to plasma proteins. Trimethoprim is widely distributed to various tissues and fluids including kidneys, liver, lung and bronchial secretions, saliva, aqueous humour, prostatic tissue and fluid, and vaginal secretions; concentrations in many of these tissues are reported to be higher than serum concentrations but concentrations in the CSF are about one-quarter to one-half of those in serum. Trimethoprim readily crosses the placenta and it appears in breast milk. The half-life is about 8 to 10 hours in adults and somewhat less in children, but is prolonged in severe renal impairment and in neonates, whose renal function is immature.

Trimethoprim is excreted mainly by the kidneys through glomerular filtration and tubular secretion. About 10 to 20% of trimethoprim is metabolised in the liver and small amounts are excreted in the faeces via the bile, but most, about 40 to 60% of a dose, is excreted in urine, mainly as unchanged drug, within 24 hours. Trimethoprim is removed from the blood by haemodialysis to some extent.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Alprim; Triprim; ***Austria***: Infectotrimet; Motrim; Solotrim†; Triprim; ***Cz.***: Triprim; ***Denm.***: Trimopan; ***Fin.***: Trimetin; Trimex†; Trimopan; ***Ger.***: InfectoTrimet; ***Hong Kong***: Primsol; ***Irl.***: Monotrim; Trimoptin; ***Malaysia***: Alprim†; ***NZ***: TMP; ***Pol.***: Trimesan; Urotrim; ***S.Afr.***: Purium†; ***Singapore***: Alprim; ***Spain***: Tediprima; ***Swed.***: Idotrim; ***Thai.***: Trimethop; Utisept†; ***UAE***: Trimol-A; ***UK***: Monotrim; Trimopan; ***USA***: Primsol; Proloprim; Trimpex.

Multi-ingredient Preparations. ***Arg.***: Adrenol; Bacti-Uril; Bacticel; Bactrim Balsamico; Bactrim; Cotrizol-G; Danferane; Dosulfin Bronquial; Dosulfin Fuerte; Enterobacticel; Neoftalm Dexa; Neoftalm; Neolag; Netocur Balsamico; Netocur; Neumobacticel; Novidrine; Rifaprim; Sulfagrand; Trimepol D†; Trimepol†; Tritenk; Urisept NF; ***Austral.***: Bactrim; Resprim; Septrin; Trimoxazole†; ***Austria***: Bactrim; Cotribene; Eusaprim; Lidaprim; Oecotrim†; ***Belg.***: Bactrim; Cotrim†; Eusaprim; Polytrim; ***Braz.***: Assepium Balsamico; Assepium; Bac-Sulfitrin; Bacfar; Bacprotin†; Bacteracin; Bactrim; Bactrisan; Bactrizol†; Bactropin; Batrox; Belfactrim F; Benectrin Balsamico; Benectrin; Diazol; Dientrin; Dispeptrin†; Ectrin Balsamico; Ectrin; Gamacutrin†; Imuneprim†; Infectrin; Metoprin Balsamico†; Metoprin; Neotrin; Pulkrin†; Qiftrim; Roytrin; Selectrin Balsamico; Selectrin†; Teutrin; Triclan; Triglobe; Trimexazol; Uroctrim; Uropol†; ***Canad.***: Apo-Sulfatrim; Novo-Trimel; Nu-Cotrimox; PMS-Polytrimethoprim; Polytrim; Protrin; Septra; Trisulfa; ***Chile***: Bacterol; Bactrimel; Entero Micinovo; Septrin; Trelibec; Uro-Micinovo; ***China***: An Li Kang (安立康); Fu Fang Xin Nuo Ming Pian (复方新诺明片); Kui Jian (奎建); Morbifurb (诺德菲); Nuo Da Ming (诺达明); Ou Lin (欧林); Pixian (彼先); Xiaoke (消刻); Xindabao (新达宝); Yu An Li Qing (玉安立清); Zengxiao Lianhuangpian (增效联磺); ***Cz.***: Biseptol; Bismoral†; Primotren†; Sumetrolim; ***Fin.***: Cotrim; Ditrim; Trimetin Duplo†; ***Fr.***: Bactrim; ***Ger.***: Berlocid†; Cotrim-Diolan; Cotrim; CotrimHefa†; Cotrimhexal†; Cotrimox-Wolff†; Cotrimstada†; Drylin†; Eusaprim; Kepinol; TMS†; ***Gr.***: Bactrimel; Bioprim; Blaxezan; Biexon; Epahol; Lidaprim; Oradin; Santafurin; Septrin; Solfoton; Stremycil-T; Sunicol; Trilogan; Ylestrom; ***Hong Kong***: Chemoprim; Cotrim; Dhatrin; Letus; Lidaprim; Resprim†; Septol†; Septrin†; Suprim†; Synco-SMZT†; Trimetrin†; Trisul†; Uni-Sulfaprim†; ***Hung.***: Cotripharm; Sumetrolim; ***India***: Alcorim-F; Antrima; Aubril; Bactrim; Cadiprim; Chemotrin; Ciplin; Colizole; Cortina; Cotribid Kid; Cotrimox; Cotrizole; Kombina; L-Trim; Larprim; Methoxaprim; Moly Kid; Mountrim; Neoprim; Okatrim DS; Oriprim-P; Oriprim; Otrim; Sepmax; Septran; Supristol; Tabrol; Trisulfose; ***Indon.***: Bactoprim Combi; Bactricid; Bactrim; Bactrizol; Cotrim†; Cotrimol†; Dotrim; Dumotrim†; Erphatrim; Ikaprim; Infatrim; Kaftrim; Lapikot; Licoprima; Meditrim†; Meprotrin; Moxalas; Nufaprim; Ottoprim; Pehatrim; Primadex; Primazole; Primsulfon; Sanprima; Septrin; Spectrem; Sulprim†; Sultrimmix†; Trimezol; Triminex†; Trimoxsul; Trixzol†; Trizole; Ulfaprim†; Wiatrim; Xepaprim; Zoltrim; Zultrop; ***Irl.***: Septrin; ***Israel***: Diseptyl; Resprim; Septrin; ***Ital.***: Bactrim; Chemitrim; Eusaprim†; ***Jpn***: Bactramin; Baktar; ***Malaysia***: Bacin; Bactrim; Balin; Beaglobe; Chemix; Cotrim; Oftalmotrim; Resprim†; Trimexazole; Trizine; Trizole; ***Mex.***: Andoprim†; Anitrim; Apo-Trinelax; Bacpiryl; Bactelan; Bacteric†; Bactide†; Bactilen; Bactiver; Bactrim Compositum; Bactrim; Bactropin; Bateral; Batrizol; Bioprim; Bisultrim; Brogamax; Dertrin; Dibaprim; Ectaprim; Esteprim; Eutrim; Partropin; Fectri; Guayaprin; Kaltrim; Maxtrim; Metoxiprim; Mixange; Neofatrim; Octex; Octiban; Odisulfan; Pisatrina†; Polibatrin; Pribac; Protaxol†; Protrim; Rifaprim; Sadocin; Septrin; Servitrim; Soltrim; Sulfawal; Sulfoid Trimetho; Sulfort; Sulprim; Sultral; Thriazol; Tribakin; Trimetoger; Trimetox; Trimexazol; Trimexole Compositum; Trimexole; Trimzol; TS-Bac; Vanadyl; ***Neth.***: Bactrimel; Lidatrim†; Polytrim; Rokiprim; ***Norw.***: Bactrim; ***NZ***: Apo-Sulfatrim†; Deprim; Trisul; ***Philipp.***: Bacidal; Bactille; Bactrim; Bactrinol; Bacxal; Baczole†; Bantizol; Chromo-Z; Combi-Methoxan; Comsid; Costazole†; Cozole†; CTR; Doctrimox; Drilozole; Embatrim; Fedimed; Forteprim; Frocimole; Globaxol; Ivatrim†; Kassemox; Kathrex; Lictora†; Macromed; Moxadden; Moxzole; Neotrim; Onetrim; Oprizole†; Pediatrim; Prizogen; Procor; Renatrim; Rimezone; Rotrace; Scribcin; Septrin; Suprex; Syltrifil; Syndal; Synermed; Timizol; Tricomed; Triforam; Triglobe†; Trim-S; Trimephar; Trimetazole; Trimitrix; Trimocom; Trimoxis; Triphimox; Trizine; Trizole; Xanazole; Zamboprim†; Zolmed; ***Pol.***: Bactrim; Biseptol; Septrin†; ***Swed.***: Bactrim; Microcetim†; Oftalmotrim; Septrin; ***Rus.***: Bactrim (Бактрим); Biseptol (Бисептол); Brifeseptol (Брифесептол); Cotrimol (Котримол); Cotripharm (Котрифарм); Groseptol (Гросептол); Lidaprim (Лидаприм)†; Oriprim (Ориприм); Rancotrim (Ранкотрим)†; Sumetrolim (Суметролим); ***S.Afr.***: Acuco†; Adco-Bencole; Bactrim; Casicot; Co Trim; Cocydal†; Cozole; Doctrim; Durobac; Dynazole; Ilvitrim; Lagatrim; Meditrim; Nucotrim; Purbac; Septran; Spectrim; Trimethox; Trimzol†; Trixazole; Ultrasept; Xerazole; ***Singapore***: Apo-Sulfatrim; Bacin; Balin; BS; Chemix; Co-Trimexazole; Dhatrin; Mortin; Primzole; Suprim; Synco-SMZT; Trimaxazole; Trizine; ***Spain***: Bactopumon; Balsoprim; Bronco Aseptilex Fuerte†; Broncovir; Bronquicisteina†; Bronquidiazina CR; Bronquimar†; Cotrazol†; Eduprim Mucolitico†; Momentol†; Oftalmotrim; Otix; Septrin; Soltrim; ***Swed.***: Bactrim; Eusaprim; ***Switz.***: Bactrim; Cotrim; Escoprim; Lagatrim; Nopil; ***Thai.***: Actin; Actrim; Addtrim; Agsulfa; Babytrim; Bacin; Bactin; Bactoprim; Bactrim; Baczole; Co-Fatrim; Co-Star; Co-Tasian; Co-Tri; Co-Trimed; Co-tromoxazole†; Comox; Comoxole; Coprim†; Coprim; Cotamox; Cotrim; D-Med; GPO-Trim; Herocetine-D; KB Famate; Ko-Cap†; Ko-Kure†; Ladar†; Lastrim; Letus†; M-Moxa; M-Trim; Mano-Trim; Maxitrin; Maxtrim; Medcotrim; Mega-Prim; Metrim; Metxaprim; Mezine; Mycosamthong; Pantrim; Patartim; Po-Trim; Spectrim; Sulbacta†; Sulfometh; Sulprim; Suntrim; Sutrim; Tactrim; Tampo; Toprim; Trifatrim; Trimexazole; Triprim†; Trixzol†; Ximeprim; Zoleprim; ***Turk.***: Bactrim; Bakton; Co-Tripirim; Cotriver; Kemoprim; Metoprim; Mikrosid; Oftalmotrim†; Polycilline†; Polytrim; Septrin; Sulfaprim; Sulfatrim†; Trifen; Trimoks; ***UAE***: Trimol; ***UK***: Fectrim; Septrin; ***Ukr.***: Bactrim (Бактрим); Biseptol (Бисептол); Groseptol (Гросептол); Soluseptol (Солюсептол); Sumetrolim (Суметролим); ***USA***: Bactrim; Cotrim†; Polytrim; Septra; SMZ-TMP; Sulfatrim; ***Venez.***: Bactrimel; Co-Sultrin; Forcrim; Trimecor; Tripur.

Pharmacopoeial Preparations

BP 2014: Co-trimoxazole Infusion; Co-trimoxazole Oral Suspension; Co-trimoxazole Tablets; Dispersible Co-trimoxazole Tablets; Paediatric Co-trimoxazole Oral Suspension; Paediatric Co-trimoxazole Tablets; Trimethoprim Oral Suspension; Trimethoprim Tablets;

USP 36: Polymyxin B Sulfate and Trimethoprim Ophthalmic Solution; Sulfamethoxazole and Trimethoprim Injection; Sulfamethoxazole and Trimethoprim Oral Suspension; Sulfamethoxazole and Trimethoprim Tablets; Trimethoprim Tablets.

Troleandomycin *(BAN, USAN, rINN)*

NSC-108166; Triacetyloleandomycin; Troleandomicina; Troleandomisin; Troléandomycine; Troleandomycinum; Troleandomysiini; Тролеандомицин.

The triacetyl ester of oleandomycin .

$C_{41}H_{67}NO_{15}$=814.0

CAS — 2751-09-9.

ATC — J01FA08.

ATC Vet — QJ01FA08.

UNII — C4DZ64560D.

Pharmacopoeias. In *Fr.*

Profile

Troleandomycin is a prodrug of the macrolide antibacterial oleandomycin that has actions similar to those of erythromycin (p. 291.2). It has been given orally in the treatment of susceptible infections although more effective antibacterials are generally preferred.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Triocetin†; ***Turk.***: Tekmisin.

Tulathromycin *(USAN, rINN)*

CP-472295 (component A); CP-547272 (component B); Tulathromycine; Tulathromycinum; Tulatromicina; Тулатромицин.

$C_{41}H_{79}N_3O_{12}$=806.1

CAS — 217500-96-4 (component A); 280755-12-6 (component B).

ATC Vet — QJ01FA94.

UNII — Q839I13422 (tulathromycin); 897A3KN7AP (tulathromycin component A); T5PDD839DA (tulathromycin component B).

NOTE. The name Draxxin has been used as a trade mark for tulathromycin.

Profile

Tulathromycin is a macrolide antibacterial used in veterinary medicine for the treatment of susceptible infections in cattle and pigs.

Tylosin *(BAN, rINN)*

Tilosina; Tilozin; Tylosiini; Tylosine; Tylosinum; Tylozyna; Типозин.

$C_{46}H_{77}NO_{17}$=916.1

CAS — 1401-69-0.

ATC Vet — QJ01FA90; QJ51FA90.

UNII — YEF4JXN031.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*, both for veterinary use.

Ph. Eur. 8: (Tylosin for Veterinary Use; Tylosin BP 2014; Tylosin BP(Vet) 2014). A mixture of macrolide antibiotics produced by a strain of *Streptomyces fradiae* or by any other means. The main component of the mixture is tylosin A, but tylosin B (desmycosin), tylosin C (macrocin), and tylosin D (relomycin) may also be present. An almost white or slightly yellow powder. Slightly soluble in water; freely soluble in dehydrated alcohol and in dichloromethane. It dissolves in dilute solutions of mineral acids. A 2.5% suspension in water has a pH of 8.5 to 10.5. Protect from light.

USP 36: (Tylosin). A macrolide antibiotic substance or mixture of such substances produced by the growth of *Streptomyces fradiae* or by any other means. A white to buff-coloured powder. Slightly soluble in water; soluble in alcohol, in amyl acetate, in chloroform, and in dilute mineral acids; freely soluble in methyl alcohol. It loses not more than 5% of its weight on drying. Protect from light, moisture, and temperatures exceeding 40 degrees.

Tylosin Tartrate *(BANM, rINNM)*

Tartrato de tilosina; Tilosina, tartrato de; Tilozin-tartarát; Tylosiinitartraatti; Tylosin tartarát; Tylosine, Tartrate de; Tylosini tartras; Tylosintartrat; Tylozyny winian; Тилозина Тартрат.

$(C_{46}H_{77}NO_{17})_2.C_4H_6O_6$=1982.3

CAS — 1405-54-5.

UNII — 5P4625C51T.

Pharmacopoeias. In *Eur.* (see p. vii) and *US* for veterinary use.

Ph. Eur. 8: (Tylosin Tartrate for Veterinary Use; Tylosin Tartrate BP 2014; Tylosin Tartrate BP(Vet) 2014). An almost white or slightly yellow hygroscopic powder. Freely soluble in water and in dichloromethane; slightly soluble in dehydrated alcohol. It dissolves in dilute solutions of mineral acids. A 2.5% solution in water has a pH of 5.0 to 7.2. Store in airtight containers. Protect from light.

USP 36: (Tylosin Tartrate). A tartrate of a mixture of macrolide antibiotic substances, or the mixture of such substances, produced by the growth of *Streptomyces fradiae*, or by any other means. Its potency is not less than 800 micrograms of tylosin per mg, calculated on the dried basis.

An almost white or slightly yellow, hygroscopic powder. Freely soluble in water and in dichloromethane; slightly soluble in alcohol. It dissolves in dilute solutions of mineral acids. pH of a 2.5% solution in water is between 5.0 and 7.2. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Profile

Tylosin is a macrolide antibacterial with actions similar to those of erythromycin (p. 291.2). Tylosin and its phosphate and tartrate salts are used in veterinary medicine in the prophylaxis and treatment of infections caused by susceptible organisms.

Tylosin and tylosin phosphate have been added to animal feeding stuffs as growth promotors for pigs.

Tylvalosin Tartrate *(USAN, rINNM)*

Acetyl Isovaleryl Tylosin Tartrate; Acetylisovaleryltylosin Tartrate; Tartrato de tilvalosina; Tylvalosine, Tartrate de; Tylvalosini Tartras; Тильвальозина Тартрат.

(4*R*,5*S*,6*S*,7*R*,9*R*,11*E*,13*E*,15*S*,16*R*)-15-[[(6-Deoxy-2,3-di-*O*-methyl-β-*D*-allopyranosyl)oxy]methyl]-6-({3,6-dideoxy-4-*O*-[2,6-dideoxy-3-*C*-methyl-4-*O*-(3-methylbutanoyl)-α-L-*ribo*-hexopyranosyl]-3-(dimethylamino)-β-D-glucopyranosyl}oxy)-16-ethyl-5,9,13-trimethyl-2,10-dioxo-7-(2-oxoethyl)oxacyclohexadeca-11,13-dien-4-yl acetate (2*R*,3*R*)-2,3-dihydroxybutanedioate.

$C_{53}H_{83}NO_{19}.C_4H_6O_6$

CAS — 63409-12-1 (tylvalosin); 63428-13-7 (tylvalosin tartrate).

ATC Vet — QJ01FA92.

UNII — AL5667FY0W.

The symbol † denotes a preparation no longer actively marketed

Profile

Tylvalosin is a derivative of tylosin (p. 383.3) and is used similarly as the tartrate in veterinary medicine.

Tyrothricin *(BAN, rINN)*

Tirotricina; Tirotricinas; Tirotrisin; Tyrothricine; Tyrothricinum; Tyrotricin; Tyrotrisiini; Тиротрицин.

CAS — 1404-88-2.
ATC — D06AX08; R02AB02; S01AA05.
ATC Vet — QD06AX08; QR02AB02; QS01AA05.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Tyrothricin). A mixture of antimicrobial linear and cyclic polypeptides, isolated from the fermentation broth of *Bacillus brevis*. It consists mainly of gramicidins and tyrocidins; other related compounds may be present in smaller amounts. The potency is 180 to 280 international units/mg, calculated with reference to the dried substance. A white or almost white powder. Practically insoluble in water; soluble in alcohol and in methyl alcohol. Store in airtight containers. Protect from light.

USP 36: (Tyrothricin). An antibacterial substance produced by the growth of *Bacillus brevis*. It is a mixture consisting chiefly of gramicidin and tyrocidine, the latter being usually present as the hydrochloride. Store in airtight containers.

Uses and Administration

Tyrothricin is unsuitable for systemic use. It is active *in vitro* against many Gram-positive bacteria and has been used either alone or with other antibacterials in the local treatment of infections mainly of the skin and mouth.

Adverse Effects and Precautions

Tyrothricin is too toxic to be used systemically; effects that have been reported include hepatic and renal toxicity as well as Stevens-Johnson syndrome. It damages the sensory epithelium of the nose and instances of prolonged loss of smell have occurred after its use as a nasal spray or instillation. Tyrothricin should not be instilled into the nasal cavities or into closed body cavities.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Tyrosur; *Gr.*: Triciderm; Tyrex Dermose; *Ital.*: Faringotricina; Hydrotricine; Rinotricina; *Port.*: Hydrotricine; *Turk.*: Hydrotricine; *Ukr.*: Tyrosur (Тирозур).

Multi-ingredient Preparations. *Arg.*: Acemuk L; Algiodent; Aseptobron Caramelos; Bagocletas; Biotaer an Caramelos; Biotaer Nebulizable; Bucotricin; Caramelos Antibioticos Lefmar; Caramelos Antibioticos; Caramelos Antibioticos; Collubiazol; Fanaletas; Filotricin A; Fonergine; Gineseptina; Oralsone C; Pulmosan Caramelos; Solumerin; Sulfanoral T; Tavinex; Vagicural; Vagisan Compuesto; Vagisan; *Austria*: Dorithricin; Lemocin; Limexx†; Tyrothricin comp; *Belg.*: Lemocin; Tyro-Drops†; *Braz.*: Amidalin; Amigdagen†; Amigdalol; Anapyon; Anginotricin; Auritricin; Colpagex-N†; Colpolase†; Gynax-N; Lacto Vagin; Malvatricin Ginecologico†; Malvatricin Pastilhas; Malvatricin Pronto; Malvatricin Solucao para diluir; Malvatricin Spray; Malvatricin; Oturga; Trivagel N; Vagitrin-N; *Canad.*: Antibiotic Cold Sore Ointment†; Soropon†; *China*: Deq (得益); *Ger.*: Dorithricin; Lemocin†; Tyrosur; *Gr.*: Evex; Oulogram; Trachisan; *Hong Kong*: Deq; Tyricine; Tyrocaine†; Tyrothricin Co; *Hung.*: Dorithricin; Tyrosur; *India*: Tytin; *Indon.*: Lemocin; *Irl.*: Tyrozets; *Israel*: Clearocin; Kalgaron; Lemocin; Rafathricin with Benzocaine; *Ital.*: Bioarscolloid; Deltavagin; Purotricina; Golamixin; Kinogen; Rinocidina; *Malaysia*: Deq; Upha Lozenges; *Mex.*: Angenovag; *Port.*: Mebocaina; Medifon†; Mentocaina R; *Singapore*: Beathricin; Deq; Dorithricin; Trachisan; Tyrocaine; *Spain*: Anginovag; Bucometasana; Cicatral; Cohortan; Denticelso; Diformiltricina†; Miozets; Pastillas Koki Mentol Tirotricina; Piorlist†; Roberfarin; Viberol Tirotricina; *Switz.*: Citropain nouvelle formule; Gem nouvelle formule contre le mal de gorge; Impuls†; Lemocin; Mebu; Mebucaine; Mebucasol †; Otothricinol; Rotpunkt Apotheke nouvelle formule pastilles contre le mal de gorge†; Sangerol; Solmucaine; Swidro nouvelle formule pastilles contre le mal de gorge†; Tyroqualine; Tyrothricin†; Tyrothricine + Gramicidine†; Zurcher Bahnhof Apotheke pastilles contre le mal de gorge nouvelle formule†; *Thal.*: Deq; Iwazin; Jawkepta; Sigatricin†; Tonsilon; Trocacin; Troneo; *Turk.*: Neolet; *UAE*: B-Cool; *UK*: Tyrozets; *Ukr.*: Anginovag (Ангіноваг); Trachisan (Трахісан); *Venez.*: Otan.

Valnemulin *(BAN, rINN)*

Valnemulinii; Valnemulina; Valnémuline; Valnemulinum; Вальнемулин.

((2-[(*R*)-2-Amino-3-methylbutyramido]-1,1-dimethylethyl) thio)acetic acid 8-ester with (3a*S*,4*R*,5*S*,6*S*,8*R*,9*R*,9a*R*,10*R*)-octahydro-5,8-dihydroxy-4,6,9,10-tetramethyl-6-vinyl-3a,9-propano-3a*H*-cyclopentacycloocten-1(4*H*)-one.

$C_{31}H_{52}N_2O_5S$=564.8

CAS — 101312-92-9 (valnemulin); 133868-46-9 (valnemulin hydrochloride).
ATC Vet — QJ01XQ02.
UNII — 2AHC415BQG.

Pharmacopoeias. *Eur.* (see p. vii) includes the hydrochloride for veterinary use.

Profile

Valnemulin is an antibacterial used as the hydrochloride in veterinary medicine.

Vancomycin *(BAN, rINN)*

Vancomicina; Vancomycine; Vancomycinum; Vankomycin; Vankomysiini; Ванкомицин.

(*S*$_a$)-(3*S*,6*R*,7*R*,22*R*,23*S*,26*S*,36*R*,38a*R*)-44-[[2-*O*-(3-Amino-2,3,6-trideoxy-3-*C*-methyl-α-L-*lyxo*-hexopyranosyl)-β-D-glucopyranosyl]oxy]-3-(carbamoylmethyl)-10,19-dichloro-2,3,4,5,6,7,23,24,25,26,36,37,38,38a-tetradecahydro-7,22,28,30,32-pentahydroxy-6-[(2*R*)-4-methyl-2-(methylamino)valeramido]-2,5,24,38,39-pentaoxo-22*H*-8,11:18,21-dietheno-23,36-(iminomethano)-13,16:31,35-dimetheno-1*H*,16*H*-[1,6,9]oxadiazacyclohexadecino[4,5-*m*][10,2,16]-benzoxadiazacyclotetracosine-26-carboxylic acid.

$C_{66}H_{75}Cl_2N_9O_{24}$=1449.3

CAS — 1404-90-6.
ATC — A07AA09; J01XA01.
ATC Vet — QA07AA09; QJ01XA01.
UNII — 6Q205EH1VU.

Description. A glycopeptide antimicrobial substance or mixture of glycopeptides produced by the growth of certain strains of *Amycolatopsis orientalis* (*Nocardia orientalis*, *Streptomyces orientalis*), or by any other means.

Pharmacopoeias. In *US.*

USP 36: (Vancomycin). Store in airtight containers.

Vancomycin Hydrochloride *(BANM, rINNM)*

Hidrocloruro de vancomicina; Vancomicina, hidrocloruro de; Vancomycine, Chlorhydrate de; Vancomycinhydrochlorid; Vancomycin-hydrochlorid; Vancomycini Hydrochloridum; Vankomicinhidroklorid; Vankomicino hidrochloridas; Vankomisin Hidroklorür; Vankomycinhydroklorid; Vankomysiinihydrokloridi; Wankomycyny chlorowodorek; Ванкомицина гидрохлорид.

$C_{66}H_{75}Cl_2N_9O_{24}$.HCl=1485.7

CAS — 1404-93-9.
ATC — A07AA09; J01XA01.
ATC Vet — QA07AA09; QJ01XA01.
UNII — 71WO621TJD.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Vancomycin Hydrochloride). A mixture of related glycopeptides, consisting mainly of vancomycin B, a substance produced by certain strains of *Amycolatopsis orientalis* or obtained by any other means. A white or almost white, hygroscopic powder. Freely soluble in water; slightly soluble in alcohol. A 5% solution in water has a pH of 2.5 to 4.5. Store in airtight containers. Protect from light.

USP 36: (Vancomycin Hydrochloride). A substance or mixture of substances produced by the growth of *Streptomyces orientalis*. A white, almost white, or tan to brown, odourless, free-flowing powder. Freely soluble in water; insoluble in chloroform and in ether. A 5% solution in water has a pH of 2.5 to 4.5. Store in airtight containers.

Incompatibility. Solutions of vancomycin hydrochloride have an acid pH and incompatibility may reasonably be expected with alkaline preparations, or with drugs unstable at low pH. Reports of incompatibility are not always consistent, and other factors such as the composition of the vehicles used may play a part.

Strength of solution may also be important; evidence of physical incompatibility was seen in solutions containing citrate 4% and vancomycin 20 mg/mL (as may be used in catheter lock solutions), but when the concentration of vancomycin was reduced to either 10 mg/mL or 5 mg/mL, no evidence of incompatibility was seen.[1]

1. Dotson B, *et al.* Physical compatibility of 4% sodium citrate with selected antimicrobial agents. *Am J Health-Syst Pharm* 2010; 67: 1195–8.

Stability. Although licensed product information recommends storage at 2 degrees to 8 degrees, solutions of vancomycin hydrochloride in various diluents (sodium chloride 0.9%, glucose 5%, and peritoneal dialysis solution) have been found to be stable for at least 14 days at room temperature.[1-3]

The stability of vancomycin in ophthalmic solution has also been studied.[4]

1. Das Gupta V, *et al.* Stability of vancomycin hydrochloride in 5% dextrose and 0.9% sodium chloride injections. *Am J Hosp Pharm* 1986; 43: 1729–31.
2. Walker SE, Birkhans B. Stability of intravenous vancomycin. *Can J Hosp Pharm* 1988; 41: 233–8.
3. Mauhinuey WM, *et al.* Stability of vancomycin hydrochloride in peritoneal dialysis solution. *Am J Hosp Pharm* 1992; 49: 137–9.
4. Fuhrman LC, Stroman RT. Stability of vancomycin in an extemporaneously compounded ophthalmic solution. *Am J Health-Syst Pharm* 1998; 55: 1386–8.

Uses and Administration

Vancomycin is a glycopeptide antibacterial that is used intravenously in the treatment and prophylaxis of serious staphylococcal or other susceptible Gram-positive infections, traditionally when other drugs cannot be used because of resistance or patient intolerance. It is used particularly in the treatment of MRSA infections (p. 208.2). It may also be used as part of a multidrug regimen for the treatment of inhalation and gastrointestinal anthrax, and orally in the treatment of antibiotic-associated colitis. For details of all these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Vancomycin may be used with other antibacterials to extend or increase efficacy notably with gentamicin or other aminoglycosides, or with rifampicin (but see Antimicrobial Action, p. 389.1).

Administration and dosage. Vancomycin is given as the hydrochloride but doses are expressed in terms of the base. 1.03 g of vancomycin hydrochloride is equivalent to about 1 g of vancomycin. It is given intravenously, preferably by intermittent infusion, although continuous infusion has been used. For intermittent infusion, a concentrated solution containing the equivalent of 500 mg of vancomycin in 10 mL of water is prepared and then added to glucose 5% or sodium chloride 0.9% to produce a diluted solution containing not more than 5 mg/mL; this diluted solution is then infused over at least 60 minutes for a 500-mg dose or 100 minutes for a 1-g dose. Final concentrations of up to 10 mg/mL may be used for patients requiring fluid restriction, although there is an increased risk of adverse events. For continuous intravenous infusion when intermittent infusion is not feasible, the equivalent of 1 to 2 g is added to a sufficiently large volume of glucose or sodium chloride to permit the daily dose to be given over a period of 24 hours.

The usual adult dose is the equivalent of 500 mg of vancomycin every 6 hours or 1 g every 12 hours (but see also Administration, p. 387.1). Response is generally seen within 48 to 72 hours in sensitive infections. In patients with staphylococcal endocarditis, treatment for at least 3 weeks has been recommended.

Where vancomycin is required for surgical infection prophylaxis, a single 1-g dose given by intravenous infusion is recommended by the *BNF*.

For doses in children and neonates, see p. 387.2.

Dose adjustment and monitoring. It has been recommended that dosage should be adjusted if necessary according to plasma-vancomycin concentrations, and this is particularly important where factors such as age or renal impairment (see also p. 388.1) may predispose to toxicity, or where there is a risk of subtherapeutic concentrations. There has been some dispute about the relationship between plasma concentrations and toxicity, and this, complicated by differences in the sampling time after the end of infusion and by differences in the regimens and assay method used, has meant that suggested peak and trough concentrations have varied considerably (see Precautions, p. 388.3).

Other routes. Vancomycin hydrochloride is given orally in the treatment of staphylococcal enterocolitis and antibiotic-associated colitis, including pseudomembranous colitis associated with the overgrowth of *Clostridium difficile*. It is given in a dose of 0.5 to 2 g daily in 3 or 4 divided doses for 7 to 14 days; the lowest dose of 500 mg daily is often considered adequate.

In meningitis or other CNS infections, vancomycin has sometimes been given by the intrathecal or intraventricular route in order to ensure adequate CSF concentrations of antibiotic. Vancomycin has also been applied topically to the eye or given by subconjunctival or intravitreal injection; it has also been given by inhalation. Vancomycin has been added to dialysis solutions in the treatment of peritonitis associated with continuous ambulatory peritoneal dialysis.

General references.

1. Stevens DL. The role of vancomycin in the treatment paradigm. *Clin Infect Dis* 2006; 42 (suppl 1): S51–S57.
2. Deresinski S. Vancomycin: does it still have a role as an antistaphylococcal agent? *Expert Rev Anti Infect Ther* 2007; 5: 393–401.
3. Cunha BA. Vancomycin revisited: a reappraisal of clinical use. *Crit Care Clin* 2008; 24: 393–420.
4. Levine DP. Vancomycin: understanding its past and preserving its future. *South Med J* 2008; 101: 284–91.
5. Niu SC, *et al.* Modified vancomycin dosing protocol for treatment of diabetic foot infections. *Am J Health-Syst Pharm* 2008; 65: 1740–3.

Administration. A consensus review[1] considered that, for most patients with normal renal function, doses of 15 to 20 mg/kg (based on actual body-weight) given every 8 to 12 hours will be necessary for adequate serum-vancomycin trough concentrations. For seriously ill patients an initial loading dose of 25 to 30 mg/kg can be considered so that optimal serum-vancomycin trough concentrations will occur more quickly. For patients infected with strains having an MIC of 2 micrograms/mL or more this was not likely to be adequate, and alternative therapies should be considered. Trough concentrations should always be maintained above 10 micrograms/mL to avoid the development of resistance in *Staph. aureus*. When individual doses exceed 1 g the infusion period should be extended to 1.5 to 2 hours.

Weight-based dosing is particularly important for obese patients. A multicentre study in patients of various body-weights indicated that although fixed doses of vancomycin 1 g twice daily achieved satisfactory initial dosing (determined as 10 mg/kg or more per dose) in underweight, normal, and overweight patients, only about 28% of obese patients could be considered to be adequately dosed.[2] If more stringent dose limits of at least 15 mg/kg per dose were used as recommended in several guidelines, less than 1% of obese patients were given adequate initial doses, and this was rarely corrected in the subsequent 24 hours. It has therefore been recommended[1] that initial doses for all patients, including the obese, should be calculated based on absolute body-weight, and then adjusted based on serum-vancomycin concentrations.

1. Rybak M, *et al.* Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am J Health-Syst Pharm* 2009; 66: 82–98. Correction. *ibid.*: 887. Also available at: http://www.ajhp.org/cgi/reprint/66/1/82 (accessed 12/11/10)
2. Hall RG, *et al.* Multicenter evaluation of vancomycin dosing: emphasis on obesity. *Am J Med* 2008; 121: 515–18.

Administration in children. Vancomycin is licensed for use in children. In children and infants over 1 month of age, an *intravenous* dose of 10 mg/kg four times a day or 15 mg/kg three times a day, up to the usual adult maximum of 1 to 2 g daily, may be given for mild to moderate infections; for severe infections, the daily dose may be increased to 60 mg/kg daily up to a maximum of 2 to 4 g daily.

In neonates, various dosage schedules have been suggested. UK licensed product information states that neonates up to 1 month old may be given an initial intravenous dose of 15 mg/kg; this is followed by 10 mg/kg every 12 hours in the first week of life or by 10 mg/kg every 8 hours in those aged 1 week to 1 month. The *BNFC* recommends the following intravenous doses for neonates:

- less than 29 weeks postmenstrual age: 15 mg/kg every 24 hours
- 29 to 35 weeks postmenstrual age: 15 mg/kg every 12 hours
- over 35 weeks postmenstrual age: 15 mg/kg every 8 hours

In the USA, the American Academy of Pediatrics[1] suggests that intravenous doses for neonates are based are on serum-creatinine concentrations as follows:

- serum-creatinine concentrations < 0.7 mg/dL: 15 mg/kg every 12 hours
- serum-creatinine concentrations 0.7 to 0.9 mg/dL: 20 mg/kg every 24 hours
- serum-creatinine concentrations 1 to 1.2 mg/dL: 15 mg/kg every 24 hours
- serum-creatinine concentrations 1.3 to 1.6 mg/dL: 10 mg/kg every 24 hours
- serum-creatinine concentrations > 1.6 mg/dL: 15 mg/kg every 48 hours

Note. For neonates with a gestation of 28 weeks or less, a value of 0.2 is added to the measured serum-creatinine concentration when the algorithm is used.

One group of workers,[2] found that continuous infusion of vancomycin in premature neonates could achieve the required therapeutic range in most cases and had produced good bacteriological efficacy. The regimen they proposed for the first 48 hours was 20 mg/kg daily in premature neonates with a serum-creatinine concentration of more than 90 micromol/litre and 30 mg/kg daily in those with a serum-creatinine concentration of 90 micromol/litre or less. Thereafter the dosage was increased or decreased if necessary by 5 mg/kg daily to maintain serum-vancomycin concentrations between 10 and 25 micrograms/mL.

Vancomycin may also be given *orally* to treat staphylococcal enterocolitis and antibiotic-associated colitis. A suggested dose for children in licensed product information is 40 mg/kg daily in 3 or 4 divided doses; the *BNFC* suggests the following doses given four times daily, usually for 10 to 14 days:

- 1 month up to 5 years: 5 mg/kg
- 5 to 12 years: 62.5 mg
- over 12 years: 125 mg

Higher oral doses may be considered if the infection is life-threatening or fails to respond to treatment.

Review[3] of the use of vancomycin in neonates.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.
2. Plan O, *et al.* Continuous-infusion vancomycin therapy for preterm neonates with suspected or documented Gram-positive infections: a new dosage schedule. *Arch Dis Child Fetal Neonatal Ed* 2008; 93: F418–21.
3. de Hoog M, *et al.* Vancomycin: pharmacokinetics and administration regimens in neonates. *Clin Pharmacokinet* 2004; 43: 417–40.

Administration in renal impairment. Various methods, including predictive nomograms based on creatinine clearance and pharmacokinetic methods such as those using Bayesian statistics, have been suggested for calculating vancomycin dosage requirements in patients with reduced renal function. One suggested approach has been a loading dose of 15 mg/kg followed by a daily dose in mg equivalent to about 15 times the glomerular filtration rate in mL/minute; or in anuric patients a dose of 1 g every 7 to 10 days. However, individualised dosage based on plasma concentrations is generally to be preferred.

Vancomycin is significantly dialysable via high-flux intermittent haemodialysis and it has been suggested that once-weekly vancomycin dosing in this setting will result in inadequate trough concentrations. A review[1] of antimicrobial dosing in renal replacement therapy has recommended that patients on intermittent haemodialysis should receive a loading dose of 15 to 25 mg/kg intravenously on day 1, followed by a 5 to 10 mg/kg maintenance dose after each dialysis run; dose adjustments should be made based on both the targeted, and reported serum-vancomycin concentrations.

For critically ill patients undergoing continuous renal replacement therapy, the same loading dose is recommended; maintenance doses (which should be adjusted based on serum-vancomycin concentration) are as follows:[1]

- continuous venovenous haemofiltration (CVVH): 10 to 15 mg/kg every 24 to 48 hours
- continuous venovenous haemodialysis (CVVHD): 10 to 15 mg/kg every 24 hours (7.5 mg/kg every 12 hours may be required when higher serum-vancomycin concentrations are needed)
- continuous venovenous haemodiafiltration (CVVHDF): 7.5 to 10 mg/kg every 12 hours

1. Heintz BH, *et al.* Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 2009; 29: 562–77.

Adverse Effects

The intravenous use of vancomycin may be associated with the so-called 'red-neck' or 'red-man' syndrome, characterised by erythema, flushing, or rash over the face and upper torso, and sometimes by hypotension and shock-like symptoms. The effect appears to be due in part to the release of histamine and is usually related to rapid infusion.

Hypersensitivity reactions may occur in about 5% of patients and include rashes, fever, chills, and rarely, anaphylactoid reactions, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and vasculitis. Drug rash with eosinophilia and systemic symptoms (DRESS syndrome) has also been reported. Many reactions have become less frequent with the availability of more highly purified preparations. Reversible neutropenia, eosinophilia, and rarely thrombocytopenia and agranulocytosis have been reported; neutropenia is stated to be more common in patients who have received a total dose of 25 g or more. Nephrotoxicity, including rare cases of interstitial nephritis, may occur, particularly at high doses or in patients with predisposing factors, but has declined in frequency with greater awareness of the problem and appropriate monitoring of plasma concentrations and renal function.

Ototoxicity is also associated with vancomycin, and is more likely in patients with high plasma concentrations, or with renal impairment or pre-existing hearing loss. It may progress after drug withdrawal, and may be irreversible. Hearing loss may be preceded by tinnitus, which must be regarded as a sign to stop treatment.

Vancomycin is irritant; intravenous use may be associated with thrombophlebitis, although this can be minimised by the slow infusion of dilute solutions, and by using different infusion sites. Extravasation may cause tissue necrosis.

Because of its poor absorption, relatively few adverse effects have been reported after the oral use of vancomycin, although mild gastrointestinal disturbances have occurred.

Effects on the ears. Reviews[1,2] of ototoxicity associated with vancomycin therapy have indicated that the actual number of cases is quite small, and close examination suggests that in most cases where hearing loss occurred patients had also received an aminoglycoside. The degree, and the reversibility, of ototoxicity associated with vancomycin alone is uncertain.

1. Baille GR, Neal D. Vancomycin ototoxicity and nephrotoxicity: a review. *Med Toxicol* 1988; 3: 376–86.
2. Brummett RE, Fox KE. Vancomycin- and erythromycin-induced hearing loss in humans. *Antimicrob Agents Chemother* 1989; 33: 791–6.

Effects on the gastrointestinal tract. Exposure to antibacterials, particularly broad-spectrum antibacterials, is the most significant risk factor for development of antibiotic-associated colitis (AAC). Antibacterials usually used to treat the disease such as vancomycin and metronidazole have also been shown to cause AAC. A 25-year-old woman developed AAC after a course of vancomycin and metronidazole, both orally, for pelvic inflammatory disease.[1] The condition resolved after treatment with vancomycin given alone. In another case,[2] *C. difficile* colitis developed after the use of intravenous vancomycin in a patient who had recently had other antibacterial treatment. For further reports on AAC caused by metronidazole see under Metronidazole, p. 940.1.

1. Bingley PJ, Harding GM. Clostridium difficile colitis following treatment with metronidazole and vancomycin. *Postgrad Med J* 1987; 63: 993–4.
2. Szczesny A, *et al.* Incidence of pseudomembranous colitis after vancomycin-treated MRSA infection. *Clin Microbiol Infect* 2002; 8: 58–9.

Effects on the heart. Cardiac arrest associated with an inadvertent rapid intravenous dose of vancomycin 150 mg has been reported[1] in a neonate.

1. Boussemart T, *et al.* Cardiac arrest associated with vancomycin in a neonate. *Arch Dis Child* 1995; 73: F123.

Effects on the kidneys. In a study,[1] nephrotoxicity was seen in 14 of 101 patients given vancomycin 1 g before and after vascular surgery for infection prophylaxis compared with 2 of 99 given saline placebo, suggesting that even short regimens of vancomycin can affect renal function. In another study involving 224 patients, nephrotoxicity was seen in 8 of 168 given vancomycin alone, 14 of 63 given vancomycin with an aminoglycoside, and 11 of 103 given an aminoglycoside without vancomycin.[2] This latter study found that use with aminoglycosides, trough serum concentrations of vancomycin greater than 10 micrograms/mL, and prolonged vancomycin therapy (for more than 21 days) were associated with an increased risk of nephrotoxicity. A later retrospective study[3] suggested that a relationship between exposure and nephrotoxicity existed, and that the most useful measure of the former was trough concentration of vancomycin. (In these studies nephrotoxicity was defined in terms of increased serum creatinine.) The use of high-dose vancomycin, in an effort to overcome resistance in meticillin-resistant staphylococci, has therefore led to concerns that aggressive dosing may increase the risk of nephrotoxicity; however, a review[4] has pointed out that the risk of nephrotoxicity with the drug remains minimal in patients without other risk factors.

1. Gudmundsson GH, Jensen LJ. Vancomycin and nephrotoxicity. *Lancet* 1989; i: 625.
2. Rybak MJ, *et al.* Nephrotoxicity of vancomycin, alone and with an aminoglycoside. *J Antimicrob Chemother* 1990; 25: 679–87.
3. Lodise TP, *et al.* Relationship between initial vancomycin concentration-time profile and nephrotoxicity among hospitalized patients. *Clin Infect Dis* 2009; 49: 507–14.
4. Hazlewood KA, *et al.* Vancomycin-associated nephrotoxicity: grave concern or death by character assassination? *Am J Med* 2010; 123: 182. e1–e7.

Effects on the liver. A 57-year-old man with multiple medical conditions developed raised liver enzyme values, on 5 different occasions, while being treated with oral vancomycin for episodes of *Clostridium difficile*-associated enterocolitis; liver enzymes returned to normal values each time the vancomycin was stopped.[1]

1. Cadle RM, *et al.* Vancomycin-induced elevation of liver enzyme levels. *Ann Pharmacother* 2006; 40: 1186–9.

Effects on the nervous system. Encephalopathy[1] (associated with high CSF concentrations after oral doses) and peripheral neuropathy[2] has been associated with vancomycin.

1. Thompson CM, *et al.* Absorption of oral vancomycin—possible associated toxicity. *Int J Pediatr Nephrol* 1983; 4: 1–4.
2. Leibowitz G, *et al.* Mononeuritis multiplex associated with prolonged vancomycin treatment. *BMJ* 1990; 300: 1344.

Effects on the skin. Rashes, erythema, or pruritus are the most common skin reactions associated with vancomycin but there have also been reports of linear IgA dermatosis,[1-4] Stevens-Johnson-like reaction,[5] bullous eruption,[6] local skin necrosis,[7] and exfoliative dermatitis.[6] In an analysis, risk factors for adverse cutaneous reactions were suggested to be age under 40 years and duration of therapy greater than 7 days.[6] See also under Hypersensitivity, p. 388.3.

1. Piketty C, *et al.* Linear IgA dermatosis related to vancomycin. *Br J Dermatol* 1994; 130: 130–1.
2. Nousari HC, *et al.* Vancomycin-associated linear IgA bullous dermatosis. *Ann Intern Med* 1998; 129: 507–8.

3. Bernstein EF, Schuster M. Linear IgA bullous dermatosis associated with vancomycin. *Ann Intern Med* 1998; 129: 508–9.
4. Danielsen AG, Thomsen K. Vancomycin-induced linear IgA bullous disease. *Br J Dermatol* 1999; 141: 756–7.
5. Laurencin CT, *et al.* Stevens-Johnson-like reaction with vancomycin treatment. *Ann Pharmacother* 1992; 26: 1520–1.
6. Korman TM, *et al.* Risk factors for adverse cutaneous reactions associated with intravenous vancomycin. *J Antimicrob Chemother* 1997; 39: 371–81.
7. Hoelen DW, *et al.* Severe local vancomycin induced skin necrosis. *Br J Clin Pharmacol* 2007; 64: 553–4.

Hypersensitivity. Skin reactions to vancomycin are common (see Effects on the Skin, p. 385.3), and may occur as part of a hypersensitivity reaction. The DRESS syndrome (drug rash with eosinophilia and systemic symptoms) has been reported rarely,[1] in patients given vancomycin. In general, the onset of DRESS occurred within 2 to 5 weeks of starting treatment, and was associated with hepatitis (and sometimes nephritis and pneumonitis); all patients survived after immediate withdrawal of vancomycin and treatment with intravenous corticosteroids.

1. Vauthey L, *et al.* Vancomycin-induced DRESS syndrome in a female patient. *Pharmacology* 2008; 82: 138–41.

Red-man syndrome. References[1-3] to the 'red-man syndrome', and evidence that pretreatment with an antihistamine can provide significant protection against it.[4,5] Similar reactions appear to be much less of a problem with teicoplanin and substitution of teicoplanin for vancomycin may be a viable alternative in patients at risk.[2,3,6] Skin tests are reported[7] to be of little value in predicting the severity of 'red-man syndrome'.

1. Wallace MR, *et al.* Red man syndrome: incidence, etiology, and prophylaxis. *J Infect Dis* 1991; 164: 1180–5.
2. Polk RE. Anaphylactoid reactions to glycopeptide antibiotics. *J Antimicrob Chemother* 1991; 27 (suppl B): 17–29.
3. Rybak MJ, *et al.* Absence of "red man syndrome" in patients being treated with vancomycin or high-dose teicoplanin. *Antimicrob Agents Chemother* 1992; 36: 1204–7.
4. Renz CL, *et al.* Oral antihistamines reduce the side effects from rapid vancomycin infusion. *Anesth Analg* 1998; 87: 681–5.
5. Renz CL, *et al.* Antihistamine prophylaxis permits rapid vancomycin infusion. *Crit Care Med* 1999; 27: 1732–7.
6. Smith SR. Vancomycin and histamine release. *Lancet* 1990; 335: 1341.
7. Polk RE, *et al.* Vancomycin skin tests and prediction of "red man syndrome" in healthy volunteers. *Antimicrob Agents Chemother* 1993; 37: 2139–43.

AFTER ORAL ADMINISTRATION. Reports of rash[1] and 'red-man syndrome'[2,3] after oral vancomycin.

1. McCullough JM, *et al.* Oral vancomycin-induced rash: case report and review of the literature. *DICP Ann Pharmacother* 1991; 25: 1326–8.
2. Killian AD, *et al.* Red man syndrome after oral vancomycin. *Ann Intern Med* 1991; 115: 410–11.
3. Bergeron L, Boucher FD. Possible red-man syndrome associated with systemic absorption of oral vancomycin in a child with normal renal function. *Ann Pharmacother* 1994; 28: 581–4.

Precautions

Vancomycin should not be given again to patients who have had a hypersensitivity reaction to it. It should not be given intramuscularly, and care should be taken when it is given intravenously to avoid extravasation, because of the risk of tissue necrosis. The adverse effects of infusion may be minimised by dilution of each 500 mg of vancomycin in at least 100 mL of fluid, and by infusion of doses over not less than 60 minutes. Infusion sites should be changed regularly.

Because the risk of ototoxicity and nephrotoxicity is thought to be increased at high plasma concentrations it may be desirable to adjust dosage requirements according to plasma-vancomycin concentrations. However, uncertainty about the optimum methods and sampling times for monitoring, as well as some uncertainty about the degree of risk, means that there is less general agreement than for the aminoglycosides. UK licensed product information suggests that peak concentrations should be kept below 30 micrograms/mL and trough concentrations should not exceed 5 to 10 micrograms/mL, although the *BNF* suggests trough concentrations of 10 to 15 micrograms/mL, or 15 to 20 micrograms/mL when treating endocarditis or less susceptible strains of MRSA. It is generally agreed, however, that vancomycin should be avoided in patients with a history of impaired hearing and that particular care is necessary in patients with renal impairment, in neonates (especially if premature), and in the elderly, all of whom may be at increased risk of toxicity. Renal function and blood counts should be monitored regularly in all patients, and monitoring of auditory function is advisable, especially in high-risk patients. Vancomycin should be stopped in patients who develop tinnitus.

Since vancomycin is poorly absorbed, toxicity is much less of a problem after oral use than with the intravenous route, but care is required in patients with inflammatory gastrointestinal disorders, including antibiotic-associated colitis, in whom absorption may be enhanced.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies vancomycin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 09/08/11)

Interactions

Other ototoxic or nephrotoxic drugs, such as aminoglycosides, polymyxins, ciclosporin, cisplatin, and loop diuretics, are likely to increase the risk of toxicity and if they need to be given with vancomycin caution and appropriate monitoring are recommended.

Some of the adverse effects of vancomycin may be enhanced by the use of general anaesthetics; it has been suggested that, where patients require both, vancomycin infusions should be completed before the induction of anaesthesia.

Vancomycin may increase neuromuscular blockade produced by drugs such as suxamethonium or vecuronium.

Antimicrobial Action

Vancomycin is a glycopeptide antibacterial with a mainly bactericidal action against a variety of Gram-positive bacteria.

Mechanism of action. Vancomycin exerts its action by inhibiting the formation of the peptidoglycan polymers of the bacterial cell wall. Unlike penicillins, which act mainly to prevent the cross-linking of peptidoglycans which gives the cell wall its strength, vancomycin prevents the transfer and addition of the muramylpentapeptide building blocks that make up the peptidoglycan molecule itself. Vancomycin may also exert some effects by damaging the cytoplasmic membrane of the protoplast, and by inhibiting bacterial RNA synthesis.

Spectrum of activity. Staphylococci, notably *Staph. aureus* and *Staph. epidermidis* (including meticillin-resistant strains), *Streptococcus pneumoniae*, *Str. pyogenes*, some strains of Group B streptococci, and the viridans streptococci are reported to be susceptible to vancomycin. Enterococci such as *Enterococcus faecalis*, are often 'tolerant', i.e. inhibition, but no bactericidal effect, can be achieved at usual plasma concentrations (but see Activity with other Antimicrobials and Resistance, below).

Clostridium difficile is usually highly susceptible as are most other clostridia. *Actinomyces* spp., *Bacillus anthracis*, *Corynebacterium* spp., some lactobacilli, and *Listeria* are usually susceptible. Virtually all Gram-negative organisms, as well as mycobacteria and fungi, are intrinsically resistant.

Activity with other antimicrobials. Vancomycin exhibits synergy with the aminoglycosides against enterococci; such combinations are usually bactericidal, even against vancomycin-tolerant strains. The synergistic effect is reported to be greater with gentamicin than with streptomycin. Combinations with an aminoglycoside are also reported to show synergy against *Staph. aureus*; however, variable results, including antimicrobial antagonism, or lack of synergy, have been reported against strains of *Staph. aureus* when vancomycin was combined with rifampicin. Synergy has been reported with the third-generation cephalosporins against *Staph. aureus* and enterococci.

Resistance to vancomycin in normally susceptible organisms has until recently remained relatively uncommon, although high-level intrinsic resistance has been seen in some species of *Lactobacillus*, *Leuconostoc*, and *Erysipelothrix*. However, there are an increasing number of reports of high-level acquired resistance amongst enterococci, apparently plasmid-mediated and transferable to other Gram-positive organisms, notably *Staph. aureus*, which are causing considerable concern (see p. 389.1).

Resistance to vancomycin among enterococci, possibly driven in part by the use of antibiotics as growth promotors for livestock (see under Avoparcin, p. 221.1) has been well established.[1,2] Six resistance patterns have been reported, known as VanA, VanB, VanC, VanD, VanE, and VanG. VanA strains are inducibly resistant to high concentrations of vancomycin and teicoplanin; VanB strains retain susceptibility to teicoplanin. VanC strains have constitutive resistance to low concentrations of vancomycin, but not teicoplanin. VanE and VanG strains acquire low level resistance to vancomycin but again, may retain some susceptibility to teicoplanin.[3] Many genes may produce resistance, but they generally do so by resulting in production of cell-wall peptidoglycans with variant end chains that have a reduced affinity for vancomycin.[3]

Enterococci are capable of transferring resistance genes to other bacteria. Because of the first-line role played by vancomycin in the management of infections due to MRSA there is particular concern about the emergence of vancomycin resistance among staphylococci. Strains of *Staph. aureus* with intermediate resistance to vancomycin and/or other glycopeptide antibacterials (VISA or GISA), now usually defined as an MIC of 4 to 8 micrograms/mL, have been reported from several countries,[3-8] and there have been some reports of high-level resistance (vancomycin-resistant *Staph. aureus*, VRSA; MIC greater than 16 micrograms/mL), thought to result from transferred VanA resistance.[9,10] The emergence of heteroresistant strains (hVISA, in which most of a population is susceptible but it contains subpopulations that have intermediate resistance) appears to be increasing, and is of some concern since it is likely to result in selection of more resistant organisms.[3,11]

Guidelines have been issued[12,13] in an attempt to reduce the spread of vancomycin resistance.

1. Murray BE. Vancomycin-resistant enterococci. *Am J Med* 1997; 102 284–93.
2. Tacconelli E, Cataldo MA. Vancomycin-resistant enterococci (VRE) transmission and control. *Int J Antimicrob Agents* 2008; 31: 99–106.
3. Levine DP. Vancomycin: a history. *Clin Infect Dis* 2006; 42 (suppl 1): S5-S12.
4. Hiramatsu K, *et al.* Methicillin-resistant Staphylococcus aureus clinical strain with reduced vancomycin susceptibility. *J Antimicrob Chemother* 1997; 40: 135–6.
5. Johnson AP. Intermediate vancomycin resistance in Staphylococcus aureus: a major threat or a minor inconvenience? *J Antimicrob Chemother* 1998; 42: 289–91.
6. Ploy MC, *et al.* First clinical isolate of vancomycin-intermediate Staphylococcus aureus in a French hospital. *Lancet* 1998; 351: 1212.
7. Cosgrove SE, *et al.* Staphylococcus aureus with reduced susceptibility to vancomycin. *Clin Infect Dis* 2004; 39: 539–45.
8. Appelbaum PC. Reduced glycopeptide susceptibility in methicillin-resistant Staphylococcus aureus (MRSA). *Int J Antimicrob Agents* 2007; 30: 398–408.
9. Chang S, *et al.* Infection with vancomycin-resistant Staphylococcus aureus containing the VanA resistance gene. *N Engl J Med* 2003; 348: 1342–7.
10. Sievert DM, *et al.* Vancomycin-resistant Staphylococcus aureus in the United States, 2002-2006. *Clin Infect Dis* 2008; 46: 668–74.
11. Liu C, Chambers HF. Staphylococcus aureus with heterogeneous resistance to vancomycin: epidemiology, clinical significance, and critical assessment of diagnostic methods. *Antimicrob Agents Chemother* 2003; 47: 3040–5.
12. Hospital Infection Control Practices Advisory Committee (HICPAC). Recommendations for preventing the spread of vancomycin resistance. *Infect Control Hosp Epidemiol* 1995; 16: 105–13.
13. CDC. Investigation and control of vancomycin-intermediate and resistant Staphylococcus aureus (VISA/VRSA): a guide for health departments and infection control personnel (updated September 2006). Available at: http://www.cdc.gov/ncidod/dhqp/pdf/ar/visa_vrsa_guide.pdf (accessed 06/07/08)

Pharmacokinetics

Vancomycin is only poorly absorbed from the gastrointestinal tract, although absorption may be somewhat greater when the gastrointestinal tract is inflamed. Infusion of a 1-g dose intravenously over 60 minutes has reportedly been associated with plasma concentrations of up to about 60 micrograms/mL immediately after completion of the infusion, and about 25 micrograms/mL 2 hours later, falling to under 10 micrograms/mL after 11 hours. However, there may be considerable interindividual variation in the pharmacokinetics of vancomycin: a range of half-lives between 3 and 13 hours has been reported, with an average of about 6 hours, in patients with normal renal function. Half-life may be prolonged in patients with renal impairment, to 7 days or more in anephric patients. About 55% is bound to plasma proteins, although large variations have been reported.

Vancomycin diffuses into extracellular fluid, including pleural, pericardial, ascitic, and synovial fluid. Small amounts are found in bile. Vancomycin concentration in lung tissue is relatively low, accounting for 20 to 30% of serum concentration. There is little diffusion into the CSF and even when the meninges are inflamed effective concentrations may not be achieved. Vancomycin crosses the peritoneal cavity; about 60% of an intraperitoneal dose is reported to be absorbed in 6 hours. It is reported to cross the placenta. It is also distributed into breast milk.

Little or no metabolism of vancomycin is thought to take place. It is excreted unchanged by the kidneys, mostly by glomerular filtration. Some 80 to 90% of the dose is excreted in urine within 24 hours. There appears to be a small amount of non-renal clearance, although the mechanism for this has not been determined.

The pharmacokinetics of vancomycin may be altered by conditions which affect renal clearance: clearance of vancomycin has been reported to be enhanced in burn patients, whereas in those with renal impairment, or reduced renal function (such as neonates or the elderly), clearance is reduced and plasma-concentrations and half-lives increased. Dosage adjustment is often necessary in patients with reduced or impaired renal function; ideally, this should be based on plasma-concentration monitoring. Although clearance is also altered in hepatic impairment, it has been suggested that dosage adjustment is not necessary in the absence of other factors.

Plasma concentrations of vancomycin are reported to be little affected by conventional haemodialysis, although the use of high-flux membranes may significantly reduce vancomycin concentrations. Peritoneal dialysis, although it may decrease concentrations, is also thought not to do so by significant amounts, but haemoperfusion or haemofiltration effectively removes vancomycin from the blood.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Fabomicina†; Icoplax; Rivervan; Vancomax; Vancotenk; Varedet; *Austral.*: Vancocin; *Austria*: Vancocin; *Belg.*: Vamysin; Vancocin; *Braz.*: Amplobac†; Vancomin; Vancoabbott; Vancocina; Vancoson; Vancotrat; *Canad.*: Val-Vanco†; Vancocin; *Chile*: Kovan; *China*: Laikexin (来可信); Vancocin (稳可信); Vanconal (万君雅); Vancorin (方刻林); *Cz.*: Edicin; Vancocin; *Denm.*: Vancocin; *Fin.*: Vancosan; *Ger.*: Vanco-ratiopharm; Vanco-saar; Vanco; *Gr.*: Rulvon; Vamistol; Vancosan; Voncon; Vondem; Voxin; *Hong Kong*: Lyphocin; Vancocin†; *Hung.*: Vancocin; *India*: Covancin; Cytovan; Forstaf; Vancocin; Vancogram; Vanlid; *Indon.*: Vancep; *Irl.*: Vancocin; *Israel*: Vanco-Teva; *Ital.*: Copovan; Farmadiclin; Levovanox; Maxivanil; Vancodina; Vancotex; Zengac; *Malaysia*: Vancotex; *Mex.*: Estavam; Havac†; Vacsol; Vanaurus; Vancocin; Vancox; *Neth.*: Norimko; Vancocin; *Philipp.*: Kavocil; Vakocil†; Vancin; Vancocin; Vancomet; Vanosyn; *Pol.*: Acviscin; Edicin; Vancocin†; Vancotex; *Port.*: Glipep†; *Rus.*: Edicin (Эдицин); Vancocin (Ванкоцин); Vancomabol (Ванкомабол); Vancorus (Ванкорус); *S.Afr.*: Vancocin; *Singapore*: Dhacocin; *Swed.*: Vancocin; *Switz.*: Vancocin; *Thai.*: Edicin; Vancin-S; Vancogen; *Turk.*: Edicin; Vancocin; Vancorin; Vancotek; *UAE*: Vancolon; *UK*: Vancocin; *Ukr.*: Edicin (Эдицин); Tancofeto (Танкофето); Vancogen (Ванкоген)†; *USA*: Lyphocin; Vancocin; Vancoled†; *Venez.*: Vagran.

Multi-ingredient Preparations. *India*: Cefirone-V.

Pharmacopoeial Preparations

BP 2014: Vancomycin Capsules; Vancomycin Infusion; Vancomycin Oral Solution;

USP 36: Vancomycin Hydrochloride Capsules; Vancomycin Hydrochloride for Injection; Vancomycin Hydrochloride for Oral Solution; Vancomycin Injection.

Virginiamycin *(BAN, USAN, rINN)*

Antibiotic 899; SKF-7988; Virgimycin; Virginiamicina; Virginiamycine; Virginiamycinum; Виргиниамицин.

CAS — 11006-76-1; 21411-53-0 (virginiamycin M_1); 23152-29-6 (virginiamycin S_1).

ATC — D06AX10.

ATC Vet — QD06AX10; QJ01FG90.

UNII — C49WS9N75L.

Profile

Virginiamycin is a streptogramin antibacterial mixture consisting mainly of 2 antimicrobial substances, virginiamycin M_1, and virginiamycin S_1, produced by the growth of *Streptomyces virginiae*. It has been used for the treatment of infections due to sensitive organisms, particularly Gram-positive cocci. It has been given orally and applied locally. It may cause gastrointestinal disturbances including diarrhoea and vomiting. A few instances of hypersensitivity have been seen.

Virginiamycin has been used in animal feeding stuffs as a growth promotor.

Xibornol *(BAN, rINN)*

1BX; 1HP; CP3H; Xibornolum; Ксиборнол.

6-(Isoborn-2-yl)-3,4-xylenol; 6-[(1*R*,2*S*,4*S*)-Born-2-yl]-3,4-xylenol.

$C_{18}H_{26}O$=258.4.

CAS — 38237-68-2; 13741-18-9.

ATC — J01XX02.

ATC Vet — QJ01XX02.

UNII — RQ12GMY0FZ.

Profile

Xibornol is an antibacterial that is reported to have a bacteriostatic action on Gram-positive organisms such as staphylococci and streptococci, as well as activity against *Haemophilus influenzae*. It has been given orally, as an oral spray, and rectally.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Bornilene.

Antidementia Drugs

This chapter includes some drugs used or promoted in the management of dementia, including centrally acting anticholinesterases such as donepezil, galantamine, rivastigmine, and tacrine, the *N*-methyl-D-aspartate receptor antagonist memantine, and drugs considered to have nootropic properties, such as piracetam and idebenone.

Many other drugs have been tried in various forms of dementia (see p. 390.1) and are discussed elsewhere in *Martindale*.

Dementia

Dementia is a syndrome in which impairment of cortical or subcortical function leads to deterioration of cognitive processes or intellectual abilities including memory, judgement, language, communication, and abstract thinking. Unlike delirium there is no gross clouding of consciousness. There may be changes in personality and behaviour disturbances. Dementia is usually progressive, though not always irreversible, and loss of social and other skills often leads to complete dependence on others.

Although dementia is more prevalent in the elderly it is not an inevitable consequence of ageing. Dementia can result from many conditions including:

- *neurodegenerative diseases*: Alzheimer's disease, Pick's disease, Huntington's chorea, Parkinson's disease, Lewy-body disease, multiple sclerosis, progressive supranuclear palsy
- *vascular diseases*: multiple cerebral infarcts, occlusion of carotid artery, cranial arteritis
- *trauma*: subdural haematoma
- *neoplasms*
- *CNS infections*: encephalitis, syphilis, toxoplasmosis, AIDS, Creutzfeldt-Jakob disease
- *endocrine/metabolic disorders*: hypothyroidism, uraemia, hepatic failure, cardiac failure, respiratory failure, hypoxia, hyponatraemia
- *toxic insults*: alcohol, solvents, heavy metals, drug therapy
- *hydrocephalus*
- *nutritional deficiency*: vitamin B_{12}, folic acid, thiamine
- *depression*
- *sleep disorders*: obstructive sleep apnoea, narcolepsy

Alzheimer's disease is the most common cause of dementia and accounts for over half of all patients; about one-third of dementia cases are due to vascular disease.

Treatment of dementia can be broadly divided into control of disturbed behaviour (p. 1030.2) and attempts to improve or preserve cognitive function (see below). Although many drugs have been tfied in the management of cognitive impairment most have produced little or no benefit.

Alzheimer's disease is a progressive degenerative condition affecting mainly patients over 65 years of age. The rare early-onset form of Alzheimer's disease (familial Alzheimer's disease) has been referred to as pre-senile dementia. Death usually occurs within 10 years of onset.[1] Apart from age other risk factors include Down's syndrome and a family history of Alzheimer's disease.[1-3] Presence of the ε4 allele of apolipoprotein E is another risk factor; it correlates with prevalence and age of onset in some forms of Alzheimer's disease but use for routine clinical or predictive testing is not recommended.[2,4-6] Elevated levels of plasma homocysteine have been linked with the development of dementia and Alzheimer's disease.[7] Cardiovascular risk factors such as diabetes, hypercholesterolaemia, hypertension, and obesity have also been associated with an increased risk.[2,8] Dialysis dementia, an irreversible condition which has occurred in dialysis patients, has been associated with excess aluminium in the dialysing fluid but the role of aluminium in Alzheimer's disease, if any, is unclear.[4]

Deficiencies in numerous neurotransmitters have been found in patients with Alzheimer's disease but reduced choline acetyltransferase activity leading to reduced synthesis of acetylcholine remains the most consistent defect correlating with the severity of the condition.[9-12] Attempts to increase acetylcholine concentrations in the brain have included use of *cholinesterase inhibitors, acetylcholine precursors, enhancers of acetylcholine release*, and *cholinergic agonists*. However, none replace lost cholinergic neurones and therefore none affect overall progression of the disease.

Donepezil, galantamine, and rivastigmine are the main *cholinesterase inhibitors*.[3,5,6,8,11-20] All have produced modest improvement in cognition and global clinical impression in patients with mild to moderately severe disease. However, there is a lack of long-term studies and little evidence of their effectiveness in advanced disease although donepezil is licensed for the treatment of severe dementia in many countries. A systematic review found no evidence of any difference between these 3 drugs with regard to efficacy although there appeared to be fewer adverse effects associated with donepezil compared with rivastigmine.[21] In the UK, NICE[22] states that donepezil, galantamine, and rivastigmine may be used in patients with mild to moderate dementia if given under the following conditions:

- treatment should only be started under specialist supervision
- patients who continue on the drug should be reviewed regularly
- treatment should only be continued if there was evidence of benefit

Tacrine was formerly used but is often poorly tolerated and may cause serious hepatotoxicity. Other cholinesterase inhibitors that have been tried in Alzheimer's disease include metrifonate and physostigmine.

Treatments using *precursors of acetylcholine* such as lecithin or choline alone are not generally considered to produce useful improvements,[10-12] although it has been suggested that choline alfoscerate may be of some benefit.

Fampridine, which *enhances acetylcholine release from nerve terminals* has also been tried in Alzheimer's disease but there is little evidence of clinical benefit.

Limited improvement has been reported with some *cholinergic agonists* and pilocarpine may even exacerbate the dementia. Muscarinic M_1 agonists such as cevimeline and xanomeline have been investigated[12,23] on the basis that muscarinic M_1 receptors appear to be preserved throughout the course of Alzheimer's disease. However, these drugs have not been successful in improving symptoms of the disease. An alternative line of investigation has been the *stimulation of nicotinic receptors* using nicotine.[12]

The *N-methyl-D-aspartate (NMDA) receptor antagonist* memantine has shown some benefit in various dementias[3,6,8,14,19,20,24,25] and is recommended in the treatment of moderate to severe Alzheimer's disease.[6,22] In the UK, NICE[22] recommends that in moderate disease memantine is used only in patients who cannot take acetylcholine esterase inhibitors. It is thought to act through modulation of the effects of the neurotransmitter glutamate.

A hypothesis that free radicals may initiate and maintain mechanisms responsible for neurodegeneration in Alzheimer's disease has prompted the investigation of drugs such as vitamin E (e.g. α-tocopherol), ginkgo biloba, idebenone, and selegiline for *antioxidant* therapy but their value remains to be confirmed.[6,10,15,24,26] Although some older US guidelines[12] have suggested consideration of vitamin E supplementation in an attempt to slow progression of the disease, more recent US[27] and European guidelines[6] do not recommend it for the treatment of cognitive symptoms because of limited evidence of efficacy as well as safety concerns. Selegiline has produced mixed results in a large number of controlled studies and US guidelines[27] note that few clinicians actually use the drug in clinical practice. A systematic review[28] has found no convincing evidence that ginkgo biloba is effective in the treatment of dementia or cognitive impairment; its use is not recommended in European guidelines.[6]

Neurotropic or *nootropic drugs* such as piracetam are considered to enhance memory and cognition. They have been tried in preventing cognitive deficits associated with Alzheimer's disease and other dementias but there is little convincing evidence of clinical usefulness.[6,12]

Many drugs with *vasodilator activity* were originally tried in dementia when it was believed that the condition was due to 'cerebrovascular insufficiency' (p. 1269.2), but overall there was little convincing evidence of benefit.[29] Ergot derivatives such as codergocrine mesilate and nicergoline have been the most commonly used; however, any effectiveness is now attributed to their action as metabolic enhancers or nootropic drugs and their place in therapy has still to be established.[30]

The *calcium-channel blocker* nimodipine has been of benefit in dementia of various aetiologies but its role in therapy remains unclear.[25,30]

Observations have suggested that *oestrogens* may reduce the risk and delay the onset of Alzheimer's disease in postmenopausal women receiving HRT.[3,5,6,12] However, a large controlled study found that combined HRT increased the risk of substantial decline in global cognitive function, did not prevent the development of mild cognitive impairment, and doubled the risk of dementia. A beneficial effect of oestrogens on cognitive function in postmenopausal women who already have mild or moderate Alzheimer's disease has not been shown in controlled studies (see p. 2244.3).

Some retrospective studies also indicate an inverse association between the use of *anti-inflammatory drugs* such as NSAIDs and the risk of developing Alzheimer's disease.[6,12,14] However, there is currently insufficient evidence to support the use of NSAIDs in the treatment of Alzheimer's disease.[3,6,8,14,31]

The possibility of an association between *statin* therapy and a reduced risk of developing dementia has also been mooted. However, a systematic review[32] concluded that there was good evidence that statins given in later life have no effect in preventing Alzheimer's disease and dementia, and that they should not be prescribed to that end.

Other drugs under investigation for Alzheimer's disease include latrepirdine dihydrochloride, an antihistamine that is reported to also have neuroprotective effects, and methylthioninium chloride, which is thought to dissolve and prevent the aggregation of tau protein filaments in the brain. It is hoped that these and other immune-based therapies in development will have disease-modifying effects.[33] A vaccine for Alzheimer's disease is being investigated.[8,14,27]

A less marked degree of impaired memory, without dementia, is seen in some patients. Many, but not all, patients with such **mild cognitive impairment** (MCI) go on to develop Alzheimer's disease, and there has been considerable interest in treating them, in the hope of retarding progression to the more severe condition.[20,34,35] However, appropriate strategies for management are unclear: although treatment with cholinesterase inhibitors, antioxidants, and other drugs used for Alzheimer's disease has been investigated, there has been some concern about a possibly increased risk of death in patients with MCI treated with galantamine (see Effects on the Cardiovascular and Cerebrovascular Systems, p. 394.2). In the UK, NICE[36] does not recommend the use of cholinesterase inhibitors in patients with MCI.

Vascular dementia[25,37-39] is a syndrome produced by ischaemic, hypoxic, or haemorrhagic brain lesions. Vessel occlusion is the most common cause of vascular dementia and produces a variety of cognitive deficits depending on the site of ischaemia. Among the major forms of dementia recognised are those due to multiple infarcts, single strategic infarcts, and subcortical white matter ischaemia (Binswanger's disease). Vascular dementia has a more acute onset than dementia due to Alzheimer's disease and in contrast to the continuous progression of Alzheimer's disease often has a stepwise progression. Risk factors for vascular dementia parallel those for stroke (p. 1269.2) and similar methods for prevention and treatment may be of use but there is a lack of evidence from adequately controlled trials. Cholinergic deficits are well documented in patients with vascular dementia; cholinesterase inhibitors such as *donepezil* and *galantamine* have been found to be well tolerated and effective in these patients. Positive results have also been seen with the NMDA receptor antagonist *memantine*.[25,39] However, in the UK, NICE[36] does not recommend the use of cholinesterase inhibitors or memantine for cognitive decline in vascular dementia.

Lewy-body dementia[37,40-42] is distinguished from other types of dementia by a state of fluctuating cognitive impairment and confusion; hallucinations, paranoid delusions, a tendency to fall for no apparent reason, and transient clouding or loss of consciousness are also characteristic symptoms. In addition, mild extrapyramidal symptoms may be present and there is increased susceptibility to the extrapyramidal adverse effects of antipsychotics (see the Elderly, under Precautions of Chlorpromazine on p. 1051.1). Severe cholinergic deficits in patients with Lewy-body dementia have prompted treatment with cholinesterase inhibitors. *Donepezil* and *rivastigmine* have been shown to be well tolerated and effective, but further studies are needed to establish their role.

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Aniracetam *(USAN, rINN)*

Aniracetam; Aniracetamum; Ro-13-5057; Анирацетам

1-(4-Methoxybenzoyl)-2-pyrrolidinone

$C_{12}H_{13}NO_3$=219.2

CAS — 72432-10-1.

ATC — N06BX11.

ATC Vet — QN06BX11.

UNII — 5L16LKN964.

Profile

Aniracetam is a nootropic drug that has been tried in senile dementia (p. 388.1). It is given orally in usual doses of 1.5 g daily.

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Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Aniran; Pergamid; *China*: Bi Si Ling (毕思灵); Bo Bang Lin (博邦邻); San Le Xi (三乐喜); Shuntan (顺坦); Yi Ling Shu (益灵舒); *Gr.*: Memodrin; Referan; *Ital.*: Ampamet.

Bifemelane *(rINN)*

Bifémélane; Bifemelano; Bifemelanum; MCI-2016 (bifemelane hydrochloride); Бифеменан.

N-Methyl-4-[(α-phenyl-*o*-tolyl)oxy]butylamine.

$C_{18}H_{23}NO$=269.4

CAS — 90293-01-9 (bifemelane); 62232-46-6 (bifemelane hydrochloride).

ATC — N06AX08.

ATC Vet — QN06AX08.

UNII — Z4501GN13G.

Profile

Bifemelane is a nootropic that has been given orally in a usual dose of 150 mg of the hydrochloride daily in divided doses for the treatment of cerebrovascular disorders including some forms of dementia (p. 388.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Cordinal; Neurocine.

Choline Alfoscerate *(rINN)*

Alfoscerato de colina; Choline, Alfoscérate de; Choline Alphoscerate; Choline Glycerophosphate; Cholini Alfosceras; Colina, alfoscerato de; L-α-Glycerylphosphorylcholine; Холина Альфосцерат.

Choline hydroxide, (*R*)-2,3-dihydroxypropyl hydrogen phosphate, inner salt.

$C_8H_{20}NO_6P$=257.2

CAS — 28319-77-9.

ATC — N07AX02.

ATC Vet — QN07AX02.

UNII — 60M225GW66.

Profile

Choline alfoscerate is a precursor of acetylcholine and has been tried in the treatment of Alzheimer's disease and other dementias (p. 391.2). The usual oral dose is 0.8 to 1.2 g daily in divided doses; doses of 1 g daily have been given by intramuscular or slow intravenous injection.

Dementia. Treatment with precursors of acetylcholine is not generally thought to be of benefit in dementia (p. 388.1). However, in an analysis[1] of 8 controlled clinical studies the use of choline alfoscerate shared some benefit in patients with Alzheimer's disease or vascular dementia or with acute cerebrovascular disease. Results of a further 3 uncontrolled studies in the same review suggested that it might favour functional recovery in patients with cerebral stroke.

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Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Gliatilin; Noebra; *Ital.*: Brezal; Delecit; Gliatilin; *Pol.*: Gliatilin; *Rus.*: Cerepro (Церепро); Cereton (Церетон); Cholitilin (Холитилин); Cholitiline (Холитилин); Gleacer (Глеацер); Gliatilin (Глиатилин); *Ukr.*: Gliatilin (Глиатилин).

Codergocrine Mesilate *(BAN)*

Codergocrina, mesilato de; Co-dergocrine Mesilate; Codergocrine, mésilate de; Co-dergocrine Mesylate; Co-dergocrine Methanesulphonate; Codergocrini Mesilas; Codergocrinme-silat; Dihydroergotoxine Mesylate; Dihydroergotoxine Methanesulphonate; Dihydrogenated Ergot Alkaloids; Ergoloid Mesylates (USAN); Hydrogenated Ergot Alkaloids; Kodergokriinimesilaatti; Ko-dergokrin Mesilat; Kodergokrin-mesilat; Kodergokrin-mesylát; Kodergokrino mesilatas.

CAS — 11032-41-0 (codergocrine); 8067-24-1 (codergocrine mesilate).

ATC — C04AE01.

ATC Vet — QC04AE01.

UNII — X3S33EX3KW.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Codergocrine Mesilate). A mixture of dihydroergocornine mesilate ($C_{31}H_{41}N_5O_5$, CH_4O_3S = 659.8), dihydroergocristine mesilate, α-dihydroergocryptine mesilate, and β-dihydroergocryptine mesilate (epicriptine mesilate). It contains 30 to 35% of dihydroergocornine, 30 to 35% of dihydroergocristine, 20 to 25% of α-dihydroergocryptine, and 10 to 13% of β-dihydroergocryptine. A white or yellowish powder. Sparingly soluble in water; sparingly soluble to soluble in alcohol; slightly soluble in dichloromethane. A 0.5% solution in water has a pH of 4.2 to 5.2. Protect from light.

USP 36: (Ergoloid Mesylates). A mixture of the methanesulfonate salts of the three hydrogenated alkaloids, dihydroergocristine, dihydroergocornine, and dihydroergocryptine, in an approximate weight ratio of 1:1:1. Dihydroergocryptine mesilate exists as a mixture of alpha- and beta-isomers. The ratio of alpha- to beta-isomers is not less than 1.5:1.0 and not more than 2.5:1.0. A white to off-white, microcrystalline or amorphous, practically odourless powder. Slightly soluble in water; soluble in alcohol and in methyl alcohol; sparingly soluble in acetone. A 0.5% solution in water has a pH of 4.2 to 5.2. Store in airtight containers. Protect from light.

Uses and Administration

Unlike the natural ergot alkaloids (see Ergotamine, p. 674.2), codergocrine mesilate has only limited vasoconstrictor effects.

A mixture of hydrogenated ergot alkaloids, codergocrine mesilate is used as an adjunct in the symptomatic treatment of mild to moderate dementia in the elderly (see also p. 391.3). It is given in oral doses of 1 mg three times daily or 4.5 mg once daily in the morning, preferably before meals. Higher doses have also been used. It has been given sublingually, intramuscularly, subcutaneously, or by intravenous infusion.

In some countries, codergocrine mesilate has been used in the treatment of hypertension, migraine, and in peripheral vascular disease.

Codergocrine esilate has been used similarly to the mesilate.

Dementia. Codergocrine has been used for many years in dementia (p. 388.1) but its value is not established.[1-3] Originally its effects were thought to be mediated through peripheral and cerebral vasodilatation but it is now classified as a metabolic enhancer.

1. Wadworth AN, Chrisp P. Co-dergocrine mesylate: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in age-related cognitive decline. *Drugs Aging* 1992; 2: 153–73.
2. Schneider LS, Olin JT. Overview of clinical trials of Hydergine in dementia. *Arch Neurol* 1994; 51: 787–98.
3. Schneider L, *et al.* Hydergine for dementia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2000 (accessed 13/02/06).

Erectile dysfunction. For reference to the use of creams containing codergocrine mesilate, isosorbide dinitrate, and either aminophylline or testosterone in the treatment of erectile dysfunction, see under Glyceryl Trinitrate, p. 1392.3.

Adverse Effects

Adverse effects occasionally reported with codergocrine mesilate include abdominal cramps, nausea, vomiting, headache, blurred vision, skin rashes, nasal congestion, flushing of the skin, dizziness, bradycardia, and orthostatic hypotension.

Local irritation has occurred after sublingual use.

Effects on the cardiovascular system. Of 8 patients given codergocrine mesilate 1.5 mg three times daily for the treatment of dementia, 3 developed severe sinus bradycardia associated with general deterioration in their condition, necessitating withdrawal of the treatment.[1] However, no sinus bradycardia had been seen in 40 elderly patients in whom the dose was built up to 1.5 mg three times daily over 3 weeks.[2]

1. Cayley ACD, *et al.* Sinus bradycardia following treatment with Hydergine for cerebrovascular insufficiency. *BMJ* 1975; 4: 384–5.
2. Cohen C. Sinus bradycardia following treatment with Hydergine. *BMJ* 1975; 4: 581.

Precautions

Codergocrine mesilate should be used with caution in patients with severe bradycardia.

Interactions

Ticlopidine. Codergocrine mesilate reduces plasma concentrations of ticlopidine, see p. 1513.1.

Pharmacokinetics

Codergocrine is rapidly absorbed from the gastrointestinal tract; peak plasma concentrations are reached in about 1 to 2 hours after an oral dose. Oral bioavailability is low; this has been attributed to incomplete absorption from the gastrointestinal tract and extensive first-pass metabolism. It is 81% bound to plasma proteins. Elimination is biphasic with a short half-life of 1.5 to 2.5 hours (α phase) and a longer half-life of 13 to 15 hours (β phase). Codergocrine is mainly excreted with bile in the faeces, although small amounts are eliminated in the urine as metabolites and unchanged drug.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Coplexina; Ergoxina; Hydergina; Vimotadine; ***Austria***: Dorehydrin†; Ergomed; Hydergin; ***Belg.***: Hydergine; Ibexone; Stofilan; ***Braz.***: Codergine; Hydergine; ***Canad.***: Hydergine; ***China***: Hydergine (喜得镇); Perenan (培磊能); Si Qing (思清); Trigogine (弟哥静); ***Cz.***: Secatoxin Forte; ***Fin.***: Hydergin; ***Fr.***: Capergyl†; Hydergine; ***Ger.***: DCCK†; Hydergin; Hydro-Cebral; Orpholt; ***Gr.***: Bordersin†; Ecuor; Engestol-Hyd; Hidrosan; Huperloid; Hydergine; Ibergal; Iresolamin; Kerasex; Normanomin; Nulin; Pallotrinate; Phenyramon; Primarocin; Resinat; Santamin; Uvu; Zidrol; Zinvalon; Zodalin; ***Hong Kong***: Headgen†; Hydergine; Stofilan†; Trigogine; ***India***: Cereloid; Hydergine; ***Indon.***: Cirloid; Ergotika; Exergin; Fontula; Hydergin; Procere; Xepadergin; ***Israel***: Hydergine; ***Ital.***: Hydergina; ***Malaysia***: Headgen; Hydergine; ***Mex.***: Hydergina; ***Philipp.***: Hydergine; ***Port.***: Hydeggine; ***Singapore***: Headgen; Hydergine; Trigogine; ***Spain***: Hydergina; ***Swed.***: Hydergin; ***Switz.***: Ergohydrine†; Hydergine; ***Thai.***: Alergot; Helcon; Hyceral; Hydergine; Hydrine; Hymed; Naline; Togine; Trigogine; Vasculin†; Vasian; ***Turk.***: Segol; ***USA***: Gerimal†; Hydergine; ***Venez.***: Astergina.

Multi-ingredient Preparations. ***Arg.***: Difusil; Reagin Vascular; ***Ukr.***: Distonin (Дистонин)†.

Pharmacopoeial Preparations
BP 2014: Codergocrine Tablets;
USP 36: Ergoloid Mesylates Capsules; Ergoloid Mesylates Oral Solution; Ergoloid Mesylates Tablets.

Dihydroergocristine Mesilate *(BANM)*

Dihidroergocristina, mesilato de; Dihidroergokristino mesilatas; Dihidroergokrisztin-mezilát; Dihydroergocristine, mésilate de; Dihydroergocristine Mesylate; Dihydroergocristine Methanesulphonate; Dihydroergocristini Mesilas; Dihydroergocristinmesilat; Dihydroergokristiinimesilaatti; Dihydroergokristinmesilat; Dihydroergokristin-mesylát.

(6a*R*,9*R*,10a*R*)-*N*-[(2*R*,5*S*,10a*S*,10b*S*)-5-Benzyl-10b-hydroxy-2-isopropyl-3,6-dioxooctahydro-8*H*-[1,3]oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide methanesulphonate.

$C_{35}H_{41}N_5O_5.CH_4O_3S$=707.8

CAS — 17479-19-5 (dihydroergocristine); 24730-10-7 (dihydroergocristine mesilate).

ATC — C04AE04.

ATC Vet — QC04AE04.

UNII — DS7CL18UAM.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Dihydroergocristine Mesilate). A white or almost white, fine crystalline powder. Slightly soluble in water; soluble in methyl alcohol. A 0.5% solution in water has a pH of 4.0 to 5.0. Protect from light.

Profile

Dihydroergocristine mesilate is a component of codergocrine mesilate (p. 389.2) and has similar actions. In some countries it has been given orally in doses of 3 to 6 mg daily in divided doses in the symptomatic treatment of mental deterioration associated with cerebrovascular insufficiency. It has also been given by intramuscular or intravenous injection.

References.

1. Franciosi A, Zavattini G. Dihydroergocristine in the treatment of elderly patients with cognitive deterioration: a double-blind, placebo-controlled, dose-response study. *Curr Ther Res* 1994; **55**: 1391–1401.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Nehydrin†; ***Braz.***: Iskemil; ***Gr.***: Agiobita; Alfacrist; Ancef; Beytina; Cristil; Diertina; Ergobel; Ergocrist; Ergofil; Fenitina; Guadal; Memotil; Mentidose; Normocedon; Thriolan; Tonergon; ***Port.***: Diertina; ***Spain***: Diertine; Ergodavur†.

Multi-ingredient Preparations. ***Arg.***: Cervilane; Cinacris; Micerfin; ***Austria***: Brinerdin; ***Braz.***: Isketam; Norogil; Vertizine D; ***Chile***: Cervilane; ***Cz.***: Anavenol; Crystepin†; Ersilan; Neocrystepin†; ***Fr.***: Iskedyl; ***Ital.***: Brinerdina; ***Mex.***: Cervilan; ***Pol.***: Anavenol†; Normatens; Venacorn; ***Rus.***: Anavenol (Анавенол); Brinerdin (Бринердин); Crystepin (Кристепин); Normatens (Нормотенс); ***S.Afr.***: Brinerdin; ***Spain***: Clinadil; Diemil; ***Switz.***: Brinerdine; ***Thai.***: Bedin; Brinerdin; Briscotin†; ***Ukr.***: Normatens (Нормотенс).

Dihydroergocryptine Mesilate

Dihidroergocriptina, mesilato de; Dihydroergocryptine Mesylate; Dihydroergocryptine Methanesulphonate; Dihydroergokryptine Mesylate.

$C_{32}H_{43}N_5O_5.CH_4O_3S$=673.8

CAS — 25447-66-9 (dihydroergocryptine, α-isomer); 19467-62-0 (dihydroergocryptine, β-isomer); 14271-05-7 (dihydroergocryptine mesilate, α-isomer); 65914-79-6 (dihydroergocryptine mesilate, β-isomer).

ATC — N04BC03.

ATC Vet — QN04BC03.

UNII — 5AAV003TAQ (dihydroergocryptine mesilate); Z4I7BU58DN (dihydroergocryptine mesilate α-isomer); 79Y4U49I29 (dihydroergocryptine mesilate β-isomer).

Profile

Dihydroergocryptine mesilate is a component of codergocrine mesilate (p. 389.2) and has similar actions. It has been given orally in doses of up to 20 mg daily for migraine, and in maintenance doses of up to 60 to 120 mg daily for parkinsonism. It has also been used for age-related dementia and to inhibit lactation. In some countries it has been given with caffeine for cerebrovascular and peripheral vascular disorders.

References.

1. Scarzella L, *et al.* Dihydroergocryptine in the management of senile psycho-organic syndrome. *Int J Clin Pharmacol Res* 1992; **12**: 37–46.
2. Battistin L, *et al.* Alpha-dihydroergocryptine in Parkinson's disease: a multicentre randomized double blind parallel group study. *Acta Neurol Scand* 1999; **99**: 36–42.
3. Bergamasco B, *et al.* Alpha-dihydroergocryptine in the treatment of de novo parkinsonian patients: results of a multicentre, randomized, double-blind, placebo-controlled study. *Acta Neurol Scand* 2000; **101**: 372–80.
4. Micieli G, *et al.* Alpha-dihydroergocryptine and predictive factors in migraine prophylaxis. *Int J Clin Pharmacol Ther* 2001; **39**: 144–51.
5. Tergau F, *et al.* Treatment of restless legs syndrome with the dopamine agonist alpha-dihydroergocryptine. *Mov Disord* 2001; **16**: 731–5.
6. Albanese A, Colosimo C. Dihydroergocriptine in Parkinson's disease: clinical efficacy and comparison with other dopamine agonists. *Acta Neurol Scand* 2003; **107**: 349–55.
7. Mailland E, *et al.* Alpha-dihydroergocryptine in the long-term therapy of Parkinson's disease. *Arzneimittelforschung* 2004; **54**: 647–54.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Cripar (克瑞帕); ***Cz.***: Almirid†; ***Ger.***: Almirid†; Cripar†; ***Gr.***: Daverium; ***Irl.***: Almirid†; ***Ital.***: Daverium; Myrol; ***Mex.***: Diamin; ***Pol.***: Almirid; ***Port.***: Striatal; ***Rus.***: Vasobral (Вазобрал); ***Switz.***: Cripar†.

Multi-ingredient Preparations. ***China***: Vasobral (洛斯宝); ***Fr.***: Vasobral; ***Hong Kong***: Vasobral.

Donepezil Hydrochloride

(BANM, USAN, rINNM)

BNAG; Donépézil, Chlorhydrate de; Donepezil Hidroklorür; Donepezili Hydrochloridum; Donepezilo, hidrocloruro de; E-2020; ER-4111 (donepezil); Hidrocloruro de donepezilo; Донепезила Гидрохлорид.

(±)-2-[(1-Benzyl-4-piperidyl)methyl]-5,6-dimethoxy-1-indanone hydrochloride.

$C_{24}H_{29}NO_3.HCl$=416.0

CAS — 120014-06-4 (donepezil); 142057-79-2 (donepezil); 120011-70-3 (donepezil hydrochloride); 142057-77-0 (donepezil hydrochloride).

ATC — N06DA02.

ATC Vet — QN06DA02.

UNII — 3O2T2PJB9D.

Pharmacopoeias. In *US.*

USP 36: (Donepezil Hydrochloride). A white to off-white, crystalline powder. Soluble in water and in glacial acetic acid; slightly soluble in alcohol and in acetonitrile; freely soluble to soluble in chloroform; practically insoluble in ethyl acetate and in *n*-hexane. Store at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Donepezil hydrochloride, a piperidine derivative, is a reversible and selective inhibitor of acetylcholinesterase with actions similar to those of neostigmine (p. 687.2). It is highly selective for the CNS and is used for the symptomatic treatment of dementia in Alzheimer's disease (p. 392.3). In the UK, the licensed use of donepezil is limited to those patients with mild to moderately severe dementia (but see p. 392.3); in the USA it is also licensed for use in those with severe symptoms.

Regardless of severity, donepezil hydrochloride is given in an initial oral dose of 5 mg once daily increased if necessary after 4 to 6 weeks to 10 mg once daily; the dose should be taken just before bedtime. In those with severe symptoms, after 3 months, a further increase to a dose of 23 mg once daily may be considered. Clinical benefit should be reassessed on a regular basis.

In some countries, donepezil is also licensed for use in patients with vascular dementia (p. 392.3); doses are similar to those used for the treatment of mild to moderate dementia in Alzheimer's disease.

Dementia. Donepezil hydrochloride is used in the symptomatic treatment of dementia in *Alzheimer's disease* (p. 388.1). In individual studies, it appears to produce modest benefits in some patients with mild to moderately severe dementia.[1-4] These findings are also supported by a systematic review[5] which concluded that, for treatment periods of up to 1 year, donepezil produces modest improvements in cognitive function and global clinical state. Benefit has also been reported in patients with more severe dementia.[5-8]

In the UK, NICE states that donepezil may be used in patients with mild to moderate dementia if given under the following conditions:[9]

- treatment should only be started under specialist supervision
- patients who continue on the drug should be reviewed regularly
- treatment should only be continued if there was evidence of benefit

Donepezil has also been tried in patients with *mild cognitive impairment* (MCI).[10,11] Findings from a double-blind study[11] have suggested that although donepezil therapy was associated with a lower rate of progression to Alzheimer's disease during the first year of treatment when compared with placebo, the rate of progression after 3 years of therapy was not lower than that of the placebo group. The authors of a systematic review[12] of these 2 studies found no evidence to support the use of donepezil in patients with MCI. Any benefits were considered to be minor, short-lived, and associated with significant adverse effects. A more recent study[13] conducted over 48 weeks found a small but significant improvement in the score of one cognitive measure with donepezil when compared with placebo; however, there were no changes in other measures of global impairment or function. The authors considered that such measures may not be sensitive enough to detect changes in patients with MCI.

Donepezil may be effective in the treatment of *vascular dementia*. Results from a randomised, controlled study[14] have shown an improvement in cognition and global function in patients with probable or possible vascular dementia. A systematic review also concluded that donepezil improved mild to moderate vascular cognitive impairment in the short term (treatment for 6 months).[15] The manufacturer has reported[16] that out of a total of 3 studies of donepezil in vascular dementia, one (Study 319) showed an apparently increased mortality compared with placebo: 1.7% and 0%, respectively. In a combined analysis of the other 2 studies, the mortality rate was 1.7% in the donepezil group and 2% in the placebo group. Combined analysis of all 3 studies showed no statistically significant difference in the mortality rates between the donepezil (1.7%) and placebo (1.1%) groups; the risk of vascular events such as stroke and myocardial infarction was also similar for each group. The unexpectedly low mortality rate with placebo in Study 319 was unusual given the age and pathology of the subjects. An increased risk of death has also been reported with another acetylcholinesterase inhibitor, *galantamine*, when used in patients who did not have Alzheimer's disease (see Effects on the Cardiovascular and Cerebrovascular Systems, p. 394.2).

1. Rogers SL, *et al.* A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. *Neurology* 1998; **50**: 136–45.
2. Mohs RC, *et al.* A 1-year, placebo-controlled preservation of function survival study of donepezil in AD patients. *Neurology* 2001; **57**: 481–8.

3. Winblad B, *et al.* A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD. *Neurology* 2001; **57**: 489–95.
4. Holmes C, *et al.* The efficacy of donepezil in the treatment of neuropsychiatric symptoms in Alzheimer disease. *Neurology* 2004; **63**: 214–19.
5. Birks J, Harvey RJ. Donepezil for dementia due to Alzheimer's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 13/02/06).
6. Feldman H, *et al.* A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease. *Neurology* 2001; **57**: 613–20.
7. Winblad B, *et al.* Donepezil in patients with severe Alzheimer's disease: double-blind, parallel-group, placebo-controlled study. *Lancet* 2006; **367**: 1057–65.
8. Black SE, *et al.* Donepezil preserves cognition and global function in patients with severe Alzheimer disease. *Neurology* 2007; **69**: 459–69.
9. NICE. Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review) (issued March 2011). Available at: http://www.nice.org.uk/nicemedia/live/13419/53619/53619.pdf (accessed 11/04/11)
10. Salloway S, *et al.* Efficacy of donepezil in mild cognitive impairment: a randomized placebo-controlled trial. *Neurology* 2004; **63**: 651–7.
11. Petersen RC, *et al.* Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med* 2005; **352**: 2379–88.
12. Birks J, Flicker L. Donepezil for mild cognitive impairment. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 09/08/07).
13. Doody RS, *et al.* Donepezil treatment of patients with MCI: a 48-week randomized, placebo-controlled trial. *Neurology* 2009; **72**: 1555–61.
14. Black S, *et al.* Efficacy and tolerability of donepezil in vascular dementia: positive results of a 24-week, multicenter, international, randomized, placebo-controlled clinical trial. *Stroke* 2003; **34**: 2323–30.
15. Malouf R, Birks J. Donepezil for vascular cognitive impairment. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 13/02/06).
16. Eisai, Jpn. Eisai reports results from latest donepezil study in vascular dementia (issued 16th March, 2006). Available at: http://www.eisai.co.jp/enews/enews200609pdf.pdf (accessed 09/08/07)

Parkinsonism. Although acetylcholinesterase inhibitors such as donepezil hydrochloride may theoretically worsen parkinsonism symptoms, particularly tremor, it has been tried for use in the treatment of drug-induced psychosis in patients with Parkinson's disease (see Disturbed Behaviour, p. 1030.2).

Adverse Effects and Treatment

Adverse effects of acetylcholinesterase inhibitors such as donepezil notably include nausea, vomiting, anorexia, diarrhoea, fatigue, and dizziness. Other common adverse effects include abdominal pain, dyspepsia, rash, pruritus, headache, somnolence, muscle cramps, insomnia, sweating, tremor, and syncope; upper-respiratory-tract and urinary-tract infections have been noted. Rare cases of angina, sinoatrial and AV blocks, bradycardia, peptic ulcers, gastrointestinal haemorrhage, extrapyramidal symptoms, and seizures have been observed. Psychiatric disturbances, including depression, hallucinations, agitation, aggressive behaviour, and confusion have also been reported. There is a potential for bladder outflow obstruction. Minor increases in serum-creatine kinase have also occurred with donepezil.

Increased liver transaminases have been noted with acetylcholinesterase inhibitors; hepatotoxicity may be severe with the acetylcholinesterase inhibitor tacrine (see p. 398.3).

The use of acetylcholinesterase inhibitors has been associated with weight loss and consequently some licensed product information has recommended that a patient's weight is monitored during treatment. Female patients have been found to be more susceptible to nausea, vomiting, anorexia, and weight loss.

Overdosage with cholinesterase inhibitors may result in 'cholinergic crisis', the details of which are described under Adverse Effects of Neostigmine, p. 688.2.

Reviews of the safety profile of donepezil.

1. CSM/MCA. Donepezil (Aricept). *Current Problems* 1999; **25**: 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023235&RevisionSelectionMethod=LatestReleased (accessed 13/08/07)
2. Jackson S, *et al.* The safety and tolerability of donepezil in patients with Alzheimer's disease. *Br J Clin Pharmacol* 2004; **58** (suppl 1): 1–8.

Effects on the cardiovascular system. The Australian Adverse Drug Reactions Advisory Committee noted in October 2004 that it had received 32 reports of cardiac arrhythmias associated with donepezil (14 of bradycardia, 1 bundle branch block, 5 AV blocks, 10 cases of syncope, and 2 unspecified), as well as 7 cases of myocardial infarction or cardiac arrest.[1] There had been 7 reports of similar cardiovascular effects with rivastigmine and 6 with galantamine; the larger number with donepezil was almost certainly due to wider usage of this drug. Most patients recovered when the drug was stopped or the dose reduced, though many were hospitalised and in 4 cases a pacemaker was required.

One study in vascular dementia reported an increased death rate with donepezil (see Dementia, p. 390.3) but no increase in vascular events.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Cholinesterase inhibitors and cardiac arrhythmias. *Aust Adverse Drug React Bull* 2004; **23**: 19–20. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0410.pdf (accessed 13/02/06)

Effects on the nervous system. Restless legs, mumbling, and stuttering developed in an elderly patient after increasing the dose of donepezil to 10 mg daily.[1] Symptoms resolved when donepezil was withdrawn and recurred on rechallenge.

1. Amouyal-Barkate K, *et al.* Abnormal movements with donepezil in Alzheimer disease. *Ann Pharmacother* 2000; **34**: 1347.

Effects on the urinary tract. Urinary incontinence is a recognised adverse effect of the older anticholinesterases such as neostigmine; not unexpectedly there have also been cases associated with donepezil.[1]

1. Hashimoto M, *et al.* Urinary incontinence: an unrecognised adverse effect with donepezil. *Lancet* 2000; **356**: 568.

Precautions

Donepezil and other acetylcholinesterase inhibitors should be used with caution, if at all, in patients with gastrointestinal or urinary-tract obstruction; their use is not recommended in patients recovering from bladder or gastrointestinal surgery. Care is also required in patients with a history of asthma, obstructive pulmonary disease, Parkinson's disease, or seizures, and in those, with, or at risk of developing, peptic ulcer disease. Patients with cardiovascular conduction disorders such as sick-sinus syndrome may be susceptible to the vagotonic effects of acetylcholinesterase inhibitors.

Dizziness, somnolence, fatigue, and muscle cramps may occur especially when starting treatment with or increasing the dose of acetylcholinesterase inhibitors; the performance of skilled tasks such as driving may be affected.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies donepezil as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 25/10/11)

Interactions

As for Neostigmine, p. 688.3. Hepatic metabolism of donepezil via the cytochrome P450 system has been demonstrated; plasma concentrations of donepezil may be raised by drugs that inhibit the isoenzyme CYP3A4 such as ketoconazole, itraconazole, and erythromycin, and by those that inhibit the isoenzyme CYP2D6 such as fluoxetine and quinidine. Conversely, plasma-donepezil concentrations may be reduced by enzyme inducers such as rifampicin, phenytoin, carbamazepine, and alcohol.

Antimuscarinics. Although antimuscarinics are expected to antagonise the effects of anticholinesterases, such combinations are sometimes used in patients with dementia who are distressed by symptoms of urge incontinence.[1] There have been, however, a few cases[2] of agitation, anxiety, confusion, aggression, and delusion precipitated by *tolterodine* in patients who had been stable on donepezil or rivastigmine. The interaction appeared to cause a state of cholinergic neurogenic hypersensitivity, similar to sudden withdrawal of the anticholinesterase.

1. Siegler EL, Reidenberg M. Treatment of urinary incontinence with anticholinergics in patients taking cholinesterase inhibitors for dementia. *Clin Pharmacol Ther* 2004; **75**: 484–8.
2. Edwards KR, O'Connor JT. Risk of delirium with concomitant use of tolterodine and acetylcholinesterase inhibitors. *J Am Geriatr Soc* 2002; **50**: 1165–6.

Pharmacokinetics

Donepezil hydrochloride is well absorbed from the gastrointestinal tract, maximum plasma concentrations being achieved within 3 to 4 hours after ingestion. It is about 95% bound to plasma proteins, mainly albumin. Donepezil undergoes partial metabolism via the cytochrome P450 isoenzyme CYP3A4, and to a lesser extent by CYP2D6, to 4 major metabolites. About 11% of a dose is present in plasma as 6-*O*-desmethyldonepezil, which has similar activity to the parent compound. Over 10 days, about 57% of a dose is recovered from the urine as unchanged drug and metabolites, and about 15% from the faeces; 28% remains unrecovered suggesting accumulation. The elimination half-life is about 70 hours. Steady-state concentrations are achieved within 3 weeks of the start of therapy.

References.

1. Tiseo PJ, *et al.* Metabolism and elimination of ^{14}C-donepezil in healthy volunteers: a single-dose study. *Br J Clin Pharmacol* 1998; **46** (suppl 1): 19–24.
2. Reyes JF, *et al.* Steady-state pharmacokinetics, pharmacodynamics and tolerability of donepezil hydrochloride in hepatically impaired patients. *Br J Clin Pharmacol* 2004; **58** (suppl 1): 9–17.
3. Nagy CF, *et al.* Steady-state pharmacokinetics and safety of donepezil HCl in subjects with moderately impaired renal function. *Br J Clin Pharmacol* 2004; **58** (suppl 1): 18–24.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Alzaimax; Cebrocal; Crialix; Cristaclar; Donepes; Donnox; Donpex; Donzeimer†; Endoclar; Eranz; Lirpan; Oldinot; Onefin; Valpex; ***Austral.***: Aricept; ***Austria***: Aricept; ***Belg.***: Aricept; ***Braz.***: Epez; Eranz; Ziledon; ***Canad.***: Aricept; ***Chile***: Dazolin; Dopaben; Eranz; Evimal; Fincip; ***China***: A Rui Si (阿瑞斯); Aricept (安理申); Fang Qing (方清); Fu Si Ke (扶斯克); Gai Fei (盖菲); Jia Qi (加奇); Nuo Chong (诺冲); Sai Ling Si (赛灵斯); Si Bo Hai (思博海); ***Cz.***: Adonep; Alzhedon†; Alzil; Aricept; Calofra; Dobedipil; Donpethon; Dospelin; Ezida; Landex; Mazil; Nepla; Oneza; Promemore; Tolerdilan; Yasnal; ***Denm.***: Aricept; Dobedipil†; Domethan; Doneprion; Doneratio†; Donespes; Memac†; ***Fin.***: Aricept; Doneratio; Yasnal; ***Fr.***: Aricept; ***Ger.***: Aricept; ***Gr.***: Aricept; Aripezil; Dementis; Donegal; Donelet; Donesan; Donester; Donopez; Dozilax; Hania; Kibilis; Nepezil; Penezil; Pezale; Razil; Sulbenin; Tactrol; Venaxen; ***Hong Kong***: Aricept; ***Hung.***: Aricept; Donecept; Donectil; Donesyn; Palixid; ***India***: Aricep; Deprizil; Donasure; Donaz; Donecept; Donep; Dopezil; Dorent; Nozil; ***Indon.***: Aldomer; Alzim; Aricept; Fordesia; ***Irl.***: Aricept; Aripez; Aripil; Arizime; Dentap; Donecept; Donelinn; Donesyn; Dozept; ***Israel***: Aricept; Asenta; Memorit; ***Ital.***: Aricept; Lizidra; Memac; Yasnoro; ***Jpn***: Aricept; ***Malaysia***: Aricept; ***Mex.***: Eranz; ***Norw.***: Aricept; ***NZ***: Aricept; Concorda; Donaccord; Donezil; ***Philipp.***: Aricept; Done; Donezel; ***Pol.***: Alzdone; Alzepezil; Apo-Doperil; Aricept; Cogiton; Cognezil; Dobedipil; Donecept; Donecleus; Donectil; Donemed; Donepex; Doneprion; Donesyn; Memocept; *Mensapex*; *Redumas*; Ricordo; Symepezil; Yasnal; ***Port.***: Alizil; Alkimus; Aricept; Damzipil†; Dilpeze†; Dizil; Dolizi†; Premptel; Paxel†; ***Rus.***: Aricept (Арисепт); Yasnal (Яснал); ***S. Afr.***: Aricept; Ariknow; Donecept; ***Singapore***: Aricept; ***Spain***: Aricept; Lixben; Yasnal; ***Swed.***: Aricept; Azepezil; ***Switz.***: Aricept; ***Thai.***: Aricept; Donept; Tonizep; ***Turk.***: Alzancer; Aricept; Arypez; Dement; Divare; Doenza; Dozyl; Nopez; Zhedon; ***UK***: Aricept; ***Ukr.***: Almer (Альмер); Alzepil (Алзепил); ***USA***: Aricept; ***Venez.***: Eranz.

Pharmacopoeial Preparations

USP 36: Donepezil Hydrochloride Orally Disintegrating Tablets; Donepezil Hydrochloride Tablets.

Fonturacetam *(rINN)* ⊗

BRN-5030440; *N*-Carbamoyl-methyl-4-phenyl-2-pyrrolidone; Carphedon; Fonturacétam; Fonturacetamum; Karfedon; 4-Phenylpiracetam; Фонтурацетам.

rac-2-(2-Oxo-4-phenylpyrolidin-1-yl)acetamide.

$C_{12}H_{14}N_2O_2$=218.3

CAS — 77472-70-9.

UNII — 99QW5JU66Y.

Profile

Fonturacetam is a nootropic and has been used in the management of various cerebrovascular disorders. It has also been abused in sport.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Phenotropil (Фенотропил); ***Ukr.***: Entrop (Энтроп); Phenotropil (Фенотропил).

Galantamine Hydrobromide

(BANM, USAN, rINNM)

Galantamina, hidrobromuro de; Galantamine, Bromhydrate de; Galantaminhydrobromid; Galantamini hydrobromidum; Galanthamine Hydrobromide; Galanthamini Hydrobromidum; Hidrobromuro de galantamina; Галантамина Гидробромид.

(4a*S*,6*R*,8a*S*)-4a,5,9,10,11,12-Hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol hydrobromide.

$C_{17}H_{21}NO_3HBr$=368.3

CAS — 357-70-0 (galantamine); 1953-04-4 (galantamine hydrobromide).

ATC — N06DA04.

ATC Vet — QN06DA04.

UNII — MJ4PTD2VVW.

Description. The hydrobromide of galantamine, an alkaloid which has been obtained from the Caucasian snowdrop (Voronov's snowdrop), *Galanthus woronowii* (Amaryllidaceae), and related species.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Galantamine Hydrobromide). A white or almost white, crystalline or amorphous powder. Sparingly soluble in water; very slightly soluble in dehydrated alcohol; it dissolves in dilute solutions of alkali hydroxides. pH of a 2% solution in water is 4.0 to 5.5.

USP 36: (Galantamine Hydrobromide). A white to almost white powder. Sparingly soluble in water; very slightly

soluble in alcohol; soluble in 0.1N sodium hydroxide; insoluble in propyl alcohol.

Uses and Administration

Galantamine hydrobromide is a reversible inhibitor of acetylcholinesterase activity, with actions similar to those of neostigmine (p. 687.2). It also has an intrinsic action on nicotinic receptors. It is used in the symptomatic treatment of mild to moderately severe dementia in Alzheimer's disease (but see p. 394.1).

Galantamine is given as the hydrobromide although doses are expressed in terms of the base; 5.1 mg of galantamine hydrobromide is equivalent to about 4 mg of galantamine. An initial oral dose of 4 mg is given twice daily with food for 4 weeks, then increased to 8 mg twice daily. This dose should be maintained for at least 4 weeks; thereafter, the dose may be further increased to 12 mg twice daily according to response and tolerance. A modified-release preparation is also available for once-daily use. The clinical benefit of galantamine should be reassessed, preferably within the first 3 months, and thereafter on a regular basis. Reductions in dose may be necessary in patients with hepatic or renal impairment (see p. 394.1) or in those also taking certain cytochrome P450 isoenzyme inhibitors (see Interactions, p. 394.2).

Galantamine hydrobromide has also been used in various neuromuscular disorders, and to curtail the muscle relaxation produced by competitive neuromuscular blockers.

Administration in hepatic impairment. No dose adjustment of galantamine is necessary in mild hepatic impairment. Patients with moderate impairment should begin with an oral dose of 4 mg once daily (or 8 mg every other day if using a modified-release preparation), preferably taken in the morning, for at least one week; thereafter the dose may be increased to 4 mg twice daily (or its once-daily equivalent if using a modified-release preparation) for at least 4 weeks, with subsequent increases up to a maximum of 8 mg twice daily (or its once-daily equivalent if using a modified-release preparation). Galantamine is contra-indicated in severe impairment (Child-Pugh score greater than 9) due to lack of data.

Administration in renal impairment. UK licensed product information states that no dose adjustment is necessary for galantamine in mild or moderate renal impairment. However, US licensed product information recommends that the dose should not exceed 16 mg daily in patients with moderate impairment.

Galantamine is contra-indicated in severe impairment (creatinine clearance less than 9 mL/minute) due to lack of data.

Dementia. Reviews[1-3] suggest that galantamine is of benefit in patients with mild to moderate symptoms of *Alzheimer's disease* (p. 388.1); evidence in more severely impaired subjects is lacking. In the UK, NICE states that galantamine may be used in patients with mild to moderate dementia if given under the following conditions:[4]

- treatment should only be started under specialist supervision
- patients who continue on the drug should be reviewed regularly
- treatment should only be continued if there was evidence of benefit

Galantamine may also be effective in the treatment of *vascular dementia*. Results from a randomised, controlled study[5] have shown a trend towards improved cognition in patients with probable vascular dementia, although patients numbers were too small for this to be significant. A more recent multicentre study[6] in patients with probable vascular dementia found cognitive improvement with galantamine to be greater than with placebo; however, improvement in daily activities with galantamine was similar to that seen with placebo.

A systematic review[3] concluded that galantamine could not be recommended for treatment in patients with *mild cognitive impairment* because of limited clinical benefit and an unexplained association with an excess death rate (see also Effects on the Cardiovascular and Cerebrovascular Systems, p. 394.2).

1. Scott LJ, Goa KL. Galantamine: a review of its use in Alzheimer's disease. *Drugs* 2000; 60: 1095–1122.
2. Pearson VE. Galantamine: a new Alzheimer drug with a past life. *Ann Pharmacother* 2001; 35: 1406–13.
3. Loy C, Schneider L. Galantamine for Alzheimer's disease and mild cognitive impairment. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 14/02/06).
4. NICE. Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review) (issued March 2011). Available at: http://www.nice.org.uk/nicemedia/live/13419/53619/53619.pdf (accessed 11/04/11)
5. Erkinjuntti T, *et al.* Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomised trial. *Lancet* 2002; 359: 1283–90.
6. Auchus AP, *et al.* Galantamine treatment of vascular dementia: a randomized trial. *Neurology* 2007; 69: 448–58.

Adverse Effects, Treatment, and Precautions

As for Donepezil, p. 391.1. Hypertension has also been reported with galantamine.

For details regarding dose adjustments in moderate hepatic or renal impairment, see under Uses and Administration, above. There are no data on the use of galantamine in patients with severe hepatic or renal impairment and consequently in the licensed product information it is contra-indicated in such patients; it should also not be given to patients with both significant hepatic and renal impairment.

Effects on the cardiovascular and cerebrovascular systems. Results from 2 studies of the use of galantamine in mild cognitive impairment (an unlicensed indication) have suggested that there may be an increased risk of death in patients given galantamine compared with those on placebo: out of a total of about 2000 patients, 13 died in the galantamine groups with only 1 death reported in the placebo groups.[1,2] About half of the deaths were caused by cardiovascular or cerebrovascular events.

For a suggestion of possibly increased mortality with *donepezil* in patients with vascular dementia, see Dementia, p. 390.3.

1. Janssen-Ortho Inc. Safety information from investigational studies with Reminyl (galantamine hydrobromide) in mild cognitive impairment (MCI) (issued 18th April, 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/reminyl_hpc-eng.pdf (accessed 05/08/08)
2. Ortho-McNeil Neurologics, Inc. Important prescribing information: deaths in subjects with mild cognitive impairment (MCI) (issued 31st March, 2005). Available at: http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM164870.pdf (accessed 19/08/10)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies galantamine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 25/10/11)

Interactions

As for Neostigmine, p. 688.3. Galantamine is partially metabolised by the cytochrome P450 isoenzymes CYP2D6 and CYP3A4. Consequently its bioavailability may be increased by drugs that inhibit CYP2D6, such as quinidine, fluoxetine, fluvoxamine, and paroxetine, and by those that inhibit CYP3A4, such as ketoconazole and ritonavir. Dose reduction of galantamine may be required when given with such drugs.

Pharmacokinetics

Galantamine is well absorbed from the gastrointestinal tract. Peak plasma concentrations are reached in about 1 hour after ingestion from conventional formulations; with modified-release formulations, peak concentrations occur about 4 to 5 hours after a dose and are somewhat lower. The absolute oral bioavailability of galantamine is about 90%. The presence of food delays the rate of absorption although the extent of absorption is not affected. Protein binding is about 18%. Galantamine is partially metabolised by the cytochrome P450 isoenzymes CYP2D6 and CYP3A4; a number of active metabolites are formed. The elimination half-life is about 7 to 8 hours. After 7 days, the majority of a single oral dose is recovered in the urine with up to about 6% detected in the faeces; about 20 to 30% of the dose is excreted in the urine as unchanged galantamine. Clearance is reported to be 20% lower in females than in males and 25% lower in poor metabolisers than in extensive metabolisers.

References.

1. Zhao Q, *et al.* Pharmacokinetics and safety of galantamine in subjects with hepatic impairment and healthy volunteers. *J Clin Pharmacol* 2002; 42: 428–36.
2. Piotrovsky V, *et al.* Galantamine population pharmacokinetics in patients with Alzheimer's disease: modeling and simulations. *J Clin Pharmacol* 2003; 43: 514–23.
3. Farlow MR. Clinical pharmacokinetics of galantamine. *Clin Pharmacokinet* 2003; 42: 1383–92.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Intelec; Memolos; Numencial; Reminyl; ***Austral.***: Galantyl; Reminyl; ***Austria***: Reminyl; ***Belg.***: Reminyl; ***Braz.***: Reminyl; ***Canad.***: Reminyl; ***Chile***: Galamed; Reminyl; ***China***: Hui Min (慧敏); Jin Kang Ling Li (金康灵力); Qi Er Neng (奇尔能); Reminyl (力益临); Shi Wei Bao (施维宝); Yi You Li Ning (易优利宁); *Cz.*: Apo-Galant; Flashemel†; Galamed†; Kurement†; OxyGal†; Reminyl; ZapTron†; ***Denm.***: Reminyl; ***Fin.***: Reminyl; ***Fr.***: Reminyl; ***Ger.***: Galnora; Reminyl; ***Gr.***: Aneprosil; Galanyl; Memo-Farmellas; Memoto; Life; Reminyl; Riminyl; Zoroflog; ***Hong Kong***: Reminyl; ***Indic***: Galamer; ***Indon.***: Reminyl; ***Irl.***: Galsya; Reminyl; ***Israel***: Reminyl; ***Ital.***: Galema; Reminyl; ***Jpn***: Reminyl; ***Malaysia***: Reminyl; ***Mex.***: Reminyl; ***Neth.***: Bergal; Galantagen; Galantex; Reminyl; ***Norw.***: Reminyl; ***NZ***: Galantyl; Reminyl; ***Philipp.***: Reminyl; ***Pol.***: Nivalin; ***Port.***: Reminyl; ***Rus.***: Nivalin (Нивалин); Reminyl (Реминил); ***S.Afr.***: Reminyl; ***Singapore***: Reminyl; ***Spain***: Galnora; Reminyl; ***Swed.***: Reminyl; ***Switz.***: Reminyl; ***Thai.***: Reminyl; ***Turk.***: Reminyl; ***UK***: Elmino; Galsya; Gatalin; Lotprosin Reminyl; ***Ukr.***: Nivalin (Нивалин); ***USA***: Razadyne; ***Venez.***: Proneurax.

Pharmacopoeial Preparations

USP 36: Galantamine Tablets.

Idebenone (rINN)

CV-2619; Idebenona; Idébénone; Idebenonum; Идебенон.

2-(10-Hydroxydecyl)-5,6-dimethoxy-3-methyl-*p*-benzoquinone.

$C_{19}H_{30}O_5$=338.4

CAS — 58186-27-9.

ATC — N06BX13.

ATC Vet — QN06BX13.

UNII — H86PN45W4J.

Profile

Idebenone has been described as a nootropic and an antoxidant. It is used in the treatment of mental impairment associated with cerebrovascular disorders. A dose of 90 mg daily has been given orally in 2 divided doses after food. Idebenone has also been tried in Alzheimer's disease.

Idebenone is used in the symptomatic management of various clinical manifestations of Friedreich's ataxia in patients aged 8 years and over. Doses are given orally with food according to body-weight: initial doses of 300 mg three times daily in patients weighing over 45 kg or of 150 mg three times daily in those weighing 45 kg or under are recommended. After at least 6 months this may be increased, according to response and tolerance, to 750 mg three times daily in patients over 45 kg or 450 mg three times daily in those weighing 45 kg or under. If no additional improvement is seen after 6 months on the higher dose, the dosage should be reduced to the initial dose.

Alternatively, in some countries, idebenone may be licensed specifically for the treatment of cardiomyopathy associated with Friedreich's ataxia; for example, in Switzerland, a dose of 5 mg/kg daily in 3 divided doses is recommended for such use in patients aged 4 years and over.

Leucocytopenia and agranulocytosis have been reported rarely with the use of idebenone. Some licensed product information recommends that a complete blood cell count and liver function tests should be performed before starting treatment and regularly thereafter, and also before and after dose increases. Idebenone should not be used in patients with moderate or severe hepatic impairment and used with caution in those with mild impairment.

Idebenone is also being investigated for the treatment of Duchenne muscular dystrophy, Leber's optic atrophy, and the multisystem syndrome of mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS).

Idebenone is available as a 1% cream for the cosmetic treatment of wrinkles.

Dementia. Idebenone was found to be safe and effective in patients with mild to moderate Alzheimer's disease (p. 388.1) when followed for up to 2 years.[1,2] In a further study,[3] its safety and efficacy were comparable to tacrine. However, another study[4] found no clinically significant slowing of cognitive decline in patients with Alzheimer's disease treated with idebenone.

1. Weyer G, *et al.* Efficacy and safety of idebenone in the long-term treatment of Alzheimer's disease: a double-blind, placebo controlled multicentre study. *Hum Psychopharmacol Clin Exp* 1996; 11: 53–65.
2. Gutzmann H, Hadler D. Sustained efficacy and safety of idebenone in the treatment of Alzheimer's disease: update on a 2-year double-blind multicentre study. *J Neural Transm* 1998; 54 (suppl): 301–10.
3. Gutzmann H, *et al.* Safety and efficacy of idebenone versus tacrine in patients with Alzheimer's disease: results of a randomized, double-blind, parallel-group multicenter study. *Pharmacopsychiatry* 2002; 35: 12–18.
4. Thal LJ, *et al.* Idebenone treatment fails to slow cognitive decline in Alzheimer's disease. *Neurology* 2003; 61: 1498–1502.

Friedreich's ataxia. Preliminary studies of idebenone in the treatment of Friedreich's ataxia.[1-7]

1. Hausse AO, *et al.* Idebenone and reduced cardiac hypertrophy in Friedreich's ataxia. *Heart* 2002; 87: 346–9.
2. Artuch R, *et al.* Friedreich's ataxia: idebenone treatment in early stage patients. *Neuropediatrics* 2002; 33: 190–3.
3. Mariotti C, *et al.* Idebenone treatment in Friedreich patients: one-year-long randomized placebo-controlled trial. *Neurology* 2003; 60: 1676–9.

4. Buyse G, *et al.* Idebenone treatment in Friedreich's ataxia: neurological, cardiac, and biochemical monitoring. *Neurology* 2003; 60: 1679–81.
5. Rustin P, *et al.* Idebenone treatment in Friedreich patients: one-year-long randomized placebo-controlled trial. *Neurology* 2004; 62: 524–5.
6. Di Prospero NA, *et al.* Safety, tolerability, and pharmacokinetics of high-dose idebenone in patients with Friedreich ataxia. *Arch Neurol* 2007; 64: 803–8.
7. Di Prospero NA, *et al.* Neurological effects of high-dose idebenone in patients with Friedreich's ataxia: a randomised, placebo-controlled trial. *Lancet Neurol* 2007; 6: 878–86.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Esanic†; Geniceral; Idesole; Nemocebral; Pavertrin; Sicoplus; Ulcourona; *Canad.*: Catena; *China*: Jin Bo Rui (金博瑞); *Ital.*: Mnesis; *Mex.*: Lucebanol; *Port.*: Amizal; Cerestabon; Idecortex; *Rus.*: Neiromet (Нейромет); Noben (Нобен); *Switz.*: Mnesis†; *USA*: Prevage.

Multi-ingredient Preparations. *Arg.*: Idenimo; Idesole Plus; Nemocebral Plus; *India*: Hi-Q Plus; Hi-Q.

Memantine Hydrochloride

(BANM, USAN, rINNM)

1-Amino-3,5-dimethyladamantane Hydrochloride; D-145 (memantine); 3,5-Dimethyl-1-adamantanamine hydrochloride; DMAA (memantine); Hidrocloruro de memantina; Memantin Hidroklorür; Memantina, hidrocloruro de; Mémantine, Chlorhydrate de; Memantini Hydrochloridum; Мемантина Гидрохлорид.

3,5-Dimethyltricyclo[3.3.1.1.^{3,7}]decan-1-amine hydrochloride.

$C_{12}H_{21}N,HCl$=215.8

CAS — 19982-08-2 (memantine); 41100-52-1 (memantine hydrochloride).

ATC — N06DX01.

ATC Vet — QN06DX01.

UNII — JY0WD0UA60.

Uses and Administration

Memantine is a derivative of amantadine (p. 891.3) and is likewise an antagonist of *N*-methyl-D-aspartate receptors. It is given in the treatment of moderate to severe Alzheimer's disease (see Dementia, p. 395.1). Memantine has also been given in the treatment of parkinsonism and central spasticity, and in other disorders such as brain injury or comatose states. It is given orally as the hydrochloride.

In the treatment of **Alzheimer's disease**, the initial dose of memantine hydrochloride is 5 mg once daily for the first week; this should be increased in weekly increments of 5 mg to a maximum dose of 20 mg daily. In the USA, licensed product information states that doses of 10 mg daily and over should be taken in 2 divided doses; however, once-daily dosing is recommended in the UK. Dosage adjustment may be required in patients with renal impairment (see p. 395.1). Clinical benefit should be reassessed on a regular basis.

Memantine hydrochloride has also been given by slow intravenous injection.

Memantine is under investigation in the treatment of glaucoma and peripheral neuropathy.

Administration in renal impairment. UK licensed product information advises that no dose adjustment is needed when memantine hydrochloride is given for Alzheimer's disease in patients with mild renal impairment (creatinine clearance [CC] 50 to 80 mL/minute). However, in those with moderate impairment (CC 30 to 49 mL/minute) an oral dose of 10 mg daily may be used (after starting at 5 mg daily) and if well tolerated for at least 7 days, it may be increased to 20 mg daily as described above (see above). In those with severe impairment (CC 5 to 29 mL/minute) the maximum daily dose is 10 mg. In the USA, licensed product information states that no dose reduction is required in those with mild or moderate impairment; a target dose of 10 mg daily is recommended in patients with severe impairment (CC 5 to 29 mL/minute).

Dementia. A systematic review[1] of the use of memantine in dementia (p. 388.1) concluded that it did have a small beneficial effect on cognitive and functional decline at 6 months in patients with moderate to severe Alzheimer's disease; the effects were not clinically discernible in those with mild to moderate vascular dementia but were discernible in those with mild to moderate Alzheimer's disease. In the UK, NICE[2] has recommended memantine in the treatment of moderate disease in patients who cannot take acetylcholine esterase inhibitors, and also in the treatment of severe disease. A general review, including a safety profile, of memantine in Alzheimer's disease has also been published.[3]

1. McShane R, *et al.* Memantine for dementia. Available in The Cochrane Database of Systematic Reviews: Issue 2. Chichester: John Wiley; 2006 (accessed 23/05/08).
2. NICE. Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review) (issued March 2011). Available at: http://www.nice.org.uk/nicemedia/live/13419/53619/53619.pdf (accessed 11/04/11)
3. Robinson DM, Keating GM. Memantine: a review of its use in Alzheimer's disease. *Drugs* 2006; 66: 1515–34.

Adverse Effects and Precautions

Common adverse effects with memantine include constipation, dizziness, headache, hypertension, and somnolence. Less common reactions such as anxiety, hallucinations, confusion, fatigue, abnormal gait, hypertonia, vomiting, fungal infections, cystitis, thromboembolism, and increased libido have also occurred. Isolated cases of psychotic reactions and pancreatitis have been reported.

Dosage adjustment may be required in renal impairment, but recommendations vary (see under Uses and Administration, above).

Only limited clinical data are available for patients with recent myocardial infarction, uncompensated congestive heart failure, and uncontrolled hypertension and use of memantine in these patients should be closely monitored. Seizures have occurred rarely and caution is recommended in patients at risk of convulsions. Conditions that increase urinary pH, such as drastic changes in diet, renal tubular acidosis, or severe infections of the urinary tract, may decrease elimination of memantine resulting in increased plasma levels; patient monitoring is recommended in such cases.

References.
1. Factow MR, *et al.* Memantine for the treatment of Alzheimer's disease: tolerability and safety data from clinical trials. *Drug Safety* 2008; 31: 577–85.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies memantine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 25/10/11)

Interactions

Use of other *N*-methyl-D-aspartate antagonists such as amantadine, ketamine, or dextromethorphan with memantine may increase both the incidence and severity of adverse effects and should be avoided. The effects of dopaminergics and antimuscarinics may also be enhanced whereas memantine may reduce the actions of barbiturates and antipsychotics.

Memantine may alter the effects of the antispasmodics baclofen and dantrolene. The clearance of memantine is reduced under alkaline urine conditions and drugs such as carbonic anhydrase inhibitors and sodium bicarbonate should be used with caution.

Pharmacokinetics

Memantine is well absorbed after oral doses. Peak plasma concentrations are achieved in about 3 to 8 hours. Plasma protein binding is about 45%. Memantine undergoes partial hepatic metabolism; the main metabolites include *N*-3,5-dimethyl-gludantan and 1-nitroso-3,5-dimethyl-adamantane. The majority of a dose is excreted unchanged via the kidney; some active renal tubular secretion and reabsorption occurs. The terminal half-life ranges from 60 to 100 hours although under alkaline conditions the rate of elimination is reduced.

References.
1. Pericliou A, *et al.* Pharmacokinetic study of memantine in healthy and renally impaired subjects. *Clin Pharmacol Ther* 2006; 79: 134–43.
2. Kornhuber J, *et al.* Memantine pharmacotherapy: a naturalistic study using a population pharmacokinetic approach. *Clin Pharmacokinet* 2007; 46: 599–612. Correction. *ibid.*; 712.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Akatinol; Carrier; Conexline; Ebixa; Fentina; Lucidex; Merital; Neuroplus; Prilben; Pronervon; Tonibral; *Austral.*: Ebixa; Memanxa; Memanxa; *Austria*: Axura; Ebixa; *Belg.*: Ebixa; *Braz.*: Alois; Clomenac; Ebix; Heimer; *Canad.*: Ebixa; *Chile*: Ebixa; Eutebrol; Lindex; Memax; Mimetix; Vivimex; *China*: Ebixa (易倍申); *Cz.*: Axura; Ebixa; *Denm.*: Axura; Ebixa; *Fin.*: Ebixa; Mentixa; *Fr.*: Ebixa; *Ger.*: Axura; Ebixa; *Gr.*: Ebixa; *Hong Kong*: Ebixa; *Hung.*: Ebixa; *India*: Admenta; Mentadem; Mentra; *Irl.*: Axura; Ebixa; *Israel*: Ebixa; Memox; *Ital.*: Ebixa; *Jpn*: Memary; *Malaysia*: Ebixa; *Mex.*: Akatinol; Ebixa; Eutebrol; *Neth.*: Axura; Ebixa; *Norw.*: Ebixa; *NZ*: Ebixa; *Philipp.*: Abixa; Zimerz; *Pol.*: Axura; Ebixa; *Port.*: Axura; Ebixa; *Rus.*: Akatinol (Акатинол); Noojerone (Нооджерон); *S.Afr.*: Ebixa; *Singapore*: Ebixa; *Spain*: Axura; Ebixa; *Swed.*: Axura; Ebixa; *Switz.*: Axura; Ebixa; *Thai.*: Ebixa; Neumantine; *Turk.*: Alzant; Alzmex; Cogito; Demax; Ebitex; Ebixa; Korint; Melanda; Memanzaks; Memorix; Mexia; *UK*: Ebixa; Maruxa; Nemdatine; *Ukr.*: Abixa (Абикса); Mema (Мема); *USA*: Namenda.

Nizofenone *(rINN)*

Nizofenona; Nizofénone; Nizofenonum; Y-9179; Низофенон.

2'-Chloro-2-[2-[(diethylamino)methyl]imidazol-1-yl]-5-nitrobenzophenone.

$C_{21}H_{21}ClN_4O_3$=412.9

CAS — 54533-85-6.

ATC — N06BX10.

ATC Vet — QN06BX10.

UNII — 7A2NOC3R88.

Nizofenone Fumarate *(rINNM)*

Fumarato de nizofenona; Midafenone Fumarate; Nizofénone, Fumarate de; Nizofenoni Fumaras; Низофенона Фумарат.

$C_{21}H_{21}ClN_4O_3C_4H_4O_4$=528.9

CAS — 54533-86-7; 93929-95-4.

ATC — N06BX10.

ATC Vet — QN06BX10.

UNII — 1I1Z517Z3Y.

Profile

Nizofenone has been described as a nootropic and cerebral vasodilator. It is used parenterally, as the fumarate, to minimise cerebral ischaemic damage after subarachnoid haemorrhage.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Ekonal.

Oxiracetam *(BAN, rINN)*

CGP-21690E; CT-848; ISF-2522; Oksirasetaami; Oxiracétam; Oxiracetamum; Oxracetam; Оксирацетам.

4-Hydroxy-2-oxo-1-pyrrolidineacetamide.

$C_6H_{10}N_2O_3$=158.2

CAS — 62613-82-5.

ATC — N06BX07.

ATC Vet — QN06BX07.

UNII — P7U817352G.

Profile

Oxiracetam has been used as a nootropic in organic brain syndromes and senile dementia.

Dementia. Clinical benefit has been reported in patients with dementia (p. 388.1) given oxiracetam,[1] but in the USA it was withdrawn from phase II clinical studies in patients with Alzheimer's disease due to lack of efficacy.[2]

1. Maina G, *et al.* Oxiracetam in the treatment of primary degenerative and multi-infarct dementia: a double-blind, placebo-controlled study. *Neuropsychobiology* 1990; 21: 141–5.
2. Parnetti L. Clinical pharmacokinetics of drugs for Alzheimer's disease. *Clin Pharmacokinet* 1995; 29: 110–29.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Bei Qing Xing (倍清星); Jian Lang Xing (健朗星); Ou Lai Ning (欧来宁); Ou Lan Tong (欧兰同).

Piracetam *(BAN, USAN, rINN)*

CI-871; Piracétam; Piracetamas; Piracetamum; Pirasetaami; Pirasetam; Pyrrolidone Acetamide; UCB-6215; Пирацетам.

2-(2-Oxopyrrolidin-1-yl)acetamide.

$C_6H_{10}N_2O_2$=142.2

CAS — 7491-74-9.

ATC — N06BX03.

ATC Vet — QN06BX03.

UNII — ZH516LNZ10.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Ph. Eur. 8: (Piracetam). A white or almost white powder. It exhibits polymorphism. Freely soluble in water; soluble in alcohol. Protect from light.

Uses and Administration

Piracetam acts on the CNS and has been described as a nootropic; it is said to protect the cerebral cortex against hypoxia. It is also reported to inhibit platelet aggregation and reduce blood viscosity at high doses. Piracetam is used as an adjunct in the treatment of myoclonus of cortical origin, and has also been used in dementia (see also p. 396.2). Other disorders or states in which it has been tried (on the basis of a supposed 'cerebrocortical insufficiency' responsive to piracetam) include alcoholism, vertigo,

cerebrovascular accidents, dyslexia, behavioural disorders in children, and after trauma or surgery.

In cortical myoclonus, piracetam is given in oral doses of 7.2 g daily increasing by 4.8 g daily every 3 or 4 days up to a maximum of 24 g daily. It is given in 2 or 3 divided doses. Once the optimal dose of piracetam has been established, attempts should be made to reduce the dose of other drugs. For dosage in renal impairment see p. 396.1.

Piracetam has been given for various other disorders in a usual oral dose of up to 2.4 g daily in 2 or 3 divided doses; doses of up to 4.8 g daily or higher have been used in severe cases. In severe disorders it has also been given by intramuscular or intravenous injection.

General references.

1. Winblad B. Piracetam: a review of pharmacological properties and clinical uses. *CNS Drug Rev* 2005; 11: 169–82.
2. Malykh AG, Sadaie MR. Piracetam and piracetam-like drugs: from basic science to novel clinical applications to CNS disorders. *Drugs* 2010; 70: 287–312.

Administration in renal impairment. The usual oral dose of piracetam (see p. 393.3) should be reduced in patients with renal impairment according to creatinine clearance (CC):

- CC between 50 and 79 mL/minute: two-thirds of the usual dose, given in 2 or 3 divided doses
- CC between 30 and 49 mL/minute: one-third of the usual dose, given in 2 divided doses
- CC between 20 and 29 mL/minute: one-sixth of the usual dose, given as a single dose

Use of piracetam is contra-indicated in those with a CC of less than 20 mL/minute.

Dementia. Although piracetam is used in some countries in the management of cognitive impairment and dementia (p. 388.1), a systematic review[1] concluded that the evidence from the published literature did not support this use.

1. Flicker L, Grimley Evans J. Piracetam for dementia or cognitive impairment. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 14/02/06).

Myoclonus. A review[1] of 62 case reports, 3 open studies, and 2 double-blind studies concluded that piracetam is beneficial in the treatment of disabling myoclonus (p. 511.3), either as adjunctive treatment or as monotherapy. Similar conclusions were made in another review[2] in which experience of 12 patients with progressive myoclonus epilepsy, 8 of whom benefited from piracetam in doses of up to 45 g daily without significant adverse effects, was described.

1. Van Vleymen B, Van Zandijcke M. Piracetam in the treatment of myoclonus: an overview. *Acta Neurol Belg* 1996; 96: 270–80.
2. Genton P, *et al.* Piracetam in the treatment of cortical myoclonus. *Pharmacopsychiatry* 1999; 32 (suppl): 49–53.

Stroke. Piracetam did not influence the outcome if given within 12 hours of the onset of acute ischaemic stroke in a multicentre, randomised, double-blind study,[1] although post hoc analyses suggested that it might confer benefit when given within 7 hours of onset, particularly in patients with stroke of moderate to severe degree. Further analyses of the same data concluded that piracetam did not produce significant adverse effects when given in high doses to patients with acute stroke,[2] and significantly more patients had recovered from aphasia on piracetam than placebo.[3] The results of two further randomised, double-blind, placebo-controlled studies supporting the role of piracetam as an adjunct to intensive speech therapy in improving aphasia following stroke were also reported.[3] In contrast, a systematic review including the first study considered that the trend towards an increased risk of early death in patients allocated to piracetam was of concern, and concluded that the data did not support routine use of piracetam in acute ischaemic stroke.[4]

1. De Deyn PP, *et al.* Treatment of acute and ischemic stroke with piracetam. *Stroke* 1997; 28: 2347–52.
2. De Reuck J, Van Vleymen B. The clinical safety of high-dose piracetam—its use in the treatment of acute stroke. *Pharmacopsychiatry* 1999; 32 (suppl): 33–7.
3. Huber W. The role of piracetam in the treatment of acute and chronic aphasia. *Pharmacopsychiatry* 1999; 32 (suppl): 38–43.
4. Ricci S, *et al.* Piracetam for acute ischaemic stroke. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 23/05/08).

Vertigo. Piracetam has been reported to be of benefit in patients with vertigo (p. 612.3) of both central or peripheral origin.[1]

1. Oosterveld WJ. The effectiveness of piracetam in vertigo. *Pharmacopsychiatry* 1999; 32 (suppl): 54–60.

Adverse Effects and Precautions

Piracetam is reported to produce insomnia or somnolence, weight gain, hyperkinesia, nervousness, and depression. Other reported adverse effects include gastrointestinal disorders such as abdominal pain, diarrhoea, nausea and vomiting, hypersensitivity reactions, ataxia, vertigo, confusion, hallucinations, angioedema, and rashes. Piracetam should not be given to patients with hepatic impairment or severe renal impairment; dosage reduction is recommended for those with mild to moderate renal impairment (see under Uses and Administration, above). Therapy with piracetam should not be withdrawn abruptly in myoclonic patients due to the risk of inducing seizures. When used to treat cortical myoclonus, piracetam is contra-indicated in patients with cerebral haemorrhage, and should be used with caution after major surgery and in those with haemostatic disorders or severe haemorrhage.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies piracetam as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 25/10/11)

Interactions

Anticoagulants. For reference to the effect of piracetam on *warfarin* therapy, see p. 1535.1.

Pharmacokinetics

Piracetam is rapidly and extensively absorbed from the gastrointestinal tract; peak plasma concentrations are reached within 1.5 hours after oral doses. The plasma half-life is reported to be 5 hours and it crosses the blood-brain barrier. Piracetam is excreted almost completely in the urine. It crosses the placenta and is distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Noostan; ***Austria***: Cerebryl; Nootropil; Novocephal; Pirabene; ***Belg.***: Braintop; Docpiracet†; Geratam; Noodis; Nootropil; Piracemed†; Piracetop†; ***Braz.***: Cintilan; Nootron; Nootropil; ***Chile***: Nootropyl; ***China***: Hong Wei Li Di (宏威利迪); Kang Ling (康灵); Kang Rong (康容); Lu Si Qi (路思齐); Ning Xiu Xin (宁秀欣); Qing Da (庆达); Si Bi Ke (斯必克); Si Tai (思泰); Tan Fu (坦复); Tong Tan Kang (通坦康); Xin Ao Xin (欣奥欣); Yi An Nuo (益安诺); YiTing (易汀); Zhen Xi (真昔); ***Cz.***: Geratam; Kalicor†; Nootropil; Oikamid; Pirabene; ***Fin.***: Nootropil; ***Fr.***: Gabacet; Nootropyl; ***Ger.***: Cerepar N†; Nootrop; Normabrain†; Piracebral†; Piracetrop†; ***Gr.***: Aminotrophylle-88; Arterosol; Cebragil; Celebral; Centracetam; Cetrop; Cosmoxim; Espritam; Latys; Lobelo; Logofren; Lowtens; Meclivin; Meditam; Noforit; Nootrop†; Oxynium; Piracem; Psycoton; Stamin; Zalipan; ***Hong Kong***: Nootropil; Piratin; ***Hung.***: Cerebryl; Lucetam; Memoril; Nootropil; Pirabene; ***India***: Alcetam; Amritam; Axetam; Brentor; Ceact; Cerecetam; Cetam; E-Tam; Enpir; Etotam; Floracetam; Gencephal; Mincetam; Neopiram; Neurocetam; Neuropil; Nicetam; Nootropil; Normabrain; Normenta†; Nupic; Nurest; Nutam; Orotam; Piramet; Piratam; ***Indon.***: Antikun; Benocetam; Brenaris; Cervas; Cetoros; Chepamed; Ciclobrain; Cytropil; Encebion†; Ethopil; Fepiram; Gotropil; Gracetam; Latropil; Lutrotam; Mersitropil; Neurocet; Neurotam; Noocephal; Noocetam; Nootropil; Notrotam; Nufacetam; Piratrof; Pratropil; Primatam; Procetam; Resibron; Revolan; Scantropil; Sevotam; Sotropil; Tropilex; ***Irl.***: Nootropil†; ***Ital.***: Nootropil; Psycoton; ***Jpn***: Myocalm; Nootropil†; ***Malaysia***: Cebrotonin; Ceretam; Knowful; Nootropil; Syntam; ***Mex.***: Dinagen†; Nootropil; ***Neth.***: Nootropil; ***Norw.***: Nootropil; ***Philipp.***: Irahex; Neurocetam; Neuroton; Nootrocet; Nootropil; Normabrain; Nurocer; Pirasam†; ***Pol.***: Biotropil; Lucetam; Memotropil; Nootropil; ***Port.***: Acetar; Noostan; Nootropil†; Oxibran; ***Rus.***: Eskotropil (Эскотропил); Lucetam (Луцетам); Memotropil (Мемотропил); Nootropil (Ноотропил); Phezam (Фезам); Piratropil (Пиратропил); ***S.Afr.***: Nootropil†; ***Singapore***: Cebrotonin; Cetam; Neurocetam; Nootropil; Piratam; Racetam; ***Spain***: Ciclofalina; Nootropil; ***Swed.***: Nootropil; ***Switz.***: Nootropil; Pirax†; ***Thai.***: Embol; Knofuli†; Mancetam; Mempil; Noocetam; Nootropil; Scarda; ***Turk.***: Cerebrofil; Nootropil; Norotrop; ***UK***: Nootropil; ***Ukr.***: Lucetam (Луцетам); Nootropil (Ноотропил); ***Venez.***: Breinox.

Multi-ingredient Preparations. ***Braz.***: Energiclin†; Energivit; Exit; Isketam; ***India***: Neuromin-M; Nutam Plus; ***Port.***: Anacervix; ***Rus.***: Combitropil (Комбитропил); NooCam (НооКам); Omaron (Омарон); Piracezine (Пирацезин); Vinpotropile (Винпотропил); ***Spain***: Anacervix; Devincal†; Diemil; ***Ukr.***: Cinatropil (Цинатропил)†; Evrisam (Эвризам); Memosam (Мемозам); Neuro-Norm (Нейро-Норм); Olatropil (Олатропил); Omaron (Омарон); Phezam (Фезам); Tiocetam (Тиоцетам).

Pramiracetam Sulfate *(USAN, rINNM)*

Amacetam Sulphate; CI-879; Pramiracétam, Sulfate de; Pramiracetam, sulfato de; Pramiracetam Sulphate; Pramiracetami Sulfas; Sulfato de pramiracetam; Прамирацетама Сульфат.

N-[2-(Diisopropylamino)ethyl]-2-oxo-1-pyrrolidineacetamide sulphate.

$C_{14}H_{27}N_3O_2.H_2SO_4$=367.5

CAS — 68497-62-1 (pramiracetam); 72869-16-0 (pramiracetam sulfate).

ATC — N06BX16.

ATC Vet — QN06BX16.

UNII — OP7O7MN59P.

Profile

Pramiracetam sulfate has been used in age-related memory impairment and senile dementia. It has also been tried, without much success, as an adjunct to ECT in severe depression.

References.

1. McLean A, *et al.* Placebo-controlled study of pramiracetam in young males with memory and cognitive problems resulting from head injury and anoxia. *Brain Inj* 1991; 5: 375–80.
2. Auteri A, *et al.* Pharmacokinetics of pramiracetam in healthy volunteers after oral administration. *Int J Clin Pharmacol Res* 1992; 12: 129–32.
3. Scarpazza P, *et al.* Multicenter evaluation of pramiracetam for the treatment of memory impairment of probable vascular origin. *Adv Therapy* 1993; 10: 217–25.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ukr.***: Pramistar (Прамистар).

Pyritinol Hydrochloride *(BANM, rINNM)*

Hidrocloruro de piritinol; Piritinol, hidrocloruro de; Pirytynolu dichlorowodorek; Pyrithioxine Hydrochloride; Pyritino Chlorhydrate de; Pyritinoli Dihydrochloridum; Pyritinol Hydrochloridum; Пиритинола Гидрохлорид.

5,5-Dihydroxy-6,6-dimethyl-3,3-dithiodimethylenebis(4-pyridylmethanol) dihydochloride monohydrate.

$C_{16}H_{20}N_2O_4S_2.2HCl.H_2O$=459.4

CAS — 1098-97-1 (pyritinol); 10049-83-9 (anhydrous pyritinol hydrochloride).

ATC — N06BX02.

ATC Vet — QN06BX02.

UNII — 0OE436N2Y2.

Pharmacopoeias. In *Chin.* and *Pol.*

Profile

Pyritinol hydrochloride has been described as a nootropic that promotes the uptake of glucose by the brain. It has been used in the treatment of various cerebrovascular and mental function disorders. It has been given in a usual oral dose of 600 mg daily in 3 divided doses. Pyritinol hydrochloride has also been given as an alternative to penicillamine in rheumatoid arthritis. It is also an ingredient of various preparations promoted as tonics.

References.

1. Knezevic S, *et al.* Pyritinol treatment of SDAT patients: evaluation by psychiatric and neurological examination, psychometric testing and rCBF measurements. *Int Clin Psychopharmacol* 1989; 4: 25–38.
2. Lemmel EM. Comparison of pyritinol and auranofin in the treatment of rheumatoid arthritis. *Br J Rheumatol* 1993; 32: 375–82.
3. Straumann A, *et al.* Acute pancreatitis due to pyritinol: an immune-mediated phenomenon. *Gastroenterology* 1998; 115: 452–4.
4. Maria V, *et al.* Severe cholestatic hepatitis induced by pyritinol. *BMJ* 2004; 328: 572–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Encephabol; ***Chile***: Encefabol; ***China***: Ai Nao Xing (爱瑙幸); An Jie De Xin (安洁德欣); Ling Bo Kang (灵博康); Tian Shu Qing (天叔清); Xin Te (信特); Yi Shou (益寿); Ying Luo En (英罗恩); ***Cz.***: Encephabol; Enerbol†; ***Ger.***: Encephabol; ***Gr.***: Encephabol; ***Hong Kong***: Encephabol; ***India***: Encephabol; ***Indon.***: Encepan; Encephabol; Enerbol; ***Malaysia***: Pyritil; ***Mex.***: Encephabol; ***Philipp.***: Encephabol; ***Port.***: Cerbon; ***Rus.***: Encephabol (Энцефабол); Enerbol (Энербол)†; ***S.Afr.***: Encephabol†; ***Thai.***: Encephabol; Memonol; Pyritil; ***Ukr.***: Encephabol (Энцефабол); ***Venez.***: Acon; Bonifen; Bonitrop; Fitina.

Multi-ingredient Preparations. ***Arg.***: Ciprovit Energizante; Gabimex Plus; Levantol Procaina; ***Spain***: Refulgin†; Tomevit†.

Rivastigmine *(BAN, USAN, rINN)*

ENA-713 (rivastigmine or rivastigmine hydrogen tartrate); Rivastigmiini; Rivastigmin; Rivastigmina; Rivastigminum; SDZ-212-713; SDZ-ENA-713 (rivastigmine or rivastigmine hydrogen tartrate); Ривастигмин.

(-)-*m*-[(*S*)-1-(Dimethylamino)ethyl]phenyl ethylmethylcarbamate.

$C_{14}H_{22}N_2O_2$=250.3

CAS — 123441-03-2.

ATC — N06DA03.

ATC Vet — QN06DA03.
UNII — PKI06M31W0.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Rivastigmine). A viscous, clear, colourless or yellow or very slightly brown, hygroscopic liquid. Sparingly soluble in water; very soluble in dehydrated alcohol and in heptane. Store in airtight containers under an inert gas at a temperature of 2 degrees to 8 degrees. Protect from light.

USP 36: (Rivastigmine). Store in airtight containers under an inert gas at a temperature of 2 degrees to 8 degrees. Protect from light.

Rivastigmine Hydrogen Tartrate

(BANM, rINNM)

ENA-713 (rivastigmine or rivastigmine hydrogen tartrate); Hidrogenotartrato de rivastigmina; Rivastigmina, hidrogenotartrato de; Rivastigmine Bitartrate; Rivastigmine, Hydrogénotartrate de; Rivastigmine Tartrate; Rivastigmini Hydrogenotartras; SDZ-ENA-713 (rivastigmine or rivastigmine hydrogen tartrate); Ривастигмина Гидротартрат.

$C_{14}H_{22}N_2O_2.C_4H_6O_6$=400.4
CAS — 129101-54-8.
ATC — N06DA03.
ATC Vet — QN06DA03.
UNII — 9IY2357JPE.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Rivastigmine Hydrogen Tartrate). A white or almost white, very hygroscopic, crystalline or fine crystalline powder. It shows polymorphism. Very soluble in water; soluble in methyl alcohol; very slightly soluble in ethyl acetate. Store in airtight containers. Protect from light.

USP 36: (Rivastigmine Tartrate). A white to off-white powder. Very soluble in water and in methyl alcohol; very slightly soluble in ethyl acetate. Store in airtight containers.

Uses and Administration

Rivastigmine is a carbamate type reversible acetylcholinesterase inhibitor; it also inhibits butyrylcholinesterase. Rivastigmine is selective for the CNS and is used for the symptomatic treatment of mild to moderately severe dementia in Alzheimer's disease (but see p. 398.1) and idiopathic Parkinson's disease (p. 398.1). It is given orally as the hydrogen tartrate or in transdermal patches as the base. For both routes doses are expressed in terms of the base; 2.4 mg of rivastigmine hydrogen tartrate is equivalent to about 1.5 mg of rivastigmine.

An initial oral dose is 1.5 mg given twice daily with food. Thereafter, the dose may be increased according to response and tolerance by increments of 1.5 mg twice daily at intervals of at least 2 weeks to a maximum dose of 6 mg twice daily. In the USA, licensed product information recommends dose increments at intervals of at least 4 weeks when treating dementia associated with Parkinson's disease.

Transdermal patches delivering 4.6, 9.5, or 13.3 mg of rivastigmine over 24 hours are also available for once-daily application. In the USA, rivastigmine patches are licensed for use in the treatment of dementia in Alzheimer's disease or Parkinson's disease; however, in the UK, the licensed use is restricted to dementia in Alzheimer's disease. An initial transdermal dose is 4.6 mg daily; after at least 4 weeks and if well tolerated, the dose should be increased to 9.5 mg daily. US licensed product information states that the dose may be further increased to 13.3 mg daily after at least another 4 weeks; UK licensed product information states that this increase should only be considered after a minimum of 6 months of treatment at the lower dose. A maintenance dose of 4.6 mg daily may be sufficient for patients with a low body-weight (below 50 kg) who develop adverse effects; conversely, those who weigh more than 100 kg may need doses higher than 9.5 mg daily.

Patients already taking oral rivastigmine may be changed to the patches as follows:

- those taking 6 mg daily or less of oral rivastigmine may be switched to patches delivering 4.6 mg over 24 hours
- those taking more than 6 mg daily orally may be switched to patches delivering 9.5 mg over 24 hours

The first patch should be applied on the day following the last oral dose. The patch should be applied to intact skin on the upper or lower back, or on the upper arm or chest; it should not be applied to the abdomen or thigh due to decreased bioavailability. Re-application to the same site should be avoided for 14 days. Only one patch should be applied at a time.

Doses may need to be adjusted in those with hepatic or renal impairment (see p. 398.1).

If treatment with oral or transdermal rivastigmine is interrupted for more than a few days, it should be restarted at the low initial dose, and then increased as described above. Clinical benefit should be reassessed on a regular basis; treatment should be stopped if there is no improvement after 3 months.

Administration in hepatic impairment. Exposure to rivastigmine is increased in patients with hepatic impairment and those with significant impairment may experience more adverse reactions. Recommendations to titrate the dose of rivastigmine to patients' requirements should be closely followed.

Based on pharmacokinetic studies with oral rivastigmine, licensed product information for rivastigmine transdermal patches suggests to consider a dose of 4.6 mg daily as both initial and maximum therapy in patients with mild to moderate hepatic impairment (Child Pugh score of 5 to 9). There is a lack of data on its use in severe hepatic impairment.

Administration in renal impairment. Exposure to rivastigmine may be increased in patients with renal impairment and those with significant impairment may experience more adverse reactions. Recommendations to titrate the dose of rivastigmine to patients' requirements should be closely followed.

Based on pharmacokinetic studies with oral rivastigmine, UK licensed product information for rivastigmine transdermal patches suggests to consider a dose of 4.6 mg daily as both initial and maximum therapy in patients with significant renal impairment. However, US product information does not consider dose adjustment to be necessary in this patient group due to the lack of a clear effect of creatinine clearance on the steady state concentrations of rivastigmine or its metabolite.

Dementia. Rivastigmine may be of benefit in the management of patients with mild to moderate dementia in *Alzheimer's disease*[1,2] (see Dementia, p. 388.1). In the UK, NICE states that it may be used in patients with mild to moderate dementia if given under the following conditions:[3]

- treatment should only be started under specialist supervision
- patients who continue on the drug should be reviewed regularly
- treatment should only be continued if there was evidence of benefit

Rivastigmine given in titrated doses of up to 6 mg twice daily was also found to be well tolerated, and to produce some improvement in behavioural and psychiatric symptoms, in a group of patients with *Lewy-body dementia*.[4] However, a systematic review[5] that included this study noted that rivastigmine did not have significant benefit in cognitive function compared with placebo; the authors considered that the evidence for its use in such patients was weak and that further trials were needed.

Rivastigmine has also been tried in the treatment of *vascular dementia*. A systematic review[6] concluded that although there is some evidence of benefit in these patients, available data are inadequate and further trials were wartanted before rivastigmine could be recommended.

For the use of rivastigmine in the treatment of dementia in Parkinson's disease, see p. 398.1.

1. Birks J, *et al.* Rivastigmine for Alzheimer's disease. Available in The John Wiley; 2009 (accessed 01/03/10).
2. Dhillon S. Rivastigmine transdermal patch: a review of its use in the management of dementia of the Alzheimer's type. *Drugs* 2011; 71: 1209–31.
3. NICE. Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review) (issued March 2011). Available at: http://www.nice.org.uk/nicemedia/live/13419/53619/53619.pdf (accessed 11/04/11)
4. McKeith I, *et al.* Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study. *Lancet* 2000; 356: 2031–36.
5. Wild R, *et al.* Cholinesterase inhibitors for dementia with Lewy bodies. Available in the Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 14/02/06).
6. Craig D, Birks J. Rivastigmine for vascular cognitive impairment. Available in the Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 14/02/06).

Parkinsonism. Although acetylcholinesterase inhibitors such as rivastigmine may theoretically worsen parkinsonian symptoms, particularly tremor, it has been tried for use in the treatment of drug-induced psychosis in patients with Parkinson's disease (see Disturbed Behaviour, p. 1030.2). In 2 large studies,[1,2] rivastigmine was found to produce some improvement in symptoms of dementia associated with Parkinson's disease when compared with placebo. Furthermore, a retrospective analysis[3] that included one of these studies concluded that rivastigmine did not induce clinically significant exacerbation of motor dysfunction in this patient group; emergent or worsening rest tremor had been reported, however, this effect was transient and associated with dose titration.

1. Emre M, *et al.* Rivastigmine for dementia associated with Parkinson's disease. *N Engl J Med* 2004; 351: 2509–18.
2. Wesnes KA, *et al.* Benefits of rivastigmine on attention in dementia associated with Parkinson disease. *Neurology* 2005; 65: 1654–6.
3. Oertel W, *et al.* Effects of rivastigmine on tremor and other motor symptoms in patients with Parkinson's disease dementia: a retrospective analysis of a double-blind trial and an open-label extension. *Drug Safety* 2008; 31: 79–94.

Adverse Effects, Treatment, and Precautions

As for Donepezil, p. 391.1. Application site reactions such as erythema, pruritus, rash, and vesicles have been seen with transdermal use of rivastigmine. Serious adverse effects, including fatalities, have occurred after incorrect use of transdermal patches, the most frequent causes being the failure to remove the previous patch before applying a new one and application of more than one patch at a time. In such cases of overdose all patches should be removed immediately and no further patch applied for the next 24 hours.

Rivastigmine blood levels are dependent on body-weight and careful titration of dosage is recommended in those with a low or high body-weight; for further details, see under Uses and Administration, above.

Rivastigmine should be used with care in patients with impaired hepatic or renal function.

Reviews.

1. Darreh-Shori T, Jelic V. Safety and tolerability of transdermal and oral rivastigmine in Alzheimer's disease and Parkinson's disease dementia. *Expert Opin Drug Safety* 2010; 9: 167–76.
2. Greenspoon J, *et al.* Transdermal rivastigmine: management of cutaneous adverse events and review of the literature. *CNS Drugs* 2011; 25: 575–83.

Effects on the gastrointestinal tract. A 67-year-old woman experienced severe vomiting after rivastigmine, in an oral dose of 4.5 mg, was mistakenly reintroduced without the recommended titration phase;[1] the vomiting was so severe that the patient also suffered a rupture of the oesophagus that needed corrective surgery. The authors commented that careful dose titration of rivastigmine is necessary even when restarting treatment.

1. Babic T, *et al.* Spontaneous rupture of oesophagus (Boerhaave's syndrome) related to rivastigmine. *Age Ageing* 2000; 29: 370–1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies rivastigmine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 25/10/11)

Interactions

As for Neostigmine, p. 688.3. See also Antimuscarinics, under Donepezil, p. 391.2, for mention of an interaction between rivastigmine and tolterodine.

Pharmacokinetics

Rivastigmine is readily absorbed from the gastrointestinal tract and peak plasma concentrations are reached in about 1 hour after oral doses. Food delays absorption by about 1.5 hours and reduces maximum plasma concentrations. Absorption from transdermal patches is slow and peak plasma concentrations are reached in 10 to 16 hours after applying the first patch; with subsequent patches, peak concentrations are reached in about 8 hours. Exposure to rivastigmine is highest when the patch is applied to the upper back, chest, or upper arm, and about 20 to 30% lower when applied to the abdomen or thigh. Rivastigmine is about 40% bound to plasma proteins and readily crosses the blood-brain barrier; it is widely distributed throughout the body. Rivastigmine is rapidly and extensively metabolised, primarily by cholinesterase-mediated hydrolysis to the weakly active decarbamylated metabolite. The plasma half-life is about 1 hour after oral doses and about 3 hours after patch removal. After oral use, more than 90% of a dose is excreted in the urine within 24 hours; no unchanged rivastigmine is detected in the urine. Less than 1% of a dose appears in the faeces.

References.

1. Hossain M, *et al.* Estimation of the absolute bioavailability of rivastigmine in patients with mild to moderate dementia of the Alzheimer's type. *Clin Pharmacokinet* 2002; 41: 225–34.
2. Kurz A, *et al.* Pharmacokinetics of a novel transdermal rivastigmine patch for the treatment of Alzheimer's disease: a review. *Int J Clin Pract* 2009; 63: 799–805.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Donadox; Exelon; Luneste; Remizeral; Rivasmina; *Austral.*: Exelon; *Austria*: Exelon; *Belg.*: Exelon; *Braz.*: Exelon; Prometax; *Canad.*: Exelon; *Chile*: Exelon; Probrain; *China*: Exelon (艾斯能); *Cz.*: Evertas; Exelon; Ivagalmin; Kerstipon; Nimvastid; Prometax; Ristidic; Vastigmex; *Denm.*: Exelon; Nimvastid; Prometax; *Fin.*: Exelon; *Fr.*: Exelon; *Ger.*: Exelon; *Gr.*: Exelon; Prometax; *Hong Kong*: Exelon; *Hung.*: Exelon; *India*: Exelon; *Indon.*: Exelon; *Irl.*: Exelon; Nimvastid; Prometax; *Israel*: Exelon; *Ital.*: Exelon; Prometax; *Jpn*: Exelon; Rivastach; *Malaysia*: Exelon; *Mex.*: Exelon; *Neth.*:

Exelon; Ivagalmin; Niddastig†; Nimvastid; Prometax; Ristidic; Rivalong; Rivarlau; Rivaxon; Signelon†; ***Norw.***: Exelon; ***NZ***: Exelon; Rimane; ***Philipp.***: Exelon; ***Pol.***: Exelon; Ivagalmin; Nimvastid; Prometax; Ristidic; Rivaller; Rivastinorm; Riveka; Symelon; Velastina; ***Port.***: Exelon; Nimvastid; Prometax; ***Rus.***: Exelon (Экселон); ***S.Afr.***: Exelon; ***Singapore***: Exelon; ***Spain***: Exelón; Prometax; ***Swed.***: Exelon; Nimvastid; ***Switz.***: Exelon; ***Thai.***: Exelon; ***Turk.***: Altigmin; Exelon; Ristart; Rivaxel; ***UK***: Exelon; ***USA***: Exelon; ***Venez.***: Exelon.

Pharmacopoeial Preparations
USP 36: Rivastigmine Tartrate Capsules.

Tacrine Hydrochloride

(BANM, USAN, rINNM)

Ci-970; Hidrocloruro de tacrina; Hidrocloruro de tetrahidroaminoacridina; Tacrina, hidrocloruro de; Tacrine, Chlorhydrate de; Tacrini hydrochloridum; Tetrahydroaminoacridine Hydrochloride; THA; Такрина Гидрохлорид.

1,2,3,4-Tetrahydroacridin-9-ylamine hydrochloride.

$C_{13}H_{14}N_2$,HCl=234.7

CAS — 321-64-2 (tacrine); 1684-40-8 (tacrine hydrochloride).

ATC — N06DA01.

ATC Vet — QN06DA01.

UNII — 4966RNG0BU.

Pharmacopoeias. In *US* as the monohydrate.

USP 36: (Tacrine Hydrochloride). The monohydrate occurs as a white powder. Freely soluble in water, in alcohol, in dimethyl sulfoxide, in methyl alcohol, in propylene glycol, and in 0.1N hydrochloric acid; sparingly soluble in linoleic acid and in macrogol 400.

Profile

Tacrine hydrochloride is a centrally acting reversible inhibitor of acetylcholinesterase activity that has been used in the treatment of mild to moderately severe dementia in Alzheimer's disease. However, hepatotoxicity was common and sometimes severe (see under Adverse Effects, p. 398.3).

Tacrine has also been used intravenously to antagonise competitive neuromuscular blockers and as a postoperative respiratory stimulant.

Adverse effects. *EFFECTS ON THE LIVER.* Examination of data from 2446 patients who were at least 50 years old and received tacrine for Alzheimer's disease suggested that raised serum-alanine aminotransferase (ALT) concentrations are likely to occur in about 50% of patients.[1] Most cases developed within the first 12 weeks of therapy,[1] but an asymptomatic increase in ALT concentrations has been reported in a patient after more than 80 weeks of therapy.[2] The increase is usually asymptomatic and mild, and resolves upon dosage reduction or stopping treatment. However, a small percentage of patients may develop unpredictable life-threatening hepatotoxicity although frequent monitoring of ALT concentrations during the first 12 weeks of therapy can identify susceptible individuals. No significant correlation has been found between plasma-tacrine concentrations and hepatotoxicity.[3]

1. Watkins PB, *et al.* Hepatotoxic effects of tacrine administration in patients with Alzheimer's disease. *JAMA* 1994; 271: 992–8.
2. Terrell PS, *et al.* Late-onset alanine aminotransferase increase with tacrine. *Ann Pharmacother* 1996; 30: 301.
3. Ford JM, *et al.* Serum concentrations of tacrine hydrochloride predict its adverse effects in Alzheimer's disease. *Clin Pharmacol Ther* 1993; 53: 691–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Talem; ***Austral.***: THA†; ***Br.***: Cognex†; ***USA***: Cognex†.

Pharmacopoeial Preparations
USP 36: Tacrine Capsules.

Xanomeline *(USAN, rINN)*

LY-246708; NNC-11-0232; Xanomelina; Xanoméline; Xanomelinum; Ксаномелин.

3-[4-(Hexyloxy)-1,2,5-thiadiazol-3-yl]-1,2,5,6-tetrahydro-1-methylpyridine.

$C_{14}H_{23}N_3OS$=281.4

CAS — 131986-45-3.

UNII — 9ORI6L73CJ.

Profile

Xanomeline is a selective muscarinic M_1 agonist. Xanomeline tartrate has been studied in the management of Alzheimer's disease but drugs of this type have not generally produced benefit.

References.

1. Sramek JJ, *et al.* The safety and tolerance of xanomeline tartrate in patients with Alzheimer's disease. *J Clin Pharmacol* 1995; 35: 800–80 i.
2. Bodick NC, *et al.* Effects of xanomeline, a selective muscarinic receptor agonist, on cognitive function and behavioral symptoms in Alzheimer disease. *Arch Neurol* 1997; 54: 465–73.

Antidepressants

Bipolar disorder, p. 399
Depression, p. 400
Mania, p. 402

This chapter describes drugs used principally in the treatment of affective disorders. Affective disorders are disorders of mood that may manifest as ***depression*** or ***mania*** or, in some cases, as ***mixed affective states*** in which depressive and manic or hypomanic episodes may coexist or rapidly alternate.

- The core features of ***depressive disorders*** are low mood, anhedonia (the loss of interest in former pleasures or activities), pessimism, and lethargy. They were formerly classified either as ***endogenous***, in which the symptoms were independent of external factors and considered to be a consequence of factors within the patient, or ***reactive***, in which depressive symptoms were a result of external stressors (i.e. exogenous). It is now recognised that depressive disorders are composed of both endogenous and reactive factors. Similarly, the classification of ***neurotic depression*** is no longer considered useful because it encompasses several different syndromes.
  Depressive episodes generally last for at least 2 weeks and are classified according to severity as mild, moderate, severe, or severe with psychosis. ***Recurrent brief depression*** is defined as depressive episodes that last a few days and recur regularly. Depression is often accompanied by characteristic ***somatic*** symptoms, including anorexia, weight loss, insomnia, early morning waking, and psychomotor retardation. Symptoms associated with ***atypical depression*** include overeating and oversleeping. Some classifications distinguish between major depressive episodes and minor (and hence ***major*** or ***minor depression***) based on the number and type of symptoms.
- The main symptoms of ***mania*** are overactivity, mood changes ranging from elation to irritability, expansive ideas, and inflated self-importance. Manic episodes are classified according to severity in a similar manner to depressive disorders: namely, mild, moderate, severe, or severe with psychosis. ***Hypomania*** is differentiated from mania in terms of a reduction in intensity of symptoms and social incapacity.
- Alternating episodes of mania or hypomania and depression are termed ***bipolar disorder (bipolar affective disorder)***. (To differentiate between alternating episodes of depression and mania or depression and hypomania, some classification systems use the terms ***bipolar I disorder*** and ***bipolar II disorder***, respectively.) Since it is very rare for repeated episodes of mania to occur without alternating episodes of depression, it is accepted practice to include mania without depression within the bipolar category. The term ***unipolar disorder (unipolar depression)*** is reserved for depressive disorders without mania.
- States of persistent but mild disturbances of mood exist in which the symptoms are not severe enough to meet the criteria for classification as a major depressive or hypomanic disorder, but may nevertheless cause considerable suffering to the patient. ***Subthreshold depressive symptoms*** and ***dysthymia*** are terms used to describe a milder depressive state whereas ***cyclothymia*** has some similarity to bipolar disorder, the instability characterised by long periods of hypomania and mild depression.
- The term ***seasonal affective disorder*** has been applied to depressive disorders repeatedly occurring seasonally, but not related to seasonal stressful life events; the depressive symptoms usually occur during the autumn and winter months. There have also been reports of patients developing seasonal bipolar disorder with hypomania or mania occurring in the summer months.
- Anxiety is often associated with depressive disorders at all levels of severity and it may be difficult to distinguish between the two conditions, especially in the milder forms. ***Mixed anxiety and depressive disorder*** defines a state in which anxiety and depressive symptoms coexist but neither component is severe enough to merit classification as an anxiety disorder or a depressive disorder.

Classification of antidepressants. Antidepressants are classified into different groups either structurally or depending on which central neurotransmitters they act upon. The older tricyclic (e.g. amitriptyline) and related cyclic antidepressants and the monoamine oxidase inhibitors (MAOIs) (e.g. phenelzine) have now been joined by the selective serotonin reuptake inhibitors (SSRIs) (e.g. fluoxetine), the reversible inhibitors of monoamine oxidase type A (RIMAs) (e.g. moclobemide), and more recently by the serotonin and noradrenaline reuptake inhibitors (SNRIs) (e.g. venlafaxine). Other antidepressants that do not fit exactly into these groups include bupropion, the herbal preparation St John's wort, mirtazapine, reboxetine, and trazodone.

Lithium salts provide a source of lithium ions that compete with sodium ions at various sites in the body and thus have an action and adverse effects distinct and separate from those of other antidepressants.

Bipolar disorder

Bipolar disorder (manic depression) is a mixed affective disorder in which the patient has alternating episodes of hypomania or mania and depression. Although isolated episodes of mania may occur, they are more usually part of bipolar disorder; for the purposes of classification, mania without depression is therefore included in the bipolar category. Manic episodes usually start suddenly and last on average for about 4 months. The depressive phase may last longer with an average duration of 6 months. The course of the illness is unpredictable; most patients will suffer a relapse after an initial manic episode, and of these, probably 10 to 20% will have more than 3 episodes a year with partial or full remission in between, or switch to the alternative phase (rapid cycling). The diagnosis of bipolar disorder can be difficult, particularly if patients are only seen during the depressive phase. The morbidity of the disorder is often substantial especially during the depressive phase. Suicide is a significant risk and up to one-third of patients may attempt to take their own life.

The treatment of bipolar disorder is generally divided into the following phases:

- acute manic or mixed episode
- acute depressive episode
- maintenance and long-term treatment

Guidelines have been issued in the UK[1-3] and USA[4,5] to facilitate treatment choice in the management of bipolar disorder; international guidelines and expert consensus statements are also available.[6-9] The choice of drug therapy should be guided by severity, the type of episode (including associated symptoms), and patient preference.

In patients with severe **manic** or mixed episodes, initial treatment with an antipsychotic or the mood stabiliser valproate should be considered because of their rapid onset of action; for less severe cases lithium, another mood stabiliser, may also be appropriate.[1,3,6,8] The choice between lithium or valproate as first-line treatment has been a matter of debate: although there is more reliable evidence for the use of lithium, its narrow therapeutic index and monitoring requirements[10-12] (see Pharmacokinetics of Lithium, p. 434.3) have led to the increased use of valproate in some countries.[10] Lithium must also be given in high doses in acute mania and its antimanic actions may be delayed by at least a week.[11,13] Nonetheless, lithium is still widely used[11] and may be most effective in pure euphoric mania.[6,8] However, valproate may be a better first-choice drug in rapid cycling bipolar disorder, for which it is particularly effective, and in mixed or dysphoric states.[1,4,6-8] Carbamazepine and its derivative oxcarbazepine are sometimes used as alternatives to lithium or valproate although their efficacy is not as well established and they are considered a second-line choice by most guidelines.[3,4,6,8] Treatment with carbamazepine is also complicated by its numerous drug interactions.[10,12,13]

Patients with mania and co-existing psychotic features usually require treatment with an antipsychotic to produce a rapid tranquillising effect.[4] Traditionally, classical antipsychotics such as the phenothiazine chlorpromazine and the butyrophenone haloperidol have been used although most guidelines now recommend the atypical antipsychotics, particularly olanzapine, quetiapine, and risperidone, because of their more favourable adverse effect profile.[1,3-6,8] Nevertheless, classical antipsychotics still appear to be widely used in the treatment of mania although high-dose therapy should be avoided because of the risk of extrapyramidal effects.[8] If sedation is required the short-term use of a benzodiazepine such as clonazepam or lorazepam should be considered instead of high-dose antipsychotics;[1,3,4] however, such treatments should be stopped as soon as symptoms subside in order to reduce the risk of dependence.[12]

The initial treatment should be continued at an optimal dose for at least 1 week before making any change to the regimen if the patient is unresponsive; if there is a partial response it may be appropriate to wait at least another week before considering the treatment ineffective. Options for patients who are inadequately controlled on optimised first-line treatment include a trial of lithium or valproate with an antipsychotic.[1,3,4,6,8] (Combination therapy has also been recommended as first-line treatment in patients with particularly severe symptoms.[3,4]) Another option is to try an alternative mood stabiliser or antipsychotic.[6] Clozapine may be considered in more refractory cases[3,4] and ECT is effective in patients who are severely ill or resistant to treatment.[1,3,4,8]

The treatment of the acute **depressive phase** of bipolar disorder depends on the severity of the depression and whether any psychotic symptoms are still present. Less severe cases may be adequately controlled by lithium, which has a modest antidepressant action.[3] Alternatively, treatment with lamotrigine or an antidepressant may be considered although most guidelines[1,3,4,9] recommend that antidepressants should be given with a mood stabiliser such as lithium or valproate to reduce the risk of antidepressant-induced switching (see below). The atypical antipsychotic quetiapine also has an antidepressant action and is another monotherapy alternative for managing the acute depressive phase.[3,9]

The selection of an antidepressant for bipolar depression generally involves the same considerations as those for unipolar depression (see p. 400.1) although the risk of switching to mania should also be taken into account. Antidepressants have also been implicated in the induction of rapid cycling;[4,12] they should be tapered and stopped if either switching or rapid cycling occurs.[1,3,6] The SSRIs and possibly bupropion are usually first-choice antidepressants as they have a low risk of switching when compared with other antidepressants.[3,4,6,9,14] Tricyclic antidepressants should only be used in resistant cases as the risk of switching to mania is higher than with other antidepressant groups.[1,3] Data for the newer antidepressants such as nefazodone and venlafaxine are limited; it has been suggested that the risk of switching with venlafaxine is increased.[6,9] MAOIs may be less likely to induce mania than other antidepressants, but troublesome adverse effects and safety issues have limited their use.

As with the manic phase, treatment should be tried at an optimal dose and for an adequate time before it is considered ineffective.[6,9] If there is no response, second-line options include adding an antidepressant or lamotrigine in those patients on monotherapy with a mood stabiliser such as lithium, or in those patients already on an antidepressant, an alternative antidepressant may be tried or a second mood stabiliser added.[4,6,9] Additional treatment with an antipsychotic may be necessary if psychotic symptoms are also present.[3,4] In addition, some atypical antipsychotics have been shown to be of benefit in non-psychotic bipolar depression when given with an antidepressant[6,9] and one such combination preparation (olanzapine with fluoxetine) is available in some countries. Quetiapine is another atypical antipsychotic that may be added to therapy.[2,3] ECT is a valuable alternative and should be considered for resistant or severe bipolar depression.[1,3,4,9]

Once the acute phase has been brought under control, drug therapy should be continued until the patient is thought unlikely to suffer a relapse; this might entail **maintaining treatment** for several months.[3,4,15] When full remission has been achieved treatment should be gradually stopped over several weeks unless long-term treatment is planned (see below). Antipsychotics and antidepressants are usually stopped unless residual symptoms persist.

Some guidelines[3,4] recommend that **long-term** treatment should be started after a single episode of mania although others generally wait until a patient has had at least 2 manic episodes.[6] Lithium is often the drug of choice for the long-term treatment of bipolar disorder.[1,3,4] It reduces the risk of relapse, particularly mania,[3] although its prophylactic effects on depression are less obvious.[16] Long-term lithium treatment has also been associated with an anti-suicide effect.[3,15] Other treatment options include valproate, lamotrigine (particularly if bipolar depression is a burden), aripiprazole olanzapine, quetiapine, and possibly carbamazepine or oxcarbazepine.[1,3-7] Combination therapy may be necessary in those who fail on monotherapy; ECT and clozapine have also been tried in treatment-resistant patients.[3,7] However, it is usual practice for patients to continue with their acute treatment, given at the same doses, if effective.[3,4,6]

There is no consensus on the appropriate duration of long-term treatment and in some patients with severe

disorders it may be necessary to continue treatment indefinitely.

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Depression

Clinical depression (unipolar depression) is a disturbance of mood that is distinguishable from the usual mood fluctuations of everyday life. A depressed mood is usually the major symptom, which may be accompanied by other mental or somatic symptoms representing several depressive syndromes (see p. 397.1). Suicide is a significant risk and up to half of all patients with depression may attempt suicide during their lifetime. Risk factors for developing depression include female gender and a positive family history.

The aetiology of depression is unknown but it may represent an interaction between psychological and biochemical mechanisms rather than any single factor. The symptoms appear to be mediated through alterations in levels of some central neurotransmitters, although it is not certain that this represents a cause of the disorder. However, it is at this level that the antidepressant drugs currently in clinical use exert their action.

Guidelines have been issued nationally in, for example, the UK[1,2] and the USA,[3-5] and internationally,[6,7] which provide evidence-based recommendations for the treatment of depression. The decision to start treatment should be based on the severity of the condition and the risks to the patient.

- Patients with *subthreshold depressive symptoms* do not routinely require treatment with antidepressants unless symptoms have been present for a long period, typically 2 years or more.[1,2]
- Patients with *mild depression* may improve while being monitored without any additional help; in others simple interventions such as problem-solving, counselling, or exercise may be effective.[2] The evidence for the efficacy of antidepressants in mild depression is lacking and initial treatment with antidepressants is not recommended;[1,2,4] however, patients with persistent mild depression or those with a history of depression may benefit from antidepressant treatment.[1,2]
- Patients with *moderate* depression should be treated with an antidepressant; psychological treatments (particularly cognitive behavioural therapy) are also effective.[1,2]
- A combination of antidepressants and psychological treatments should be considered in patients with *severe* depression.[1,2] ECT may also be of value, particularly when a rapid improvement of symptoms is essential (e.g. in patients at high risk of suicide) or in patients with depressive psychosis or psychomotor retardation.[8,9]
- For patients with *psychotic depression*, an antipsychotic may be required in addition to any antidepressant treatment;[1,2,4] ECT should also be considered.[4]
- Light therapy appears to be effective in patients with *seasonal affective disorder*.[10,11] Exposure to bright artificial light may take place at any time of the day, and the therapy should continue until the natural seasonal remission of the disorder; antidepressant drugs may also be used.

Choice of antidepressant. In more recent years many newer drugs have been licensed and added to the original treatments for depression. The role of these drugs relative to the older drugs is established for some of the newer drug groups, particularly the SSRIs, and evidence suggests that efficacy is comparable. In addition, many new drugs have been promoted on the basis of superior tolerability and this is also supported by clinical studies (see below for further details). The improved choice of treatment options offered by the newer antidepressants has meant that therapy is increasingly tailored to individual patient requirements.

- Tricyclic antidepressants have long been preferred over MAOIs because of the problem of drug interactions and the need for strict dietary precautions with the latter group. Tricyclics with sedative properties may be more suitable for agitated and anxious patients, whereas those with less sedative properties may be preferred for withdrawn and apathetic patients. Unfortunately, the traditional tricyclics such as amitriptyline have antimuscarinic and cardiotoxic adverse effects that can limit their use. Their cardiotoxicity also means that they are associated with a high risk of fatality in patients taking overdoses (see toxicity in overdosage, below).
- Continuing development produced lofepramine and drugs related to the tricyclic group such as mianserin that are less cardiotoxic than the earlier tricyclics.
- The subsequent introduction of SSRIs such as fluoxetine provided a group of drugs with still fewer antimuscarinic and cardiotoxic adverse effects. However, the SSRIs themselves have characteristic adverse effects; gastrointestinal symptoms such as nausea and vomiting may be a problem, and sleep disturbances and anxiety may be exacerbated at the start of treatment. Moreover, those in current clinical use interact to varying degrees with cytochrome P450 isoenzymes, which carries a potential for interaction with many drugs.
- More recently serotonin and noradrenaline reuptake inhibitors (SNRIs) such as duloxetine and venlafaxine have been developed, as well as reversible inhibitors of monoamine oxidase type A (RIMAs) such as moclobemide. RIMAs offer a safer alternative to the MAOIs and fewer dietary restrictions are necessary. Nefazodone, mirtazapine, and reboxetine, which have slightly different biochemical profiles from the major groups, are also more recent introductions. Bupropion, another unrelated antidepressant, is also available in some countries. With the exception of nefazodone, which causes hepatotoxicity and venlafaxine, which is cardiotoxic, most of these newer drugs seem to be associated with fewer severe adverse effects; their efficacy is also comparable to that of the tricyclics and SSRIs.[12-14]
- Other drugs used in the treatment of depression include flupentixol, the antidepressant dose of which is lower than that used for the treatment of psychoses. Agomelatine, an agonist at melatonergic MT_1 and MT_2 receptors and an antagonist at $5\text{-}HT_{2C}$ receptors, is used in the treatment of depression. Ademetionine, the active derivative of methionine, has been tried in depressive disorders, and extracts of the plant St John's wort are widely used in some countries for depression. Transdermal patches containing selegiline, an irreversible inhibitor of monoamine oxidase type B, are available in the USA for the treatment of depression. Lithium may be used for the prophylaxis of recurrent unipolar depression as an alternative to standard antidepressants, although it is more commonly used in the management of bipolar disorder (see p. 397.2); its role in unipolar depression is more usually to augment the effect of standard antidepressants in treatment-resistant disease.

An area of particular concern with regard to initial choice of an antidepressant is the most appropriate drug for patients considered to be a high suicide risk.[15] It is important to remember that suicide is an inherent risk in depression; it is generally accepted that with all antidepressant therapies the risk of suicide may increase in the early stages of recovery (for further details, see Effects on Mental State, under Fluoxetine, p. 422.2). Varying relative risks of **toxicity in overdosage** for different groups of antidepressant have been assessed:[16-19]

- older tricyclics and the tetracyclic maprotiline[20] appear to be more toxic in overdosage than the tetracyclic mianserin[21] and the SSRIs[18,22]
- MAOIs have an intermediate risk[22,23]
- within the tricyclic group, desipramine[16,17,22] has been reported to be associated more frequently with fatal overdosage although some[24] assign this status to dosulepin. The *BNF* considers amitriptyline and dosulepin to be particularly dangerous in overdosage; lofepramine[19,22,25] may be one of the safer tricyclics
- toxicity of the SNRI venlafaxine in overdose appears to be greater than other new serotonergic antidepressants and comparable to some of the less toxic tricyclics[22]

Although such analyses cannot determine to what extent the data reflect prescribing patterns and patient selection as opposed to drug toxicity[16,17,25] it is widely accepted that the older tricyclics are more toxic in overdosage, and that the SSRIs[26,27] and the newer tricyclic and related cyclic antidepressants are safer.[27] In practice, it is often difficult to identify patients at high risk for suicide, and it has therefore been suggested that a routine strategy should be to begin antidepressant therapy in all patients with drugs that have low toxicity in overdose.[15,27] However, whichever antidepressant is chosen, all patients should be closely monitored during early therapy until significant improvement in depression occurs and limited quantities of antidepressants should be prescribed at any one time.

Current guidelines recommend that choice of antidepressant should be based on superior tolerability, safety in overdose, and efficacy at prescribed doses.[1,2,4,6] Meta-analyses[28-31] comparing the efficacy of SSRIs and tricyclics in general find no difference in efficacy although there is the suggestion of a greater efficacy for some tricyclics when given to inpatients. However, drop-out rates due to adverse effects have generally been higher in patients receiving tricyclics than in those taking SSRIs. Based on these findings, most guidelines recommend that an SSRI[1,2,4,6] should be used as first-line treatment. In addition some consider that lofepramine, nortriptyline, or newer antidepressants such as mirtazapine or reboxetine are suitable alternatives.[1,4,6] Bupropion, which is marketed as an antidepressant in the USA, is considered to be a first-line choice in US guidelines.[4] Older tricyclics may, however, be more appropriate in severely ill patients or in other situations where maximising efficacy is important.[1] The use of an MAOI may be considered in patients with atypical depression[4,6] although, in practice, SSRIs are often tried initially because of their more favourable adverse effects profile.[4]

The sedative properties of some of the antidepressants may adversely affect the performance of potentially hazardous tasks such as driving and the operation of machinery. One of the less sedative antidepressants should be used where appropriate, although care is needed with all psychotropic drugs, especially at the start of treatment.

Regardless of antidepressant choice, certain principles of management apply when **starting antidepressant therapy.**

- A low initial dose will minimise adverse effects; this is then increased until an adequate response occurs.[4] When the newer antidepressants, including the SSRIs, are used the dose can generally be increased after a few days; for the tricyclics the increase should be more gradual.[32] Gradual introduction of treatment is of particular importance in the elderly who may be more susceptible to adverse effects.
- Although some adverse effects of antidepressant drugs appear soon after treatment is started, there is a delay of about 2 weeks before any therapeutic benefit is seen, and at least 6 weeks before maximum improvement in depressive symptoms occurs.[33] Claims of a fast onset of action have been made for several antidepressants, but in a review[34] of data relating to onset of action with currently available antidepressants, none have been shown conclusively to work faster than any other. This delay in benefit may relate to a combination of pharmacokinetic and neurochemical factors.
- A patient's response to the chosen drug should not be considered inadequate until they have been maintained at an adequate dose for at least 3 to 4 weeks[1,2] (the *BNF* has recommended 6 weeks in the elderly). Patients with a partial response should continue for a further 2 to 4 weeks (possibly longer in the elderly) before considering further adjustments in therapy. Treatment failure is often due to subtherapeutic doses,[1] particularly with the older tricyclics whose adverse effects limit maximum tolerable doses in many patients.[35] Where lack of compliance leads to subtherapeutic doses therapeutic drug monitoring may be of value.[6]

In those who show little or no response to an adequate trial of the first-choice antidepressant the following options exist:

- switching to an alternative antidepressant
- adding another drug (augmentation), particularly if there has been a partial response
- introducing psychological treatments such as cognitive behavioural therapy if not previously used

Guidelines generally consider it preferable to try an alternative single antidepressant before giving combinations of drugs (augmentation).[1–4,6]

If **switching antidepressants** the choice is between a drug from the same pharmacological group or one from a different group.[1–4,6] In the UK, venlafaxine is usually reserved for patients with more severe depression, or when two different SSRIs have failed, because of its adverse cardiovascular effects and toxicity in overdose.[1,2] MAOIs can also be tried in patients who are refractory to or intolerant of treatment with other antidepressants.[1,2,4]

When changing a patient from one type of antidepressant to another an appropriate drug-free interval may be needed. An MAOI (including a RIMA and selegiline) should not be started until at least one week after stopping a tricyclic antidepressant, an SSRI, or any related antidepressant; in the case of bupropion, mirtazapine, and the SSRI sertraline the drug-free interval is extended to 2 weeks, and for fluoxetine to 5 weeks, because of their longer half-lives. For the tricyclics clomipramine and imipramine a drug-free interval of 3 weeks should be allowed. Conversely, 2 weeks should elapse between stopping MAOI (including selegiline) therapy and starting patients on a tricyclic antidepressant (3 weeks in the case of clomipramine or imipramine), an SSRI, or any related antidepressant. No treatment-free period is necessary between stopping a reversible inhibitor of monoamine oxidase type A (RIMA) and starting an SSRI or another antidepressant.

Drugs that have been used in **augmentation strategies** for resistant depression include lithium,[1,2,4,6] thyroid hormones (liothyronine),[1,4,6,36] and central stimulants[4,36] such as methylphenidate. Atypical antipsychotics, such as aripiprazole, olanzapine, quetiapine, and risperidone may be added to therapy.[1,2,37] Pindolol has also been studied as an augmentation agent with several SSRIs and other serotonergic antidepressants.[4,36] Another method is to combine different classes of antidepressants. Although this has been used successfully in the treatment of drug-resistant depression,[2,4,6,36] it may result in enhanced adverse reactions or interactions and should only be done under expert supervision. For further details of the interactions between different antidepressants, see under Interactions of Phenelzine, p. 447.2.

If the response to treatment is good, the patient should continue with the same treatment for at least 4 to 6 months after full remission,[1–4] and perhaps 12 months in the elderly;[4] symptoms are likely to recur if treatment is stopped too soon.[38–40] In general, the dose should not be reduced for this **continuation phase**.[1,3,4,7] Continuing therapy beyond this phase[1,2,4,7,41] is a matter of clinical judgement and should take into account the number of prior episodes, any residual symptoms, and the severity of the episode. **Maintenance therapy** should be considered for recurrent depressive disorders,[1,2,4,7,38,40,42] and may be necessary for several years, if not indefinitely, in some cases. Again, full therapeutic doses are recommended for prophylaxis rather than reduced doses.[1,2,4,7,39,42]

Suddenly stopping antidepressant therapy after regular use for 8 weeks or more may precipitate withdrawal symptoms.[43–45] Common symptoms seen after antidepressant withdrawal include headache, anorexia, nausea, insomnia, and anxiety; the SSRIs have also been associated with episodes of dizziness and paraesthesia which are rarely seen with the tricyclics.[46] Withdrawal reactions may be more severe with the MAOIs especially tranylcypromine.[46] To minimise symptoms, most guidelines[1,2,4] and authorities such as the *BNF* recommend reducing the dose over a period of about 4 weeks, although considerably longer periods (6 months) may be required when withdrawing maintenance therapy.

Depressive disorders may arise in **childhood and adolescence**, the prevalence increasing with age.[6] Concerns about a possible increased risk of suicide with antidepressant treatment, have led to considerable uncertainty about appropriate management in young patients.[47–51] In the UK, guidelines issued by NICE state that the mainstay of treatment for this patient group should be psychological therapy;[47] treatment with antidepressants should only be offered alongside psychological therapy. For children and adolescents with mild depression, as for adults, a period of watchful waiting may be appropriate before starting any treatment. If symptoms have not resolved after several weeks, patients should be started on an appropriate course of psychological therapy such as group cognitive behavioural therapy or guided self-help which should be continued for 2 to 3 months. Antidepressants should not be used for the initial treatment of mild depression. Children or adolescents with moderate to severe depression (or those with mild depression unresponsive to the above measures) should be given more specific psychological treatment such as individual cognitive behavioural therapy, interpersonal therapy, or short-term family therapy. Combined treatment with an antidepressant (which, as in adults, appears more effective than either alone[52]) should only be considered if there is a lack of response to psychotherapy alone.[47] The SSRI fluoxetine is considered the first-choice antidepressant in children aged 12 and over because of proven efficacy and low toxicity in overdose;[6,47] although the evidence for its efficacy in younger children has been questioned,[47] a review by the EMEA concluded that studies showed a positive effect and approved its use throughout the EU in children from 8 years of age.[53] In the USA, escitalopram and fluoxetine are the only SSRIs licensed for the treatment of depression in young patients. The other SSRIs should not be used in children (but see below) because of unproven efficacy and/or an increased risk of a harmful outcome (see Effects on Mental State under Fluoxetine, p. 422.2 for further details). Similar recommendations have been made for the SNRI venlafaxine (see p. 457.2) and the serotonergic antidepressant, mirtazapine (see p. 438.2). Patients who remain unresponsive to combined treatment should be initially tried on an alternative psychological therapy.[47] A change in antidepressant may also be warranted and NICE guidelines have suggested that citalopram and sertraline may be appropriate, provided certain criteria have been met.[47] (Paroxetine and venlafaxine should not be used.[47]) Lithium has also been tried[6] and ECT may be considered for older children with severe, unresponsive depression.[6,47] Tricyclics may have a modest effect in the treatment of depression in adolescents; however, they are not effective in the treatment of younger children.[54] In practice they have often been reserved for refractory cases in adolescents[55] although evidence to support this role is lacking[54] and NICE guidelines[47] do not recommend their use. There have also been reports of death due to cardiotoxicity in children taking tricyclic antidepressants, in particular desipramine and imipramine.

Following the concerns raised about the possible increased risk of suicide in children and adolescents treated with antidepressants, the FDA undertook a meta-analysis of 372 studies in adults. From 295 studies in psychiatric patients, the overall risk of suicide was not increased, but there was a trend toward increased risk with younger age. Although the effect was not statistically significant, the FDA considered the trend sufficiently convincing to warn that, like children and adolescents, **young adults** (aged 18 to 24 years) treated with antidepressants of any type may be at increased risk of suicidal thinking and behaviour.[56] In the UK, an Expert Working Group of the CSM found no clear evidence that use of SSRIs in young adults increased the risk of self-harm or suicidal thoughts;[57] however, it was noted that such patients have a higher background risk of suicidal behaviour than older adults and consequently should be closely monitored during treatment.

Depression in the **elderly** is not uncommon and may affect up to 4% of this population.[58] Suicide is also more frequent in the elderly than in the general population and depressive symptoms are present in about 80% of patients aged over 74 years who commit suicide.[58] Depression in the elderly is often undertreated and prognosis is poor; treatment is also often complicated by co-existing medical conditions.[4,6,58,59] SSRIs are often the first choice of treatment in the elderly because of their favourable adverse effect profile and low toxicity in overdose.[4,6,58,59] They may be especially appropriate in patients with an existing cardiovascular disease or in those taking other medications that may lower the blood pressure. Tricyclics such as amitriptyline and imipramine are probably best avoided in the elderly as their cardiotoxic, antimuscarinic, and sedative effects may be particularly troublesome. However, the tricyclics desipramine and nortriptyline are considered by some[4,6,58] to be an alternative first-choice as they are less cardiotoxic and have fewer antimuscarinic and sedative actions compared with amitriptyline or imipramine. Other newer antidepressants may also be useful in specific situations; bupropion, which has the advantage of a relative lack of cardiotoxicity and drug interactions, may be an appropriate option.[4] Lower initial doses of antidepressant drugs are often recommended in the elderly to minimise adverse effects but individual differences in metabolism and excretion may mean that some patients are undertreated. The elderly tend to respond more slowly to antidepressants than younger patients[4] and additional psychosocial or psychotherapeutic management is often warranted.[4,58] The management of inadequate responses to initial therapies in elderly patients should follow the same principles as in younger patients.[6,58] ECT is also safe and effective in the elderly, and should be considered in those at high risk for suicide or who are refractory to or intolerant of antidepressant drugs.[6,58] Depression late in life may require long-term antidepressant treatment beyond the recovery phase, even after first episodes of depression and should be a continuation of the treatment that was successful in the initial acute phase (see above).

Treatment of **women** with depressive disorders during and after **pregnancy** raises concerns about the risk of teratogenicity, fetal growth retardation, or perinatal problems (see also individual drug monographs); the ratio of risk to the child versus the benefit to the mother must therefore be considered very carefully.[6,60,61] It should also be remembered that untreated depression during pregnancy has been associated with poor neonatal outcomes such as low birth-weight.[61] In some cases starting treatment with an antidepressant will be appropriate although psychotherapy and ECT should also be considered as alternatives.[6,61] Treatment should not be stopped as a matter of routine in early pregnancy in women who become pregnant while taking an antidepressant.[60] Maternal mood disorders in the immediate postpartum period are related to hormonal changes, particularly falling progesterone levels; the symptoms are mild and resolve spontaneously after several days, therefore no treatment is required.[4,6] Of greater concern are major depressive episodes that occur beyond this initial phase, which are clinically identical to depressive disorders in general and call for the same principles of management[60] (although there are few studies to support this[62]). These depressive episodes have been found to be related to the presence of immediate postpartum mood disorders, although no hormonal basis to this association has been identified.[60] Nevertheless, there has been interest in the use of oestrogen as a treatment.

As with use of any medicine in **women who breastfeed**, the risks to the infant from drugs distributed into breast milk must be considered. The American Academy of Pediatrics[63] considers that the effect of all antidepressants on nursing infants could be of concern.

Symptoms of **anxiety and depression** often coexist and it may be difficult to distinguish which is the predominant disorder, especially in milder forms. Depression is generally treated before anxiety,[2] using antidepressants such as SSRIs that also have anxiolytic effects.[64] Where anxiety predominates, comorbid mild depression may also respond to psychological treatment of anxiety.[64] Anxiolytics and antipsychotics can be useful adjuncts in agitated depression, but a sedative antidepressant might be preferable. Combination preparations of antidepressants with antipsychotics or anxiolytics should not be used because the dosage of the individual components should be adjusted separately. Also, anxiolytics should only be prescribed on a short-term basis whereas antidepressants are given for longer periods.

The efficacy of antidepressants in **chronic fatigue syndrome** in clinical studies have been equivocal although it has been suggested that antidepressant therapy should be tried in patients with co-existing depression.[65] Cognitive therapy may also be useful.

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Mania

Although isolated episodes of mania (see p. 397.1) may occur, mania is usually followed by depression when it is considered to be part of bipolar disorder. It is accepted practice to include mania without depression within the bipolar category. The treatment and prophylaxis of acute mania are therefore described under Bipolar Disorder, p. 397.2.

Agomelatine *(BAN, rINN)*

Agomelatina; Agomélatine; Agomelatinum; S-20098; Агомелатин.

N-[2-(7-Methoxy-1-naphthyl)ethyl]acetamide.

$C_{15}H_{17}NO_2$=243.3

CAS — 138112-76-2.

ATC — N06AX22.

ATC Vet — QN06AX22.

UNII — 137R1N49AD.

Uses and Administration

Agomelatine is an agonist at melatonergic MT_1 and MT_2 receptors, and an antagonist at 5-HT_{2C} receptors. It is given orally in the treatment of depression (p. 398.1) at a dose of 25 mg once daily at bedtime. After 2 weeks, the dose may be increased to 50 mg at bedtime if necessary. Unlike many other antidepressants, there is no need to taper the dose of agomelatine when treatment is stopped.

Agomelatine is under investigation in the management of anxiety.

References.

1. Zupancic M, Guilleminault C. Agomelatine: a preliminary review of a new antidepressant. *CNS Drugs* 2006; **20:** 981–92.
2. Ghosh A, Hellewell JSE. A review of the efficacy and tolerability of agomelatine in the treatment of major depression. *Expert Opin Invest Drugs* 2007; **16:** 1999–2004.
3. Eser D, *et al.* Evidence of agomelatine's antidepressant efficacy: the key points. *Int Clin Psychopharmacol* 2007; **22** (suppl 2): S15–S19.
4. Dolder CR, *et al.* Agomelatine treatment of major depressive disorder. *Ann Pharmacother* 2008; **42:** 1822–31.
5. Stein DJ, *et al.* Efficacy of agomelatine in generalized anxiety disorder: a randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol* 2008; **28:** 561–6,
6. Stahl SM, *et al.* Agomelatine in the treatment of major depressive disorder: an 8-week, multicenter, randomized, placebo-controlled trial. *J Clin Psychiatry* 2010; **71:** 616–26.

Adverse Effects and Precautions

The most common adverse effects that occur in the first few weeks of agomelatine treatment are transient nausea and dizziness, which are usually mild or moderate. Other gastrointestinal disturbances, headache, somnolence, insomnia, migraine, hyperhidrosis, back pain, and fatigue are also reported as being common adverse effects. There have been cases of paraesthesia, blurred vision, and eczema.

Increases in serum transaminases are common during agomelatine therapy, and the drug is contra-indicated in patients with hepatic impairment. Liver function should be tested before starting agomelatine, and after about 6, 12, and 24 weeks of treatment. Liver function tests should be repeated within 48 hours in any patient who has increased serum transaminase values. The drug should be stopped if values increase to more than 3 times the upper limit of normal, and liver function should be monitored until they return to normal. Liver function should also be tested in any patient who develops symptoms of hepatic dysfunction, and agomelatine should be stopped if jaundice occurs.

Patients should be closely monitored during early antidepressant therapy until significant improvement in depression is noted because suicide is an inherent risk in depressed patients. For further details, see under Depression, p. 398.1. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions followed when treating patients with depression should therefore be followed when treating patients with other disorders.

Agomelatine should be used with caution in patients with bipolar disorder because of the risk of precipitating mania.

As with other antidepressants, agomelatine may impair performance of skilled tasks and, if affected, patients should not drive or operate machinery.

Children. Agomelatine has not been studied for the treatment of depression in adolescents and children; consequently its use in patients under 18 years of age is not recommended. In addition, other antidepressants have been shown to increase the risk of suicidal thoughts and behaviour in such patients (see Effects on Mental State, under Fluoxetine, p. 422.2).

Interactions

Drugs that inhibit or induce the cytochrome P450 isoenzyme CYP1A2 have the potential to interact with agomelatine. By this mechanism, fluvoxamine can markedly inhibit the metabolism of agomelatine and increase systemic exposure by about sixtyfold. The use of agomelatine with potent CYP1A2 inhibitors is therefore contra-indicated. Moderate CYP1A2 inhibitors, such as oestrogens, may also increase exposure to agomelatine, and such combinations should be used with caution.

Pharmacokinetics

Agomelatine is rapidly and well absorbed after oral dosage and peak plasma concentrations occur within 1 to 2 hours however, it has a low absolute bioavailability of less than 5% with substantial interindividual variability. It is about 95% bound to plasma proteins. Systemic exposure increases proportionally with dose, and first-pass metabolism becomes saturated at higher doses. Agomelatine is rapidly metabolised, mainly by the hepatic cytochrome P450 isoenzyme CYP1A2; the isoenzymes CYP2C9 and CYP2C19 also make a minor contribution. It has a mean plasma half-life of between 1 and 2 hours and is mainly excreted in the urine as inactive metabolites. Systemic exposure to agomelatine is substantially increased in patients with liver impairment.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Valdoxan; ***Austral.***: Valdoxan; ***Austria***: Valdoxan; ***Belg.***: Valdoxan; ***Braz.***: Valdoxan; ***China***: Valdoxan (维度新); ***Cz.***: Thymanax; Valdoxan; ***Denm.***: Valdoxan; ***Fr.***: Valdoxan; ***Ger.***: Valdoxan; ***Gr.***: Valdoxan; ***Hong Kong***: Valdoxan; ***Hung.***: Valdoxan; ***Irl.***: Thymanax; Valdoxan; ***Malaysia***: Valdoxan; ***Neth.***: Thymanax; Valdoxan; ***Pol.***: Thymanax; Valdoxan; ***Port.***: Thymanax; Valdoxan; ***Rus.***: Valdoxan (Вальдоксан); ***Singapore***: Valdoxan; ***Spain***: Thymanax; Valdoxan; ***Swed.***: Valdoxan; ***Switz.***: Valdoxan; ***Thai.***: Valdoxan; ***Turk.***: Valdoxan; ***UK***: Valdoxan; ***Ukr.***: Melitor (Мелитор).

Amineptine Hydrochloride *(rINNM)*

Amineptina, hidrocloruro de; Amineptine, Chlorhydrate d'; Amineptini Hydrochloridum; Hidrocloruro de amineptina; S-1694; Аминептина гидрохлорид.

7-[(10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)amino] heptanoic acid hydrochloride.

$C_{22}H_{27}NO_2$,HCl=373.9

CAS — 57574-09-1 (amineptine); 30272-08-3 (amineptine hydrochloride).

ATC — N06AA19.

ATC Vet — QN06AA19.

UNII — A5P604A12R.

Profile

Amineptine hydrochloride is a tricyclic antidepressant (see Amitriptyline, p. 403.1). It has been given orally in the treatment of depression.

Hepatic adverse effects seem to be more common than with most other tricyclic antidepressants (see Effects on the Liver, p. 405.3). Also amineptine has been subject to abuse and withdrawal has been both prolonged and difficult; for these reasons, it is no longer marketed in many countries.

Adverse effects. In 5 patients very severe acne-type lesions were associated with the chronic self-increased use of high doses of amineptine (0.2 to 1 g daily).[1] Unusual lactam metabolites were found in all patients and in 2 these were still present, along with the lesions, 3 months after stopping therapy. In another case, a 48-year-old woman developed acne-like eruptions after long-term use of amineptine 400 mg daily.[2] There was no clinical improvement 6 months after amineptine withdrawal.

1. Vexiau P, *et al.* Severe acne-like lesions caused by amineptine overdose. *Lancet* 1988; **i:** 585.
2. De Gálvez Aranda MV, *et al.* Acneiform eruption caused by amineptine: a case report and review of the literature. *J Eur Acad Dermatol Venereol* 2001; **15:** 337–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Survector.

Amitriptyline (BAN, rINN)

Amitriptilina; Amitriptylini; Amitriptylín; Amitriptylinum; Амитриптилин.

3-(10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ylidene) propyldimethylamine; 10,11-Dihydro-*N*,*N*-dimethyl-5*H*-dibenzo[*a*,*d*]cycloheptene-$\Delta^{5,\gamma}$-propylamine.

$C_{20}H_{23}N$=277.4

CAS — 50-48-6.

ATC — N06AA09.

ATC Vet — QN06AA09.

UNII — 1806D8D52K.

Amitriptyline Embonate (BANM, rINNM)

Amitriptilina, embonato de; Amitriptyline, Embonate d'; Amitriptylini Embonas; Embonato de amitriptilina; Амитриптилина Эмбонат.

$(C_{20}H_{23}N)_2C_{23}H_{16}O_6$=943.2

CAS — 17086-03-2.

Pharmacopoeias. In *Br.*

BP 2014: (Amitriptyline Embonate). A pale yellow to brownish-yellow, odourless or almost odourless powder. Practically insoluble in water; slightly soluble in alcohol; freely soluble in chloroform. Protect from light.

Amitriptyline Hydrochloride (BANM, rINNM)

Amitriptilin Hidroklorür; Amitriptilina, hidrocloruro de; Amitriptilin-hidroklorid; Amitriptilino hidrochloridas; Amitriptyliinihydrokloridi; Amitriptyline, chlorhydrate d'; Amitriptylinhydrochlorid; Amitriptylin-hydrochlorid; Amitriptylinhydroklorid; Amitriptylini Hydrochloridum; Amitrypтyliny chlorowodorek; Hidrocloruro de amitriptilina; Амитриптилина Гидрохлорид.

$C_{20}H_{23}N.HCl$=313.9

CAS — 549-18-8.

UNII — 26LUD4JO9K.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 8: (Amitriptyline Hydrochloride). A white or almost white powder or colourless crystals. Freely soluble in water, in alcohol, and in dichloromethane. Protect from light.

USP 36: (Amitriptyline Hydrochloride). A white or practically white, odourless or practically odourless, crystalline powder or small crystals. Freely soluble in water, in alcohol, in chloroform, and in methyl alcohol; insoluble in ether. pH of a 1% solution in water is between 5.0 and 6.0.

Stability. Decomposition occurred when solutions of amitriptyline hydrochloride in water or phosphate buffers were autoclaved at 115 degrees to 116 degrees for 30 minutes in the presence of excess oxygen.[1]

The decomposition of amitriptyline as the hydrochloride in buffered aqueous solution stored at 80 degrees in the dark was accelerated by metal ions.[2] Disodium edetate 0.1% significantly reduced the decomposition rate of these amitriptyline solutions but propyl gallate and hydroquinone were less effective. Sodium metabisulfite produced an initial lowering of amitriptyline concentration and subsequently an acceleration of decomposition. The rate of decomposition was also much greater in amber glass ampoules than in clear glass ones (the metal ion content of amber glass is higher than that of clear glass). However, there were considerable variations between different batches of amber glass and, since amitriptyline is photolabile, its solutions are likely to be stored in amber containers.

Solutions of amitriptyline hydrochloride in water are stable for at least 8 weeks at room temperature if protected from light either by storage in a cupboard or in amber containers.[3] Decomposition to ketone and, to a lesser extent, other unidentified products was found to occur on exposure to light.

1. Enever RP, *et al.* Decomposition of amitriptyline hydrochloride in aqueous solution: identification of decomposition products. *J Pharm Sci* 1975; 64: 1497–9.
2. Enever RP, *et al.* Factors influencing decomposition rate of amitriptyline hydrochloride in aqueous solution. *J Pharm Sci* 1977; 66: 1087–9.
3. Buckles J, Walters V. The stability of amitriptyline hydrochloride in aqueous solution. *J Clin Pharm* 1976; 1: 107–12.

Uses and Administration

Tricyclic antidepressants such as amitriptyline were developed from phenothiazine compounds related to chlorpromazine and, as the name suggests, possess a 3-ring molecular structure. They inhibit the neuronal reuptake of noradrenaline in the CNS; some, in addition, inhibit the reuptake of serotonin (5-HT). Prevention of the reuptake of these monoamine neurotransmitters, which potentiates their action in the brain, appears to be associated with antidepressant activity. Tricyclic antidepressants also possess affinity for muscarinic and histamine H_1 receptors to varying degrees, see under Adverse Effects, p. 404.3. Amitriptyline is one of the more sedating tricyclics. Antidepressants with one, two, or four rings have also been developed, and these share only some of the properties of the tricyclics.

While the sedative action and other adverse effects of amitriptyline and other tricyclics are soon apparent, it may be several weeks before any antidepressant effect is seen. After a response has been obtained, maintenance therapy should be continued at the optimum dose for at least 6 months (12 months in the elderly) to avoid relapse on stopping therapy. Patients with a history of recurrent depression should continue to receive maintenance treatment for at least 2 years. It is important to use doses that are sufficiently high for effective treatment, but not so high as to cause toxic effects.

Amitriptyline, a dibenzocycloheptadiene, is usually given orally as the hydrochloride and doses are expressed in terms of this salt. Amitriptyline hydrochloride is also given by intramuscular or slow intravenous injection; doses may be expressed in terms of the base or the hydrochloride. Amitriptyline hydrochloride 75 mg is equivalent to about 66.3 mg of the base. Amitriptyline has also been given orally as the embonate and as the oxide (amitriptylinoxide).

In the treatment of **depression**, amitriptyline hydrochloride is given initially in a daily dose of 50 to 75 mg orally in divided doses (or as a single dose at night). Thereafter, the dose may be gradually increased, if necessary, to 150 mg daily, the additional doses being given in the late afternoon or evening. Doses of up to 200 mg daily and, occasionally, up to 300 mg daily have been used in severely depressed patients in hospital.

Adolescent and elderly patients often have reduced tolerance to tricyclic antidepressants and UK licensed product information states that initial doses of amitriptyline hydrochloride as low as 25 mg daily may be used in these groups, given either in divided doses or as a single dose, preferably at bedtime. The *BNF* suggests a minimum initial dose of 30 mg daily. In the UK, the use of amitriptyline in children under 16 years for the treatment of depression is not recommended.

In the initial stages of treatment, if oral dosage is impracticable or inadvisable, amitriptyline hydrochloride may be given by intramuscular injection, but the oral route should be substituted as soon as possible. Doses are similar to those usually given orally. The intravenous route has also been used.

Dose adjustments have been suggested for patients with genetic polymorphisms in the cytochrome P450 isoenzymes CYP2D6 and CYP2C19 (see Administration in Genetic Variation, p. 403.2).

Tricyclic antidepressants, including amitriptyline, may be helpful in some **anxiety disorders** such as panic disorder, and in the *management* of **neuropathic pain** (see p. 404.2). For the uses of amitriptyline in children, see p. 403.2.

Amitriptyline should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Administration in children. Amitriptyline is used for the treatment of **nocturnal enuresis** in children in whom organic pathology has been excluded. However, drug therapy for nocturnal enuresis should be reserved for when other methods have failed and should preferably only be given to cover periods away from home. Tricyclic antidepressants are not recommended in children under 6 years of age. For a discussion of tricyclic use in nocturnal enuresis, see Micturition Disorders, p. 404.1.

Oral doses of amitriptyline hydrochloride that may be used are:

- 10 to 20 mg for children aged 6 to 10 years
- 25 to 50 mg for children 11 years and over

The dose should be given at night and treatment, including a period of gradual withdrawal, should not continue for longer than 3 months. A full physical examination, including an ECG, is recommended before a further course.

For the use of amitriptyline in children with **neuropathic pain**, see p. 404.2.

Administration in genetic variation. The effect of cytochrome P450 isoenzymes CYP2D6 and CYP2C19 genotypes on tricyclic antidepressant dosage has been reviewed,[1] and the following adjustments, based on phenotype, have been suggested for their use in depression:

CYP2D6 phenotype and amitriptyline or nortriptyline use

- ultrarapid metaboliser: avoid due to potential lack of efficacy; if use is warranted, consider increasing the initial dose (see Uses and Administration, above) and use therapeutic drug monitoring to guide dose adjustments
- extensive metaboliser (77 to 92% of Caucasian population): the usual initial dose may be given
- intermediate metaboliser: consider reducing the initial dose by 25% and use therapeutic drug monitoring to guide dose adjustments
- poor metaboliser: avoid due to increased potential for adverse effects; if use is warranted, consider decreasing the initial dose by 50% and use therapeutic drug monitoring to guide dose adjustments

CYP2C19 phenotype and amitriptyline use

- ultrarapid metaboliser: consider alternative drug; if use is warranted, use therapeutic drug monitoring to guide dose adjustments
- extensive metaboliser (35 to 50% of multiethnic population): the usual initial dose may be given
- intermediate metaboliser: the usual initial dose may be given
- poor metaboliser: consider decreasing the initial dose by 50% and use therapeutic drug monitoring to guide dose adjustments

The authors suggested that because tricyclics have comparable pharmacokinetic profiles, the above guidance may be applied to other tricyclics including clomipramine, desipramine, doxepin, imipramine, and trimipramine; however, it was noted that there are fewer data to support such dosage adjustments in these drugs.

1. Hicks JK, *et al.* Clinical Pharmacogenetics Implementation Consortium guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. *Clin Pharmacol Ther* 2013; 93: 402–8.

Anxiety disorders. For the use of tricyclic antidepressants in anxiety disorders, see under Clomipramine, p. 414.2.

Bulimia nervosa. A combination of counselling, support, psychotherapy, and antidepressants is the usual treatment for bulimia nervosa. Antidepressants can help to reduce the frequency of overeating and some other symptoms of bulimia but relapse tends to occur when stopped. Many antidepressants have been tried, but the tricyclic desipramine and the SSRI fluoxetine have been the most commonly used and are considered to be well tolerated.

References.

1. Hay PPJ, *et al.* Antidepressants versus psychological treatments and their combination for bulimia nervosa. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 28/07/10).
2. Bacaltchuk J, Hay PPJ. Antidepressants versus placebo for people with bulimia nervosa. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 28/07/10).

Ciguatera poisoning. Amitriptyline has relieved some of the neurological symptoms associated with ciguatera poisoning (see Mannitol, p. 1428.2).

Cocaine dependence. For the use of tricyclic antidepressants in cocaine dependence, see under Desipramine, p. 415.2.

Depression. As discussed on p. 398.1, there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effect profile. Although less well tolerated than the newer antidepressants, tricyclic antidepressants may still be chosen because of wide experience with their use and familiarity with their pharmacological actions. The more sedating tricyclics such as amitriptyline, clomipramine, dosulepin, doxepin, and trimipramine may be of value in depression with associated agitation or anxiety. The less sedating tricyclics such as amoxapine, desipramine, imipramine, lofepramine, nortriptyline, and protriptyline may be of value for withdrawn or apathetic depressed patients. However, the *BNF* considers amitriptyline and dosulepin to be particularly dangerous in overdosage and not recommended for treatment of depression, and that dosulepin should only be prescribed by specialists.

Combination therapy with differing classes of antidepressants, including the tricyclics, has been used in the treatment of refractory or drug-resistant depression. However, such therapy may result in enhanced adverse reactions or interactions and requires expert supervision. For further details, see Antidepressants under Interactions of Phenelzine, p. 447.2.

References.

1. Deisenhammer EA, *et al.* Intravenous versus oral administration of amitriptyline in patients with major depression. *J Clin Psychopharmacol* 2000; 20: 417–22.
2. Guaiana G, *et al.* Amitriptyline for depression. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 07/05/08).

Headache. Tricyclic antidepressants can be effective in the management of some types of headache and, although they are especially useful when the headache is accompanied by depression, their beneficial effects appear to be independent of their antidepressant action. They are used for the prophylaxis of migraine (p. 670.3) when drugs such as propranolol have proved ineffective. Amitriptyline is the tricyclic usually used but others have been tried. It

has also been investigated in children. The *BNF* suggests an initial adult dosage for amitriptyline hydrochloride in the prophylaxis of migraine of 10 mg orally at night, increased if necessary to a dose of 50 to 75 mg (maximum of 150 mg) at night; the need for continuing prophylaxis should be reviewed at intervals of about 6 months. Tricyclics are also used prophylactically in the control of chronic tension-type headache (p. 671.3) although benefit is rarely complete. Improvement is generally seen with low doses, but full antidepressant doses are necessary in the presence of underlying depression. Amitriptyline may be used in the management of symptoms during withdrawal in patients with medication-overuse headache (p. 670.2).

References.

1. Mathew NT. Prophylaxis of migraine and mixed headache: a randomized controlled study. *Headache* 1981; 21: 105–9.
2. Pfaffenrath V, *et al.* Combination headache: practical experience with a combination of a β-blocker and an antidepressive. *Cephalalgia* 1986; 6 (suppl 5): 25–32.
3. Wörz R, Scherhag R. Treatment of chronic tension headache with doxepin or amitriptyline—results of a double-blind study. *Headache Q* 1990; 1: 216–23.
4. Ziegler DK, *et al.* Propranulol and amitriptyline in prophylaxis of migraine: pharmacokinetic and therapeutic effects. *Arch Neurol* 1993; 50: 825–30.
5. Pfaffenrath V, *et al.* Efficacy and tolerability of amitriptylinuxide in the treatment of chronic tension-type headache: a multi-centre controlled study. *Cephalalgia* 1994; 14: 149–55.
6. Hershey AD, *et al.* Effectiveness of amitriptyline in the prophylactic management of childhood headaches. *Headache* 2000; 40: 539–49.
7. Holroyd KA, *et al.* Management of chronic tension-type headache with tricyclic antidepressant medication, stress management therapy, and their combination: a randomized controlled trial. *JAMA* 2001; 285: 2208–15.
8. Descombes S, *et al.* Amitriptyline treatment in chronic drug-induced headache: a double-blind comparative pilot study. *Headache* 2001; 41: 178–82.
9. Jackson JL, *et al.* Tricyclic antidepressants and headaches: systematic review and meta-analysis. *BMJ* 2010; 341: c5222.

Hiccup. Amitriptyline is one of many drugs for which there are anecdotal reports[1] of success in the treatment of intractable hiccup (p. 1046.3).

1. Stalnikowicz R, *et al.* Amitriptyline for intractable hiccups. *N Engl J Med* 1986; 315: 64–5.

Hyperactivity. When drug therapy is required for attention deficit hyperactivity disorder (p. 2314.1), initial treatment is usually with a central stimulant. Tricyclic antidepressants such as imipramine or desipramine are reserved for patients who fail to respond to or who are intolerant of stimulants. They may also be of use for selected patients with certain co-existing disorders.

Interstitial cystitis. Tricyclic antidepressants have been found to be of benefit in the treatment of interstitial cystitis (p. 2348.1). In a placebo-controlled study in 48 patients with interstitial cystitis, amitriptyline treatment (in doses ranging from 25 to 100 mg daily) significantly reduced the symptom score and improved pain and urgency when compared with placebo;[1] however, in some patients the antimuscarinic adverse effects of amitriptyline were troublesome. Amitriptyline or imipramine have also been given at night, with methenamine hippurate during the day, in the treatment of interstitial cystitis.[2]

1. van Ophoven A, *et al.* A prospective, randomized, placebo controlled, double-blind study of amitriptyline for the treatment of interstitial cystitis. *J Urol (Baltimore)* 2004; 172: 533–6.
2. Cardozo L. Postmenopausal cystitis. *BMJ* 1996; 313: 129.

Irritable bowel syndrome. A tricyclic antidepressant may be tried in irritable bowel syndrome (p. 1813.3), particularly where diarrhoea and abdominal pain are presenting symptoms.

Micturition disorders. Tricyclic antidepressants are among the drugs used as an alternative or adjunct to nonpharmacological methods for the treatment of **nocturnal enuresis** in children (p. 2349.1) in whom organic pathology has been excluded. However, because of their potentially fatal toxicity in overdosage, there has been concern over the safety of using tricyclics in households with children. Most experience in nocturnal enuresis has been with imipramine, but other tricyclics such as amitriptyline, nortriptyline, and clomipramine have also been used. Their mechanism of action in nocturnal enuresis is unclear. It may be the result of their antimuscarinic and antispasmodic actions as well as their effect on sleep patterns and possible stimulation of antidiuretic hormone secretion. Imipramine appears to be most effective in older children, but many patients develop tolerance and increasingly higher doses are required.

Tricyclic antidepressants are also sometimes used in the management of **urinary incontinence** (p. 2349.2).

References.

1. Glazener CMA, *et al.* Tricyclic and related drugs for nocturnal enuresis in children. Available in The Cochrane Database of Systematic Reviews: Issue 3. Chichester: John Wiley; 2003 (accessed 24/11/05).

Narcoleptic syndrome. Tricyclic antidepressants are the primary treatment for cataplexy and sleep paralysis associated with narcolepsy (p. 2314.3). Imipramine has been widely used for these symptoms although some consider clomipramine more effective. The onset of action is quicker than when used for depression and doses required appear to be lower (typically 10 to 75 mg of imipramine daily) although tolerance may develop. Doses should be titrated to provide maximal protection for the time of day when symptoms usually occur.

Pain. Tricyclic antidepressants, usually amitriptyline, are useful in alleviating some types of pain when given in subantidepressant doses. An initial oral dose of amitriptyline hydrochloride 10 mg at night increased gradually if necessary to about 75 mg daily has been suggested by the *BNF* for the management of neuropathic pain in adults. Similar doses of amitriptyline hydrochloride are also suggested by the *BNFC* for the treatment of neuropathic pain, either chronic or in palliative care, in children aged 12 years and over; in addition, younger children aged 2 years and above may receive an initial dose of 200 to 500 micrograms/kg (to a maximum of 10 mg) once daily at night, increased if necessary to a maximum of 1 mg/kg twice daily on specialist advice.

Chronic neuropathic pain as seen in cancer (p. 7.1), central post-stroke pain (p. 7.3), diabetic neuropathy (p. 8.2), phantom limb pain (p. 10.3), and postherpetic neuralgia (p. 10.3) responds to therapy with tricyclics. Tricyclics are also often of benefit in the treatment of idiopathic orofacial pain (p. 10.2), and may be of value for patients with complex regional pain syndrome (p. 8.1). Pain and sleep quality may be improved by tricyclics in patients with fibromyalgia (see Soft-tissue Rheumatism, p. 14.2), a condition that responds poorly to analgesics and anti-inflammatory drugs. See also Choice of Analgesic on p. 4.2. Patients with migraine or chronic tension-type headache may also benefit from tricyclics (see Headache, p. 401.3). There is little evidence for an analgesic effect of tricyclics in acute or arthritic pain.

References.

1. Onghena P, Van Houdenhove, B. Antidepressant-induced analgesia in chronic non-malignant pain: a meta-analysis of 39 placebo-controlled studies. *Pain* 1992; 49: 205–19.
2. McQuay HJ, *et al.* A systematic review of antidepressants in neuropathic pain. *Pain* 1996; 68: 217–27.
3. Godfrey RG. A guide to the understanding and use of tricyclic antidepressants in the overall management of fibromyalgia and other chronic pain syndromes. *Arch Intern Med* 1996; 156: 1047–52.
4. McQuay HJ, Moore RA. Antidepressants and chronic pain. *BMJ* 1997; 314: 763–4.
5. Joss JD. Tricyclic antidepressant use in diabetic neuropathy. *Ann Pharmacother* 1999; 33: 996–1000.
6. Arnold LM, *et al.* Antidepressant treatment of fibromyalgia: a meta-analysis and review. *Psychosomatics* 2000; 41: 104–13.
7. Lynch ME. Antidepressants as analgesics: a review of randomized controlled trials. *J Psychiatry Neurosci* 2001; 26: 30–6.
8. Reisner L. Antidepressants for chronic neuropathic pain. *Curr Pain Headache Rep* 2003; 7: 24–33.

Pathological crying or laughing. Pathological crying or laughing can result from lesions in certain areas of the brain. Attempts at treatment have mostly been with antidepressants and favourable results have been reported in double-blind studies with amitriptyline[1] and nortriptyline.[2]

1. Schiffer RB, *et al.* Treatment of pathologic laughing and weeping with amitriptyline. *N Engl J Med* 1985; 312: 1480–2.
2. Robinson RG, *et al.* Pathological laughing and crying following stroke: validation of a measurement scale and a double-blind treatment study. *Am J Psychiatry* 1993; 150: 286–93.

Premenstrual syndrome. For reference to the tricyclic antidepressant, clomipramine, in premenstrual syndrome, see p. 414.3.

Schizophrenia. Antidepressants such as the tricyclics are considered worth trying as an adjunct in the treatment of patients with schizophrenia (p. 1031.3) who develop depression during the recovery phase after an acute episode of psychosis. There is, however, no clear evidence that they are effective during acute psychotic episodes or for depression during periods of remission in patients with chronic schizophrenia.[1]

1. Anonymous. The drug treatment of patients with schizophrenia. *Drug Ther Bull* 1995; 33: 81–6.

Sexual dysfunction. Impotence or ejaculatory problems have been reported as adverse effects of tricyclic antidepressants (see Effects on Sexual Function in Adverse Effects, p. 406.1). Such properties have been studied as a potential form of treatment for men with premature ejaculation (see Clomipramine, p. 414.3).

Skin disorders. See under Doxepin, p. 416.3, for use of tricyclic antidepressants in skin disorders.

Smoking cessation. Tricyclic antidepressants are among the drugs that have been tried with varying degrees of success as alternatives to nicotine replacement therapy (NRT) to alleviate the withdrawal syndrome associated with smoking cessation (p. 2570.2). Nortriptyline is recommended by some as a second-line treatment in those patients who cannot tolerate or relapse after NRT.

References.

1. Hughes JR, *et al.* Antidepressants for smoking cessation. Available in The Cochrane Database of Systematic Reviews: Issue 1. Chichester: John Wiley; 2007 (accessed 14/08/08).

Adverse Effects

Many adverse effects of amitriptyline and similar tricyclic antidepressants are caused by their antimuscarinic actions. Antimuscarinic effects are relatively common and occur before an antidepressant effect is obtained. They include dry mouth, constipation occasionally leading to paralytic ileus, urinary retention, blurred vision and disturbances in accommodation, increased intra-ocular pressure, and hyperthermia. Tolerance is often achieved if treatment is continued and adverse effects may be less troublesome if treatment is begun with small doses and then increased gradually, although this may delay the clinical response.

Drowsiness may also be common, although a few tricyclic antidepressants possess little or no sedative potential and may produce nervousness and insomnia. Other neurological adverse effects include headache, peripheral neuropathy, tremor, ataxia, epileptiform seizures, tinnitus, and occasional extrapyramidal symptoms including speech difficulties (dysarthria). Confusion, hallucinations, or delirium may occur, particularly in the elderly, and mania or hypomania, and behavioural disturbances (particularly in children) have been reported.

Gastrointestinal complaints include sour or metallic taste, stomatitis, and gastric irritation with nausea and vomiting.

Effects on the cardiovascular system are discussed in more detail below (p. 405.1). Orthostatic hypotension and tachycardia can occur in patients without a history of cardiovascular disease, and may be particularly troublesome in the elderly.

Hypersensitivity reactions, such as urticaria and angioedema, and photosensitisation have been reported and, rarely, cholestatic jaundice and blood disorders, including eosinophilia, bone-marrow depression, thrombocytopenia, leucopenia, and agranulocytosis.

Endocrine effects include testicular enlargement, gynaecomastia and breast enlargement, and galactorrhoea. Sexual dysfunction may also occur. Changes in blood sugar concentrations may also occur, and, very occasionally, hyponatraemia associated with inappropriate secretion of antidiuretic hormone.

Other adverse effects that have been reported are increased appetite with weight gain (or occasionally anorexia with weight loss). Sweating may be a problem.

Symptoms of **overdosage** may include excitement and restlessness with marked antimuscarinic effects, including dryness of the mouth, hot dry skin, dilated pupils, tachycardia, urinary retention, and intestinal stasis. Severe symptoms include unconsciousness, convulsions and myoclonus, hyperreflexia, hypothermia, hypotension, metabolic acidosis, and respiratory and cardiac depression, with life-threatening cardiac arrhythmias that may recur some days after apparent recovery. Delirium, with confusion, agitation and hallucinations, is common during recovery.

Antimuscarinic and antihistaminic properties. Studies *in vitro*[1] showed antidepressant affinities for human muscarinic acetylcholine receptors and therefore the likelihood of antimuscarinic effects to be, in descending order:

- amitriptyline
- protriptyline
- clomipramine
- trimipramine
- doxepin
- imipramine
- nortriptyline
- desipramine
- amoxapine
- maprotiline
- trazodone

The effect of affinities for other receptor sites was less certain, although those antidepressants with high affinity for histamine H_1 receptors might be expected to be more sedating. Affinities for *murine* histamine H_1 receptors in descending order were:

- doxepin
- trimipramine
- amitriptyline
- maprotiline
- amoxapine
- nortriptyline
- imipramine
- clomipramine
- protriptyline

- trazodone
- desipramine

1. Richelson E. Antimuscarinic and other receptor-blocking properties of antidepressants. *Mayo Clin Proc* 1983; 58: 40–6.

Effects on the blood. After a case report of agranulocytosis linked with imipramine, review of the literature suggested that agranulocytosis associated with tricyclic antidepressant use was a rare idiosyncratic condition, resulting from a direct toxic effect rather than an allergic mechanism, and particularly affected the elderly from 4 to 8 weeks after beginning treatment.[1]

Between 1963 and 1993 the UK CSM received 912 reports of drug-induced agranulocytosis of which 38 were due to tricyclic antidepressants (12 fatal) and 1499 cases of neutropenia of which 46 were due to tricyclics (none fatal).[2] In a report[3] on a patient who developed aplastic anaemia associated with use of remoxipride and dosulepin it was noted that up to May 1993 the CSM had also received 11 reports of aplastic anaemia secondary to use of dosulepin.

Neutropenia reported[4] in a patient after separate exposure to imipramine and nortriptyline, indicated that there might be cross-intolerance between the tricyclic antidepressants and if neutropenia developed with one member of the group the use of others on future occasions should be avoided.

1. Albertini RS, Penders TM. Agranulocytosis associated with tricyclics. *J Clin Psychiatry* 1978; 39: 483–5.
2. CSM/MCA. Drug-induced neutropenia and agranulocytosis. *Current Problems* 1993; 19: 10–11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2044566&RevisionSelectionMethod=LatestReleased (accessed 14/08/08)
3. Philpott NJ, *et al.* Aplastic anaemia and remoxipride. *Lancet* 1993; 342: 1244–5.
4. Draper BM, Manoharan A. Neutropenia with cross-intolerance between two tricyclic antidepressant agents. *Med J Aust* 1987; 146: 452–3.

Effects on bone. A review of 9 epidemiological studies, mainly in patients aged 50 years or older, found an increased risk of fracture in those receiving tricyclic antidepressants. However, no definite conclusions could be made about a dose-response relationship, time relationship, or the possible mechanism.[1]

1. MHRA/CHM. Antidepressants: risk of fractures. *Drug Safety Update* 2010; 3 (10): 3–4. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON0818666&RevisionSelectionMethod=LatestReleased (accessed 28/07/10)

Effects on the cardiovascular system. The cardiotoxic potential of tricyclic antidepressants after **overdosage** is widely acknowledged; symptoms include arrhythmias, conduction defects, and hypotension. This factor was, in part, responsible for the development of antidepressants with different chemical structures and pharmacological properties that are less cardiotoxic. It also led to some concern over whether tricyclic antidepressants had adverse effects on the heart or cardiovascular system when used in usual therapeutic doses.

Since the introduction of the tricyclic antidepressants, reports, often anecdotal, have been published of adverse cardiovascular effects at **therapeutic doses** and have included malignant hypertension with amitriptyline,[1] and cardiomyopathy in a patient given amitriptyline and imipramine.[2] QT prolongation, which in some cases progressed to torsade de pointes, has also been associated with some tricyclics.[3,4] Sudden cardiac death in patients with pre-existing cardiac disease has been linked with amitriptyline[5-7] or imipramine,[6] although the Boston Collaborative Drug Surveillance Program failed to confirm these findings.[8] In a more recent analysis, it has been suggested that the risk of sudden cardiac death may increase with high doses of tricyclic antidepressants.[9] Using patient medication records, it was found that the rate of sudden cardiac death in patients taking less than 100 mg of amitriptyline or its equivalent, [presumably as a daily dose although this is not specified], did not differ from that among non-users of antidepressants even in those with cardiovascular disease or other conditions considered to increase the risk of sudden death; however, the risk was significantly increased in those patients on doses of 100 mg or more when compared with non-users, regardless of any predisposing conditions.

There have also been reports of sudden death in children given desipramine[10-12] or imipramine;[12-14] in at least some of these cases plasma concentrations were not elevated and the children had no cardiac abnormality. Again, however, evaluation of much of the evidence suggests the association is weak;[15] nonetheless, the American Heart Association recommends baseline ECG monitoring in children who are to be treated with tricyclic antidepressants, and a repeat ECG when steady-state dosage is achieved.[16]

Re-evaluations and reviews of this topic[17,18] concluded that the only significant or serious cardiovascular adverse effects, seen in *patients with no history* of cardiovascular disease given therapeutic doses of tricyclic antidepressants, are orthostatic hypotension and tachycardia, and that these effects may be particularly troublesome in elderly patients. However, a later study[19] also considered that prolongation of the QT interval might occur with therapeutic doses of tricyclics in non-risk patients.

In *patients with overt heart disease* it was considered[17] that increased risk was likely in those with intraventricular conduction abnormalities; in patients with a history of myocardial infarction or angina, but free of conduction defects, the use of tricyclics appeared to be mainly limited by how often they developed orthostatic hypotension and to what degree. In a re-evaluation of the risks and benefits of tricyclics in patients with ischaemic heart disease no consensus was reached.[20] In practice the authors used SSRIs or bupropion as first-choice therapy in patients with ischaemic heart disease who were mildly or moderately depressed; tricyclics were reserved for unresponsive patients and were also used as first-choice therapy for patients with more severe depression despite cardiac risks. More recently an increased risk of myocardial infarction has been found in patients taking tricyclic antidepressants (but not SSRIs) with treatment for heart disease.[21] Results of a later case-control study[22] examining the risk of ischaemic heart disease for different types of antidepressants and individual antidepressants support these findings. After adjustment for confounders and use of other antidepressants the risk of ischaemic heart disease was significantly raised in patients who had ever taken tricyclics but not in those given other antidepressants. When the risk was calculated for the tricyclics amitriptyline, dosulepin, and lofepramine, and confounders had been adjusted for, an increased risk of ischaemic heart disease remained only for dosulepin with evidence of a dose-response relationship.

1. Dunn FG. Malignant hypertension associated with use of amitriptyline hydrochloride. *South Med J* 1982; 75: 1124–5.
2. Howland JS, *et al.* Cardiomyopathy associated with tricyclic antidepressants. *South Med J* 1983; 76: 1455–6.
3. Baker B, *et al.* Electrocardiographic effects of fluoxetine and doxepin in patients with major depressive disorder. *J Clin Psychopharmacol* 1997; 17: 15–21.
4. Vieweg WVR, Wood MA. Tricyclic antidepressants, QT interval prolongation, and torsade de pointes. *Psychosomatics* 2004; 45: 371–7.
5. Coull DC, *et al.* Amitriptyline and cardiac disease. *Lancet* 1970; ii: 590–1.
6. Moir DC, *et al.* Cardiotoxicity of amitriptyline. *Lancet* 1972; ii: 561–4.
7. Moir DC, *et al.* Medicines evaluation and monitoring group: a follow-up study of cardiac patients receiving amitriptyline. *Eur J Clin Pharmacol* 1973; 6: 98–101.
8. Boston Collaborative Drug Surveillance Program. Adverse reactions to the tricyclic-antidepressant drugs: report from Boston Collaborative Drug Surveillance Program. *Lancet* 1972; i: 529–31.
9. Ray WA, *et al.* Cyclic antidepressants and the risk of sudden cardiac death. *Clin Pharmacol Ther* 2004; 75: 234–41.
10. Anonymous. Sudden death in children treated with a tricyclic antidepressant. *Med Lett Drugs Ther* 1990; 32: 53.
11. Riddle MA, *et al.* Another sudden death in a child treated with desipramine. *J Am Acad Child Adolesc Psychiatry* 1993; 32: 792–7.
12. Varley CK, McClellan J. Case study: two additional sudden deaths with tricyclic antidepressants. *J Am Acad Child Adolesc Psychiatry* 1997; 36: 390–4.
13. Swanson JR, *et al.* Death of two subjects due to imipramine and desipramine metabolite accumulation during chronic therapy: a review of the literature and possible mechanisms. *J Forensic Sci* 1997; 42: 335–9.
14. Varley CK. Sudden death of a child treated with imipramine: case study. *J Child Adolesc Psychopharmacol* 2000; 10: 321–5.
15. Biederman J, *et al.* Estimation of the association between desipramine and the risk for sudden death in 5- to 14-year-old children. *J Clin Psychiatry* 1995; 56: 87–93.
16. Gutgesell H, *et al.* Cardiovascular monitoring of children and adolescents receiving psychotropic drugs: a statement for healthcare professionals from the Committee on Congenital Cardiac Defects, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation* 1999; 99: 979–82. Also available at: http://circ.ahajournals.org/cgi/reprint/99/7/979 (accessed 24/11/05)
17. Glassman AH. Cardiovascular effects of tricyclic antidepressants. *Annu Rev Med* 1984; 35: 503–11.
18. Mortensen SA. Cyclic antidepressants and cardiotoxicity. *Practitioner* 1984; 228: 1180–3.
19. Reilly JG, *et al.* QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. *Lancet* 2000; 355: 1048–52.
20. Glassman AH, *et al.* The safety of tricyclic antidepressants in cardiac patients: risk-benefit reconsidered. *JAMA* 1993; 269: 2673–5.
21. Cohen HW, *et al.* Excess risk of myocardial infarction in patients treated with antidepressant medications: association with use of tricyclic agents. *Am J Med* 2000; 108: 2–8.
22. Hippisley-Cox J, *et al.* Antidepressants as risk factor for ischaemic heart disease: case-control study in primary care. *BMJ* 2001: 323: 666–9.

EFFECTS ON THE PERIPHERAL CIRCULATION. Painful vasospastic episodes, characterised by cold and blue hands and feet, occurred in a woman each time she received imipramine 150 mg daily and also with amitriptyline, but only when the dose was increased to 200 mg daily.[1] This suggested that the ability of tricyclic antidepressants to induce vasospasm was not limited to imipramine and that the effect might be partly dose-dependent. Additionally, acrocyanosis of the hands and feet has been reported in a child receiving imipramine for nocturnal enuresis.[2]

1. Appelbaum PS, Kapoor W. Imipramine-induced vasospasm: a case report. *Am J Psychiatry* 1983; 140: 913–15.
2. Anderson RP, Morris BAP. Acrocyanosis due to imipramine. *Arch Dis Child* 1988; 63: 204–5.

Effects on the endocrine system. The *syndrome of inappropriate antidiuretic hormone secretion with hyponatraemia* has been reported in patients receiving tricyclics and other antidepressants. The UK CSM, commenting on reports it had received of hyponatraemia associated with antidepressants (fluoxetine, paroxetine, lofepramine, clomipramine, and imipramine), considered that it was likely to occur with any antidepressant and usually involved elderly patients.[1] Case reports of hyponatraemia in 24 patients treated with tricyclics and 20 patients treated with other antidepressants have been summarised.[2]

In a review covering the effects of drugs on *prolactin secretion*[3] it was stated that antidepressants could affect prolactin secretion by disturbing the balance of catecholaminergic inhibition and serotonergic stimulation of prolactin release, although any change is less than with antipsychotic therapy. Clomipramine and nortriptyline had been reported to stimulate prolactin release whereas amitriptyline, desipramine, and imipramine had been reported to be without effect. Such stimulation may account for symptoms of galactorrhoea or amenorrhoea reported with some tricyclics.

1. CSM/MCA. Antidepressant-induced hyponatraemia. *Current Problems* 1994; 20: 5–6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015616&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)
2. Spigset O, Hedenmalm K. Hyponatraemia and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) induced by psychotropic drugs. *Drug Safety* 1995; 12: 209–25.
3. Heil K, Wernze H. Drug-induced changes in prolactin secretion: clinical implications. *Med Toxicol* 1988; 3: 463–98.

Effects on the gastrointestinal tract. Rare cases of ileus and pseudo-obstruction have apparently resulted from the antimuscarinic effects of tricyclic antidepressants.[1-4] An early report[1] from the UK CSM noted no evidence that any tricyclic was especially liable to cause ileus.

1. CSM. Tricyclic antidepressants and ileus. *Current Problems* 3 1978. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2044106&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)
2. McMahon AJ. Amitriptyline overdose complicated by intestinal pseudo-obstruction and caecal perforation. *Postgrad Med J* 1989; 65: 948–9.
3. Sood A, Kumar R. Imipramine induced acute colonic pseudo-obstruction (Ogilvie's syndrome): a report of two cases. *Indian J Gastroenterol* 1996; 15: 70–1.
4. Ross JP, *et al.* Imipramine overdose complicated by toxic megacolon. *Am Surg* 1998; 64: 242–4.

Effects on the kidneys and urine. Haematuria has been seen in a patient receiving amitriptyline and carbamazepine;[1] carbamazepine had previously been taken alone for a long period without producing this effect.

Amitriptyline may have produced a blue-green colour in urine,[2] although it was considered to be a rare phenomenon.

1. Gillman MA, Sandyk R. Hematuria following tricyclic therapy. *Am J Psychiatry* 1984; 141: 463–4.
2. Beeley L. *BMJ* 1986; 293: 750.

Effects on the liver. In a report of 91 cases of hepatitis due to antidepressant therapy, 63 occurred in patients receiving the tricyclic antidepressant amineptine, sometimes with other psychotropic drugs; in about 50% of these amineptine cases, benzodiazepines had also been taken and it was postulated that the benzodiazepines may have increased the oxidation of amineptine to a toxic metabolite.[1] Most patients presented with abdominal pain and mixed liver damage with predominant cholestasis. One died after myocardial infarction, but all the others recovered. The mean amineptine dosage was 200 mg daily. In comparison, only a few cases were attributed to other tricyclic antidepressants—amitriptyline (4 cases), clomipramine (3 cases), and dibenzepin (1 case). Cross-hepatotoxicity between amineptine and clomipramine has also been reported in a patient.[2]

Hepatotoxicity has also been noted with lofepramine. The UK CSM had by the end of 1987 received 57 reports of abnormal liver function tests associated with lofepramine.[3] They included hepatic failure (1 case), jaundice (9 cases), and hepatitis (5 cases). All reactions occurred within the first 8 weeks of treatment and all were reversible on stopping the drug.

1. Lefebure B, *et al.* Hépatites aux antidépresseurs. *Therapie* 1984; 39: 509–16.
2. Larrey D, *et al.* Cross hepatotoxicity between tricyclic antidepressants. *Gut* 1986; 27: 726–7.
3. CSM. Lofepramine (Gamanil) and abnormal blood tests of liver function. *Current Problems 23* 1988. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2044306&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)

Effects on the mouth. The inhibition of salivation caused by tricyclic antidepressants (in this case clomipramine) has been implicated in dental caries formation.[1]

1. deVries MW, Peeters P. Dental caries with longterm use of antidepressants. *Lancet* 1995; 346: 1640.

Effects on the nervous system. Effects on the nervous system attributed to tricyclic antidepressants include drowsiness (especially with those with antihistaminic activity), peripheral neuropathy, tremor, ataxia, confusion, and delirium. Of particular concern is a reduction in the seizure threshold (see Epileptogenic Effect, p. 406.1). Extrapyramidal effects (p. 406.1) and neuroleptic malignant syndrome (see p. 406.2) may also occasionally occur.

Effects on sexual function. Loss of libido and impotence are common in depression, often making the role of drugs in producing sexual dysfunction difficult to assess.[1]

Sedation due to tricyclic antidepressants may lead to loss of libido and many of the tricyclics have been reported to cause impotence.[1,2] Amitriptyline, clomipramine, desipramine, doxepin, nortriptyline, and trimipramine have been stated to delay or inhibit ejaculation, and amoxapine, imipramine, and protriptyline, also to cause painful ejaculation. However, some tricyclics have been used for their effect on ejaculation in the management of premature ejaculation (see Sexual Dysfunction under Clomipramine, p. 414.3).

In women, anorgasmia or delayed orgasm has been reported with amitriptyline, amoxapine, clomipramine, and imipramine,[1-3] although spontaneous orgasm associated with yawning has been reported with clomipramine.[4]

1. Beeley L. Drug-induced sexual dysfunction and infertility. *Adverse Drug React Acute Poisoning Rev* 1984; 3: 23–42.
2. Anonymous. Drugs that cause sexual dysfunction. *Med Lett Drugs Ther* 1987; 29: 65–70.
3. Shen WW, Sata LS. Inhibited female orgasm resulting from psychotropic drugs: a clinical review. *J Reprod Med* 1983; 28: 497–9.
4. McLean JD, *et al.* Unusual side effects of clomipramine associated with yawning. *Can J Psychiatry* 1983; 28: 569–70.

Effects on the skin. Hypersensitivity reactions to tricyclic antidepressants are said to be uncommon.[1] Urticaria and angioedema have occurred, the urticaria occasionally clearing without drug withdrawal. Pruritus is also uncommon, but may be associated with transient erythema. Photosensitivity reactions are far less common than with phenothiazines; protriptyline has been the tricyclic most frequently implicated.[2,3] Rarely, exfoliative dermatitis has developed, and purpura, pigmentation, and lichen planus have been noted in isolated reports. In some cases pigmentation changes may be permanent.[4] Toxic epidermal necrolysis has been reported in a patient 2 weeks after starting therapy with amoxapine.[5] Hypersensitivity reactions to tricyclic antidepressants usually occur between 14 and 60 days after the start of treatment.[6]

Amitriptyline and fluoxetine have been implicated in the development of atypical cutaneous lymphoid hyperplasia in 8 patients, 7 of whom either had an underlying immunosuppressant systemic disease or were also receiving immunomodulatory drugs.[7] The lesions improved or resolved on stopping the antidepressant, although in some patients other factors may have contributed to lesional resolution.

1. Almeyda J. Drug reactions XIII: cutaneous reactions to imipramine and chlordiazepoxide. *Br J Dermatol* 1971; 84: 298–9.
2. Smith AG. Drug-induced photosensitivity. *Adverse Drug React Bull* 1989; 136 (June): 508–11.
3. Barth Y, Rapoport M. Photosensitivity associated with antipsychotics, antidepressants and anxiolytics. *Drug Safety* 1996; 14: 252–9.
4. Dean CE, Grund FM. Imipramine-associated hyperpigmentation. *Ann Pharmacother* 2003; 37: 825–8.
5. Camisa C, Grines C. Amoxapine: a cause of toxic epidermal necrolysis? *Arch Dermatol* 1983; 119: 709–10.
6. Quitkin F. Cross-tolerance of tricyclic antidepressant drugs. *JAMA* 1979; 241: 1625.
7. Crowson AN, Magro CM. Antidepressant therapy: a possible cause of atypical cutaneous lymphoid hyperplasia. *Arch Dermatol* 1995; 131: 925–9.

Epileptogenic effect. Seizures have been reported after therapeutic doses of tricyclic antidepressants as well as after overdosage, although the mechanism by which the seizures are induced is unclear.[1] Seizures usually appear within a few days of starting the drug or changing to a higher dose but in patients with no history of epilepsy or no predisposing medical condition the frequency seems[1] to be very low with an incidence of about 1 in 1000. An incidence of 0.4 per 1000 was reported[2] based on 16 cases out of an estimated group of 42 000 patients receiving tricyclics and who had no predisposing factors, but in another review[3] a reasonable estimate of the incidence was considered to be 3 to 6 per 1000. However, it is widely agreed that tricyclics should be used very cautiously in patients with epilepsy or those with a low convulsive threshold.

In a retrospective analysis of 1313 cases[4] of overdosage involving cyclic antidepressants, seizures occurred more commonly with the tricyclics amoxapine (24.5%) and desipramine (17.9%), and the tetracyclic maprotiline (12.2%). In another analysis of 302 consecutive cases of tricyclic overdosage a higher rate of seizures was seen with dosulepin in overdosage (13%) than other tricyclics.[5]

1. Zaccara G, *et al.* Clinical features, pathogenesis and management of drug-induced seizures. *Drug Safety* 1990; 5: 109–51.
2. Jick SS, *et al.* Antidepressants and convulsions. *J Clin Psychopharmacol* 1992; 12: 241–5.
3. Rosenstein DL, *et al.* Seizures associated with antidepressants: a review. *J Clin Psychiatry* 1993; 54: 289–99.
4. Wedin GP, *et al.* Relative toxicity of cyclic antidepressants. *Ann Emerg Med* 1986; 15: 797–804.
5. Buckley NA, *et al.* Greater toxicity in overdose of dothiepin than of other tricyclic antidepressants. *Lancet* 1994; 343: 159–62.

Extrapyramidal effects. Extrapyramidal effects such as orofacial and choreoathetoid movements, and dyskinesias have been attributed to treatment with tricyclic antidepressants. Dysarthria has also been reported[1] and was said to be not uncommon in those taking higher doses of tricyclic antidepressants, but unusual at lower doses.[2]

Some patients with panic disorder may be sensitive to imipramine, developing symptoms of insomnia, jitteriness, and irritability.[3] Symptoms have also been seen in patients with panic disorder treated with low doses of desipramine although the symptoms usually subsided when the dose of the tricyclic was gradually increased. It has been suggested[4] that these symptoms may be related to akathisia and are more likely to occur with those tricyclics that have a more potent effect on inhibition of noradrenaline reuptake.

Reviews of adverse effects of drugs on the nervous system have also listed acute torsion dystonias and tremors[5] as being caused or exacerbated by tricyclic antidepressants.

1. Quader SE. Dysarthria: an unusual side effect of tricyclic antidepressants. *BMJ* 1977; 2: 97.
2. Saunders M. Dysarthria with tricyclic antidepressants. *BMJ* 1977; 2: 317.
3. Yeragani VK, *et al.* Tricyclic induced jitteriness—a form of akathisia? *BMJ* 1986; 292: 1529.
4. Cole JO, Bodkin JA. Antidepressant drug side effects. *J Clin Psychiatry* 1990; 51 (suppl): 21–6.
5. Llau M-E, *et al.* Mouvements anormaux d'origine médicamenteuse: l'expérience d'un centre de pharmacovigilance sur cinq ans. *Therapie* 1995; 50: 425–7.

Hypersensitivity. A hypersensitivity syndrome developed in a 24-year-old woman 3 weeks after starting amitriptyline 50 mg daily for the treatment of depression;[1] symptoms included generalised erythroderma with mild scaling, sinus tachycardia, haematological abnormalities such as eosinophilia, and raised liver enzyme values. The patient recovered after drug withdrawal and treatment with intravenous prednisolone.

See also under Effects on the Skin, above.

1. Millonis HJ, *et al.* Hypersensitivity syndrome caused by amitriptyline administration. *Postgrad Med J* 2000; 76: 361–3.

Hyponatraemia. See Effects on the Endocrine System, p. 403.2.

Neuroleptic malignant syndrome. Of 16 cases of neuroleptic malignant syndrome reported to the UK CSM by July 1986, 3 cases occurred in patients receiving a tricyclic antidepressant: amitriptyline with perphenazine had been taken by one patient and dosulepin or clomipramine alone by 2 other patients. The clomipramine case was fatal.[1] Other reports have been associated with amoxapine,[2] clomipramine alone,[3] clomipramine with triazolam,[4] and nortriptyline.[5]

1. CSM. Neuroleptic malignant syndrome—an underdiagnosed condition? *Current Problems 18* 1986. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON20244256&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)
2. Madakasira S. Amoxapine-induced neuroleptic malignant syndrome. *DICP Ann Pharmacother* 1989; 23: 50–1.
3. Haddow AM, *et al.* Clomipramine induced neuroleptic malignant syndrome and pyrexia of unknown origin. *BMJ* 2004; 329: 1333–5.
4. Domingo P, *et al.* Benign type of malignant syndrome. *Lancet* 1989; i: 50.
5. June R, *et al.* Neuroleptic malignant syndrome associated with nortriptyline. *Am J Emerg Med* 1999; 17: 736–7.

Overdosage. In a 1993 report[1] tricyclic antidepressants were associated with a higher risk of fatality after suicide attempts by drug overdose compared with the non-tricyclics available at the time. Some reports[2] have considered desipramine to be associated more frequently than other tricyclic antidepressants with fatal overdosage, although others[3] assign this status to dosulepin. The *BNF* considers amitriptyline and dosulepin to be particularly dangerous in overdosage.

Later reviews continue to cite tricyclic antidepressants as one of the most commonly ingested substances in fatal cases of self-poisoning.[3,4]

1. Anonymous. Antidepressant drugs and the risk of suicide. *WHO Drug Inf* 1993; 7: 18–20.
2. Amital Y, Prischer H. The toxicity and dose of desipramine hydrochloride. *JAMA* 1994; 272: 1719–20.
3. Kerr GW, *et al.* Tricyclic antidepressant overdose: a review. *Emerg Med J* 2001; 18: 236–41.
4. Glauser J. Tricyclic antidepressant poisoning. *Cleve Clin J Med* 2000; 67: 704–19.

Treatment of Adverse Effects

The basis of the management of tricyclic antidepressant poisoning is intensive supportive care and symptomatic therapy.

Since tricyclic antidepressants slow gastrointestinal transit time, absorption may be delayed in overdosage. Activated charcoal may be given if a toxic dose of a tricyclic antidepressant has been ingested (see p. 406.3) and the patient presents within 1 hour, provided the airway can be protected; a second dose may be considered after 1 to 2 hours in patients with central features of toxicity. Gastric lavage is rarely used but may be considered in life-threatening overdoses.

The patient should be monitored for cardiac arrhythmias. UK authorities consider that although cardiac arrhythmias are of concern they are best treated by correction of hypoxia and acidosis with intravenous sodium bicarbonate; the use of antiarrhythmic drugs is best avoided. Intravenous sodium bicarbonate should also be given to treat arrhythmias or significant ECG abnormalities even in the absence of acidosis.

Convulsions can be managed by giving diazepam, lorazepam, or midazolam intravenously. Phenytoin should be avoided because it may increase the risk of arrhythmias. Oral or intravenous diazepam may be given to sedate agitated patients; if ineffective, oral or parenteral haloperidol may be considered.

Forced diuresis, haemodialysis, and haemoperfusion are not of value in tricyclic antidepressant poisoning, and charcoal haemoperfusion is of doubtful benefit.

Activated charcoal. The UK Poisons Information Service considers the benefit of gastric decontamination in the management of overdosage with tricyclic antidepressants to be uncertain. However, it is suggested that activated charcoal given orally or by nasogastric tube may be considered if this is given within 1 hour of ingestion of any amount of tricyclic antidepressant in children, and the following amounts or more in adults, provided that the airway can be protected:

- amitriptyline: 3 mg/kg
- clomipramine: 4 mg/kg
- desipramine: 3 mg/kg
- dosulepin: 3 mg/kg
- doxepin: 4 mg/kg
- imipramine: 4 mg/kg
- lofepramine: 15 mg/kg
- nortriptyline: 3 mg/kg
- trimipramine: 5 mg/kg

Precautions

The antimuscarinic effects of tricyclic antidepressants warrant care in patients with urinary retention, prostatic hyperplasia, or chronic constipation; caution has also been advised in untreated angle-closure glaucoma and in phaeochromocytoma.

The epileptogenic potential of tricyclic antidepressants requires care in patients with a history of epilepsy. In addition, because of their potential cardiotoxicity, tricyclics should be used with caution in patients with cardiovascular disease and avoided in those with heart block, cardiac arrhythmias, or in the immediate recovery period after myocardial infarction. Caution has also been recommended in patients with hyperthyroidism as tricyclics may increase the risk of developing cardiac arrhythmias.

Blood-sugar concentrations may be altered in diabetic patients.

Because tricyclic antidepressants are metabolised and inactivated in the liver they should be used with caution in patients with hepatic impairment and avoided in severe liver disease.

Patients should be closely monitored during early antidepressant therapy until significant improvement in depression occurs because suicide is an inherent risk in depressed patients. For further details, see under Depression, p. 398.1. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be followed when treating patients with other disorders.

If tricyclic antidepressants are used for the depressive component of bipolar disorder, mania may be precipitated; similarly, psychotic symptoms may be aggravated if tricyclics are used for a depressive component of schizophrenia.

Drowsiness often occurs, particularly at the start of therapy, and patients, if affected, should not drive or operate machinery.

Tricyclic antidepressants may inhibit salivation and regular dental check-ups are recommended for patients on long-term therapy, particularly when taking those with marked antimuscarinic actions.

Elderly patients can be particularly sensitive to the adverse effects of tricyclic antidepressants and a reduced dose, especially initially, should be used.

Tricyclic antidepressants are not recommended for depression in children. If they are used for nocturnal enuresis in children they should be limited to short courses with a full physical examination before subsequent courses.

Tricyclic antidepressants should be withdrawn gradually to reduce the risk of withdrawal symptoms (see p. 407.3).

Licensed product information recommends that, where possible, tricyclic antidepressants should be stopped several days before elective surgery, and that they should be used with caution in patients requiring ECT; however, see also under Anaesthesia, p. 406.3.

Anaesthesia. Patients receiving tricyclic antidepressants are at an increased risk of developing hypotension or car-

diac arrhythmias during anaesthesia. Tricyclics may also dangerously potentiate the cardiovascular effects of vasopressor drugs such as sympathomimetics that may be required during anaesthesia. Although some licensed product information recommends stopping tricyclics several days before elective surgery where possible, the *BNF* advises that this is unnecessary as long as the anaesthetist is informed.

Commenting on the anaesthetic considerations relevant to ECT,[1] it was considered that therapy with tricyclic antidepressants should not be a contra-indication to anaesthesia for ECT. A major consideration, though, was said to be the interaction of tricyclics with barbiturates resulting in increased sleep time and duration of anaesthesia. This meant that lower doses of barbiturate anaesthetics should be used.

Antidepressants with significant serotonergic effects such as the tricyclic clomipramine may increase the risk of bleeding during surgery; for further details see under Precautions in Fluoxetine, p. 425.3.

1. Gaines GY, Rees DI. Electroconvulsive therapy and anesthetic considerations. *Anesth Analg* 1986; 65: 1345–56.

Breast feeding. In general, only small amounts of tricyclic antidepressants are distributed into breast milk. Nevertheless, the American Academy of Pediatrics[1] considers that the effect of all antidepressants, including tricyclics, on nursing infants is unknown but may be of concern. In addition, most manufacturers advise that tricyclics should be avoided by women during breast feeding.

Case reports indicate that amitriptyline and its metabolite (nortriptyline),[2,3] clomipramine,[4] desipramine and its metabolite (2-hydroxydesipramine),[5] dosulepin and its primary metabolites (nordothiepin, dothiepin-*S*-oxide, and nordothiepin-*S*-oxide),[6] doxepin and its metabolite (*N*-desmethyldoxepin),[7-9] imipramine and its metabolite (desipramine),[10] and maprotiline[11] are all present in breast milk in concentrations similar to those in maternal blood; amoxapine and its metabolite (8-hydroxyamoxapine)[12] have also been found in breast milk but in concentrations lower than in maternal blood. In all but 2 of the above cases the infants were breast fed without having adverse effects and tricyclics were undetectable in the infant's blood or present only in minute amounts. In one of the affected infants,[8] adverse effects included sedation and shallow respiration. Although the doxepin given to the mother was almost undetectable in the infant's serum, its desmethyl metabolite appeared to have accumulated. In the other infant, drowsiness, poor suckling, and difficulty in swallowing were noted[9] but the concentrations of both doxepin and its desmethyl metabolite were below the lower level of quantification. However, it was considered that the infant may have been at a greater risk for adverse effects because he had also developed hyperbilirubinaemia. There were no data for the effects of amoxapine on breast-fed infants because the case reported[12] involved samples of milk taken from a woman who had galactorrhoea as an adverse effect of tricyclic use. No adverse effects were seen during a 27-month follow-up of 14 breast-fed infants whose mothers had taken imipramine 100 to 225 mg daily for 4 to 24 weeks.[13]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 24/11/05)
2. Bader TF, Newman K. Amitriptyline in human breast milk and the nursing infant's serum. *Am J Psychiatry* 1980; 137: 855–6.
3. Brixen-Rasmussen L, *et al.* Amitriptyline and nortriptyline excretion in human breast milk. *Psychopharmacology (Berl)* 1982; 76: 94–5.
4. Schimmell MS, *et al.* Toxic neonatal effects following maternal clomipramine therapy. *Clin Toxicol* 1991; 29: 479–84.
5. Stancer HC, Reed KL. Desipramine and 2-hydroxydesipramine in human breast milk and the nursing infant's serum. *Am J Psychiatry* 1986; 143: 1597–1600.
6. Ilett KF, *et al.* The excretion of dothiepin and its primary metabolites in breast milk. *Br J Clin Pharmacol* 1992; 33: 635–9.
7. Kemp J, *et al.* Excretion of doxepin and N-desmethyldoxepin in human milk. *Br J Clin Pharmacol* 1985; 20: 497–9.
8. Matheson I, *et al.* Respiratory depression caused by N-desmethyldoxepin in breast milk. *Lancet* 1985; II: 1124.
9. Frey OR, *et al.* Adverse effects in a newborn infant breast-fed by a mother treated with doxepin. *Ann Pharmacother* 1999; 33: 690–3.
10. Sovner R, Orsulak PJ. Excretion of imipramine and desipramine in human breast milk. *Am J Psychiatry* 1979; 136: 451–2.
11. Lloyd AH. Practical considerations in the use of maprotiline (Ludiomil) in general practice. *J Int Med Res* 1977; 5 (suppl 4): 122–38.
12. Gelenberg AJ. Amoxapine, a new antidepressant, appears in human milk. *J Nerv Ment Dis* 1979; 167: 635–6.
13. Misri S, Sivertz K. Tricyclic drugs in pregnancy and lactation: a preliminary report. *Int J Psychiatry Med* 1991; 21: 157–71.

Cardiovascular disease. For comments on the potential cardiotoxicity of tricyclic antidepressants and precautions to be observed in patients with pre-existing cardiovascular disorders, see under Effects on the Cardiovascular System in Adverse Effects, p. 403.1.

Contact lenses. Based on reports involving amitriptyline[1] and maprotiline[2] it has been considered that the antimuscarinic action of tricyclic antidepressants may decrease tear flow enough to cause corneal drying and staining of contact lenses.[3]

1. Litovitz GL. Amitriptyline and contact lenses. *J Clin Psychiatry* 1984; 45: 188.
2. Troiano G. Amitriptyline and contact lenses. *J Clin Psychiatry* 1985; 46: 199.
3. Anonymous. Drugs interfering with contact lenses. *Aust J Hosp Pharm* 1987; 17: 55–6.

Diabetes mellitus. The fact that tricyclic antidepressants may cause alterations in blood-glucose concentrations has led to the recommendation that these drugs should be used with caution in diabetic patients. Amitriptyline has also been reported[1] to cause hypoglycaemic unawareness; a patient did not have the usual adrenergic symptoms that preceded or accompanied her hypoglycaemic episodes.

1. Sherman KE, Bornemann M. Amitriptyline and asymptomatic hypoglycemia. *Ann Intern Med* 1988; 109: 683–4.

Driving. While affective disorders probably adversely affect driving skill,[1,2] treatment with antidepressant drugs may also be hazardous,[1] although patients may be safer drivers with medication than without.[2] Impairment of performance is largely related to sedative and antimuscarinic effects both of which are more pronounced at the start of treatment; sedative tricyclics, such as amitriptyline and doxepin, are likely to cause greater psychomotor impairment than less sedative tricyclics such as imipramine and nortriptyline.[1] However, an epidemiological study[3] was unable to confirm any increased risk of road-traffic accidents in those drivers receiving tricyclic antidepressants or SSRIs. In healthy subjects fluoxetine (an SSRI) and dosulepin appeared to have a similar but apparently small potential for impairing psychomotor and driving performance.[4]

In the UK, the Driver and Vehicle Licensing Authority (DVLA) considers that drugs such as the older tricyclic antidepressants may have pronounced antimuscarinic and antihistaminic effects, which may impair driving.[5] In addition, all drugs acting on the CNS can impair alertness, concentration, and driving performance, particularly at the start of treatment or when the dose is increased; driving must cease if patients are adversely affected. Patients with severe depressive illnesses complicated by significant memory or concentration problems, agitation, behavioural disturbances, or suicidal thoughts should cease driving pending the outcome of medical enquiry.

1. Ashton H. Drugs and driving. *Adverse Drug React Bull* 1983; 98: 360–3.
2. Cremona A. Mad drivers: psychiatric illness and driving performance. *Br J Hosp Med* 1986; 35: 193–5.
3. Barbone F, *et al.* Association of road-traffic accidents with benzodiazepine use. *Lancet* 1998; 352: 1331–6.
4. Ramaekers JG, *et al.* A comparative study of acute and subchronic effects of dothiepin, fluoxetine and placebo on psychomotor and actual driving performance. *Br J Clin Pharmacol* 1995; 39: 397–404.
5. Driver and Vehicle Licensing Agency. For medical practitioners: at a glance guide to the current medical standards of fitness to drive (issued November 2013). Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/258991/aagv1.pdf (accessed 20/11/13)

ECT. For comments concerning precautions in patients receiving ECT, see under Anaesthesia, p. 404.3.

Epilepsy. For comments on the epileptogenic effect of tricyclic antidepressants and the need for caution in patients with a history of epilepsy or other risk factors for development of seizures, see under Epileptogenic Effect in Adverse Effects, p. 404.1.

Food. A high-fibre diet reduced or abolished the efficacy of doxepin in 2 patients and desipramine in one.[1]

1. Stewart DE. High-fiber diet and serum tricyclic antidepressant levels. *J Clin Psychopharmacol* 1992; 12: 438–40.

Gastro-oesophageal reflux disease. The antimuscarinic action of tricyclic antidepressants may cause relaxation of the lower oesophageal sphincter and could aggravate nocturnal symptoms of gastro-oesophageal reflux if given in the late evening.[1]

1. Atkinson M. Use and misuse of drugs in the treatment of gastro-oesophageal reflux. *Prescribers' J* 1982; 22: 129–36.

Glaucoma. Manufacturers have stated that, because of their antimuscarinic actions, tricyclic antidepressants should be used with caution in patients with angle-closure glaucoma or raised intra-ocular pressure. There have been few reports of glaucoma associated with tricyclics, although acute angle-closure glaucoma was reported in 4 patients with narrow angles while taking imipramine in usual doses,[1] and in another patient taking clomipramine.[2] In the latter case, the presenting sign was amaurosis fugax, caused by the combination of raised intra-ocular pressure and an abnormally large drop in blood pressure on standing.

1. Ritch R, *et al.* Oral imipramine and acute angle closure glaucoma. *Arch Ophthalmol* 1994; 112: 67–8.
2. Schlingemann RO, *et al.* Amaurosis fugax on standing and angle-closure glaucoma with clomipramine. *Lancet* 1996; 347: 465.

Phaeochromocytoma. Use of imipramine[1,2] or desipramine[3] has caused adverse effects such as seizures and cardiovascular abnormalities (tachycardia and hypertension or hypotension) in patients with previously undiagnosed phaeochromocytoma. It has been suggested[3] that imipramine and its metabolite, desipramine, may be particularly effective in unmasking phaeochromocytoma and that this may be a reflection of their relative potency in inhibiting the noradrenaline reuptake mechanism.

1. Kaufmann JS. Pheochromocytoma and tricyclic antidepressants. *JAMA* 1974; 229: 1282.
2. Mok J, Swann I. Diagnosis of phaeochromocytoma after ingestion of imipramine. *Arch Dis Child* 1978; 53: 676–7.
3. Achong MR, Keane PM. Pheochromocytoma unmasked by desipramine therapy. *Ann Intern Med* 1981; 94: 358–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies amitriptyline as probably porphyrinogenic: it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Pregnancy. Management of depression during pregnancy can be difficult, and one report[1] on experience in 8 pregnant women being treated with a tricyclic antidepressant suggested that the dose might need to be increased during the second half of pregnancy to achieve a response. There are obvious concerns about such treatment (see also Depression, p. 398.1). However, although there have been isolated reports[2] attributing *congenital malformations* to the use of tricyclic antidepressants during pregnancy, large-scale studies and case-control data[3,4] have failed to substantiate any association.

The effects of tricyclics on *fetal neurodevelopment* were studied[5] in 80 pregnant women by later assessing global IQ of the children; no differences were seen in those exposed to tricyclics *in utero* in the first trimester compared with those exposed to fluoxetine or no adverse developmental influences. A subsequent study indicated that exposure to tricyclic antidepressants or fluoxetine throughout gestation did not appear to adversely affect cognition.[6]

Fetal tachyarrhythmia detected at 37 weeks of gestation was attributed to maternal use of dosulepin during pregnancy. When this was stopped, no abnormalities in fetal heart rate were found and an uneventful labour led to a healthy infant being delivered. However, the authors expressed concern that fetal tachycardias might result in *in-utero* cardiac failure and considered that tricyclic antidepressants should be used during pregnancy only if there were compelling reasons.[7]

Withdrawal syndromes manifesting as hypothermia and jitteriness,[8] convulsions,[9,10] or myoclonus[11] have been reported in neonates whose mothers took clomipramine during pregnancy. Management has been with phenobarbital or clomipramine. Licensed product information advises that if it is justifiable to do so, clomipramine should be withdrawn at least 7 weeks before the calculated date of delivery.

1. Wisner KL, *et al.* Tricyclic dose requirements across pregnancy. *Am J Psychiatry* 1993; 150: 1541–2.
2. Barson AJ. Malformed infant. *BMJ* 1972; 2: 45.
3. Greenberg G, *et al.* Maternal drug histories and congenital abnormalities. *BMJ* 1977; 2: 853–6.
4. Winship KA, *et al.* Maternal drug histories and central nervous system anomalies. *Arch Dis Child* 1984; 59: 1052–60.
5. Nulman I, *et al.* Neurodevelopment of children exposed in utero to antidepressant drugs. *N Engl J Med* 1997; 336: 258–62.
6. Nulman I, *et al.* Child development following exposure to tricyclic antidepressants or fluoxetine throughout fetal life: a prospective, controlled study. *Am J Psychiatry* 2002; 159: 1889–95.
7. Prentice A, Brown R. Fetal tachyarrhythmia and maternal antidepressant treatment. *BMJ* 1989; 298: 190.
8. Musa AB, Smith CS. Neonatal effects of maternal clomipramine therapy. *Arch Dis Child* 1979; 54: 405.
9. Cowe L, *et al.* Neonatal convulsions caused by withdrawal from maternal clomipramine. *BMJ* 1982; 284: 1837–8.
10. Bromiker R, Kaplan M. Apparent intrauterine fetal withdrawal from clomipramine hydrochloride. *JAMA* 1994; 272: 1722–3.
11. Bloem BR, *et al.* Clomipramine withdrawal in newborns. *Arch Dis Child Fetal Neonatal Ed* 1999; 81: F77–F79.

Surgery. For comments regarding precautions in patients undergoing surgery, see under Anaesthesia, p. 404.3.

Withdrawal. Suddenly stopping antidepressant therapy after regular use for 8 weeks or more may precipitate withdrawal symptoms. The symptoms associated with withdrawal of tricyclic antidepressants appear to form 4 distinct syndromes:[1]

- gastrointestinal disturbances and generalised somatic symptoms such as malaise, chills, headache, and increased perspiration, which may also be accompanied by anxiety and agitation
- sleep disturbances characterised by insomnia followed by excessive and vivid dreams
- parkinsonism or akathisia
- hypomania or mania

Tricyclic withdrawal has also resulted in cardiac arrhythmias in some patients. Withdrawal symptoms seem to be more common and more severe in children.[2]

Many of the symptoms associated with stopping tricyclics may be produced by cholinergic rebound[1] and can be minimised by a gradual reduction in dosage. The *BNF* recommends that any antidepressant, including a tricyclic, that has been given regularly for 8 weeks or more should be stopped gradually over a period of at least 4 weeks, or as much as 6 months in patients who have been receiving long-term maintenance therapy. If withdrawal symptoms do occur, they can be managed by restarting at a dose sufficient to eliminate them, and then stopping gradually.[1,2] On the occasions that it may be necessary to stop a tricyclic abruptly, the withdrawal symptoms can be treated with a centrally active antimuscarinic such as atropine or benzatropine,[1] or alternatively, if withdrawal symptoms are just gastrointestinal, an antimuscarinic that does not cross the blood-brain barrier such as propantheline.[1] Awareness of the possibility of withdrawal syndromes helps to avoid misinterpreting new symptoms after withdrawal as evidence of relapse.

Tricyclic antidepressants have been included in some classifications as drugs of dependence because of their potential to produce withdrawal syndromes, but a review[3] of several substance abuse studies challenged this on finding no evidence of abuse or dependence of the barbiturate type developing with the tricyclics.

For reports of withdrawal symptoms in neonates born to mothers who took tricyclic antidepressants during pregnancy, and their management, see under Pregnancy, p. 405.3.

1. Dilsaver SC. Withdrawal phenomena associated with antidepressant and antipsychotic agents. *Drug Safety* 1994; 10: 103–14.
2. Anonymous. Problems when withdrawing antidepressives. *Drug Ther Bull* 1986; 24: 29–30.
3. Lichtigfeld PJ, Gillman MA. The possible abuse of and dependence on major tranquillisers and tricyclic antidepressants. *S Afr Med J* 1994; 84: 5–6.

Interactions

Interactions involving tricyclic antidepressants often result from additive toxicity or from altered metabolism of one drug by the other. Drugs that inhibit or induce the cytochrome P450 isoenzyme CYP2D6 may affect tricyclic metabolism and produce marked alterations in plasma concentrations.

Adverse effects may be enhanced by antimuscarinic drugs or CNS depressants, including alcohol. Barbiturates and other enzyme inducers such as rifampicin and some antiepileptics can increase the metabolism of tricyclic antidepressants and may lower plasma concentrations and reduce antidepressant response. Cimetidine, methylphenidate, antipsychotics, and calcium-channel blockers can reduce the metabolism of the tricyclics, leading to the possibility of increased plasma concentrations and accompanying toxicity.

Patients taking thyroid preparations may show an accelerated response to tricyclic antidepressants and occasionally liothyronine has been used to produce this effect in patients with refractory depression. However, the use of tricyclics with thyroid hormones may precipitate cardiac arrhythmias.

The antihypertensive effects of debrisoquine, guanethidine, and clonidine may be reduced by tricyclic antidepressants. The pressor effects of sympathomimetics, especially those of the direct-acting drugs adrenaline and noradrenaline, can be enhanced by tricyclic antidepressants; however, there is no clinical evidence of dangerous interactions between adrenaline-containing local anaesthetics and tricyclic antidepressants. Great care should, however, be taken to avoid inadvertent intravenous injection of the local anaesthetic preparation.

Drugs that prolong the QT interval, including antiarrhythmics such as amiodarone or quinidine, the antihistamines astemizole and terfenadine, some antipsychotics (notably pimozide, sertindole, and thioridazine), cisapride, halofantrine, and sotalol, may increase the likelihood of ventricular arrhythmias when taken with tricyclic antidepressants. This may be exacerbated where the interacting drug (such as quinidine or some antipsychotics) also reduces tricyclic metabolism.

Although different antidepressants have been used together under expert supervision in refractory cases of depression, severe adverse reactions including the serotonin syndrome (see p. 445.2) may occur. For this reason an appropriate drug-free interval should elapse between stopping some types of antidepressant and starting another. Tricyclic antidepressants should not generally be given to patients receiving MAOIs or for at least 2 weeks (3 weeks if starting clomipramine or imipramine) after their withdrawal. No treatment-free period is necessary after stopping a reversible inhibitor of monoamine oxidase type A (RIMA) and starting a tricyclic. At least 1 to 2 weeks (3 weeks in the case of clomipramine or imipramine) should elapse between withdrawing a tricyclic antidepressant and starting any drug liable to provoke a serious reaction (e.g. phenelzine).

Further details concerning some of the above interactions, and others, are given below.

Alcohol. For reference to the effect of alcohol on amitriptyline, see under CNS depressants, p. 409.1.

Analgesics. Doubling of plasma-doxepin concentrations with associated lethargy has been reported in a patient after the addition of *dextropropoxyphene* to the tricyclic.[1] This was consistent with previous studies indicating that dextropropoxyphene can impair the hepatic metabolism of other drugs.

For general reference to the effect of tricyclic antidepressants, notably amitriptyline and clomipramine, on *opioid analgesics*, see under Morphine, p. 95.3.

1. Abernethy DR, *et al.* Impairment of hepatic drug oxidation by propoxyphene. *Ann Intern Med* 1982; 97: 223–4.

Antiarrhythmics. Antiarrhythmics that prolong the QT interval may increase the likelihood of ventricular arrhythmias when given with tricyclic antidepressants. This includes various class I antiarrhythmics such as *disopyramide, flecainide, procainamide, propafenone,* and *quinidine,* and the class III antiarrhythmic *amiodarone.*

Raised serum-desipramine concentrations and signs of toxicity were noted[1] in a patient taking desipramine after starting treatment with digoxin and propafenone for paroxysmal atrial fibrillation. It was considered that propafenone probably reduced the metabolism and clearance of desipramine.

1. Katz MR. Raised serum levels of desipramine with the antiarrhythmic propafenone. *J Clin Psychiatry* 1991; 52: 432–3.

Anticoagulants. For the effect of tricyclic antidepressants on anticoagulants, see under Warfarin, p. 1531.3.

Antidepressants. Combination therapy with differing classes of antidepressants has been used successfully in the treatment of drug-resistant depression. It should be emphasised, however, that such combinations may result in interactions or enhanced adverse reactions, and should be used only under expert supervision. For further details of the interactions between different antidepressants when used together, see Phenelzine, p. 447.2. For details of the serotonin syndrome that can arise when two serotonergic drugs with different mechanisms of action are given, see under Adverse Effects of Phenelzine, p. 445.2.

Antidiabetics. For the effect of tricyclic antidepressants on *sulfonylureas* and *insulin*, see Interactions, p. 504.3 and p. 488.3, respectively.

Antiepileptics. Antidepressants may antagonise the activity of antiepileptics by lowering the convulsive threshold.

A review[1] of drug interactions with *phenytoin* noted that although there had been reports of interactions between antiepileptics and tricyclic or related antidepressants, most involved enzyme-inducing antiepileptics other than phenytoin or phenytoin with other drugs. In the only report where phenytoin could be identified as the sole antiepileptic used, 2 patients required high doses of desipramine to achieve an antidepressant effect and to maintain plasma-desipramine concentrations in the range usually associated with therapeutic efficacy.

Carbamazepine has been reported to induce the metabolism of several tricyclic antidepressants (amitriptyline, desipramine, doxepin, imipramine, and nortriptyline) and to reduce their plasma concentrations. The clinical importance of the interaction is unclear. Use of nortriptyline with carbamazepine in a patient led to a decrease in serum-nortriptyline concentration requiring an increase in nortriptyline dose.[2] In another patient a prolonged QT interval was noted after use of desipramine with carbamazepine;[3] the authors hypothesised that the accelerated metabolism of desipramine had resulted in high levels of a cardiotoxic metabolite.

Valproate has been reported to increase plasma concentrations of amitriptyline,[4] clomipramine,[5] and nortriptyline.[4,6]

For the effect of the cyclic antidepressants desipramine and viloxazine on carbamazepine, see p. 516.2. For the effects of tricyclic antidepressants on phenytoin, see p. 543.1.

See also under Barbiturates, p. 408.3.

1. Nation RL, *et al.* Pharmacokinetic drug interactions with phenytoin (part II). *Clin Pharmacokinet* 1990; 18: 131–50.
2. Brøsen K, Kragh-Sørensen P. Concomitant intake of nortriptyline and carbamazepine. *Ther Drug Monit* 1993; 15: 258–60.
3. Baldessarini RJ, *et al.* Anticonvulsant cotreatment may increase toxic metabolites of antidepressants and other psychotropic drugs. *J Clin Psychopharmacol* 1988; 8: 381–2.
4. Wong SL, *et al.* Effects of divalproex sodium on amitriptyline and nortriptyline pharmacokinetics. *Clin Pharmacol Ther* 1996; 60: 48–53.
5. Fehr C, *et al.* Increase in serum clomipramine concentrations caused by valproate. *J Clin Psychopharmacol* 2000; 20: 493–4.
6. Pu C, *et al.* Valproate/nortriptyline interaction. *J Clin Psychopharmacol* 1994; 14: 205–6.

Antifungals. Increased serum concentrations of nortriptyline[1] or amitriptyline[2,3] have occurred in patients also taking *fluconazole.* In some patients the use of amitriptyline with fluconazole has led to syncope[3] or torsade de pointes.[4] Raised serum concentrations of nortriptyline and associated symptoms of intoxication have been reported in 2 patients during treatment with *terbinafine;*[5,6] the interaction was confirmed on rechallenge. In another case, dizziness, dry mouth, and muscle twitching were reported in a patient on long-term imipramine treatment after starting terbinafine;[7] serum imipramine concentrations were found to be elevated and symptoms subsided after the dose of imipramine was reduced. A study in healthy subjects also indicated that terbinafine similarly inhibited the metabolism of desipramine.[8]

1. Gannon RH. Fluconazole-nortriptyline drug interaction. *Ann Pharmacother* 1992; 26: 1456.
2. Newberry DL, *et al.* A fluconazole/amitriptyline drug interaction in three male adults. *Clin Infect Dis* 1997; 24: 270–1.
3. Robinson RF, *et al.* Syncope associated with concurrent amitriptyline and fluconazole therapy. *Ann Pharmacother* 2000; 34: 1406–1409.
4. Dorsey ST, Biblo LA. Prolonged QT interval and torsades de pointes caused by the combination of fluconazole and amitriptyline. *Am J Emerg Med* 2000; 18: 227–9.
5. van der Kuy P-HM, *et al.* Nortriptyline intoxication induced by terbinafine. *BMJ* 1998; 316: 441.
6. van der Kuy P-HM, *et al.* Pharmacokinetic interaction between nortriptyline and terbinafine. *Ann Pharmacother* 2002; 36: 1712–14.
7. Teitelbaum ML, Pearson VE. Imipramine toxicity and terbinafine. *Am J Psychiatry* 2001; 158: 2086.
8. Madani S, *et al.* Effect of terbinafine on the pharmacokinetics and pharmacodynamics of desipramine in healthy volunteers identified as cytochrome P450 2D6 (CYP2D6) extensive metabolizers. *J Clin Pharmacol* 2002; 42: 1211–18.

Antihypertensives. In general, the hypotensive effect of antihypertensives is enhanced by tricyclic antidepressants, but there may be antagonism of the effect of *adrenergic neurone blockers* and of *clonidine.*

Antimigraine drugs. For the effects when some tricyclics are used with *dihydroergotamine,* see p. 675.2.

Antineoplastics. For the effects when tricyclic antidepressants are used with *altretamine,* see p. 739.1.

Antiprotozoals. Toxic psychosis developed in a patient on amitriptyline after starting *furazolidone,* an antiprotozoal with monoamine oxidase inhibiting activity.[1]

1. Aderhold RM, Muniz CE. Acute psychosis with amitriptyline and furazolidone. *JAMA* 1970; 213: 2080.

Antipsychotics. For a discussion of interactions between antipsychotics and tricyclic antidepressants, see *Chlorpromazine* (p. 1052.1). For details of a possible interaction between clomipramine and *clozapine,* see p. 1061.3.

Antivirals. HIV-protease inhibitors may increase the plasma concentrations of tricyclic antidepressants whose metabolism is mediated through common cytochrome P450 isoenzymes. *Ritonavir* has produced moderate increases in the plasma concentrations of desipramine and a lower initial dose of desipramine may be appropriate. Licensed product information for ritonavir has warned that a similar increase may occur for other tricyclics; monitoring of therapeutic and adverse effects is recommended when tricyclics are used with ritonavir.

Anxiolytics. For a suggestion that *benzodiazepines* may increase the oxidation of amineptine to a toxic metabolite, see under Effects on the Liver in Adverse Effects, p. 403.1. For a possible interaction of desipramine and other antidepressants with *zolpidem* see p. 1117.2.

Barbiturates. Antidepressants may antagonise the antiepileptic activity of some barbiturates by lowering the convulsive threshold.

Barbiturates can increase the metabolism of tricyclic antidepressants and thereby produce lower plasma concentrations.

For details of the interaction of tricyclic antidepressants with barbiturate anaesthetics, see under Anaesthesia in Precautions, p. 404.3.

Beta blockers. Raised imipramine plasma concentrations were noted in two 9-year-old children also given *propranolol;*[1] in both cases, no significant adverse effects were reported. *Labetalol* has also increased the bioavailability of imipramine in healthy subjects and inhibited its metabolism.[2]

The risk of ventricular arrhythmias may be increased when tricyclic antidepressants are taken with *sotalol.*

1. Gillette DW, Tannery LP. Beta blocker inhibits tricyclic metabolism. *J Am Acad Child Adolesc Psychiatry* 1994; 33: 223–4.
2. Hermann DJ, *et al.* Comparison of verapamil, diltiazem, and labetalol on the bioavailability and metabolism of imipramine. *J Clin Pharmacol* 1992; 32: 176–83.

Calcium-channel blockers. *Diltiazem* and *verapamil* each increased the bioavailability of imipramine in healthy subjects; second-degree heart block developed in 2 subjects.[1] Diltiazem also increased the bioavailability of nortriptyline in one patient,[2] probably by reducing the first-pass metabolism of nortriptyline. Increased serum concentrations of trimipramine have been reported when taken with diltiazem,[3] although there was no evidence of toxicity.

1. Hermann DJ, *et al.* Comparison of verapamil, diltiazem, and labetalol on the bioavailability and metabolism of imipramine. *J Clin Pharmacol* 1992; 32: 176–83.
2. Krähenbühl S, *et al.* Pharmacokinetic interaction between diltiazem and nortriptyline. *Eur J Clin Pharmacol* 1996; 49: 417–19.
3. Cotter PA, *et al.* Asymptomatic tricyclic toxicity associated with diltiazem. *Br J Psychol Med* 1996; 13: 168–9.

CNS depressants. Drugs with depressant actions on the CNS may be expected to enhance the drowsiness and related effects produced by the sedating type of tricyclic antidepressants. Such an interaction may occur between *alcohol* and tricyclic antidepressants and a study has shown that alcohol decreases the hepatic first-pass extraction of amitriptyline resulting in increased free plasma-amitriptyline concentrations, especially during the period of drug absorption.[1]

The problems that may be encountered with *barbiturate anaesthetics* are discussed under Anaesthesia in Precautions, p. 404.3.

1. Dorian P, *et al.* Amitriptyline and ethanol: pharmacokinetic and pharmacodynamic interaction. *Eur J Clin Pharmacol* 1983; 25: 325–31.

Disulfiram. Acute organic brain syndrome has been reported in 2 patients after the addition of amitriptyline to their disulfiram treatment.[1] It was suspected that the syndrome was potentiated by the combined action of the drugs and the synergistic elevation in dopamine concentration.

For a report of the enhancement of the disulfiram-alcohol reaction by amitriptyline, see p. 2496.3.

1. Maany I, *et al.* Possible toxic interaction between disulfiram and amitriptyline. *Arch Gen Psychiatry* 1982; 39: 743–4.

Dopaminergics. Serious adverse effects have been reported[1] when *selegiline*, an irreversible selective inhibitor of monoamine oxidase type B, was used with tricyclic antidepressants. In some instances effects resembled the potentially fatal serotonin syndromes reported when tricyclics are given with non-selective MAOIs (see under Phenelzine, p. 445.2).

Some manufacturers of selegiline advise that tricyclic antidepressants should not generally be given at the same time, or for at least 2 weeks after it has been discontinued. Similarly, at least one week should elapse between withdrawing a tricyclic antidepressant and starting selegiline.

For reference to the effect when tricyclic antidepressants are taken with *levodopa*, see p. 908.2.

1. Anonymous. Selegiline and antidepressants: risk of serious interactions. *WHO Drug Inf* 1995; 9: 160–1.

General anaesthetics. For the effect of amitriptyline on *enflurane*, see p. 1903.2. For the effects of using tricyclic antidepressants with *barbiturates* see under Anaesthesia in Precautions, p. 404.3.

Histamine. For the effect of tricyclic antidepressants on histamine given exogenously, see p. 2525.3.

Histamine H_2-antagonists. *Cimetidine* is a known inhibitor of hepatic metabolism of drugs and symptoms of tricyclic toxicity have been reported in patients given cimetidine with desipramine,[1] doxepin,[2] or imipramine;[1] there has been a report of psychosis developing in a patient given imipramine and cimetidine.[3] Elevated tricyclic concentrations during combined therapy or reductions in tricyclic concentrations after withdrawal of cimetidine have been reported for imipramine[4] and nortriptyline.[5] Studies in healthy subjects have also indicated increased bioavailability and/or impaired hepatic metabolism of amitriptyline,[6] doxepin,[7,8] and imipramine[9] during cimetidine therapy. Adjustment of tricyclic antidepressant dosage may therefore be required if cimetidine therapy is begun or stopped.

Ranitidine has been reported not to alter the pharmacokinetics of amitriptyline,[10] doxepin,[8] or imipramine.[9]

1. Miller DD, Macklin M. Cimetidine-imipramine interaction: a case report. *Am J Psychiatry* 1983; 140: 351–2.
2. Brown BA, *et al.* Cimetidine-doxepin interaction. *J Clin Psychopharmacol* 1985; 5: 245–7.
3. Miller ME, *et al.* Psychosis in association with combined cimetidine and imipramine treatment. *Psychosomatics* 1987; 28: 217–19.
4. Shapiro PA. Cimetidine-imipramine interaction: case report and comments. *Am J Psychiatry* 1984; 141: 152.
5. Miller DD, *et al.* Cimetidine's effect on steady-state serum nortriptyline concentrations. *Drug Intell Clin Pharm* 1983; 17: 904–5.
6. Curry SH, *et al.* Cimetidine interaction with amitriptyline. *Eur J Clin Pharmacol* 1985; 29: 429–33.
7. Abernethy DR, Todd EL. Doxepin-cimetidine interaction: increased doxepin bioavailability during cimetidine treatment. *J Clin Psychopharmacol* 1986; 6: 8–12.
8. Sutherland DL, *et al.* The influence of cimetidine versus ranitidine on doxepin pharmacokinetics. *Eur J Clin Pharmacol* 1987; 32: 159–64.
9. Wells BG, *et al.* The effect of ranitidine and cimetidine on imipramine disposition. *Eur J Clin Pharmacol* 1986; 31: 285–90.
10. Curry SH, *et al.* Lack of interaction of ranitidine with amitriptyline. *Eur J Clin Pharmacol* 1987; 32: 317–20.

Muscle relaxants. There has been an isolated report[1] of a patient taking *baclofen* for spasticity who had weakness in his legs and was unable to stand after starting treatment with nortriptyline. Symptoms improved on stopping nortriptyline but recurred when imipramine was given.

1. Silverglat MJ. Baclofen and tricyclic antidepressants: possible interaction. *JAMA* 1981; 246: 1659.

Sex hormones. There have been anecdotal reports of interactions between tricyclic antidepressants and *oestrogens*[1-3] resulting in a lack of antidepressant response and/or tricyclic toxicity but the significance of these interactions is unknown.

1. Prange AJ, *et al.* Estrogen may well affect response to antidepressant. *JAMA* 1972; 219: 143–4.
2. Khurana RC. Estrogen-imipramine interaction. *JAMA* 1972; 222: 702–3.
3. Somani SM, Khurana RC. Mechanism of estrogen-imipramine interaction. *JAMA* 1973; 223: 560.

Smoking. Tobacco smoke has been reported to reduce the plasma levels of tricyclic antidepressants.[1-3] The clinical significance is not, however, fully established as the plasma concentration of unbound drug may not be affected.[3] The mechanism is probably by stimulation of hepatic drug metabolism by components present in cigarette smoke.

1. Perel JM, *et al.* Pharmacodynamics of imipramine in depressed patients. *Psychopharmacol Bull* 1973; 11: 16–18.
2. John VA, *et al.* Effects of age, cigarette smoking and the oral contraceptive on the pharmacokinetics of clomipramine and its desmethyl metabolite during chronic dosing. *J Int Med Res* 1980; 8 (suppl 3): 88–95.
3. Perry PJ, *et al.* Effects of smoking on nortriptyline plasma concentrations in depressed patients. *Ther Drug Monit* 1986; 8: 279–84.

Sympathomimetics. The pressor effects of sympathomimetics can be enhanced by tricyclic antidepressants.

For prescribing precautions in patients on tricyclic therapy who may require sympathomimetics during anaesthesia, see under Anaesthesia in Precautions, p. 404.3.

Thyroid hormones. An increase in receptor sensitivity to catecholamines produced by thyroid hormones has been proposed as the reason for an increase in response to tricyclic antidepressants given with *liothyronine*.[1,2]

1. Banki CM. Cerebrospinal fluid amine metabolites after combined amitriptyline-triiodothyronine treatment of depressed women. *Eur J Clin Pharmacol* 1977; 11: 311–15.
2. Goodwin FK, *et al.* Potentiation of antidepressant effects by L-triiodothyronine in tricyclic nonresponders. *Am J Psychiatry* 1982; 139: 34–8.

Pharmacokinetics

Amitriptyline is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur within about 6 hours after oral doses.

Amitriptyline undergoes extensive first-pass metabolism and is demethylated in the liver by the cytochrome P450 isoenzymes CYP3A4, CYP2C9, and CYP2D6 to its primary active metabolite, nortriptyline. Other paths of metabolism of amitriptyline include hydroxylation (possibly to active metabolites) by CYP2D6 and *N*-oxidation; nortriptyline follows similar paths. Amitriptyline is excreted in the urine, mainly in the form of its metabolites, either free or in conjugated form.

Amitriptyline and nortriptyline are widely distributed throughout the body and are extensively bound to plasma and tissue protein. Amitriptyline has been estimated to have an elimination half-life ranging from about 9 to 25 hours, which may be considerably extended in overdosage. Plasma concentrations of amitriptyline and nortriptyline vary very widely between individuals and no simple correlation with therapeutic response has been established.

Amitriptyline and nortriptyline cross the placenta and are distributed into breast milk (see Breast Feeding under Precautions, p. 405.1).

References.
1. Schulz P, *et al.* Discrepancies between pharmacokinetic studies of amitriptyline. *Clin Pharmacokinet* 1985; 10: 257–68.
2. Brøsen K, Gram LF. Clinical significance of the sparteine/debrisoquine oxidation polymorphism. *Eur J Clin Pharmacol* 1989; 36: 537–47.
3. Caccia S, Garattini S. Formation of active metabolites of psychotropic drugs: an updated review of their significance. *Clin Pharmacokinet* 1990; 18: 434–59.
4. Wood AJJ, Zhou HH. Ethnic differences in drug disposition and responsiveness. *Clin Pharmacokinet* 1991; 20: 350–73.
5. Llerena A, *et al.* Debrisoquin and mephenytoin hydroxylation phenotypes and CYP2D6 genotype in patients treated with neuroleptic and antidepressant agents. *Clin Pharmacol Ther* 1993; 54: 606–11.
6. Ghahramani P, *et al.* Cytochromes P450 mediating the N-demethylation of amitriptyline. *Br J Clin Pharmacol* 1997; 43: 137–44.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Florda; Tryptalgin; Triptanol; Uxen; *Austral.*: Endep; Tryptanol†; *Austria*: Saroten; Tryptizol†; *Belg.*: Redomex; *Braz.*: Amytril; Neurotrypt; Protanol; Tripsol; Trisomatol; Tryptanol; *Canad.*: Elavil; Levate; Novo-Triptyn; *Denm.*: Saroten; *Fin.*: Triptyl; *Fr.*: Elavil; Laroxyl; *Ger.*: Amineurin†; Amloxid; Equilibrin; Saroten; Syneudon; *Gr.*: Maxivalet; Saroten; Stelminal; Thymonil; *Hong Kong*: Endep†; Qualitriptine; *Hung.*: Teperin; *India*: Amit; Amitone; Amitor; Amitrip; Amrea; Amypres; Crypton; Eliwel; Gentrip; Kamitrin; Latilin; Mitryp-10; Odep; Sarotena; Tryptomer; *Israel*: Elatrol; Elatrolet; Tryptal†; *Ital.*: Adepril; Laroxyl; Triptizol; *Malaysia*: Tripta; Tryptanol†; *Mex.*: Anapsique; Tryptanol; *Neth.*: Sarotex; Tryptizol; *Norw.*: Sarotex; *NZ*: Amitrol; Amitrip; *Port.*: ADT; Tryptizol; *Rus.*: Amyzol (Амизол)†; Eliwel (Эливел)†; Saroten (Саропен); *S.Afr.*: Norilline†; Saroten†; Trepiline; Tryptanol; *Singapore*: Tripta; *Spain*: Deprelio; Tryptizol; *Swed.*: Saroten; Tryptizol; *Switz.*: Saroten; Tryptizol†; *Thal.*: Amitec; Amitryn; Conmitrip; Polytanol; Tripsyline; Tripta; Triptyline; Tripzol; Tryptanol; *Turk.*: Laroxyl; Triptilin; *UK*: Elavil; *Ukr.*: Saroten (Саропен); *Venez.*: Tryptanol.

Multi-ingredient Preparations. *Austria*: Limbitrol; *Braz.*: Limbitrol; *Canad.*: Apo-Peram†; PMS-Levazine; *Chile*: Antalin; Limbatrilin; Morelin; Tiperin; *Fin.*: Klotriptyl; Limbitrol; Pertriptyl; *Gr.*: Minitran; Triphenaze; *India*: Amichlor; Amixide H; Amize; Amizep; Amrea-C; Amypres-C; Chlotrip; Emotrip; Febl; Gentrip Forte; Gentrip Plus; Libotryp; Librodep; Limbitrol; Limbival; Mirip; Mitryp; Normaline Plus; Normaline-H; *Indon.*: Limbitrol; Mutabon-D; Mutabon-M; *Ital.*: Diapatol; Limbitryl; Mutabon; Sedans; *Mex.*: Adepsique; *Port.*: Mutabon; *Rus.*: Amixide (Амиксид); *S.Afr.*: Limbitrol†; *Spain*: Mutabase; Nobritol; *Switz.*: Limbitrol; *Thal.*: Neuragon†; Polybon; *UK*: Triptafen; *USA*: Etrafon†; Limbitrol.

Pharmacopoeial Preparations

BP 2014: Amitriptyline Tablets;

USP 36: Amitriptyline Hydrochloride Injection; Amitriptyline Hydrochloride Tablets; Chlordiazepoxide and Amitriptyline Hydrochloride Tablets; Perphenazine and Amitriptyline Hydrochloride Tablets.

Amoxapine *(BAN, USAN, rINN)*

Amoksapiini; Amoksapin; Amoxapin; Amoxapina; Amoxapinum; CL-67772; Амоксапин.

2-Chloro-11-(piperazin-1-yl)dibenz[*b*,*f*][1,4]oxazepine.

$C_{17}H_{16}ClN_3O$=313.8

CAS — 14028-44-5.

ATC — N06AA17.

ATC Vet — QN06AA17.

UNII — R63VQ857OT.

Pharmacopoeias. In *Jpn* and *US*.

USP 36: (Amoxapine). A white to yellowish crystalline powder. Practically insoluble in water; slightly soluble in acetone; freely soluble in chloroform; sparingly soluble in methyl alcohol and in toluene; soluble in tetrahydrofuran. Store in airtight containers.

Uses and Administration

Amoxapine, the *N*-desmethyl derivative of loxapine (p. 1082.2), is a dibenzoxazepine tricyclic antidepressant with actions and uses similar to those of amitriptyline (p. 401.1). Amoxapine is one of the less sedating tricyclics and its antimuscarinic effects are mild; it also inhibits the reuptake of dopamine.

In the treatment of depression (p. 398.1) amoxapine is given in oral doses of 50 mg two or three times daily initially, gradually increased as necessary up to 100 mg two or three times daily by the end of the first week. Higher doses of up to 600 mg daily may also be given, if required, in severely depressed patients in hospital. A suggested dose for the elderly is 25 mg two or three times daily initially, increased as necessary up to 50 mg two or three times daily by the end of the first week; further increases to a maximum of 300 mg daily are permitted, if required.

Once-daily dosage regimens, usually given at night, are suitable for amoxapine up to 300 mg daily once an effective dosage has been established; divided-dosage regimens are recommended for doses above 300 mg daily.

It has been claimed that, in the treatment of depression, amoxapine has a more rapid onset of action than amitriptyline or imipramine with a clinical effect possibly appearing 4 to 7 days after starting therapy, although this has been disputed.

Amoxapine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Amoxapine has also been investigated for its potential as an antipsychotic.

References.
1. Jue SG, *et al.* Amoxapine: a review of its pharmacology and efficacy in depressed states. *Drugs* 1982; 24: 1–23.

2. Sa DS, *et al.* Amoxapine shows an antipsychotic effect but worsens motor function in patients with Parkinson's disease and psychosis. *Clin Neuropharmacol* 2001; 24: 242–4.
3. Apiquian R, *et al.* Amoxapine shows atypical antipsychotic effects in patients with schizophrenia: results from a prospective open-label study. *Schizophr Res* 2003; 59: 35–9.
4. Fitzgerald PB, *et al.* Amoxapine in schizophrenia: a negative double-blind controlled trial. *J Clin Psychopharmacol* 2004; 24: 448–50.
5. Apiquian R, *et al.* Amoxapine as an atypical antipsychotic: a comparative study vs risperidone. *Neuropsychopharmacology* 2005; 30: 2236–44.
6. Chaudhry IB, *et al.* Amoxapine as an antipsychotic: comparative study versus haloperidol. *J Clin Psychopharmacol* 2007; 27: 575–81.

Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p. 402.3).

Rare cases of tardive dyskinesias and the neuroleptic malignant syndrome have been reported with amoxapine.

Antidopaminergic effects. Amoxapine is a derivative of the antipsychotic loxapine (p. 1082.2) and possesses some antipsychotic activity. It also has dopamine-receptor blocking properties as do its hydroxylated metabolites. Adverse effects that are symptoms of such blockade have been reported and reviewed[1,2] and include akinesia, akathisia, withdrawal dyskinesia, reversible tardive dyskinesia, persistent dyskinesia, elevated serum concentration of prolactin, and galactorrhoea. Chorea[3] and oculogyric crisis[4] have also been reported.

1. Tao GK, *et al.* Amoxapine-induced tardive dyskinesia. *Drug Intell Clin Pharm* 1985; 19: 548–9.
2. Devarajan S. Safety of amoxapine. *Lancet* 1989; ii: 1455.
3. Patterson JF. Amoxapine-induced chorea. *South Med J* 1983; 76: 1077.
4. Hunt-Fugate AK, *et al.* Adverse reactions due to dopamine blockade by amoxapine. *Pharmacotherapy* 1984; 4: 35–9.

Antimuscarinic effects. Amoxapine therapy has been reported to produce adverse effects associated with antimuscarinic activity (such as constipation, blurred vision, and dry mouth), but such reports did not reflect *in-vitro* findings that amoxapine had considerably less affinity for muscarinic binding sites than amitriptyline;[1] this was supported by results in healthy subjects. The adverse effects described as antimuscarinic could possibly be explained by amoxapine affecting noradrenergic mechanisms.

1. Bourne M, *et al.* A comparison of the effects of single doses of amoxapine and amitriptyline on autonomic functions in healthy volunteers. *Eur J Clin Pharmacol* 1993; 44: 57–62.

Breast feeding. For comments on the use of tricyclic antidepressants in breast feeding patients, see under Precautions for Amitriptyline, p. 405.1.

Effects on the endocrine system. Reversible nonketotic hyperglycaemia developed in a 49-year-old woman with no history of diabetes mellitus within 5 days of oral therapy with amoxapine 50 mg three times daily.[1] She had previously had nonketotic hyperglycaemic coma after loxapine 150 mg daily. 7-Hydroxyamoxapine, a metabolite common to both amoxapine and loxapine, was implicated.

See also Antidopaminergic Effects, above, for mention of galactorrhoea and hyperprolactinaemia.

1. Tollefson G, Lesar T. Nonketotic hyperglycemia associated with loxapine and amoxapine: case report. *J Clin Psychiatry* 1983; 44: 347–8.

Overdosage. In overdosage, amoxapine is reported to cause acute renal failure with rhabdomyolysis,[1,2] coma, and seizures.[3-5] Although there has been some debate as to whether the incidence of seizures and death is higher with overdosage of amoxapine than with other tricyclic antidepressants, some[6] consider that evidence does seem to favour increased neurological consequences.

It has been reported that amoxapine is not cardiotoxic in overdosage[3] but later evidence would suggest that there is cardiotoxic potential.[6,7]

1. Pumariega AJ, *et al.* Acute renal failure secondary to amoxapine overdose. *JAMA* 1982; 248: 3141–2.
2. Jennings AE, *et al.* Amoxapine-associated acute renal failure. *Arch Intern Med* 1983; 143: 1525–7.
3. Kulig K, *et al.* Amoxapine overdose: coma and seizures without cardiotoxic effects. *JAMA* 1982; 248: 1092–4.
4. Litovitz TL, Troutman WG. Amoxapine overdose: seizures and fatalities. *JAMA* 1983; 250: 1069–71.
5. Jefferson JW. Convulsions associated with amoxapine. *JAMA* 1984; 251: 603–4.
6. Leonard BE. Safety of amoxapine. *Lancet* 1989; ii: 808.
7. Sørensen MR. Acute myocardial failure following amoxapine intoxication. *J Clin Psychopharmacol* 1988; 8: 75.

Interactions

For interactions associated with tricyclic antidepressants, see Amitriptyline, p. 406.1.

Pharmacokinetics

Amoxapine is readily absorbed from the gastrointestinal tract. It bears a close chemical relationship to loxapine (p. 1082.2) and is similarly metabolised by hydroxylation. It is excreted in the urine, mainly as its metabolites in conjugated form as glucuronides.

Amoxapine has been reported to have a plasma half-life of 8 hours and its major metabolite, 8-hydroxyamoxapine, has been reported to have a biological half-life of 30 hours; 7-hydroxyamoxapine has been identified as another metabolite. Both metabolites are pharmacologically active. Amoxapine is about 90% bound to plasma proteins.

Amoxapine and its metabolite 8-hydroxyamoxapine are distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Defanyl; *India*: Amolife; Demolox; Oxamine; Oxcap; *Indon.*: Asendin†.

Pharmacopoeial Preparations
USP 36: Amoxapine Tablets.

Benactyzine Hydrochloride *(BANM, rINNM)*

Amizylum; Benacticina, hidrocloruro de; Bénactyzine, Chlorhydrate de; Benactyzini Hydrochloridum; Hidrocloruro de benacticina; Бенактизина Гидрохлорид.
2-Diethylaminoethyl benzilate hydrochloride.
$C_{20}H_{23}NO_3$,HCl=363.9
CAS — 302-40-9 (benactyzine); 57-37-4 (benactyzine hydrochloride).
UNII — 26R628272Q.

Profile

Benactyzine has antidepressant and antimuscarinic activity. It has been used as the hydrochloride in the management of depression and associated anxiety. It is also used as a pharmacological tool. Methylbenactyzium bromide (p. 1864.3), the methobromide of benactyzine, has been used for its antimuscarinic activity in the treatment of gastrointestinal spasm and nocturnal enuresis.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Dimaval.

Bupropion *(BAN, rINN)*

Amfebutamone; Bupropión; Bupropione; Bupropionum; Бупропион.
(±)-2-(*tert*-Butylamino)-3′-chloropropiophenone.
$C_{13}H_{18}ClNO$=239.7
CAS — 34911-55-2.
ATC — N06AX12.
ATC Vet — QN06AX12.
UNII — 01ZG3TPX31.

Bupropion Hydrobromide *(BANM, USAN, rINNM)*

Bupropione, Bromhydrate de; Bupropioni Hydrobromidum; BVF-033; Hidrobromuro de bupropión; Бупропиона Гидробромид.
(2*RS*)-1-(3-Chlorophenyl)-2-[(1,1-dimethylethyl)amino]propan-1-one hydrobromide.
$C_{13}H_{18}ClNO$,HBr=320.7
CAS — 905818-69-1.
ATC — N06AX12.
ATC Vet — QN06AX12.
UNII — E70G3G5863.

Bupropion Hydrochloride *(BANM, USAN, rINNM)*

Amfebutamone Hydrochloride; Bupropión, hidrocloruro de; Bupropione, Chlorhydrate de; Bupropionhydrokloríd; Bupropioni Hydrochloridum; Bupropionihydrokloridi; BW-323; Hidrocloruro de anfebutamona; Hidrocloruro de bupropión; Бупропиона Гидрохлорид.
(±)-2-(*tert*-Butylamino)-3′-chloropropiophenone hydrochloride.
$C_{13}H_{18}ClNO$,HCl=276.2
CAS — 31677-93-7.
ATC — N06AX12.
ATC Vet — QN06AX12.
UNII — ZG7E5POY8O.

Pharmacopoeias. In *US*.

USP 36: (Bupropion Hydrochloride). A white powder. Soluble in water, in alcohol, and in 0.1N hydrochloric acid. Protect from light.

Uses and Administration

Bupropion is a chlorpropiophenone antidepressant chemically unrelated to other classes of antidepressants but similar in structure to the central stimulant diethylpropion (p. 2321.1). It is a weak blocker of neuronal reuptake of serotonin and noradrenaline compared with tricyclic antidepressants; it also inhibits the neuronal reuptake of dopamine. The antidepressant effect may not be evident until after 4 weeks of therapy. Bupropion is also used as an aid to smoking cessation.

Bupropion is given orally as the hydrochloride or the hydrobromide; 150 mg of bupropion hydrochloride is equivalent to about 174 mg of the hydrobromide. To minimise agitation, anxiety, and insomnia that often occur at the start of therapy, and to reduce the risk of seizures, doses should be increased gradually; the total daily dose should be given in equally divided doses and the maximum recommended single and total daily doses should not be exceeded. Insomnia at the start of therapy may be minimised by avoiding bedtime doses. Patients with hepatic or renal impairment should be given reduced doses and monitored for toxic effects (see p. 410.3).

In the treatment of **depression** bupropion hydrochloride is given in initial doses of 100 mg twice daily increased, if necessary, after at least 3 days to 100 mg three times daily. In severe cases, if no improvement has occurred after several weeks of therapy, the dose may be increased further to a maximum of 150 mg three times daily. Bupropion hydrochloride is also available as a modified-release preparation given in an initial dose of 150 mg once daily in the morning increased, if necessary, after at least 3 days to 150 mg twice daily; in severe cases, the dose of the modified-release preparation may be increased further after several weeks to 200 mg twice daily. A modified-release preparation that is given once daily is also available; the maximum daily dose for this preparation is 450 mg as a single dose in the morning. Bupropion hydrobromide is also given as a modified-release preparation for once-daily use; doses are equivalent to those of the hydrochloride, when given once daily.

A modified-release preparation of bupropion hydrochloride is also licensed for the prevention of depression in patients with seasonal **affective disorder**; the maximum dose for this disorder is 300 mg once daily. A once-daily modified-release preparation of bupropion hydrobromide is also given in doses equivalent to those of the hydrochloride for this indication.

Bupropion hydrochloride is given as a modified-release preparation as an aid to **smoking cessation** in an initial dose of 150 mg once daily for 6 days, increasing to 150 mg twice daily on day 7. In the USA, the dose may be increased after 3 days. In the UK, the maximum recommended dose in the elderly, or in patients with predisposing risk factors for seizure (see Precautions, p. 412.1), is 150 mg daily. Treatment should be started about 1 to 2 weeks before the patient attempts to stop smoking, to allow steady-state blood concentrations of bupropion to be reached, and normally continues for 7 to 12 weeks; if there is no significant progress towards smoking abstinence by the seventh week, then therapy should be stopped. Use with nicotine transdermal patches may be warranted in some patients, although there is a risk of hypertension with such therapy (see Interactions, p. 412.2).

Administration in hepatic impairment. When used as an aid to *smoking cessation* in patients with mild to moderate hepatic impairment, bupropion hydrochloride should be given at a reduced frequency; UK licensed product information suggests an oral dose of 150 mg once daily. The use of bupropion hydrochloride in patients with severe hepatic cirrhosis is contra-indicated in the UK although doses of 150 mg every other day are permitted in the USA.

In the treatment of *depression*, a reduction in the frequency and/or the dose of bupropion should be considered in patients with mild to moderate impairment. In patients with severe hepatic cirrhosis the dose varies according to the preparation given. For modified-release bupropion hydrochloride (or its equivalent as the hydrobromide) the suggested maximum oral dose is 100 mg once daily or 150 mg every other day, while the maximum dose of immediate-release bupropion hydrochloride is 75 mg once daily. Similar recommendations apply to modified-release preparations when used for the prevention of depression in *seasonal affective disorder*.

Administration in renal impairment. When used as an aid to *smoking cessation* in patients with renal impairment, bupropion hydrochloride should be given at a reduced frequency; UK licensed product information suggests an oral dose of 150 mg once daily.

In the treatment of *depression*, a reduction in the frequency and/or the dose of bupropion should be considered.

Depression. As discussed on p. 398.1, there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effect profile. Bupropion has a different biochemical profile from both the tricyclics and the SSRIs; however, like the SSRIs, it may be safer in overdosage than the older tricyclics.

References.
1. Nieuwstraten CE, Dolovich LR. Bupropion versus selective serotonin-reuptake inhibitors for treatment of depression. *Ann Pharmacother* 2001; 35: 1608–13.
2. Weihs KL, *et al.* Continuation phase treatment with bupropion SR effectively decreases the risk for relapse of depression. *Biol Psychiatry* 2002; 51: 753–61.
3. Glod CA, *et al.* Open trial of bupropion SR in adolescent major depression. *J Child Adolesc Psychiatr Nurs* 2003; 16: 123–30.
4. Rush AJ, *et al.* The STAR*D Study Team. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. *N Engl J Med* 2006; 354: 1231–42.
5. Trivedi MH, *et al.* The STAR*D Study Team. Medication augmentation after the failure of SSRIs for depression. *N Engl J Med* 2006; 354: 1243–52.
6. Papakostas GI, *et al.* Comparing the rapidity of response during treatment of major depressive disorder with bupropion and the SSRIs: a pooled survival analysis of 7 double-blind, randomized clinical trials. *J Clin Psychiatry* 2007; 68: 1907–12.
7. Dhillon S, *et al.* Bupropion: a review of its use in the management of major depressive disorder. *Drugs* 2008; 68: 653–89.
8. Papakostas GI, *et al.* Efficacy of bupropion and the selective serotonin reuptake inhibitors in the treatment of major depressive disorder with high levels of anxiety (anxious depression): a pooled analysis of 10 studies. *J Clin Psychiatry* 2008; 69: 1287–92.

Hyperactivity. When drug therapy is indicated for attention deficit hyperactivity disorder (p. 2314.1) initial treatment is usually with a central stimulant. Antidepressants may be used for patients who fail to respond to, or who are intolerant of, central stimulants. Data from open and controlled studies involving small numbers of patients suggest that bupropion is effective in adults and children.[1,2]

1. Cantwell DP. ADHD through the life span: the role of bupropion in treatment. *J Clin Psychiatry* 1998; 59 (suppl 4): 92–4.
2. Wilens TE, *et al.* A controlled clinical trial of bupropion for attention deficit hyperactivity disorder in adults. *Am J Psychiatry* 2001; 158: 282–8.

Obesity. Bupropion is under investigation in the management of obesity. It is being studied as combination therapy with naltrexone (see Eating Disorders, p. 1565.3) or zonisamide (see Obesity, p. 561.1).

Smoking cessation. Bupropion is effective in the management of smoking cessation (p. 2570.2) and may be used as a first-line alternative to nicotine replacement therapy (NRT); its action is said to be independent of its antidepressant activity. Bupropion with NRT has also been used successfully although there is an increased risk of hypertension with this combination (see Interactions, p. 412.2).

References:
1. Holm KJ, Spencer CM. Bupropion: a review of its use in the management of smoking cessation. *Drugs* 2000; 59: 1007–1024.
2. Tashkin DP, *et al.* Smoking cessation in patients with chronic obstructive pulmonary disease: a double-blind, placebo-controlled, randomised trial. *Lancet* 2001; 357: 1571–5.
3. Gonzales DH, *et al.* Bupropion SR as an aid to smoking cessation in smokers treated previously with bupropion: a randomized placebo-controlled study. *Clin Pharmacol Ther* 2001; 69: 438–44.
4. Hays JT, *et al.* Sustained-release bupropion for pharmacologic relapse prevention after smoking cessation: a randomized, controlled trial. *Ann Intern Med* 2001; 135: 423–33.
5. Fagerström K, *et al.* Smoking cessation treatment with sustained-release bupropion: optimising approaches to management. A seminar-in-print. *Drugs* 2002; 62 (suppl 2): 1–70.
6. Hays JT, Ebbert JO. Bupropion sustained release for treatment of tobacco dependence. *Mayo Clin Proc* 2003; 78: 1020–4.
7. Tonnesen P, *et al.* A multicentre, randomized, double-blind, placebo-controlled, 1-year study of bupropion SR for smoking cessation. *J Intern Med* 2003; 254: 184–92.
8. Simon JA, *et al.* Bupropion for smoking cessation: a randomized trial. *Arch Intern Med* 2004; 164: 1797–1803.
9. Roddy E. ABC of smoking cessation: bupropion and other non-nicotine pharmacotherapies. *BMJ* 2004; 328: 509–11.
10. Paluck EC, *et al.* Outcomes of bupropion therapy for smoking cessation during routine clinical use. *Ann Pharmacother* 2006; 40: 185–90.
11. Hughes JR, *et al.* Antidepressants for smoking cessation. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 14/08/08).

Adverse Effects and Treatment

Agitation, anxiety, and insomnia often occur during the initial stages of bupropion therapy. Other relatively common adverse effects reported with bupropion include fever, dry mouth, headache or migraine, dizziness, urinary frequency, nausea and vomiting, constipation, tremor, sweating, and skin rashes. Hypersensitivity reactions, ranging from pruritus and urticaria to, less commonly, angioedema, dyspnoea, and anaphylactoid reactions, have occurred, as have symptoms suggestive of serum sickness. There have been rare reports of Stevens-Johnson syndrome and erythema multiforme. Tachycardia, chest pain, and hypertension (sometimes severe), or occasionally vasodilatation, orthostatic hypotension, palpitations, and syncope have been reported. Psychotic episodes, confusion, nightmares, impaired memory, dysgeusia, anorexia with weight loss, paraesthesia, tinnitus, and visual disturbances have also been reported.

Hyponatraemia, possibly due to inappropriate secretion of antidiuretic hormone, has been associated with the use of antidepressants, particularly in the elderly.

Seizures, which appear to be partially dose-related, may occur with bupropion and have been particularly notable in patients with anorexia nervosa or bulimia nervosa; the risk is also increased in patients with a history of seizure disorders or other predisposing factor. The manufacturers state that the overall incidence of seizure in patients receiving bupropion at recommended doses is about 0.1 to 0.4%.

Symptoms of overdosage include hallucinations, nausea and vomiting, tachycardia, loss of consciousness, and death (following massive overdose); seizures have occurred in about one-third of all bupropion overdose cases. Activated charcoal should be considered in adult patients who have taken more than 450 mg and in all children, if they present within 1 hour of ingestion and provided the airway can be protected; gastric lavage may also be used to decrease absorption. Treatment is supportive. Benzodiazepines may be tried for seizures. Diuresis, dialysis, and haemoperfusion are unlikely to be of benefit.

Incidence of adverse effects. Up to 24 July 2002 (the first 25 months of marketing), the UK CSM had received 7630 reports of suspected adverse reactions associated with the use of bupropion.[1] Of these reports, 60 were associated with a fatal outcome although in most cases underlying conditions could have been responsible. Cardiovascular and cerebrovascular disorders such as myocardial infarction and stroke were reported as the cause of death in 70% of cases. The CSM also commented that adverse reactions were mainly recognised ones and listed in the licensed product information.

In January 2005 the German pharmacovigilance network reviewed[2] 273 reports of adverse effects associated with bupropion, received between June 2000 and September 2004. The most frequent adverse effects were: psychiatric disorders (79.3%), including suicide attempts (17.6%), and tachycardia (11.15%), seizures (8.8%), and dyspnoea (8.8%). There were also 4 cases of pancreatitis and one of raised pancreatic enzyme activity three times greater than normal.

1. CSM/MCA. Zyban (bupropion hydrochloride) - safety update (issued 26th July, 2002). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON019524&RevisionSelectionMethod=LatestReleased (accessed 08/06/06)
2. Arzneimittelkommission der deutschen Ärzteschaft. Erhöhte Pankreasenzyme oder akute Pankreatitis unter Bupropion (Zyban) (aus der UAW-Datenbank; issued 10th January, 2005). Available at: http://www.akdae.de/Arzneimittelsicherheit/Bekanntgaben/Archiv/2005/800_20050110.html (accessed 28/07/10)

Effects on the cardiovascular system. Up to the end of December 2001 the national pharmacovigilance centre in the Netherlands had received 591 adverse reaction reports associated with the use of bupropion for smoking cessation since its marketing 2 years earlier;[1] of these, 45 concerned cardiac complaints such as palpitations (21 reports), arrhythmias (7 reports), myocardial infarction (3 reports), anginal pain (2 reports), and cardiac arrest (1 report). Twenty-two reports also mentioned chest pain or tightness, although these were considered to be of noncardiac origin. In another report a 43-year-old male suffered an acute myocardial infarction 2 weeks after starting bupropion for smoking cessation;[2] he had experienced central chest and arm pain 3 days before the infarction. The authors of the report said that up to 30 April 2001 the UK CSM had received 238 reports of chest pain and 134 reports of chest tightness associated with bupropion use.

1. de Graaf L, Diemont WL. Chest pain during use of bupropion as an aid in smoking cessation. *Br J Clin Pharmacol* 2003; 56: 451–2.
2. Patterson RN, Herity NA. Acute myocardial infarction following bupropion (Zyban). *Q J Med* 2002; 95: 58–9.

Effects on the cerebrovascular system. A 67-year-old male had paraesthesia, dizziness, tinnitus, confusion, and gait impairment after taking bupropion for smoking cessation.[1] Although a transient ischaemic attack was suspected symptoms resolved on stopping bupropion and recurred on rechallenge.

1. Humma LM, Swims MP. Bupropion mimics a transient ischemic attack. *Ann Pharmacother* 1999; 33: 305–7.

Effects on the pancreas. See under Incidence of Adverse Effects, above.

Effects on the skin. *Erythema multiforme* developed in a 31-year-old woman several weeks after starting modified-release bupropion for depression.[1] Symptoms resolved on drug withdrawal. In another report, 3 patients with controlled *psoriasis* had an exacerbation of their psoriatic symptoms after starting bupropion for smoking cessation.[2] All 3 patients required hospitalisation to control their symptoms. There have also been several reports of patients developing *generalised acute urticaria*;[3,4] systemic symptoms resembling serum sickness were also reported in 1 case[4] (see also Hypersensitivity, p. 411.3).

1. Lineberry TW, *et al.* Bupropion-induced erythema multiforme. *Mayo Clin Proc* 2001; 76: 664–6.
2. Cox NH, *et al.* Generalized pustular and erythrodermic psoriasis associated with bupropion treatment. *Br J Dermatol* 2002; 146: 1061–3.
3. Fays S, *et al.* Bupropion and generalized acute urticaria: eight cases. *Br J Dermatol* 2003; 148: 177–8.
4. Loo WJ, *et al.* Bupropion and generalized acute urticaria: a further case. *Br J Dermatol* 2003; 149: 660.

Extrapyramidal effects. A 44-year-old man had acute head and neck dystonia while taking buspirone and modified-release bupropion.[1] No recurrence was noted on rechallenge with buspirone although symptoms did develop on rechallenge with bupropion when the dose was increased from 150 mg once daily to 150 mg twice daily. In another case, a 42-year-old woman had gross involuntary movements of her torso, arms, and legs (diagnosed as ballism) 8 days after starting bupropion for smoking cessation;[2] the dose had been increased from 150 mg once daily to 150 mg twice daily on the fourth day. She recovered when bupropion was stopped and treatment with haloperidol and oxazepam was given.

1. Detweiler MB, Harpold GJ. Bupropion-induced acute dystonia. *Ann Pharmacother* 2002; 36: 251–4.
2. de Graaf L, *et al.* Ballism associated with bupropion use. *Ann Pharmacother* 2003; 37: 302–3.

Hypersensitivity. Eosinophilia has been reported[1] in a patient 12 days after bupropion was added to her existing treatment regimen of glibenclamide and tolmetin. The eosinophil count returned to normal after all medication was stopped. Bupropion appeared to be the causative drug.

Serum sickness or symptoms suggestive of serum sickness has also been associated with bupropion use.[2-5] In one case,[5] although the initial presentation resembled serum sickness, the patient went on to develop multisystem complications that included hepatitis, cholestasis, and myocarditis.

Angioedema affecting the feet, hands, arms, lower lip, and tongue occurred in a patient about 20 days after starting bupropion.[6] He also had a pruritic rash and urticaria, and developed watery diarrhoea and slight swelling and soreness of the knees and heals. The reaction was treated symptomatically and bupropion therapy was stopped.

See also Effects on the Skin, above.

1. Malesker MA, *et al.* Eosinophilia associated with bupropion. *Ann Pharmacother* 1995; 29: 867–8.
2. Yolles JC, *et al.* Serum sickness induced by bupropion. *Ann Pharmacother* 1999; 33: 931–3.
3. McCollom RA, *et al.* Bupropion-induced serum sickness-like reaction. *Ann Pharmacother* 2000; 34: 471–3.
4. Benson E. Bupropion-induced hypersensitivity reactions. *Med J Aust* 2001; 174: 650–1.
5. Bagshaw SM, *et al.* Drug-induced rash with eosinophilia and systemic symptoms syndrome with bupropion administration. *Ann Allergy Asthma Immunol* 2003; 90: 572–5.
6. Tackett AE, Smith KM. Bupropion-induced angioedema. *Am J Health-Syst Pharm* 2008; 65: 1627–30.

Overdosage. Unlike the tricyclic antidepressants, bupropion appears to lack any significant cardiovascular or antimuscarinic adverse effects when taken in overdose. In an early review[1] of 58 overdose cases involving immediate-release bupropion alone, the most common symptoms were sinus tachycardia, lethargy, tremor, and seizures; other effects included confusion, lightheadedness, hallucinations, paraesthesias, and vomiting. Most patients had minor effects or none at all. Similar symptoms have also been noted in reviews of overdose cases involving modified-release bupropion.[2,3] UK licensed prescribing information for bupropion also lists ECG changes such as conduction disturbances, arrhythmias, and tachycardia although a literature review[4] concluded that cardiotoxicity appeared to be rare with bupropion overdosage. Although rare, there have been fatalities after overdose; in some cases other drugs may have been involved.[3,5,6]

More recent case reports and reviews with modified-release preparations have highlighted that seizures are a particular feature of bupropion overdose.[2,3,7,8]

1. Spiller HA, *et al.* Bupropion overdose: a 3-year multi-center retrospective analysis. *Am J Emerg Med* 1994; 12: 43–5.
2. Balit CR, *et al.* Bupropion poisoning: a case series. *Med J Aust* 2003; 178: 61–3.
3. Shepherd G, *et al.* Intentional bupropion overdoses. *J Emerg Med* 2004; 27: 147–51.
4. Druteika D, Zed PJ. Cardiotoxicity following bupropion overdose. *Ann Pharmacother* 2002; 36: 1791–5.
5. Friel PN, *et al.* Three fatal drug overdoses involving bupropion. *J Anal Toxicol* 1993; 17: 436–8.
6. Harris CR, *et al.* Fatal bupropion overdose. *J Toxicol Clin Toxicol* 1997; 35: 321–4.
7. Bhattacharjee C, *et al.* Bupropion overdose: a potential problem with the new 'miracle' anti-smoking drug. *Int J Clin Pract* 2001; 55: 221–2.
8. Paoloni R, Szekely I. Sustained-release bupropion overdose: a new entity for Australian emergency departments. *Emerg Med (Fremantle)* 2002; 14: 109–12.

Precautions

Bupropion may induce seizures and consequently its use is contra-indicated in patients with epilepsy. It is also contra-indicated in patients with a history of anorexia nervosa or bulimia nervosa, as a higher incidence of seizures has been noted in such patients treated with bupropion, and in those undergoing abrupt withdrawal from alcohol or benzodiazepines. It should be used with extreme caution, if at all, in patients with a history of seizure disorders or other predisposing factors such as severe hepatic cirrhosis or a CNS tumour. The use of bupropion in patients with other risk factors for seizures (for example, alcohol abuse, a history of head trauma, diabetes, and drugs known to lower the seizure threshold) should only be undertaken when there are compelling clinical reasons.

Bupropion should be used with caution in patients with bipolar disorder or psychoses because of the risk of precipitating mania; use for smoking cessation in such patients may be contra-indicated. It should also be used cautiously in patients with a recent history of myocardial infarction or unstable heart disease, and in hepatic or renal impairment.

When bupropion is used for depression, patients should be closely monitored during early therapy until significant improvement occurs because suicide is an inherent risk in depressed patients. For further details, see under Depression, p. 398.1. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be observed when treating patients with other disorders.

As with other CNS-active drugs, the ability to perform tasks requiring motor or cognitive skills or judgement may be impaired by bupropion, and patients, if affected, should not drive or operate machinery.

Breast feeding. The American Academy of Pediatrics considers[1] that the effect of bupropion on nursing infants is unknown but may be of concern.

In a study[2] in 10 women, bupropion and its active metabolites were found in breast milk, and the average breast milk to plasma bupropion ratio was 2.8. The authors estimated that for a breast-fed infant the total exposure to bupropion and its metabolites would be 2% of the weight-normalised maternal bupropion dose, and that this should not be of concern for most infants. No adverse effects were noted in an infant breast fed twice daily by a mother who had breast-milk concentrations of bupropion higher than those in her plasma;[3] neither bupropion nor its metabolites were detected in the infant's plasma. Similar findings were noted in a study in 2 breast-fed infants whose mothers took bupropion for postpartum depression.[4] Bupropion was found in the urine of 1 of 4 breast-fed infants whose mothers were taking bupropion; the infant was reported to be nearly 6 weeks premature.[5] In these women, the average milk to serum ratio of bupropion was 1.30, and the infant dose estimated to be 5.7% of the maternal dose. In this report, too, the authors considered the risk of systemic exposure in the infants to be minimal. However, in another report, a 6-month-old infant had a seizure after being fed breast milk that had been expressed and stored 2 days earlier, after the infant's mother had taken a single dose of bupropion.[6] Before the seizure, the mother had taken 2 doses of bupropion and breast fed the infant several times with no adverse effects.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 24/11/05)
2. Haas JS, *et al.* Bupropion in breast milk: an exposure assessment for potential treatment to prevent post-partum tobacco use. *Tob Control* 2004; 13: 52–6.
3. Briggs GG, *et al.* Excretion of bupropion in breast milk. *Ann Pharmacother* 1993; 27: 431–3.
4. Baab SW, *et al.* Serum bupropion levels in 2 breastfeeding mother-infant pairs. *J Clin Psychiatry* 2002; 63: 910–11.
5. Davis MP, *et al.* Bupropion levels in breast milk for 4 mother-infant pairs: more answers to lingering questions. *J Clin Psychiatry* 2009; 70: 297–8.
6. Chaudron LH, Schoenecker CJ. Bupropion and breastfeeding: a case of a possible infant seizure. *J Clin Psychiatry* 2004; 65: 881–2.

Children. Bupropion has not been studied for the treatment of depression in adolescents and children; consequently its use in patients under 18 years of age, regardless of indication, is not recommended. In addition, other antidepressants have been shown to increase the risk of suicidal thoughts and behaviour in these patients (see Effects on Mental State, under Fluoxetine, p. 422.2).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies bupropion as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Pregnancy. The safety of bupropion in pregnancy has not been established. In a study of 136 women who took bupropion for either depression or smoking cessation in at least the first trimester of pregnancy, there were 105 live births, 20 spontaneous abortions, 10 therapeutic abortions, 1 still-birth, and 1 neonatal death; no major congenital malformations were reported.[1] Compared with a control group not exposed to teratogens, the rate of spontaneous abortions was significantly higher in the bupropion group when both indications were considered; however, there was no difference in the rate when women taking bupropion for depression were compared with this control group and another control group of women taking other antidepressants.

Complications at birth requiring prolonged hospitalisation, breathing support, and tube feeding have been reported with some of the newer antidepressants such as bupropion.[2] Other reported symptoms have included seizures, muscle rigidity, jitteriness, and prolonged crying. It is unknown whether such symptoms represent a direct toxicity of bupropion or a possible withdrawal syndrome.

1. Chun-Fai-Chan B, *et al.* Pregnancy outcome of women exposed to bupropion during pregnancy: a prospective comparative study. *Am J Obstet Gynecol* 2005; 192: 932–6.
2. Health Canada. Health Canada advises of potential adverse effects of SSRIs and other anti-depressants on newborns (issued 9th August 2004). Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2004/2004_44-eng.php (accessed 14/08/08)

Interactions

Bupropion should not be given with or within 14 days of stopping an MAOI; however, no treatment-free period is necessary after stopping a reversible inhibitor of monoamine oxidase type A (RIMA) and starting bupropion.

The use of alcohol with bupropion should be minimised or avoided completely because it may alter the seizure threshold. Similarly, extreme caution is needed if other drugs that lower the seizure threshold, such as other antidepressants, antimalarials, antipsychotics, sedating antihistamines, quinolones, tramadol, theophylline, or systemic corticosteroids are used with bupropion. In the UK, where it is licensed as a modified-release product for smoking cessation, a maximum dose of 150 mg daily is recommended if patients are also taking such drugs.

Use of nicotine transdermal patches with bupropion has been associated with hypertension, and patients using both should therefore have their blood pressure monitored.

Caution has been advised in patients receiving either amantadine or levodopa with bupropion because of reports of a higher incidence of adverse effects in patients receiving these combinations.

Animal studies have indicated that bupropion may induce drug-metabolising enzymes and pharmacokinetic interactions with other drugs are therefore a possibility. Bupropion is itself metabolised by hepatic enzyme systems and drugs known to affect such systems may interact with bupropion. For example carbamazepine, phenobarbital, or phenytoin may induce the metabolism of bupropion while other drugs such as cimetidine or valproate may inhibit its metabolism. *In-vitro* studies have shown that bupropion is metabolised by the cytochrome P450 isoenzyme CYP2B6. Consequently interactions may occur between bupropion and drugs that affect this isoenzyme, for example orphenadrine, cyclophosphamide, and ifosfamide.

In-vitro studies have also shown that bupropion is also an inhibitor of the isoenzyme CYP2D6; caution should be exercised when it is given with drugs metabolised by this isoenzyme and they should be started at the lower end of their dose range. Such drugs include some antidepressants, antipsychotics, beta blockers, and type Ic antiarrhythmics.

Antiepileptics. Plasma-bupropion concentrations became undetectable in 2 patients who were also receiving *carbamazepine*; plasma concentrations of hydroxybupropion, an active metabolite of bupropion, were high.[1]

1. Popli AP, *et al.* Bupropion and anticonvulsant drug interactions. *Ann Clin Psychiatry* 1995; 7: 99–101.

Antivirals. There is some evidence from study *in vitro* that the antivirals *efavirenz*, *nelfinavir*, and *ritonavir* can inhibit the cytochrome P450 isoenzyme CYP2B6.[1] However, evidence of clinically significant interaction with bupropion is lacking: a small case series of 10 patients who took bupropion with low-dose ritonavir (100 mg twice daily), or efavirenz or nelfinavir, did not note any episodes of seizures.[2] A study[3] in 7 healthy male subjects also found that 2 days of low-dose ritonavir (200 mg twice daily) had little impact on the pharmacokinetics of a single bupropion dose.

In contrast, UK licensed product information for bupropion states that studies in healthy subjects found that ritonavir (100 mg or 600 mg, twice daily) reduced the exposure to bupropion and its major metabolites in a dose-dependent manner, possibly by inducing its metabolism. In another study[4] in healthy subjects, the plasma concentrations and AUC of bupropion and its active metabolite hydroxybupropion, from a single dose of bupropion, were reduced by about 50% after 14 days of a *lopinavir/ritonavir* combination (400 mg/100 mg twice daily). This effect was attributed to induction of CYP2B6 and UDP-glucuronosyltransferase by the HIV-protease inhibitor combination. In discussing the contrasting results that have been reported, the authors suggested that the higher ritonavir concentrations achieved *in-vitro* had an inhibitory effect, compared with the inducing effect of lower steady-state concentrations achieved *in-vivo*. In practice, UK licensed product information for bupropion suggests that the dose may need to be increased in patients also taking ritonavir, but that the maximum dose of bupropion should not be exceeded.

1. Hesse LM, *et al.* Ritonavir, efavirenz, and nelfinavir inhibit CYP2B6 activity in vitro: potential drug interactions with bupropion. *Drug Metab Dispos* 2001; 29: 100–102.
2. Park-Wyllie LY, Antoniou T. Concurrent use of bupropion with CYP2B6 inhibitors, nelfinavir, ritonavir and efavirenz: a case series. *AIDS* 2003; 17: 638–40.
3. Hesse LM, *et al.* Ritonavir has minimal impact on the pharmacokinetic disposition of a single dose of bupropion administered to human volunteers. *J Clin Pharmacol* 2006; 46: 567–76.
4. Hogeland GW, *et al.* Lopinavir/ritonavir reduces bupropion plasma concentrations in healthy subjects. *Clin Pharmacol Ther* 2007; 81: 69–75.

Histamine H_2-antagonists. A randomised controlled study in 24 subjects found that *cimetidine* had no effect on the pharmacokinetics of modified-release bupropion or its active metabolite, hydroxybupropion.[1]

1. Kustra R, *et al.* Lack of effect of cimetidine on the pharmacokinetics of sustained-release bupropion. *J Clin Pharmacol* 1999; 39: 1184–8.

Pharmacokinetics

Bupropion is well absorbed from the gastrointestinal tract but may undergo extensive first-pass metabolism. Several metabolites of bupropion are pharmacologically active and have longer half-lives, and achieve higher plasma concentrations, than the parent compound. Hydroxybupropion is the major metabolite, produced by the metabolism of bupropion by the cytochrome P450 isoenzyme CYP2B6; in *animal* studies hydroxybupropion was one-half as potent as bupropion. Threohydrobupropion and erythrohydrobupropion are produced by reduction and are about one-fifth the potency of the parent compound. Bupropion is 80% or more bound to plasma proteins. The terminal plasma half-life of immediate-release bupropion is about 14 hours; the terminal plasma half-life of modified-release bupropion is about 20 hours. The metabolites of bupropion are excreted mainly in the urine; less than 1% of the parent drug is excreted unchanged. Bupropion and its metabolites cross the placenta and are distributed into breast milk.

References.

1. Sweet RA, *et al.* Pharmacokinetics of single- and multiple-dose bupropion in elderly patients with depression. *J Clin Pharmacol* 1995; 35: 876–84.

Smoking. No clinically significant differences were seen between the pharmacokinetics of bupropion or its metabolites in cigarette smokers and non-smokers.[1]

1. Hsyu P-H, *et al.* Pharmacokinetics of bupropion and its metabolites in cigarette smokers versus nonsmokers. *J Clin Pharmacol* 1997; 37: 737–43.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Lung; Odranal†; Wellbutrin; ***Austral.***: Clorprax†; Prexaton; Zyban; ***Austria***: Elontril; Wellbutrin; Zyban; ***Belg.***: Wellbutrin; Zyban; ***Braz.***: Bup; Wellbutrin; Zetron; Zyban; ***Canad.***: Wellbutrin; Zyban; ***Chile***: Buxon; Wellbutrin; ***China***: Le Fu Ting (乐孚亭); Yue Ting (悦亭); *Cz.*: Elontril; Wellbutrin; Zyban†; ***Denm.***: Wellbutrin; Zyban; ***Fin.***: Voxra; Zyban; ***Fr.***: Zyban; ***Ger.***: Elontril; Zyban; ***Gr.***: Wellbutrin; Zyban; ***Hong Kong***: Wellbutrin; Zyban; ***Hung.***: Elontril; Wellbutrin; ***India***: Bupep; Bupisure; Bupron; Ession; Nicotex; Zyban; ***Irl.***: Zyban; ***Israel***: Wellbutrin; Zyban; ***Ital.***: Elontril; Wellbutrin; Zyban; ***Malaysia***: Zyban; ***Mex.***: Butrew; Wellbutrin; ***Neth.***: Elontril; Quomem; Wellbutrin; Zyban; Zyntabac; ***Norw.***: Wellbutrin; Zyban; ***NZ***: Zyban; ***Pol.***: Wellbutrin; Zyban; ***Port.***: Elontril; Wellbutrin; Zyban; Zyntabac†; ***S.Afr.***: Wellbutrin; Zyban; ***Singapore***: Wellbutrin; Zyban†; ***Spain***: Elontril; Quomem†; Zyntabac; ***Swed.***: Voxra; Zyban; ***Switz.***: Wellbutrin; Zyban; ***Thal.***: Quomem; Wellbutrin; ***Turk.***: Wellbutrin; Zyban; ***UK***: Zyban; ***USA***: Aplenzin; Budeprion†; Buproban; Forfivo; Wellbutrin; Zyban; ***Venez.***: Wellbutrin.

Pharmacopoeial Preparations

USP 36: Bupropion Hydrochloride Extended-Release Tablets; Bupropion Hydrochloride Tablets.

Citalopram *(BAN, rINN)*

Citalopramum; Lu-10-171; Sitalopraami; Циталопрам.
1-(3-Dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile.
$C_{20}H_{21}FN_2O$=324.4
CAS — 59729-33-8.
ATC — N06AB04.
ATC Vet — QN06AB04.
UNII — 0DHU588D6V.

Citalopram Hydrobromide
(BANM, USAN, rINNM)

Citalopram, Bromhydrate de; Citalopram, hidrobromuro de; Citalopramhydrobromid; Citalopraami Hydrobromidum; Hidrobromuro de citalopram; Lu-10-1718; Nitalapram Hydrobromide; Sitalopram Hidrobromür; Циталопрама Гидробромид.
$C_{20}H_{21}FN_2O,HBr$=405.3
CAS — 59729-32-7.
UNII — J1E9D14F36.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Citalopram Hydrobromide). A white or almost white, crystalline powder. Sparingly soluble in water and in dehydrated alcohol.

USP 36: (Citalopram Hydrobromide). A white to almost white, crystalline powder. Sparingly soluble in water and in dehydrated alcohol; soluble in alcohol. A 0.5% solution in water has a pH of 5.5 to 6.5.

Citalopram Hydrochloride *(BANM, rINNM)*

Citalopram, Chlorhydrate de; Citalopram, hidrocloruro de; Citalopramhydrochlorid; Citalopraami hydrochloridum; Hidrocloruro de citalopram; Циталопрама Гидрохлорид.
$C_{20}H_{21}FN_2O,HCl$=360.9
UNII — 4DY48G26JY.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Citalopram Hydrochloride). A white or almost white, crystalline powder. Very soluble in water; freely soluble in dehydrated alcohol.

Uses and Administration

Citalopram, a phthalane derivative, is an SSRI with actions and uses similar to those of fluoxetine (p. 419.1). Citalopram is given orally as the hydrobromide or hydrochloride, usually as a single daily dose. Doses are expressed in terms of citalopram; citalopram hydrobromide 25.0 mg and citalopram hydrochloride 22.3 mg are each equivalent to about 20.0 mg of citalopram.

In the treatment of **depression**, the initial oral dose (given as tablets or a liquid) is the equivalent of 20 mg daily. After at least one week, the dose may be increased to a maximum of 40 mg daily. In some countries citalopram is also given as the hydrochloride in the form of concentrated oral drops containing the equivalent of 40 mg/mL of citalopram. The bioavailability of the drops is about 25% greater than that of the tablets and consequently daily doses appear to be lower: a 20-mg tablet dose is equivalent to a 16-mg (8 drops) dose of the concentrate. Citalopram hydrochloride has also been given by intravenous infusion in doses of 20 to 40 mg when the oral route is impracticable.

In the treatment of **panic disorder** with or without agoraphobia, the initial oral dose is 10 mg (or the equivalent as the concentrate) daily increasing to 20 mg daily after one week. The dose may be increased thereafter as required up to a maximum of 40 mg daily. In some countries citalopram is also used in the treatment of **obsessive-compulsive disorder** in doses similar to those used in depression (see above).

Elderly patients should be given half the recommended adult doses, up to a maximum of 20 mg (or their equivalents as the concentrate) daily. In addition, patients who are poor CYP2C19 metabolisers should be given an initial dose of 10 mg daily for the first 2 weeks of treatment, increasing to a maximum of 20 mg daily thereafter, according to response. Similarly, a maximum dose of 20 mg daily is recommended in those also taking CYP2C19 inhibitors. For dosage in hepatic and renal impairment, see p. 413.2, and for doses used in children, see p. 413.2.

Citalopram should be withdrawn gradually to reduce the risk of withdrawal symptoms (see also Withdrawal, under Precautions of Fluoxetine, p. 425.3).

The *S*-enantiomer of citalopram, escitalopram (p. 418.2) is given for the treatment of depression and some anxiety disorders.

Reviews.

1. Milne RJ, Goa KL. Citalopram: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in depressive illness. *Drugs* 1991; 41: 450–77.

Administration in children. There are concerns about the use of SSRIs in children (see Effects on Mental State, under Adverse Effects of Fluoxetine, p. 422.2) and citalopram therapy is unlicensed in those under 18 years of age. Nonetheless, the *BNFC* suggests that it may be used by specialists for the treatment of major depression in those aged 12 years and over. The initial oral dose is 10 mg daily, increased if necessary to 20 mg daily over 2 to 4 weeks; the maximum dose is 40 mg daily. It may also be given in the form of concentrated oral drops, see Uses and Administration, above for details of equivalence and bioavailability.

Administration in hepatic or renal impairment. Citalopram should be used with caution in patients with hepatic impairment, particularly those with severe impairment. An initial oral dose of 10 mg (or the equivalent as the concentrate) daily is recommended for the first 2 weeks of treatment in those with mild or moderate impairment; thereafter, the dose may be increased, according to response, to a maximum of 20 mg daily.

There is no need for dose adjustment in mild to moderate renal impairment although information is lacking on appropriate dosage in severe impairment.

Anxiety disorders. Citalopram has been given in anxiety disorders (p. 1028.1) including panic disorder (p. 1029.1), obsessive-compulsive disorder (p. 1028.2), post-traumatic stress disorder (p. 1029.2), and social anxiety disorder (see under Phobic Disorders, p. 1029.1).

References.

1. Bouwer C, Stein DJ. Use of the selective serotonin reuptake inhibitor citalopram in the treatment of generalized social phobia. *J Affect Disord* 1998; 49: 79–82.
2. Lepola UM, *et al.* A controlled, prospective, 1-year trial of citalopram in the treatment of panic disorder. *J Clin Psychiatry* 1998; 59: 528–34.
3. Seedat S, *et al.* Open trial of citalopram in adults with post-traumatic stress disorder. *Int J Neuropsychopharmacol* 2000; 3: 135–40.
4. Montgomery SA, *et al.* Citalopram 20 mg, 40 mg and 60 mg are all effective and well tolerated compared with placebo in obsessive-compulsive disorder. *Int Clin Psychopharmacol* 2001; 16: 75–86.
5. Perna G, *et al.* A comparison of citalopram and paroxetine in the treatment of panic disorder: a randomized, single-blind study. *Pharmacopsychiatry* 2001; 34: 85–90.
6. Marazziti D, *et al.* Citalopram in refractory obsessive-compulsive disorder: an open study. *Int Clin Psychopharmacol* 2001; 16: 215–19.
7. Atmaca M, *et al.* Efficacy of citalopram and moclobemide in patients with social phobia: some preliminary findings. *Hum Psychopharmacol* 2002; 17: 401–5.
8. Varia I, Rauscher F. Treatment of generalized anxiety disorder with citalopram. *Int Clin Psychopharmacol* 2002; 17: 103–7.
9. Mukaddes NM, *et al.* Citalopram treatment of children and adolescents with obsessive-compulsive disorder: a preliminary report. *Psychiatry Clin Neurosci* 2003; 57: 405–8.
10. Lenze EJ, *et al.* Efficacy and tolerability of citalopram in the treatment of late-life anxiety disorders: results from an 8-week randomized, placebo-controlled trial. *Am J Psychiatry* 2005; 162: 146–50.

Depression. As discussed on p. 398.1, there is very little difference in efficacy between the different groups of antidepressant drugs. SSRIs such as citalopram are widely used as an alternative to the older tricyclics as they have fewer adverse effects and are safer in overdosage.

References.

1. Montgomery SA, *et al.* The optimal dosing regimen for citalopram—a meta-analysis of nine placebo-controlled studies. *Int Clin Psychopharmacol* 1994; 9 (suppl 1): 35–40.
2. Keller MB. Citalopram therapy for depression: a review of 10 years of European experience and data from US trials. *J Clin Psychiatry* 2000; 61: 896–908.
3. Parker NG, Brown CS. Citalopram in the treatment of depression. *Ann Pharmacother* 2000; 34: 761–71.
4. Guelfi JD, *et al.* Efficacy of intravenous citalopram compared with oral citalopram for severe depression. Safety and efficacy data from a double-blind, double-dummy trial. *J Affect Disord* 2000; 58: 201–9.
5. Hochstrasser B, *et al.* Prophylactic effect of citalopram in unipolar, recurrent depression: placebo-controlled study of maintenance therapy. *Br J Psychiatry* 2001; 178: 304–10.
6. Klysner R, *et al.* Efficacy of citalopram in the prevention of recurrent depression in elderly patients: placebo-controlled study of maintenance therapy. *Br J Psychiatry* 2002; 181: 29–35.
7. Roose SP, *et al.* Antidepressant pharmacotherapy in the treatment of depression in the very old: a randomized, placebo-controlled trial. *Am J Psychiatry* 2004; 161: 2050–9.
8. Trivedi MH, *et al.* The STAR*D Study Team. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry* 2006; 163: 28–40.
9. McGrath PJ, *et al.* Response to a selective serotonin reuptake inhibitor (citalopram) in major depressive disorder with melancholic features: a STAR*D report. *J Clin Psychiatry* 2008; 69: 1847–55.

Pathological crying or laughing. Inappropriate or uncontrolled crying or laughing can occur in patients with lesions in certain areas of the brain. Attempts at treatment have mostly been with antidepressant drugs, including SSRIs. Favourable results with citalopram have been reported in a double-blind placebo-controlled study[1] and in case reports.[2-4]

1. Andersen G, *et al.* Citalopram for post-stroke pathological crying. *Lancet* 1993; 342: 837–9.
2. Andersen G, *et al.* Citalopram treatment of traumatic brain damage in a 6-year-old boy. *J Neurotrauma* 1999; 16: 341–4.
3. Kaschka WP, *et al.* Treatment of pathological crying with citalopram. *Pharmacopsychiatry* 2001; 34: 254–8.
4. Giacobbe P, Flint A. Pharmacological treatment of post-stroke pathological laughing and crying. *J Psychiatry Neurosci* 2007; 32: 384.

Schizophrenia. The treatment of schizophrenia consists mainly of a combination of social therapy and antipsychotic drugs (see p. 1031.3). Like other antidepressants, citalopram has been examined for its potential value as an adjuvant in schizophrenia.[1-4] In a preliminary placebo-controlled study[1] in 15 patients with chronic schizophrenia who had signs of impulsive aggression, adding citalopram to existing antipsychotic therapy significantly reduced the frequency, but not the average severity, of aggressive incidents. In a subsequent study involving 90 patients, citalopram appeared to improve subjective well-being but had no clear effect on psychopathological symptoms.[2]

1. Vartiainen H, *et al.* Citalopram, a selective serotonin reuptake inhibitor, in the treatment of aggression in schizophrenia. *Acta Psychiatr Scand* 1995; 91: 348–51.
2. Salokangas RKR, *et al.* Citalopram as an adjuvant in chronic schizophrenia: a double-blind placebo-controlled study. *Acta Psychiatr Scand* 1996; 94: 175–80.
3. Talminen TJ, *et al.* Citalopram as an adjuvant in schizophrenia: further evidence for a serotonergic dimension in schizophrenia. *Int Clin Psychopharmacol* 1997; 12: 31–5.
4. Kasckow JW, *et al.* Citalopram augmentation of antipsychotic treatment in older schizophrenia patients. *Int J Geriatr Psychiatry* 2001; 16: 1163–7.

Sexual dysfunction. SSRIs have been tried in the treatment of premature ejaculation, but results with citalopram have been conflicting, see under Fluoxetine, p. 421.1.

Adverse Effects, Treatment, and Precautions

As for SSRIs in general (see Fluoxetine, p. 421.1) although increased appetite and weight gain have also been reported with citalopram.

Citalopram may cause dose-dependent prolongation of the QT interval and torsade de pointes has been reported. It should be used with caution, if at all, in patients at risk of developing such arrhythmias including those with congenital QT prolongation, congestive heart failure, bradycardia, or a predisposition to hypokalaemia or hypomagnesaemia. ECG and/or electrolyte monitoring is recommended in these patients; citalopram should be stopped in those with a persistent QTc of greater than 500 milliseconds. Use with other drugs that may prolong the QT interval or inhibit the metabolism of citalopram may also increase the risk (see Interactions, p. 413.3).

Citalopram may be more cardiotoxic in overdosage than other SSRIs; for further details, see Overdosage, under Fluoxetine, p. 423.3.

Breast feeding. For comments on the use of SSRIs in breast feeding patients, see under Precautions for Fluoxetine, p. 424.2.

Children. SSRIs are associated with an increased risk of potentially suicidal behaviour when used for the treatment of depression in children and adolescents under 18 years old; for further details, see under Effects on Mental State in Fluoxetine, p. 422.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies citalopram as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

For interactions associated with SSRIs, see Fluoxetine, p. 426.1.

The use of citalopram with other drugs that may prolong the QT interval is contra-indicated, and a maximum oral dose of citalopram 20 mg daily is recommended in patients also taking inhibitors of the cytochrome P450 isoenzyme CYP2C19.

Pharmacokinetics

Citalopram is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur 2 to 4 hours after oral doses. Citalopram is widely distributed throughout the body; protein binding is less than 80%. Citalopram is metabolised by demethylation, deamination, and oxidation to active and inactive metabolites. The demethylation of citalopram to one of its active metabolites, demethylcitalopram, involves the cytochrome P450 isoenzymes CYP3A4 and CYP2C19; the metabolism of citalopram is also partly dependent on CYP2D6. Didemethylcitalopram has also been identified as a metabolite of citalopram. The elimination half-life of citalopram is reported to be about 36 hours. It is excreted mainly via the liver (85%) with the remainder via the kidneys. About 12% of the daily dose is excreted in the urine as unchanged drug. Citalopram is distributed into breast milk in very low concentrations (see Breast Feeding under Precautions in Fluoxetine, p. 424.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Humorap; Psiconor; Seropram; Zentius; ***Austral.***: Celapram; Celica; Ciazil; Cipramil; Citalo; Talam; Talohexal†; ***Austria***: Citalostad; Eostar†; Pram; Seropram; ***Belg.***: Cipramil; ***Braz.***: Alcytam; Celapram; Cipramil; Citaforin; Citagran; Citaprass; Citta; Denyl; Maxapran; Procimax; Tensiopax; Zoxipan; Zycitapran; ***Canad.***: Celexa; CTP; Ran-Citalo; ***Chile***: Actipram; Cimal; Cipramil; Cortran; Finap†; Pramcil; Prisma; Setronil; Temperax; Zebrak; Zentius; ***China***: Cipramil (喜普妙); Duo Fo (多弗); Te Lin Na (特林那); Wang You (望悠); Yi Tai Na (一泰纳); YiTeAn (易特安); ***Cz.***: Apo-Cital; Cerotor; Cipram†; Cita; Citalec; Citalon; Citaratio†; Dalsan; Pram; Seropram; Zyloram; ***Denm.***: Akarin†; Cipramil; Citacip; Citaham†; Citalonte; Seropram; ***Fin.***: Cipramil; Sepram; ***Fr.***: Seropram; ***Ger.***: Cipramil; CitaLich†; Citalo-Q†; Citalogamma†; Citalon; Futuril†; Serital†; ***Gr.***: A-Depress-Therapy; Acelopram; Adeprenal; Alepram; Atinorm; Belmazol; Bibien†; Bivien; Celius; Cilopress; Cinapen; Cipram; Cipraned; Citalgert; Citaloprol; Citopram; Decilop; Depretal; Ecloram; Erlicon; Espinal; Etapiam; Eumitol; Exenadil; Galopran; Goldamit; Kylipram; Lodeprem; Lopracil; Lopraxer; Loptar; Malicon; Pralotam; Pramital; Prefucet; Pricital; Renevil; Ropramin; Selon; Seproc; Seretover; Serocel; Seropram; Seror; Siloam; Sitaleau; Sotovon; Talopram; Talopron; Taloram; Talosin; Taprocil; Tasonade; Unstress; Varom; Verus; Vesema; Xadorek; Zanipram; Zeclicid; ***Hong Kong***: Arpolax; Cipram; Cital; Talam†; ***Hung.***: Citagen; Citalodep; Citalon†; Citalowin†; Citapram; Dalsan; Oropram†; Seropram; Serotor; Zyloram; ***India***: C-Pram; C-Talo; Celepra; Celica; Citadep; Citalomine; Citalop; Citara; Citola; Citopam; Cytop; Feliz; Lopram; Madam; Nevdep; Palocit; ***Indon.***: Cipram†; ***Irl.***: Bellcital; Cipager; Cipralam†; Cipramil; Ciprapine; Ciprotan; Citrol; ***Israel***: Cipramil; Recital; ***Ital.***: Elopram; Felipram; Feliximir; Frimaind; Kaidor; Lampopram†; Marpram; Percitale; Pramexyl†; Return; Ricap; Seropram; Sintopram; Verisan; ***Malaysia***: Cipram; Cital†; ***Mex.***: Cibrom; Citox; Norecsero; Prepram; Seropram; Xylorane†; ***Neth.***: Cipramil; Ciprapine†; Lontax†; ***Norw.***: Cipramil; ***NZ***: Celapram; Cipramil; ***Philipp.***: Feliz; Lupram; Tazen; ***Pol.***: Aurex; Cilon†; Cilonast; Cipramil; Citabax; Cital; Citaratio; Citaxin†; Citronil; Oropram; ***Port.***: Citadep†; Zitolex; ***Rus.***: Cipramil (Ципрамил); Citalift (Циталифт); Citalon (Циталон); Citalorin (Циталорин); Citol (Цитол); Humorap (Умоpап); Opra (Опра); Pram (Прам); Sedopram (Седопрам); Siozam (Сиозам); ***S.Afr.***: Adco-Talomil; Cilate; Cilift; Ciloram; Cipramil; CitaloHexal; Depramil; ***Singapore***: Cipram; ***Spain***: Calton; Citalvir; Genprol†; Prisdal; Relapaz; Seregra; Seropram; Somac†; ***Swed.***: Cipramil; ***Switz.***: Claropram; Seropram; ***Thai.***: Cipram†; ***Turk.***: Atopran; Cipram; Citara; Citexam; Citol; Citolap; Citolixin; Citrex; Copsam; Eslopram; Laira; Pasilopram; Relaxol; Sintab; Vodelax; ***UK***: Cipramil; ***Ukr.***: Cipramil (Ципрамил); Cita Sandoz (Цита Сандоз); ***USA***: Celexa; ***Venez.***: Seropram.

Pharmacopoeial Preparations

USP 36: Citalopram Oral Solution; Citalopram Tablets.

Clomipramine Hydrochloride

(BANM, USAN, rINNM)

Chlorimipramine Hydrochloride; Clomipramina, hidrocloruro de; Clomipramine, chlorhydrate de; Clomipraminhydrochlorid; Clomipramini Hydrochloridum; G-34586; Hidrocloruro de clomipramina; Hidrocloruro de monoclorimipramina; Klomipramiinihydrokloridi; Klomipramin Hidroklorür; Klomipramin hydrochlorid; Klomipramin-hidroklorid; Klomipraminhydroklorid; Klomipramino hidrochloridas; Monochlorimipramine Hydrochloride; Кломипрамина Гидрохлорид.

3-(3-Chloro-10,11-dihydro-5*H*-dibenz[*b,f*]azepin-5-yl)propyldimethylamine hydrochloride.

$C_{19}H_{23}ClN_2,HCl=351.3$

CAS — 303-49-1 (clomipramine); 17321-77-6 (clomipramine hydrochloride).

ATC — N06AA04.

ATC Vet — QN06AA04.

UNII — 2LXW0L6GWJ.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Clomipramine Hydrochloride). A white or slightly yellow, slightly hygroscopic, crystalline powder. Freely soluble in water and in dichloromethane; soluble in alcohol. A 10% solution in water has a pH of 3.5 to 5.0. Protect from light.

USP 36: (Clomipramine Hydrochloride). A white to faintly yellow crystalline powder. Very soluble in water. pH of a 10% solution in water is between 3.5 and 5.0.

Uses and Administration

Clomipramine is a dibenzazepine tricyclic antidepressant with actions and uses similar to those of amitriptyline (p. 401.1). It has antimuscarinic properties and is also a potent serotonin reuptake inhibitor. Clomipramine is one of the more sedating tricyclics. It is used as the hydrochloride.

In the treatment of **depression**, clomipramine hydrochloride is given in oral doses of 10 mg daily initially, increasing gradually to 30 to 150 mg daily if required; up to 250 mg daily or higher may be given in severe cases or in patients who also have obsessional or phobic disorders. A suggested initial dose for the elderly is 10 mg daily increasing gradually over 10 days to 30 to 75 mg daily if required. Clomipramine may be given in divided doses throughout the day, but since it has a prolonged half-life, once-daily dosage regimens are also suitable, usually given at night.

In the treatment of **obsessive-compulsive disorder and phobias**, clomipramine hydrochloride may be given in an initial oral dose of 25 mg daily (or 10 mg daily for elderly patients or those sensitive to tricyclics). The dose may be increased gradually over two weeks to 100 to 150 mg daily; in some countries, maximum doses of 250 mg daily have been used. Similar doses have also been used in the management of **panic disorder**. Clomipramine hydrochloride may also be used for the treatment of obsessive-compulsive disorder in children and adolescents aged 10 years and over (see p. 414.2 for doses).

Clomipramine has been given for depression or obsessive-compulsive disorder by the intramuscular or intravenous routes if giving it orally is impracticable or inadvisable. The initial dose of clomipramine hydrochloride by intramuscular injection is 25 to 50 mg daily, increasing to a maximum of 100 to 150 mg daily; oral dosage should be substituted as soon as possible. Clomipramine hydrochloride may also be given by intravenous infusion in doses of 50 to 75 mg daily diluted in 250 to 500 mL of sodium chloride 0.9% or glucose 5% and infused over 1.5 to 3 hours. When a satisfactory response to parenteral doses has been obtained oral therapy should be substituted, initially giving double the parenteral dose by mouth and subsequently adjusting if necessary. Patients must be carefully supervised during intravenous infusion of clomipramine hydrochloride and the blood pressure carefully monitored owing to the risk of hypotension.

In the adjunctive treatment of **cataplexy associated with narcolepsy**, clomipramine hydrochloride is given in an initial oral dose of 10 mg daily and gradually increased until a satisfactory response occurs, usually within the range of 10 to 75 mg daily.

For all indications, an oral modified-release preparation, containing clomipramine hydrochloride 75 mg, may be given once daily for maintenance.

Clomipramine has also been used in the management of **nocturnal enuresis** in children (see p. 414.2 for doses).

Clomipramine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Administration in children. In the UK, the use of clomipramine in children under 18 years is not recommended in the treatment of depressive states, phobias, or cataplexy associated with narcolepsy. However, in some countries clomipramine hydrochloride is licensed for the treatment of **obsessive-compulsive disorder** in children and adolescents aged 10 years and over. Initial oral doses are 25 mg daily, increased gradually during the first 2 weeks to a maximum daily dose of 3 mg/kg or 100 mg, whichever is smaller, and given in divided doses. Further increases are permitted, over several weeks to a maximum daily dose of 3 mg/kg or 200 mg, whichever is smaller. Once titration has been achieved the dose may be given as a single dose at bedtime.

Clomipramine hydrochloride is also licensed for oral use in the management of **nocturnal enuresis** in some countries (for a discussion of tricyclic use in nocturnal enuresis see Micturition Disorders under Amitriptyline, p. 402.1). The age ranges and licensed doses vary somewhat from country to country, however. For example, in *France*, use is licensed in children over 6 years of age, at a daily dose of 10 to 30 mg, or 0.5 to 1 mg/kg, whereas in *Austria* and *Switzerland* the licensed dose is: 6 to 8 years, 20 to 30 mg; 9 to 12 years, 25 to 50 mg; over 12 years, 25 to 75 mg.

Anxiety disorders. Tricyclic antidepressants that inhibit serotonin reuptake, such as clomipramine and imipramine, have been given in the management of anxiety disorders (p. 1028.1) including obsessive-compulsive disorder (p. 1028.2), panic disorder (p. 1029.1), post-traumatic stress disorder (p. 1029.2), and trichotillomania.

References.

1. Swedo SE, *et al.* A double-blind comparison of clomipramine and desipramine in the treatment of trichotillomania (hair pulling). *N Engl J Med* 1989; **321:** 497–501.
2. McTavish D, Benfield P. Clomipramine: an overview of its pharmacological properties and a review of its therapeutic use in obsessive compulsive disorder and panic disorder. *Drugs* 1990; **39:** 136–53.
3. Kelly MW, Myers CW. Clomipramine: a tricyclic antidepressant effective in obsessive compulsive disorder. *DICP Ann Pharmacother* 1990; **24:** 739–44.
4. Papp LA, *et al.* Clomipramine treatment of panic disorder: pros and cons. *J Clin Psychiatry* 1997; **58:** 423–5.
5. Fallon BA, *et al.* Intravenous clomipramine for obsessive-compulsive disorder refractory to oral clomipramine: a placebo-controlled study. *Arch Gen Psychiatry* 1998; **55:** 918–24.
6. Sasson Y, *et al.* A double-blind crossover comparison of clomipramine and desipramine in the treatment of panic disorder. *Eur Neuropsychopharmacol* 1999; **9:** 191–6.

Autism. Clomipramine reduced adventitious movements when tried in 5 boys with autistic disorder.[1] However, in a small study in 7 children no improvement in symptoms was noted and adverse effects were common and serious.[2] In another study,[3] although clomipramine was found to be as effective as haloperidol in the treatment of some autistic symptoms, patients on clomipramine were significantly less likely to complete the study for reasons that included the onset of adverse effects.

1. Brasic JR, *et al.* Clomipramine ameliorates adventitious movements and compulsions in prepubertal boys with autistic disorder and severe mental retardation. *Neurology* 1994; **44:** 1309–12.
2. Sanchez LE, *et al.* A pilot study of clomipramine in young autistic children. *J Am Acad Child Adolesc Psychiatry* 1996; **35:** 537–44.
3. Remington G, *et al.* Clomipramine versus haloperidol in the treatment of autistic disorder: a double-blind, placebo-controlled, crossover study. *J Clin Psychopharmacol* 2001; **21:** 440–4.

Micturition disorders. In some countries, clomipramine is used in children for the treatment of nocturnal enuresis; for further details, see Administration in Children, above.

Pain. Antidepressants, usually amitriptyline or another tricyclic, are useful in alleviating some types of pain (see Choice of Analgesic, p. 4.2). In several countries, clomipramine hydrochloride is licensed for the treatment of chronic pain; oral doses range from 10 to 150 mg daily. Parenteral doses may also be given.

Premenstrual syndrome. Clomipramine reduced premenstrual irritability and depressed mood when given during the luteal phase;[1] oral doses of clomipramine ranged from 25 to 75 mg daily. It was postulated that the efficacy of clomipramine in relieving premenstrual symptoms is related to its serotonin reuptake inhibitor activity. For the overall management of premenstrual syndrome, see p. 2272.3.

1. Sundblad C, *et al.* Clomipramine administered during the luteal phase reduces the symptoms of premenstrual syndrome: a placebo-controlled trial. *Neuropsychopharmacology* 1993; **9:** 133–45.

Sexual dysfunction. Clomipramine has been used for its inhibitory effect on ejaculation in the management of premature ejaculation[1-5] (p. 2350.2). In some men with very short latencies (less than 1 minute) continuous therapy with a low daily dose of clomipramine, typically 20 or 30 mg, may be more effective than taking 25 mg as required.[5] Any benefits may relate to its effect as a serotonin reuptake inhibitor; other antidepressants with serotonin reuptake inhibiting actions, such as fluoxetine and sertraline, have also been tried in this condition.[4]

1. Hawton K. Erectile dysfunction and premature ejaculation. *Br J Hosp Med* 1988; **40:** 428–36.
2. Althof SE, *et al.* A double-blind crossover trial of clomipramine for rapid ejaculation in 15 couples. *J Clin Psychiatry* 1995; **56:** 402–7.
3. Haensel SM, *et al.* Clomipramine and sexual function in men with premature ejaculation and controls. *J Urol (Baltimore)* 1996; **156:** 1310–15.
4. Kim SC, Seo KK. Efficacy and safety of fluoxetine, sertraline and clomipramine in patients with premature ejaculation: a double-blind, placebo controlled study. *J Urol (Baltimore)* 1998; **159:** 425–7.
5. Rowland DL, *et al.* Effective daily treatment with clomipramine in men with premature ejaculation when 25 mg (as required) is ineffective. *BJU Int* 2001; **87:** 357–60.

Stuttering. Clomipramine was of modest success in a controlled study[1] of 17 patients with developmental stuttering (p. 1078.1). It was suggested that its efficacy may be related to its serotonin reuptake inhibitor activity.

1. Gordon CT, *et al.* A double-blind comparison of clomipramine and desipramine in the treatment of developmental stuttering. *J Clin Psychiatry* 1995; **56:** 238–42.

Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p. 402.3).

Breast feeding. For comments on the use of tricyclic antidepressants in breast-feeding patients, see under Precautions for Amitriptyline, p. 405.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies clomipramine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

For interactions associated with tricyclic antidepressants, see Amitriptyline, p. 406.1.

MAOIs. The combination of clomipramine and *tranylcypromine* is considered particularly hazardous.

The serotonin syndrome (p. 445.2) has occurred in patients receiving clomipramine and *moclobemide* (see under Interactions of Antidepressants in Phenelzine, p. 447.2).

Pharmacokinetics

Clomipramine is readily absorbed from the gastrointestinal tract, and extensively demethylated during first-pass metabolism in the liver to its primary active metabolite, desmethylclomipramine.

Clomipramine and desmethylclomipramine are widely distributed throughout the body and are extensively bound to plasma and tissue protein. Clomipramine has been estimated to have a plasma elimination half-life of about 21 hours, which may be considerably extended in overdosage; that of desmethylclomipramine is longer (about 36 hours).

Paths of metabolism of both clomipramine and desmethylclomipramine include hydroxylation and *N*-oxidation. About two-thirds of a single dose of clomipramine is excreted in the urine, mainly in the form of its metabolites, either free or in conjugated form; the remainder of the dose appears in the faeces. Clomipramine crosses the placenta and is distributed into breast milk.

References.

1. Gex-Fabry M, *et al.* Clomipramine metabolism: model-based analysis of variability factors from drug monitoring data. *Clin Pharmacokinet* 1990; **19:** 241–55.
2. Balant-Gorgia AE, *et al.* Clinical pharmacokinetics of clomipramine. *Clin Pharmacokinet* 1991; **20:** 447–62.
3. Nielsen KK, *et al.* Single-dose kinetics of clomipramine: relationship to the sparteine and S-mephenytoin oxidation polymorphisms. *Clin Pharmacol Ther* 1994; **55:** 518–27.
4. Herrera D, *et al.* Pharmacokinetics of a sustained-release dosage form of clomipramine. *J Clin Pharmacol* 2000; **40:** 1488–93.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Anafranil; ***Austral.***: Anafranil; Clopram†; Placil; ***Austria***: Anafranil; ***Belg.***: Anafranil; ***Braz.***: Anafranil; Clo; Clomipran; Fenatil; ***Canad.***: Anafranil; Novo-Clopamine; ***Chile***: Anafranil; Atenual; Ausentron; Deprelin†; ***China***: Anafranil (安拿芬尼); ***Cz.***: Anafranil; ***Denm.***: Anafranil; ***Fin.***: Anafranil; ***Fr.***: Anafranil; ***Ger.***: Anafranil; ***Gr.***: Anafranil; ***Hong Kong***: Anafranil; Clopress†; Zoiral†; ***Hung.***: Anafranil; ***India***: Anafranil; Clofranil; Clom; Clomine; Clomip; Clomistar; Clomizil; Clonil; Depnil; Mario; Ocifril; ***Indon.***: Anafranil; ***Irl.***: Anafranil; ***Israel***: Anafranil; Maronil; ***Ital.***: Anafranil; ***Malaysia***: Anafranil; Denapranil; ***Mex.***: Anafranil; ***Neth.***: Anafranil; ***Norw.***: Anafranil; ***NZ***: Clopress†; ***Philipp.***: Anafranil; ***Pol.***: Anafranil; Hydiphen†; ***Port.***: Anafranil; ***Rus.***: Anafranil (Анафранил); Clofranil (Клофранил); ***S.Afr.***: Anafranil; Clomidep; Equinorm; ***Singapore***: Anafranil; Depranil; ***Spain***: Anafranil; ***Swed.***: Anafranil; ***Switz.***: Anafranil; ***Thai.***: Anafranil; Clofranil; ***Turk.***: Anafranil; ***UK***: Anafranil; ***Ukr.***: Anafranil (Анафранил); ***USA***: Anafranil; ***Venez.***: Anafranil.

Pharmacopoeial Preparations

BP 2014: Clomipramine Capsules; Prolonged-release Clomipramine Tablets;

USP 36: Clomipramine Hydrochloride Capsules.

Desipramine Hydrochloride

(BANM, USAN, rINNM)

Desipramiinihydrokloridi; Desipramina, hidrocloruro de; Désipramine, chlorhydrate de; Desipramin-hydrochlorid; Desipraminhydrochlorid; Desipraminhydroklorid; Desipramini Hydrochloridum; Desmethylimipramine Hydrochloride; Dezipramin-hidroklorid; Dezipramino hidrochloridas; Dezypraminy chlorowodorek; DMI; EX-4355; G-35020; Hidrocloruro de desipramina; Hidrocloruro de desmetilimipramina; JB-8181; NSC-114901; RMI-9384A; Дезипрамина Гидрохлорид.

3-(10,11-Dihydro-5*H*-dibenz[*b*,*f*]azepin-5-yl)propyl(methyl) amine hydrochloride.

$C_{18}H_{22}N_2$,HCl=302.8

CAS — 50-47-5 (desipramine); 58-28-6 (desipramine hydrochloride).

ATC — N06AA01.

ATC Vet — QN06AA01.

UNII — 1Y58DO4MY1.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Desipramine Hydrochloride). A white or almost white crystalline powder. Soluble in water and in alcohol. Protect from light.

USP 36: (Desipramine Hydrochloride). A white to off-white crystalline powder. Soluble 1 in 12 of water, 1 in 14 of alcohol, and 1 in 3.5 of chloroform; insoluble in ether; freely soluble in methyl alcohol. Store in airtight containers.

Uses and Administration

Desipramine, the principal active metabolite of imipramine (p. 428.2), is a dibenzazepine tricyclic antidepressant with actions and uses similar to those of amitriptyline (p. 401.1). It is one of the less sedating tricyclics and its antimuscarinic effects are mild. Desipramine is used as the hydrochloride.

In the treatment of depression, desipramine hydrochloride is given orally in daily doses of 100 to 200 mg; higher doses of up to 300 mg daily may be required in severely depressed patients in hospital. Lower doses should be used in adolescents and the elderly and are usually 25 to 100 mg daily; up to 150 mg daily may be required for severe depression. Initial doses should be low and gradually increased according to tolerance and clinical response. Therapy may initially be given as a single daily dose or in divided doses; maintenance therapy may be given as a single daily dose usually at night.

Desipramine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Cocaine dependence. Since dopamine depletion may be the cause of the depression often associated with cocaine craving and with relapse, drugs such as desipramine that interact with dopaminergic systems have been tried in managing cocaine withdrawal symptoms (see p. 1990.1). However, a systematic review[1] was unable to find evidence to support the use of antidepressants in the treatment of cocaine dependence although the efficacy of desipramine was suggested in some individual studies.

1. Lima MS, *et al.* Antidepressants for cocaine dependence [withdrawn]. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 24/11/05).

Hyperactivity. When drug therapy is required for attention deficit hyperactivity disorder (see p. 2314.1) tricyclic antidepressants such as imipramine or desipramine[1-4] are usually reserved for patients who fail to respond to, or who are intolerant of, stimulants. They may also be of use for selected patients with co-existing disorders such as Tourette's syndrome, anxiety, and enuresis.

1. Rapport MD, *et al.* Methylphenidate and desipramine in hospitalized children: I. separate and combined effects on cognitive function. *J Am Acad Child Adolesc Psychiatry* 1993; **32:** 333–42.
2. Pataki CS, *et al.* Side effects of methylphenidate and desipramine alone and in combination in children. *J Am Acad Child Adolesc Psychiatry* 1993; **32:** 1065–72.
3. Singer HS, *et al.* The treatment of attention-deficit hyperactivity disorder in Tourette's syndrome: a double-blind placebo-controlled study with clonidine and desipramine. *Pediatrics* 1995; **95:** 74–81.
4. Spencer T, *et al.* A double-blind comparison of desipramine and placebo in children and adolescents with chronic tic disorder and comorbid attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* 2002; **59:** 649–56.

Pain. Antidepressants, usually amitriptyline or another tricyclic, are useful in alleviating some types of pain (see Choice of Analgesic, p. 4.2) when given in subantidepressant doses.

References to the use of desipramine.

1. Kishore-Kumar R, *et al.* Desipramine relieves postherpetic neuralgia. *Clin Pharmacol Ther* 1990; **47:** 305–12.
2. Max MB, *et al.* Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. *N Engl J Med* 1992; **326:** 1250–6.
3. Coquoz D, *et al.* Central analgesic effects of desipramine, fluvoxamine, and moclobemide after single oral dosing: a study in healthy volunteers. *Clin Pharmacol Ther* 1993; **54:** 339–44.
4. Gordon NC, *et al.* Temporal factors in the enhancement of morphine analgesia by desipramine. *Pain* 1993; **53:** 273–6.

Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p. 402.3).

Breast feeding. For comments on the use of tricyclic antidepressants in breast-feeding patients, see under Precautions for Amitriptyline, p. 405.1.

Interactions

For interactions associated with tricyclic antidepressants, see Amitriptyline, p. 406.1.

Pharmacokinetics

Desipramine is the principal active metabolite of imipramine (p. 429.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Distonal; ***Ger.***: Petylyl†; ***Israel***: Deprexan; ***Ital.***: Nortimil; ***Pol.***: Petylyl†; ***Turk.***: Desipram; ***USA***: Norpramin.

Pharmacopoeial Preparations

BP 2014: Desipramine Tablets;

USP 36: Desipramine Hydrochloride Tablets.

Desvenlafaxine Succinate *(BANM, USAN, rINNM)*

O-Desmethylvenlafaxine succinate; Desvenlafaxine Succinate de; Desvenlafaxini Succinas; DVS-233 (base or succinate); Succinato de desvenlafaxina; Wy-45233; Десвенлафаксина Сукцинат.

1-[(1*RS*)-2-(Dimethylamino)-1-(4-hydroxyphenyl)ethyl]cyclohexanol hydrogen butanedioate monohydrate.

$C_{16}H_{25}NO_2,C_4H_6O_4,H_2O$=399.5

CAS — 93413-62-8 (desvenlafaxine); 386750-22-7 (desvenlafaxine succinate).

ATC — N06AX23.

ATC Vet — QN06AX23.

UNII — ZB22ENF0XR.

Profile

Desvenlafaxine, the major active metabolite of venlafaxine, is a serotonin and noradrenaline reuptake inhibitor (SNRI) (see Venlafaxine, p. 456.2). It is given orally as the succinate but doses are expressed in terms of the base; desvenlafaxine succinate 75.8 mg is equivalent to about 50 mg of desvenlafaxine. The succinate is given in the treatment of depression (p. 398.1) as a modified-release preparation providing a dose equivalent to desvenlafaxine 50 mg once daily. Higher doses of up to 400 mg daily have been studied, but provide no additional benefit and are associated with more frequent adverse effects. The dose may need to be reduced in patients with hepatic or renal impairment (see p. 415.3).

Desvenlafaxine should be withdrawn gradually to reduce the risk of withdrawal symptoms (see also Withdrawal, under Precautions of Fluoxetine, p. 425.3).

Desvenlafaxine is under investigation in the management of menopausal vasomotor symptoms, neuropathic pain, and fibromyalgia.

References.

1. DeMartinis NA, *et al.* A double-blind, placebo-controlled study of the efficacy and safety of desvenlafaxine succinate in the treatment of major depressive disorder. *J Clin Psychiatry* 2007; **68:** 677–88.
2. Septien-Velez L, *et al.* A randomized, double-blind, placebo-controlled trial of desvenlafaxine succinate in the treatment of major depressive disorder. *Int Clin Psychopharmacol* 2007; **22:** 338–47.
3. Liebowitz MR, *et al.* A randomized, double-blind, placebo-controlled trial of desvenlafaxine succinate in adult outpatients with major depressive disorder. *J Clin Psychiatry* 2007; **68:** 1663–72.
4. Archer DF, *et al.* A double-blind, randomly assigned, placebo-controlled study of desvenlafaxine efficacy and safety for the treatment of vasomotor symptoms associated with menopause. *Am J Obstet Gynecol* 2009; **200:** 172.e1–172.e10.

Administration in hepatic or renal impairment. The usual desvenlafaxine oral dose of 50 mg daily may be given to patients with moderate to severe hepatic impairment; doses above 100 mg daily are not recommended.

Patients with moderate renal impairment (creatinine clearance [CC] of 30 to 50 mL/min) may be given a maximum dose of 50 mg daily. In severe impairment (CC less than 30 mL/min) or end-stage renal disease, 50 mg may be given on alternate days. Supplemental doses should not be given after dialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Pristiq; ***Austral.***: Pristiq; ***Braz.***: Pristiq; ***Canad.***: Pristiq; ***Chile***: Pristiq; ***Hong Kong***: Pristiq; ***Israel***: Pristiq; ***Malaysia***: Pristiq; ***Singapore***: Pristiq; ***Thai.***: Pristiq; ***USA***: Pristiq.

Dibenzepin Hydrochloride

(BANM, USAN, rINNM)

Dibenzepina, hidrocloruro de; Dibenzépine, Chlorhydrate de; Dibenzepini Hydrochloridum; HF-1927; Hidrocloruro de dibenzepina; Дибензепина Гидрохлорид.

10-(2-Dimethylaminoethyl)-5,10-dihydro-5-methyl-dibenzo[*b*,*e*][1,4]diazepin-11-one hydrochloride.

$C_{18}H_{21}N_3O$,HCl=331.8

CAS — 4498-32-2 (dibenzepin); 315-80-0 (dibenzepin hydrochloride).

ATC — N06AA08.

ATC Vet — QN06AA08.

UNII — JLN027354Z.

Profile

Dibenzepin hydrochloride is a tricyclic antidepressant (see Amitriptyline, p. 401.1).

In the treatment of depression dibenzepin hydrochloride is given in oral doses of 480 mg daily; higher doses of up to 720 mg daily may be required in some patients with severe depression. Elderly patients should be given reduced doses of 240 mg daily initially, increased to a maximum of 480 mg daily if required.

Dibenzepin hydrochloride has also been given by intravenous infusion.

In some countries it has also been used for nocturnal enuresis.

Dibenzepin should be withdrawn gradually to reduce the risk of withdrawal symptoms.

References.
1. Wirtheim E, Bloch Y. Dibenzepin overdose causing pulmonary edema. *Ann Pharmacother* 1996; 30: 789–90.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Noveril†; ***Cz.***: Noveril; ***Hung.***: Noveril†; ***Israel***: Noveril†; ***Pol.***: Noveril†; ***Switz.***: Noveril.

Dosulepin Hydrochloride *(BANM, rINNM)*

Dosulepiinihydrokloridl; Dosulepina, hidrocloruro de; Dosulépine, Chlorhydrate de; Dosulepin-hydrochlorid; Dosulepinhydrochlorid; Dosulepinhydroklorid; Dosulepini hydrochloridum; Dosulepino hidrochloridas; Doszulepinhidroklorid; Dothiepin Hydrochloride (USAN); Dothiepin Hydrochloride; Hidrocloruro de dosulepina; Hidrocloruro de dotiepina; Досулепина Гидрохлорид.

3-(Dibenzo[*b*,*e*]thiepin-11-ylidene)propyldimethylamine hydrochloride.

$C_{19}H_{21}NS,HCl$=331.9

CAS — 113-53-1 (dosulepin); 897-15-4 (dosulepin hydrochloride).

ATC — N06AA16.

ATC Vet — QN06AA16.

UNII — 3H0042311V.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Dosulepin Hydrochloride). A white or faintly yellow crystalline powder. It consists chiefly of the *E*-isomer. Freely soluble in water, in alcohol, and in dichloromethane. A 10% solution in water has a pH of 4.2 to 5.2. Protect from light.

Uses and Administration

Dosulepin hydrochloride is a tricyclic antidepressant with actions and uses similar to those of amitriptyline (p. 401.1). It is one of the more sedating tricyclics. In the UK, the MHRA suggests that the use of dosulepin for depression should be limited, because of the small margin of safety between the maximum therapeutic dose and potentially fatal overdose. It advises that treatment should only be started by a specialist-care prescriber, and that the quantity issued per prescription should be limited. In patients with increased risk factors for suicide at the start of treatment, during dose adjustment, and until improvement occurs, the MHRA suggests a maximum supply equivalent to 2 weeks of treatment with 75 mg daily.

In the treatment of depression, dosulepin hydrochloride is given in oral doses of 25 mg three times daily initially, gradually increased to 50 mg three times daily if necessary; alternatively a single dose at night may be given. Higher doses of up to 225 mg daily have been given to severely depressed patients in hospital. The recommended initial dose for the elderly is 50 to 75 mg daily.

Dosulepin should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p. 402.3).

Breast feeding. For comments on the use of tricyclic antidepressants in breast-feeding patients, see under Precautions for Amitriptyline, p. 405.1.

Effects on the cardiovascular system. For reference to an increased risk of ischaemic heart disease in patients treated with dosulepin, see under Amitriptyline, p. 403.1.

Overdosage. After an overdose of 1 g of dosulepin, the ECG of a 41-year-old man showed cardiac abnormalities mimicking an acute myocardial infarction.[1] However, as cardiac enzymes did not confirm an ischaemic event, the abnormalities were thought to be due to either the quinidine-like effect of dosulepin or changes in potassium membrane permeability.

1. Steeds RP, Muthusamy R. Abnormal ventricular conduction following dothiepin overdose simulating acute myocardial infarction. *Heart* 2000; 83: 289.

Interactions

For interactions associated with tricyclic antidepressants, see Amitriptyline, p. 406.1.

Pharmacokinetics

Dosulepin hydrochloride is readily absorbed from the gastrointestinal tract, and extensively demethylated by first-pass metabolism in the liver to its primary active metabolite, desmethyldothiepin (also termed northiaden). Paths of metabolism also include *S*-oxidation.

Dosulepin is excreted in the urine, mainly in the form of its metabolites; small amounts are also excreted in the faeces. Elimination half-lives of about 14 to 24 and 23 to 46 hours have been reported for dosulepin and its metabolites, respectively.

Dosulepin is distributed into breast milk (see Breast Feeding under Precautions in Amitriptyline, p. 405.1).

References.
1. Maguire KP, *et al.* Clinical pharmacokinetics of dothiepin: single-dose kinetics in patients and prediction of steady-state concentrations. *Clin Pharmacokinet* 1983; 8: 179–85.
2. Yu DK, *et al.* Pharmacokinetics of dothiepin in humans: a single dose dose-proportionality study. *J Pharm Sci* 1986; 75: 582–5.
3. Ilett KF, *et al.* The excretion of dothiepin and its primary metabolites in breast milk. *Br J Clin Pharmacol* 1992; 33: 635–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Dothep; Prothiaden; ***Belg.***: Prothiaden; ***Cz.***: Prothiaden; ***Denm.***: Prothiaden; ***Fr.***: Prothiaden; ***Ger.***: Idom†; ***Hong Kong***: Prothiaden†; Qualiaden; Vick-Thiaden; ***India***: Dothcin; Dothip; Othtric; Prothiaden; ***Irl.***: Dothep; Prothiaden; ***Ital.***: Protiaden; ***Malaysia***: Depropin; Dothep†; Prothiaden; ***Neth.***: Prothiaden; ***NZ***: Dopress; Prothiaden†; ***Philipp.***: Prothiaden†; ***Port.***: Protiadene; ***S.Afr.***: Prothiaden; Thaden; ***Singapore***: Espin; Prothiaden; ***Spain***: Prothiaden†; ***UK***: Prepadine; Prothiaden.

Multi-ingredient Preparations. ***Austria***: Harmomed.

Pharmacopoeial Preparations

BP 2014: Dosulepin Capsules; Dosulepin Oral Solution; Dosulepin Tablets.

Doxepin Hydrochloride

(BANM, USAN, rINNM)

Doksepiinihydrokloridi; Doksepin Hidroklorür; Doksepino hidrochloridas; Doksepiny chlorowodorek; Doxepina, hidrocloruro de; Doxépine, Chlorhydrate de; Doxepin-hidroklorid; Doxepinhydrochlorid; Doxepin-hydrochlorid; Doxepinhydroklorid; Doxepini hydrochloridum; Hidrocloruro de doxepina; NSC-108160; P-3693A; Доксепина Гидрохлорид.

(*E*)-3-(Dibenz[*b*,*e*]oxepin-11-ylidene)propyldimethylamine hydrochloride.

$C_{19}H_{21}NO,HCl$=315.8

CAS — 1668-19-5 (doxepin); 1229-29-4 (doxepin hydrochloride); 4698-39-9 (doxepin hydrochloride, E-isomer); 25127-31-5 (doxepin hydrochloride, Z-isomer).

ATC — N06AA12.

ATC Vet — QN06AA12.

UNII — 3U9A0FE9N5 (doxepin hydrochloride); CU61C5RH24 (E-doxepin hydrochloride).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Doxepin Hydrochloride). A white or almost white crystalline powder. Freely soluble in water, in alcohol, and in dichloromethane. Protect from light.

USP 36: (Doxepin Hydrochloride). It consists of a mixture of *Z*- and *E*-isomers.

Uses and Administration

Doxepin is a dibenzoxepine tricyclic antidepressant with actions and uses similar to those of amitriptyline (p. 401.1). It has moderate antimuscarinic and marked sedative properties and has serotonin reuptake inhibitor activity.

In the treatment of **depression** doxepin is given orally as the hydrochloride although doses are expressed in terms of the base; doxepin hydrochloride 84.8 mg is equivalent to about 75 mg of doxepin. The initial dose is 75 mg daily, gradually adjusted according to response. Doses of up to 300 mg daily may be required in severely depressed patients; mildly affected patients may respond to as little as 25 to 50 mg daily. Lower doses may be required in the elderly who may be more susceptible to developing adverse effects. Daily doses up to 100 mg may be given in divided doses or as a single dose at bedtime. If the total daily dose exceeds 100 mg, it should be given in 3 divided doses, although the largest portion, up to a maximum of 100 mg, may be given at bedtime. In the USA, the recommended maximum single dose is 150 mg.

Doxepin hydrochloride has also been given by intramuscular or intravenous injection.

Doxepin should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Low doses of doxepin may be used in the management of **insomnia** characterised by difficulty in sleep maintenance. Doxepin hydrochloride is given orally to provide a dose equivalent to doxepin 6 mg once daily at night; the dose should be taken within 30 minutes of bedtime. A dose of 3 mg may be sufficient for some patients, which is also the recommended starting dose for elderly patients aged 65 years and older. It is recommended that the dose should not be taken within 3 hours of a meal, to minimise the potential for effects continuing into the next day.

Doxepin has histamine H_1- and H_2-antagonist activity and is used topically in a cream containing 5% of the hydrochloride for the short-term (up to 8 days) relief of moderate pruritus associated with various types of dermatitis (see p. 416.3). A thin film should be applied 3 or 4 times daily to the affected area. To reduce the incidence of drowsiness, maximum coverage should be less than 10% of the body-surface; this equates to no more than 12 g of the cream daily. Occlusive dressings should be used with caution, if at all.

Headache. Tricyclic antidepressants can be effective in the management of some types of headache—see p. 401.3.

References to the use of doxepin.

1. Wörz R, Scherhag R. Treatment of chronic tension headache with doxepin or amitriptyline—results of a double-blind study. *Headache Q* 1990; 1: 216–23.

Insomnia. Doxepin is used in low doses in the management of insomnia (p. 1033.2).[1,2]

1. Roth T, *et al.* Efficacy and safety of doxepin 1 mg, 3 mg, and 6 mg in adults with primary insomnia. *Sleep* 2007; 30: 1555–61.
2. Scharf M, *et al.* Efficacy and safety of doxepin 1 mg, 3 mg, and 6 mg in elderly patients with primary insomnia: a randomized, double-blind, placebo-controlled crossover study. *J Clin Psychiatry* 2008; 69: 1557–64.

Skin disorders. Tricyclic antidepressants have several pharmacological activities and some drugs in this group have notable antihistaminic actions. Doxepin in particular has very potent antihistaminic activity. It has been shown to be an effective oral alternative to conventional antihistamines in the treatment of chronic urticaria,[1-3] and to be an effective oral treatment for idiopathic cold urticaria.[4,5] In the case of cold urticaria doxepin may act by inhibiting release of a platelet-activating factor-like lipid.[5]

For an overview of the possible treatments for the various urticarias, including mention of the use of doxepin, see p. 1689.2.

As with conventional antihistamines (p. 612.1) doxepin has also been used topically for the relief of pruritus (see also p. 1687.3) associated with various types of allergic and inflammatory skin disorders[6,7] although some authorities remain to be convinced of its efficacy.[8,9] Topical application of doxepin can also produce contact dermatitis (see Effects on the Skin, p. 416.3) and drowsiness and other systemic effects.

1. Greene SL, *et al.* Double-blind crossover study comparing doxepin with diphenhydramine for the treatment of chronic urticaria. *J Am Acad Dermatol* 1985; 12: 669–75.
2. Harto A, *et al.* Doxepin in the treatment of chronic urticaria. *Dermatologica* 1985; 170: 90–3.
3. Goldsobel AB, *et al.* Efficacy of doxepin in the treatment of chronic idiopathic urticaria. *J Allergy Clin Immunol* 1986; 78: 867–73.
4. Neittaanmäki H, *et al.* Comparison of cinnarizine, cyproheptadine, doxepin, and hydroxyzine in treatment of idiopathic cold urticaria: usefulness of doxepin. *J Am Acad Dermatol* 1984; 11: 483–9.
5. Grandel KE, *et al.* Association of platelet-activating factor with primary acquired cold urticaria. *N Engl J Med* 1985; 313: 405–9.
6. Drake LA, *et al.* Relief of pruritus in patients with atopic dermatitis after treatment with topical doxepin cream. *J Am Acad Dermatol* 1994; 31: 613–16.
7. Smith PF, Corelli RL. Doxepin in the management of pruritus associated with allergic cutaneous reactions. *Ann Pharmacother* 1997; 31: 633–5.
8. Anonymous. Doxepin cream for pruritus. *Med Lett Drugs Ther* 1994; 36: 99–100.
9. Anonymous. Doxepin cream for eczema? *Drug Ther Bull* 2000; 38: 31–2.

Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p. 402.3). Drowsiness and other systemic effects can also occur after topical application. In addition, local effects, most commonly burning and stinging, have been reported.

Breast feeding. For comments on the use of tricyclic antidepressants in breast-feeding patients, see under Precautions for Amitriptyline, p. 405.1.

Effects on the skin. Up to January 2002 the FDA was aware of 26 cases of allergic contact dermatitis associated with the use of doxepin 5% cream;[1] manifestations included eczema, urticaria, purpura, and papulovesicular lesions. Of the 20 cases where details were known, 13 occurred after use for more than the recommended 8 days. Patch testing was positive in the 21 cases where it was performed, supporting an allergic reaction rather than an exacerbation of the original condition.

1. Bonnel RA, *et al.* Allergic contact dermatitis from topical doxepin: Food and Drug Administration's postmarketing surveillance experience. *J Am Acad Dermatol* 2003; 48: 294–6.

Overdosage. An infant became difficult to arouse after the application of doxepin cream 5% to about 50% of her body-surface; an entire 30-g tube of the cream was used in only 2 applications.[1] The cream is not recommended for use in children.

1. Zell-Kanter M, *et al.* Doxepin toxicity in a child following topical application. *Ann Pharmacother* 2000; 34: 328–9.

Interactions

For interactions associated with tricyclic antidepressants, see Amitriptyline, p. 406.1.

Pharmacokinetics

Doxepin is readily absorbed from the gastrointestinal tract after oral doses, and is extensively demethylated by first-pass metabolism in the liver, to its primary active metabolite, desmethyldoxepin. Doxepin is also absorbed through the skin after topical application.

Paths of metabolism of both doxepin and desmethyldoxepin include hydroxylation and *N*-oxidation. Doxepin is excreted in the urine, mainly in the form of its metabolites, either free or in conjugated form.

Doxepin and desmethyldoxepin are widely distributed throughout the body; the plasma protein binding of doxepin is about 76%. Doxepin has been estimated to have a plasma elimination half-life ranging from 8 to 24 hours, which may be considerably extended in overdosage; that of desmethyldoxepin is longer.

Doxepin crosses the blood-brain barrier and the placenta. It is distributed into breast milk (see Breast Feeding under Precautions in Amitriptyline, p. 405.1).

References.
1. Faulkner RD, *et al.* Multiple-dose doxepin kinetics in depressed patients. *Clin Pharmacol Ther* 1983; 34: 509–15.
2. Joyce PR, Sharman JR. Doxepin plasma concentrations in clinical practice: could there be a pharmacokinetic explanation for low concentrations? *Clin Pharmacokinet* 1985; 10: 365–70.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Deptran; Sinequan; *Austria*: Sinequan†; *Belg.*: Sinequan; *Canad.*: Sinequan; Zonalon; *China*: Li Ke Ning (丽科宁); *Denm.*: Sinequan; *Fin.*: Doxal; *Fr.*: Quitaxon; *Ger.*: Aponal; Doneurin†; Doxe†; Mareen; *Gr.*: Sinequan; *Hong Kong*: Qualiquan; Sinequan; *India*: Doxedep; Doxetar; Doxin; Doxyril; Noctaderm; Spectra; *Indon.*: Sagalon; *Irl.*: Sinequan†; Xepin†; *Israel*: Gilex; *Mex.*: Sinequan; *Neth.*: Sinequan; *Norw.*: Sinequan; *NZ*: Anten; *Pol.*: Sinequan†; *Spain*: Sinequan; *Switz.*: Sinquane; *Thai.*: Sinequan; *Turk.*: Antimax; *UK*: Sinepin; Xepin; *USA*: Prudoxin; Silenor; Sinequan†; Zonalon.

Multi-ingredient Preparations. *India*: Doxure.

Pharmacopoeial Preparations
BP 2014: Doxepin Capsules;
USP 36: Doxepin Hydrochloride Capsules; Doxepin Hydrochloride Oral Solution.

Duloxetine Hydrochloride

(BANM, USAN, rINNM)

Duloxetina, hidrocloruro de; Duloxétine, Chlorhydrate de; Duloxetini Hydrochloridum; Hidrocloruro de duloxetina; LY-248686 (duloxetine); Дулоксетина Гидрохлорид.

(+)-(*S*)-*N*-Methyl-γ-(1-naphthyloxy)-2-thiophenepropylamine hydrochloride.

$C_{18}H_{19}NOS,HCl$=333.9

CAS — 116539-59-4 (duloxetine); 136434-34-9 (duloxetine hydrochloride).

ATC — N06AX21.

ATC Vet — QN06AX21.

UNII — 9044SC542W.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Duloxetine Hydrochloride). A white or almost white powder. Sparingly soluble in water; freely soluble in methyl alcohol; practically insoluble in hexane. Protect from light.

USP 36: (Duloxetine Hydrochloride). A white to brownish-white solid. Slightly soluble in water. Protect from light.

Uses and Administration

Duloxetine hydrochloride is a serotonin and noradrenaline reuptake inhibitor (SNRI) (see Venlafaxine, p. 456.2). It is given orally as the hydrochloride although doses are expressed in terms of the base; duloxetine hydrochloride 22.5 mg is equivalent to about 20 mg of duloxetine.

Duloxetine is used in the treatment of **depression** in usual initial doses of 20 or 30 mg twice daily, or 60 mg once daily. A lower starting dose of 30 mg once daily for the first week may be suitable for some patients, to allow them to adjust to the effects of duloxetine before increasing the dose. Patients should be continued on a dose of 60 mg once daily. Those with a history of repeated episodes of depression who respond to duloxetine may require long-term treatment using 60 to 120 mg daily.

Duloxetine is also used in the treatment of **generalised anxiety disorder**, in a usual initial dose of 30 or 60 mg once daily. A dose of 60 mg daily is usually adequate, but doses of 90 or 120 mg daily may be needed in some patients.

In the treatment of diabetic **peripheral neuropathic pain** the usual dose is 60 mg once daily. Some patients who respond insufficiently to this dose may benefit from up to 120 mg daily in divided doses. Response to therapy should be evaluated after 2 months and every 3 months thereafter.

In **fibromyalgia**, an initial dose of 30 mg daily is given for the first week to allow patients to adjust to the effects of duloxetine, then increased to 60 mg once daily. A similar dose is used in the management of **chronic musculoskeletal pain** such as low back pain and pain due to osteoarthritis.

Duloxetine is also used in the treatment of moderate to severe **stress urinary incontinence** in women. Usual initial doses are 40 mg twice daily; however, some patients may benefit from an initial dose of 20 mg twice daily for 2 weeks before increasing to 40 mg twice daily.

For dosage in hepatic or renal impairment, see p. 417.2.

Duloxetine should be withdrawn gradually to reduce the risk of withdrawal symptoms (see Precautions, p. 417.3).

Administration in hepatic or renal impairment. Duloxetine should not be used in patients with hepatic impairment.

UK licensed product information for duloxetine states that no dosage adjustment is necessary in mild to moderate renal impairment (creatinine clearance 30 mL/min or above). However, US information suggests that a lower starting dose and gradual dose increase may be warranted for patients, such as diabetics, with renal impairment. Both UK and US information recommend that duloxetine should not be used in more severe renal impairment (creatinine clearance less than 30 mL/min).

Anxiety disorders. Duloxetine is used in the treatment of generalised anxiety disorder (p. 1028.1).

References.
1. Koponen H, *et al.* Efficacy of duloxetine for the treatment of generalized anxiety disorder: implications for primary care physicians. *Prim Care Companion J Clin Psychiatry* 2007; 9: 100–107.
2. Endicott J, *et al.* Duloxetine treatment for role functioning improvement in generalized anxiety disorder: three independent studies. *J Clin Psychiatry* 2007; 68: 518–24. Corrections. *ibid.* 2007; 518, 806.
3. Hartford J, *et al.* Duloxetine as an SNRI treatment for generalized anxiety disorder: results from a placebo and active-controlled trial. *Int Clin Psychopharmacol* 2007; 22: 167–74.
4. Allgulander C, *et al.* Pharmacotherapy of generalized anxiety disorder: results of duloxetine treatment from a pooled analysis of three clinical trials. *Curr Med Res Opin* 2007; 23: 1245–52.
5. Rynn M, *et al.* Efficacy and safety of duloxetine in the treatment of generalized anxiety disorder: a flexible-dose, progressive-titration, placebo-controlled trial. *Depress Anxiety* 2008; 25: 182–9.

Depression. As discussed on p. 398.1, there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effect profile. SSRIs are widely used as an alternative to the older tricyclics as they have fewer adverse effects and are safer in overdosage. Similar properties may also favour the use of serotonin and noradrenaline reuptake inhibitors such as duloxetine.

References.
1. Goldstein DJ, *et al.* Duloxetine in the treatment of major depressive disorder: a double-blind clinical trial. *J Clin Psychiatry* 2002; 63: 225–31.
2. Detke MJ, *et al.* Duloxetine, 60 mg once daily, for major depressive disorder: a randomized double-blind placebo-controlled trial. *J Clin Psychiatry* 2002; 63: 308–15.
3. Raskin J, *et al.* Duloxetine in the long-term treatment of major depressive disorder. *J Clin Psychiatry* 2003; 64: 1237–44.
4. Goldstein DJ, *et al.* Duloxetine in the treatment of depression: a double-blind placebo-controlled comparison with paroxetine. *J Clin Psychopharmacol* 2004; 24: 389–99.
5. Detke MJ, *et al.* Duloxetine in the acute and long-term treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. *Eur Neuropsychopharmacol* 2004; 14: 457–70.
6. Dugan SE, Fuller MA. Duloxetine: a dual reuptake inhibitor. *Ann Pharmacother* 2004; 38: 2078–85.
7. Whitmyer VG, *et al.* A comparison of initial duloxetine dosing strategies in patients with major depressive disorder. *J Clin Psychiatry* 2007; 68: 1921–30.
8. Perahia DGS, *et al.* Duloxetine in the prevention of depressive recurrences: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 2009; 70: 706–16.

Micturition disorders. Duloxetine is used[1-3] to increase urethral tone in the treatment of women with moderate to severe stress urinary incontinence (p. 2349.2). A systematic review[3] concluded that duloxetine treatment reduced the frequency of incontinence episodes and significantly improved the patient's quality of life; however, it was unclear if these benefits were sustained. In addition, the review showed that adverse effects, particularly nausea, were common with duloxetine and led some patients to stop treatment.

1. McCormack PL, Keating GM. Duloxetine in stress urinary incontinence. *Drugs* 2004; 64: 2567–73.
2. Ghoniem GM, *et al.* A randomized controlled trial of duloxetine alone, pelvic floor muscle training alone, combined treatment and no active treatment in women with stress urinary incontinence. *J Urol (Baltimore)* 2005; 173: 1647–53.
3. Mariappan P, *et al.* Serotonin and noradrenaline reuptake inhibitors (SNRI) for stress urinary incontinence in adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 14/09/06).

Pain. Duloxetine is used[1-5] in the treatment of diabetic peripheral neuropathic pain (p. 8.2) and fibromyalgia (see Soft-tissue Rheumatism, p. 14.2), a condition that responds poorly to analgesics and anti-inflammatory drugs. It is also used in the management of chronic musculoskeletal pain such as low back pain (p. 9.2) and pain due to osteoarthritis (p. 12.3).

1. Lunn MPT, *et al.* Duloxetine for treating painful neuropathy or chronic pain. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 01/03/11).
2. Chappell AS, *et al.* Duloxetine, a centrally acting analgesic, in the treatment of patients with osteoarthritis knee pain: a 13-week, randomized, placebo-controlled trial. *Pain* 2009; 146: 253–60.
3. Skljarevski V, *et al.* Efficacy and safety of duloxetine in patients with chronic low back pain. *Spine* 2010; 35: E578–E585.
4. Skljarevski V, *et al.* Duloxetine versus placebo in patients with chronic low back pain: a 12-week, fixed-dose, randomized, double-blind trial. *J Pain* 2010; 11: 1282–90.
5. Chappell AS, *et al.* A double-blind, randomized, placebo-controlled study of the efficacy and safety of duloxetine for the treatment of chronic pain due to osteoarthritis of the knee. *Pain Pract* 2011; 11: 33–41.

Adverse Effects and Treatment

Adverse effects reported most frequently with duloxetine include nausea, headache, insomnia, fatigue, somnolence, dry mouth, dizziness, and constipation. Other common adverse effects include anorexia, diarrhoea, dyspepsia, vomiting, anxiety, visual disturbances, tremor, weight gain or loss, sexual dysfunction, nervousness, lethargy, yawning, hot flushes, increased sweating, and pruritus. Dose-related increases in blood pressure have also been seen in some patients. Reports of tachycardia, ecchymosis, urinary hesitation, rashes, and photosensitivity reactions are less common, and convulsions and activation of mania or hypomania have occurred rarely. Increases in liver enzyme values, hepatitis, and acute liver injury are uncommon, usually occurring within a few months of starting duloxetine. There have been reports of hepatic failure with or without jaundice (sometimes fatal), with a mixed or hepatocellular pattern of damage. Cases of orthostatic hypotension and syncope, serotonin syndrome, and akathisia have also been reported. Suicidal ideation may occur in some patients.

Hyponatraemia, possibly due to inappropriate secretion of antidiuretic hormone, has been associated with the use of antidepressants, particularly in the elderly.

In the treatment of overdosage the value of gastric decontamination is uncertain; however, oral activated charcoal should be considered if more than 5 mg/kg of duloxetine has been ingested and the patient presents within 1 hour of ingestion. Symptomatic and supportive therapy should be given thereafter as necessary. Dialysis, haemoperfusion, exchange perfusion, and measures to increase urine production are considered unlikely to be of benefit.

Incidence of adverse effects. References.

1. Brunton S, *et al.* Profile of adverse events with duloxetine treatment: a pooled analysis of placebo-controlled studies. *Drug Safety* 2010; 33: 393–407.

Precautions

Duloxetine should not be used in patients with hepatic or severe renal impairment and is contra-indicated in patients with uncontrolled narrow-angle glaucoma or hypertension. Patients with raised intra-ocular pressure or at risk of angle-closure glaucoma should be monitored closely. Blood pressure should also be monitored because of the risk of hypertension. Increases in fasting blood glucose and in total cholesterol have been reported in diabetic patients. It should be used with caution in patients with a history of seizures, of bleeding disorders, or of hypomania or mania.

Patients should be closely monitored during early antidepressant therapy until significant improvement in depression occurs because suicide is an inherent risk in depressed patients. For further details, see under Depression, p. 398.1. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be observed when treating patients with other disorders.

As with other antidepressants, duloxetine may impair performance of skilled tasks and, if affected, patients should not drive or operate machinery.

Symptoms reported when duloxetine therapy was stopped abruptly include headache, nausea, vomiting, dizziness, insomnia, anxiety, and paraesthesia. It is therefore recommended that duloxetine should be withdrawn gradually and the patient monitored to minimise the risk of withdrawal reactions (see also Withdrawal, under Precautions of Fluoxetine, p. 425.3).

Children. Duloxetine has not been studied for the treatment of depression in adolescents and children; consequently its use in patients under 18 years of age is not generally recommended. In addition, other antidepressants have been shown to increase the risk of suicidal thoughts

and behaviour in such patients (see Effects on the Mental State, under Fluoxetine, p. 422.2).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies duloxetine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Pregnancy. Neonatal behavioural syndrome developed about 3 days after birth in an infant whose mother had taken duloxetine during pregnancy.[1] The infant developed jerky rhythmic movements, twitching, and episodes of shaking, which were managed with phenobarbital for about 7 weeks. At 2 years of age, the child was healthy with normal neurobehavioural development.

1. Eyal R, Yaeger D. Poor neonatal adaptation after in utero exposure to duloxetine. *Am J Psychiatry* 2008; **165**: 651.

Interactions

Duloxetine should not be used with MAOIs and at least 14 days should elapse between stopping an MAOI and starting treatment with duloxetine. At least 5 days should elapse between stopping duloxetine and starting any drug liable to provoke a serious reaction (e.g. phenelzine). The use of duloxetine with other antidepressants including the SSRIs, other serotonin and noradrenaline reuptake inhibitors, and the reversible inhibitors of monoamine oxidase is not recommended. For further details, see Antidepressants under Interactions of Phenelzine, p. 447.2.

Caution is advised when using duloxetine with other centrally acting drugs including alcohol and those with sedative properties.

Duloxetine is metabolised by the cytochrome P450 isoenzymes CYP1A2 and CYP2D6. It should not be given with potent inhibitors of CYP1A2 such as fluvoxamine, ciprofloxacin, and enoxacin as such combinations are likely to result in increased duloxetine concentrations. Similarly, caution is recommended when duloxetine is given with potent CYP2D6 inhibitors such as paroxetine. Duloxetine itself is also a moderate inhibitor of CYP2D6 and, consequently, licensed product information recommends that it should be used cautiously with drugs that have a narrow therapeutic index and are extensively metabolised by this isoenzyme. In particular, use with thioridazine is contra-indicated because of the risk of serious ventricular arrhythmias and sudden death associated with raised thioridazine concentrations.

As duloxetine may increase the risk of bleeding, caution is advised when it is given with warfarin or drugs known to affect platelet function.

Duloxetine is highly protein-bound and adverse effects may occur if given with other highly protein-bound drugs.

References.

1. Skinner MH, *et al.* Duloxetine is both an inhibitor and a substrate of cytochrome P4502D6 in healthy volunteers. *Clin Pharmacol Ther* 2003; **73**: 170–7.
2. Lobo ED, *et al.* In vitro and in vivo evaluations of cytochrome P450 1A2 interactions with duloxetine. *Clin Pharmacokinet* 2008; **47**: 191–202.

Antimigraine drugs. There have been rare reports of serotonin syndrome associated with the use of serotonin and noradrenaline reuptake inhibitors (SNRIs) with serotonin ($5\text{-}HT_1$) agonists such as *sumatriptan* (see p. 681.3).

Pharmacokinetics

Duloxetine is well absorbed from the gastrointestinal tract and peak plasma concentrations occur about 6 hours after an oral dose. Food delays the time to reach peak concentrations to 10 hours. Protein binding is about 96%, mainly to albumin and $alpha_1$-acid glycoprotein. Duloxetine is extensively metabolised by the cytochrome P450 isoenzymes CYP1A2 and CYP2D6; two major, but inactive, metabolites are formed, 4-hydroxy duloxetine glucuronide and 5-hydroxy, 6-methoxy duloxetine sulfate. These and other metabolites are mainly excreted in the urine; about 20% is excreted in the faeces. Less than 1% of a dose is excreted in the urine as unchanged duloxetine. The elimination half-life of duloxetine is 8 to 17 hours with an average of about 12 hours. Duloxetine is distributed into breast milk.

References.

1. Lantz RJ, *et al.* Metabolism, excretion, and pharmacokinetics of duloxetine in healthy human subjects. *Drug Metab Dispos* 2003; **31**: 1142–50.
2. Skinner MH, *et al.* Effect of age on the pharmacokinetics of duloxetine in women. *Br J Clin Pharmacol* 2004; **57**: 54–61.
3. Lobo ED, *et al.* Population pharmacokinetics of orally administered duloxetine in patients: implications for dosing recommendation. *Clin Pharmacokinet* 2009; **48**: 189–97.
4. Lobo ED, *et al.* Effects of varying degrees of renal impairment on the pharmacokinetics of duloxetine: analysis of a single-dose phase I study and pooled steady-state data from phase II/III trials. *Clin Pharmacokinet* 2010; **49**: 311–21.

Distribution into breast milk. A study in 6 women, who were given duloxetine 40 mg orally twice daily, found that the drug was distributed into breast milk.[1] The concentration of duloxetine was consistently lower in milk than in plasma, at a ratio of about 0.25. No infants were breast fed during the study, but the dose they would have been likely to receive was calculated to be about 2 micrograms/kg daily, or about 0.14% of the maternal dose.

1. Lobo ED, *et al.* Pharmacokinetics of duloxetine in breast milk and plasma of healthy postpartum women. *Clin Pharmacokinet* 2008; **47**: 103–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Cymbalta; Duxetin; *Austral.*: Cymbalta; *Austria*: Cymbalta; Yentreve; *Belg.*: Cymbalta; Yentreve; *Braz.*: Cymbalta; *Canad.*: Cymbalta; *Chile*: Cymbalta; Duceten; Lervitan; Nitexol; Yentreve; *China*: Ao Si Ping (奥思平); Cymbalta (欣百达); *Cz.*: Ariclaim; Cymbalta; Xeristar; Yentreve; *Denm.*: Cymbalta; Xeristar; Yentreve; *Fin.*: Cymbalta; Yentreve; *Fr.*: Cymbalta; *Ger.*: Ariclaim; Cymbalta; Yentreve; *Gr.*: Ariclaim; Cymbalta; Xeristar; Yentreve; *Hong Kong*: Cymbalta; *Hung.*: Cymbalta; *India*: C-Pact; Delok; Dulife; Dumore; Duvanta; Duxet; Duzela; Nudep; *Indon.*: Cymbalta; *Irl.*: Ariclaim; Cymbalta; Xeristar; Yentreve; *Israel*: Cymbalta; Yentreve; *Ital.*: Cymbalta; Xeristar; Yentreve; *Jpn*: Cymbalta; *Malaysia*: Cymbalta; *Mex.*: Cymbalta; Yentreve; *Neth.*: Ariclaim; Cymbalta; Xeristar; Yentreve; *Norw.*: Cymbalta; *Philipp.*: Cymbalta; *Pol.*: Ariclaim; Cymbalta; Xeristar; Yentreve; *Port.*: Ariclaim; Cymbalta; Xeristar; Yentreve; *Rus.*: Cymbalta (Симбалта); *S.Afr.*: Cymbalta; *Singapore*: Cymbalta; *Spain*: Cymbalta; Xeristar; *Swed.*: Ariclaim; Cymbalta; Yentreve; *Switz.*: Cymbalta; *Thai.*: Cymbalta; *Turk.*: Cymbalta; *UK*: Cymbalta; Yentreve; *USA*: Cymbalta.

Multi-ingredient Preparations. *India*: Duzela-M.

Pharmacopoeial Preparations
USP 36: Duloxetine Delayed-Release Capsules.

Escitalopram Oxalate

(BANM, USAN, rINNM)

S-Citalopram Oxalate; Escitalopram, Oxalate d'; Escitalopram, oxalato de; Escitalopramі Oxalas; Lu-26-054/0; Oxalato de escitalopram; Эсциталопрама Оксалат.

(+)-(*S*)-1-[3-(dimethylamino)propyl]-1-(*p*-fluorophenyl)-5-phthalancarbonitrile oxalate.

$C_{20}H_{21}FN_2O.C_2H_2O_4$=414.4

CAS — 128196-01-0 (escitalopram); 219861-08-2 (escitalopram oxalate).

ATC — N06AB10.

ATC Vet — QN06AB10.

UNII — 5U85DBW7LO.

Pharmacopoeias. In *US*.

USP 36: (Escitalopram Oxalate). A fine, white to slightly yellow powder. Sparingly soluble in water and in alcohol; freely soluble in methyl alcohol and in dimethyl sulfoxide; very slightly soluble in ethyl acetate and in isopropyl alcohol; insoluble in heptane.

Uses and Administration

Escitalopram, the *S*-enantiomer of citalopram (p. 411.1), is an SSRI with actions and uses similar to those of fluoxetine (p. 419.1). It is given orally as the oxalate although doses are expressed in terms of the base; escitalopram oxalate 12.8 mg is equivalent to about 10 mg of escitalopram.

In the treatment of **depression**, the usual dose is 10 mg once daily increased, after at least a week, to a maximum of 20 mg once daily if necessary.

Escitalopram is also used in the treatment of **panic disorder** with or without agoraphobia. Initial doses are 5 mg once daily, increased after a week to 10 mg once daily; further increases up to a maximum of 20 mg daily may be necessary in some patients.

Doses of escitalopram used in the treatment of **generalised anxiety disorder, social anxiety disorder,** and **obsessive-compulsive disorder** are similar to those used in depression.

Initial treatment with half the usual recommended dose and a lower maximum dose should be considered in elderly patients; a maximum of 10 mg daily has been recommended. Patients with hepatic impairment or those who are poor metabolisers with respect to the cytochrome P450 isoenzyme CYP2C19 may also require lower doses (see p. 418.3). For doses in children, see p. 418.2.

Escitalopram should be withdrawn gradually to reduce the risk of withdrawal symptoms (see also Withdrawal, under Precautions of Fluoxetine, p. 425.3).

Administration in children. There are concerns about the use of SSRIs in children (see Effects on Mental State, under Adverse Effects of Fluoxetine, p. 422.2) and, in the UK, escitalopram therapy is unlicensed in those under 18 years of age. In the USA, however, escitalopram may be given for the treatment of major depression in children and adolescents aged 12 years and over. Initial oral doses of 10 mg once daily can be increased, if necessary, to 20 mg once daily after at least 3 weeks.

Administration in hepatic impairment. Increases of 51% and 69% in the area under the concentration-time curve occurred in a single-dose study of escitalopram in patients with mild and moderate hepatic impairment (Child-Pugh score 5 or 6, and 7 to 9, respectively).[1] This study also reported that activity of the cytochrome P450 isoenzyme CYP2C19 was a better predictor of escitalopram clearance than the Child-Pugh classification.

UK licensed product information for escitalopram suggests that patients with mild to moderate hepatic impairment or those who are poor metabolisers with respect to the cytochrome P450 isoenzyme CYP2C19 should receive an initial oral dose of 5 mg daily, increased to 10 mg daily after 2 weeks depending on response; more careful dose titration is advised in those with severe impairment. US licensed product information recommends 10 mg daily as a suitable dose for patients with hepatic impairment.

1. Areberg J, *et al.* The pharmacokinetics of escitalopram in patients with hepatic impairment. *AAPS J* 2006; **8**: E14–E19.

Anxiety disorders. Escitalopram has been given in anxiety disorders (p. 1028.1) including panic disorder (p. 1029.1), obsessive-compulsive disorder (p. 1028.2), and social anxiety disorder (see under Phobic Disorders, p. 1029.1).

References.

1. Stahl SM, *et al.* Escitalopram in the treatment of panic disorder: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 2003; **64**: 1322–7.
2. Davidson JR, *et al.* Escitalopram in the treatment of generalized anxiety disorder: double-blind, placebo controlled, flexible-dose study. *Depress Anxiety* 2004; **19**: 234–40.
3. Lader M, *et al.* Efficacy and tolerability of escitalopram in 12- and 24-week treatment of social anxiety disorder: randomised, double-blind, placebo-controlled, fixed-dose study. *Depress Anxiety* 2004; **19**: 241–8.
4. Kasper S, *et al.* Escitalopram in the treatment of social anxiety disorder: randomised, placebo-controlled, flexible-dosage study. *Br J Psychiatry* 2005; **186**: 222–6.
5. Stein DJ, *et al.* Escitalopram in obsessive-compulsive disorder: a randomized, placebo-controlled, paroxetine-referenced, fixed-dose, 24-week study. *Curr Med Res Opin* 2007; **23**: 701–11.

Depression. As discussed on p. 398.1, there is very little difference in efficacy between the different groups of antidepressant drugs. SSRIs such as escitalopram are widely used as an alternative to the older tricyclics as they have fewer adverse effects and are safer in overdosage.

References.

1. Burke WJ, *et al.* Fixed-dose trial of the single isomer SSRI escitalopram in depressed outpatients. *J Clin Psychiatry* 2002; **63**: 331–6.
2. Wade A, *et al.* Escitalopram 10mg/day is effective and well tolerated in a placebo-controlled study in depression in primary care. *Int Clin Psychopharmacol* 2002; **17**: 95–102.
3. Lepola UM, *et al.* Escitalopram (10-20 mg/day) is effective and well tolerated in a placebo-controlled study in depression in primary care. *Int Clin Psychopharmacol* 2003; **18**: 211–17.
4. Rapaport MH, *et al.* Escitalopram continuation treatment prevents relapse of depressive episodes. *J Clin Psychiatry* 2004; **65**: 44–9.
5. Montgomery SA, *et al.* A randomised study comparing escitalopram with venlafaxine XR in primary care patients with major depressive disorder. *Neuropsychobiology* 2004; **50**: 57–64.
6. Murdoch D, Keam SJ. Escitalopram: a review of its use in the management of major depressive disorder. *Drugs* 2005; **65**: 2379–2404.
7. Cipriani A, *et al.* Escitalopram versus other antidepressive agents for depression. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 07/08/09).

Adverse Effects, Treatment, and Precautions

As for Citalopram, p. 411.3.

Children. SSRIs are associated with an increased risk of potentially suicidal behaviour when used for the treatment of depression in children and adolescents under 18 years old; for further details, see under Effects on Mental State in Fluoxetine, p. 422.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies escitalopram as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Pharmacokinetics

Escitalopram has similar pharmacokinetics to those of racemic citalopram (p. 411.3).

References.

1. Søgaard B, *et al.* The pharmacokinetics of escitalopram after oral and intravenous administration of single and multiple doses to healthy subjects. *J Clin Pharmacol* 2005; **45**: 1400–6.
2. Rao N. The clinical pharmacokinetics of escitalopram. *Clin Pharmacokinet* 2007; **46**: 281–90.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Aramix; Axiomat; Beaplen; Citalax; Esciprox; Esciterokam; Ex3; Lexapro; Lextor; Meridian; Novo Humorap; Talpram; Zenvas; *Austral.*: Esipram; Esitalo; Lexam; Lexapro; Loxalate; *Austria*: Cipralex; *Belg.*: Sipralexa; *Braz.*: Espran; Exodus; Lexapro; Reconter; *Canad.*: Cipralex; *Chile*: Celtium; Eciprax; Ectiban; Ipran; Lexapro; Neopresol; Neozentius; Nexipram; Reposil; Zepaz; *China*: Lexapro (来士普); *Cz.*: Anxila; Cipralex; Depresinal; Despra; Elicea; Escirdec; Escitil; Escitralix; Esoprex; Esprolan; Isozyloram; Itakem; Lenuxin; *Denm.*: Cipralex; Entact; Escinapram†; Esertia; Lieropram; Lorepram†; Mylopram; Scippa†; Seroplex; Solatct; Talogen; Talomam; *Fin.*: Cipralex; Esipral; *Fr.*: Seroplex; *Ger.*: Cipralex; *Gr.*: Cipralex; Entact; *Hong Kong*: Lexapro; *Hung.*: Cipralex; *India*: Alivate-E; Alwel; Ambulax-AD; Articalm; C-Pram-S; Cilentra; Cipralex; Cita-S; Citalop-S; Citel; Citofast; Deplam-S; Deptune; Ecitalop; Elcit; Emdes; Escin; Escita; Escitapax; Escitrac; Esdep; Esfancy; Esfany; Esitonic; Esitor; Esjoy; Espam; Espar; Estomine; Feliz-S; Firsito; Jolivel; Jopram; Monopram; Nestilo; Nexito; Recita; S-Citadep; *Indon.*: Cipralex†; *Irl.*: Esciprex; Escitasan; Escitomar; Escitotab; Etalopro; Lexapro; Scippa; *Israel*: Cipralex; Esto; *Ital.*: Cipralex; Entact; *Jpn*: Lexapro; *Malaysia*: Lexapro; *Mex.*: Lexapro; *Neth.*: Cipralex†; Escitaburg†; Escitafloc†; Escitalis†; Escitalodeon†; Escitalofil†; Lexapro; *Norw.*: Cipralex; *NZ*: Lexapro; Loxalate; *Philipp.*: Jovia; Lexapro; *Pol.*: Depralin; Deprigen; Elicea; Escertal; Escitasan; Escitil; Lenuxin; Lexapro; Mozarin; Pramatis; *Port.*: Aloce†; Cipralex; Depart†; Ecitrix†; Escitaham†; Espax†; Rasec; Sades; Scipral; Tacipram†; Tacipram; Ticofarma; Zecidec†; Zocital†; *Rus.*: Cipralex (Ципралекс); Selectra (Селектра); *S.Afr.*: Cipralex; Citraz; Lexamil; Zytomil; *Singapore*: Lexapro; *Spain*: Cipralex; Entact†; Escilan; Escimylan; Esertia; Heipram; *Swed.*: Cipralex; Premalex; *Switz.*: Cipralex; *Thai.*: Lexapro; *Turk.*: Avertyn; Cipralex; Citoles; Eslorex; Esmax; Esram; Losiram; Secita; Tiopram†; Zendor; *UK*: Cipralex; *Ukr.*: Cipralex (Ципралекс); Esopram (Эзопрам); Essobel (Эссобел); *USA*: Lexapro; *Venez.*: Lexapro.

Multi-ingredient Preparations. *India*: C-Pram-S Plus; Cita-S Forte; Cita-S Plus; Ecitalop-C; Escin Plus; Escita Plus; Escitrac-CZ; Esfany-CZ; Esitor Forte; Esjoy Plus; Espar-CL; Estomine Zee; Estomine-SF; Feliz-S Plus; Nexito Forte; Nexito-Plus.

Pharmacopoeial Preparations
USP 36: Escitalopram Tablets.

Fluoxetine Hydrochloride

(BANM, USAN, rINNM)

Fluoksetiinihydrokloridi; Fluoksetin Hidroklorür; Fluoksetino hidrochloridas; Fluoksetyny chlorowodorek; Fluoxetina, hidrocloruro de; Fluoxétine, chlorhydrate de; Fluoxetin-hidroklorid; Fluoxetinhydrochlorid; Fluoxetin-hydrochlorid; Fluoxetinhydroklorid; Fluoxetini hydrochloridum; Hidrocloruro de fluoxetina; Lilly-103472; LY-110140; Флуоксетина гидрохлорид.

(±)-*N*-Methyl-3-phenyl-3-(α,α,α-trifluoro-*p*-tolyloxy)propylamine hydrochloride.

$C_{17}H_{18}F_3NO,HCl$=345.8

CAS — 54910-89-3 (fluoxetine); 59333-67-4 (fluoxetine hydrochloride).

ATC — N06AB03.

ATC Vet — QN06AB03.

UNII — I9W7N6B1KJ (fluoxetine hydrochloride); 7C4D25ST1T (R-fluoxetine hydrochloride).

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of fluoxetine:

Distas; Green and whites; Greens; Limes; Pros; Zacs.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Fluoxetine Hydrochloride). A white or almost white crystalline powder. Sparingly soluble in water and in dichloromethane; freely soluble in methyl alcohol. A 1% solution in water has a pH of 4.5 to 6.5.

USP 36: (Fluoxetine Hydrochloride). A white to off-white crystalline powder. Sparingly soluble in water and in dichloromethane; freely soluble in alcohol and in methyl alcohol; practically insoluble in ether. Store in airtight containers.

Uses and Administration

Prevention of the reuptake of monoamine transmitters such as serotonin, which potentiates their action in the brain, appears to be associated with antidepressant activity. SSRIs such as fluoxetine preferentially inhibit the reuptake of serotonin compared with noradrenaline, and have limited direct action at other neurotransmitter sites, including muscarinic receptors. They therefore cause fewer antimuscarinic or sedative adverse effects than the tricyclic antidepressants and are less cardiotoxic. Citalopram is the most selective of the SSRIs currently available, whereas paroxetine is the most potent.

SSRIs provide an alternative to the tricyclics for the treatment of depression. As with the tricyclics, it may be several weeks before an antidepressant effect is seen. Once depression has then resolved, maintenance therapy should be continued for at least 6 months (12 months in the elderly) to avoid relapse on stopping therapy. Patients with a history of recurrent depression should continue to receive maintenance treatment for at least 2 years.

Some SSRIs are also used as part of the management of generalised anxiety disorder, obsessive-compulsive disorder, panic disorders with or without agoraphobia, social phobia, and post-traumatic stress disorder, and as part of the management of bulimia nervosa. Fluoxetine is also used in the treatment of premenstrual dysphoric disorder.

Fluoxetine, a phenylpropylamine derivative, is given orally as the hydrochloride, but doses are expressed in terms of the base; fluoxetine hydrochloride 22.4 mg is equivalent to about 20 mg of fluoxetine.

In the treatment of **depression** the usual initial dose of fluoxetine is 20 mg once daily; US licensed product information recommends giving this dose in the morning. If no clinical response is seen after several weeks, the daily dose may be gradually increased, up to a maximum of 80 mg daily (60 mg in the elderly). Doses above 20 mg daily may be given in 2 divided doses, for example in the morning and at noon, or as a once daily dose. A once-weekly, modified-release preparation equivalent to 90 mg of fluoxetine is available in the USA for use in patients whose depressive symptoms have stabilised, and who require long-term treatment; it is recommended that weekly dosing is started 7 days after the last daily dose of fluoxetine. Fluoxetine may also be given as a combination preparation with olanzapine (p. 1089.3) in the management of depressive episodes associated with bipolar disorder, and in treatment-resistant depression. The daily dose of fluoxetine is usually within the range of 20 to 50 mg, and the combination is given as a single dose in the evening.

Fluoxetine is used in the management of **bulimia nervosa** in a dose of 60 mg daily, which may be given as a single morning dose or in divided doses.

In the management of **obsessive-compulsive disorder** the initial dose of fluoxetine is 20 mg once daily increased after several weeks if there is no response to up to 60 mg daily. Up to 80 mg daily has been used, sometimes divided into 2 doses.

Fluoxetine may be used in the treatment of **panic disorder** in initial doses of 10 mg once daily. After a week the dose should be increased to 20 mg daily; further increases to 60 mg daily may be considered after several weeks if no improvement is seen.

A dose of 20 mg daily is used in the treatment of **premenstrual dysphoric disorder**. Intermittent dosing is also permitted: for each new cycle, fluoxetine should be started 14 days before the onset of menstruation and continued until the first full day of menstruation. Treatment may be continued for 6 months; benefit should then be reassessed before continuing further.

A lower or less frequent dosage is recommended in elderly patients. For dose adjustment in hepatic or renal impairment, see p. 419.2, and for doses in children, see p. 419.2.

It should be noted that because fluoxetine and norfluoxetine have prolonged half-lives several weeks of therapy are required before steady-state concentrations are attained; similarly after dosage adjustments a time lag will occur before steady-state concentrations are again achieved. Although SSRIs should generally be withdrawn gradually to reduce the risk of withdrawal symptoms, the long half-life may reduce the need for dose tapering with fluoxetine.

Administration in children. Fluoxetine may be used for the treatment of **depression** in children aged 8 years and over. Initial oral doses of 10 mg daily can be increased to 20 mg daily after 1 to 2 weeks (except in low-weight children when such increases should not be made for several weeks, and then only if the clinical response is insufficient). Because of concerns about the use of SSRIs in children (see Effects on Mental State, p. 422.2), fluoxetine is licensed in the EU only as an adjunct to psychological therapy in children and adolescents with moderate to severe depression who have not responded to psychological therapy alone.

Fluoxetine is also licensed in the USA for the management of **obsessive-compulsive disorder** in children aged 7 years and over, starting with an oral dose of 10 mg daily. In low-weight children this may be increased after several weeks to 20 to 30 mg daily, if required. The dose in adolescents and heavier children may be increased to 20 mg daily after 2 weeks; further increases to 60 mg daily may be made after several weeks, as necessary.

Administration in hepatic or renal impairment. Fluoxetine is subject to hepatic metabolism, and, therefore, lower doses, such as alternate-day dosing, have been recommended in patients with significant hepatic impairment.

It is also excreted by the kidneys and licensed information for some UK products recommends a similar dose reduction in patients with mild to moderate renal impairment and that fluoxetine should be avoided in those with severe impairment. However, other UK and US product information states that plasma concentrations of fluoxetine or its metabolite norfluoxetine in patients with severe impairment requiring dialysis did not differ from those in controls with normal renal function when given fluoxetine 20 mg daily for 2 months.

Anorexia nervosa. Counselling and psychotherapy form the major part of treatment of anorexia nervosa and there is little or no role for specific drug therapy. Antidepressants may be indicated when there is co-existing depression or obsessive-compulsive disorder but malnourished anorexic patients may be more susceptible to adverse effects and less responsive than other patients with depression. Fluoxetine has been studied in the prevention of relapse once weight gain has been achieved, with mixed results.

References.
1. Bergh C, *et al.* Selective serotonin reuptake inhibitors in anorexia. *Lancet* 1996; 348: 1459–60.
2. Mayer LES, Walsh BT. The use of selective serotonin reuptake inhibitors in eating disorders. *J Clin Psychiatry* 1998; 59 (suppl 15): 28–34.
3. Kaye WH, *et al.* Double-blind placebo-controlled administration of fluoxetine in restricting- and restricting-purging-type anorexia nervosa. *Biol Psychiatry* 2001; 49: 644–52.
4. Kim SS. Role of fluoxetine in anorexia nervosa. *Ann Pharmacother* 2003; 37: 890–2.
5. Walsh BT, *et al.* Fluoxetine after weight restoration in anorexia nervosa: a randomized controlled trial. *JAMA* 2006; 295: 2605–12. Corrections. *ibid.*; 296: 934 and 2007; 298: 2008.

Anxiety disorders. SSRIs have been given in a variety of anxiety disorders but their role in these disorders is most well established in the treatment of *obsessive-compulsive disorder* (p. 1028.2). Efficacy in obsessive-compulsive disorder appears to have been best shown for fluvoxamine and fluoxetine but other SSRIs are also effective and patients unresponsive to one SSRI may respond to another. SSRIs are also of use in the treatment of *generalised anxiety disorder* (p. 1028.1), *panic disorder* (p. 1029.1), and *post-traumatic stress disorder* (p. 1029.2). SSRIs are considered to be the first choice for the treatment of *social anxiety disorder* (see under Phobic Disorders, p. 1029.1). Fluoxetine is one of the SSRIs that has been tried in the treatment of *trichotillomania*.

References.
1. Tollefson GD, *et al.* A multicenter investigation of fixed-dose fluoxetine in the treatment of obsessive-compulsive disorder. *Arch Gen Psychiatry* 1994; 51: 559–67.
2. Yanchick JK, *et al.* Efficacy of fluoxetine in trichotillomania. *Ann Pharmacother* 1994; 28: 1245–6.
3. Boyer W. Serotonin uptake inhibitors are superior to imipramine and alprazolam in alleviating panic attacks: a meta-analysis. *Int Clin Psychopharmacol* 1995; 10: 45–9.
4. Michelson D, *et al.* Continuing treatment of panic disorder after acute response: randomised, placebo-controlled trial with fluoxetine. *Br J Psychiatry* 1999; 174: 213–18.
5. Connor KM, *et al.* Fluoxetine in post-traumatic stress disorder: randomised, double-blind study. *Br J Psychiatry* 1999; 175: 17–22.
6. Meltzer-Brody S, *et al.* Symptom-specific effects of fluoxetine in post-traumatic stress disorder. *Int Clin Psychopharmacol* 2000; 15: 227–31.
7. Geller DA, *et al.* Fluoxetine treatment for obsessive-compulsive disorder in children and adolescents: a placebo-controlled clinical trial. *J Am Acad Child Adolesc Psychiatry* 2001; 40: 773–9.
8. Romano S, *et al.* Long-term treatment of obsessive-compulsive disorder after an acute response: a comparison of fluoxetine versus placebo. *J Clin Psychopharmacol* 2001; 21: 46–52.
9. Barnett SD, *et al.* Tolerability of fluoxetine in posttraumatic stress disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2002; 26: 363–7.
10. Liebowitz MR, *et al.* Fluoxetine in children and adolescents with OCD: a placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry* 2002; 41: 1431–8.
11. Birmaher B, *et al.* Fluoxetine for the treatment of childhood anxiety disorders. *J Am Acad Child Adolesc Psychiatry* 2003; 42: 415–23.
12. Davidson JR, *et al.* Fluoxetine, comprehensive cognitive behavioral therapy, and placebo in generalized social phobia. *Arch Gen Psychiatry* 2004; 61: 1005–13.

Bipolar disorder. Treatment of the depressive phase of bipolar disorder (p. 397.2) with antidepressants needs caution since these drugs may precipitate mania or hypomania. SSRIs such as fluoxetine have nonetheless been used in bipolar disorder with some success. In some countries, fluoxetine is also available as a fixed-dose combination with the atypical antipsychotic olanzapine for use in the depressive phase of bipolar disorder.

References.
1. Amsterdam JD, *et al.* Efficacy and safety of fluoxetine in treating bipolar II major depressive episode. *J Clin Psychopharmacol* 1998; 18: 435–40.
2. Megna JL, Devitt PJ. Treatment of bipolar depression with twice-weekly fluoxetine: management of antidepressant-induced mania. *Ann Pharmacother* 2001; 35: 45–7.
3. Tohen M, *et al.* Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Arch Gen Psychiatry* 2003; 60: 1079–88. Correction. *ibid.* 2004; 61: 176.
4. Amsterdam JD, *et al.* Short-term fluoxetine monotherapy for bipolar type II or bipolar NOS major depression - low manic switch rate. *Bipolar Disord* 2004; 6: 75–81.
5. Deeks ED, Keating GM. Olanzapine/fluoxetine: a review of its use in the treatment of acute bipolar depression. *Drugs* 2008; 68: 1115–37.

Bulimia nervosa. A combination of counselling, support, psychotherapy, and antidepressants is the usual treatment for bulimia nervosa. Fluoxetine and the tricyclic desipramine have been suggested as the antidepressants of choice because they have been used extensively and are considered to be well tolerated. Other SSRIs that have been tried include sertraline, fluvoxamine, and paroxetine. Antidepressants in general do not appear to alter the patient's disturbed self-image, although disturbed attitudes might improve during short-term therapy with fluoxetine.

References.

1. Goldbloom DS, Olmsted MP. Pharmacotherapy of bulimia nervosa with fluoxetine: assessment of clinically significant attitudinal change. *Am J Psychiatry* 1993; 150: 770–4.
2. Mayer LES, Walsh BT. The use of selective serotonin reuptake inhibitors in eating disorders. *J Clin Psychiatry* 1998; 59 (suppl 15): 28–34.
3. Hay PPJ, *et al.* Antidepressants versus psychological treatments and their combination for bulimia nervosa. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 29/07/10).
4. Bacaltchuk J, Hay PPJ. Antidepressants versus placebo for people with bulimia nervosa. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 29/07/10).

Congenital myasthenia. Fluoxetine may be used as an alternative to quinidine sulfate in the treatment of the slow-channel congenital myasthenic syndrome (p. 685.1).

Depression. As discussed on p. 398.1, there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effect profile. SSRIs such as fluoxetine are widely used as an alternative to the older tricyclics as they have fewer adverse effects and are safer in overdosage.

Combination therapy with differing classes of antidepressants, including the SSRIs, has been used in the treatment of drug-resistant depression. However, such therapy may result in enhanced adverse reactions or interactions, and should be used only under expert supervision. For further details see Antidepressants, under Interactions of Phenelzine, p. 447.2.

References to the use of SSRIs in general and to the use of fluoxetine are given below.

1. Anderson IM, Tomenson BM. Treatment discontinuation with selective serotonin reuptake inhibitors compared with tricyclic antidepressants: a meta-analysis. *BMJ* 1995; 310: 1433–8.
2. Brown WA, Harrison W. Are patients who are intolerant to one serotonin selective reuptake inhibitor intolerant to another? *J Clin Psychiatry* 1995; 56: 30–4.
3. Fava M, *et al.* Relapse in patients on long-term fluoxetine treatment: response to increased fluoxetine dose. *J Clin Psychiatry* 1995; 56: 52–5.
4. Mourilhe P, Stokes PE. Risks and benefits of selective serotonin reuptake inhibitors in the treatment of depression. *Drug Safety* 1998; 18: 57–82.
5. Anderson IM. SSRIs versus tricyclic antidepressants in depressed inpatients: a meta-analysis of efficacy and tolerability. *Depress Anxiety* 1998; 7 (suppl 1): 11–17.
6. Cheer SM, Goa KL. Fluoxetine: a review of its therapeutic potential in the treatment of depression associated with physical illness. *Drugs* 2001; 61: 81–110.
7. Sampson SM. Treating depression with selective serotonin reuptake inhibitors: a practical approach. *Mayo Clin Proc* 2001; 76: 739–44.
8. Wagstaff AJ, Goa KL. Once-weekly fluoxetine. *Drugs* 2001; 61: 2221–8.
9. Bull SA, *et al.* Discontinuing or switching selective serotonin-reuptake inhibitors. *Ann Pharmacother* 2002 36: 578–84.
10. Emslie GJ, *et al.* Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. *J Am Acad Child Adolesc Psychiatry* 2002; 41: 1205–15.
11. March J, *et al.* Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA* 2004; 292: 807–20.
12. Devanand DP, *et al.* Randomized, double-blind, placebo-controlled trial of fluoxetine treatment for elderly patients with dysthymic disorder. *Am J Geriatr Psychiatry* 2005; 13: 59–68.
13. Trivedi MH, *et al.* An integrated analysis of olanzapine/fluoxetine combination in clinical trials of treatment-resistant depression. *J Clin Psychiatry* 2009; 70: 387–96.

Disturbed behaviour. SSRIs appear to have been of some benefit in controlling symptoms such as impulsiveness and aggression[1-4] when tried in various disorders for the management of disturbed behaviour (see p. 1030.2). There have been several case reports of fluoxetine being used with some success in the control of fantasies associated with various paraphilias.[5]

1. Cornelius JR, *et al.* Fluoxetine trial in borderline personality disorder. *Psychopharmacol Bull* 1990; 26: 151–4.
2. Vartiainen H, *et al.* Citalopram, a selective serotonin reuptake inhibitor, in the treatment of aggression in schizophrenia. *Acta Psychiatr Scand* 1995; 91: 348–51.
3. Coccaro EF, Kavoussi RJ. Fluoxetine and impulsive aggressive behavior in personality-disordered subjects. *Arch Gen Psychiatry* 1997; 54: 1081–8.
4. Coccaro EF, *et al.* A double-blind, randomized, placebo-controlled trial of fluoxetine in patients with intermittent explosive disorder. *J Clin Psychiatry* 2009; 70: 653–62.
5. Richer M, Crismon ML. Pharmacotherapy of sexual offenders. *Ann Pharmacother* 1993; 27: 316–19.

Headache. A systematic review[1] of 13 studies found that the SSRIs were no better than placebo in the prevention of migraine or tension-type headache; when compared with the tricyclic antidepressants, the SSRIs were as effective for migraine but less effective for tension-type headache. However, it was noted that studies were small, of short duration (8 to 12 weeks), and most had methodological faults.

Guidelines for the management of migraine or tension-type headache (see p. 670.3 and p. 671.3, respectively) do not recommend the use of SSRIs for prophylaxis.

1. Moja L, *et al.* Selective serotonin re-uptake inhibitors (SSRIs) for preventing migraine and tension-type headaches. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 27/01/09).

Hot flushes. HRT with oestrogens is usually the mainstay of acute treatment for symptoms such as hot flushes associated with the menopause (see Menopausal Disorders, p. 2245.1); however, HRT has potentially tumour-stimulating effects and may be unsuitable in some patients, particularly those with a history of breast cancer (see Malignant Neoplasms, under Precautions of HRT, p. 2250.2). Preliminary studies have shown that some SSRIs (fluoxetine, paroxetine, and sertraline) have a modest effect on alleviating hot flushes and may be an alternative to HRT in peri- and postmenopausal women and in women with a history of breast cancer.[1-4] Indeed, low-dose paroxetine is used for the treatment of moderate to severe vasomotor symptoms associated with the menopause;[5] however, there is some concern that paroxetine may interact with tamoxifen treatment in patients with breast cancer (see Antidepressants under Interactions in Tamoxifen, p. 863.3 for details).

In addition, paroxetine has been tried in the treatment of hot flushes in men receiving anti-androgen therapy for prostate cancer.[6]

The serotonergic antidepressant venlafaxine has also been tried with some success in men and women with hot flushes in whom other treatments were unsuitable.[7]

1. Stearns V, *et al.* Paroxetine controlled release in the treatment of menopausal hot flashes: a randomized controlled trial. *JAMA* 2003; 289: 2827–34.
2. Kockler DR, McCarthy MW. Antidepressants as a treatment for hot flashes in women. *Am J Health-Syst Pharm* 2004; 61: 287–92.
3. De Sloover Koch Y, Ernst ME. Selective serotonin-reuptake inhibitors for the treatment of hot flashes. *Ann Pharmacother* 2004; 38: 1293–6.
4. Stearns V, *et al.* Paroxetine is an effective treatment for hot flashes: results from a prospective randomized clinical trial. *J Clin Oncol* 2005; 23: 6919–30. Correction. *Ibid.*: 8549.
5. Simon JA, *et al.* Low-dose paroxetine 7.5 mg for menopausal vasomotor symptoms: two randomized controlled trials. *Menopause* 2013; 20: 1027–35.
6. Loprinzi CL, *et al.* Pilot evaluation of paroxetine for treating hot flashes in men. *Mayo Clin Proc* 2004; 79: 1247–51.
7. Schober CE, Ansani NT. Venlafaxine hydrochloride for the treatment of hot flashes. *Ann Pharmacother* 2003; 37: 1703–7.

Hyperactivity. When drug therapy is indicated for attention deficit hyperactivity disorder (ADHD—p. 2314.1) initial treatment is usually with a central stimulant. SSRIs such as fluoxetine have produced beneficial effects as an adjunct to central stimulants in small numbers of patients with comorbid disorders such as depression or obsessive-compulsive disorder;[1-3] although there is insufficient evidence to assess their efficacy in ADHD alone.

1. Gammon GD, Brown TE. Fluoxetine and methylphenidate in combination for treatment of attention deficit disorder and comorbid depressive disorder. *J Child Adolesc Psychopharmacol* 1993; 3: 1–10.
2. Bussing R, Levin GM. Methamphetamine and fluoxetine treatment of a child with attention-deficit hyperactivity disorder and obsessive-compulsive disorder. *J Child Adolesc Psychopharmacol* 1993; 3: 53–8.
3. Finding RL. Open-label treatment of comorbid depression and attentional disorders with co-administration of serotonin reuptake inhibitors and psychostimulants in children, adolescents and adults: a case series. *J Child Adolesc Psychopharmacol* 1996; 6: 165–75.

Hypochondriasis. SSRIs may be of benefit in patients with hypochondriasis.[1] Fluoxetine in an initial dose of 20 mg daily gradually increased up to 80 mg daily produced some beneficial results in 10 of 14 patients with hypochondriasis (p. 1030.2) who completed 12 weeks of treatment.[2] Fluvoxamine[3] and paroxetine[4] have also been tried.

1. Fallon BA, *et al.* The pharmacotherapy of hypochondriasis. *Psychopharmacol Bull* 1996; 32: 607–11.
2. Fallon BA, *et al.* Fluoxetine for hypochondriacal patients without major depression. *J Clin Psychopharmacol* 1993; 13: 438–41.
3. Fallon BA, *et al.* An open trial of fluvoxamine for hypochondriasis. *Psychosomatics* 2003; 44: 298–303.
4. Oosterbaan DB, *et al.* An open study of paroxetine in hypochondriasis. *Prog Neuropsychopharmacol Biol Psychiatry* 2001; 25: 1023–33.

Hypotension. SSRIs have been used in patients with neurally mediated hypotension refractory to standard treatment (see p. 1277.2), although evidence of benefit is mainly anecdotal. However, a small study[1] found that paroxetine reduced the incidence of both tilt-induced and spontaneous syncope.

See also Orthostatic Hypotension, p. 420.3.

1. Di Girolamo E, *et al.* Effects of paroxetine hydrochloride, a selective serotonin reuptake inhibitor, on refractory vasovagal syncope: a randomized, double-blind, placebo-controlled study. *J Am Coll Cardiol* 1999; 33: 1227–30.

Obesity. Fluoxetine has been tried with some success as part of the management of obesity (p. 2315.1). Fluoxetine's mechanism of action in obesity is unknown. Serotonin is believed to be involved in the regulation of satiety[1] but fluoxetine has also been shown to increase resting energy expenditure and raise basal body temperature.[2] A common dose for fluoxetine in the management of obesity has been 60 mg daily; it appears that fluoxetine has a dose-related effect on weight loss.[3] Reviews[1,4,5] agree that fluoxetine can aid weight reduction in the short term but after 16 to 20 weeks some patients have started to regain weight and its long-term efficacy is unknown. Troublesome adverse effects can occur.[1] Some patients treated with fluoxetine for depression have had an increase of appetite and some have gained weight. There has been a report[6] of a patient who lost weight during treatment with fluoxetine for depression despite an increased appetite and food intake.

1. Anonymous. Fluoxetine (Prozac) and other drugs for treatment of obesity. *Med Lett Drugs Ther* 1994; 36: 107–8.
2. Bross R, Hoffer LJ. Fluoxetine increases resting energy expenditure and basal body temperature in humans. *Am J Clin Nutr* 1995; 61: 1020–5.
3. Levine LR, *et al.* Use of fluoxetine, a selective serotonin-uptake inhibitor, in the treatment of obesity: a dose-response study. *Int J Obes* 1989; 13: 635–45.
4. Bray GA. Use and abuse of appetite-suppressant drugs in the treatment of obesity. *Ann Intern Med* 1993; 119: 707–13.
5. Mayer LE, Walsh BT. The use of selective serotonin reuptake inhibitors in eating disorders. *J Clin Psychiatry* 1998; 59 (suppl 15): 28–34.
6. Fichtner CG, Braun BG. Hyperphagia and weight loss during fluoxetine treatment. *Ann Pharmacother* 1994; 28: 1350–2.

Orthostatic hypotension. Although orthostatic hypotension has been reported in some patients taking SSRIs, there has been a report[1] that fluoxetine 20 mg daily for 6 to 8 weeks produced beneficial effects in 4 of 5 patients with chronic symptomatic orthostatic hypotension (p. 1634.3) refractory to other treatment. Modest benefits have also been seen in patients with orthostatic hypotension associated with parkinsonism.[2]

1. Grubb BP, *et al.* Fluoxetine hydrochloride for the treatment of severe refractory orthostatic hypotension. *Am J Med* 1994; 97: 366–8.
2. Montastruc JL, *et al.* Fluoxetine in orthostatic hypotension of Parkinson's disease: a clinical and experimental pilot study. *Fundam Clin Pharmacol* 1998; 12: 398–402.

Pain. SSRIs have been tried in the treatment of painful disorders including fibromyalgia and diabetic neuropathy.

See also Headache, above.

References.

1. Goldenberg D, *et al.* A randomized, double-blind crossover trial of fluoxetine and amitriptyline in the treatment of fibromyalgia. *Arthritis Rheum* 1996; 39: 1852–9.
2. Jung AC, *et al.* The efficacy of selective serotonin reuptake inhibitors for the management of chronic pain. *J Gen Intern Med* 1997; 12: 384–9.
3. Smith AJ. The analgesic effects of selective serotonin reuptake inhibitors. *J Psychopharmacol* 1998; 12: 407–13.
4. Anderberg UM, *et al.* Citalopram in patients with fibromyalgia—a randomized, double-blind, placebo-controlled study. *Eur J Pain* 2000; 4: 27–35.
5. Shimodozono M, *et al.* Reduction of central poststroke pain with the selective serotonin reuptake inhibitor fluvoxamine. *Int J Neurosci* 2002; 112: 1173–81.
6. Arnold LM, *et al.* A randomized, placebo-controlled, double-blind, flexible-dose study of fluoxetine in the treatment of women with fibromyalgia. *Am J Med* 2002; 112: 191–7.

Parkinsonism. It has been suggested that fluoxetine might be of use in the management of selected patients with Parkinson's disease (p. 890.1) who have levodopa-induced dyskinesias unresponsive to other measures.[1] However, although fluoxetine has been reported to have produced beneficial results in such patients[2] there has also been a report of increased disability in patients with Parkinson's disease given fluoxetine.[3] Extrapyramidal effects have also been reported in other patients taking fluoxetine (see under Adverse Effects, p. 423.2). Fluoxetine has been tried in parkinsonism-related orthostatic hypotension (above).

1. Giron LT, Koller WC. Methods of managing levodopa-induced dyskinesias. *Drug Safety* 1996; 14: 365–74.
2. Durif F, *et al.* Levodopa-induced dyskinesias are improved by fluoxetine. *Neurology* 1995; 45: 1855–8.
3. Steur ENHJ. Increase of Parkinson disability after fluoxetine medication. *Neurology* 1993; 43: 211–3.

Pathological crying or laughing. Inappropriate or uncontrolled crying or laughing can occur in patients with lesions in certain areas of the brain. Attempts at treatment have mostly been with antidepressant drugs, including SSRIs. Beneficial effects have been claimed for fluoxetine in several uncontrolled studies and reports.[1-4]

1. Seliger GM, *et al.* Fluoxetine improves emotional incontinence. *Brain Inj* 1992; 6: 267–70.
2. Sloan RL, *et al.* Fluoxetine as a treatment for emotional lability after brain injury. *Brain Inj* 1992; 6: 315–19.
3. Hanger HC. Emotionalism after stroke. *Lancet* 1993; 342: 1235–6.
4. Tsai WC, *et al.* Treatment of emotionalism with fluoxetine during rehabilitation. *Scand J Rehabil Med* 1998; 30: 145–9.

Peripheral vascular disease. Anecdotal reports[1,2] and a small pilot study[3] of fluoxetine (in a daily dose of 20 to 60 mg) suggest it may produce favourable therapeutic responses in patients with Raynaud's syndrome (see Vasospastic Arterial Disorders, p. 1275.3).

1. Bolte MA, Avery D. Case of fluoxetine-induced remission of Raynaud's phenomenon—a case report. *Angiology* 1993; 44: 161–3.
2. Jaffe IA. Serotonin reuptake inhibitors in Raynaud's phenomenon. *Lancet* 1995; 345: 1378.

3. Coleiro B, *et al.* Treatment of Raynaud's phenomenon with the selective serotonin reuptake inhibitor fluoxetine. *Rheumatology (Oxford)* 2001; 40: 1038–43.

Premenstrual syndrome. Fluoxetine is used to control both the psychological and somatic symptoms of women with premenstrual dysphoric syndrome, a severe form of premenstrual syndrome (p. 2272.3). Other SSRIs also appear to be useful.

References.

1. Carr RR, Ensom MHH. Fluoxetine in the treatment of premenstrual dysphoric disorder. *Ann Pharmacother* 2002; 36: 713–17.
2. Pearlstein T. Selective serotonin reuptake inhibitors for premenstrual dysphoric disorder: the emerging gold standard? *Drugs* 2002; 62: 1869–85.
3. Luisi AF, Pawasauskas JE. Treatment of premenstrual dysphoric disorder with selective serotonin reuptake inhibitors. *Pharmacotherapy* 2003; 23: 1131–40.
4. Brown J, *et al.* Selective serotonin reuptake inhibitors for premenstrual syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 30/07/10).

Sexual dysfunction. Impotence or ejaculatory problems have been reported as adverse effects of SSRIs (see Effects on Sexual Function in Adverse Effects, p. 423.1). Such properties of the SSRIs have been studied as a potential form of treatment for men with premature ejaculation[1-3] (p. 2350.2). The relative effects of the SSRIs on delaying ejaculation have also been studied.[4] Paroxetine was found to cause the strongest delay, followed by fluoxetine and then sertraline; fluvoxamine caused a slight delay although the effect was not significantly different from that seen with placebo. (Citalopram was unavailable at the time of the study; later studies of its effect have been conflicting.[3])

1. Waldinger MD, *et al.* Paroxetine treatment of premature ejaculation: a double-blind, randomized, placebo-controlled study. *Am J Psychiatry* 1994; 151: 1377–9.
2. Mendels J, *et al.* Sertraline treatment for premature ejaculation. *J Clin Psychopharmacol* 1995; 15: 341–6.
3. Moreland AJ, Makela EH. Selective serotonin-reuptake inhibitors in the treatment of premature ejaculation. *Ann Pharmacother* 2005; 39: 1296–1301.
4. Waldinger MD, *et al.* Effect of SSRI antidepressants on ejaculation: a double-blind, randomized, placebo-controlled study with fluoxetine, fluvoxamine, paroxetine and sertraline. *J Clin Psychopharmacol* 1998; 18: 274–81.

Adverse Effects

SSRIs such as fluoxetine are less sedating than tricyclic antidepressants and have fewer antimuscarinic and cardiotoxic effects. Adverse effects reported with SSRIs include dry mouth and gastrointestinal disturbances such as nausea, vomiting, dyspepsia, constipation, and diarrhoea. Anorexia and weight loss may also occur. Neurological adverse effects have included either anxiety, restlessness, nervousness, and insomnia, or drowsiness and fatigue; headache, tremor, dizziness, seizures, hallucinations, confusion, agitation, extrapyramidal effects, depersonalisation, mania, panic attacks, sexual dysfunction, and symptoms suggestive of a serotonin syndrome (p. 445.2) have also occurred. The concern that SSRIs may be associated with increased suicidal ideation is discussed under Effects on Mental State, p. 422.2.

Excessive sweating, pruritus, rashes, alopecia, photosensitivity, and urticaria have also been reported. Angioedema and anaphylactoid reactions have occurred. In some patients who have developed rashes while taking fluoxetine, systemic hypersensitivity reactions involving the lungs, kidneys, or liver, and possibly related to vasculitis, have developed; it has therefore been advised that fluoxetine therapy should be stopped in any patient who develops a skin rash.

Hyponatraemia, possibly due to inappropriate secretion of antidiuretic hormone, has been associated with the use of antidepressants, particularly in the elderly. Hyperprolactinaemia and galactorrhoea have occurred, as have changes in blood sugar, in patients receiving SSRIs.

Arthralgia and myalgia have been reported and there have also been cases of orthostatic hypotension, yawning, urinary retention, and abnormal vision including blurred vision and mydriasis. Abnormal liver function tests have been reported rarely. SSRIs have occasionally been associated with bleeding disorders such as ecchymosis and purpura and other effects on the blood.

In overdosage nausea, vomiting, and excitation of the CNS are considered to be prominent features; death has been reported.

Incidence of adverse effects. In June 1992 the UK CSM had received 1236 reports of adverse effects with fluvoxamine (from about 280 000 prescriptions) compared with 2422 for fluoxetine (from about 480 000 prescriptions).[1] The overall patterns of adverse effects were similar but dermatological reactions were more likely with fluoxetine and gastrointestinal reactions with fluvoxamine. Reports of attempted suicide increased after adverse publicity about SSRIs in 1990, and the number of reports per million prescriptions were similar for the 2 drugs (25 for fluoxetine and 20 for fluvoxamine); at that time such figures were not considered disconcerting given that features of depression, including attempted suicide, can worsen after the introduction of any antidepressant (see also Effects on Mental State, p. 422.2). A later review[2] by the CSM of the 5 SSRIs available in the UK (citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) found that the SSRIs were broadly similar with respect to their safety profile. A list of adverse reactions common to all SSRIs was provided.

A review[3] of 1861 adverse reactions to citalopram, fluoxetine, fluvoxamine, paroxetine, or sertraline reported to the Swedish Adverse Drug Reactions Advisory Committee found that the most commonly reported reactions were neurological (22.4% of all reports), psychiatric (19.5%), and gastrointestinal (18.0%). Compared with other SSRIs, gastrointestinal symptoms were more common with fluvoxamine, psychiatric symptoms with sertraline, and dermatological symptoms with fluoxetine.

A later meta-analysis[4] has compared the adverse effect profile of fluoxetine with other antidepressants including the tricyclics and other SSRIs. The overall risk of any adverse effect with fluoxetine was less than that for the tricyclic antidepressants; however, there was no difference in risk when fluoxetine was compared with other SSRIs. When considering individual adverse reactions, fluoxetine was more likely to cause activating effects such as insomnia, agitation, tremor, and anxiety, and gastrointestinal disturbances such as nausea, vomiting, diarrhoea, weight loss, and anorexia than other antidepressants. In contrast, the tricyclics were associated with a greater risk of sedation, antimuscarinic effects (such as dry mouth, dizziness, and blurred vision), constipation, and weight gain, than fluoxetine.

1. CSM. Safety of fluoxetine (Prozac): comparison with fluvoxamine (Faverin). *Current Problems* 34 1992. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024526&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)
2. CSM/MCA. Selective serotonin reuptake inhibitors (SSRIs). *Current Problems* 2000; 26: 11–12. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON0074606&RevisionSelectionMethod=LatestReleased (accessed 27/11/05)
3. Spigset O. Adverse reactions of selective serotonin reuptake inhibitors: reports from a spontaneous reporting system. *Drug Safety* 1999; 20: 277–87.
4. Brambilla P, *et al.* Side-effect profile of fluoxetine in comparison with other SSRIs, tricyclic and newer antidepressants: a meta-analysis of clinical trial data. *Pharmacopsychiatry* 2005; 38: 69–77.

Effects on the blood. Abnormalities in platelet aggregation were associated with fluoxetine given to a severely underweight patient.[1] Platelet activity returned to normal when fluoxetine was stopped. Fluoxetine was also suspected of being the cause of bruising in a patient whose blood clotting parameters were within normal limits.[2] Purpura and bruising have been reported to be the commonest adverse blood effects associated with fluoxetine, paroxetine, or sertraline although cases of thrombocytopenia have been recorded for all three antidepressants.[3] The suggested mechanism was inhibition of uptake of serotonin into platelets, thereby disrupting platelet aggregation; caution was recommended when treating patients with a history of bleeding disorders with SSRIs. However, a subsequent cohort study based on prescription-event monitoring provided only weak evidence of a link between the use of SSRIs and the development of bleeding disorders.[4] A similar study[5] found no evidence of a major increased risk of intracranial haemorrhage with the use of SSRIs, although smaller increases in risk could not be ruled out.

For mention of a possibly increased risk of gastrointestinal bleeding, see Effects on the Gastrointestinal Tract, p. 422.1.

1. Alderman CP, *et al.* Abnormal platelet aggregation associated with fluoxetine therapy. *Ann Pharmacother* 1992; 26: 1517–19.
2. Pai VB, Kelly MW. Bruising associated with the use of fluoxetine. *Ann Pharmacother* 1996; 30: 786–8.
3. Anonymous. Bruising and bleeding with SSRIs. *Aust Adverse Drug React Bull* 1998; 17: 10. Also available at: http://www.tga.gov.au/adr/aadrb/aadr9808.pdf (accessed 14/08/08)
4. Layton D, *et al.* Is there an association between selective serotonin reuptake inhibitors and risk of abnormal bleeding? Results from a cohort study based on prescription event monitoring in England. *Eur J Clin Pharmacol* 2001; 57: 167–76.
5. de Abajo FJ, *et al.* Intracranial haemorrhage and use of selective serotonin reuptake inhibitors. *Br J Clin Pharmacol* 2000; 50: 43–7.

Effects on bone. A review of 9 epidemiological studies, mainly in patients aged 50 years or older, found an increased risk of fracture in those receiving SSRIs. However, no definite conclusions could be made about a dose-response relationship, time relationship, or the possible mechanism.[1]

1. MHRA/CHM. Antidepressants: risk of fractures. *Drug Safety Update* 2010; 3 (10): 3–4. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON081866&RevisionSelectionMethod=LatestReleased (accessed 28/07/10)

Effects on the cardiovascular system. SSRIs are not usually associated with the same degree of cardiotoxicity as the tricyclic antidepressants (see p. 403.1), although orthostatic hypotension has been reported in some patients. A decrease in heart rate with ECG changes has been noted with fluvoxamine. However, a study[1] on long-term fluvoxamine treatment in 311 patients followed for 1 year revealed no significant effect on ECG findings compared with patients given placebo.

Concern over the use of sertraline in patients with coronary heart disease was raised after a report[2] of a 53-year-old man with a history of coronary heart disease who had attacks of sudden precordial chest pain on starting treatment with sertraline. The pain responded to glyceryl trinitrate. The manufacturers[3] pointed out that there had been no ECG changes confirming an ischaemic origin of the disorder in this patient and that in studies sertraline had had no demonstrable clinical effects on intraventricular conduction or ECG intervals. Furthermore, no significant changes in cardiovascular indices had been recorded in patients who had taken overdoses of up to 6 g of sertraline. It was suggested that this might have been an effect on the gastrointestinal tract possibly at the oesophageal level.

Citalopram has been associated with dose-dependent prolongation of the QT interval and torsade de pointes; for further details, see Adverse Effects, Treatment, and Precautions of Citalopram, p. 411.3.

1. Hochberg HM, *et al.* Electrocardiographic findings during extended clinical trials of fluvoxamine in depression: one years experience. *Pharmacopsychiatry* 1995; 28: 253–6.
2. Iruela LM. Sudden chest pain with sertraline. *Lancet* 1994; 343: 1106.
3. Berti CA, Doogan DP. Sudden chest pain with sertraline. *Lancet* 1994; 343: 1510–11.

Effects on the cerebrovascular system. There have been rare reports of cerebral ischaemic events associated with the use of SSRIs. In one case[1] a 57-year-old man receiving long-term treatment for atrial fibrillation and hypercholesterolaemia presented with a facial droop and slurred speech 3 days after starting paroxetine 20 mg twice daily. Symptoms resolved after anticoagulant therapy and stopping paroxetine but recurred when paroxetine was reintroduced at a dose of 10 mg twice daily. Paroxetine was stopped and no further episodes had occurred within 4 months at follow-up.

For a report that there is no major increased risk of intracranial haemorrhage associated with the SSRIs, see Effects on the Blood, above.

1. Manos GH, Wechsler SM. Transient ischemic attack reported with paroxetine use. *Ann Pharmacother* 2004; 38: 617–20.

Effects on the endocrine system. The *syndrome of inappropriate antidiuretic hormone secretion (SIADH)* with *hyponatraemia* has been reported in patients receiving antidepressants. The UK CSM, commenting on reports it had received of hyponatraemia associated with antidepressants (fluoxetine, paroxetine, lofepramine, clomipramine, and imipramine), considered that it was likely to occur with any antidepressant, and usually involved elderly patients.[1] However, the results of a later study[2] have suggested that cases are more likely to occur with serotonergic antidepressants such as the SSRIs, clomipramine, and venlafaxine. Case reports of hyponatraemia in 16 patients treated with SSRIs have been summarised.[3] A further review[4] of reports on 15 patients with hyponatraemia with SIADH induced by fluoxetine (12 cases), fluvoxamine (2 cases), and paroxetine (1 case) showed that the risk was greatest during the early treatment phase. This is borne out by single-case reports[5-12] of hyponatraemia with SIADH in elderly patients receiving either citalopram, paroxetine, or sertraline. A retrospective study[13] of hyponatraemia associated with either fluoxetine or paroxetine use also showed the early onset of the condition and identified low body-weight as being another risk factor for developing hyponatraemia. Not unexpectedly, replacing one SSRI with another has resulted in a recurrence of hyponatraemia; however, in one report,[14] the symptoms of hyponatraemia did not recur until about 16 months after switching SSRIs.

SSRI-associated *hyperprolactinaemia* has been reported.[15] Lactation and raised prolactin levels occurred in a teenager 3 days after fluoxetine was added to her existing therapy which included pimozide. Stopping fluoxetine had no effect on lactation, which only ceased after withdrawing pimozide. In another report,[16] hyperprolactinaemia and galactorrhoea in an elderly woman receiving fluoxetine resolved on stopping the drug.

Gynaecomastia, unrelated to prolactin concentrations, was associated with the start of fluoxetine therapy in a 49-year-old man. Symptoms subsided 10 months after withdrawing fluoxetine.[17]

Although SSRIs may be favoured for the management of depression in patients with diabetes, there is some evidence that sertraline and fluoxetine can induce *hypoglycaemia*.[18,19] Licensed product information for other SSRIs also warns of similar risks with these products.

1. CSM/MCA. Antidepressant-induced hyponatraemia. *Current Problems* 1994; 20: 5–6. Also available at: http://www.mhra.gov.uk/home/idcplg?

IdcService=GET_FILE&dDocName=CON2015616&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)
2. Movig KLL, *et al.* Serotonergic antidepressants associated with an increased risk for hyponatraemia in the elderly. *Eur J Clin Pharmacol* 2002; 58: 143–8.
3. Spigset O, Hedenmalm K. Hyponatraemia and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) induced by psychotropic drugs. *Drug Safety* 1995; 12: 209–25.
4. Canadian Medical Association. Hyponatraemia and selective serotonin reuptake inhibitors. *Can Med Assoc J* 1996; 154: 63.
5. Bluff DD. SIADH in a patient receiving sertraline. *Ann Intern Med* 1995; 123: 811.
6. Adverse Drug Reactions Advisory Committee. Selective serotonin reuptake inhibitors and SIADH. *Med J Aust* 1996; 164: 562.
7. Kessler J, Samuels SC. Sertraline and hyponatremia. *N Engl J Med* 1996; 335: 524.
8. Robinson D, *et al.* SIADH—compulsive drinking or SSRI influence? *Ann Pharmacother* 1996; 30: 885.
9. Monmany J, *et al.* Syndrome of inappropriate secretion of antidiuretic hormone induced by paroxetine. *Arch Intern Med* 1999; 159: 2089–90.
10. Odeh M, *et al.* Severe life-threatening hyponatremia during paroxetine therapy. *J Clin Pharmacol* 1999; 39: 1290–1.
11. Barclay TS, Lee AJ. Citalopram-associated SIADH. *Ann Pharmacother* 2002; 36: 1558–63.
12. Flores G, *et al.* Severe symptomatic hyponatremia during citalopram therapy–a case report. *BMC Nephrol* 2004; 5: 2.
13. Wilkinson TJ, *et al.* Incidence and risk factors for hyponatraemia following treatment with fluoxetine or paroxetine in elderly people. *Br J Clin Pharmacol* 1999; 47: 211–17.
14. Arinzon ZH, *et al.* Delayed recurrent SIADH associated with SSRIs. *Ann Pharmacother* 2002; 36: 1175–7.
15. Arya DK, *et al.* Lactation associated with fluoxetine treatment. *Aust N Z J Psychiatry* 1995; 29: 697.
16. Peterson MC. Reversible galactorrhea and prolactin elevation related to fluoxetine use. *Mayo Clin Proc* 2001; 76: 215–16.
17. Sahin M, *et al.* A possible case of gynecomastia with fluoxetine. *Ann Pharmacother* 2005; 39: 1369.
18. Deeg MA, Lipkin EW. Hypoglycemia associated with the use of fluoxetine. *West J Med* 1996; 164: 262–3.
19. Pollak PT, *et al.* Sertraline-induced hypoglycemia. *Ann Pharmacother* 2001; 35: 1371–4.

Effects on the eyes. Symptoms of glaucoma that developed in a patient receiving fluoxetine subsided within 2 days of drug withdrawal.[1] Similar symptoms have been reported with citalopram,[2] fluvoxamine,[3] paroxetine,[2,4] and sertraline.[2] In some cases, the SSRI may have aggravated pre-existing glaucoma.[2,3] Intra-ocular pressure after oral doses of fluoxetine was recorded in 20 patients in a placebo-controlled crossover double-blind study.[5] Significant increases were found in all patients 2 hours after receiving fluoxetine; some patients still had raised intra-ocular pressure after 8 hours. A review of case reports documenting SSRI-associated changes in intra-ocular pressure concluded that such changes were difficult to predict;[6] however, it was recommended that those with risk factors for glaucoma, such as elderly patients with a family history, should be considered for ophthalmic consultations before starting an SSRI and regularly throughout treatment.

Anisocoria (uneven pupillary dilatation) has been reported[7] in a patient taking paroxetine and in another taking sertraline. It was noted that the UK CSM had received 21 reports of mydriasis associated with paroxetine but it appeared that noticeably asymmetrical mydriasis as seen in these 2 patients had not previously been reported.

1. Ahmad S. Fluoxetine and glaucoma. *DICP Ann Pharmacother* 1991; 25: 436.
2. Anonymous. SSRIs and increased intraocular pressure. *Aust Adverse Drug React Bull* 2001; 20: 3. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0102.pdf (accessed 14/08/08)
3. Jiménez-Jiménez FJ, *et al.* Aggravation of glaucoma with fluvoxamine. *Ann Pharmacother* 2001; 35: 1565–6.
4. Eke T, Carr S. Acute glaucoma, chronic glaucoma, and serotoninergic drugs. *Br J Ophthalmol* 1998; 82: 976–7.
5. Costagliola C, *et al.* Fluoxetine oral administration increases intraocular pressure. *Br J Ophthalmol* 1996; 80: 678.
6. Costagliola C, *et al.* SSRIs and intraocular pressure modifications: evidence, therapeutic implications and possible mechanisms. *CNS Drugs* 2004; 18: 475–84.
7. Barrett J. Anisocoria associated with selective serotonin reuptake inhibitors. *BMJ* 1994; 309: 1620.

Effects on the gastrointestinal tract. A case-control study[1] suggested that treatment with SSRIs produced a moderately increased risk of upper gastrointestinal bleeding (adjusted relative risk 3.0). The risk was greatly increased if SSRIs were given with NSAIDs (relative risk 15.6). Treatment with SSRIs did not appear to increase the risk of ulcer perforation. The absolute risk of bleeding was estimated at one case per 8000 prescriptions, a risk similar to that of low-dose ibuprofen. A more recent cohort study[2] found a similar increase in risk. However, others have questioned whether such an association exists.[3]

A retrospective cohort study[4] in *elderly* patients found that there was an increasing risk of upper gastrointestinal bleeding as the extent of inhibition of serotonin reuptake by the antidepressant used increased. The effect was considered to be clinically important for patients with a high risk of such bleeding, namely the very elderly and those with a history of previous upper gastrointestinal bleeding.

Some[5] consider that gastroprotection is unlikely to be justified in those given SSRIs alone and furthermore there are no studies to suggest that gastroprotective drugs reduce the risk of SSRI-associated haemorrhage. However, it has been recommended[5] that such protection should be considered when SSRIs and NSAIDs are used together because of the increased risk.

1. de Abajo FJ, *et al.* Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding: population based case-control study. *BMJ* 1999; 319: 1106–9.
2. Dalton SO, *et al.* Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal tract bleeding: a population-based cohort study. *Arch Intern Med* 2003; 163: 59–64.
3. Dunn NR, *et al.* Association between SSRIs and upper gastrointestinal bleeding. *BMJ* 2000; 320: 1405–6.
4. van Walraven C, *et al.* Inhibition of serotonin reuptake by antidepressants and upper gastrointestinal bleeding in elderly patients: retrospective cohort study. *BMJ* 2001; 323: 655–8.
5. Paton C, Ferrier IN. SSRIs and gastrointestinal bleeding. *BMJ* 2005; 331: 529–30.

Effects on the hair. A report[1] on 2 patients who had hair loss associated with the use of fluoxetine noted 4 other published cases and stated that, up to the end of 1991, the US manufacturers had received 498 reports of fluoxetine-associated alopecia.

1. Ogilvie AD. Hair loss during fluoxetine treatment. *Lancet* 1993; 342: 1423.

Effects on the liver. Acute hepatitis occurred in 2 patients after several months of fluoxetine treatment;[1] it was noted that 5 other cases of acute hepatitis with fluoxetine had been reported.

Abnormal liver function tests were seen in a patient after a suicide attempt with sertraline and cefalexin.[2] The patient was then started on venlafaxine but, again abnormal liver function tests were noted. When these abnormal values had decreased, sertraline was restarted at therapeutic doses, with a subsequent increase in liver function tests. Values returned to normal once all medications were stopped. Auto-immune hepatitis has been reported after therapeutic doses of sertraline;[3] rechallenge in this case was also positive.

Hepatotoxicity has also been rarely associated with citalopram[4] and with paroxetine use.[5]

1. Cai Q, *et al.* Acute hepatitis due to fluoxetine therapy. *Mayo Clin Proc* 1999; 74: 692–4.
2. Kim KY, *et al.* Acute liver damage possibly related to sertraline and venlafaxine ingestion. *Ann Pharmacother* 1999; 33: 381–2.
3. Persky S, Reinus JF. Sertraline hepatotoxicity: a case report and review of the literature on selective serotonin reuptake inhibitor hepatotoxicity. *Dig Dis Sci* 2003; 48: 939–44.
4. López-Torres E, *et al.* Hepatotoxicity related to citalopram. *Am J Psychiatry* 2004; 161: 923–4.
5. Azaz-Livshits T, *et al.* Paroxetine associated hepatotoxicity: a repon of 3 cases and a review of the literature. *Pharmacopsychiatry* 2002; 35: 112–15.

Effects on mental state. As early as 1990 there was concern that the SSRIs increased the risk of *suicidal ideation* after the publication of a case series of such events with fluoxetine.[1] Meta-analyses[2,3] performed around that time (criticism of statistical power notwithstanding[4]) did not confirm an increased risk and this was supported by the results of prescription-event monitoring.[5] Nevertheless, reports of suicidal ideation as well as suicide and self-harm have continued to be published for the SSRIs and the issue remains controversial. A subsequent meta-analysis[6] of 702 randomised controlled studies found an increased risk for attempted suicide in those taking SSRIs when compared with placebo but not when compared with tricyclic antidepressants.

Risk analysis of suicidal behaviour with any antidepressant is confounded by the rarity of suicide even in patients with depression, and by the possibility that such behaviour is a manifestation of the underlying disease. Furthermore, the more favourable safety profile of the SSRIs, particularly in overdosage (see Depression, p. 398.1), when compared with the older MAOIs and tricyclic antidepressants may have resulted in the SSRIs being prescribed to those patients at greater risk of suicidal behaviour.

In 2003, the UK CSM established an Expert Working Group to address increasing public concerns regarding the safety of the SSRIs. The serotonergic antidepressants venlafaxine and mirtazapine were also included and the conclusions given below also apply to these drugs. In its final report[7] issued in December 2004, the Working Group concluded that the risk of suicide may increase in the early stages of treatment for depression in adults and consequently careful and frequent monitoring is important, particularly if a patient has worsening of symptoms or new symptoms after starting therapy. However, the Working Group noted that increases in the prescribing of SSRIs have not been associated with an increase in suicide rates, although they acknowledged that the interpretation of these findings was difficult. They could not rule out that there might be a modest increase in the risk of suicidal ideation and self-harm with the SSRIs when compared with placebo. However, there was insufficient evidence from clinical studies to determine any differences between the SSRIs as a group, or between the SSRIs and other antidepressants regarding the risk of suicidal behaviour; evidence from the General Practice Research database has suggested that there is no increased risk of such behaviour with the SSRIs when compared with the tricyclic antidepressants. The Working Group also concluded that the evidence for a relationship between suicidal behaviour and a change in dose was not robust; however, patients should be monitored for any new symptoms or worsening of disease around the time of any dose change.

The Expert Working Group of the CSM has also commented[7] on the use of SSRIs in young adults. They concluded that although there was no clear evidence of an increased risk of self-harm or suicidal thoughts in young adults of 18 years or over, such patients have a higher background risk of suicidal behaviour than older adults and consequently those treated with SSRIs should be closely monitored. Furthermore, the results of a meta-analysis undertaken by the FDA found that although the overall risk of suicide was not increased in adult patients receiving antidepressants, there was a non-significant trend toward increased risk with younger age. The FDA considered the trend sufficiently convincing to warn that, like children and adolescents, young adults aged between 18 and 24 years treated with antidepressants of any type may be at increased risk of suicidal thinking and behaviour.[8]

In 2003 the CSM recommended (on the basis of their Expert Working Group's finding) that paroxetine should not be used to treat depressive illness in children under 18 years old. Data from studies received by CSM in May 2003 failed to show that paroxetine was effective in depressive illness in this age group and indicated that the risk of harmful outcome, including self-harm and potentially suicidal behaviour, was 1.5 to 3.2 times greater in those given paroxetine when compared with placebo.[9] Following a further review,[10] the CSM extended their recommendation to include the SSRIs citalopram, escitalopram, and sertraline; subsequent analysis had also associated these antidepressants with an unfavourable risk to benefit ratio in the treatment of depression in children under 18. The CSM also included fluvoxamine in their recommendation as its risk to benefit ratio was unassessable. Fluoxetine was not included and the CSM acknowledged that clinical studies had shown a favourable risk to benefit ratio for fluoxetine in the treatment of depression in young patients. The European Medicines Agency (EMEA) has also recommended that serotonergic antidepressants, including the SSRIs, should not be used in children and adolescents except within their approved indications,[11] but considered[12] that studies with fluoxetine in children and adolescents have shown a positive effect that outweighs any potential risks, and recommended that it should be licensed for use where needed, as an adjunct to psychological therapies in children from 8 years of age. Nevertheless, it is recognised that specialists may decide to use these drugs according to clinical need and, although unlicensed, guidelines issued by NICE suggest that citalopram and sertraline may be given for the treatment of depression in those aged 12 years and over (for further details, see Depression, p. 398.1).

The FDA has not issued advice contra-indicating the use of these antidepressants in those under 18 years old in the USA, although they have stressed that all patients, including adolescents and children, should be closely monitored for worsening depression or suicidal behaviour, especially at the beginning of treatment. Apart from escitalopram and fluoxetine, the SSRIs are not licensed in the USA for the treatment of depression in young patients.

The use of SSRIs has been associated with the development of *akathisia, restlessness,* and *psychomotor agitation* such as an inability to sit or stand still, particularly in the first few weeks of treatment.[13] In some patients these symptoms have precipitated suicidal behaviour. However, the Expert Working Group of the CSM considered that it was not possible to draw any conclusions on the link between the development of these symptoms and the risk of suicidal behaviour, as such data were not included in the majority of cases.[7]

There have been suggested links between the use of fluoxetine and *irritability, hostility, and aggression.*[14] However, one review[15] noted that an unpublished analysis had indicated that patients taking fluoxetine for a variety of disorders were not more likely to be aggressive than those taking placebo. Prescription-event monitoring has also found no evidence to suggest that fluoxetine increases the frequency of aggression.[5]

Initiation of antidepressant therapy with paroxetine or sertraline has been associated with either worsening or a new onset of *flashback syndrome* in 2 patients with a history of lysergide abuse.[16]

There have been isolated reports of *memory loss* associated with the use of SSRIs.[17]

For further effects on mental function, see also under Withdrawal (p. 425.3) and under Mania in Precautions, p. 425.1.

1. Teicher MH, *et al.* Emergence of intense suicidal preoccupation during fluoxetine treatment. *Am J Psychiatry* 1990; 147: 207–10.
2. Beasley CM, *et al.* Fluoxetine and suicide: a meta-analysis of controlled trials of treatment for depression. *BMJ* 1991; 303: 685–92. Correction. *ibid.*; 968.

3. Goldstein DJ, *et al.* Analyses of suicidality in double-blind, placebo-controlled trials of pharmacotherapy for weight reduction. *J Clin Psychiatry* 1993; 54: 309–16.
4. Li Wan Po A. Fluoxetine and suicide: meta-analysis and Monte-Carlo simulations. *Pharmacoepidemiol Drug Safety* 1993; 2: 79–84.
5. Nakielny J. Fluoxetine and suicide. *Lancet* 1994; 343: 1359.
6. Fergusson D, *et al.* Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomised controlled trials. *BMJ* 2005; 330: 396. Correction. *ibid.*: 653.
7. Weller IVD. *Report of the CSM Expert Working Group on the safety of selective serotonin reuptake inhibitor antidepressants.* London: The Stationery Office, 2005. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON019472&RevisionSelectionMethod=LatestReleased (accessed 14/08/08)
8. Friedman RA, Leon AC. Expanding the black box — depression, antidepressants, and the risk of suicide. *N Engl J Med* 2007; 356: 2343–6.
9. MHRA. Safety of Seroxat (paroxetine) in children and adolescents under 18 years - contraindication in the treatment of depressive illness. Epinet message from Professor G Duff, Chairman of Committee on Safety of Medicines (issued 10th June, 2003). Available at: http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con019507.pdf (accessed 14/08/08)
10. MHRA. Selective Serotonin Reuptake Inhibitors - use in children and adolescents with major depressive disorder. Epinet message from Professor G Duff, Chairman of Committee on Safety of Medicines (issued 10th December, 2003). Available at: http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con019492.pdf (accessed 08/09/10)
11. European Medicines Agency. European Medicines Agency finalises review of antidepressants in children and adolescents (issued 25th April, 2005). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/SSRI_31/WC500013082.pdf (accessed 29/07/10)
12. Committee for Medicinal Products for Human Use, European Medicines Agency. European Medicines Agency adopts a positive opinion for the use of Prozac in the treatment of children and adolescents suffering from depression (issued 6th June, 2006). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/12/WC500017468.pdf (accessed 29/07/10)
13. Lane RM. SSRI-induced extrapyramidal side-effects and akathisia: implications for treatment. *J Psychopharmacol* 1998; 12: 192–214.
14. Anonymous. Fluoxetine, suicide and aggression. *Drug Ther Bull* 1992; 30: 5–6.
15. Power AC, Cowen PJ. Fluoxetine and suicidal behaviour; some clinical and theoretical aspects of a controversy. *Br J Psychiatry* 1992; 161: 735–41.
16. Markel H, *et al.* LSD flashback syndrome exacerbated by selective serotonin reuptake inhibitor antidepressants in adolescents. *J Pediatr* 1994; 125: 817–19.
17. Joss JD, *et al.* Memory loss in a patient treated with fluoxetine. *Ann Pharmacother* 2003; 37: 1800–3.

Effects on sexual function. Sexual dysfunction is often noted in patients with depression and may be due to their antidepressant medication or to the disease itself. Complaints include a decrease in or loss of libido, delayed ejaculation, erectile difficulty, or anorgasmia in men;[1] loss of libido, delayed orgasm, or anorgasmia have been reported in women.[1,2] Early identification is important since drug-induced sexual dysfunction is a common cause of non-compliance; in addition, it may adversely affect the quality of life of patients and hamper their recovery.[3,4]

It has been considered that sexual dysfunction occurs in up to 1.9% of patients taking fluoxetine, with impotence or ejaculatory problems occurring in less than 1% of patients.[5] However, these figures, which were based on information supplied by the US manufacturer, have been disputed[6,7] and the incidence of sexual dysfunction may be higher than the manufacturer's data suggest. Earlier studies and anecdotal reports quoted rates of 7.8 to 75% for sexual dysfunction with fluoxetine but it appears that only small numbers of men were studied.[8] A later review[9] also estimated the incidence of SSRI-induced sexual dysfunction at between 10 and 75%.

The incidence of sexual dysfunction may differ between types of antidepressants. A large, observational study[3] found the rate of sexual dysfunction to be higher with the SSRIs (citalopram, fluoxetine, paroxetine, and sertraline) and the SNRI venlafaxine than with bupropion or nefazodone. However, no significant difference in rate was found among the SSRIs as a group. The study also identified other risk factors for developing sexual dysfunction which included increasing age, the use of high doses, and use with other medications. Gender, race, and length of treatment were not associated with an increased risk.

Suggested[1,4,10] strategies for managing SSRI-induced sexual dysfunction include reducing the dosage of the SSRI or altering the timing of doses, or changing to another antidepressant. In some cases tolerance may develop, particularly if the dysfunction occurred early in treatment. One small study[11] has indicated that spontaneous improvement may occur even up to 6 months after the start of therapy.[11] Evidence of efficacy for drug treatments is mainly anecdotal. Cyproheptadine seems to have been tried most often, but the SSRI may become less effective (see Antihistamines, under Interactions, p. 426.2) and patients should be monitored for worsening symptoms of depression.

The effects of the SSRIs on sexual function have been studied as a potential form of treatment for men with premature ejaculation (see Sexual Dysfunction in Uses, p. 419.1).

1. Frye CB, Berger JE. Treatment of sexual dysfunction induced by selective serotonin-reuptake inhibitors. *Am J Health-Syst Pharm* 1998; 55: 1167–9.
2. Feiger A, *et al.* Nefazodone versus sertraline in outpatients with major depression: focus on efficacy, tolerability, and effects on sexual function and satisfaction. *J Clin Psychiatry* 1996; 57 (suppl 2): 53–62.
3. Clayton AH, *et al.* Prevalence of sexual dysfunction among newer antidepressants. *J Clin Psychiatry* 2002; 63: 357–66.
4. Hirschfeld RMA. Long-term side effects of SSRIs: sexual dysfunction and weight gain. *J Clin Psychiatry* 2003; 64 (suppl 18): 20–4.
5. Hollander JB. Fluoxetine and sexual dysfunction. *JAMA* 1994; 272: 242.
6. Balon R. Fluoxetine and sexual dysfunction. *JAMA* 1995; 273: 1489.
7. Hopkins HS, Gelenberg AJ. Fluoxetine and sexual dysfunction. *JAMA* 1995; 273: 1489–90.
8. Hollander JB. Fluoxetine and sexual dysfunction. *JAMA* 1995; 273: 1490.
9. Gregorian RS, *et al.* Antidepressant-induced sexual dysfunction. *Ann Pharmacother* 2002; 36: 1577–89.
10. Woodrum ST, Brown CS. Management of SSRI-induced sexual dysfunction. *Ann Pharmacother* 1998; 32: 1209–15.
11. Haberfellner EM, Rittmannsberger H. Spontaneous remission of SSRI-induced orgasm delay. *Pharmacopsychiatry* 2004; 37: 127–30.

Effects on the skin. *Toxic epidermal necrolysis* developed in a 16-year-old girl 8 days after beginning fluvoxamine therapy.[1] Other drugs, which included metoclopramide, clorazepate, and clomipramine were discounted as possible causes.

Amitriptyline and fluoxetine have been implicated in the development of *atypical cutaneous lymphoid hyperplasia* in 8 patients, 7 of whom either had an underlying immunosuppressant systemic disease or were also receiving immunomodulatory drugs.[2] The lesions improved or resolved on stopping the antidepressant, although in some patients other factors may have contributed to the improvement.

Bullous pemphigoid induced by fluoxetine has been reported in a 75-year-old woman.[3] Spontaneous resolution followed within 3 weeks of stopping the drug.

Paroxetine treatment has been associated with the development of *cutaneous vasculitis*, which involved several fingers, in a 20-year-old woman;[4] rechallenge was positive. On both occasions the patient recovered when paroxetine was withdrawn.

A severe *bullous reaction with full-thickness skin necrosis* has been reported in a 48-year-old woman after 6 months of treatment with sertraline.[5] The lesions required extensive skin grafts and recovery was prolonged, with drug-induced scleroderma developing in the affected area.

1. Wolkenstein P, *et al.* Toxic epidermal necrolysis after fluvoxamine. *Lancet* 1993; 342: 304–5.
2. Crowson AN, Magro CM. Antidepressant therapy: a possible cause of atypical cutaneous lymphoid hyperplasia. *Arch Dermatol* 1995; 131: 925–9.
3. Rault S, *et al.* Bullous pemphigoid induced by fluoxetine. *Br J Dermatol* 1999; 141: 755–6.
4. Margolese HC, *et al.* Cutaneous vasculitis induced by paroxetine. *Am J Psychiatry* 2001; 158: 497.
5. Kirkup ME, *et al.* Delayed onset of bullous reaction with severe deep skin necrosis in association with sertraline. *Br J Dermatol* 2004; 150: 164–6.

Epileptogenic effect. Generalised seizures have been reported in 2 patients with no history of seizures after starting fluoxetine therapy.[1,2] Although convulsions have been noted in patients taking fluvoxamine (see Incidence of Adverse Effects, p. 428.1), a small clinical study involving 35 depressed epileptic patients[3] found no change in the number of seizures or in their nature when fluvoxamine was given in doses of up to 200 mg daily.

1. Weber JJ. Seizure activity associated with fluoxetine therapy. *Clin Pharm* 1989; 8: 296–8.
2. Ware MR, Stewart RB. Seizures associated with fluoxetine therapy. *DICP Ann Pharmacother* 1989; 23: 428.
3. Harmant J, *et al.* Fluvoxamine: an antidepressant with low (or no) epileptogenic effect. *Lancet* 1990; 336: 386.

Extrapyramidal effects. Extrapyramidal effects, such as tics[1] and akathisia,[2,3] have been reported with fluoxetine. By 1993, the UK CSM had received 39 reports of extrapyramidal reactions with paroxetine including 15 of dystonia of the face and mouth.[4] Although extrapyramidal effects might occur with other SSRIs, orofacial dystonias appeared to be more common with paroxetine. However, evidence from monitoring prescriptions within the UK showed that the overall incidence of extrapyramidal effects was the same for paroxetine as for other SSRIs.[5] Orofacial dystonias (teeth clenching) or dyskinesias (teeth grinding), resulting in severe damage to teeth and gums in many cases, have been reported[6] in 6 patients receiving fluoxetine, fluvoxamine, paroxetine, or sertraline. The authors concluded that these adverse effects were not specific for any particular SSRI. Analysis of spontaneous adverse reaction reports received by the national pharmacovigilance centre in The Netherlands found that there had been 41 reports of extrapyramidal effects associated with the SSRIs over a period of nearly 15 years;[7] parkinsonism and dystonia were the most frequently reported effects. Over the same time period, 14 reports had been received in total for other antidepressants. The authors commented that the results might be biased by the selective reporting of adverse reactions to the SSRIs.

Dyskinesia associated with withdrawal of citalopram and risperidone has been reported in a patient.[8]

The onset of akathisia may be linked to suicidal ideation; for further details, see Effects on Mental State, p. 420.2.

1. Eisenhauer G, Jermain DM. Fluoxetine and tics in an adolescent. *Ann Pharmacother* 1993; 27: 725–6.
2. Lipinski JF, *et al.* Fluoxetine-induced akathisia: clinical and theoretical implications. *J Clin Psychiatry* 1989; 50: 339–42.
3. Rothschild AJ, Locke CA. Reexposure to fluoxetine after serious suicide attempts by three patients: the role of akathisia. *J Clin Psychiatry* 1991; 52: 491–3.
4. CSM/MCA. Dystonia and withdrawal symptoms with paroxetine (Seroxat). *Current Problems* 1993; 19: 1. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON20244546-RevisionSelectionMethod=LatestReleased (accessed 04/08/08)
5. Choo V. Paroxetine and extrapyramidal reactions. *Lancet* 1993; 341: 624.
6. Fitzgerald K, Healy D. Dystonias and dyskinesias of the jaw associated with the use of SSRIs. *Hum Psychopharmacol Clin Exp* 1995; 10: 215–19.
7. Schillevoort I, *et al.* Extrapyramidal syndromes associated with selective serotonin reuptake inhibitors: a case-control study using spontaneous reports. *Int Clin Psychopharmacol* 2002; 17: 75–9.
8. Miller LJ. Withdrawal-emergent dyskinesia in a patient taking risperidone/citalopram. *Ann Pharmacother* 2000; 34: 269.

Hypersensitivity. Hypersensitivity reactions to SSRIs are well documented. Interestingly, despite structural dissimilarities, there have been a few reports of cross-sensitivity between SSRIs. A young man who had previously developed a maculopapular rash while taking paroxetine suffered a similar reaction after starting sertraline;[1] both episodes resolved after the SSRI was withdrawn.

1. Warnock CA, Azadian AG. Cross-sensitivity between paroxetine and sertraline. *Ann Pharmacother* 2002; 36: 631–3.

Hyponatraemia. See Effects on the Endocrine System, p. 419.3.

Overdosage. SSRIs are generally regarded as being less toxic in overdosage than tricyclic antidepressants or MAOIs. A review[1] of SSRI overdosage, covering the period 1985 to 1997, noted that there had been remarkably few fatal overdoses when taken alone. Moderate overdoses (up to about 30 times the usual daily dose) were generally associated with minor symptoms at most; only at very high doses (more than 75 times the usual daily dose) did more serious effects such as seizures, ECG abnormalities, and decreased consciousness tend to occur. Toxicity was greatly increased, however, when overdoses of SSRIs were taken with alcohol or other drugs. There was no evidence of a difference in the various SSRIs with respect to safety in overdosage. The results of a more recent cohort study[2] have also confirmed the relative safety of the SSRIs in overdosage. However, the study also found that citalopram was potentially more cardiotoxic than other SSRIs in overdose, causing significant prolongation of the QT interval (see below). In addition, serotonin syndrome was noted as being a common feature of SSRI overdosage although in most cases symptoms were not severe or life-threatening.

- Fatal overdose was reported with *citalopram* in 6 patients,[3] although the suggested cause of death as cardiac dysfunction rather than seizures was disputed.[4] Nonetheless, cases[2,5] of cardiac abnormalities (including prolongation of the QT interval) associated with citalopram overdose have continued to be reported, and routine ECG monitoring may be necessary in the management of overdosage. Some authors consider that a metabolite, didemethylcitalopram, rather than citalopram itself, may be responsible for the cardiotoxicity seen with citalopram overdose.[5] At therapeutic doses, concentrations of didemethylcitalopram are much lower than those of citalopram and, in general, significant cardiotoxicity is not seen; however, in overdosage the amount of didemethylcitalopram may be sufficient to induce cardiac conduction abnormalities.
- A report involving 87 cases in which *fluoxetine* was taken in overdosage without other drugs found that the main symptoms were tachycardia, drowsiness, tremor, and nausea and vomiting.[6] These were considered relatively minor, and were of short duration, and supportive care was considered to be the only intervention necessary.
- Of 41 cases of self-poisoning with *fluvoxamine*, only one patient died and even here fluvoxamine was not implicated.[7] Prolonged cerebral depression occurred in a patient after fluvoxamine overdose,[7] but this may have been due to an interaction with temazepam which the patient also took in overdose.
- One hour after taking 2 g of *sertraline* in a suicide attempt a 42-year-old woman was flushed, angry, emotionally labile, and easily distracted but not psychotic.[8] Apart from watery bowel movements recovery was mainly uneventful after treatment with gastric lavage, oral activated charcoal with sorbitol, and intravenous hydration. In another case,[9] symptoms resembling serotonin syndrome developed in a 51-year-old woman after an overdose attempt with sertraline; it was believed that the patient may have taken as much as 8 g of sertraline. She recovered with supportive treatment. Abnormal liver function tests have also been noted after

a suicide attempt with sertraline (see Effects on the Liver, p. 420.2).

For a discussion of choice of antidepressant with respect to toxicity in overdosage, see under Depression, p. 398.1.

1. Barbey JT, Roose SP. SSRI safety in overdose. *J Clin Psychiatry* 1998; 59 (suppl 15): 42–8.
2. Isbister GK, *et al.* Relative toxicity of selective serotonin reuptake inhibitors (SSRIs) in overdose. *J Toxicol Clin Toxicol* 2004; 42: 277–85.
3. Östrom M, *et al.* Fatal overdose with citalopram. *Lancet* 1996; 348: 339–40.
4. Brion F, *et al.* Fatal overdose with citalopram? *Lancet* 1996; 348: 1380.
5. Catalano G, *et al.* QTc interval prolongation associated with citalopram overdose: a case report and literature review. *Clin Neuropharmacol* 2001; 24: 158–62.
6. Borys DJ, *et al.* Acute fluoxetine overdose: a report of 234 cases. *Am J Emerg Med* 1992; 10: 115–20.
7. Banerjee AK. Recovery from prolonged cerebral depression after fluvoxamine overdose. *BMJ* 1988; 296: 1774.
8. Brown DF, Kerr HD. Sertraline overdose. *Ann Pharmacother* 1994; 28: 1307.
9. Brendel DH, *et al.* Massive sertraline overdose. *Ann Emerg Med* 2000; 36: 524–6.

Treatment of Adverse Effects

Treatment of overdosage with an SSRI involves appropriate symptomatic and supportive therapy. Activated charcoal may be given orally if the amount ingested was large (see p. 424.1) and treatment is within an hour of ingestion, provided the airway can be protected. Dialysis, haemoperfusion, exchange transfusion, and measures to increase urine production are considered unlikely to be of benefit.

Activated charcoal. The UK Poisons Information Service considers the benefit of gastric decontamination in the management of overdosage with SSRIs to be uncertain. However, it is suggested that oral activated charcoal may be considered in adults and children if this is given within 1 hour of ingestion and the quantity of SSRI exceeds the following amount, provided that the airway can be protected:

- citalopram: 2 mg/kg
- escitalopram: 1 mg/kg
- fluoxetine: 6 mg/kg
- fluvoxamine maleate: 15 mg/kg
- paroxetine: 3 mg/kg
- sertraline: 7 mg/kg

Precautions

Because of their epileptogenic effect SSRIs should be used with caution in patients with epilepsy or a history of such disorders (and should be avoided if the epilepsy is poorly controlled). Treatment should be stopped if seizures develop or when there is an increase in seizure frequency. Care is advised in patients receiving ECT as prolonged seizures have occurred rarely. SSRIs should also be used with caution in patients with cardiac disease or a history of bleeding disorders. Although SSRIs are preferred to tricyclics for the treatment of depression in patients with diabetes, they may alter glycaemic control and therefore caution is also warranted in diabetic subjects. SSRIs should be used with caution in patients with angle-closure glaucoma.

Fluoxetine should be stopped in patients who develop a rash since systemic effects, possibly related to vasculitis, have occurred in such patients. Fluoxetine undergoes hepatic metabolism and should be used with caution and in reduced doses in patients with impaired hepatic function.

Patients should be closely monitored during early therapy until significant improvement in depression occurs because suicide is an inherent risk in depressed patients. For further details, see under Depression, p. 398.1. For a discussion of the concern that SSRIs may increase suicidal ideation, and concerns about their use for depression in children and adolescents, see Effects on Mental State in Adverse Effects, p. 420.2. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be observed when treating patients with other disorders. If SSRIs are given for the depressive component of bipolar disorder, mania may be precipitated. Symptoms may also worsen during the initial treatment of panic disorder with SSRIs.

SSRIs may impair performance of skilled tasks and, if affected, patients should not drive or operate machinery.

Some licensed product information recommends reduced or less frequent dosage of SSRIs for elderly patients.

SSRIs should generally be withdrawn gradually to reduce the risk of withdrawal symptoms although this may be unnecessary for fluoxetine because of its long half-life.

Abuse. There have been occasional reports of individuals abusing fluoxetine.[1,2]

1. Pagliaro LA, Pagliaro AM. Fluoxetine abuse by an intravenous drug user. *Am J Psychiatry* 1993; 150: 1898.
2. Tinsley JA, *et al.* Fluoxetine abuse. *Mayo Clin Proc* 1994; 69: 166–8.

Blood disorders. For a reference recommending cautious use of SSRIs in patients with a history of bleeding disorders, see Effects on the Blood in Adverse Effects, p. 419.2.

Breast feeding. The American Academy of Pediatrics[1] considers that the effect of all antidepressants, including SSRIs (fluoxetine, fluvoxamine, paroxetine, and sertraline) on nursing infants is unknown but may be of concern. In addition, most licensed product information advises that SSRIs should be avoided by women during breast feeding.

- *Citalopram* and its metabolites have been detected in breast milk; however, in one study, the plasma concentrations in exposed infants were either very low or undetectable and no adverse effects were reported.[2] In another study, 3 out of 31 breast-fed infants whose mothers were taking citalopram had adverse effects, specifically one case each of colic, decreased feeding, and irritability.[3] However, there was no significant increase in the risk of adverse events in this group of infants when compared with either infants of depressed mothers not taking citalopram, or infants of healthy controls.
- Symptoms of colic were reported[4] in a 6-week-old infant whose mother was taking *fluoxetine* 20 mg daily. The concentrations of fluoxetine and its active metabolite norfluoxetine were 69 nanograms/mL and 90 nanograms/mL respectively in breast milk, and 340 nanograms/mL and 208 nanograms/mL respectively in the infant's plasma. The infant's symptoms resolved when he was formula fed. Post-natal weight gain has been reduced in infants exposed to fluoxetine during breast feeding, although in all cases the reduction was less than 2 standard deviations below the norm.[5] In another report,[6] several seizure-like episodes occurred in a breast-fed infant whose mother was taking fluoxetine in addition to carbamazepine and buspirone; however, plasma drug concentrations in the infant were significant only for fluoxetine and norfluoxetine. In a study[7] of 10 women taking fluoxetine while breast feeding 11 infants, breast milk concentrations of fluoxetine ranged from 17.4 to 293 nanograms/mL and of norfluoxetine from 23.4 to 379.1 nanograms/mL. No adverse effects were noted in the infants. Similar concentrations have occurred in other breast-fed infants without any apparent drug-induced adverse effects.[8-10] Fluoxetine and norfluoxetine were detected in the milk of 14 nursing women.[11] Blood samples were taken from 9 of the infants in the study, and of these, fluoxetine was detected in the plasma of 5 and norfluoxetine in 7. Although it was felt that many infants would tolerate the mean combined dose of fluoxetine and norfluoxetine transmitted via breast milk in this study, there was considerable interpatient variability in estimated infant dose and caution should be exercised; neonates in particular had higher concentrations of norfluoxetine than older infants. Moreover, since both fluoxetine and norfluoxetine have long half-lives, neonates already exposed *in utero* may have an additional risk of adverse effects during breast feeding.
- The excretion of *fluvoxamine* into breast milk was studied[12] in a woman who had been receiving fluvoxamine maleate 100 mg twice daily for 2 weeks. The concentration of fluvoxamine base 4.75 hours after a dose was 310 nanograms/mL in maternal plasma and 90 nanograms/mL in breast milk. It was estimated that an infant would ingest only 0.5% of the daily maternal intake. It was considered that these data supported the notion that the use of fluvoxamine by nursing mothers posed little risk to the infant. A subsequent study[13] found no detectable drug concentrations in the plasma of breast-fed infants exposed to fluvoxamine; the authors suggested that fluvoxamine was a reasonable choice for nursing mothers requiring treatment for depression.
- Although *paroxetine* was detected in measurable concentrations in the breast milk of a group of 10 nursing mothers receiving paroxetine no adverse effects were reported in any of their breast-fed infants.[14] Paroxetine could not be detected in the plasma of 7 of the 8 infants from whom samples were obtained and in the other infant, concentrations were not quantifiable. Another study involving 7 women suggested that the dose of paroxetine to suckling infants would be 0.7 to 2.9% of the weight-adjusted maternal dose.[15] A later study[13] also found no detectable drug concentrations in the plasma of breast-fed infants exposed to paroxetine; the authors suggested that paroxetine was a reasonable choice for nursing mothers requiring treatment for depression. In a prospective cohort study, weight gain at 6 and 12 months of age in infants whose mothers took paroxetine during breast feeding was not adversely affected when compared with the infants of mothers who either did not breast feed or breast fed without taking any drugs during lactation;[16] in addition, there was no difference in reaching the usual developmental milestones between the infants of the 3 groups.
- Plasma concentrations of *sertraline* were undetectable in a breast-fed infant despite the presence of concentrations in the mother's breast milk ranging from 8.8 to 43 nanograms/mL over a 24-hour period.[17] However, the authors pointed out that metabolite concentrations were not measured and that sertraline may have been present in the infant at a concentration below the level of sensitivity of the assay. Other studies[13,18-21] have found desmethylsertraline in breast milk, which was also detected in the plasma of some of the infants in several studies[13,18,20,21] but not all.[19] The authors of at least one study[13] suggested that sertraline was a reasonable choice for nursing mothers requiring treatment for depression. In addition, some authors recommend expressing and discarding breast milk 8 to 9 hours after a maternal dose when levels of desmethylsertraline and sertraline are maximal, in order to significantly reduce infant exposure to sertraline.[21]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 24/11/05)
2. Heikkinen T, *et al.* Citalopram in pregnancy and lactation. *Clin Pharmacol Ther* 2002; 72: 184–91.
3. Lee A, *et al.* Frequency of infant adverse events that are associated with citalopram use during breast-feeding. *Am J Obstet Gynecol* 2004; 190: 218–21.
4. Lester BM, *et al.* Possible association between fluoxetine hydrochloride and colic in an infant. *J Am Acad Child Adolesc Psychiatry* 1993; 32: 1253–5.
5. Chambers CD, *et al.* Weight gain in infants breastfed by mothers who take fluoxetine. *Pediatrics* 1999; 104: 1120–1.
6. Brent NB, Wisner KL. Fluoxetine and carbamazepine concentrations in a nursing mother/infant pair. *Clin Pediatr (Phila)* 1998; 37: 41–4.
7. Taddio A, *et al.* Excretion of fluoxetine and its metabolite, norfluoxetine, in human breast milk. *J Clin Pharmacol* 1996; 36: 42–7.
8. Isenberg KE. Excretion of fluoxetine in human breast milk. *J Clin Psychiatry* 1990; 51: 169.
9. Burch KJ, Wells BG. Fluoxetine/norfluoxetine concentrations in human milk. *Pediatrics* 1992; 89: 676–7.
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12. Wright S, *et al.* Excretion of fluvoxamine in breast milk. *Br J Clin Pharmacol* 1991; 31: 209.
13. Hendrick V, *et al.* Use of sertraline, paroxetine and fluvoxamine by nursing women. *Br J Psychiatry* 2001; 179: 163–6.
14. Begg EJ, *et al.* Paroxetine in human milk. *Br J Clin Pharmacol* 1999; 48: 142–7.
15. Öhman R, *et al.* Excretion of paroxetine into breast milk. *J Clin Psychiatry* 1999; 60: 519–23.
16. Merlob P, *et al.* Paroxetine during breast-feeding: infant weight gain and maternal adherence to counsel. *Eur J Pediatr* 2004; 163: 135–9.
17. Altshuler LL, *et al.* Breastfeeding and sertraline: a 24-hour analysis. *J Clin Psychiatry* 1995; 56: 243–5.
18. Stowe ZN, *et al.* Sertraline and desmethylsertraline in human breast milk and nursing infants. *Am J Psychiatry* 1997; 154: 1255–60.
19. Kristensen JH, *et al.* Distribution and excretion of sertraline and N-desmethylsertraline in human milk. *Br J Clin Pharmacol* 1998; 45: 453–7.
20. Epperson N, *et al.* Maternal sertraline treatment and serotonin transport in breast-feeding mother-infant pairs. *Am J Psychiatry* 2001; 158: 1631–7.
21. Stowe ZN, *et al.* The pharmacokinetics of sertraline excretion into human breast milk: determinants of infant serum concentrations. *J Clin Psychiatry* 2003; 64: 73–80.

Children. SSRIs are associated with an increased risk of potentially suicidal behaviour when used for the treatment of depression in children and adolescents under 18 years old; for further details, see under Effects on Mental State, p. 420.2.

Diabetes mellitus. A patient with type 1 diabetes mellitus lost hypoglycaemic awareness after starting therapy with fluoxetine.[1] Awareness returned on tapered withdrawal of fluoxetine. Changes in blood sugar concentrations may occur in patients with diabetes treated for depression with SSRIs (see also Effects on the Endocrine System, p. 419.3); however, these may represent an improvement in glycaemic control.[2]

1. Sawka AM, *et al.* Loss of hypoglycemia awareness in an adolescent with type 1 diabetes mellitus during treatment with fluoxetine hydrochloride. *J Pediatr* 2000; 136: 394–6.
2. Lustman PJ, *et al.* Fluoxetine for depression in diabetes: a randomized double-blind placebo-controlled trial. *Diabetes Care* 2000; 23: 618–23.

Driving. While affective disorders probably adversely affect driving skill,[1,2] treatment with antidepressants can also be hazardous,[1] although patients may be safer drivers with medication than without.[2] Impairment of performance is largely related to sedative and antimuscarinic effects. These are more pronounced with older antidepressants such as the tricyclic antidepressants than with the SSRIs, but a comparative study[3] of fluoxetine (an SSRI) and dosulepin (a tricyclic) in healthy subjects showed a similar but apparently small potential for impairing psychomotor and driving performance. A later epidemiological study[4] was unable to confirm any increased risk of road-traffic accidents in those drivers receiving tricyclic antidepressants or SSRIs.

In the UK, the Driver and Vehicle Licensing Authority (DVLA)[5] considers that drugs such as SSRIs may have fewer adverse effects on drivers than antidepressants with pronounced antimuscarinic or antihistaminic adverse

effects, such as tricyclic antidepressants. However, all drugs acting on the CNS can impair alertness, concentration, and driving performance, particularly at the start of treatment or when the dose is increased; driving must cease if patients are adversely affected. Patients with severe depressive illnesses complicated by significant memory or concentration problems, agitation, behavioural disturbances, or suicidal thoughts should also cease driving pending the outcome of medical enquiry.

1. Ashton H. Drugs and driving. *Adverse Drug React Bull* 1983; 98: 360–3.
2. Cremona A. Mad drivers: psychiatric illness and driving performance. *Br J Hosp Med* 1986; 35: 193–5.
3. Ramaekers JG, *et al.* A comparative study of acute and subchronic effects of dothiepin, fluoxetine and placebo on psychomotor and actual driving performance. *Br J Clin Pharmacol* 1995; 39: 397–404.
4. Barbone F, *et al.* Association of road-traffic accidents with benzodiazepine use. *Lancet* 1998; 352: 1331–6.
5. Driver and Vehicle Licensing Agency. For medical practitioners: at a glance guide to the current medical standards of fitness to drive (issued November 2013). Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/258991/aagv1.pdf (accessed 20/11/13)

Gastrointestinal disorders. For the opinion that the SSRIs may produce a clinically important increase in the risk of upper gastrointestinal bleeding in patients with a high risk of such bleeding, see under Effects on the Gastrointestinal Tract, p. 420.1.

Glaucoma. For reference to SSRIs precipitating or exacerbating symptoms of glaucoma, see Effects on the Eyes, p. 420.1.

Mania. Hypomania or mania have been reported with the SSRIs; consequently, UK licensed product information recommends that SSRIs should be withdrawn in any patient entering a manic phase.

Fluvoxamine was associated with manic behaviour in 8 patients who were being treated for major depression;[1] 3 also had obsessive-compulsive disorder. Daily doses of fluvoxamine ranged from 75 to 300 mg and duration of therapy to development of manic behaviour from 2 to 6 weeks. The authors were unable to determine whether fluvoxamine had induced mania or unmasked latent bipolar disorder in these patients. However, they recommended that fluvoxamine-treated patients should be monitored for manic behaviour.

Symptoms of manic behaviour also developed in a 7-year-old girl after taking *sertraline* for about 2 weeks for the treatment of major depression.[2] She recovered within a few weeks of stopping sertraline.

1. Dorevitch A, *et al.* Fluvoxamine-associated manic behavior: a case series. *Ann Pharmacother* 1993; 27: 1455–7.
2. Ghaziuddin M. Mania induced by sertraline in a prepubertal child. *Am J Psychiatry* 1994; 151: 944.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fluoxetine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Pregnancy. In an early prospective study[1] comparing 128 pregnant women exposed to a mean daily dose of about 26 mg of fluoxetine during their first trimester with control groups given tricyclic antidepressants or non-teratogens, the incidence of **neonatal malformations** was similar in all groups and did not exceed that in the general population. However, there was a tendency to a higher incidence of miscarriages in the groups given fluoxetine or tricyclics. A later prospective study[2] comparing 228 pregnant women taking fluoxetine with a control group taking non-teratogens also failed to find a significant increased incidence in major fetal abnormalities in the fluoxetine group; it also did not reveal an increased risk of miscarriage. There was an increase in the incidence of minor fetal abnormalities in infants exposed to fluoxetine during the first trimester. Also, infants exposed to fluoxetine during the third trimester had more perinatal complications such as prematurity, low full-term birthweight and length, and poor neonatal adaptation compared with infants exposed only during the first and second trimesters. However, the design of this study was criticised[3] because of several methodological problems such as unmatched controls and a higher maternal age in the fluoxetine group, which may partly explain the excess of poor perinatal outcomes.

The manufacturer evaluated the outcome of 796 pregnancies in which the mother received fluoxetine during the first trimester and considered that it was unlikely that fluoxetine increased the risk of miscarriage or fetal malformation.[4] A prospective controlled study[5] on pregnancy outcome in women exposed to fluvoxamine, paroxetine, or sertraline also found that, when used in recommended doses, there appeared to be no increase in the risk of major congenital malformations, miscarriages, or still-births when compared with women exposed to non-teratogens. Nonetheless, the results from a more recent meta-analysis which included some of the above studies have suggested that maternal exposure to antidepressant treatment (specifically SSRIs, tricyclics, nefazodone, trazodone, or venlafaxine) may significantly increase the risk of miscarriage in comparison to women not exposed to antidepressants.[6] However, the authors acknowledged that the underlying depression itself might be a contributing factor to the increased risk.

There is some evidence that paroxetine may be more teratogenic than other antidepressants. In 2005, the manufacturer *GlaxoSmithKline* commented[7] on the results of 2 studies on the use of antidepressants in pregnant women. Data from a retrospective US epidemiological study showed a non-significant, 1.5-fold increase in the risk of cardiovascular malformations, particularly ventricular septal defects, in the infants of mothers who had taken paroxetine during pregnancy when compared with those whose mothers had taken other antidepressants. The data also showed a significant increase in the overall risk of major congenital malformations (including cardiovascular defects) in those infants exposed to paroxetine. A second study using data from the Swedish national birth registry also found a twofold increase in the risk of cardiovascular malformations in infants exposed to paroxetine when compared with the general population; however, this study did not find an increase in the overall risk of major congenital malformations in those infants exposed to paroxetine. Based on these findings, the manufacturer revised the product literature for paroxetine to strengthen the warnings on its use in pregnancy. More recently, a Danish study[8] concluded that there was a significant, twofold increase in the risk of septal heart defects with the SSRIs as a group (specifically citalopram, fluoxetine, paroxetine, and sertraline) when compared with a general population of pregnant women. However, when considered individually, the increase in risk was only statistically significant for citalopram and sertraline. The risk of major congenital malformations overall was not increased in this study. These somewhat conflicting results may be explained by methodological differences between the studies.

Maternal use of SSRIs has been associated with **neonatal complications**. CNS toxicity and an increased heart rate were reported in a neonate whose mother had received 20 mg of fluoxetine daily throughout most of her pregnancy.[9] The neonate's symptoms resolved 96 hours after delivery. In another neonate whose mother took up to 30 mg daily of fluoxetine throughout the third trimester cardiac arrhythmias were noted.[10] In a matched-control study[11] the rate of complications after delivery in 55 infants exposed to paroxetine during the third trimester was higher than in a control group who had been exposed to paroxetine or non-teratogenic agents during the first or second timesters. Complications that occurred in the infants exposed in the third trimester included respiratory distress (9 cases), hypoglycaemia (2 cases), bradycardia (1 case), jaundice (1 case), and suckling problems (1 case). More recently, another matched-control study[12] has suggested that exposure to SSRIs (in this case fluoxetine, paroxetine, and sertraline) after the 20th week of gestation may increase the risk of persistent pulmonary hypertension of the newborn (PPHN). Of 377 infants with a confirmed diagnosis of PPHN, the mothers of 14 (3.7%) had taken an SSRI after the 20th week of gestation, compared with only 6 out of 836 infants (0.7%) in the matched-control group. Although these figures represent about a sixfold increase in the risk of PPHN in infants exposed to SSRIs *in utero*, the absolute risk remains relatively low (about 6 to 12 per 1000 women).

Several reports[2,13-17] have described symptoms such as jitteriness, irritability, sleep disturbances, and altered muscle tone in neonates who had been exposed to SSRIs *in utero*, especially during the third trimester; in the majority of cases the symptoms are mild and self-limiting. Although withdrawal symptoms have been reported with most SSRIs, they have been more commonly reported in those neonates exposed to paroxetine.[18] More recently, some authors have used the term neonatal behavioural syndrome to refer to such symptoms.[16] It is unclear whether the symptoms represent a withdrawal syndrome or direct serotonin toxicity;[15,17,19] however, it has been suggested by some that *in-utero* exposure to SSRIs with a short half-life such as paroxetine may lead to a neonatal withdrawal syndrome whereas exposure to an SSRI with a long half-life, particularly fluoxetine, may manifest as neonatal serotonin toxicity.[16] There have been case reports of intraventricular haemorrhage in neonates whose mothers took SSRIs during late pregnancy but there is currently not enough data to determine whether the frequency of such bleeds in infants exposed to SSRIs is higher than normal.[17]

The effects of fluoxetine on fetal **neurodevelopment** were studied[20] in 55 pregnant women by later assessing global IQ of the children; no differences were seen in those exposed to fluoxetine *in utero* during the first trimester compared with those exposed to tricyclic antidepressants or adverse developmental influences. A subsequent study indicated that exposure to fluoxetine or tricyclic antidepressants throughout gestation did not appear to affect cognition adversely.[21] In another follow-up study, subtle differences in motor development and control, in particular tremulousness and inappropriate fine motor movements, were noted in the infants and children of depressed mothers who had taken SSRIs during pregnancy when compared with the infants of depressed mothers who had not taken any medication.[22] However, in other measures of mental development no differences between the two groups were seen.

1. Pastuszak A, *et al.* Pregnancy outcome following first-trimester exposure to fluoxetine (Prozac). *JAMA* 1993; 269: 2246–8.
2. Chambers CD, *et al.* Birth outcomes in pregnant women taking fluoxetine. *N Engl J Med* 1996; 335: 1010–15.
3. Robert E. Treating depression in pregnancy. *N Engl J Med* 1996; 335: 1056–8.
4. Goldstein DJ, *et al.* Effects of first-trimester fluoxetine exposure on the newborn. *Obstet Gynecol* 1997; 89: 713–18.
5. Kulin NA, *et al.* Pregnancy outcome following maternal use of the new selective serotonin reuptake inhibitors: a prospective controlled multicenter study. *JAMA* 1998; 279: 609–10.
6. Hemels MEH, *et al.* Antidepressant use during pregnancy and the rates of spontaneous abortions: a meta-analysis. *Ann Pharmacother* 2005; 39: 803–9.
7. GlaxoSmithKline USA. Important prescribing information (issued December 2005). Available at: http://www.gsk.com/media/paroxetine/pregnancy_hcp_letter.pdf (accessed 23/02/10)
8. Pedersen LH, *et al.* Selective serotonin reuptake inhibitors in pregnancy and congenital malformations: population based cohort study. *BMJ* 2009; 339: b3569.
9. Spencer MJ. Fluoxetine hydrochloride (Prozac) toxicity in a neonate. *Pediatrics* 1993; 92: 721–2.
10. Abebe-Campino G, *et al.* Cardiac arrhythmia in a newborn infant associated with fluoxetine use during pregnancy. *Ann Pharmacother* 2002; 36: 533–4.
11. Costei AM, *et al.* Perinatal outcome following third trimester exposure to paroxetine. *Arch Pediatr Adolesc Med* 2002; 156: 1129–32.
12. Chambers CD, *et al.* Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *N Engl J Med* 2006; 354: 579–87.
13. Nijhuis IJM, *et al.* Withdrawal reactions of a premature neonate after maternal use of paroxetine. *Arch Dis Child Fetal Neonatal Ed* 2001; 84: F77.
14. Stiskal JA, *et al.* Neonatal paroxetine withdrawal syndrome. *Arch Dis Child Fetal Neonatal Ed* 2001; 84: F134–F135.
15. Zeskind PS, Stephens LE. Maternal selective serotonin reuptake inhibitor use during pregnancy and newborn neurobehavior. *Pediatrics* 2004; 113: 368–75.
16. Moses-Kolko EL, *et al.* Neonatal signs after late in utero exposure to serotonin reuptake inhibitors: literature review and implications for clinical applications. *JAMA* 2005; 293: 2372–83.
17. Nordeng H, Spigset O. Treatment with selective serotonin reuptake inhibitors in the third trimester of pregnancy: effects on the infant. *Drug Safety* 2005; 28: 565–81.
18. Sanz EJ, *et al.* Selective serotonin reuptake inhibitors in pregnant women and neonatal withdrawal syndrome: a database analysis. *Lancet* 2005; 365: 482–7.
19. Isbister GK, *et al.* Neonatal paroxetine withdrawal syndrome or actually serotonin syndrome? *Arch Dis Child Fetal Neonatal Ed* 2001; 85: F147–F148.
20. Nulman I, *et al.* Neurodevelopment of children exposed in utero to antidepressant drugs. *N Engl J Med* 1997; 336: 258–62.
21. Nulman I, *et al.* Child development following exposure to tricyclic antidepressants or fluoxetine throughout fetal life: a prospective, controlled study. *Am J Psychiatry* 2002; 159: 1889–95.
22. Casper RC, *et al.* Follow-up of children of depressed mothers exposed or not exposed to antidepressant drugs during pregnancy. *J Pediatr* 2003; 142: 402–8.

Surgery. In patients undergoing orthopaedic surgery, the risk of perioperative blood loss was significantly increased in those taking serotonergic antidepressants (specifically clomipramine, fluoxetine, fluvoxamine, paroxetine, sertraline, and venlafaxine) when compared with those on non-serotonergic antidepressants.[1] In addition, there was a significant increase in the need for blood transfusion during surgery in those on serotonergic antidepressants compared with those not receiving antidepressant medication.

1. Movig KLL, *et al.* Relationship of serotonergic antidepressants and need for blood transfusion in orthopedic surgical patients. *Arch Intern Med* 2003; 163: 2354–8.

Withdrawal. Withdrawal reactions have been reported for all SSRIs and the related antidepressants mirtazapine and venlafaxine on dosage reduction or stopping treatment, although the frequency of such reactions may vary.[1-5] Paroxetine and venlafaxine have been associated with withdrawal reactions more often than other serotonergic antidepressants; in the case of paroxetine this may be due, in part, to its short half-life. Fluvoxamine also has a short half-life and has been shown in some studies to have a high risk of withdrawal reactions. The apparent lower risk of withdrawal reactions with fluoxetine may be due to its long half-life. Other factors that increase the risk of withdrawal reactions include abrupt withdrawal, the use of high doses, and prolonged therapy.[5]

In general, withdrawal reactions tend to occur within 3 days of stopping an SSRI or related antidepressant,[1,4,5] although a delay of up to 2 weeks may be noted with fluoxetine.[5] Common symptoms include dizziness, numbness and tingling, gastrointestinal disturbances (particularly nausea and vomiting), headache, sweating, anxiety, and sleep disorders. In some cases withdrawal symptoms may be severe and disabling. There has also been a report[6] of 2

patients without a history of major psychiatric disorder who developed severe behavioural symptoms when paroxetine was withdrawn. Withdrawal was abrupt in one patient and more gradual, over a 12-day period, in the other. Symptoms were mainly hypomanic over the first few days, followed by a period of escalated ego-dystonic aggression, behavioural dyscontrol, and suicidal ideation.

Antidepressant dose tapering appears to reduce the frequency and severity of withdrawal reactions.[5] The *BNF* recommends that any antidepressant, including an SSRI, that has been taken regularly for 8 weeks or more should be stopped gradually over a period of about 4 weeks, or as much as 6 months in patients who have been receiving long-term maintenance therapy.

The withdrawal syndrome of the SSRIs is not considered to be a consequence of dependence.[4,5]

See also Extrapyramidal Effects under Adverse Effects, p. 421.2. For debate about whether a withdrawal syndrome exists in neonates whose mothers have received SSRIs see Pregnancy, p. 423.1.

1. Price JS, *et al.* A comparison of the post-marketing safety of four selective serotonin re-uptake inhibitors including the investigation of symptoms occurring on withdrawal. *Br J Clin Pharmacol* 1996; **42**: 757–63.
2. Adverse Drug Reactions Advisory Committee (ADRAC). SSRI's and withdrawal syndrome. *Aust Adverse Drug React Bull* 1996; **15**: 3. Also available at: http://www.tga.gov.au/adr/aadrb/aadr9602.htm (accessed 14/08/08)
3. Coupland NJ, *et al.* Serotonin reuptake inhibitor withdrawal. *J Clin Psychopharmacol* 1996; **16**: 356–62.
4. CSM/MCA. Selective serotonin reuptake inhibitors (SSRIs). *Current Problems* 2000; **26**: 11–12. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007460&RevisionSelectionMethod=LatestReleased (accessed 24/11/05)
5. Weller IVD. *Report of the CSM Expert Working Group on the safety of selective serotonin reuptake inhibitor antidepressants.* London: The Stationery Office, 2005. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON019472&RevisionSelectionMethod=LatestReleased (accessed 14/08/08)
6. Bloch M, *et al.* Severe psychiatric symptoms associated with paroxetine withdrawal. *Lancet* 1995; **346**: 57.

Interactions

SSRIs interact with other drugs mainly as a result of their inhibitory activity on hepatic cytochrome P450 isoenzymes. Individual SSRIs do not all show the same degree of inhibition nor do they react with the same isoenzymes. The drugs inhibited by specific SSRIs depends on the isoenzyme affected.

As SSRIs have occasionally been associated with bleeding disorders and other effects on the blood, caution is advised when they are given with drugs known to affect platelet function.

Although different antidepressants have been used together under expert supervision in refractory cases of depression, adverse reactions including the *serotonin syndrome* (see p. 445.2) may occur; in its more severe form, serotonin syndrome can resemble neuroleptic malignant syndrome. Sequential prescribing of different types of antidepressant may also produce adverse reactions, and an appropriate drug-free interval should elapse between stopping one type of antidepressant and starting another. SSRIs should not generally be given to patients receiving MAOIs or for at least 2 weeks after their use. No treatment-free period is necessary after stopping a reversible inhibitor of monoamine oxidase type A (RIMA) and starting an SSRI. At least one week should elapse between withdrawing an SSRI and starting any drug liable to provoke a serious reaction (e.g. phenelzine); in the case of the SSRI sertraline the drug-free interval is extended to 2 weeks, and for fluoxetine 5 weeks, because of their longer half-lives. (For fluoxetine, the interval may need to be further extended if therapy has been prolonged or if high doses have been given.) Adverse effects such as the serotonin syndrome may also occur when the SSRIs are given with other drugs known to act on the same neurotransmitter, a consequence of synergistic interaction.

Further details concerning some of these interactions, and others, are given below.

References.

1. Mitchell PB. Drug interactions of clinical significance with selective serotonin reuptake inhibitors. *Drug Safety* 1997; **17**: 390–406.
2. Sproule BA, *et al.* Selective serotonin reuptake inhibitors and CNS drug interactions: a critical review of the evidence. *Clin Pharmacokinet* 1997; **33**: 454–71.
3. Bemeryck A, Belpaire FM. Selective serotonin reuptake inhibitors and cytochrome P-450 mediated drug-drug interactions: an update. *Curr Drug Metab* 2002; **3**: 13–37.

Antibacterials. Rapid development of delirium was reported[1] in a patient when *clarithromycin* was added to his existing regimen of fluoxetine and nitrazepam. It was suggested that his delirium was a result of increased plasma-fluoxetine concentrations produced by the inhibition of cytochrome P450 enzymes by clarithromycin. Serotonin syndrome developed in a patient given *erythromycin* in addition to sertraline;[2] this was attributed to inhibition of CYP3A4 by the antibacterial, resulting in accumulation of the SSRI. There have also been reports of serotonin syndrome when *linezolid* was given with fluoxetine,[3] sertraline,[4] paroxetine,[5] and citalopram[6]; in the latter case the patient developed complications including metabolic acidosis and ultimately fatal cardiac arrest.[6] Reviews of serotonin syndrome associated with the use of linezolid suggest that serotonergic antidepressants such as the SSRIs are the interacting drug most often implicated.[7-9] However, it has been suggested that if warranted, linezolid may be given to patients receiving serotonergic antidepressants provided the patient is carefully monitored for signs and symptoms of serotonin syndrome.[8]

1. Pollak PT, *et al.* Delirium probably induced by clarithromycin in a patient receiving fluoxetine. *Ann Pharmacother* 1995; **29**: 486–8.
2. Lee DO, Lee CD. Serotonin syndrome in a child associated with erythromycin and sertraline. *Pharmacotherapy* 1999; **19**: 894–6.
3. Steinberg M, Morin AK. Mild serotonin syndrome associated with concurrent linezolid and fluoxetine. *Am J Health-Syst Pharm* 2007; **64**: 59–62.
4. Lavery S, *et al.* Linezolid and serotonin syndrome. *Psychosomatics* 2001; **42**: 432–4.
5. Wigen CL, Goetz MB. Serotonin syndrome and linezolid. *Clin Infect Dis* 2002; **34**: 1651–2.
6. Bernard L, *et al.* Serotonin syndrome after concomitant treatment with linezolid and citalopram. *Clin Infect Dis* 2003; **36**: 1197.
7. Lawrence KR, *et al.* Serotonin toxicity associated with the use of linezolid: a review of postmarketing data. *Clin Infect Dis* 2006; **42**: 1578–83.
8. Taylor JJ, *et al.* Linezolid and serotonergic drug interactions: a retrospective survey. *Clin Infect Dis* 2006; **43**: 180–7.
9. FDA. Drug Safety Communication: updated information about the drug interaction between linezolid (Zyvox) and serotonergic psychiatric medications (issued 20th October, 2011). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm276251.htm (accessed 06/11/12)

Anticoagulants. SSRIs may increase the anticoagulant activity of some anticoagulants including *acenocoumarol* and *warfarin* (see p. 1531.3).

Antidepressants. Combination therapy with differing classes of antidepressants has been used successfully in the treatment of drug-resistant depression. It should be emphasised, however, that such combinations may result in enhanced adverse reactions or interactions, and should be used only under expert supervision. For further details of the interactions between different antidepressants when given together, see Phenelzine, p. 447.2. For details of the serotonin syndrome that can arise when two serotonergic drugs with different mechanisms of action are given, see under Adverse Effects of Phenelzine, p. 445.2.

Antiepileptics. Antidepressants may antagonise the activity of antiepileptics by lowering the convulsive threshold.

There has been a report of the serotonin syndrome (see p. 445.2) developing in a patient 14 days after fluoxetine had been added to *carbamazepine* therapy.[1]

Phenobarbital has been reported to reduce serum concentrations of paroxetine.[2] Steady-state serum concentrations of paroxetine were found to be lower in patients taking *phenytoin* than in those taking carbamazepine or valproate.[3]

Low serum concentrations of citalopram have been reported in 2 patients also taking carbamazepine.[4] Serum concentrations increased when carbamazepine was changed to oxcarbazepine.

Some SSRIs have been reported to increase plasma concentrations of carbamazepine (see p. 516.2) and phenytoin (see p. 543.1). For conflicting reports of the effect of fluoxetine on serum-*valproate* concentrations, see p. 557.2.

1. Dursun SM, *et al.* Toxic serotonin syndrome after fluoxetine plus carbamazepine. *Lancet* 1993; **342**: 442–3.
2. Greb WH, *et al.* The effect of liver enzyme inhibition by cimetidine and enzyme induction by phenobarbitone on the pharmacokinetics of paroxetine. *Acta Psychiatr Scand* 1989; **80** (suppl 350): 95–8.
3. Andersen BB, *et al.* No influence of the antidepressant paroxetine on carbamazepine, valproate and phenytoin. *Epilepsy Res* 1991; **10**: 201–4.
4. Leinonen E, *et al.* Substituting carbamazepine with oxcarbazepine increases citalopram levels. A report on two cases. *Pharmacopsychiatry* 1996; **29**: 156–8.

Antihistamines. *Cyproheptadine* given to male and female patients as treatment for sexual dysfunction induced by fluoxetine or paroxetine has produced re-emergence of previously controlled depressive symptoms[1,2] or bulimia nervosa[3] in some patients.

Citalopram, fluoxetine, and fluvoxamine may increase plasma concentrations of *astemizole* or *terfenadine* by inhibition of their hepatic cytochrome P450 metabolism, increasing the risk of ventricular arrhythmias; use together should be avoided.

1. Feder R. Reversal of antidepressant activity of fluoxetine by cyproheptadine in three patients. *J Clin Psychiatry* 1991; **52**: 163–4.
2. Christensen RC. Adverse interaction of paroxetine and cyproheptadine. *J Clin Psychiatry* 1995; **56**: 433–4.
3. Goldbloom DS, Kennedy SH. Adverse interaction of fluoxetine and cyproheptadine in two patients with bulimia nervosa. *J Clin Psychiatry* 1991; **52**: 261–2.

Antimalarials. For mention of the effect of the SSRI fluvoxamine on the metabolism of *proguanil*, see p. 662.2.

Antimigraine drugs. There have been rare reports of serotonin syndrome associated with the use of SSRIs with serotonin (5-HT_1) agonists such as *sumatriptan* (see p. 681.3). Fluvoxamine may inhibit the metabolism of *frovatriptan* and *zolmitriptan* (see p. 676.3 and p. 682.3, respectively). For the effects when some SSRIs are used with *dihydroergotamine*, see p. 675.2.

Antimuscarinics. For the effect when SSRIs were taken with *benzatropine*, see p. 896.1. For the effect of paroxetine on *procyclidine*, see p. 913.3.

Antineoplastics. Paroxetine may inhibit the metabolism of *tamoxifen*; for further details, see p. 863.3.

Antipsychotics. For reports of adverse effects in patients treated with SSRIs and antipsychotics, see under *Chlorpromazine*, p. 1052.1. Interactions between SSRIs and atypical antipsychotics are also mentioned under *clozapine*, p. 1061.3, *olanzapine*, p. 1092.1, *risperidone*, p. 1105.3, and *sertindole*, p. 1107.3.

Antivirals. Plasma concentrations of fluoxetine and other SSRIs are possibly increased by HIV-protease inhibitors, such as *ritonavir*, which may inhibit metabolism of the SSRI. Unexpectedly, however, total exposure to paroxetine was about halved by a *ritonavir-boosted fosamprenavir* combination in a study in healthy subjects.[1] Although the free fraction of paroxetine in plasma was increased, suggesting that it had been displaced from protein binding, the maximum concentration of free paroxetine was reduced.

The serotonin syndrome has been described[2] in a few patients given regimens that included fluoxetine and antiretroviral-dose ritonavir. The reaction also occurred in another patient given fluoxetine and *efavirenz*.

1. van der Lee MJ, *et al.* Interaction study of the combined use of paroxetine and fosamprenavir-ritonavir in healthy subjects. *Antimicrob Agents Chemother* 2007; **51**: 4098–4104.
2. DeSilva KE, *et al.* Serotonin syndrome in HIV-infected individuals receiving antiretroviral therapy and fluoxetine. *AIDS* 2001; **15**: 1281–5

Anxiolytics. Fluoxetine and fluvoxamine increase plasma concentrations of some *benzodiazepines* (see under Diazepam, p. 1068.3). For mention of possible interactions between some SSRIs and *buspirone*, see p. 1043.2.

Beta blockers. For the effect when fluoxetine or fluvoxamine was taken with beta blockers, see p. 1321.3.

Ciclosporin. For the effect when fluoxetine or fluvoxamine was taken with ciclosporin, see p. 1956.2.

Cough suppressants. For the effects when using fluoxetine or paroxetine with *dextromethorphan*, see p. 1661.2.

Dopaminergics. *Selegiline* is an irreversible selective inhibitor of monoamine oxidase type B. Serious adverse effects have been reported when selegiline and SSRIs have been used together (see p. 917.1). In some instances, these reactions resemble the potentially fatal serotonin syndromes reported when SSRIs are given with non-selective MAOIs (see p. 445.2).

SSRIs should not generally be given to patients receiving selegiline, or for at least 2 weeks after it has been stopped. Similarly, at least one week should elapse between withdrawing an SSRI and starting selegiline; this interval should be increased to 2 weeks for sertraline, and to 5 weeks for fluoxetine because of their longer half-lives.

Gastrointestinal drugs. Acute dystonia has been noted in a patient given fluvoxamine and *metoclopramide*.[1] Similar reports have been published for other SSRIs (fluoxetine or sertraline[2]) and metoclopramide. Involuntary twitching, tremor, and stiffness of the jaw and tongue occurred or both occasions after the use of intravenous metoclopramide in a patient also taking sertraline.[4] The authors considered the adverse effects to be features of the serotonin syndrome.

For the effect of fluvoxamine on *alosetron*, and a recommendation that the combination be avoided, see p. 1820.1.

For the effect of fluvoxamine on proton pump inhibitors including *omeprazole*, see p. 1874.1.

1. Palop V, *et al.* Acute dystonia associated with fluvoxamine-metoclopramide. *Ann Pharmacother* 1999; **33**: 382.
2. Coulter DM, Pillans PI. Fluoxetine and extrapyramidal side effects. *Am. Psychiatry* 1995; **152**: 122–5.
3. Christensen RC, Byerly MJ. Mandibular dystonia associated with the combination of sertraline and metoclopramide. *J Clin Psychiatry* 1996; **57**: 596.
4. Fisher AA, Davis MW. Serotonin syndrome caused by selective serotonin reuptake-inhibitors–metoclopramide interaction. *Ann Pharmacother* 2002; **36**: 67–71.

General anaesthetics. For a report of a generalised tonic-clonic seizure in a patient receiving paroxetine and *methohexital sodium*, see p. 1910.2.

Hypnotics. For reference to visual hallucinations in patients receiving an SSRI concomitantly with *zolpidem*, see p. 1117.2.

Levothyroxine. For mention of a decreased effect of levothyroxine in patients given sertraline concomitantly, see p. 2341.2.

Local anaesthetics. For the effect of fluvoxamine on *ropivacaine*, see p. 1996.3.

Muscle relaxants. For a report of QT prolongation in a patient taking fluoxetine and *cyclobenzaprine*, see p. 2023.3.

For the effect of fluvoxamine on *tizanidine*, see p. 2027.1.

NSAIDs. For reference to an increased risk of upper gastrointestinal bleeding in patients taking SSRIs and NSAIDs together, see under Effects on the Gastrointestinal Tract, p. 420.1.

Opioid analgesics. A possible case of serotonin syndrome (p. 445.2) has been reported with *tramadol* and sertraline,[1] and another when sertraline was given with high doses of *oxycodone*.[2] There have also been occasional reports of the syndrome in patients given tramadol with citalopram,[3] fluoxetine,[4] or paroxetine.[5,6] Other reports of serotonin syndrome were associated with use of oxycodone and fluvoxamine,[7] *pethidine* and fluoxetine,[8] and citalopram with *fentanyl*[9] or pethidine.[10] For reference to SSRIs enhancing the effects and toxicity of *methadone*, see p. 90.3.

1. Mason BJ, Blackburn KH. Possible serotonin syndrome associated with tramadol and sertraline coadministration. *Ann Pharmacother* 1997; 31: 175–7.
2. Rosebraugh CJ, *et al.* Visual hallucination and tremor induced by sertraline and oxycodone in a bone marrow transplant patient. *J Clin Pharmacol* 2001; 41: 224–7.
3. Mahlberg R, *et al.* Serotonin syndrome with tramadol and citalopram. *Am J Psychiatry* 2004; 161: 1129.
4. Késavan S, Sobala GM. Serotonin syndrome with fluoxetine plus tramadol. *J R Soc Med* 1999; 92: 474–5.
5. Egberts ACG, *et al.* Serotonin syndrome attributed to tramadol addition to paroxetine therapy. *Int Clin Psychopharmacol* 1997; 12: 181–2.
6. Lantz MS, *et al.* Serotonin syndrome following the administration of tramadol with paroxetine. *Int J Geriatr Psychiatry* 1998; 13: 343–5.
7. Karunatilake H, Buckley NA. Serotonin syndrome induced by fluvoxamine and oxycodone. *Ann Pharmacother* 2006; 40: 155–7.
8. Tissot TA. Probable meperidine-induced serotonin syndrome in a patient with a history of fluoxetine use. *Anesthesiology* 2003; 98: 1511–12.
9. Ailawadhi S, *et al.* Serotonin syndrome caused by interaction between citalopram and fentanyl. *J Clin Pharm Ther* 2007; 32: 199–202.
10. Altman EM, Manos GH. Serotonin syndrome associated with citalopram and meperidine. *Psychosomatics* 2007; 48: 361–3.

Parasympathomimetics. For the effect of some SSRIs on *galantamine*, see p. 392.2.

Sibutramine. There is a risk of CNS toxicity due to synergistic serotonergic actions when an SSRI is given with sibutramine.

Smoking. Serum concentrations of fluvoxamine were lower in smokers than non-smokers in a single-dose study.[1] It was proposed that the polycyclic hydrocarbons present in cigarette smoke stimulated hepatic metabolism of fluvoxamine by cytochrome P450 isoenzymes.

1. Spigset O, *et al.* Effect of cigarette smoking on fluvoxamine pharmacokinetics in humans. *Clin Pharmacol Ther* 1995; 58: 399–403.

Stimulants. For the effect of paroxetine on the metabolism of *atomoxetine*, see p. 2317.3.

Theophylline. For the effect of fluvoxamine on theophylline, see p. 1234.3.

Pharmacokinetics

Fluoxetine is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur about 6 to 8 hours after oral doses. Systemic bioavailability does not appear to be affected by food. Fluoxetine is extensively metabolised, by demethylation, in the liver to its primary active metabolite norfluoxetine. Excretion is mainly via the urine. Protein binding is reported to be about 95%.

Fluoxetine used clinically is a racemic mixture consisting of *R*- and *S*-enantiomers in equal amounts. Both enantiomers are active according to *animal* studies, but *S*-fluoxetine is eliminated more slowly. Metabolism is believed to be mediated by cytochrome P450 isoenzyme CYP2D6 (but see p. 427.2), and leads to *R*- and *S*-enantiomers of norfluoxetine, with the *S*-enantiomer being considered as active as the parent drug; the *R*-enantiomer is considered to be much less active. This metabolism is subject to genetic polymorphism. While the small proportion of the population known as slow metabolisers do show a different spectrum of parent drug and metabolite, the overall activity does not appear to be altered.

Fluoxetine is widely distributed throughout the body.

Fluoxetine has a relatively long elimination half-life of about 1 to 3 days after acute use and 4 to 6 days after long-term use; that of its metabolite, norfluoxetine, is even longer, being about 4 to 16 days. These long half-lives have clinical implications. Steady-state plasma concentrations will only be attained after several weeks. Additionally, fluoxetine and its metabolites may persist for a considerable time after treatment, and this has led to precautions concerning the subsequent use of other serotonergic drugs (see Interactions, p. 424.1).

Fluoxetine and norfluoxetine are distributed into breast milk (see Breast Feeding under Precautions, p. 422.2).

References.
1. Altamura AC, *et al.* Clinical pharmacokinetics of fluoxetine. *Clin Pharmacokinet* 1994; 26: 201–14.
2. Baumann P. Pharmacokinetic-pharmacodynamic relationship of the selective serotonin reuptake inhibitors. *Clin Pharmacokinet* 1996; 31: 444–69.
3. Greenblatt DJ, *et al.* Inhibition of human cytochrome P450-3A isoforms by fluoxetine and norfluoxetine: in vitro and in vivo studies. *J Clin Pharmacol* 1996; 36: 792–8.
4. Hamelin BA, *et al.* The disposition of fluoxetine but not sertraline is altered in poor metabolizers of debrisoquin. *Clin Pharmacol Ther* 1996; 60: 512–21.
5. Preskorn SH. Clinically relevant pharmacology of selective serotonin reuptake inhibitors: an overview with emphasis on pharmacokinetics and effects on oxidative drug metabolism. *Clin Pharmacokinet* 1997; 32 (suppl 1): 1–21.
6. Hiemke C, Härtter S. Pharmacokinetics of selective serotonin reuptake inhibitors. *Pharmacol Ther* 2000; 85: 11–28.

Metabolism. Although fluoxetine is stated by the manufacturers to be metabolised by the cytochrome P450 isoenzyme CYP2D6, which is supported by studies[1] indicating that its disposition is altered in poor metabolisers of debrisoquine (a substrate for this enzyme), others have suggested that CYP2C19, and perhaps CYP2C9, play an important role.[2]

1. Hamelin BA, *et al.* The disposition of fluoxetine but not sertraline is altered in poor metabolizers of debrisoquin. *Clin Pharmacol Ther* 1996; 60: 512–21.
2. Liu Z-Q, *et al.* Effect of the CYP2C19 oxidation polymorphism on fluoxetine metabolism in Chinese healthy subjects. *Br J Clin Pharmacol* 2001; 52: 96–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Alental; Animex-On; Anzoldent†; Captaton; Eburnate; Equilibrane; Faboxetina; Felixina; Fibrotina†; Fluopiram†; Fluoxiram; Foxetin; Lapsus; Mitilase; Nervosal; Neupax; Neuro Laz; Prozac; Saurat; ***Austral.***: Auscap; Fluohexal†; Fluoxebell†; Lovan; Prozac; Zactin; ***Austria***: Felicium; Floccin†; Fluctine; Fluoxibene; Flux; Fluxil†; FluxoMed; Mutan; Positivum; ***Belg.***: Docfluoxetine†; Fluox†; Fluoxemed†; Fluoxone; Fontex; Prosimed†; Prozac; ***Braz.***: Daforin; Deprax; Depress; Eufor; Fluox; Fluxene; Nortec Prozac Prozen; Psiquial; Verotina; Zyfloxin; ***Canad.***: FXT†; Prozac; ***Chile***: Actan; Alentol; Anisimol; Aprinol; Clinium; Dominium; Nerbet; Pragmaten; Prozac; Sostac; Ultiflox; ***China***: Ao Mai Lun (奥麦伦); Jin Kai Ke (金开克); Kai Ke (开克); Prozac (百优解); Youke (优克); Zactin (艾旭); Cz.: Defluox; Deprex; Floxet; Fluoxin†; Fluzak; Magrilan; Portal†; Prozac; ***Denm.***: Flutin†; Fondur†; Fontex; ***Fin.***: Fluoxone; Seromex; Seronil; ***Fr.***: Prozac; ***Ger.***: Fluctin; Fluox-Puren†; Fluoxe-Q†; FluoxeLich; Fluoxgamma; Fluxet; ***Gr.***: Dagrilan; Dinalexin; Exostrept; Flonital; Fluocalm; Fluxadir; Fokeston; Hapilux; Ladose; Orthon; Sartuzin; Sofelin; Stephadilat-S; Stressless; Thiramil; Zinovat; ***Hong Kong***: Anzac†; CP-Fluoxet; Dawnex†; Deprexin†; Floxet; Fluxetin; Fluxil; Nopres; Prozac; Qualisac; ***Hung.***: Deprexin; Floxet; FluWinox†; Portal; Prozac; ***India***: Afzot; Alivate; Barozac; Curix; Dawnex; Depten; Depzac; Faa; Fadep; Faxtin; Floxikair; Fluchem; Fludac; Fludawn; Fludep; Flugen; Flumusa-20; Flunat; Flunil; Fluriv; Flutin; Flutine; Flutinol; Flutop; Flutrac; Flutric; Flux; Fluxal; Fluxin; Fluze; Fulx; Griloc; HT; Loftil; Molux; Nedep; Noc; Nuzac; Platin; ***Indon.***: Andep†; Ansi†; Antiprestin; Courage; Deprezac; Elizac; Foransi; Kalxetin; Lodep†; Nopres; Noxetine; Oxipres; Prozac; ZAC; Zactin†; ***Irl.***: Affex; Bellzac; Biozac; Fluzac; Gerozac; Norzac; Prozac; Prozamel; Prozatan†; Prozit; ***Israel***: Flutine; Prizma; Prozac; ***Ital.***: Azur; Clexiclor; Cloriflox; Diesan; Flotina; Fluoxeren; Ipsumor; Prozac; Xeredien; ***Malaysia***: Fluovex; Fluran; Fluxetil; Prozac; Salipax; Sinzac; ***Mex.***: Aniup; Auroken; Axtin; Deprozin; F-Exina; Farmaxetina; Flocet†; Florexal; Fluctine†; Fluneurin; Fluoxac; Fluralex; Flutinax†; Fusum; Indozul; Lebensart; Ovisen; Pisaurit; Prozac; Quanilene; Regultron; Siquial; Teczac; Ulmely; Zatin; ***Neth.***: Flustad; Prozac; ***Norw.***: Fontex; ***NZ***: Fluox; Plinzene†; Prozac; ***Philipp.***: Adep; Adepssir; Deprexone; Deprizac; Motivest; Neuxetin; Oxedep; Prodin; Prozac; ***Pol.***: Andepin; Bioxetin; Deprexetin; Salipax†; Seronil; Xetiran; ***Port.***: Digassim; Prozac; Psipax; Salipax; Selectus; Tuneluz; ***Rus.***: Apo-Fluoxetine (Апо-Флуоксетин); Flunisan (Флунисан); Fluval (Флувал); Framex (Фрамекс)†; Portal (Портал); Prodep (Продеп); Proflusak (Профлузак); Prozac (Прозак); ***S.Afr.***: Deprozan; Flutinol; Lorien; Nuzak; ProHexal; Prozac; Prozyn; Ranflocs; Rezak; Trizac†; ***Singapore***: Fluoxone; Fluxetin; Fluxil; Foxtin; Magrilan; Prozac; Zactin; ***Spain***: Adofen; Lecimar†; Luramon; Prozac; Reneuron; ***Swed.***: Fontex; ***Switz.***: Fluctine; Fluocim†; Fluoxifar†; ***Thai.***: Actisac; Anzac; Dawnex†; Deproxin; F-ZAC; Flulox; Flumed; Fluoxine; Flusac; Flutine; Fluxetil; Fluxetin; Fluzac; Foxetin; Hapilux; Loxetine; Magrilan; Oxetine; Oxsac; Prodep†; Prozac; Unprozy; Xetin; Zezac; ***Turk.***: Depreks; Depset; Florak; Foxeteva; Fulsac; Loksetin; Prozac; Seronil; Zedprex; ***UAE***: Flutin; ***UK***: Prozac; Prozep; Prozit; ***Ukr.***: Fluxen (Флуксен); Portal (Портал)†; ***USA***: Prozac; Sarafem; Selfemra; ***Venez.***: Anoxen; Antipres; Fluxet; Fluzac; Prozac; Psiquial.

Multi-ingredient Preparations. ***Chile***: Symbyax; ***India***: Alamflu; Alp-FT; Altin; Ateez-F; Azo-F; Cinol Forte; Cinol Plus; Cooltime; Coral-F; Depten-AZ; Depten-OZ; Depwell; Exiten Plus; Faa Plus; Faxtin-A; Fiden-AZ; Fludep Plus; Fludep-AZ; Flumusa; Fluwel; Fluxin-AL; Fluzolam; Kurelam-F; L-Peez F; M-Olan Plus; Oladay-F; Olanex-F; Olapin Forte; Olapin Plus; Olorest-F; ***Mex.***: Symbyax; ***USA***: Symbyax.

Pharmacopoeial Preparations

BP 2014: Fluoxetine Capsules; Fluoxetine Oral Solution;
USP 36: Fluoxetine Capsules; Fluoxetine Delayed-Release Capsules; Fluoxetine Oral Solution; Fluoxetine Tablets; Olanzapine and Fluoxetine Capsules.

Fluvoxamine Maleate

(BANM, USAN, rINNM)

DU-23000; Fluvoksaminimaleaatti; Fluvoksamin Maleat; Fluvoxamina, maleato de; Fluvoxamine, Maléate de; Fluvoxamini Maleas; Fluvoxaminmaleat; Maleato de fluvoxamina; MK-264; SME-3110; Флувоксамина Малеат.

(*E*)-5-Methoxy-4′-trifluoromethylvalerophenone *O*-2-aminoethyloxime maleate.

$C_{15}H_{21}F_3N_2O_2C_4H_4O_4$=434.4

CAS — 54739-18-3 (fluvoxamine); 61718-82-9 (fluvoxamine maleate).

ATC — N06AB08.

ATC Vet — QN06AB08.

UNII — 5LGN83G74V.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Fluvoxamine Maleate). A white or almost white, crystalline powder. Sparingly soluble in water; freely soluble in alcohol and in methyl alcohol.

USP 36: (Fluvoxamine Maleate). A white to off-white, crystalline powder. Sparingly soluble in water; freely soluble in alcohol and in chloroform; practically insoluble in solvent ether. Protect from light.

Uses and Administration

Fluvoxamine, an aralkylketone derivative, is an SSRI with actions and uses similar to those of fluoxetine (p. 417.1).

In the treatment of **depression** fluvoxamine maleate is given in an initial oral dose of 50 or 100 mg once daily, preferably in the evening; in some patients the dose may need to be gradually increased to a maximum of 300 mg daily. It is recommended that daily dosages exceeding 150 mg should be given in 2 or 3 divided doses.

Fluvoxamine maleate is also used in the management of **obsessive-compulsive disorder**. In the UK, doses are similar to those used in the treatment of depression. The recommended starting dose in the USA is 50 mg once daily at bedtime; this dose may be increased by increments of 50 mg every 4 to 7 days to a maximum of 300 mg daily. Doses above 100 mg daily should be given in 2 divided doses. It is recommended that if no improvement occurs within 10 weeks, treatment with fluvoxamine should be reassessed.

In the USA, a modified-release preparation of fluvoxamine maleate is available for the treatment of obsessive-compulsive disorder. The initial dose is 100 mg once daily at bedtime increased, as necessary, by increments of 50 mg at weekly intervals to a maximum of 300 mg once daily.

US licensed product information recommends that dosage modification be considered in elderly patients, in whom clearance may be decreased. For dosage in renal and hepatic impairment, see p. 427.3, and for doses used in children, see p. 427.3.

It has also been used for the treatment of **social anxiety disorder**.

Fluvoxamine should be withdrawn gradually to reduce the risk of withdrawal symptoms (see also Withdrawal, under Precautions of Fluoxetine, p. 423.3).

Administration in children. Fluvoxamine maleate may be used in the management of **obsessive-compulsive disorder** in children aged 8 years and over, including adolescents. The recommended starting dose is 25 mg given orally, once daily at bedtime. This may be increased in increments of 25 mg every 4 to 7 days to a maximum daily dose of 200 mg for children (8 to 11 years old) or 300 mg for adolescents. Daily doses of more than 50 mg should be given as 2 divided doses; if the 2 doses are unequal, the larger dose should be given at bedtime.

Administration in hepatic or renal impairment. UK licensed product information recommends that patients with hepatic or renal impairment should begin therapy with a low dose of fluvoxamine maleate and be carefully monitored. US product information only recommends that dosage modification be considered in hepatic impairment,

since it considers evidence of accumulation in renal impairment to be lacking.

Anxiety disorders. Fluvoxamine has been given in a variety of anxiety disorders including obsessive-compulsive disorder (p. 1028.2), panic disorder (p. 1029.1), and social anxiety disorder (see under Phobic Disorders, p. 1029.1).

References.
1. van Vliet IM, *et al.* Psychopharmacological treatment of social phobia: a double blind placebo controlled study with fluvoxamine. *Psychopharmacology (Berl)* 1994; **115**: 128–34.
2. Freeman CPL, *et al.* Fluvoxamine versus clomipramine in the treatment of obsessive compulsive disorder: a multicenter, randomized, double-blind, parallel group comparison. *J Clin Psychiatry* 1994; **55**: 301–5.
3. Greist JH, *et al.* Efficacy of fluvoxamine in obsessive-compulsive disorder: results of a multicentre, double blind, placebo-controlled trial. *Eur J Clin Res* 1995; **7**: 195–204.
4. Stein MB, *et al.* Fluvoxamine treatment of social phobia (social anxiety disorder): a double-blind placebo-controlled study. *Am J Psychiatry* 1999; **156**: 756–60.
5. Figgitt DP, McClellan KJ. Fluvoxamine: an updated review of its use in the management of adults with anxiety disorders. *Drugs* 2000; **60**: 925–54.
6. The Research Unit on Pediatric Psychopharmacology Anxiety Study Group. Fluvoxamine for the treatment of anxiety disorders in children and adolescents. *N Engl J Med* 2001; **344**: 1279–85.
7. Asnis GM, *et al.* Fluvoxamine in the treatment of panic disorder: a multicenter, double-blind, placebo-controlled study in outpatients. *Psychiatry Res* 2001; **103**: 1–14.
8. Hollander E, *et al.* A double-blind, placebo-controlled study of the efficacy and safety of controlled-release fluvoxamine in patients with obsessive-compulsive disorder. *J Clin Psychiatry* 2003; **64**: 640–7.
9. Stein DJ, *et al.* Fluvoxamine CR in the long-term treatment of social anxiety disorder: the 12- to 24-week extension phase of a multicentre, randomized, placebo-controlled trial. *Int J Neuropsychopharmacol* 2003; **6**: 317–23.

Hypochondriasis. For reference to the use of SSRIs, including fluvoxamine, in hypochondriasis, see under Fluoxetine, p. 418.2.

Adverse Effects, Treatment, and Precautions

As for SSRIs in general (see Fluoxetine, p. 419.1).

Bradycardia with ECG changes has been noted with fluvoxamine (but see also Effects on the Cardiovascular System in Adverse Effects of Fluoxetine, p. 419.2).

It is recommended that fluvoxamine should be withdrawn in patients who have increased serum liver enzyme concentrations.

Fluvoxamine may need to be given with caution to patients with hepatic or renal impairment, and to the elderly.

Incidence of adverse effects. The UK CSM has reported[1] that between 25 September 1986 and 23 March 1988 it had received 961 reports of adverse reactions, including 5 deaths, associated with the use of fluvoxamine. The most frequently reported reactions were nausea (183 reports) and vomiting (101 reports). Other reactions included dizziness, somnolence, agitation, headache, tremor, and, during the first few days, worsening of anxiety. There were 13 reports of convulsions. Reports of appetite stimulation and antimuscarinic reactions were unusual. The effects sometimes resolved with time or dose reduction.

The safety profile of fluvoxamine has been reviewed.[2] For a comparison of the adverse reaction profiles of other SSRIs including fluoxetine with that of fluvoxamine, see Incidence of Adverse Effects, under Adverse Effects of Fluoxetine, p. 419.1.

1. CSM. Fluvoxamine (Faverin): adverse reaction profile. *Current Problems* 22 1988. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE6dDocName=CON20244296RevisionSelectionMethod=LatestReleased (accessed 04/08/08)
2. Wagner W, *et al.* Fluvoxamine: a review of its safety profile in worldwide studies. *Int Clin Psychopharmacol* 1994; **9**: 223–7.

Breast feeding. For comments on the use of SSRIs in breast-feeding patients, see under Precautions for Fluoxetine, p. 422.2.

Children. SSRIs are associated with an increased risk of potentially suicidal behaviour when used for the treatment of depression in children and adolescents under 18 years old; for further details, see under Effects on Mental State in Fluoxetine, p. 420.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fluvoxamine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

For interactions associated with SSRIs, see Fluoxetine, p. 424.1.

Fluvoxamine can greatly increase plasma concentrations of theophylline (see p. 1234.3), and they should not be given together, or, if this is unavoidable, the dose of theophylline should be halved and plasma-theophylline concentrations monitored more closely.

For the effect of fluvoxamine on melatonin, see p. 2552.2, and on pirfenidone, see p. 2592.1.

References.
1. Wagner W, Vause EW. Fluvoxamine: a review of global drug-drug interaction data. *Clin Pharmacokinet* 1995; **29** (suppl 1): 26–32.

Pharmacokinetics

Fluvoxamine is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur 3 to 8 hours after a dose. Systemic bioavailability does not appear to be affected by food. It is extensively metabolised in the liver by oxidative demethylation and deamination, to inactive metabolites. Excretion is mainly in the urine; about 2% of a dose is excreted as unchanged drug. Fluvoxamine is widely distributed throughout the body and protein binding is reported to be about 80%; it has a plasma-elimination half-life of about 15 hours. Fluvoxamine is distributed into breast milk (see Breast Feeding under Precautions in Fluoxetine, p. 422.2).

References.
1. Perucca E, *et al.* Clinical pharmacokinetics of fluvoxamine. *Clin Pharmacokinet* 1994; **27**: 175–90.
2. van Harten J. Overview of the pharmacokinetics of fluvoxamine. *Clin Pharmacokinet* 1995; **29** (suppl 1): 1–9.
3. Xu Z-H, *et al.* In vivo inhibition of CYP2C19 but not CYP2D6 by fluvoxamine. *Br J Clin Pharmacol* 1996; **42**: 518–21.
4. DeVane CL, Gill HS. Clinical pharmacokinetics of fluvoxamine: applications to dosage regimen design. *J Clin Psychiatry* 1997; **58** (suppl 5): 7–14.
5. Spigset O, *et al.* Non-linear fluvoxamine disposition. *Br J Clin Pharmacol* 1998; **45**: 257–63.
6. Hiemke C, Härtter S. Pharmacokinetics of selective serotonin reuptake inhibitors. *Pharmacol Ther* 2000; **85**: 11–28.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Faverin; Luvox; Movox; Voxam; ***Austria***: Floxyfral; ***Belg.***: Floxyfral; ***Braz.***: Luvox; ***Canad.***: Luvox; Riva-Fluvox; ***Chile***: Luvox; ***China***: Luvox (兰释); Ruibile; Cz.: Fevarin; ***Denm.***: Dumirox; Fevarin; ***Fin.***: Fevarin†; Fluvosol; ***Fr.***: Floxyfral; ***Ger.***: Fevarin; Fluvohexal†; ***Gr.***: Dumyrox; Mytoxine; ***Hong Kong***: Faverin; ***Hung.***: Fevarin; ***India***: Fluvator; Fluvoxin; Foxa; Sorest; Uvox; ***Indon.***: Luvox; ***Irl.***: Faverin; ***Israel***: Favoxil; ***Ital.***: Dumirox; Fevarin; Maveral; ***Jpn***: Luvox; ***Malaysia***: Luvox; ***Mex.***: Luvox; Vumínix; ***Neth.***: Fevarin; ***Norw.***: Fevarin; ***Philipp.***: Faverin†; Voxamine; ***Pol.***: Fevarin; ***Port.***: Dumyrox; ***Rus.***: Fevarin (Феварин); ***S.Afr.***: Faverin; Luvox; ***Singapore***: Faverin; ***Spain***: Dumirox; ***Swed.***: Fevarin; ***Switz.***: Flox-ex; Floxyfral; ***Thai.***: Faverin; Fluvoxin; ***Turk.***: Faverin; Fluvamteva; Revoxin; ***UK***: Faverin; ***Ukr.***: Deprivox (Депривокс); Fevarin (Феварин); ***USA***: Luvox; ***Venez.***: Luvox.

Pharmacopoeial Preparations
BP 2014: Fluvoxamine Tablets;
USP 36: Fluvoxamine Maleate Tablets.

Imipramine *(BAN, rINN)*

Imipramiini; Imipramin; Imipramina; Imipraminum; Имипрамин.

3-(10,11-Dihydro-5*H*-dibenz[*b*,*f*]azepin-5-yl)propyldimethylamine.

$C_{19}H_{24}N_2$=280.4

CAS — 50-49-7.

ATC — N06AA02.

ATC Vet — QN06AA02.

UNII — OGG85SX4E4.

Imipramine Embonate *(BANM, rINNM)*

Embonato de imipramina; Imipramina, embonato de; Imipramine, Embonate d'; Imipramine Pamoate; Imipramini Embonas; Имипрамина Эмбонат.

$(C_{19}H_{24}N_2)_2C_{23}H_{16}O_6$=949.2

CAS — 10075-24-8.

UNII — MC34P30298.

Imipramine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de imipramina; Imipram. Hydrochlor.; Imipramiinihydrokloridi; Imipramin Hidroklorür; Imipramina, hidrocloruro de; Imipramine, chlorhydrate d'; Imipraminhidroklorid; Imipraminhydrochlorid; Imipramin-hydrochlorid; Imipraminhydroklorid; Imipramini Chloridum; Imipramini hydrochloridum; Imipramino hidrochloridas; Imipraminy chlorowodorek; Imizine; Имипрамина Гидрохлорид.

$C_{19}H_{24}N_2HCl$=316.9

CAS — 113-52-0.

UNII — BKE5Q1J60U.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Imipramine Hydrochloride). A white or slightly yellow crystalline powder. Freely soluble in water and in alcohol. A 10% solution in water has a pH of 3.6 to 5.0. Protect from light.

USP 36: (Imipramine Hydrochloride). A white to off-white, odourless or practically odourless, crystalline powder. Freely soluble in water and in alcohol; soluble in acetone; insoluble in ether and in benzene. Store in airtight containers.

Uses and Administration

Imipramine is a dibenzazepine tricyclic antidepressant with actions and uses similar to those of amitriptyline (p. 401.1). Imipramine is one of the less sedating tricyclics and has moderate antimuscarinic activity. Imipramine is usually given orally as the hydrochloride or embonate, with doses expressed in terms of the hydrochloride. Imipramine embonate 149.8 mg and imipramine base 88.5 mg are both equivalent to about 100 mg of imipramine hydrochloride.

In the treatment of **depression**, the usual daily dose of imipramine hydrochloride is up to 75 mg in divided doses initially, gradually increased to 150 to 200 mg daily as necessary; higher doses of up to 300 mg daily may be required in severely depressed patients in hospital. A suggested initial dose for the elderly in the UK is 10 mg daily, gradually increasing to 30 to 50 mg daily. In the USA, daily doses of 25 to 50 mg are recommended for initial therapy in the elderly and adolescents, increasing to a maximum of 100 mg daily as required. Since imipramine has a prolonged half-life, once-daily dosage regimens may also be suitable, usually given at night.

Imipramine, as the hydrochloride, has also been given by intramuscular injection in the treatment of depression.

For the uses of imipramine in children, see p. 428.3.

Imipramine oxide hydrochloride (imipraminoxide hydrochloride) has also been used as an antidepressant and for nocturnal enuresis.

Imipramine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Administration in children. Imipramine is used for the treatment of **nocturnal enuresis** in children in whom organic pathology has been excluded. However, drug therapy for nocturnal enuresis should be reserved for those in whom other methods have failed and should preferably only be given to cover periods away from home. Tricyclic antidepressants are not recommended in children under 6 years of age. For a discussion of tricyclic use in nocturnal enuresis, see Micturition Disorders under Amitriptyline, p. 402.1.

Suggested oral doses of imipramine hydrochloride are:
- 25 mg for children aged 6 to 7 years (20 to 25 kg)
- 25 to 50 mg for children aged 8 to 11 years (25 to 35 kg)
- 50 to 75 mg for children over 11 years (35 to 54 kg)

The dose should be taken just before bedtime and treatment, including a period of gradual withdrawal, should not continue for longer than 3 months. A full physical examination is recommended before a further course.

Imipramine has also been used in children with **attention deficit hyperactivity disorder** (see p. 428.3).

Anxiety disorders. See under Clomipramine, p. 412.2. In some countries, imipramine hydrochloride is licensed for the treatment of panic disorder in an initial oral dose of 10 mg daily; this dose may be increased as necessary to between 75 to 150 mg daily although doses of 200 mg daily may be needed in some patients.

Some references to the use of imipramine in anxiety disorders are given below.

1. Cross-National Collaborative Panic Study. Second Phase Investigators. Drug treatment of panic disorder: comparative efficacy of alprazolam, imipramine, and placebo. *Br J Psychiatry* 1992; **160**: 191–202.
2. Lepola UM, *et al.* Three-year follow-up of patients with panic disorder after short-term treatment with alprazolam and imipramine. *Int Clin Psychopharmacol* 1993; **8**: 115–18.
3. Rickels K, *et al.* Antidepressants for the treatment of generalised anxiety disorder: a placebo-controlled comparison of imipramine, trazodone, and diazepam. *Arch Gen Psychiatry* 1993; **50**: 884–95.
4. Clark DM, *et al.* A comparison of cognitive therapy, applied relaxation and imipramine in the treatment of panic disorder. *Br J Psychiatry* 1994; **164**: 759–69.
5. Barlow DH, *et al.* Cognitive-behavioral therapy, imipramine, or their combination for panic disorder: a randomized controlled trial. *JAMA* 2000; **283**: 2529–36. Correction. *ibid.*; **284**: 2597.

Hyperactivity. Although not licensed in the UK for use in children with attention deficit hyperactivity disorder, the *BNFC* has suggested that imipramine hydrochloride may be given to those aged 6 years and over in an oral dose of 10 to 30 mg twice daily.

See also under Desipramine, p. 413.2.

Pain. Antidepressants, usually amitriptyline or another tricyclic, are useful in alleviating some types of pain (see Choice of Analgesic, p. 4.2). In some countries, imipramine hydrochloride is also available for the treatment of chronic pain; the usual recommended oral dose is 25 to

75 mg daily, although doses of up to 300 mg daily may be necessary.

Some references to the use of imipramine are given below.

1. Walsh TD. Controlled study of imipramine and morphine in chronic pain due to advanced cancer. *Proc Am Soc Clin Oncol* 1986; 5: 237.
2. Sindrup SH, *et al.* Concentration-response relationship in imipramine treatment of diabetic neuropathy symptoms. *Clin Pharmacol Ther* 1990; 47: 509–15.
3. Hummel T, *et al.* A comparison of the antinociceptive effects of imipramine, tramadol and anpirtoline. *Br J Clin Pharmacol* 1994; 37: 325–33.
4. Cannon RO, *et al.* Imipramine in patients with chest pain despite normal coronary angiograms. *N Engl J Med* 1994; 330: 1411–17.
5. Godfrey RG. A guide to the understanding and use of tricyclic antidepressants in the overall management of fibromyalgia and other chronic pain syndromes. *Arch Intern Med* 1996; 156: 1047–52.
6. Minotti V, *et al.* Double-blind evaluation of short-term analgesic efficacy of orally administered diclofenac, diclofenac plus codeine, and diclofenac plus imipramine in chronic cancer pain. *Pain* 1998; 74: 133–7.

Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p. 402.3).

Breast feeding. For comments on the use of tricyclic antidepressants in breast-feeding patients, see under Precautions for Amitriptyline, p. 405.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies imipramine as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

For interactions associated with tricyclic antidepressants, see Amitriptyline, p. 406.1.

Pharmacokinetics

Imipramine is readily absorbed from the gastrointestinal tract, and extensively demethylated by first-pass metabolism in the liver, to its primary active metabolite, desipramine.

Paths of metabolism of both imipramine and desipramine include hydroxylation and *N*-oxidation. Imipramine is excreted in the urine, mainly in the form of its metabolites, either free or in conjugated form; small amounts are excreted in the faeces via the bile.

Imipramine and desipramine are widely distributed throughout the body and are extensively bound to plasma and tissue protein. Imipramine has been estimated to have an elimination half-life ranging from 9 to 28 hours, which may be considerably extended in overdosage. Plasma concentrations of imipramine and desipramine vary very widely between individuals but some correlation with therapeutic response has been established.

Imipramine and desipramine cross the blood-brain barrier and placenta and are distributed into breast milk (see Breast Feeding under Precautions in Amitriptyline, p. 405.1).

References.

1. Sallee FR, Pollock BG. Clinical pharmacokinetics of imipramine and desipramine. *Clin Pharmacokinet* 1990; 18: 346–64.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Elepsin†; Tofranil; *Austral.*: Melipramine†; Tofranil; Tolerade; *Belg.*: Tofranil; *Braz.*: Depramina; Imipra; Mepramin; Praminan; Tofranil; Uni Imiprax; *Canad.*: Impril; Novo-Pramine; Tofranil†; *Cz.*: Melipramin; *Fr.*: Tofranil; *Ger.*: Pryleugan†; Tofranil; *Gr.*: Depramine; Venefon; *Hung.*: Melipramin; *India*: Antidep; Antipres; Depik; Depranil; Depsol; Depsonil; Diamin; Elamin; Eldep; Impramine; Imprine; Microdep; *Indon.*: Tofranil; *Irl.*: Tofranil†; *Israel*: Primonil†; Tofranil; *Ital.*: Tofranil; *Mex.*: Fixon; Talpramin; Tofranil; *NZ*: Tofranil; *Philipp.*: Tofranil; *Port.*: Tofranil; *Rus.*: Melipramin (Мелипрамин); *S.Afr.*: Ethipramine; Mipralin†; Tofranil; *Spain*: Tofranil; *Switz.*: Tofranil; *Thai.*: Celamine; Inpramine; Mipramine; Sermonil; Topramine; *Turk.*: Tofranil; *Ukr.*: Melipramin (Мелипрамин); *USA*: Tofranil; *Venez.*: Tofranil.

Multi-ingredient Preparations. *India*: Anxitab; Depik Forte; Depik Plus; Depranil Plus; Depsodep; Depsol Forte; Depsol Plus; Depsonil-DZ; Diamin Plus; Eldep Forte; Eldep-M; Eldep-Plus; Imipam.

Pharmacopoeial Preparations

BP 2014: Imipramine Tablets;

USP 36: Imipramine Hydrochloride Injection; Imipramine Hydrochloride Tablets.

Iproniazid Phosphate *(BANM, rINNM)*

Fosfato de iproniazida; Iproniazida, fosfato de; Iproniazide, Phosphate d'; Iproniazidi Phosphas; Ипрониазида Фосфат.

2'-Isopropylisonicotinohydrazide phosphate.

$C_9H_{13}N_3O.H_3PO_4$=277.2

CAS — 54-92-2 (iproniazid); 305-33-9 (iproniazid phosphate).

ATC — N06AF05.

ATC Vet — QN06AF05.

UNII — 8DE00V62TV.

Profile

Iproniazid, a hydrazine derivative, is an irreversible inhibitor of both monoamine oxidase types A and B with actions and uses similar to those of phenelzine (p. 444.1). It has been given orally in the treatment of depression.

Iproniazid is the isopropyl derivative of isoniazid (see p. 311.2) and was developed for use in tuberculosis, but owing to its toxicity is no longer used for this purpose.

Effects on the liver. Of 91 cases of hepatitis due to antidepressant therapy, cytolytic reactions occurred in 11 treated with iproniazid.[1] Five patients died, 3 of them after involuntary rechallenge. High levels of antimitochondrial antibody were found in 5 patients.

1. Lefebure B, *et al.* Hépatites aux antidépresseurs. *Therapie* 1984; 39: 509–16.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Marsilid.

Isocarboxazid *(BAN, rINN)*

Isocarboxazida; Isocarboxazide; Isocarboxazidum; Isokarboksatsidi; Isokarboxazid; Ro-50831; Изокарбоксазид.

2'-Benzyl-5-methylisoxazole-3-carbohydrazide.

$C_{12}H_{13}N_3O_2$=231.3

CAS — 59-63-2.

ATC — N06AF01.

ATC Vet — QN06AF01.

UNII — 3423V8437.

Pharmacopoeias. In *Chin.*

Uses and Administration

Isocarboxazid, a hydrazine derivative, is an irreversible inhibitor of both monoamine oxidase types A and B with actions and uses similar to those of phenelzine (p. 444.1).

Isocarboxazid is used in the treatment of depression but because of the risks associated with irreversible non-selective MAOIs (see p. 398.1) usually other antidepressants are preferred. It is given in an initial oral dose of 30 mg daily in single or divided doses. If no improvement occurs after 4 weeks, doses of up to 60 mg daily can be tried for up to 4 to 6 weeks. Once a response has been obtained the dosage may be gradually reduced to a maintenance dose of 10 to 20 mg daily, although doses of up to 40 mg daily may be needed in some patients. Half the normal maintenance dose may be adequate in the elderly.

Isocarboxazid should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Adverse Effects, Treatment, and Precautions

As for MAOIs in general (see Phenelzine, p. 444.2).

Interactions

For interactions associated with MAOIs, see Phenelzine, p. 446.3 and p. 447.1.

Pharmacokinetics

Isocarboxazid is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur 3 to 5 hours after ingestion. It is metabolised by the liver, and is excreted in the urine mainly in the form of metabolites.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Denm.*: Marplan; *USA*: Marplan.

Levomilnacipran *(USAN, rINN)*

F-2695 (levomilnacipran or levomilnacipran hydrochloride); Levomilnaciprán; Levomilnacipran; Levomilnacipranum; Левомилнаципран.

(1*S*,2*R*)-2-(Aminomethyl)-*N*,*N*-diethyl-1-phenylcyclopropanecarboxamide.

$C_{15}H_{22}N_2O$=246.4

CAS — 96847-54-0; 96847-55-1.

UNII — UGM0326TXX.

Levomilnacipran Hydrochloride *(USAN, rINNM)*

F-2695 (levomilnacipran or levomilnacipran hydrochloride); Hidrocloruro de levomilnaciprán; Levomilnacipran, Chlorhydrate de; Levomilnacipranı Hydrochloridum; Левомилнаципрана Гидрохлорид.

$C_{15}H_{22}N_2O.HCl$=282.8

CAS — 175131-60-9.

UNII — 371U2ZK31U.

Profile

Levomilnacipran is the 1*S*,2*R*-enantiomer of milnacipran (p. 437.3), a serotonin and noradrenaline reuptake inhibitor (SNRI), and is used for the treatment of depression (p. 398.1). It is given orally as the hydrochloride although doses are expressed in terms of the base; levomilnacipran hydrochloride 45.9 mg is equivalent to about 40 mg of levomilnacipran. The usual initial dose is 20 mg once daily, increased to 40 mg daily after 2 days; thereafter, the dose may be further increased, according to response, in steps of 40 mg at intervals of 2 days or more, to a maximum of 120 mg once daily.

Levomilnacipran is metabolised mainly by the cytochrome P450 isoenzyme CYP3A4, and the dose in those who are also taking potent CYP3A4 inhibitors should not exceed 80 mg daily. For doses in patients with renal impairment, see p. 429.3.

Levomilnacipran should be withdrawn gradually to reduce the risk of withdrawal symptoms (see also Withdrawal, under Precautions of Fluoxetine, p. 423.3).

References.

1. Mago R, *et al.* Safety and tolerability of levomilnacipran ER in major depressive disorder: results from an open-label, 48-week extension study. *Clin Drug Investig* 2013; 33: 761–71. Correction. *ibid.*; 861.
2. Hair P, *et al.* Levomilnacipran extended release: first global approval. *Drugs* 2013; 73: 1639–45.
3. Citrome L. Levomilnacipran for major depressive disorder: a systematic review of the efficacy and safety profile for this newly approved antidepressant—what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? *Int J Clin Pract* 2013; 67: 1089–1104.
4. Bakish D, *et al.* Levomilnacipran ER 40 mg and 80 mg in patients with major depressive disorder: a phase III, randomized, double-blind, fixed-dose, placebo-controlled study. *J Psychiatry Neurosci* 2013; 38: 130040.

Administration in renal impairment. Usual oral doses of levomilnacipran may be given to patients with mild renal impairment (creatinine clearance [CC] of 60 to 89 mL/min). The maximum daily dose should not exceed 80 mg in those with moderate (CC of 30 to 59 mL/min), or 40 mg in those with severe (CC of 15 to 29 mL/min), impairment. Levomilnacipran should not be used in end-stage renal disease.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Fetzima.

Lithium Carbonate *(USAN)*

CP-15467-61; Dilithium Carbonate; Ličio karbonatas; Lithii Carbonas; Lithium Carb; Lithium, carbonate de; Lithiumcarbonat; Litio, carbonato de; Litiumkarbonaatti; Litiumkarbonat; Lítium-karbonát; Litu węglan; Lityum Karbonat; NSC-16895; Uhličitan lithný; Карбонат Лития.

Carbonic acid, dilithium salt.

Li_2CO_3=73.89

CAS — 554-13-2.

ATC — N05AN01.

ATC Vet — QN05AN01.

UNII — 2BMD2GNA4V.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Lithium Carbonate). A white or almost white powder. Slightly soluble in water; practically insoluble in alcohol.

USP 36: (Lithium Carbonate). A white odourless granular powder. Sparingly soluble in water, very slightly soluble in alcohol; dissolves, with effervescence, in dilute mineral acids.

Lithium Citrate

Citronan litný tetrahydrát; Ličio citratas; Lithii Citras; Lithii Citras Tetrahydricus; Lithium, citrate de; Lithiumcitrat; Litio, citrato de; Litiumcitraat; Lítium-citrát; Litiumsitraatti; Lityum Sitrat; Лития Цитрат.

$C_6H_5Li_3O_7.4H_2O$=282.0

CAS — 919-16-4 (anhydrous lithium citrate); 6080-58-6 (lithium citrate tetrahydrate).
UNII — 5Z6E9K79YV.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

US also includes lithium hydroxide.

Ph. Eur. 8: (Lithium Citrate). A white or almost white fine crystalline powder. Freely soluble in water; slightly soluble in alcohol.

USP 36: (Lithium Citrate). A white odourless deliquescent powder or granules. Freely soluble in water; slightly soluble in alcohol. pH of a 5% solution in water is between 7.0 and 10.0. Store in airtight containers.

Uses and Administration

Lithium, given as one of its salts, provides a source of lithium ions, which compete with sodium ions at various sites in the body. It thus has an action and adverse effects distinct and separate from those of other antidepressants. Its mode of action is not understood, but it is effective in the management of **mania, bipolar disorder,** and **recurrent unipolar depression**. Since the margin between therapeutic and toxic serum concentrations is narrow the decision to give lithium is usually based on specialist advice; lithium should not be prescribed unless facilities for monitoring serum concentrations are available.

Treatment with lithium needs to be monitored by measurement of serum concentrations, which must be adjusted for each patient to give a clinical response without evidence of toxicity. There is evidence that patients are most likely to respond to concentrations of 0.8 mmol/litre or above, but individual patients may respond to concentrations as low as 0.4 mmol/litre, and it is impossible to identify these patients beforehand. Because toxic effects are associated with concentrations above 1.5 mmol/litre, and may occur with concentrations as low as 1 mmol/litre in susceptible patients such as the elderly, it is therefore recommended that doses are adjusted to provide a serum-lithium concentration of 0.4 to 1 mmol/litre (at the lower end of this range for maintenance therapy and elderly patients). Patients must be taught to recognise the symptoms of early lithium intoxication (see Adverse Effects, p. 430.3) in order to omit further doses of lithium and seek medical care should it be impending.

The dose of lithium given depends on the preparation chosen since different preparations of lithium salts vary widely in bioavailability. This can be illustrated by the recommended doses for some UK preparations:

- *Camcolit* tablets (*Norgine, UK*) containing lithium carbonate; for treatment, initially 1 to 1.5 g daily; for prophylaxis, initially 300 to 400 mg daily
- *Li-Liquid* syrup (*Rosemont, UK*) containing lithium citrate; for treatment and prophylaxis, initially 1.018 to 3.054 g daily in two divided doses (elderly or patients less than 50 kg, 509 mg twice daily)
- *Liskonum* tablets (*GlaxoSmithKline, UK*) containing lithium carbonate; for treatment, initially 450 to 675 mg twice daily (elderly, 225 mg twice daily); for prophylaxis, initially 450 mg twice daily (elderly, 225 mg twice daily)
- *Priadel* tablets (*Sanofi, UK*) containing lithium carbonate; for treatment and prophylaxis, initially 400 mg to 1.2 g daily as a single dose or in two divided doses (elderly or patients less than 50 kg, 200 to 400 mg daily)
- *Priadel* syrup (*Sanofi, UK*) containing lithium citrate; for treatment and prophylaxis, initially 1.04 to 3.12 g daily in two divided doses (elderly or patients less than 50 kg, 520 mg to 1.04 g daily)

Doses of lithium are initially divided throughout the day; however, when serum-lithium concentrations are stabilised once-daily dosage may be preferred.

The initial dose given is adjusted after 4 to 7 days according to the results of serum-lithium estimations obtained under controlled conditions (samples being taken 12 hours after the preceding dose). Serum-lithium concentrations are then checked once a week until the dosage has remained constant for 4 weeks. The frequency of estimations can then be reduced to about once every 3 months. Should the patient's circumstances change such that the lithium pharmacokinetics or requirements might be affected, close control of serum concentrations should be reinstated until the concentrations stabilise once more. Such circumstances could involve a change of lithium preparation, an intercurrent illness (including a urinary-tract infection), a manic or depressive phase, a change in dietary regimen or body temperature, pregnancy, or use of other drugs (in particular, sodium-containing preparations and diuretics). For further details see Precautions, p. 432.2 and Interactions, p. 433.2. Long-term use of lithium has been associated with thyroid disorders and mild cognitive and memory impairment. Therefore, long-term treatment should only be undertaken if it is definitely indicated. Patients need to be regularly assessed and treatment should only continue after 3 to 5 years if the benefit persists.

Lithium is also used for the management of **aggressive or self-mutilating behaviour.** The doses are similar to those used in the prophylaxis of recurrent affective disorders described above.

Lithium is not licensed in the UK for use in children, although some preparations may be used in patients aged 12 years and over. The *BNFC* suggests that it may be considered, on the advice of a specialist, in the management of mania, bipolar disorder, recurrent depression, and aggressive or self-mutilating behaviour. Suggested doses are similar to those given above.

Lithium therapy should, where possible, be withdrawn slowly over a period of weeks to allay any concerns about relapse. For further details, see Withdrawal under Precautions, p. 433.2.

Other lithium salts have been used in the treatment of psychiatric disorders and these include the acetate, gluconate, glutamate, and sulfate.

Homoeopathy

Lithium carbonate has been used in homoeopathic medicines under the following names: Lithium carbonicum; Lithium carb; Lith. carb.

Lithium citrate has been used in homoeopathic medicines under the following names: Lithium citricum.

Anxiety disorders. Lithium has been tried as augmentation therapy in the treatment of obsessive-compulsive disorder (p. 1028.2).

Bipolar disorder. Lithium's main role in the management of bipolar disorder is for prophylaxis (see p. 397.2). It is sometimes used in the control of the acute manic stage, but, because of its slow onset of action, usually with an antipsychotic.

References.
1. Aronson JK, Reynolds DJM. Lithium. *BMJ* 1992; **305**: 1273–6.
2. Price LH, Heninger GR. Lithium in the treatment of mood disorders. *N Engl J Med* 1994; **331**: 591–8.
3. Jensen HV, *et al.* Lithium prophylaxis of manic-depressive disorder: daily lithium dosing schedule versus every second day. *Acta Psychiatr Scand* 1995; **92**: 69–74.
4. Jensen HV, *et al.* Twelve-hour brain lithium concentration in lithium maintenance treatment of manic-depressive disorder: daily versus alternate-day dosing schedule. *Psychopharmacology (Berl)* 1996; **124**: 275–8.
5. Maj M, *et al.* Late non-responders to lithium prophylaxis in bipolar patients: prevalence and predictors. *J Affect Disord* 1996; **39**: 39–42.
6. Burgess S, *et al.* Lithium for maintenance treatment of mood disorders. Available in The Cochrane Database of Systematic Reviews: Issue 3. Chichester: John Wiley; 2001 (accessed 24/11/05).
7. Sproule B. Lithium in bipolar disorder: can drug concentrations predict therapeutic effect? *Clin Pharmacokinet* 2002; **41**: 639–60.
8. Geddes JR, *et al.* Long-term lithium therapy for bipolar disorder: systematic review and meta-analysis of randomized controlled trials. *Am J Psychiatry* 2004; **161**: 217–22.
9. Severus WE, *et al.* What is the optimal serum lithium level in the long-term treatment of bipolar disorder—a review? *Bipolar Disord* 2008; **10**: 231–7.
10. Berghöfer A, *et al.* Long-term effectiveness of lithium in bipolar disorder: a multicenter investigation of patients with typical and atypical features. *J Clin Psychiatry* 2008; **69**: 1860–8.
11. Corvell W. Maintenance treatment in bipolar disorder: a reassessment of lithium as the first choice. *Bipolar Disord* 2009; **11** (suppl 2): 77–83.
12. Tondo L, Baldessarini RJ. Long-term lithium treatment in the prevention of suicidal behavior in bipolar disorder patients. *Epidemiol Psichiatr Soc* 2009; **18**: 179–83.

Depression. Lithium may be used in the treatment and prophylaxis of recurrent unipolar depression, usually when standard antidepressants have failed (p. 398.1). Lithium is also used to augment the efficacy of other antidepressants in refractory cases.

References.
1. Heit S, Nemeroff CB. Lithium augmentation of antidepressants in treatment-refractory depression. *J Clin Psychiatry* 1998; **59** (suppl 6): 28–33.
2. Bauer M, Dopfmer S. Lithium augmentation in treatment-resistant depression: meta-analysis of placebo-controlled studies. *J Clin Psychopharmacol* 1999; **19**: 427–34. Correction. *ibid.* 2000; **20**: 287.
3. Sackeim HA, *et al.* Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. *JAMA* 2001; **285**: 1299–1307.
4. Gurzetta F, *et al.* Lithium treatment reduces suicide risk in recurrent major depressive disorder. *J Clin Psychiatry* 2007; **68**: 380–3.
5. Crossley NA, Bauer M. Acceleration and augmentation of antidepressants with lithium for depressive disorders: two meta-analyses of randomized, placebo-controlled trials. *J Clin Psychiatry* 2007; **68**: 935–40.

Disturbed behaviour. For mention of lithium in the management of children with disturbed behaviour see p. 1030.2.

Headache. Lithium is one of many drugs that have been tried in cluster headache (p. 670.1) to prevent headache attacks during cluster periods. In a double-blind study[1] lithium and verapamil were found to be of similar efficacy for cluster headache prophylaxis although verapamil appeared to produce fewer adverse effects. However, a later placebo-controlled study[2] was stopped early when lithium was found to be no more effective than placebo.

1. Bussone G, *et al.* Double blind comparison of lithium and verapamil in cluster headache prophylaxis. *Headache* 1990; **30**: 411–17.
2. Steiner TJ, *et al.* Double-blind placebo-controlled trial of lithium in episodic cluster headache. *Cephalalgia* 1997; **17**: 673–5.

Hyperthyroidism. Lithium may be used in hyperthyroidism (p. 2332.2), though its practical value is a matter of debate and, rarely, it may even cause hyperthyroidism (see Effects on the Endocrine System in Adverse Effects, p. 431.1). Pretreatment with lithium has also been reported to prolong the exposure of the thyroid to radioactive iodine in patients with Graves' thyrotoxicosis.[1]

1. Bogazzi F, *et al.* Treatment with lithium prevents serum thyroid hormone increase after thionamide withdrawal and radioiodine therapy in patients with Graves' disease. *J Clin Endocrinol Metab* 2002; **87**: 449–53.

Schizophrenia. The addition of lithium to antipsychotic treatment has been tried in patients with schizophrenia (p. 1031.3) or schizoaffective disorders who fail to respond to an antipsychotic alone. The results of a meta-analysis have suggested that lithium augmentation is of some benefit, particularly in those with schizoaffective disorder, although the evidence is inconsistent.[1] However, significantly more patients with lithium augmentation left the studies early, suggesting adverse effects may be problematic and the danger of an interaction between the drugs should also be borne in mind (see under Interactions, p. 433.3).

1. Leucht S, *et al.* Lithium for schizophrenia revisited: a systematic review and meta-analysis of randomized controlled trials. *J Clin Psychiatry* 2007; **68**: 177–86.

Skin disorders. Some salts or derivatives of lithium (notably lithium succinate, p. 1710.3, but also lithium gluconate) have been applied topically in preparations for seborrhoeic dermatitis.

References.
1. Dreno B, *et al.* Lithium gluconate 8% vs ketoconazole 2% in the treatment of seborrhoeic dermatitis: a multicentre, randomized study. *Br J Dermatol* 2003; **148**: 1230–6.
2. Dreno B, *et al.* Gluconate de lithium gel à 8 p. 100 dans le traitement de la dermatite séborrheique. *Ann Dermatol Venereol* 2007; **134**: 347–51.

Adverse Effects

Many of the adverse effects of lithium are dose-related and the margin between the therapeutic and toxic dose is narrow.

Initial adverse effects of lithium therapy include nausea, diarrhoea, vertigo, muscle weakness, and a dazed feeling; these effects often abate with continued therapy. Fine hand tremors, polyuria, and polydipsia may, however, persist. Other adverse effects that may occur at therapeutic serum-lithium concentrations include weight gain and oedema (which should not be treated with diuretics). Hypercalcaemia, hypermagnesaemia, and hyperparathyroidism have been reported. Skin disorders such as acne, psoriasis, and rashes may be exacerbated by lithium therapy. Leucocytosis is a relatively common adverse effect. Long-term adverse effects include hypothyroidism and/or goitre, rarely hyperthyroidism, and mild cognitive and memory impairment. Histological and functional changes in the kidney have been noted after long-term use of therapeutic concentrations of lithium (but see under Effects on the Kidneys, p. 431.2).

Toxic effects may be expected at serum-lithium concentrations of about 1.5 mmol/litre, although they can appear at lower concentrations. They call for immediate withdrawal of treatment and should always be considered very seriously.

Signs of lithium toxicity include increasing diarrhoea, vomiting, anorexia, muscle weakness, lethargy, giddiness with ataxia, lack of coordination, tinnitus, blurred vision, coarse tremor of the extremities and lower jaw, muscle hyperirritability, choreoathetoid movements, dysarthria, and drowsiness. Symptoms of severe overdosage at serum lithium concentrations above 2 mmol/litre include hyperreflexia and hyperextension of limbs, syncope, toxic psychosis, seizures, polyuria, renal failure, electrolyte imbalance, dehydration, circulatory failure, coma, and occasionally death.

The hazards of lithium in pregnant patients are discussed under Pregnancy in Precautions, p. 433.1.

References.
1. McKnight RF, *et al.* Lithium toxicity profile: a systematic review and meta-analysis. *Lancet* 2012; **379**: 721–8.

Effects on the blood. A patient developed thrombocytopenia after restarting lithium therapy after a gap of some weeks.[1] Stopping lithium led to an improvement in platelet count, but the count fell when lithium therapy was tried again. This patient also had leucocytosis, a recognised effect of lithium. Although concerns about leukaemia induction have not been verified, the author noted earlier reports of aplastic and megaloblastic anaemia and a case of fatal haemolytic anaemia reported to the UK CSM.

1. Collings S. Thrombocytopenia associated with lithium carbonate. *BMJ* 1992; **305**: 159.

Effects on the cardiovascular system. Reports of adverse effects on the heart associated with lithium have included

bradycardia due to sinus node dysfunction,[1] which has persisted after stopping lithium,[2] premature ventricular contractions,[3] atrioventricular block,[4] and T-wave depression.[5] For the adverse cardiac effects associated with lithium intoxication, see under Overdosage, p. 432.1.

For mention of myocarditis possibly associated with lithium therapy, see under Effects on the Musculoskeletal System, p. 431.2.

1. Montalescot G, *et al.* Serious sinus node dysfunction caused by therapeutic doses of lithium. *Int J Cardiol* 1984; 5: 94–6.
2. Palileo EV, *et al.* Persistent sinus node dysfunction secondary to lithium therapy. *Am Heart J* 1983; 106: 1443–4.
3. Tangedahl TN, Gau GT. Myocardial irritability associated with lithium carbonate therapy. *N Engl J Med* 1972; 287: 867–9.
4. Martin CA, Piascik MT. First degree A-V block in patients on lithium carbonate. *Can J Psychiatry* 1985; 30: 114–16.
5. Demers RG, Heninger GR. Electrocardiographic T-wave changes during lithium carbonate treatment. *JAMA* 1971; 218: 381–6.

Effects on the endocrine system. There is a small, but definite, risk that patients taking lithium in therapeutic doses will develop *goitre*, clinical or subclinical *hypothyroidism*, or, rarely, both.[1-3] Published prevalence figures have varied widely although most studies have found an increased risk of hypothyroidism in patients treated with lithium when compared with the general population.[2] Prevalence also appears to be higher in women taking lithium than in men;[2] in addition, the increased risk in women may be greatest during the first 2 years of lithium therapy. Other risk factors identified include a family history of thyroid disorders.[3] However, a long-term, follow-up study[4,5] suggested that the incidence of thyroid abnormalities was no greater in lithium-treated patients than in the general population.

Early goitre and lithium-induced hypothyroidism are both reversible if lithium is withdrawn; if continued treatment with lithium is desirable the patient should be treated with levothyroxine.

There have been rare reports of *hyperthyroidism* in lithium-treated patients[6] and the association may only be one of coincidence, although it is important to realise that hyperthyroidism can precipitate mania and can also be mistaken for an attack of mania.

Increases in serum concentrations of calcium and parathyroid hormone have been described in patients receiving lithium therapy. Although generally considered to be slight, some patients have experienced *parathyroid hyperplasia*.[7,8]

Cases of *diabetes mellitus* developing in patients treated with lithium have been reported but may not be attributable to lithium.[9] A case of transient diabetes after withdrawal of lithium treatment has also been described, manifesting as excessive thirst and polyuria that progressed to diabetic ketoacidosis; insulin therapy was stopped after 7 months.[10]

1. Vincent A, *et al.* Lithium-associated hypothyroidism: a practical review. *Lithium* 1994; 5: 73–4.
2. Johnston AM, Eagles JM. Lithium-associated clinical hypothyroidism: prevalence and risk factors. *Br J Psychiatry* 1999; 175: 336–9.
3. Ozpoyraz N, *et al.* Thyroid abnormalities in lithium-treated patients. *Adv Therapy* 2002; 19: 176–84.
4. Boccheta A, *et al.* Six-year follow-up of thyroid function during lithium treatment. *Acta Psychiatr Scand* 1996; 94: 45–8.
5. Boccheta A, *et al.* Ten-year follow-up of thyroid function in lithium patients. *J Clin Psychopharmacol* 2001; 21: 594–8.
6. Yamagishi S-I, Yokoyama-Ohta M. A case of lithium-associated hyperthyroidism. *Postgrad Med J* 1999; 75: 188–9.
7. Nordenström J, *et al.* Hyperparathyroidism associated with treatment of manic-depressive disorders by lithium. *Eur J Surg* 1992; 158: 207–11.
8. Taylor JW, Bell AJ. Lithium-induced parathyroid dysfunction: a case report and review of the literature. *Ann Pharmacother* 1993; 27: 1040–3.
9. Pandit MK, *et al.* Drug-induced disorders of glucose tolerance. *Ann Intern Med* 1993; 118: 529–39.
10. Okosieme OE, *et al.* Transient diabetes associated with withdrawal of lithium therapy. *Diabetes Care* 2006; 29: 1181.

Effects on the eyes. Decrease in accommodation has been reported in up to 10% of patients taking lithium; younger patients are most affected.[1] Blurred vision can also occur, most commonly early in therapy, but this may improve with time. Lithium can affect extra-ocular muscles and produce diplopia. A reduction in dosage or withdrawal of therapy may be required. It reduces lachrymal secretions and is excreted in tears in increased concentrations. In rare cases this may result in ocular irritation but this usually causes few problems when artificial tears are used. Photophobia, which occurs rarely with lithium therapy, may also be associated with the excretion of lithium in tears. Lithium can reduce dark adaptation due to a direct neural effect but whether this can progress further to cause irreversible macular or retinal degeneration is not proven. There are some rare but poorly documented reports of deposits in the cornea or conjunctiva. It was considered unlikely that lithium increased the risk of developing senile cataracts.

Lithium can cause nystagmus, many forms of which are reversible on reducing the dose or withdrawal of the drug. However, downbeat nystagmus is a serious adverse effect and is often irreversible. Irreversible oscillopsia can occur rarely secondary to nystagmus. Oculogyric crisis has been associated with lithium therapy and may be exacerbated by haloperidol.

Some ocular effects may be secondary to the effects of lithium on other systems. Exophthalmos and other thyroid-related eye disorders may occur rarely as a secondary effect of lithium on the thyroid. Lithium can also cause pseudotumor cerebri with papilloedema (benign intracranial hypertension). Most cases have occurred a few years after starting therapy but there has been a report of this condition after only 7 months of treatment. Ptosis has been reported, mainly associated with unmasking of myasthenia gravis.

1. Fraunfelder FT, *et al.* The effects of lithium on the human visual system. *J Toxicol Cutan Ocul Toxicol* 1992; 11: 97–169.

Effects on the kidneys. Polyuria with associated polydipsia, due to drug-induced nephrogenic diabetes insipidus, is the most common result of the effects of lithium on the kidney; an early review[1] stated that the incidence ranged from 4 to 50%. In some patients, irreversible kidney damage, associated with renal histological changes that included tubular atrophy, focal interstitial nephropathy and focal fibrosis, and impairment of glomerular filtration rate, was reported. However, although patients on long-term maintenance lithium therapy did appear to be susceptible to the development of progressive impairment of urinary concentrating ability it was most noticeable in patients with a history of acute lithium toxicity. The risk of renal damage and impaired glomerular filtration rate was thought to be extremely small in patients on stable maintenance lithium therapy with no history of acute lithium intoxication.[1]

A similar review considered that, although it was necessarily an oversimplified view, many, and perhaps all, of the renal adverse effects of lithium were induced by excessive dosage.[2] Others have also defended lithium with respect to its renal toxicity and stated that long-term therapy, if properly controlled, does not necessarily lead to chronic or irreversible renal damage.[3-5]

1. Walker RG, Kincaid-Smith P. Kidneys and the fluid regulatory system. In: Johnson FN, ed. *Depression & mania: modern lithium therapy*. Oxford: IRL Press,1987: 206–13.
2. George CRP. Renal aspects of lithium toxicity. *Med J Aust* 1989; 150: 291–2.
3. Schou M. Serum lithium monitoring of prophylactic treatment: critical review and updated recommendations. *Clin Pharmacokinet* 1988; 15: 283–6.
4. Schou M. Lithium treatment of manic-depressive illness: past, present, and perspectives. *JAMA* 1988; 259: 1834–6.
5. Gidlin M. Lithium and the kidney: an updated review. *Drug Safety* 1999; 20: 231–43.

Effects on the musculoskeletal system. The effects of lithium on skeletal muscle are represented mainly by varying degrees of weakness and tremor (for further details see under Effects on the Nervous and Neuromuscular Systems, p. 431.2). Aggravation of myasthenia gravis has been reported. Acute or subacute painful proximal myopathy causing myalgia, cramps, myokymia, or weakness has also been described. An association with myocarditis has been proposed[1] but it is unclear whether this is causal.

1. Coulter DM, *et al.* Antipsychotic drugs and heart muscle disorder in international pharmacovigilance: data mining study. *BMJ* 2001; 322: 1207–9.

Effects on the nervous and neuromuscular systems. Neurotoxicity has long been recognised as a potential adverse effect of lithium. Minor effects of lithium on the nervous system can be minimised by reduction of lithium dose during maintenance therapy but severe effects warrant immediate and complete withdrawal of the drug.[1] Minor effects have been considered to include impaired concentration, comprehension, and short-term memory, restlessness and anxiety, depression, fine rapid tremors, and easy fatigue. Serious or severe effects might include declining cognition and mental status, gait disturbances, movement disorders such as choreoathetosis, myoclonus, and parkinsonism, seizures, cerebellar signs, pseudotumor cerebri (although this was rare), neuroleptic malignant syndrome, myopathy, axonal neuropathy, a myasthenic syndrome, and exacerbation of underlying neuromuscular disease. The cognitive effects of lithium such as mental slowing may be subtle.[2]

There are 2 types of lithium-induced tremor.[3] The first is a coarse tremor occurring with impending and actual lithium toxicity and appears to have both cerebellar and parkinsonian components. It is often associated with incoordination, facial spasms, twitching of muscles and limbs, hyperactive reflexes, and more general systemic signs of toxicity. With this type of tremor it was mandatory to stop or decrease the dose of lithium. The second type, which is more common, is a fine tremor, usually occurring within normal therapeutic concentrations, either transiently within a few days of starting treatment or later as a long-standing adverse effect. With this type of fine tremor there was evidence to show that a slight decrease in dose may be beneficial.

In addition to the effects mentioned above, impairment of taste perception (mainly involving butter and celery)[4] and speech disturbances with few other signs of toxicity[5-8] have been reported.

Neurotoxicity persisting for at least 2 months after stopping lithium therapy (SILENT; syndrome of irreversible lithium-effectuated neurotoxicity) has been described.[9] Common presentations included cerebellar dysfunction, extrapyramidal symptoms, brainstem dysfunction, and dementia with varying degrees of organic mental syndromes.

For further effects of lithium on the nervous system, see under Effects on the Eyes above, Effects on the Musculoskeletal System, above, and under Epileptogenic Effect, p. 431.3.

1. Sansone ME, Ziegler DK. Brain and nervous system. In: Johnson FN, ed. *Depression & mania: modern lithium therapy*. Oxford: IRL Press, 1987: 240–5.
2. Pachet AK, Wisniewski AM. The effects of lithium on cognition: an updated review. *Psychopharmacology (Berl)* 2003; 170: 225–34.
3. Johns S, Harris B. Tremor. *BMJ* 1984; 288: 1309.
4. Himmelhoch JM, Hanin I. Side effects of lithium carbonate. *BMJ* 1974; 4: 233.
5. Solomon K, Vickers R. Dysarthria resulting from lithium carbonate: a case report. *JAMA* 1975; 231: 280.
6. Worrall EP, Gillham RA. Lithium-induced constructional dyspraxia. *BMJ* 1983; 286: 189.
7. McGovern GP. Lithium induced constructional dyspraxia. *BMJ* 1983; 286: 646.
8. Netski AL, Piasecki M. Lithium-induced exacerbation of stutter. *Ann Pharmacother* 2001; 35: 961.
9. Adityanjee, *et al.* The syndrome of irreversible lithium-effectuated neurotoxicity. *Clin Neuropharmacol* 2005; 28: 38–49.

Effects on respiration. Lithium is not generally recognised as a respiratory depressant but an episode of reversible respiratory failure about 3 weeks after the start of lithium therapy has been described in a patient with stable chronic airways obstruction.[1] Recovery of consciousness and resolution of hypercapnia occurred within 24 to 36 hours of stopping lithium.

1. Weiner M, *et al.* Effect of lithium on the responses to added respiratory resistances. *N Engl J Med* 1983; 308: 319–22.

Effects on sexual function and fertility. Lithium does not seem to interfere with sexual function in most patients, but there have been isolated reports of impotence and loss of libido attributed to lithium therapy.[1]

Studies *in vitro* have shown that lithium can inhibit sperm motility in concentrations comparable with those reported to be achieved in semen,[2] but concentrations found in cervico-vaginal mucus were considered unlikely to affect motility.[3]

1. Beeley L. Drug-induced sexual dysfunction and infertility. *Adverse Drug React Acute Poisoning Rev* 1984; 3: 23–42.
2. Raoof NT, *et al.* Lithium inhibits human sperm motility in vitro. *Br J Clin Pharmacol* 1989; 28: 715–17.
3. Salas IG, *et al.* Lithium carbonate concentration in cervico-vaginal mucus and serum after repeated oral dose administration. *Br J Clin Pharmacol* 1989; 28: 751P.

Effects on the skin and hair. Patients taking lithium may develop skin disorders, though these are not necessarily serious or severe.[1-3] Male patients may be more susceptible to such effects than female, although early results suggested the reverse.[3] Onset can vary from 2 or 3 weeks to 7 or more years, but many reactions start to appear once optimal serum-lithium concentrations have been attained. Effects reported include psoriasis which may be severe and require lithium withdrawal. Seborrhoeic dermatitis and follicular keratosis also occur and can improve spontaneously or after stopping lithium. Acneform eruptions are found in areas not usually affected by acne vulgaris; in general the face is less affected or not affected at all.

Hair loss, not always severe, is more frequent than cutaneous effects. About 6% of patients may be affected and all forms of alopecias have been found. The onset occurs several weeks or months after the start of lithium therapy. The hair usually regrows despite continuing therapy but in some cases regrowth only occurs after withdrawal of lithium. In a review[4] of the effects on the ocular system, loss of eyebrows and eyelashes was noted as a rare event. Hair loss due to lithium-induced hypothyroidism can be corrected by thyroid replacement therapy.

For references to the association of lithium with lupus, see under Lupus, p. 432.1.

1. Lambert D, Dalac S. Skin, hair and nails. In: Johnson FN, ed. *Depression & mania: modern lithium therapy*. Oxford: IRL Press, 1987: 232–4.
2. Gupta AK, *et al.* Lithium therapy associated with hidradenitis suppurativa: case report and a review of the dermatologic side effects of lithium. *J Am Acad Dermatol* 1995; 32: 382–6.
3. Yeung CK, Chan HHL. Cutaneous adverse effects of lithium: epidemiology and management. *Am J Clin Dermatol* 2004; 5: 3–8.
4. Fraunfelder FT, *et al.* The effects of lithium on the human visual system. *J Toxicol Cutan Ocul Toxicol* 1992; 11: 97–169.

Epileptogenic effect. Seizures during lithium therapy usually indicate toxicity or impending toxicity. There have, however, been a few isolated reports of seizures in patients with serum-lithium concentrations within the normally accepted therapeutic range.[1,2]

1. Demers R, *et al.* Convulsion during lithium therapy. *Lancet* 1970; ii: 315–16.

2. Massey EW, Polger WN. Seizures activated by therapeutic levels of lithium carbonate. *South Med J* 1984; 77: 1173–5.

Lupus. Studies have found that antinuclear antibodies were more common in patients taking lithium carbonate than in controls.[1,2] The absence of anti-DNA antibodies indicated that they did not have true SLE but it was considered that patients ingesting lithium might be at risk. Dermatological manifestations of lupus with the presence of antinuclear antibodies have been reported in a patient taking lithium.[3]

1. Johnstone EC, Whaley K. Antinuclear antibodies in psychiatric illness: their relationship to diagnosis and drug treatment. *BMJ* 1975; 2: 724–5.
2. Presley AP, *et al.* Antinuclear antibodies in patients on lithium carbonate. *BMJ* 1976; 2: 280–1.
3. Shukla VR, Borison RL. Lithium and lupuslike syndrome. *JAMA* 1982; 248: 921–2.

Overdosage. Nausea, vomiting, and diarrhoea are common early features of lithium toxicity, and are followed by coarse tremor, increased muscle tone, cogwheel rigidity, fasciculation, and myoclonus.[1] Coma and convulsions may occur in serious cases and cardiac effects (first-degree heart block and QRS and QT prolongation) have been described rarely. A patient may appear to be aware with open eyes but have an expressionless face and be unable to move or speak (coma vigil). Acute renal failure and nephrogenic diabetes insipidus may develop.

In **acute overdosage**[2] vomiting often occurs within an hour of ingestion due to the high concentration of lithium in the stomach, but significant amounts of lithium can still reach the systemic circulation. The typical clinical symptoms often appear after a delay and gastrointestinal symptoms can re-appear at a later time. The symptoms of overdosage are reported to be mainly related to the gastrointestinal and nervous systems and include abdominal pain, anorexia, nausea, and vomiting, occasionally mild diarrhoea, giddiness, tremor, ataxia, slurring speech, myoclonus, twitching, asthenia, and depression; renal symptoms have also been noted by some investigators. Efficient detoxification procedures (see Treatment of Adverse Effects, p. 432.2) should be started as rapidly as possible.

Symptoms associated with **chronic intoxication** can be more severe and neurotoxicity may be a particular feature.[3,4] One reviewer considered that the majority of lithium intoxications reported had occurred in patients with renal impairment or in patients who had been given too high a dose.[2] The patient usually has a prodromal period of days to a few weeks with minor 'nervous' symptoms which are signs of a manifest slight intoxication. At an unpredictable point renal function starts to deteriorate and within hours or, at the most, a few days, the patient will become severely intoxicated. By this point lithium should have been stopped and efficient detoxification measures (see Treatment of Adverse Effects, p. 432.2) begun if the patient is to make a complete recovery. Other risk factors[3-5] for developing chronic intoxication include use with certain medications (see Interactions, p. 433.2), older age, and the presence of other conditions such as neurogenic diabetes insipidus and thyroid dysfunction (see also Precautions, p. 432.2).

In a series of 28 patients with lithium self-poisoning or therapeutic intoxication many of the features and symptoms mentioned above were noted.[6] Other workers[7,8] have also reported cases that illustrate the differences between acute and chronic toxicity encountered clinically.

Serum concentrations of lithium should be measured routinely throughout treatment to ensure that values do not rise to levels associated with toxicity. However, some patients may have concentrations considered to be toxic without showing any symptoms and others may develop signs of toxicity at therapeutic serum concentrations.[9]

Other symptoms that have been noted in case reports of lithium intoxication in individual patients include photophobia,[10] acute polyarthritis involving several large joints,[11] severe hypertension,[12] deep venous thrombophlebitis,[13] reduction of central temperature,[14] and severe leucopenia.[15]

1. Proudfoot AT. Acute poisoning with antidepressants and lithium. *Prescribers' J* 1986; 26: 97–106.
2. Amdisen A. Clinical features and management of lithium poisoning. *Med Toxicol* 1988; 3: 18–32.
3. Oakley PW, *et al.* Lithium toxicity: an iatrogenic problem in susceptible individuals. *Aust N Z J Psychiatry* 2001; 35: 833–40.
4. Chen K-P, *et al.* Implication of serum concentration monitoring in patients with lithium intoxication. *Psychiatry Clin Neurosci* 2004; 58: 25–9.
5. Montagnon F, *et al.* Lithium: poisonings and suicide prevention. *Eur Psychiatry* 2002; 17: 92–5.
6. Dyson EH, *et al.* Self-poisoning and therapeutic intoxication with lithium. *Hum Toxicol* 1987; 6: 325–9.
7. Ananth J, *et al.* Acute and chronic lithium toxicity: case reports and a review. *Lithium* 1992; 3: 139–45.
8. Bailey B, McGuigan M. Lithium poisoning from a poison control center perspective. *Ther Drug Monit* 2000; 22: 650–5.
9. Stern R. Lithium in the treatment of mood disorders. *N Engl J Med* 1995; 332: 127–8.
10. Caplan RP, Fry AH. Photophobia in lithium intoxication. *BMJ* 1982; 285: 1314–15.
11. Black DW, Waziri R. Arthritis associated with lithium toxicity: case report. *J Clin Psychiatry* 1984; 45: 135–6.
12. Michaeli J, *et al.* Severe hypertension and lithium intoxication. *JAMA* 1984; 251: 1680.
13. Lyles MR. Deep venous thrombophlebitis associated with lithium toxicity. *J Natl Med Assoc* 1984; 76: 633–4.
14. Follézou J-Y, Bleibel J-M. Reduction of temperature and lithium poisoning. *N Engl J Med* 1985; 313: 1609.
15. Green ST, Dunn FG. Severe leucopenia in fatal lithium poisoning. *BMJ* 1985; 290: 517.

Treatment of Adverse Effects

In recent acute overdosage with lithium, consideration should be given to gastric lavage to empty the stomach if ingestion has occurred within 1 hour of presentation. However this may be of limited value after overdosage with modified-release preparations, which do not disintegrate in the stomach and may be too large to pass through a lavage tube. Activated charcoal is of no value. Whole-bowel irrigation has been suggested although there do not appear to be clinical studies to confirm efficacy.

Further measures may involve procedures to enhance the renal clearance of lithium or its active removal. Adequate hydration should be ensured and any electrolyte imbalance corrected, but forced diuresis or diuretics are contra-indicated. Appropriate supportive care may include measures to control hypotension and convulsions. Maintenance of fluid and electrolyte balance is particularly important because of the risk of hypernatraemia. The ECG should be monitored in symptomatic patients.

In severe poisoning, haemodialysis is the treatment of choice (particularly if there is renal impairment). Although effective in reducing serum-lithium concentrations, substantial rebound increases can be expected when dialysis is stopped, and prolonged or repeated treatments may be required. Peritoneal dialysis is less effective and only appropriate if haemodialysis facilities are not available. Haemofiltration has been tried to good effect.

Serum lithium concentrations should be monitored regularly throughout treatment. Once the serum and dialysis fluid are free of lithium, it has been recommended that serum-lithium concentrations should be monitored for at least another week so that allowance can be made for delayed diffusion from body tissues.

As a result of the narrow margin between therapeutic and toxic serum concentrations, lithium poisoning may also develop during the course of therapy. In some instances temporary withdrawal of lithium therapy and giving generous amounts of sodium and fluid may be all that is required while adverse effects abate. In any serious or severe case of intoxication active measures such as dialysis and supportive measures outlined above may need to be instituted. Gut decontamination is not useful.

References.

1. Smith SW, *et al.* Whole-bowel irrigation as a treatment for acute lithium overdose. *Ann Emerg Med* 1991; 20: 536–9.
2. Okusa MD, *et al.* Clinical manifestations and management of acute lithium intoxication. *Am J Med* 1994; 97: 383–9.
3. Swartz CM, Jones P. Hyperlithemia correction and persistent delirium. *J Clin Pharmacol* 1994; 34: 865–70.
4. Tyrer SP. Lithium intoxication: appropriate treatment. *CNS Drugs* 1996; 6: 426–39.

Precautions

The margin between the therapeutic and the toxic concentration of lithium is narrow so therapy usually requires specialist advice, and serum concentrations should be monitored regularly under controlled conditions. Patients receiving lithium therapy should be taught to recognise the symptoms of early toxicity (see Adverse Effects, p. 428.3) and, should these occur, to stop therapy and request medical aid at once. They should be warned not to compensate for an omitted dose by subsequently taking a double dose. Additionally, patients should not be switched between different formulations or preparations of lithium without therapeutic monitoring, as bioavailability may be different.

Lithium should be avoided in patients with cardiac disease or renal impairment; cardiac and renal function should be monitored regularly during treatment. It should also be avoided in Addison's disease or other conditions with a sodium imbalance and in severely debilitated or dehydrated patients.

Patients receiving lithium should be examined periodically for abnormal thyroid function, since goitre and hypothyroidism may develop. Lithium should be avoided in untreated hypothyroidism. Lithium should be used with caution in patients with myasthenia gravis because exacerbation of this disorder has been reported (see Effects on the Musculoskeletal System in Adverse Effects, p. 429.2).

Lithium should be used with special care in the elderly since this group may be particularly susceptible to toxicity owing to reduced renal function.

Impaired driving performance or machine operating skills may occur in patients receiving lithium (see Driving, p. 432.3).

It may be necessary to temporarily reduce or stop lithium therapy in patients suffering from vomiting, diarrhoea, intercurrent infection, excessive sweating, or any other condition that causes excessive sodium loss and hence increased serum-lithium concentrations. Conversely, increased sodium levels are likely to reduce serum-lithium concentrations. Patients taking lithium should therefore maintain an adequate fluid intake and should avoid increasing or decreasing sodium intake through dietary changes or ingestion of sodium-containing medicaments. Significant changes in caffeine intake may affect serum-lithium concentrations (see Xanthines under Interactions, p. 434.3).

Lithium therapy should, where possible, be withdrawn slowly over a period of weeks to allay any concerns about relapse (see Withdrawal, p. 433.2).

The risks of using lithium in pregnant patients are described under Pregnancy, p. 433.1. If lithium is used during pregnancy then dose adjustments will be required to compensate for the altered renal handling.

Lithium should be temporarily stopped 24 hours before major surgery to safeguard the patient from accumulation (see Anaesthesia, p. 432.3).

Anaesthesia. The *BNF* states that lithium should be stopped 24 hours before major surgery, but the normal dose can be continued for minor surgery if fluids and electrolytes are carefully monitored. Lithium may accumulate because of reduced renal clearance associated with anaesthesia;[1] treatment should be resumed as soon as possible after surgery, when kidney function and fluid-electrolyte balance have become normal. Patients are often not allowed oral fluids or foods the night before surgery but patients with lithium-induced polyuria should be given fluids parenterally during the night before the operation, if they vomit copiously, or if they are unconscious for several hours.

There is no clinical evidence of interaction between lithium and anaesthetics, although lithium may prolong the action of neuromuscular blockers.[1]

1. Schou M, Hippus H. Guidelines for patients receiving lithium treatment who require major surgery. *Br J Anaesth* 1987; 59: 809–10.

Breast feeding. Lithium is distributed into breast milk. Early reports suggested that serum concentrations in breast-fed infants were about one-third to one-half of those measured in mothers.[1] However, advice regarding the decision to breast feed remains equivocal. The American Academy of Pediatrics[2] considers that lithium should be given with caution to breast-feeding women but does not contra-indicate such use, and this is supported by some authors.[3,4] Conversely, most UK licensed product information and other authors[5,6] suggest that mothers receiving lithium should bottle feed their infants. It has been recommended[5] that if a mother did want to breast feed this should be done at times to avoid peak blood concentrations of lithium and the infant carefully monitored. Medication should be withheld or breast feeding stopped if the infant developed an infection or dehydration as they would be more susceptible to the adverse effects of lithium.

1. Schou M, Amdisen A. Lithium and pregnancy—III, lithium ingestion by children breast-fed by women on lithium treatment. *BMJ* 1973; 2: 138
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 24/11/05)
3. Schou M. Lithium treatment during pregnancy, delivery, and lactation an update. *J Clin Psychiatry* 1990; 51: 410–13.
4. Sykes PA, *et al.* Lithium carbonate and breast-feeding. *BMJ* 1976; 2 1299.
5. Ananth J. Lithium during pregnancy and lactation. *Lithium* 1993; 4 231–7.
6. Llewellyn A, *et al.* The use of lithium and management of women with bipolar disorder during pregnancy and lactation. *J Clin Psychiatry* 1998 59 (suppl 6): 57–64.

Cystic fibrosis. Reduced renal excretion of lithium was evident in 8 patients with cystic fibrosis compared with healthy subjects.[1] The authors recommended caution when prescribing standard doses of lithium to patients with cystic fibrosis until more definitive data were available.

1. Brager NPD, *et al.* Reduced renal fractional excretion of lithium in cystic fibrosis. *Br J Clin Pharmacol* 1996; 41: 157–9.

Driving. In the UK, the Driver and Vehicle Licensing Authority (DVLA) considers that patients with severe depressive illnesses complicated by significant memory or concentration problems, agitation, behavioural disturbances, or suicidal thoughts should cease driving pending the outcome of medical enquiry.[1] Mania or hypomania is particularly dangerous and driving should cease during the acute illness. After an isolated episode, re-licensing can be reconsidered provided the patient has remained well and stable for at least 3 months, is compliant with treatment, and has regained insight; in addition, the patient should be free from any adverse effects of medication that would impair driving. If there have been 4 or

more episodes of mood swing within the previous 12 months, at least 6 months of stability will be required before re-licensing can be considered. Drivers of heavy goods and public service vehicles are normally required to be well and stable for 3 years before driving can resume.

Treatment with antidepressant drugs, including lithium, may also be hazardous,[2] although patients may be safer drivers with medication than without.[3] Lithium has been reported[2] to adversely affect the choice reaction time (a test to assess the time taken to respond correctly to some signals but not others) to a level considered dangerous for driving. Another study has found that elderly patients taking lithium may be at an increased risk of being involved in an injurious motor vehicle accident while driving when compared with a cohort of elderly, non-lithium users.[4]

1. Driver and Vehicle Licensing Agency. For medical practitioners: at a glance guide to the current medical standards of fitness to drive (issued November 2013). Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/258991/aagv1.pdf (accessed 20/11/13)
2. Ashton H. Drugs and driving. *Adverse Drug React Bull* 1983; 98: 360–3.
3. Cremona A. Mad drivers: psychiatric illness and driving performance. *Br J Hosp Med* 1986; 35: 193–5.
4. Bjerkan M, *et al.* Use of lithium and the risk of injurious motor vehicle crash in elderly adults: case-control study nested within a cohort. *BMJ* 2004; 328: 558–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lithium as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Pregnancy. The decision whether to continue lithium treatment during pregnancy is difficult and should involve careful consideration of the risk-benefit ratio, which in some cases may favour treatment. Early case reports of mothers taking lithium during pregnancy pointed to an increased risk of congenital abnormalities with the baby's heart being mainly affected.[1] Support for this increased risk also came from a study[2] of the records of 59 children born to women who had taken lithium during pregnancy. However, another study[3] that prospectively followed 138 pregnant women being treated with lithium did not identify any difference in pregnancy outcome between them and a control group. The authors considered that lithium was not a major teratogen and felt that women with major affective disorders could continue lithium treatment during pregnancy provided that adequate fetal screening tests were carried out. A subsequent review[4] considered that the teratogenic risk was lower than previously thought, but that it would still be wise for women who wished to become pregnant to stop lithium if at all possible, at least during the period of embryogenesis. If lithium is stopped, withdrawal should be slow to prevent a relapse (see p. 433.2).

There is limited evidence that lithium treatment during pregnancy may increase the risk of fetal macrosomia, premature delivery, and perinatal mortality.[1,5] Polyhydramnios (an excess of amniotic fluid) in the last trimester of pregnancy has been reported and has been attributed to fetal lithium toxicity (polyuria and diabetes insipidus).[6,7]

Monitoring of serum-lithium concentrations is particularly important during pregnancy. The renal clearance of lithium by the mother is not constant during pregnancy; in the second half of the pregnancy clearance rises gradually by 30 to 50% but falls abruptly and significantly after delivery to pre-pregnancy values.[1,8] The increased doses of lithium that may be given during pregnancy to compensate for this increased clearance may result in lithium toxicity.[8] It is generally considered[1,9,10] advisable to stop lithium during the last few days of pregnancy to reduce the risk of maternal lithium toxicity due to accumulation of lithium but it should be started again a few days later after delivery at reduced dosage because of the increased postpartum risk of manic and depressive relapse.[1,10]

Reducing the dosage during the last few days of pregnancy also helps to reduce lithium concentrations in the neonate and avoid associated adverse effects.[1,9] Adverse effects that have been reported in neonates exposed *in utero* to lithium include cyanosis, lethargy, flaccidity, hypotonia, poor gag and sucking reflexes, feeding problems, bradycardia, tachycardia, goitre, hypothyroidism, nephrogenic diabetes, and jaundice;[9-12] withdrawal symptoms have also been seen.

1. Schou M. Lithium treatment during pregnancy, delivery, and lactation: an update. *J Clin Psychiatry* 1990; 51: 410–13.
2. Källén B, Tandberg A. Lithium and pregnancy: a cohort study on manic-depressive women. *Acta Psychiatr Scand* 1983; 68: 134–9.
3. Jacobson SJ, *et al.* Prospective multicentre study of pregnancy outcome after lithium exposure during first trimester. *Lancet* 1992; 339: 530–3.
4. Cohen LS, *et al.* A reevaluation of risk of in utero exposure to lithium. *JAMA* 1994; 271: 146–50.
5. Troyer WA, *et al.* Association of maternal lithium exposure and premature delivery. *J Perinatol* 1993; XIII: 123–7.
6. Krause S, *et al.* Polyhydramnios with maternal lithium treatment. *Obstet Gynecol* 1990; 75: 504–6.
7. Ang MS, *et al.* Maternal lithium therapy and polyhydramnios. *Obstet Gynecol* 1990; 76: 517–19.
8. Lemoine J-M. Pregnancy, delivery and lactation. In: Johnson FN, ed. *Depression & mania: modern lithium therapy*. Oxford: IRL Press, 1987: 139–46.
9. Ananth J. Lithium during pregnancy and lactation. *Lithium* 1993; 4: 231–7.
10. Pinelli JM, *et al.* Case report and review of the perinatal implications of maternal lithium use. *Am J Obstet Gynecol* 2002; 187: 245–9.
11. Frassetto P, *et al.* Goiter in a newborn exposed to lithium in utero. *Ann Pharmacother* 2002; 36: 1745–8.
12. Kozma C. Neonatal toxicity and transient neurodevelopmental deficits following prenatal exposure to lithium: another clinical report and a review of the literature. *Am J Med Genet A* 2005; 132: 441–4.

Surgery. For comments regarding the precautions to be considered in patients undergoing surgery, see under Anaesthesia, p. 430.3.

Withdrawal. Symptoms such as anxiety, tremor, fatigue, nausea, sweating, headache, sleep disturbances, diarrhoea, or blurred vision have developed within days of sudden cessation of treatment with lithium.[1] These symptoms may simply be a recurrence of the mood disorder. Uncontrolled studies of withdrawal symptoms have raised the possibility of a lithium-withdrawal state although controlled studies have been convincingly negative. It is, however, wise to reduce lithium dosage gradually rather than stop high-dosage treatment abruptly.

A frequent worry associated with stopping lithium therapy is that of relapse. Most evidence has supported the view that any relapses occurring in the first weeks after lithium withdrawal are simply part of a pattern of recurrence of bipolar disorder in general and are not indicative of a higher rate of recurrence. Some,[2] however, have found the proportion of patients relapsing on sudden withdrawal of lithium therapy to be 50%, a figure they consider to be too high to be accounted for by the natural history of the disease process. They and others[3] advise that this risk should be considered when prescribing lithium for bipolar disorder. In patients who previously had been stable on lithium for at least 18 months, the risk of early recurrence of bipolar disorder was higher when therapy was withdrawn rapidly in less than 2 weeks than when it was withdrawn gradually over 2 to 4 weeks.[4]

1. Goodnick PJ. Terminating treatment. In: Johnson FN, ed. *Depression & mania: modern lithium therapy*. Oxford: IRL Press, 1987: 115–17.
2. Mander AJ, Loudon JB. Rapid recurrence of mania following abrupt discontinuation of lithium. *Lancet* 1988; ii: 15–17.
3. Goodwin GM. Recurrence of mania after lithium withdrawal. *Br J Psychiatry* 1994; 164: 149–52.
4. Faedda GL, *et al.* Outcome after rapid vs gradual discontinuation of lithium treatment in bipolar disorders. *Arch Gen Psychiatry* 1993; 50: 448–55.

Interactions

Some diuretics may reduce lithium excretion and result in toxicity (see p. 434.2 for further details). Thiazide diuretics may also show a paradoxical antidiuretic effect. Consequently, diuretics should be avoided or used with caution in those receiving lithium; if used together, a reduction in the lithium dose may be appropriate. Other drugs affecting electrolyte balance may also alter lithium excretion and should be avoided if possible or used with care.

Further interactions reported with lithium are discussed below.

Reviews.

1. Amdisen A. Lithium and drug interactions. *Drugs* 1982; 24: 133–9.
2. Beeley L. Drug interactions with lithium. *Prescribers' J* 1986; 26: 160–2.
3. Harvey NS, Merriman S. Review of clinically important drug interactions with lithium. *Drug Safety* 1994; 10: 455–63.
4. Finley PR, *et al.* Clinical relevance of drug interactions with lithium. *Clin Pharmacokinet* 1995; 29: 172–91.

ACE inhibitors. Giving lithium with ACE inhibitors has been reported[1-5] to increase serum-lithium concentrations, resulting in some cases in lithium toxicity. ACE inhibitors such as *captopril*,[2] *enalapril*,[1,3,5] and *lisinopril*[4,5] have been implicated, although in a study[6] of enalapril and lithium in healthy subjects, the lithium levels remained unchanged. The mechanism is unclear but it has been suggested[7] that suppression of the renin-angiotensin-aldosterone system by ACE inhibitors may be responsible. Lithium excretion by the kidney is dependent on both glomerular filtration and sodium concentration in the proximal tubule, both of which are reduced by ACE inhibitors. It has also been suggested[3] that inhibition of angiotensin II production may lead to reduced fluid intake through lack of activation of the thirst stimulus and this would enhance the tendency to volume depletion caused by natriuresis. Patients considered[7] to be at risk from this reaction would include those whose renal function is largely dependent on the effect of angiotensin II, those with congestive heart failure, and those with volume depletion.

1. Douste-Blazy P, *et al.* Angiotensin converting enzyme inhibitors and lithium treatment. *Lancet* 1986; i: 1448.
2. Pullk M, Lida H. Interaction lithium-inhibiteurs de l'enzyme de conversion. *Presse Med* 1988; 17: 755.
3. Navis GJ, *et al.* Volume homeostasis, angiotensin converting enzyme inhibition, and lithium therapy. *Am J Med* 1989; 86: 621.
4. Baldwin CM, Salferman AZ. A case of lisinopril-induced lithium toxicity. *DICP Ann Pharmacother* 1990; 24: 946–7.
5. Correa FJ, Elser AR. Angiotensin-converting enzyme inhibitors and lithium toxicity. *Am J Med* 1992; 93: 108–9.
6. DasGupta K, *et al.* The effect of enalapril on serum lithium levels in healthy men. *J Clin Psychiatry* 1992; 53: 398–400.
7. Mignat C, Unger T. Ace inhibitors: drug interactions of clinical significance. *Drug Safety* 1995; 12: 334–47.

Analgesics. See NSAIDs and Opioid Analgesics, p. 434.2 and p. 434.3, respectively.

Angiotensin II receptor antagonists. There have been case reports of lithium intoxication occurring in patients after the addition of *candesartan*,[1] *losartan*,[2] or *valsartan*[3] to their therapy. The mechanism may be similar to that for ACE inhibitors (above).

1. Zwanzger P, *et al.* Lithium intoxication after administration of AT$_1$ blockers. *J Clin Psychiatry* 2001; 62: 208–9.
2. Blanche P, *et al.* Lithium intoxication in an elderly patient after combined treatment with losartan. *Eur J Clin Pharmacol* 1997; 52: 501.
3. Leung M, Remick RA. Potential drug interaction between lithium and valsartan. *J Clin Psychopharmacol* 2000; 20: 392–3.

Antidepressants. Lithium has been used to augment the effect of other antidepressants in refractory depression. However, there have been reports of adverse reactions with some of these combinations. For further details, see Antidepressants under Interactions of Phenelzine, p. 447.2.

Antiepileptics. Severe CNS toxicity despite 'normal' serum-lithium concentrations has been described in a patient also taking *phenytoin* and *phenobarbital*.[1] Symptoms indicative of lithium toxicity have also been reported in a patient taking lithium with phenytoin alone;[2] again concentrations were not abnormal.

For reports of neurotoxicity in patients receiving *carbamazepine* and lithium, see p. 516.2. Carbamazepine-induced renal failure has also resulted in toxic serum-lithium concentrations.[3]

1. Speirs J, Hirsch SR. Severe lithium toxicity with "normal" serum concentrations. *BMJ* 1978; 1: 815–16.
2. MacCallum WAG. Interaction of lithium and phenytoin. *BMJ* 1980; 280: 610–11.
3. Mayan H, *et al.* Lithium intoxication due to carbamazepine-induced renal failure. *Ann Pharmacother* 2001; 35: 560–2.

Antimicrobials. Lithium toxicity has been reported on isolated occasions in patients receiving *doxycycline*,[1] *metronidazole*,[2] *spectinomycin*,[3] and *tetracycline*.[4]

However, it has been noted that lithium and tetracycline have been used together without serious problems in many patients and that additionally tetracycline has been used to treat the acneform skin eruptions induced by lithium.[5] It has also been found[5] that in healthy subjects lithium concentrations were decreased, rather than increased, after the addition of tetracycline but this was probably of no clinical significance.

1. Miller SC. Doxycycline-induced lithium toxicity. *J Clin Psychopharmacol* 1997; 17: 54–5.
2. Teicher MH, *et al.* Possible nephrotoxic interaction of lithium and metronidazole. *JAMA* 1987; 257: 3365–6.
3. Anonymous. Possible adverse drug-drug interaction report: lithium intoxication in a spectinomycin-treated patient. *Int Drug Ther Newslett* 1978; 13: 15.
4. McGennis AJ. Lithium carbonate and tetracycline interaction. *BMJ* 1978; 1: 1183.
5. Fankhauser MP, *et al.* Evaluation of lithium-tetracycline interaction. *Clin Pharm* 1988; 7: 314–17.

Antimigraine drugs. For comment on the suggestion that there may be a risk of increased CNS toxicity when *sumatriptan* and lithium are given together, see p. 681.3.

Antineoplastics. Transient decreases in serum-lithium concentration occurred in a patient given *cisplatin*.[1] The relative contributions of cisplatin itself, or the fluid loading procedure involving intravenous fluids and mannitol, or their combined effects were unclear. The interaction, however, had no apparent clinical significance in this patient although a risk of undertreatment with lithium may occur in other patients.

1. Pietruszka LJ, *et al.* Evaluation of cisplatin-lithium interaction. *Drug Intell Clin Pharm* 1985; 19: 31–2.

Antipsychotics and anxiolytics. In the control of acute mania lithium is often too slow in onset to be used alone and therefore additional therapy with an antipsychotic may be necessary. It should be noted, however, that such combinations should be used with care as interactions and adverse reactions have occurred.

The renal excretion of lithium is increased by *chlorpromazine* treatment,[1] which means that subsequent withdrawal of chlorpromazine can result in an abrupt rise in serum-lithium concentrations.[2] The serum concentration of chlorpromazine can also be reduced by lithium,[3] and chlorpromazine toxicity may be precipitated by the abrupt withdrawal of lithium in patients previously stabilised on both drugs. Ventricular fibrillation has been described after withdrawal of lithium in a patient also taking chlorprom-

azine;[4] it was suggested that the chlorpromazine dose should be reduced if lithium is to be stopped.

There have been isolated reports of neurotoxicity or brain damage, characterised by delirium, seizures, encephalopathy, or an increased incidence of extrapyramidal symptoms in patients receiving lithium with *flupentixol decanoate*,[5] *fluphenazine decanoate*,[6] or high-dose *haloperidol*,[7-9] although two earlier retrospective studies of patients taking lithium with antipsychotics had failed to detect such adverse reactions.[10,11] Neurological reactions have also been reported in patients receiving lithium with *thioridazine*,[12,13] *sulpiride*,[14] *clozapine*,[15] and *risperidone*.[16] Although a causal relationship between these events and use of lithium with antipsychotics has not been fully established, patients should be monitored for signs of neurotoxicity if receiving such combinations.

A 1987 review considered that the neurotoxicity induced by lithium and antipsychotics was a rare entity.[17] Whether the combination produced any greater risk than either drug alone, and whether the neurotoxicity was a distinct diagnostic entity or simply represented atypical cases of lithium toxicity or the neuroleptic malignant syndrome, was debatable. The interaction between lithium and haloperidol might represent a form of neuroleptic malignant syndrome and that between lithium and the phenothiazines, especially thioridazine, a form of lithium toxicity. It was concluded that the risk from combination therapy was very small but that the clinician should, nevertheless, be aware of it.

Although lithium has been reported to interact with *diazepam* resulting in hypothermic episodes,[18] this may be an idiosyncratic response rather than a true drug interaction;[17] in general it was considered safe to use lithium with benzodiazepines.

1. Sletten I, *et al.* The effect of chlorpromazine on lithium excretion in psychiatric subjects. *Curr Ther Res* 1966; **8**: 441–6.
2. Pakes GE. Lithium toxicity with phenothiazine withdrawal. *Lancet* 1979; **ii**: 701.
3. Rivera-Calimlim L, *et al.* Effect of lithium on plasma chlorpromazine levels. *Clin Pharmacol Ther* 1978; **23**: 451–5.
4. Stevenson RN, *et al.* Ventricular fibrillation due to lithium withdrawal—an interaction with chlorpromazine? *Postgrad Med J* 1989; **65**: 936–8.
5. West A. Adverse effects of lithium treatment. *BMJ* 1977; **2**: 642.
6. Singh SV. Lithium carbonate/fluphenazine decanoate producing irreversible brain damage. *Lancet* 1982; **ii**: 278.
7. Cohen WJ, Cohen NH. Lithium carbonate, haloperidol, and irreversible brain damage. *JAMA* 1974; **230**: 1283–7.
8. Loudon JB, Waring H. Toxic reactions to lithium and haloperidol. *Lancet* 1976; **ii**: 1088.
9. Thomas C, *et al.* Lithium/haloperidol combinations and brain damage. *Lancet* 1982; **i**: 626.
10. Baastrup PC, *et al.* Adverse reactions in treatment with lithium carbonate and haloperidol. *JAMA* 1976; **236**: 2645–6.
11. Prakash R. Lithium-haloperidol combination and brain damage. *Lancet* 1982; **i**: 1468–9.
12. Standish-Barry HMAS, Shelly MA. Toxic neurological reaction to lithium/thioridazine. *Lancet* 1983; **i**: 771.
13. Cantor CH. Encephalopathy with lithium and thioridazine in combination. *Med J Aust* 1986; **144**: 164–5.
14. Dinan TG, O'Keane V. Acute extrapyramidal reactions following lithium and sulpiride co-administration: two case reports. *Hum Psychopharmacol Clin Exp* 1991; **6**: 67–9.
15. Blake LM, *et al.* Reversible neurologic symptoms with clozapine and lithium. *J Clin Psychopharmacol* 1992; **12**: 297–9.
16. Swanson CL, *et al.* Effects of concomitant risperidone and lithium treatment. *Am J Psychiatry* 1995; **152**: 1096.
17. Ross DR, Coffey CE. Neuroleptics and anti-anxiety agents. In: Johnson FN, ed. *Depression & mania: modern lithium therapy*. Oxford: IRL Press, 1987: 167–71.
18. Naylor GJ, McHarg A. Profound hypothermia on combined lithium carbonate and diazepam treatment. *BMJ* 1977; **2**: 22.

Benzodiazepines. See Antipsychotics and Anxiolytics, p. 431.3.

Calcium-channel blockers. Neurotoxicity has been reported in a patient receiving lithium after the addition of *verapamil*.[1] Serum-lithium concentrations were still inside the accepted therapeutic range and it was considered that the similar actions of lithium and verapamil on neurosecretory processes may have been responsible. Verapamil has also been reported to decrease serum-lithium concentrations.[2] Neurotoxicity has also been reported in a patient receiving lithium and *diltiazem*[3] as well as other drugs. Psychosis, possibly induced by the use of diltiazem and lithium together, has been reported in another patient.[4]

1. Price WA, Giannini AJ. Neurotoxicity caused by lithium-verapamil synergism. *J Clin Pharmacol* 1986; **26**: 717–19.
2. Weinrauch LA, *et al.* Decreased serum lithium during verapamil therapy. *Am Heart J* 1984; **108**: 1378–80.
3. Valdiserri EV. A possible interaction between lithium and diltiazem: case report. *J Clin Psychiatry* 1985; **46**: 540–1.
4. Binder EP, *et al.* Diltiazem-induced psychosis and a possible diltiazem-lithium interaction. *Arch Intern Med* 1991; **151**: 373–4.

Central stimulants. A woman who had been stabilised on lithium treatment for 15 months developed lithium toxicity within a few days of being given *mazindol*.[1]

There is a risk of CNS toxicity due to synergistic serotonergic actions when lithium is given with *sibutramine*.

1. Hendy MS, *et al.* Mazindol-induced lithium toxicity. *BMJ* 1980; **280**: 684–5.

Diuretics. *Thiazide diuretics* produce sodium depletion by inhibiting distal tubular sodium reabsorption. The consequent increase in proximal tubular reabsorption frequently results in an increase in serum-lithium concentrations.[1] Patients who are stabilised on lithium therapy and begin taking thiazide diuretics are at significant risk of developing lithium toxicity. Toxic lithium concentrations may be seen within 3 to 5 days of starting a diuretic. *Loop diuretics* (*furosemide*, *bumetanide*, and *etacrynic acid*) seem less likely to cause lithium retention, although caution is warranted, especially in patients whose dietary sodium is restricted.[1] *Amiloride*, and probably other potassium-sparing diuretics, have no effect on lithium excretion, but *acetazolamide* increases lithium excretion. However, the diuretic action of acetazolamide is short-lived and the interaction may therefore be transient.[1]

It has therefore been suggested that if diuretic therapy is necessary in patients stabilised on lithium, the lithium dose should be reduced by 25 to 50%.[1,2] lithium concentrations measured twice weekly until restabilisation occurs, and that perhaps loop diuretics such as bumetanide or furosemide would be preferable.

The topic of lithium-diuretic interaction and precautions to be considered has also been discussed.[3]

1. Beeley L. Drug interactions with lithium. *Prescribers' J* 1986; **26**: 160–3.
2. Ramsay LE. Interactions that matter: diuretics and antihypertensive drugs. *Prescribers' J* 1984; **24**: 60–5.
3. Grau E. Diuretics. In: Johnson FN, ed. *Depression & mania: modern lithium therapy*. Oxford: IRL Press, 1987: 180–3.

Gastrointestinal drugs. Giving *sodium bicarbonate* with lithium has led to reduced blood-lithium concentrations, attributed to increased renal excretion of the lithium cation in response to the extra load of bicarbonate anion to be excreted.[1] *Antacids* containing combinations of *aluminium and magnesium hydroxides* and *simeticone* had no effect on the dissolution and solubility of lithium carbonate *in vitro*[2] nor on its bioavailability *in vivo*.[3]

There has been a case report describing a possible interaction between lithium and *ispaghula* where low serum concentrations of lithium may have been due to ispaghula inhibiting intestinal absorption of lithium.[4]

Use of *cisapride* with lithium may increase the risk of ventricular arrhythmias.

1. McSwiggan C. A significant drug interaction. *Aust J Pharm* 1978; **59**: 6.
2. Schiessler DM, *et al.* Effect of antacids on lithium carbonate dissolution and solubility in vitro. *Am J Hosp Pharm* 1983; **40**: 825–8.
3. Goode DL, *et al.* Effect of antacid on the bioavailability of lithium carbonate. *Clin Pharm* 1984; **3**: 284–7.
4. Perlman BB. Interaction between lithium salts and ispaghula husk. *Lancet* 1990; **335**: 416.

Ion-exchange resins. The cation-exchange resin *sodium polystyrene sulfonate* may decrease the absorption of lithium salts.

Methyldopa. Lithium toxicity induced by methyldopa has been described on several occasions.[1-3] Symptoms of toxicity may occur even though serum-lithium concentrations remain within the therapeutic range.

1. Byrd GJ. Methyldopa and lithium carbonate: suspected interaction. *JAMA* 1975; **233**: 320.
2. O'Regan JB. Adverse interaction of lithium carbonate and methyldopa. *Can Med Assoc J* 1976; **115**: 385–6.
3. Osanloo E, Deglin JH. Interaction of lithium and methyldopa. *Ann Intern Med* 1980; **92**: 433–4.

Muscle relaxants. For reports of hypothermic episodes occurring with lithium and *diazepam*, see under Antipsychotics and Anxiolytics, p. 431.3.

Severe aggravation of hyperkinetic symptoms occurred in 2 patients with Huntington's chorea when *baclofen* was added to their treatment with lithium and haloperidol.[1]

1. Andén N-E, *et al.* Baclofen and lithium in Huntington's chorea. *Lancet* 1973; **ii**: 93.

Neuromuscular blockers. For reports of prolongation of neuromuscular blockade by lithium see under Atracurium, p. 2033.1. For further comments relating to surgery and anaesthesia, see under Anaesthesia in Precautions, p. 430.3.

NSAIDs. Decreased clearance and increased serum concentrations of lithium, resulting in toxicity on some occasions, have been reported after use of lithium with *celecoxib*,[1] *diclofenac*,[2] *ibuprofen*,[3,4] *indometacin*,[5,6] *ketorolac*,[7,8] *mefenamic acid*,[9,10] *naproxen*,[11] *piroxicam*,[12,13] *rofecoxib*,[14-16] and *tiaprofenic acid*;[17] secondary sources have also implicated *azapropazone*, *ketoprofen*,[18] *parecoxib*, and *phenylbutazone*.[18] However, serum-lithium concentration is not increased by *sulindac*.[11,19,20] Although serum-lithium concentrations were increased in a patient receiving *aspirin*[21] this has not been substantiated in others and an interaction is considered unlikely;[6,22] it has also been pointed out that control of sodium balance is necessary in such studies[22] and in the report purporting to show an interaction the diet had not been controlled.

It has been stated that for mild occasional aches, pains, and fever paracetamol was the preferred analgesic in patients receiving lithium, although occasional doses of aspirin were acceptable.[18] Sulindac appeared to be the safest NSAID for long-term use. Diclofenac, ibuprofen, indometacin, ketoprofen, naproxen, phenylbutazone, and piroxicam should be avoided where possible but if it was necessary to use one of these drugs the maintenance dose of lithium should be reduced. It was also considered that perhaps other NSAIDs, for which no information was available at that time, should be regarded as having the potential to cause a rise in serum-lithium concentrations.

1. Slørdal L, *et al.* A life-threatening interaction between lithium and celecoxib. *Br J Clin Pharmacol* 2003; **55**: 413–14.
2. Reimann IW, Frölich JC. Effects of diclofenac on lithium kinetics. *Clin Pharmacol Ther* 1981; **30**: 348–52.
3. Kristoff CA, *et al.* Effect of ibuprofen on lithium plasma and red blood cell concentrations. *Clin Pharm* 1986; **5**: 51–5.
4. Ragheb M. Ibuprofen can increase serum lithium level in lithium-treated patients. *J Clin Psychiatry* 1987; **48**: 161–3.
5. Frölich JC, *et al.* Indomethacin increases plasma lithium. *BMJ* 1979; **1**: 1115–16.
6. Reimann IW, *et al.* Indomethacin but not aspirin increases plasma lithium ion levels. *Arch Gen Psychiatry* 1983; **40**: 283–6.
7. Langlois R, Paquette D. Increased serum lithium levels due to ketorolac therapy. *Can Med Assoc J* 1994; **150**: 1455–6.
8. Iyer V. Ketorolac (Toradol) induced lithium toxicity. *Headache* 1994; **34**: 442–4.
9. Shelley RK. Lithium toxicity and mefenamic acid: a possible interaction and the role of prostaglandin inhibition. *Br J Psychiatry* 1987; **151**: 847–8.
10. MacDonald J, Neale TJ. Toxic interaction of lithium carbonate and mefenamic acid. *BMJ* 1988; **297**: 1319.
11. Ragheb M, Powell AL. Lithium interaction with sulindac and naproxen. *J Clin Psychopharmacol* 1986; **6**: 150–4.
12. Kerry RJ, *et al.* Possible toxic interaction between lithium and piroxicam. *Lancet* 1983; **i**: 418–19.
13. Walbridge DG, Bazire SR. An interaction between lithium carbonate and piroxicam presenting as lithium toxicity. *Br J Psychiatry* 1985; **147**: 206–7.
14. Sajbel TA, *et al.* Pharmacokinetic effects of rofecoxib therapy on lithium. *Pharmacotherapy* 2001; **21**: 380.
15. Lundmark J, *et al.* A possible interaction between lithium and rofecoxib. *J Clin Pharmacol* 2002; **53**: 403–4.
16. Rätz Bravo AE, *et al.* Lithium intoxication as a result of an interaction with rofecoxib. *Ann Pharmacother* 2004; **38**: 1189–93.
17. Alderman CP, Lindsay KSW. Increased serum lithium concentration secondary to treatment with tiaprofenic acid and fosinopril. *Ann Pharmacother* 1996; **30**: 1411–3.
18. Furnell MM. Non-steroidal anti-inflammatory drugs. In: Johnson FN, ed. *Depression & mania: modern lithium therapy*. Oxford: IRL Press, 1987: 183–6.
19. Furnell MM, Davies J. The effect of sulindac on lithium therapy. *Drug Intell Clin Pharm* 1985; **19**: 374–6.
20. Ragheb MA, Powell AL. Failure of sulindac to increase serum lithium levels. *J Clin Psychiatry* 1986; **47**: 33–4.
21. Bendz H, Feinberg M. Aspirin increases serum lithium ion levels. *Arch Gen Psychiatry* 1984; **41**: 310–11.
22. Reimann I. Aspirin increases serum lithium ion levels. *Arch Gen Psychiatry* 1984; **41**: 311.

Opioid analgesics. There is a risk of CNS toxicity due to synergistic serotonergic actions when lithium is given with *tramadol*.

Parasympathomimetics. For the effect of lithium on parasympathomimetics, see Interactions of Neostigmine p. 688.3.

Xanthines. It has been reported[1] that *theophylline* enhances the renal clearance of lithium, thus tending to reduce serum-lithium concentrations. Lithium blood concentrations increased by 24% when *caffeine* was eliminated from the diet of 11 patients taking lithium.[2] No toxicity was seen but these patients had been maintained on low baseline lithium concentrations; toxicity might occur in patients maintained at higher concentrations.

1. Cook BL, *et al.* Theophylline-lithium interaction. *J Clin Psychiatry* 1985; **46**: 278–9.
2. Mester R, *et al.* Caffeine withdrawal increases lithium blood levels. *Biol Psychiatry* 1995; **37**: 348–50.

Pharmacokinetics

Lithium is readily and completely absorbed from the gastrointestinal tract when taken as one of its salts. Absorption can be affected by the formulation of the preparation taken. Peak serum concentrations occur between 0.5 and 3 hours after ingestion from conventional tablets, capsules, or liquids; with modified-release formulations peak concentrations are delayed and may occur between 2 and 12 hours after a dose. Lithium is distributed throughout the body and distribution is complete within about 6 to 10 hours; higher concentrations occur in the bones, the thyroid gland, and portions of the brain, than in the serum.

Lithium is excreted mainly in the urine; only a small amount can be detected in the faeces, saliva, and sweat. It is not bound to plasma proteins. It crosses the placenta and is distributed into breast milk. The elimination half-life in patients with normal renal function is about 12 to 24 hours, but increases with decreasing renal function; half-lives of up to 36 hours have been reported for elderly patients and 40 to 50 hours for patients with renal impairment. Steady-state concentrations may not, therefore, be attained until 4 to 7 days after starting treatment.

There is wide intersubject variation in the serum concentrations obtained after a given dose, and also in those required for therapeutic effect. Concentrations also vary considerably according to factors such as the dosage regimen (whether given in single or divided daily doses), renal function, the dietary regimen of the patient, the patient's state of health, the time at which the blood sample is taken, and other medication, such as sodium salts or diuretics, as well as by formulation and bioavailability. Moreover, there is only a narrow margin between the therapeutic and the toxic serum concentration of lithium. Therefore, not only is individual titration of lithium dosage essential to ensure constant appropriate concentrations for the patient, but the conditions under which the blood samples are taken for monitoring must be carefully controlled. In practice, a blood sample drawn 12 hours after the last dose of lithium following a consistent dosing schedule for 4 to 7 days is used for measurement of serum-lithium concentrations. Under these conditions the distribution of the last dose of lithium is complete, and steady-state concentrations will have been attained. The usual maintenance therapeutic serum concentrations of lithium are 0.4 to 1 mmol/litre; toxic effects may be expected at concentrations exceeding 1.5 mmol/litre. For further details regarding monitoring of serum concentrations of lithium, see Uses and Administration, p. 428.1. Estimation of lithium concentrations in other body fluids such as saliva has been investigated as a less invasive method of monitoring. However, results have been equivocal and these methods have not replaced serum monitoring in general practice.

References.
1. Ward ME, *et al.* Clinical pharmacokinetics of lithium. *J Clin Pharmacol* 1994; **34**: 280–5.
2. Reiss RA, *et al.* Lithium pharmacokinetics in the obese. *Clin Pharmacol Ther* 1994; **55**: 392–8.
3. Thomsen K, Schou M. Avoidance of lithium intoxication: advice based on knowledge about the renal lithium clearance under various circumstances. *Pharmacopsychiatry* 1999; **32**: 83–6.
4. Sproule BA, *et al.* Differential pharmacokinetics of lithium in elderly patients. *Drugs Aging* 2000; **16**: 165–77.

Administration. References concerning the pharmacokinetic methods of predicting lithium dosage requirements.

1. Marken PA, *et al.* Preliminary comparison of predictive and empiric lithium dosing: impact on patient outcome. *Ann Pharmacother* 1994; **28**: 1148–52.
2. Taright N, *et al.* Nonparametric estimation of population characteristics of the kinetics of lithium from observational and experimental data: individualization of chronic dosing regimen using a new Bayesian approach. *Ther Drug Monit* 1994; **16**: 258–69.
3. Sproule BA, *et al.* Fuzzy logic pharmacokinetic modeling: application to lithium concentration prediction. *Clin Pharmacol Ther* 1997; **62**: 29–40.
4. Wright R, Crimson ML. Comparison of three a priori methods and one empirical method in predicting lithium dosage requirements. *Am J Health-Syst Pharm* 2000; **57**: 1698–1702.

Cystic fibrosis. For a reference to reduced renal excretion of lithium in patients with cystic fibrosis, see under Precautions, p. 430.3.

Distribution into breast milk. For references to the distribution of lithium into breast milk, see under Precautions, p. 430.3.

Pregnancy. For references to changes in renal clearance of lithium during pregnancy, see under Precautions, p. 431.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Ceglution; Eskalit; Karlit; Lithiun; *Austral.*: Lithicarb; Quilonum; *Austria*: Neurolepsin; Quilonorm; *Belg.*: Camcolit; Maniprex; Priadel; *Braz.*: Carbolim; Carbolitium; Neurolithium; *Canad.*: Carbolith; Lithane; *Chile*: Cade L; Carbolit; Carboron; Psicolit; *Denm.*: Litarex; *Fin.*: Lito; *Fr.*: Lithioderm; Neurolithium†; Teralithe; *Ger.*: Hypnorex; Lithiofor; Quilonum; *Gr.*: Lithiofor; Milithin; Priadel; *Hong Kong*: Licarb; Lithicarb; Lithiofor; *Hung.*: Liticarb; *India*: Alkalith; Elcab; Genlith; Indlith; Licab; Lithocent; Lithopik; Lithosun; Staleth; *Indon.*: Frimania; *Irl.*: Camcolit; Priadel; *Israel*: Licarbium; *Ital.*: Carbolithium; *Jpn*: Limas; *Mex.*: Carbolit; Litheum; *Neth.*: Camcolit; Litarex†; Priadel; *Norw.*: Lithionit; *NZ*: Lithicarb; Priadel; *Philipp.*: Quilonium-R; *Port.*: Priadel; *Rus.*: Sedalit (Седалит); *S.Afr.*: Camcolit; Lentolith†; Quilonum; *Singapore*: Camcolit; *Spain*: Plenur; *Swed.*: Lithionit; *Switz.*: LiDCO; Litarex; Lithiofor; Priadel; Quilonorm; *Thai.*: Licarb; Limed; Lit-300; Phanate†; *Turk.*: Kilonum; Lithuril; *UK*: Camcolit; Li-Liquid; Liskonum; Lithonate; Priadel; *USA*: Lithobid.

Multi-ingredient Preparations. *Austral.*: Caprilate†; *Ger.*: Togal Classic†; *Spain*: Citinoides†.

Homoeopathic Preparations. *Chile*: Artroplex; *Fr.*: Natrum Carbonicum Complexe No 10†; Rhus Toxicodendron Compose; Ricinus Compose; *Ger.*: Arthriselect; Girheulit HM†; Girheulit HOM; Heweurat N; rheuma-loges; *Neth.*: Rhodolith-Gastreu R46; *Rus.*: Helidonium-Plus (Хелидониум-Плюс); Rhus-Plus (Рус-Плюс); *Switz.*: Lithiumeel; Regenaplex Nr. 21c; Regenaplex Nr. 51c.

Pharmacopoeial Preparations
BP 2014: Lithium Carbonate Tablets; Lithium Citrate Oral Solution; Prolonged-release Lithium Carbonate Tablets;
USP 36: Lithium Carbonate Capsules; Lithium Carbonate Extended-release Tablets; Lithium Carbonate Tablets; Lithium Citrate Syrup.

Lofepramine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de lofepramina; Leo-640; Lofepramina, hidrocloruro de; Lofépramine, Chlorhydrate de; Lofepramini Hydrochloridum; Lopramine Hydrochloride; WHR-2908A; Лофепрамина Гидрохлорид.

5-[3-[*N*-(Chlorophenacyl)-*N*-methylamino]propyl]-10,11-5*H*-dihydrodibenz[*b*,*f*]azepine hydrochloride.

$C_{26}H_{27}ClN_2O,HCl$=455.4

CAS — 23047-25-8 (lofepramine); 26786-32-3 (lofepramine hydrochloride).

ATC — N06AA07.

ATC Vet — QN06AA07.

UNII — Z24K96F991.

Pharmacopoeias. In *Br.*

BP 2014: (Lofepramine Hydrochloride). A fine, yellowish-white to green-yellow powder with a faint characteristic odour. It exhibits polymorphism. Very slightly soluble in alcohol and in methyl alcohol; slightly soluble in acetone. Store in airtight containers. Protect from light.

Uses and Administration

Lofepramine is a dibenzazepine tricyclic antidepressant with actions and uses similar to those of amitriptyline (p. 401.1). One of its metabolites is desipramine (p. 413.1). Lofepramine is one of the less sedating tricyclics.

In the treatment of depression (p. 398.1) lofepramine is given orally as the hydrochloride although doses are expressed in terms of the base. Lofepramine hydrochloride 76.1 mg is equivalent to about 70 mg of lofepramine. The usual dose is the equivalent of 70 mg two or three times daily.

Lofepramine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Administration in the elderly. UK licensed product information suggests that some elderly patients may respond to lower than usual doses of lofepramine, but in a study[1] involving 46 elderly patients with various grades of depression lofepramine 70 mg once daily was no more effective than placebo at the end of 28 days of treatment.

1. Tan RSH, *et al.* The effect of low dose lofepramine in depressed elderly patients in general medical wards. *Br J Clin Pharmacol* 1994; **37**: 321–4.

Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p. 402.3) although it has a lower incidence of antimuscarinic adverse effects. Lofepramine should be avoided in patients with severe hepatic or severe renal impairment.

Effects on the liver. See under Amitriptyline, p. 403.3.

Overdosage. Lofepramine may be less toxic in overdosage than earlier tricyclics.[1] An analysis of data from the Office of National Statistics in England and Wales has also shown that the risk of death after an overdose with lofepramine was not significantly different from that associated with the SSRIs which, as a group, are considered to be safer in overdose than the tricyclics.[2]

1. Reid F, Henry JA. Lofepramine overdosage. *Pharmacopsychiatry* 1990; **23**: 23–27.
2. Mason J, *et al.* Fatal toxicity associated with antidepressant use in primary care. *Br J Gen Pract* 2000; **50**: 366–70.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lofepramine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

For interactions associated with tricyclic antidepressants, see Amitriptyline, p. 406.1.

Pharmacokinetics

Lofepramine is readily absorbed from the gastrointestinal tract; peak plasma concentrations occur within 1 hour of oral doses. Since lofepramine slows gastrointestinal transit time absorption can, however, be delayed, particularly in overdosage. It is extensively demethylated by first-pass metabolism in the liver to its active, primary metabolite, desipramine (p. 413.1). Paths of metabolism also include *N*-oxidation and hydroxylation. The plasma half-life is about 5 hours. Lofepramine is mainly excreted in the urine, chiefly in the form of its metabolites. Up to 99% of lofepramine is bound to plasma proteins. Lofepramine is distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Gamonil; *Irl.*: Gamanil; *S. Afr.*: Emdalen; *UK*: Lomont.

Pharmacopoeial Preparations
BP 2014: Lofepramine Tablets.

Maprotiline *(BAN, USAN, rINN)*

Maprotilini; Maprotilin; Maprotilina; Maprotilinum; Манротилин.

3-(9,10-Dihydro-9,10-ethanoanthracen-9-yl)propyl(methyl)amine; *N*-Methyl-9,10-ethanoanthracene-9(10*H*)-propylamine.

$C_{20}H_{23}N$=277.4

CAS — 10262-69-8.

ATC — N06AA21.

ATC Vet — QN06AA21.

UNII — 2U1W68TROF.

Maprotiline Hydrochloride *(BANM, rINNM)*

Ba-34276; Hidrocloruro de maprotilina; Maprotilinihydroklorid; Maprotilin Hidroklorür; Maprotilina, hidrocloruro de; Maprotiline, chlorhydrate de; Maprotilin-hidroklorid; Maprotilinhydrochlorid; Maprotilin-hydrochlorid; Maprotilinhydroklorid; Maprotilini Hydrochloridum; Maprotilino hidrochloridas; Манротилина Гидрохлорид.

$C_{20}H_{23}N,HCl$=313.9

CAS — 10347-81-6.

UNII — 7C8J54PVFI.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Maprotiline Hydrochloride). A white or almost white crystalline powder. It shows polymorphism. Slightly soluble in water; soluble in alcohol; very slightly soluble in acetone; sparingly soluble in dichloromethane; freely soluble in methyl alcohol.

USP 36: (Maprotiline Hydrochloride). A fine white to off-white, practically odourless, crystalline powder. Slightly soluble in water; freely soluble in chloroform and in methyl alcohol; practically insoluble in isooctane. Store in airtight containers.

Uses and Administration

Maprotiline is a tetracyclic antidepressant with actions and uses similar to those of tricyclic antidepressants (see Amitriptyline, p. 401.1). It is one of the more sedating antidepressants but antimuscarinic effects are less marked. Like the tricyclics, maprotiline is an inhibitor of the reuptake of noradrenaline; it also has weak affinity for central adrenergic (α_1) receptors.

Maprotiline is usually given orally as the hydrochloride but it has also been given by injection as the mesilate and in oral drops as the resinate.

In the treatment of depression (p. 398.1) maprotiline hydrochloride is given orally, and the total daily dose may be given in single or divided doses. It is usually given in initial doses of 75 mg daily. After 2 weeks the dosage should be adjusted according to response, and may be gradually increased in steps of 25 mg up to a daily dose of 150 mg if necessary. Severely depressed, hospitalised patients may be given initial doses of 100 to 150 mg daily. Adjustment of the dose up to 225 mg daily may be required in some severely depressed patients. A suggested initial dose for elderly patients is 25 mg daily, gradually increased according to response to 50 to 75 mg daily.

Maprotiline should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Adverse Effects, Treatment, and Precautions

Adverse effects with maprotiline, a tetracyclic antidepressant, are broadly similar to those with tricyclic antidepressants (see Amitriptyline, p. 402.3) but antimuscarinic effects are less frequent.

Rashes seem more common with maprotiline than with tricyclic antidepressants. Seizures have occurred in patients with no history of such disorders as well as in those with a history of epilepsy and the risk is increased if high doses of maprotiline are given. It should not be used in patients with epilepsy or a lowered seizure threshold.

Incidence of adverse effects. By March 1985 the UK CSM[1] had received reports of the following adverse reactions associated with maprotiline from a cumulative total of 2.5 million prescriptions: convulsions (124 cases), hepatic reactions (4 cases), and haematological reactions (8 cases). There had also been 454 reports of rashes.

1. CSM. Dangers of newer antidepressants. *Current Problems 15* 1985. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2044226&RevisionSelectionMethod=LatestReleased (accessed 05/08/08)

Effects on the skin. In addition to many recorded instances of rashes with maprotiline (see Incidence of Adverse Effects, above) cutaneous vasculitis, which resolved on stopping therapy, has also been seen.[1]

1. Oakley AMM, Hodge L. Cutaneous vasculitis from maprotiline. *Aust N Z J Med* 1985; 15: 256–7.

Epileptogenic effect. In a retrospective review of 186 psychiatric patients with no history of seizures, 5 of 32 patients taking maprotiline developed generalised tonic-clonic seizures, compared with 1 of 45 receiving a tricyclic antidepressant.[1] There were no seizures in those patients who received other medications, or no drug treatment. Two of the 5 patients having seizures with maprotiline were taking doses of 75 to 150 mg daily, 2 were taking daily doses of 200 to 300 mg, and one patient had partial complex seizures with a daily dose of 150 mg and generalised tonic-clonic seizures after increasing the daily dose to 300 mg.

1. Jabbari B, *et al.* Incidence of seizures with tricyclic and tetracyclic antidepressants. *Arch Neurol* 1985; 42: 480–1.

Overdosage. Apart from seizures being more common with maprotiline, features of overdosage are similar to those seen with tricyclic antidepressant poisonings (see Adverse Effects of Amitriptyline, p. 402.3).

For a discussion of choice of antidepressant with respect to toxicity in overdosage, see under Depression, p. 398.1.

References.

1. Crome P, Newman B. Poisoning with maprotiline and mianserin. *BMJ* 1977; 2: 260.
2. Curtis RA, *et al.* Fatal maprotiline intoxication. *Drug Intell Clin Pharm* 1984; 18: 716–20.
3. Knudsen K, Heath A. Effects of self poisoning with maprotiline. *BMJ* 1984; 288: 601–3.
4. Crome P, Ali C. Clinical features and management of self-poisoning with newer antidepressants. *Med Toxicol* 1986; 1: 411–20.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies maprotiline as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

Interactions associated with maprotiline are similar to those associated with tricyclic antidepressants (see Amitriptyline, p. 406.1).

Pharmacokinetics

Maprotiline is slowly but completely absorbed from the gastrointestinal tract. Peak plasma concentrations occur within 8 hours of an oral dose. It is widely distributed throughout the body and plasma protein binding is about 88 to 89%.

Maprotiline is extensively demethylated in the liver to its principal active metabolite, desmethylmaprotiline; paths of metabolism of both maprotiline and desmethylmaprotiline include *N*-oxidation, aliphatic and aromatic hydroxylation, and the formation of aromatic methoxy derivatives. In addition to desmethylmaprotiline, maprotiline-*N*-oxide is also reported to be pharmacologically active. The average elimination half-life of maprotiline is reported to be about 43 hours and that of its active metabolite even longer (range 60 to 90 hours). Maprotiline is excreted in the urine, mainly in the form of its metabolites, either in free or in conjugated form; appreciable amounts are also excreted in the faeces.

Maprotiline is distributed into breast milk (see Breast Feeding under Precautions of Amitriptyline, p. 405.1).

References.

1. Maguire KP, *et al.* An evaluation of maprotiline: intravenous kinetics and comparison of two oral doses. *Eur J Clin Pharmacol* 1980; 18: 249–54.
2. Alkalay D, *et al.* Bioavailability and kinetics of maprotiline. *Clin Pharmacol Ther* 1980; 27: 697–703.
3. Firkusny L, Gleiter H. Maprotiline metabolism appears to co-segregate with the genetically-determined CYP2D6 polymorphic hydroxylation of debrisoquine. *Br J Clin Pharmacol* 1994; 37: 383–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Ludiomil; ***Belg.***: Ludiomil; ***Braz.***: Ludiomil; ***Chile***: Mapromil†; ***China***: Ludiomil (路滴美); ***Cz.***: Ludiomil; Maprotibene†; ***Denm.***: Ludiomil; ***Fr.***: Ludiomil; ***Ger.***: Ludiomil; Maprolu†; ***Gr.***: Aprotilin; Klimastress; Ludiomil; Retinyl; ***Hung.***: Ludiomil; ***Indon.***: Ludiomil; Ludios; Sandepril; Tilsan; ***Israel***: Melodil; ***Ital.***: Ludiomil; ***Malaysia***: Ludiomil; Lunaline; ***Mex.***: Ludiomil; ***NZ***: Ludiomil; ***Pol.***: Ludiomil†; ***Port.***: Ludiomil; ***Rus.***: Ludiomil (Людиомил); ***S.Afr.***: Ludiomil; ***Singapore***: Ludiomil; Lunaline; ***Spain***: Ludiomil; ***Swed.***: Ludiomil; ***Switz.***: Ludiomil; ***Thai.***: Ludiomil†; ***Turk.***: Ludiomil; Maprotil; ***Ukr.***: Ludiomil (Людиомил); ***Venez.***: Ludiomil.

Pharmacopoeial Preparations

USP 36: Maprotiline Hydrochloride Tablets.

Melitracen Hydrochloride *(USAN, rINNM)*

Hidrocloruro de melitraceno; Mélitracène, Chlorhydrate de; Melitraceni Hydrochloridum; Melitraceno, hidrocloruro de; N-7001; U-24973A; Мелитрацена Гидрохлорид.

3-(9,10-Dihydro-10,10-dimethyl-9-anthrylidene)propyldimethylamine hydrochloride.

$C_{21}H_{25}N,HCl$=327.9

CAS — 5118-29-6 (melitracen); 10563-70-9 (melitracen hydrochloride).

ATC — N06AA14.

ATC Vet — QN06AA14.

UNII — J3448GKP5W.

Profile

Melitracen is a tricyclic antidepressant (see Amitriptyline, p. 401.1). It is given orally as the hydrochloride although doses are expressed in terms of the base; melitracen hydrochloride 28.1 mg is equivalent to about 25 mg of melitracen.

Melitracen is given with flupentixol (p. 1074.1) in the management of depression with anxiety (p. 398.1). A combination of melitracen 10 mg and flupentixol 500 micrograms is given orally in the morning and at midday. In severe cases the morning dose may be doubled. The total daily dose should not exceed melitracen 40 mg and flupentixol 2 mg. Elderly patients may be given melitracen 10 mg with flupentixol 500 micrograms in the morning; in severe cases this dose may be given in the morning and at midday. Melitracen has also been used alone in the treatment of depression. It was given in initial doses of 25 mg two to three times daily, increased as necessary to a maximum of 225 mg daily.

Melitracen should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Novoxit.

Multi-ingredient Preparations. ***Austria***: Deanxit; ***Belg.***: Deanxit; ***China***: Deanxit (锭力新); ***Hong Kong***: Anfree; Danxipress; Deanxit; Quali-Xit; ***India***: Ambulax-FM; Deanxit; Delewal; Denxol; Flupen-M; Forcalm; Franxit; Fycida-M; Melicen-FP; Meliyos; Melthix; Metflu; ***Singapore***: Deanxit; ***Spain***: Deanxit; ***Switz.***: Deanxit; ***Thai.***: Deanxit.

Mianserin Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de mianserina; Mianserinihydrokloridi; Mianserin Hidroklorür; Mianserina, hidrocloruro de; Mianserine, Chlorhydrate de; Mianserinhydrochlorid; Mianserin-hydrochlorid; Mianserinhydroklorid; Mianserini Hydrochloridum; Mianserino hidrochloridas; Mianseryny chlorowodorek; Mianszerin-hidroklorid; Org-GB-94; Миансерина Гидрохлорид.

1,2,3,4,10,14b-Hexahydro-2-methyldibenzo[*c,f*]pyrazino[1,2-*a*]azepine hydrochloride.

$C_{18}H_{20}N_2,HCl$=300.8

CAS — 24219-97-4 (mianserin); 21535-47-7 (mianserin hydrochloride).

ATC — N06AX03.

ATC Vet — QN06AX03.

UNII — 2X03TN217S.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Mianserin Hydrochloride). A white or almost white crystalline powder or crystals. Sparingly soluble in water; slightly soluble in alcohol; soluble in dichloromethane. A 1% solution in water has a pH of 4.0 to 5.5. Protect from light.

Uses and Administration

Mianserin is a tetracyclic antidepressant. It does not appear to have significant antimuscarinic properties, but has a marked sedative action. Unlike the tricyclic antidepressants (see Amitriptyline, p. 401.1), mianserin does not prevent the peripheral reuptake of noradrenaline; it blocks presynaptic adrenergic (α_2) receptors and increases the turnover of brain noradrenaline. Mianserin is also an antagonist of postsynaptic serotonin receptors in some parts of the brain.

In the treatment of depression (p. 398.1) mianserin hydrochloride is given in initial oral doses of 30 to 40 mg daily increased gradually thereafter as necessary. The effective daily dosage is usually between 30 and 90 mg. The daily dosage may be divided throughout the day or given as a single dose at night. Divided daily dosages of up to 200 mg have been given. The recommended initial daily dose in the elderly is not more than 30 mg, which may be slowly increased if necessary.

Mianserin should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Adverse Effects

Antimuscarinic and cardiac adverse effects are fewer and milder with mianserin, a tetracyclic antidepressant, than with tricyclic antidepressants but effects are otherwise broadly similar (see Amitriptyline, p. 402.3); mianserin may be associated with a lower risk of cardiotoxicity in overdosage.

The most common adverse effect associated with mianserin is drowsiness. Mianserin also causes bone-marrow depression usually presenting as leucopenia, granulocytopenia, or agranulocytosis: aplastic anaemia has been reported. These adverse haematological reactions generally occur during the first few weeks of therapy and especially in the elderly.

Other adverse effects reported include disturbances of liver function and jaundice, breast disorders (gynaecomastia, nipple tenderness, and non-puerperal lactation), and polyarthropathy.

Effects on the blood. Between 1976 and the end of 1988 the UK CSM had received 239 reports of adverse haematological reactions associated with mianserin use.[1] The reports included 68 of agranulocytosis and 84 of granulocytopenia or leucopenia where mianserin was considered to be the probable or possible cause; there had been 17 fatalities. Allowing for the pattern of prescribing there was a greater number of reports of white blood cell disorders in patients over 65 years of age but there was no sex difference. The data also indicated that the adverse reactions were most likely to develop during the first 3 months of therapy. By the end of 1992 the number of reports of mianserin-induced agranulocytosis or neutropenia received by the CSM[2] had risen to 79 and 105, respectively.

A case of fatal aplastic anaemia associated with mianserin use has also been reported.[3]

Proposed mechanisms of mianserin haematotoxicity have included a direct toxicity[4] and an immunologically mediated mechanism.[5] There is evidence from studies *in vitro* of a significant correlation between the desmethyl metabolite and cytotoxicity. Mianserin is given as a racemic preparation and the formation of metabolites was greater with the *R* (-)-enantiomer than with the *S*(+)-enantiomer.[6]

1. CSM. Mianserin and white blood cell disorders in the elderly. *Current Problems 25* 1989. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024411&RevisionSelectionMethod=LatestReleased (accessed 05/08/08)
2. CSM/MCA. Drug-induced neutropenia and agranulocytosis. *Current Problems* 1993; 19: 10–11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024456&RevisionSelectionMethod=LatestReleased (accessed 05/08/08)
3. Durrant S, Read D. Fatal aplastic anaemia associated with mianserin. *BMJ* 1982; 285: 437.
4. O'Donnell JL, *et al.* Possible mechanism for mianserin induced neutropenia associated with saturable elimination kinetics. *BMJ* 1985; 291: 1375–6.
5. Stricker BHC, *et al.* Thrombocytopenia and leucopenia with mianserin-dependent antibodies. *Br J Clin Pharmacol* 1985; 19: 102–4.
6. Riley RJ, *et al.* A stereochemical investigation of the cytotoxicity of mianserin metabolites in vitro. *Br J Clin Pharmacol* 1989; 27: 823–30.

Effects on the cardiovascular system. Although mianserin is considered to be less cardiotoxic than the tricyclic antidepressants adverse effects have been noted in individual patients. Two elderly patients developed signs of disturbed cardiac function (cardiac failure, atrial and ventricular fibrillation, bradycardia, and frequent ventricular ectopic beats) which resolved after the drug was stopped.[1] One of the patients also developed hypokalaemia which was possibly caused by mianserin. It was suggested that persons most likely to have problems were the elderly with a history of cardiovascular disorders. Further reports of mianserin-induced cardiac effects include recurrent ventricular fibrillation in a 61-year-old man after an overdose of mianserin[2] and bradycardia in a 50-year-old woman after a therapeutic dose.[3]

1. Whiteford H, *et al.* Disturbed cardiac function possibly associated with mianserin therapy. *Med J Aust* 1984; 140: 166–7.
2. Haefeli WE, *et al.* Recurrent ventricular fibrillation in mianserin intoxication. *BMJ* 1991; 302: 415–16.
3. Carcone B, *et al.* Symptomatic bradycardia caused by mianserin at therapeutic doses. *Hum Exp Toxicol* 1991; 10: 383–4.

Effects on the liver. By March 1985 the UK CSM had received 57 reports of hepatic reactions associated with mianserin use from a total of 5 million prescriptions. Reactions had included jaundice and other abnormalities of liver function, but no fatalities had been reported.[1]

Case reports have also been published concerning jaundice;[2-5] liver function returned to normal after stopping mianserin or lowering the dose.

1. CSM. Dangers of newer antidepressants. *Current Problems 15* 1985. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024422&RevisionSelectionMethod=LatestReleased (accessed 14/08/08)
2. Adverse Drug Reactions Advisory Committee. Mianserin: a possible cause of neutropenia and agranulocytosis. *Med J Aust* 1980; 2: 673–4.
3. Goldstraw PW, *et al.* Mianserin and jaundice. *N Z Med J* 1983; 96: 985.
4. Zarski J-P, *et al.* Toxicité hépatique des nouveaux anti-dépresseurs: a propos d'une observation. *Gastroenterol Clin Biol* 1983; 7: 220–1.
5. Otani K, *et al.* Hepatic injury caused by mianserin. *BMJ* 1989; 299: 519.

Effects on the musculoskeletal system. A patient developed an acute polyarthritis affecting the hands and feet 6 days after starting therapy with mianserin;[1] at that time the UK CSM had received 19 reports of arthritis and arthralgia associated with mianserin. For the suggestion that effects at serotonin receptors may be involved in such adverse effects see under Mirtazapine, p. 438.3.

1. Hughes A, Coote J. Arthropathy associated with treatment with mianserin. *BMJ* 1986; 292: 1050.

Effects on the skin. Reports of adverse dermatological reactions in individual patients related to mianserin therapy have included toxic epidermal necrolysis[1] and erythema multiforme.[2,3]

1. Randell P. Tolvon and toxic epidermal necrolysis. *Med J Aust* 1979; 2: 653.
2. Quraishy E. Erythema multiforme during treatment with mianserin—a case report. *Br J Dermatol* 1981; 104: 481.
3. Cox NH. Erythema multiforme due to mianserin—a case against generic prescribing. *Br J Clin Pract* 1985; 39: 293–4.

Effects on the tongue. Glossitis associated with mianserin therapy was reported in 2 patients.[1] Additionally, glossitis accompanied by severe facial oedema has been noted in another patient.[2] In all cases symptoms resolved after withdrawal of mianserin.

1. de la Fuente JR, Berlanga C. Glossitis associated with mianserin. *Lancet* 1984; i: 233.
2. Leibovitch G, *et al.* Severe facial oedema and glossitis associated with mianserin. *Lancet* 1989; ii: 871–2.

Epileptogenic effect. By March 1985 the UK CSM had received 64 reports of convulsions associated with mianserin use from a total of 5 million prescriptions.[1] In a previous review[2] concerning 40 of these cases it was considered that a causal connection could be established only in a minority. It was suggested that mianserin is no more epileptogenic than tricyclic antidepressants, an opinion that was also shared by other reviewers.[3]

1. CSM. Dangers of newer antidepressants. *Current Problems 15* 1985. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024422&RevisionSelectionMethod=LatestReleased (accessed 05/08/08)
2. Edwards JG, Glen-Bott M. Mianserin and convulsive seizures. *Br J Clin Pharmacol* 1983; 15: 299S–311S.
3. Richens A, *et al.* Antidepressant drugs, convulsions and epilepsy. *Br J Clin Pharmacol* 1983; 15: 295S–298S.

Overdosage. Experience with 100 consecutive cases of intoxication with mianserin[1] revealed that when it was the only drug ingested symptoms were mild and neither deep coma nor convulsions occurred. More serious symptoms and 2 fatalities were seen in patients who had taken multiple drug overdoses. The results suggested that after an acute overdose mianserin is less toxic than the tricyclic antidepressants. This conclusion was also supported by a large follow-up study[2] comparing the outcome of suicide attempts among patients who had taken mianserin in overdose with those who had taken amitriptyline.

1. Chand S, *et al.* One hundred cases of acute intoxication with mianserin hydrochloride. *Pharmakopsychiatrie* 1981; 14: 15–17.
2. Inman WHW. Blood disorders and suicide in patients taking mianserin or amitriptyline. *Lancet* 1988; ii: 90–2.

Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p. 404.3). Although mianserin is less cardiotoxic than the tricyclic antidepressants, it still should be used with caution in patients with cardiovascular disorders, such as heart block, or after recent myocardial infarction. Similarly, patients with angle-closure glaucoma or prostatic hyperplasia should be monitored even though antimuscarinic effects are rare. Mianserin should be used with caution in patients with diabetes mellitus, epilepsy, and hepatic or renal impairment; it should be avoided in severe hepatic disease.

Patients should be carefully monitored during early antidepressant therapy until significant improvement in depression occurs because suicide is an inherent risk in depressed patients. For further details, see under Depression, p. 398.1. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be observed when treating patients with other disorders.

A full blood count is recommended every 4 weeks during the first 3 months of treatment with mianserin, because of the risk of bone-marrow depression. Similarly, if a patient receiving mianserin develops fever, sore throat, stomatitis, or other signs of infection, treatment should be stopped and a full blood count obtained. The elderly are considered to be at special risk of blood disorders from mianserin. For further details see Effects on the Blood under Adverse Effects, p. 434.3.

UK licensed product information recommends that mianserin should not be given during breast feeding, but the *BNF* considers the amount distributed into breast milk too small to be harmful.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mianserin as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

It is recommended that mianserin should not be given to patients receiving MAOIs or for at least 14 days afterwards. At least one week should elapse between withdrawing mianserin and starting any drug liable to provoke a serious reaction (e.g. phenelzine). Unlike the tricyclics (p. 406.1), mianserin does not diminish the effects of the antihypertensives guanethidine, hydralazine, propranolol, or clonidine. However, it is still recommended that blood pressure be monitored when mianserin is prescribed with antihypertensive therapy. Plasma-phenytoin concentrations should be monitored carefully in patients also treated with mianserin; phenytoin has also been reported to reduce concentrations of mianserin (see p. 437.2). There may be potentiation of effects when mianserin is given with CNS depressants such as alcohol, anxiolytics, or antipsychotics.

Antiepileptics. Reduced plasma concentrations and half-lives of mianserin and desmethylmianserin were seen in 6 patients also receiving antiepileptic therapy consisting of *phenytoin* with either *carbamazepine* or *phenobarbital*.[1] Carbamazepine alone may also reduce the plasma concentration of mianserin.[2,3]

Mianserin may antagonise the action of antiepileptics by lowering the convulsive threshold.

1. Nawishy S, *et al.* Kinetic interaction of mianserin in epileptic patients on anticonvulsant drugs. *Br J Clin Pharmacol* 1982; 13: 612P–13P.
2. Leinonen E, *et al.* Effects of carbamazepine on serum antidepressant concentrations in psychiatric patients. *J Clin Psychopharmacol* 1991; 11: 313–18.
3. Eap CB, *et al.* Effects of carbamazepine coadministration on plasma concentrations of the enantiomers of mianserin and of its metabolites. *Ther Drug Monit* 1999; 21: 166–70.

Pharmacokinetics

Mianserin is readily absorbed from the gastrointestinal tract, but its bioavailability is reduced by extensive first-pass metabolism in the liver.

Paths of metabolism of mianserin include aromatic hydroxylation, *N*-oxidation, and *N*-demethylation. Desmethylmianserin and 8-hydroxymianserin are pharmacologically active.

Mianserin is excreted in the urine, almost entirely as its metabolites, either free or in conjugated form; some is also found in the faeces.

Mianserin is widely distributed throughout the body and is extensively bound to plasma proteins. It has been found to have a biphasic plasma half-life with the duration of the terminal phase ranging from about 6 to 40 hours. Mianserin crosses the blood-brain barrier and the placenta. It is distributed into breast milk.

References.

1. Hrdina PD, *et al.* Mianserin kinetics in depressed patients. *Clin Pharmacol Ther* 1983; 33: 757–62.
2. Pinder RM, Van Delft AML. The potential therapeutic role of enantiomers and metabolites of mianserin. *Br J Clin Pharmacol* 1983; 15: 269S–276S.
3. Timmer CJ, *et al.* Absolute bioavailability of mianserin tablets and solution in healthy humans. *Eur J Drug Metab Pharmacokinet* 1985; 10: 315–23.
4. Begg EJ, *et al.* Variability in the elimination of mianserin in elderly patients. *Br J Clin Pharmacol* 1989; 27: 645–51.
5. Bulst A, *et al.* Mianserin in breast milk. *Br J Clin Pharmacol* 1993; 36: 133–4.
6. Dahl M-L, *et al.* Stereoselective disposition of mianserin is related to debrisoquin hydroxylation polymorphism. *Clin Pharmacol Ther* 1994; 56: 176–83.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Lerivon; *Austral.*: Lumin; Tolvon; *Austria*: Tolvon; *Belg.*: Lerivon; *Braz.*: Tolvon; *Chile*: Athimil; Prevalina; *China*: Tolvon (特文); *Cz.*: Lerivon; Miabene; *Denm.*: Tolmin; Tolvon†; *Fin.*: Miaxan†; Tolvon; *Fr.*: Athymil†; *Ger.*: Mianeurin†; Tolvin†; *Gr.*: Tolvon; *Hong Kong*: Tolvon†; *Hung.*: Miagen; Tolvon; *India*: Depnon; *Irl.*: Tolvon†; *Israel*: Bonserin; *Ital.*: Lantanon; *Mex.*: Tolvon; *Neth.*: Tolvon; *Norw.*: Tolvon; *NZ*: Tolvon; *Pol.*: Deprexolet; Lerivon; Miansec; Miansegen; Miansemerck; Norserin†; *Port.*: Tolvon; *Rus.*: Lerivon (Леривон); *S.Afr.*: Lantanon; *Spain*: Lantanon; *Swed.*: Tolvon†; *Switz.*: Tolvon; *Thai.*: Mealin; Servin; Tolmed; Tolvon; *Turk.*: Tolvon; *Ukr.*: Lerivon (Леривон); Miaser (Миасер).

Pharmacopoeial Preparations
BP 2014: Mianserin Tablets.

Milnacipran Hydrochloride *(BANM, rINNM)*

F-2207 (milnacipran); Hidrocloruro de milnaciprán; Midalcipran Hydrochloride; Milnacipran; Chlorhydrate de; Milnacipran, hidrocloruro de; Milnaciprani Hydrochloridum; Мильнаципрана Гидрохлорид.

(±)-*cis*-2-(Aminomethyl)-*N*,*N*-diethyl-1-phenylcyclopropanecarboxamide hydrochloride.

$C_{15}H_{22}N_2O.HCl$=282.8

CAS — 92623-85-3 (milnacipran); 101152-94-7 (milnacipran hydrochloride); 175131-61-0 (milnacipran hydrochloride).

ATC — N06AX17.

ATC Vet — QN06AX17.

UNII — RNZ43O5WWS.

Profile

Milnacipran hydrochloride is a serotonin and noradrenaline reuptake inhibitor (SNRI) (see Venlafaxine, p. 456.2). It is used for the treatment of depression (p. 398.1) in usual oral doses of 50 mg twice daily. In the management of fibromyalgia (see Soft-tissue Rheumatism, p. 14.2), milnacipran hydrochloride is introduced gradually, starting with a single dose of 12.5 mg on the first day, 12.5 mg twice daily on days 2 and 3, then 25 mg twice daily on days 4 to 7, and 50 mg twice daily thereafter. The dose may need to be increased to 100 mg twice daily in some patients, according to response. For doses in renal impairment, see p. 437.3.

Milnacipran should be withdrawn gradually to reduce the risk of withdrawal symptoms (see also Withdrawal, under Precautions of Fluoxetine, p. 423.3).

References.

1. Tignol J, *et al.* Double-blind study of the efficacy and safety of milnacipran and imipramine in elderly patients with major depressive episode. *Acta Psychiatr Scand* 1998; 97: 157–65.
2. Spencer CM, Wilde MI. Milnacipran: a review of its use in depression. *Drugs* 1998; 56: 405–27.
3. Rouillon F, *et al.* Milnacipran efficacy in the prevention of recurrent depression: a 12-month placebo-controlled study. *Int Clin Psychopharmacol* 2000; 15: 133–40.
4. Clerc G. Antidepressant efficacy and tolerability of milnacipran, a dual serotonin and noradrenaline reuptake inhibitor: a comparison with fluvoxamine. *Int Clin Psychopharmacol* 2001; 16: 145–51.
5. Fukuchi T, Kanemoto K. Differential effects of milnacipran and fluvoxamine, especially in patients with severe depression and agitated depression: a case-control study. *Int Clin Psychopharmacol* 2002; 17: 53–8.
6. Clauw DJ, *et al.* Milnacipran for the treatment of fibromyalgia in adults: a 15-week, multicenter, randomized, double-blind, placebo-controlled, multiple-dose clinical trial. *Clin Ther* 2008; 30: 1988–2004. Correction. *ibid.* 2009; 31: 446.
7. Mease PJ, *et al.* The efficacy and safety of milnacipran for treatment of fibromyalgia: a randomized, double-blind, placebo-controlled trial. *J Rheumatol* 2009; 36: 398–409. Correction. *ibid.*: 661.

Administration in renal impairment. Usual doses of milnacipran hydrochloride may be given to patients with mild renal impairment, and used with caution in moderate impairment. An oral maintenance dose of 25 mg twice daily may be given to patients with severe impairment (creatinine clearance 5 to 29 mL/min), but can be increased to 50 mg twice daily according to response. The drug should not be used in end-stage renal disease.

Interactions. *ANTIMIGRAINE DRUGS.* There have been rare reports of serotonin syndrome associated with the use of serotonin and noradrenaline reuptake inhibitors (SNRIs) with serotonin (5-HT_1) agonists such as *sumatriptan* (see p. 681.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Dalcipran; Ixel; *Austria*: Dalcipran†; Ixel; *Braz.*: Ixel; *Chile*: Ixel; Misulvan; *Cz.*: Dalcipran†; Ixel; *Fin.*: Ixel; *Fr.*: Ixel; *Hong Kong*: Ixel; *India*: Milborn; Milnace; *Israel*: Ixel; *Jpn*: Toledomin; *Pol.*: Ixel†; *Port.*: Dalcipran; Ixel; *Rus.*: Ixel (Иксел); *Thai.*: Ixel; *Turk.*: Ixel; *USA*: Savella.

Mirtazapine *(BAN, USAN, rINN)*

6-Azamianserin; Mepirzapin; Mepirzepine; Mirtatsapiini; Mirtazapiini; Mirtazapina; Mirtazapinum; Org-3770; Миртазапин.

(RS)-1,2,3,4,10,14b-Hexahydro-2-methylpyrazino-[2,1-*a*]pyrido[2,3-*c*][2]benzazepine.

$C_{17}H_{19}N_3$=265.4

CAS — 61337-67-5.

ATC — N06AX11.

ATC Vet — QN06AX11.

UNII — A051Q2099Q (mirtazapine); 8Z5UNK8A61 (mirtazapine hemihydrate).

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Mirtazapine). A white or almost white powder, slightly hygroscopic to hygroscopic. It exhibits polymorphism. Practically insoluble in water; freely soluble in anhydrous alcohol. Store in airtight containers.

USP 36: (Mirtazapine). It is anhydrous or contains one-half molecule of water of hydration. A white to creamy white, crystalline powder. Practically insoluble in water; soluble in solvent ether; sparingly soluble in *n*-hexane; freely soluble in methyl alcohol and in toluene. Store in airtight containers.

Uses and Administration

Mirtazapine, a piperazinoazepine, is an analogue of mianserin (p. 434.2); it is a noradrenergic and specific serotonergic antidepressant. It enhances the release of noradrenaline and, indirectly, serotonin through blockade of central presynaptic adrenergic (α_2) receptors. The effects of released serotonin are mediated via 5-HT_1 receptors as mirtazapine blocks both 5-HT_2 and 5-HT_3 receptors. Mirtazapine is given as a racemic mixture: the *S*(+)-enantiomer blocks α_2 and 5-HT_2 receptors whereas the *R* (-)-enantiomer blocks 5-HT_3 receptors. Mirtazapine is also a potent antagonist at histamine (H_1) receptors which gives it sedative properties; it has very little antimuscarinic activity.

In the treatment of depression (p. 398.1), mirtazapine is given in an initial oral daily dose of 15 or 30 mg, which may be increased gradually according to response. Changes in dose should be made at intervals of at least 1 to 2 weeks because of the long half-life. The usual effective daily dose lies within the range of 15 to 45 mg. Daily doses may be given as a single dose, preferably at bedtime, or in 2 divided doses with the larger portion taken at night. Mirtazapine may also be given by intravenous infusion.

Mirtazapine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Anxiety disorders. Mirtazapine has been tried with some success in the treatment of anxiety disorders (p. 1028.1) including obsessive-compulsive disorder (p. 1028.2), panic disorder (p. 1029.1), and post-traumatic stress disorder (p. 1029.2).

References.

1. Boshuisen ML, *et al.* The effect of mirtazapine in panic disorder: an open label pilot study with a single-blind placebo run-in period. *Int Clin Psychopharmacol* 2001; 16: 363–8.
2. Davidson JR, *et al.* Mirtazapine vs placebo in posttraumatic stress disorder: a pilot trial. *Biol Psychiatry* 2003; 53: 188–91.
3. Chung MY, *et al.* Efficacy and tolerability of mirtazapine and sertraline in Korean veterans with posttraumatic stress disorder: a randomized open label trial. *Hum Psychopharmacol* 2004; 19: 489–94.
4. Koran LM, *et al.* Mirtazapine for obsessive-compulsive disorder: an open trial followed by double-blind discontinuation. *J Clin Psychiatry* 2005; 66: 515–20.

Depression. As discussed on p. 398.1, there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effect profile. Mirtazapine is a central presynaptic adrenergic (α_2) receptor antagonist and has a slightly different biochemical profile from both the tricyclics and the SSRIs; however, like the SSRIs, mirtazapine appears to have fewer unpleasant adverse effects in comparison with the older tricyclics.

References.

1. Kasper S, *et al.* A risk-benefit assessment of mirtazapine in the treatment of depression. *Drug Safety* 1997; 17: 251–64.
2. Montgomery SA, *et al.* Mirtazapine versus amitriptyline in the long-term treatment of depression: a double-blind placebo-controlled study. *Int Clin Psychopharmacol* 1998; 13: 63–73.
3. Puzantian T. Mirtazapine, an antidepressant. *Am J Health-Syst Pharm* 1998; 55: 44–9.
4. Holm KJ, Markham A. Mirtazapine: a review of its use in major depression. *Drugs* 1999; 57: 607–31.
5. Schatzberg AF, *et al.* Double-blind, randomized comparison of mirtazapine and paroxetine in elderly depressed patients. *Am J Geriatr Psychiatry* 2002; 10: 541–50.
6. Wade A, *et al.* A randomized, double-blind, 24-week study comparing the efficacy and tolerability of mirtazapine and paroxetine in depressed patients in primary care. *Int Clin Psychopharmacol* 2003; 18: 133–41.
7. Versiani M, *et al.* Comparison of the effects of mirtazapine and fluoxetine in severely depressed patients. *CNS Drugs* 2005; 19: 137–46.
8. Watanabe N, *et al.* Multiple Meta-Analyses of New Generation Antidepressants (MANGA) Study Group. Mirtazapine versus other antidepressants in the acute-phase treatment of adults with major depression: systematic review and meta-analysis. *J Clin Psychiatry* 2008; 69: 1404–15.

Nausea and vomiting. Mirtazapine has been investigated in the management of severe nausea and vomiting (p. 1814.3). For mention of the successful use of mirtazapine to treat hyperemesis of pregnancy see Pregnancy, under Precautions, p. 438.3.

Further references.

1. Kast RE. Mirtazapine may be useful in treating nausea and insomnia of cancer chemotherapy. *Support Care Cancer* 2001; 9: 469–70.
2. Caldis EV, Gair RD. Mirtazapine for treatment of nausea induced by selective serotonin reuptake inhibitors. *Can J Psychiatry* 2004; 49: 707.
3. Teixeira FV, *et al.* Mirtazapine (Remeron) as treatment for non-mechanical vomiting after gastric bypass. *Obes Surg* 2005; 15: 707–9.

Adverse Effects

Adverse effects commonly reported with mirtazapine are an increase in appetite and weight, and oedema; drowsiness or sedation generally occur during the first few weeks of treatment. Dizziness, headache, and increases in liver enzyme levels have been reported less commonly; jaundice may occur. Other rarely reported adverse effects include orthostatic hypotension, rashes, nightmares, agitation, mania, hallucinations, paraesthesia, convulsions, tremor, myoclonus, psychomotor restlessness including akathisia, restless legs syndrome, arthralgia, myalgia, and reversible agranulocytosis, leucopenia, and granulocytopenia.

Hyponatraemia, possibly due to inappropriate secretion of antidiuretic hormone, has been associated with the use of antidepressants, particularly in the elderly.

Incidence of adverse effects. The Australian Adverse Drug Reactions Advisory Committee has reported[1] that, up to October 2003, it had received 253 reports of adverse reactions associated with the use of mirtazapine. The most frequently reported reactions were oedema (33 reports), anxiety or agitation (24 reports), myalgia or arthralgia (24 reports), sedation (23 reports), and skin reactions (20 reports). Other reactions included hyperkinesis, diarrhoea, and nausea and vomiting. There were 16 cases of convulsions, all in patients without a history of epilepsy. Blood dyscrasias were also reported and included 8 cases of neutropenia, 6 of thrombocytopenia, and 1 each of lymphopenia and pancytopenia; in the majority of cases onset was within 2 months of starting mirtazapine.

A prescription-event monitoring study conducted in England identified 13 554 patients who had been prescribed mirtazapine during the first 2 years of marketing in the UK;[2] within this cohort, 807 adverse drug reactions were reported in 573 patients. The most common adverse reactions included drowsiness or sedation (116 reports), malaise (71 reports), dizziness (57 reports), nausea and vomiting (33 reports), weight gain (31 reports), and headache or migraine (21 reports). Facial oedema (5 reports), allergy (3 reports), bone marrow toxicity (2 reports), and myelodysplasia (1 report) were the more serious suspected adverse reactions.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Convulsions and blood dyscrasias with mirtazapine. *Aust Adverse Drug React Bull* 2003; 22: 18–19. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0310.pdf (accessed 24/11/05)
2. Biswas PN, *et al.* The pharmacovigilance of mirtazapine: results of a prescription event monitoring study on 13 554 patients in England. *J Psychopharmacol* 2003; 17: 121–6.

Effects on the endocrine system. An elderly woman developed *hyponatraemia* within 4 days of starting mirtazapine at a dose of 15 mg at night.[1] Apart from her age, other risk factors for hyponatraemia included diuretic use and a previous episode while taking venlafaxine.

1. Roxanas MG. Mirtazapine-induced hyponatraemia. *Med J Aust* 2003; 179: 453–4.

Effects on mental state. An Expert Working Group was convened in May 2003 by the UK CSM to consider the ongoing safety concerns of the SSRIs particularly the risk of suicidal behaviour in children: the safety of mirtazapine (another serotonergic antidepressant) was also considered. In its final report[1] in December 2004, the group concluded that data from studies received by the CSM had failed to show that mirtazapine was effective in the treatment of depression in **adolescents and children** under 18 years old, although the risk of suicidal behaviour was not increased. Consequently, it was considered that the balance of risks and benefits of mirtazapine for the treatment of depression in this group was unfavourable. Similar recommendations have also been issued in the EU.[2]

The risk of suicide and suicide-related events with serotonergic antidepressant treatment in **adults**, including young adults, are discussed under Fluoxetine, p. 420.2.

1. Weller IVD. *Report of the CSM Expert Working Group on the safety of selective serotonin reuptake inhibitor antidepressants.* London: The Stationery Office, 2005. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON019472&RevisionSelectionMethod=LatestReleased (accessed 14/08/08)
2. European Medicines Agency. European Medicines Agency finalises review of antidepressants in children and adolescents (issued 25th April, 2005). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/SSRI_31/WC500013082.pdf (accessed 30/07/10)

Effects on the musculoskeletal system. The Netherlands Pharmacovigilance Centre Lareb received 8 reports of arthralgia associated with the use of mirtazapine between May 1995 and October 2004; the effect usually developed within a short time of starting treatment and resolved once the drug was withdrawn.[1] The authors noted that of 4578 reported reactions to mirtazapine held in the WHO database up to March 2004, 110 concerned the development of arthralgia. Similar reactions have occurred with mianserin and nefazodone, and it was suggested that effects at serotonin 5-HT_1 or 5-HT_2 receptors might be involved.

1. Passier A, van Puijenbrock E. Mirtazapine-induced arthralgia. *Br J Clin Pharmacol* 2005; 60: 570–2.

Extrapyramidal effects. Akathisia that developed in 2 patients given mirtazapine 30 mg at night[1] resolved in one after being treated with clonazepam and in the other patient after reducing the dose of mirtazapine to 15 mg at night.

1. Girishchandra BG, *et al.* Mirtazapine-induced akathisia. *Med J Aust* 2002; 176: 242.

Serotonin syndrome. The serotonin syndrome (p. 445.2) is most commonly due to the additive adverse effects of two or more drugs that enhance serotonin activity at central receptors; rarely, a single serotonergic drug has caused the syndrome. One such case[1] occurred in an elderly patient given mirtazapine 15 mg daily; he was also taking salbutamol, ipratropium, and nimodipine, although none of these are known to have serotonergic effects.

1. Hernández JL, *et al.* Severe serotonin syndrome induced by mirtazapine monotherapy. *Ann Pharmacother* 2002; 36: 641–3.

Precautions

Mirtazapine should be used with caution in patients with epilepsy or a history of seizures, and it should be avoided completely if these disorders are unstable. Care is also required in hepatic or renal impairment, and cardiac disorders such as conduction disturbances, angina pectoris, and recent myocardial infarction; caution is further advised in patients with hypotension, diabetes mellitus, psychoses, and in those with a history of bipolar disorder. Treatment should be stopped if jaundice develops. Although mirtazapine has only weak antimuscarinic activity, it should nevertheless be used with care in patients with micturition disturbances, angle-closure glaucoma, and raised intra-ocular pressure.

Because of the risk of bone-marrow depression, patients should be advised to report any of the following symptoms during treatment: fever, sore throat, stomatitis, or other signs of infection; treatment should be stopped and a blood count performed.

Drowsiness often occurs at the start of therapy and patients, if affected, should not drive or operate machinery.

Patients should be closely monitored during early therapy until significant improvement in depression occurs because suicide is an inherent risk in depressed patients. For further details, see under Depression, p. 398.1. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be observed when treating patients with other disorders.

Mirtazapine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Breast feeding. Mirtazapine has been detected in breast milk;[1] however, the plasma concentration in a breast-fed infant was very low (200 picograms/mL) and no adverse events were detected.

1. Aichhorn W, *et al.* Mirtazapine and breast-feeding. *Am J Psychiatry* 2004; 161: 2325.

Children. The use of mirtazapine in adolescents and children with depression is not recommended; for further details, see Effects on Mental State, above.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mirtazapine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Pregnancy. A small case series followed the pregnancies of 9 women exposed to mirtazapine during the first trimester;[1] in the majority of cases the women were also exposed to other drugs. Within the group there were 7

healthy deliveries, 1 induced abortion, and 1 spontaneous abortion. In another report a mother who was given mirtazapine twice during her pregnancy for the successful treatment of hyperemesis gravidarum bore healthy male twins.[2] A follow-up examination of the twins at 6 months was normal.

Health Canada has reported that some newborn infants of mothers who took newer antidepressants such as mirtazapine mainly during the third trimester of pregnancy have had complications at birth requiring prolonged hospitalisation, breathing support, and tube feeding.[3] Reported symptoms included seizures, muscle rigidity, jitteriness, and constant crying. It was considered that these symptoms represented either direct toxicity of mirtazapine or a possible withdrawal syndrome.

1. Yaris F, *et al.* Newer antidepressants in pregnancy: prospective outcome of a case series. *Reprod Toxicol* 2004; 19: 235–8.
2. Rohde A, *et al.* Mirtazapine (Remergil) for treatment resistant hyperemesis gravidarum: rescue of a twin pregnancy. *Arch Gynecol Obstet* 2003; 268: 219–21.
3. Health Canada. Health Canada advises of potential adverse effects of SSRIs and other anti-depressants on newborns (issued 9th August 2004). Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2004/2004_44-eng.php (accessed 14/08/08)

Interactions

Mirtazapine should not be used with or within 2 weeks of stopping an MAOI; at least one week should elapse between stopping mirtazapine and starting any drug liable to provoke a serious reaction (e.g. phenelzine). Use of mirtazapine with alcohol or benzodiazepines may potentiate sedative effects.

The cytochrome P450 isoenzyme CYP3A4 is involved in the metabolism of mirtazapine and caution is advised when mirtazapine is given with potent inhibitors of this isoenzyme such as HIV-protease inhibitors, azole antifungals including ketoconazole, erythromycin, and nefazodone; raised plasma levels of mirtazapine have been noted after use with ketoconazole. Conversely, carbamazepine and other inducers of CYP3A4 increased the clearance of mirtazapine and the dose of mirtazapine may need to be increased when given with these drugs.

Cimetidine, which inhibits a range of cytochrome P450 isoenzymes, has more than doubled the bioavailability of mirtazapine; the dose of mirtazapine may need to be reduced if given with cimetidine.

Antihypertensives. For reports of hypertensive crisis occurring when mirtazapine was given with clonidine, see Antidepressants, p. 1342.1.

Pharmacokinetics

Mirtazapine is well absorbed from the gastrointestinal tract and peak plasma levels occur about 2 hours after oral use. Plasma protein binding is about 85%. Mirtazapine is extensively metabolised in the liver and the major biotransformation pathways are demethylation and oxidation followed by glucuronide conjugation; cytochrome P450 isoenzymes involved are CYP2D6, CYP1A2, and CYP3A4. The *N*-desmethyl metabolite is pharmacologically active. Elimination is via urine (75%) and faeces (15%). The mean plasma elimination half-life is 20 to 40 hours. Data from *animal* studies indicate that mirtazapine crosses the placenta. Mirtazapine is distributed into breast milk.

References.

1. Timmer CJ, *et al.* Clinical pharmacokinetics of mirtazapine. *Clin Pharmacokinet* 2000; 38: 461–74.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Bilanz; Comenter; Mitaxind; Noxibel; Remeron; Tetrazic; *Austral.*: Avanza; Axit; Mirtazon; Remeron; *Austria*: Mirtabene; Mirtaron; Mirtel; Remeron; *Belg.*: Remergon; *Braz.*: Menelat; Razapina; Remeron; *Canad.*: Remeron; *Chile*: Amirel; Ciblex; Divaril; Promyrtil; Zuleptan; *China*: Mi Er Ning (米尔宁); Paidisheng (派迪生); Remeron (瑞美隆); *Cz.*: Calixta†; Esprital; Mirtabs†; Mirtastad†; Mirzaten; Remeron; Valdren†; *Denm.*: Arintapin; Combar; Kompazin†; Miramerck†; Mirtazon†; Mirtin; Remeron; Zapatabs†; *Fin.*: Mirtachem; Mirtaril; Mirtazon†; Remeron; Trimazimyl; *Fr.*: Norset; *Ger.*: Mirta TAD; Mirtagamma; MirtaLich; Mirtazelon; Remergil; *Gr.*: Azapin; Depreram; Merdaten; Mirrador; Mirtamor; Mirtapil; Motofen; Remeron; Saxib; *Hong Kong*: Remeron; *Hung.*: Mirtadepi; Mirtel†; Mirzaten; Mizapin; Remeron; Yarocen; *India*: Matiz; Maz; Miramind; Miraz; Mirazep; Mirnite; Mirpine; Mirstar; Mirt; Mirtacin; Mirtadep; Mirtaz; Mirzest; Mitocent; Nassa; Nutaz; *Indon.*: Remeron; *Irl.*: Bexmirt†; BexZist†; Mirap; Mirtall†; Mirtaz†; Mirzaten; Tazamel†; Zismirt; Zispin; *Israel*: Miro; Remeron; *Ital.*: Remeron; *Malaysia*: Remeron; *Mex.*: Comenter; Mirzalux; Remeron; Zapex; *Neth.*: Azatrim†; Mirasol; Mirzasna; Mitabor; Remeron; *Norw.*: Remeron; *NZ*: Avanza; Remeron†; *Philipp.*: Mirazep; Remeron; *Pol.*: Esprital; Mirtagen; Mirtamerck; Mirtastad; Mirtor; Mirzaten; Remeron; Remirta; *Port.*: Mirpax; Mirtazon; Psidep; Remeron; *Rus.*: Mirtalan (Мирталан); Mirtazonal (Миртазонал); Mirzaten (Мирзатен); Noxibel (Ноксибел); Remeron (Ремерон); *S.Afr.*: Adco-Mirteron; Beron; Mytra; Remeron; *Singapore*: Remeron; *Spain*: Afloyan; Mirpik†; Mirtamylan; Rexer; Vastat†; *Swed.*: Mirtin; Remeron; *Switz.*: Mirtazap; Remeron; *Thai.*: Remeron; *Turk.*: Minelza; Mirtaron; Redepra; Remeron; Velorin; Zestat; *UK*: Zispin; *Ukr.*: Esprital (Эспритал); Mirazep (Миразеп); Mirtastadin (Миртастадин); Remeron (Ремерон); *USA*: Remeron; *Venez.*: Comenter; Remeron.

Pharmacopoeial Preparations

BP 2014: Mirtazapine Oral Solution; Mirtazapine Tablets; Orodispersible Mirtazapine Tablets;

USP 36: Mirtazapine Orally Disintegrating Tablets; Mirtazapine Tablets.

Moclobemide *(BAN, USAN, rINN)*

Moclobemida; Moclobémide; Moclobemidum; Moklobemid; Moklobemidi; Ro-11-1163; Ro-11-1163/000; Моклобемид.

4-Chloro-*N*-(2-morpholinoethyl)benzamide.

$C_{13}H_{17}ClN_2O_2$=268.7

CAS — 71320-77-9.

ATC — N06AG02.

ATC Vet — QN06AG02.

UNII — PJ0Y7AZ863.

Pharmacopoeias. In *Chin.* and *Swiss.*

Uses and Administration

Moclobemide, a benzamide derivative, is a reversible inhibitor of monoamine oxidase type A (RIMA) (see under Phenelzine, p. 444.1) used for the treatment of depression and of social anxiety disorder.

In the treatment of **depression** the usual initial oral dose of moclobemide is 300 mg daily in divided doses. This may be increased up to 600 mg daily according to response. In some patients, a maintenance dose of 150 mg daily may be sufficient.

In the treatment of **social anxiety disorder**, the initial daily dose of moclobemide is 300 mg increased after 3 days to 600 mg given in 2 divided doses. Treatment should be continued for 8 to 12 weeks to assess efficacy; patients should be periodically re-evaluated thereafter to determine the need for further treatment.

Moclobemide should be taken after food.

Reduced doses may need to be given in hepatic impairment (see p. 439.2) and in patients also taking cimetidine (see p. 440.1).

Antidepressants, particularly MAOIs, should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Reviews.

1. Bonnet U. Moclobemide: therapeutic use and clinical studies. *CNS Drug Rev* 2003; 9: 97–140.

Administration in hepatic impairment. UK licensed product information states that doses of moclobemide in patients with severe hepatic impairment may need to be reduced to half or one-third of the recommended dose (see above).

Anxiety disorders. The use of MAOIs in general in the management of anxiety disorders is discussed under Phenelzine on p. 444.2. For a discussion of the overall treatment of anxiety disorders, see p. 1028.1.

References.

1. Noyes R, *et al.* Moclobemide in social phobia: a controlled dose-response trial. *J Clin Psychopharmacol* 1997; 17: 247–54.
2. Neal LA, *et al.* An open trial of moclobemide in the treatment of post-traumatic stress disorder. *Int Clin Psychopharmacol* 1997; 12: 231–7.
3. Schneier FR, *et al.* Placebo-controlled trial of moclobemide in social phobia. *Br J Psychiatry* 1998; 172: 70–7.
4. Tiller JW, *et al.* Moclobemide and fluoxetine for panic disorder. *Eur Arch Psychiatry Clin Neurosci* 1999; 249 (suppl 1): 57–510.
5. Stein DJ, *et al.* Moclobemide is effective and well tolerated in the long-term pharmacotherapy of social anxiety disorder with or without comorbid anxiety disorder. *Int Clin Psychopharmacol* 2002; 17: 161–70.

Depression. As discussed on p. 398.1 there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effects. The traditional MAOIs such as phenelzine are rarely used as first-choice antidepressants because of the dangers of dietary and drug interactions. Reversible inhibitors of monoamine oxidase type A (RIMAs) such as moclobemide offer a safer alternative to the irreversible non-selective MAOIs and fewer dietary restrictions are necessary.

References.

1. Fitton A, *et al.* Moclobemide: a review of its pharmacological properties and therapeutic use in depressive illness. *Drugs* 1992; 43: 561–96.
2. Angst J, Stabl M. Efficacy of moclobemide in different patient groups: a meta-analysis of studies. *Psychopharmacology (Berl)* 1992; 106 (suppl): S109–S113.
3. Lonnqvist J, *et al.* Moclobemide and fluoxetine in atypical depression: a double-blind trial. *J Affect Disord* 1994; 32: 169–77.
4. Norman TR, Burrows GD. A risk-benefit assessment of moclobemide in the treatment of depressive disorders. *Drug Safety* 1995; 12: 46–54.
5. Roth M, *et al.* Moclobemide in elderly patients with cognitive decline and depression: an international double-blind, placebo-controlled trial. *Br J Psychiatry* 1996; 168: 149–57.
6. Lotufo-Neto F, *et al.* Meta-analysis of the reversible inhibitors of monoamine oxidase type A moclobemide and brofaromine for the treatment of depression. *Neuropsychopharmacology* 1999; 20: 226–47.

Smoking cessation. In a preliminary double-blind, placebo-controlled parallel-group study in 88 smokers, moclobemide facilitated smoking cessation (p. 2570.2) in highly dependent smokers.[1]

1. Berlin I, *et al.* A reversible monoamine oxidase A inhibitor (moclobemide) facilitates smoking cessation and abstinence in heavy, dependent smokers. *Clin Pharmacol Ther* 1995; 58: 444–52.

Adverse Effects

Adverse effects reported to occur with moclobemide include sleep disturbances, dizziness, agitation, feelings of anxiety, restlessness, irritability, and headache. Gastrointestinal disturbances include dry mouth, diarrhoea, constipation, and nausea and vomiting. Paraesthesia, visual disturbances, and oedema have also been reported, and skin reactions include rash, pruritus, urticaria, and flushing. Confusional states have occurred but they disappear rapidly on stopping the drug. Raised liver enzymes and galactorrhoea have been reported rarely.

Hyponatraemia, possibly due to inappropriate secretion of antidiuretic hormone, has been associated with the use of antidepressants, particularly in the elderly.

Effects on the cardiovascular system. Hypertension has been reported[1,2] rarely in patients taking moclobemide, some of whom were also taking other drugs although moclobemide was suspected to be the cause. Blood pressure usually returned to normal after stopping moclobemide.

1. Coulter DM, Pillans PI. Hypertension with moclobemide. *Lancet* 1995; 346: 1032.
2. Boyd IW. Hypertension with moclobemide. *Lancet* 1995; 346: 1498.

Effects on the endocrine system. A prescription-event monitoring study found that galactorrhoea is significantly associated with the use of moclobemide.[1]

1. Dunn NR, *et al.* Galactorrhoea with moclobemide. *Lancet* 1998; 351: 802.

Effects on the liver. An 85-year-old woman developed intrahepatic cholestasis after taking moclobemide for about 1 week;[1] she had previously been taking fluoxetine and was switched to moclobemide without a washout period. She died 12 days after the onset of jaundice despite prompt moclobemide withdrawal.

1. Timmings P, Lamont D. Intrahepatic cholestasis associated with moclobemide leading to death. *Lancet* 1996; 347: 762–3.

Overdosage. Several case series[1-3] have suggested that moclobemide is relatively safe when taken alone in overdose; symptoms such as gastrointestinal irritation, agitation, aggression, behavioural disturbances, and tachycardia have been noted. However, fatalities have been reported, particularly when taken with other serotonergic drugs.[3,4]

1. Hetzel W. Safety of moclobemide taken in overdose for attempted suicide. *Psychopharmacology (Berl)* 1992; 106: S127–S129.
2. Myrenfors PG, *et al.* Moclobemide overdose. *J Intern Med* 1993; 233: 113–15.
3. Isbister GK, *et al.* Moclobemide poisoning: toxicokinetics and occurrence of serotonin toxicity. *Br J Clin Pharmacol* 2003; 56: 441–50.
4. Giroud C, *et al.* Death following acute poisoning by moclobemide. *Forensic Sci Int* 2004; 140: 101–7.

Precautions

Moclobemide is contra-indicated in patients with acute confusional states and in those with phaeochromocytoma. It should be avoided in excited or agitated patients, unless used with a sedative. Manic episodes may be provoked in patients with bipolar disorder. Care is also required in patients with thyrotoxicosis as moclobemide can theoretically precipitate a hypertensive reaction. Reduced doses should be used in patients with severe hepatic impairment.

Patients should be closely monitored during early antidepressant therapy until significant improvement in depression occurs because suicide is an inherent risk in depressed patients. For further details, see under Depression, p. 398.1. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be observed when treating patients with other disorders.

Although impairment of mental alertness is generally not expected with moclobemide, caution should be exercised with respect to driving or operating machinery until individual reactions have been assessed.

Antidepressants, particularly MAOIs, should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Breast feeding. In a study[1] of the distribution of moclobemide into the breast milk of 6 mothers given a single 300-mg dose of moclobemide, a mean of 0.057% of the dose appeared in breast milk as moclobemide and 0.031% as Ro-12-8095, its major metabolite, within 24 hours of a

dose. It was considered that this small amount of moclobemide was unlikely to be hazardous to breast-fed infants. UK licensed product information advises caution and consideration of the benefits of moclobemide therapy to the mother against possible risks to the infant.

1. Pons G, *et al.* Moclobemide excretion in human breast milk. *Br J Clin Pharmacol* 1990; 29: 27–31.

Children. Moclobemide has not been adequately studied for the treatment of depression in children and its use is not recommended in UK licensed product information. In addition, other antidepressants have been shown to increase the risk of suicidal thoughts and behaviour in these patients (see Effects on Mental State, under Fluoxetine, p. 420.2).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies moclobemide as possibly porphyrinogenic: it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Pregnancy. UK licensed product information recommends that moclobemide should only be used during pregnancy if the benefits to the mother outweigh any possible risks to the fetus.

A patient who took at least 300 mg daily of moclobemide throughout her pregnancy delivered a healthy, full-term infant after an uncomplicated pregnancy.[1] The infant was monitored from birth, and psychomotor and somatic development for the first 14 months was found to be normal.

1. Rybakowski JK. Moclobemide in pregnancy. *Pharmacopsychiatry* 2001; 34: 82–3.

Withdrawal. Withdrawal symptoms may occur if an antidepressant such as moclobemide is suddenly stopped after regular use for 8 weeks or more; the *BNF* recommends that the dose should be tapered gradually over a period of about 4 weeks, or as much as 6 months in patients who have been receiving long-term maintenance therapy.

Despite reducing the dose of moclobemide over 3 days, symptoms such as muscle cramps, shivering, headache, nausea, and hot flushes developed in a 47-year-old woman on the day that moclobemide was completely stopped.[1] The patient had been taking moclobemide for about 15 months.

1. Curtin F, *et al.* Moclobemide discontinuation syndrome predominantly presenting with influenza-like symptoms. *J Psychopharmacol* 2002; 16: 271–2.

Interactions

The dietary restrictions that need to be followed with selective reversible inhibitors of monoamine oxidase type A such as moclobemide are less stringent than those for non-selective inhibitors of monoamine oxidase types A and B (see under Interactions of Phenelzine, p. 446.3). However, UK licensed product information recommends that since some patients may be especially sensitive to tyramine, consumption of large amounts of tyramine-rich food should be avoided.

Medicines containing *sympathomimetics, dextromethorphan,* or *anorectics* should not be taken with moclobemide. Moclobemide should not be given with *other antidepressants* although, owing to its short duration of action, a treatment-free period is generally considered unnecessary after its cessation. For further details, see Antidepressants under Interactions of Phenelzine, p. 447.2. Therapy with moclobemide should not be started until at least one week after cessation of a tricyclic or related antidepressant or an SSRI or related antidepressant (2 weeks in the case of paroxetine and sertraline; at least 5 weeks in the case of fluoxetine) or for at least one week after stopping treatment with non-selective MAOIs. CNS excitation or depression may occur if moclobemide is taken with *opioid analgesics,* and there is also a risk of CNS toxicity if taken with *serotonin ($5\text{-}HT_1$) agonists.* The metabolism of moclobemide is inhibited by *cimetidine,* leading to increased plasma concentrations and a need for reduced dosage (see p. 440.1).

Antimigraine drugs. For the effects of moclobemide on *serotonin ($5\text{-}HT_1$) agonists,* see under Sumatriptan, p. 681.3.

Cimetidine. Cimetidine 1 g daily for 2 weeks increased the mean peak plasma concentration of moclobemide in 8 healthy subjects from 575 nanograms/mL to 787 nanograms/mL; several other parameters associated with moclobemide absorption and disposition were also affected.[1] It was suggested that a reduction in the dosage of moclobemide might be required. UK licensed product information for moclobemide recommends reducing its dose by half in patients also receiving cimetidine.

1. Schoerlin M-P, *et al.* Cimetidine alters the disposition kinetics of the monoamine oxidase-A inhibitor moclobemide. *Clin Pharmacol Ther* 1991; 49: 32–8.

Dopaminergics. Adverse effects including nausea, vomiting, and dizziness were noted in healthy subjects given moclobemide and *levodopa with benserazide;*[1] however, no significant hypertensive reactions were seen.

Caution is also required when *selegiline* and moclobemide are given together.[1] Dietary restrictions with this combination (see under Phenelzine, p. 446.3) are recommended by one manufacturer of selegiline, whereas others advise that this combination should be avoided (as does the manufacturer of moclobemide).

See also under Selegiline, p. 917.1.

1. Dingemanse J. An update of recent moclobemide interaction data. *Int Clin Psychopharmacol* 1993; 7: 167–80.

Omeprazole. Omeprazole, which is an inhibitor of cytochrome P450 isoenzyme CYP2C19, increased plasma concentrations and elimination half-life of moclobemide in extensive metabolisers of the drug towards values seen in poor metabolisers.[1] It had little effect on pharmacokinetic parameters in poor metabolisers. The clinical effects were uncertain but extra care might be warranted if the 2 drugs are given together.

1. Yu K-S, *et al.* Effect of omeprazole on the pharmacokinetics of moclobemide according to the genetic polymorphism of CYP2C19. *Clin Pharmacol Ther* 2001; 69: 266–73.

Opioid analgesics. Symptoms suggestive of a mild serotonin syndrome (p. 445.2) developed in a 73-year-old woman taking moclobemide, nortriptyline, and lithium after she was given *pethidine* intravenously.[1] Licensed product information recommends that moclobemide should not be given with pethidine.

1. Gillman PK. Possible serotonin syndrome with moclobemide and pethidine. *Med J Aust* 1995; 162: 554.

Pharmacokinetics

Moclobemide is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur within about 1 hour of ingestion. Absorption is virtually complete but first-pass metabolism reduces bioavailability of the drug. Moclobemide is widely distributed throughout the body and is 50% bound to plasma proteins. It undergoes extensive metabolism in the liver, in part by the cytochrome P450 isoenzymes CYP2C19 and CYP2D6. Metabolites of moclobemide and a small amount of unchanged drug are excreted in the urine. Moclobemide has a plasma elimination half-life of 2 to 4 hours. Moclobemide is distributed into breast milk.

References.
1. Mayersohn M, Guentert TW. Clinical pharmacokinetics of the monoamide oxidase-A inhibitor moclobemide. *Clin Pharmacokinet* 1995; 29: 292–332.
2. Gram LF, *et al.* Moclobemide: a substrate of CYP2C19 and an inhibitor of CYP2C19, CYP2D6, and CYP1A2: a panel study. *Clin Pharmacol Ther* 1995; 57: 670–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Amira; Arima†; Aurorix; Clobemix; Maosig; Mohexal; *Austria*: Aurorix; *Belg.*: Aurorix; *Braz.*: Aurorix; *Canad.*: Manerix; *Chile*: Aurorix; Inpront†; *China*: Bei Su (贝苏); Hai Bei Lin (海倍森); Langtian (朗天); Tian Tai (恬泰); Ya Zheng (亚正); *Cz.*: Apo-Moclob; Aurorix; *Denm.*: Aurorix; Moclostad; *Fin.*: Aurorix; *Fr.*: Moclamine; *Ger.*: Aurorix; Moclobeta; *Gr.*: Aurorix; *Hong Kong*: Aurorix†; *Hung.*: Aurorix; *Maorex*†; Moclopharm†; Mocrim; *India*: Morex; Rimarex; *Indon.*: Aurorix†; *Irl.*: Manerix; *Israel*: Mobemide†; *Malaysia*: Aurorix; *Mex.*: Aurorex; Demobal; Feraken†; *Neth.*: Aurorix; *Norw.*: Aurorix; *NZ*: Aurorix; *Philipp.*: Aurorix†; *Pol.*: Aurorix; Mobemid; Moclozil†; Moklar; *Port.*: Aurorix; Zorix; *Rus.*: Aurorix (Аурорикс); *S.Afr.*: Aurorix†; Clorix†; Depnil; *Singapore*: Aurorix; Mobemide; *Spain*: Manerix; *Swed.*: Aurorix; *Switz.*: Aurorix; Moclo A; *Thai.*: Aurorix†; *Turk.*: Aurorix; Lobem; *UK*: Manerix.

Nefazodone Hydrochloride

(BANM, USAN, rINNM)

BMY-13754; Hidrocloruro de nefazodona; MJ-13754-1; Nefazodona, hidrocloruro de; Néfazodone, Chlorhydrate de; Nefazodoni Hydrochloridum; Нефазодона Гидрохлорид.

2-[3-[4-(3-Chlorophenyl)piperazin-1-yl]propyl]-5-ethyl-2,4-dihydro-4-(2-phenoxyethyl)-1,2,4-triazol-3-one monohydrochloride.

$C_{25}H_{32}ClN_5O_2,HCl$=506.5

CAS — 83366-66-9 (nefazodone); 82752-99-6 (nefazodone hydrochloride).

ATC — N06AX06.

ATC Vet — QN06AX06.

UNII — 27X63J94GR.

Pharmacopoeias. In *US.*

USP 36: (Nefazodone Hydrochloride). A non-hygroscopic white powder. Slightly soluble in water and in macrogols; freely soluble in chloroform; soluble in propylene glycol. Store in airtight containers at a temperature between 15 degrees and 30 degrees.

Uses and Administration

Nefazodone is a phenylpiperazine antidepressant structurally related to trazodone (see p. 453.1). It blocks the reuptake of serotonin at presynaptic neurones and is an antagonist at postsynaptic $5\text{-}HT_2$ receptors. Unlike trazodone, nefazodone inhibits the reuptake of noradrenaline. It blocks α_1-adrenoceptors but has no apparent effect on dopamine receptors. Nefazodone does not appear to have very significant antimuscarinic properties compared with tricyclic antidepressants.

Nefazodone hydrochloride has been given for the treatment of depression. One manufacturer (*Bristol-Myers Squibb*) has withdrawn nefazodone worldwide (see also Effects on the Liver, p. 440.3); however, nefazodone remains available in the USA, and possibly some other countries, as a generic preparation. The usual initial oral dose is 100 mg twice daily increased if necessary, in increments of 100 to 200 mg at intervals of at least a week, to a maximum of 300 mg twice daily. Doses are restricted in elderly patients: a recommended initial dose is 50 mg twice daily.

Antidepressants should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Nefazodone has been tried in anxiety disorders, but other drugs may now be preferred.

Adverse Effects and Treatment

The most common adverse effects seen with nefazodone are weakness, dry mouth, nausea, constipation, somnolence, dizziness, insomnia, and lightheadedness. Other effects which have occurred less frequently include chills, fever, orthostatic hypotension, incoordination, vasodilatation, arthralgia, paraesthesia, confusion, memory impairment, abnormal dreams, ataxia, and amblyopia and other visual disturbances. Syncope, priapism, and seizures have occurred rarely and there have been reports of sinus bradycardia. Hepatotoxicity has occurred (see p. 440.3).

Hyponatraemia, possibly due to inappropriate secretion of antidiuretic hormone, has been associated with the use of antidepressants, particularly in the elderly.

In overdosage, the symptoms that have been reported most frequently include hypotension, dizziness, nausea, vomiting, and drowsiness. The value of gastric decontamination in the treatment of overdosage is uncertain. Activated charcoal should be considered if more than 1.5 g (in an adult) or 20 mg/kg (in a child) has been taken and treatment is within 1 hour of ingestion. US licensed product information recommends gastric lavage, although this technique is seldom practicable and should not be attempted unless the airway is protected. Supportive therapy should be given as necessary. Dialysis, haemoperfusion, exchange perfusion, and measures to increase urine production are considered unlikely to be of benefit.

Reviews.
1. Robinson DS, *et al.* The safety profile of nefazodone. *J Clin Psychiatry* 1996; 57 (suppl 2): 31–8.

Effects on the liver. Subfulminant hepatic failure developed in 3 women given nefazodone for depression.[1] Two patients required liver transplantation although this was unsuccessful in one case and the patient died. Hepatitis, positive on rechallenge, has also been reported with nefazodone.[2]

The original US manufacturer (*Bristol-Myers Squibb*) of nefazodone have stated that rare events of raised liver enzymes, hepatitis, hepatic failure and necrosis have been reported since marketing but no causal relationship has been established. In the USA, a reported rate of about 1 case of hepatic failure resulting in death or transplantation per 250 000 to 300 000 patient years of nefazodone treatment has been estimated by the manufacturer; this rate is about 3 to 4 times greater than the background rate of hepatic failure.[3] Onset times for such cases ranged from 2 weeks to 6 months. The Canadian manufacturers have indicated[4] that as of June 2001 there had been 109 reports of serious hepatic adverse events associated with nefazodone from postmarketing surveillance worldwide. These included 23 cases of hepatic failure, of which 16 led to transplantation and/or death. Most cases occurred within 4 months of beginning treatment although a few were after continuous use for up to 2 years. After a review[5] of the data available to December 2002, it was decided to withdraw nefazodone from the Canadian market in November 2003. Subse-

quently, one manufacturer (*Bristol-Myers Squibb*) withdrew nefazodone worldwide.

1. Aranda-Michel J, *et al.* Nefazodone-induced liver failure: report of three cases. *Ann Intern Med* 1999; 130: 285–8.
2. Schrader GD, Roberts-Thompson IC. Adverse effect of nefazodone: hepatitis. *Med J Aust* 1999; 170: 452.
3. Jody DM [Bristol-Myers Squibb]. Important drug warning including black box information. Available at: http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM171084.pdf (accessed 30/07/10)
4. Bristol-Myers Squibb Canada Inc/Linson Pharama Inc. Important safety information on nefazodone HCl: severe and serious hepatic events (issued June 2001). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/nefazodone_hpc-cps-eng.pdf (accessed 14/08/08)
5. Bristol-Myers Squibb Canada. Important safety information regarding the discontinuation of sales of nefazodone in Canada (issued October 2003). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/bms-nefazodone_hpc-cps-eng.pdf (accessed 14/08/08)

Overdosage. A 27-year-old woman had no serious toxicity after taking 3 g of nefazodone in a suicide attempt.[1] Somnolence was the most severe effect noted. In another case, a 31-year-old woman attempted suicide with 16.8 g of nefazodone and an unknown quantity of verapamil.[2] The patient was lethargic, and developed significant bradycardia and hypotension; she recovered after supportive therapy. The authors reported that among the 7 cases of overdose occurring during clinical studies, there were no fatalities or permanent sequelae.

In a review of 1338 cases of nefazodone-only overdoses reported to the American Association of Poison Control Centers over a 2-year period, it was found that the majority of cases were either asymptomatic or mild in nature with symptoms such as nausea, vomiting, dizziness, and drowsiness.[3] More severe symptoms were noted in only 2 patients. In one case, an 11-year-old boy with a history of seizures suffered several seizures after starting nefazodone at a dose of 100 mg twice daily; the other case involved a 47-year-old man who developed premature ventricular contractions, bradycardia, agitation, and hypotension after an intentional overdose of an unknown quantity. No deaths were recorded in any of the cases where the outcome was known.

1. Gaffney PW, *et al.* Nefazodone overdose. *Ann Pharmacother* 1998; 32: 1249–50.
2. Catalano G, *et al.* Nefazodone overdose: a case report. *Clin Neuropharmacol* 1999; 22: 63–5.
3. Benson BE, *et al.* Toxicities and outcomes associated with nefazodone poisoning: an analysis of 1,338 exposures. *Am J Emerg Med* 2000; 18: 587–92.

Precautions

Treatment with nefazodone should not generally be started in patients with active hepatic disease or elevated baseline serum transaminases. Patients who develop signs or symptoms of hepatic impairment such as jaundice, anorexia, abdominal pain, elevated transaminase levels, or malaise during treatment should be evaluated for hepatic damage and the drug withdrawn if necessary. Nefazodone is contra-indicated in patients previously withdrawn from the drug because of hepatotoxicity.

Nefazodone should be used with caution in patients with epilepsy, or a history of hypomania or mania. It should also be used with caution in cardiovascular or cerebrovascular disease that could be exacerbated by hypotension (for example recent history of myocardial infarction, unstable heart disease, angina, or ischaemic stroke), and in any condition such as dehydration or hypovolaemia that may predispose patients to hypotension.

Since nefazodone is structurally related to trazodone which is known to have caused priapism (see Effects on Sexual Function, p. 454.1), US licensed product information recommends that any patient developing inappropriate or prolonged penile erections should stop nefazodone immediately.

Patients should be closely monitored during early antidepressant therapy until significant improvement in depression occurs because suicide is an inherent risk in depressed patients. For further details, see under Depression, p. 398.1. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be observed when treating patients with other disorders.

Nefazodone may impair performance of skilled tasks and, if affected, patients should not drive or operate machinery.

Antidepressants should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Breast feeding. A study[1] in 2 nursing mothers receiving nefazodone for postpartum depression indicated that nefazodone, but not its major active metabolites, was distributed into breast milk in variable amounts; the quantity present did not seem to be dose-related. The calculated exposure of the two women's infants was 2.2% and 0.4% of the maternal dose respectively. Another report suggested that even such low exposures might result in clinically significant effects:[2] drowsiness, inability to maintain normal body temperature, and poor feeding were reported in the breast-fed infant of a woman receiving nefazodone. After breast feeding was stopped the symptoms resolved, suggesting an association between the two despite a calculated exposure in the infant of only 0.45% of the maternal dose.

1. Dodd S, *et al.* Nefazodone in the breast milk of nursing mothers: a report of two patients. *J Clin Psychopharmacol* 2000; 20: 717–18.
2. Yapp P, *et al.* Drowsiness and poor feeding in a breast-fed infant: association with nefazodone and its metabolites. *Ann Pharmacother* 2000; 34: 1269–72.

Children. US licensed product information considers that the safety and efficacy of nefazodone have not been established for the treatment of depression in adolescents and children. In addition, other antidepressants have been shown to increase the risk of suicidal thoughts and behaviour in these patients (see Effects on Mental State, under Fluoxetine, p. 420.2).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nefazodone as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Pregnancy. Licensed product information states that nefazodone should only be used during pregnancy if the benefits to the mother outweigh the risks to the fetus.

In a multicentre study of 147 women who took either nefazodone or trazodone in at least the first trimester of pregnancy there were 121 live births, 20 spontaneous abortions, 6 therapeutic abortions, and 2 reports of major malformations (Hirschsprung disease and neural tube defect);[1] no still-births were recorded. There were no significant differences in pregnancy outcome in the nefazodone/trazodone group when compared with the 2 control groups (women with depression taking non-teratogenic antidepressants and women taking non-teratogenic drugs). The rate of spontaneous abortions was non-significantly higher in both the antidepressant groups than in the other control group. It was suggested that the rate of major malformations in all 3 groups was not greater than the baseline rate of 1 to 3%.

1. Einarson A, *et al.* A multicentre prospective controlled study to determine the safety of trazodone and nefazodone use during pregnancy. *Can J Psychiatry* 2003; 48: 106–10.

Interactions

Nefazodone should not be given to patients receiving MAOIs or for at least 14 days after they are stopped; it has also been recommended that any drug liable to provoke a serious reaction (e.g. phenelzine) should not be given within one week of stopping nefazodone therapy. For further details on the combined use of antidepressants, see Antidepressants under Interactions of Phenelzine, p. 447.2.

Orthostatic hypotension can be a problem with nefazodone, and therefore caution is required for any patient also on antihypertensive therapy.

Nefazodone is an inhibitor of the cytochrome P450 isoenzyme CYP3A4 responsible for the metabolism of some benzodiazepines, and consequently it may produce clinically important increases in their plasma concentrations. Use with astemizole, cisapride, pimozide, and terfenadine (which are metabolised by the same isoenzyme) is best avoided because the potential also exists for increased plasma concentrations of these drugs, with the risk of inducing ventricular arrhythmias. Other substrates for this isoenzyme may also interact with nefazodone: atorvastatin, lovastatin, and simvastatin should be used with caution with nefazodone since there have been rare reports of rhabdomyolysis with such combinations. Increased serum concentrations of ciclosporin or tacrolimus, both substrates for CYP3A4, have been reported in patients also receiving nefazodone. Monitoring of serum ciclosporin or tacrolimus levels is recommended when either of these two drugs is given with nefazodone. Use of the vasopressin V_2-receptor antagonist tolvaptan with nefazodone is contra-indicated (see p. 2633.1).

Plasma concentrations of digoxin are increased by nefazodone, and because of digoxin's narrow therapeutic index, plasma concentrations of digoxin should be monitored if use with nefazodone is necessary.

Caution should be exercised when haloperidol is given with nefazodone as the clearance of haloperidol may be reduced. Plasma concentrations of carbamazepine are also increased when used with nefazodone. More importantly, carbamazepine may reduce nefazodone plasma concentrations to subtherapeutic levels and therefore use together is not recommended. Giving buspirone with nefazodone significantly increases the serum concentrations of buspirone; the manufacturers of nefazodone recommend that the initial dose of buspirone is reduced if these drugs are given together.

The potential for interaction between nefazodone and general anaesthetics exists and the manufacturer recommends that nefazodone should be stopped before elective surgery for as long as clinically feasible.

Benzodiazepines. For further details of interactions between nefazodone and benzodiazepines, see Diazepam, p. 1068.3.

Pharmacokinetics

Nefazodone is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur within about 2 hours after oral doses. Absorption is delayed and reduced by food but this is not considered to be clinically significant. Nefazodone undergoes extensive first-pass metabolism and is more than 99% bound to plasma proteins; it is widely distributed. It is extensively metabolised by *N*-dealkylation and hydroxylation in the liver to several metabolites, two of which, hydroxynefazodone and *m*-chlorophenylpiperazine, are known to be pharmacologically active. Excretion is mainly as metabolites via the urine (about 55%) and the faeces (20 to 30%). The plasma elimination half-life is 2 to 4 hours. Pharmacokinetic parameters are reported to be non-linear with increasing doses. Nefazodone is distributed in small amounts into breast milk (see Breast Feeding, above).

Reviews.

1. Greene DS, Barbhaiya RH. Clinical pharmacokinetics of nefazodone. *Clin Pharmacokinet* 1997; 33: 260–75.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Nefadon; Nefirel.

Pharmacopoeial Preparations
USP 36: Nefazodone Hydrochloride Tablets.

Nortriptyline Hydrochloride

(BANM, USAN, rINNM)

38489; Hidrocloruro de nortriptilina; Nortriptilina, hidrocloruro de; Nortriptilin-hidroklorid; Nortriptilino hidrochloridas; Nortriptyliinihydrokloridi; Nortriptyline, Chlorhydrate de; Nortriptylinhydrochlorid; Nortriptylin-hydrochlorid; Nortriptylinhydroklorid; Nortriptylini Hydrochloridum; Nortryptyliny chlorowodorek; Нортриптилина Гидрохлорид.

3-(10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cycloheptен-5-ylidene) propyl(methyl)amine hydrochloride.

$C_{19}H_{21}N,HCl=299.8$

CAS — 72-69-5 (nortriptyline); 894-71-3 (nortriptyline hydrochloride).

ATC — N06AA10.

ATC Vet — QN06AA10.

UNII — 00FN6IH15D.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Nortriptyline Hydrochloride). A white or almost white powder. Sparingly soluble in water; soluble in alcohol and in dichloromethane. Protect from light.

USP 36: (Nortriptyline Hydrochloride). A white to off-white powder having a slight characteristic odour. Soluble 1 in 90 of water, 1 in 30 of alcohol, 1 in 20 of chloroform, and 1 in 10 of methyl alcohol; practically insoluble in ether, in benzene, and in most other organic solvents. pH of a 1% solution in water is about 5. Store in airtight containers. Protect from light.

Uses and Administration

Nortriptyline is a dibenzocycloheptadiene tricyclic antidepressant with actions and uses similar to those of amitriptyline (p. 401.1). It is the principal active metabolite of amitriptyline. Nortriptyline is one of the less sedating tricyclics and its antimuscarinic effects are mild.

Nortriptyline is given orally as the hydrochloride although doses are expressed in terms of the base; nortriptyline hydrochloride 113.8 mg is equivalent to about 100 mg of nortriptyline. In the treatment of depression a low starting dose is given gradually increasing to the equivalent of 75 to 100 mg daily in 3 or 4 divided doses. Up to a maximum of 150 mg daily may be required in patients with severe depression. Licensed product information recommends that plasma concentrations of nortriptyline should be monitored when doses above 100 mg daily are given; however, the *BNF* considers that the evidence of any practical value is uncertain. Adolescents and the elderly may be given 30 to 50 mg daily in divided doses. Since nortriptyline has a prolonged half-life, once-daily dosage regimens are also suitable, usually given at night.

Dose adjustments have been suggested for patients with genetic polymorphisms in the cytochrome P450 isoenzyme CYP2D6 (see Administration in Genetic Variation, under Amitriptyline, p. 401.2).

For the use of nortriptyline in children, see p. 442.1.

Nortriptyline should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Administration in children. Nortriptyline is used for the treatment of nocturnal enuresis in children in whom organic pathology has been excluded. However, drug therapy for nocturnal enuresis should be reserved for those in whom other methods have failed and should preferably only be given to cover periods away from home. Tricyclic antidepressants are not recommended in children under 6 years of age. For a discussion of tricyclic use in nocturnal enuresis see Micturition Disorders under Amitriptyline, p. 402.1.

Suggested oral doses of nortriptyline are:

- 10 mg for children aged 6 to 7 years (20 to 25 kg)
- 10 to 20 mg for children aged 8 to 11 years (25 to 35 kg)
- 25 to 35 mg for children aged over 11 years (35 to 54 kg)

The dose should be given 30 minutes before bedtime and treatment, including a period of gradual withdrawal, should not continue for longer than 3 months. A full physical examination, including an ECG, is recommended before a further course.

Pain. Antidepressants, usually amitriptyline or another tricyclic, are useful in alleviating some types of pain (see Choice of Analgesic, p. 4.2). Nortriptyline has also been tried and may produce fewer adverse effects than amitriptyline. In the management of neuropathic pain, the *BNF* has suggested an initial oral dose of 10 mg daily at night, increased if necessary to 75 mg daily.

References.

1. Atkinson JH, *et al.* A placebo-controlled randomized clinical trial of nortriptyline for chronic low back pain. *Pain* 1998; 76: 287–96.
2. Watson CP, *et al.* Nortriptyline versus amitriptyline in postherpetic neuralgia: a randomized trial. *Neurology* 1998; 51: 1166–71.

Smoking cessation. For reference to the use of nortriptyline in management of smoking cessation, see under Amitriptyline, p. 402.2.

Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p. 402.3).

Breast feeding. For comments on the use of tricyclic antidepressants in breast-feeding patients, see under Precautions for Amitriptyline, p. 405.1.

Effects on ventilation. Severe hyperventilation developed in a 61-year-old man with end-stage renal disease after receiving nortriptyline 125 mg daily;[1] mechanical ventilation was necessary to correct severe respiratory alkalosis.

1. Sunderrajan S, *et al.* Nortriptyline-induced severe hyperventilation. *Arch Intern Med* 1985; 145: 746–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nortriptyline as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

For interactions associated with tricyclic antidepressants, see Amitriptyline, p. 406.1.

Pharmacokinetics

Nortriptyline is the main active metabolite of amitriptyline (p. 407.2). It has been reported to have a longer plasma half-life than amitriptyline. Nortriptyline is subject to extensive first-pass metabolism in the liver to 10-hydroxynortriptyline, which is active.

Metabolism. Individuals with a poor debrisoquine hydroxylation phenotype may be at greater risk of confusional states when taking nortriptyline.[1] This was thought to be because the polymorphic hydroxylation of debrisoquine and nortriptyline are mediated by similar enzymatic mechanisms [the cytochrome P450 isoenzyme CYP2D6], with poor oxidisers having higher plasma nortriptyline concentrations.[2,3] A nonlinear (dose-dependent) relationship between dose and plasma-nortriptyline concentrations has been seen during therapeutic drug monitoring[4] in subjects who were considered to be extensive metabolisers of debrisoquine; nonlinearity did not appear to occur in poor metabolisers. There was no significant correlation between hydroxylation phenotype and amitriptyline concentrations, suggesting that demethylation and hydroxylation of tricyclic antidepressants are mediated by different cytochrome P450 isoenzymes.[5]

The pharmacokinetics and pharmacological actions of 10-hydroxynortriptyline, the major active metabolite of nortriptyline, have been reviewed.[3]

1. Park BK, Kitteringham NR. Adverse reactions and drug metabolism. *Adverse Drug React Bull* 1987; 122: 456–9.
2. Nordin C, *et al.* Plasma concentrations of nortriptyline and its 10-hydroxy metabolite in depressed patients—relationship to the debrisoquine hydroxylation metabolic ratio. *Br J Clin Pharmacol* 1985; 19: 832–5.
3. Nordin C, Bertilsson L. Active hydroxymetabolites of antidepressants: emphasis on E-10-hydroxy-nortriptyline. *Clin Pharmacokinet* 1995; 28: 26–40.
4. Jerling M, Alván G. Nonlinear kinetics of nortriptyline in relation to nortriptyline clearance as observed during therapeutic drug monitoring. *Eur J Clin Pharmacol* 1994; 46: 67–70.
5. Bertilsson L, *et al.* Metabolism of various drugs in subjects with different debrisoquine and sparteine oxidation phenotypes. *Br J Clin Pharmacol* 1982; 14: 602P.

Therapeutic plasma concentrations. Nortriptyline appears to have an optimum antidepressant effect at plasma concentrations between 50 and 150 nanograms/mL. Outside this range, there is a poor clinical response. Plasma concentration measurements are unequivocally useful in patients who do not respond to usual oral doses or in high-risk patients for whom, because of age or medical illness, it is especially important to use the lowest possible effective dose of the drug.[1]

It has been suggested[2] that within this range of total nortriptyline concentrations there is a probability of an antidepressant response of 68% or more with free concentrations of 7 to 10 nanograms/mL.

For reference to dose-dependent kinetics of nortriptyline seen in individuals with an extensive debrisoquine hydroxylation phenotype, see under Metabolism, above.

1. Task Force on the Use of Laboratory Tests in Psychiatry. Tricyclic antidepressants—blood level measurements and clinical outcome: an APA task force report. *Am J Psychiatry* 1985; 142: 155–62.
2. Perry PJ, *et al.* The relationship of free nortriptyline levels to antidepressant response. *Drug Intell Clin Pharm* 1984; 18: 510.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Allegron; ***Belg.***: Nortrilen; ***Braz.***: Nortrip; Pamelor; ***Canad.***: Aventyl; Norventyl; ***Cz.***: Nortrilen; ***Denm.***: Noritren; ***Fin.***: Noritren; ***Ger.***: Nortrilen; ***Gr.***: Nortrilen; ***Hong Kong***: Nortrilen; ***India***: Sensival; ***Israel***: Nortylin; ***Ital.***: Noritren; ***Neth.***: Nortrilen; ***Norw.***: Noritren; ***NZ***: Norpress; ***Port.***: Norterol; ***Spain***: Norfenazin; Paxtibi; ***Swed.***: Sensaval; ***Switz.***: Nortrilen; ***Thai.***: N-Trip; Norline; Nortrilen†; Nortyline; Ortrip; ***UK***: Allegron; ***USA***: Aventyl; Pamelor.

Multi-ingredient Preparations. ***Arg.***: Karile; ***Chile***: Motitrel†; ***Indon.***: Motival†; ***Irl.***: Motival†; ***Ital.***: Dominans; ***Mex.***: Motival; ***S.Afr.***: Motival†; ***Spain***: Tropargal; ***Thai.***: Cetavol.

Pharmacopoeial Preparations

BP 2014: Nortriptyline Capsules; Nortriptyline Tablets;
USP 36: Nortriptyline Hydrochloride Capsules; Nortriptyline Hydrochloride Oral Solution.

Opipramol Hydrochloride *(BANM, USAN, rINNM)*

G-33040; Hidrocloruro de opipramol; Opipramol, Chlorhydrate d'; Opipramol, hidrocloruro de; Opipramol Hidroklorür; Opipramoli Dihydrochloridum; Opipramoli Hydrochloridum; Opipramolu dichlorowodorek; Опипрамола Гидрохлорид.

2-[4-(3-5*H*-Dibenz[*b*,*f*]azepin-5-ylpropyl)piperazin-1-yl]ethanol dihydrochloride.

$C_{23}H_{29}N_3O,2HCl$=436.4

CAS — 315-72-0 (opipramol); 909-39-7 (opipramol dihydrochloride).

ATC — N06AA05.

ATC Vet — QN06AA05.

UNII — B49OBI656M.

Pharmacopoeias. In *Pol.*

Profile

Opipramol hydrochloride is a dibenzazepine tricyclic antidepressant (see Amitriptyline, p. 401.1) given in oral doses of 50 to 300 mg daily in the treatment of depression.

It should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Insidon; ***Ger.***: Insidon†; Opipra†; Opipram; ***Gr.***: Insidon; ***Israel***: Oprimol†; ***Pol.***: Pramolan; Sympramol; ***Switz.***: Insidon; ***Turk.***: Deprenil; Insidon; Insomin; Inzeton; Opridon; Oprimol†.

Oxitriptan *(rINN)*

5-HTP; L-5-Hydroxytryptophan; Oxitriptán; Oxitriptanum; Ro-0783/B; Окситриптан.

L-2-Amino-3-(5-hydroxy-1*H*-indol-3-yl)propionic acid.

$C_{11}H_{12}N_2O_3$=220.2

CAS — 4350-09-8 (oxitriptan); 56-69-9 (DL-5-hydroxytryptophan).

ATC — N06AX01.

ATC Vet — QN06AX01.

UNII — C1UO185Q9.

Profile

Oxitriptan is the L form of 5-hydroxytryptophan, a precursor of serotonin. Like tryptophan (p. 455.2) it is used in the treatment of depression; it is given in oral doses of up to 600 mg daily.

Oxitriptan is also used in doses of up to 1 g daily in myoclonic disorders, especially posthypoxic myoclonus (p. 511.3). It has also been used in neurological conditions including migraine, pain syndromes, and sleep disorders and as an adjunct in epilepsy and parkinsonism.

DL-Oxitriptan has also been used as an antidepressant.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Tript-OH; ***Fr.***: Levotonine ***Ital.***: Tript-OH; ***Port.***: Cincofarm; ***Spain***: Cincofarm; ***Switz.***: Tript-OH†.

Multi-ingredient Preparations. ***Indon.***: Deprex; Menose; ***Ital.*** Pineal Notte; ***USA***: PowerSleep.

Paroxetine *(BAN, USAN, rINN)*

BRL-29060; FG-7051; Paroksetiini; Paroxetin; Paroxetina; Paroxétine; Paroxetinum; Пароксетин.

(-)-*trans*-5-(4-*p*-Fluorophenyl-3-piperidylmethoxy)-1,3-benzodioxole.

$C_{19}H_{20}FNO_3$=329.4

CAS — 61869-08-7.

ATC — N06AB05.

ATC Vet — QN06AB05.

UNII — 41VRH5220H.

Paroxetine Hydrochloride *(BANM, rINNM)*

BRL-29050A; Hidrocloruro de paroxetina; Paroksetiinihydrokloridihemihydraatti; Paroksetin Hidroklorür; Paroksetino hidrochloridas hemihidratas; Paroksetyny chlorowodorek; Paroxetin hydrochlorid; Paroxetina, hidrocloruro de; Paroxétine, chlorhydrate de; Paroxétine (chlorhydrate de) hémihydraté; Paroxetine Hydrochloride Hemihydrate; Paroxetinhydrochlorid-Hemihydrat; Paroxetinhydrokloridhemihydrat; Paroxetini Hydrochloridum; Paroxetini hydrochloridum hemihydricum; Пароксетина Гидрохлорид.

$C_{19}H_{20}FNO_3,HCl,½H_2O$=374.8

CAS — 78246-49-8 (anhydrous paroxetine hydrochloride); 110429-35-1 (paroxetine hydrochloride hemihydrate).

UNII — X2ELS050D8 (paroxetine hydrochloride, hemihydrate); 3I3T11UD2S (anhydrous paroxetine hydrochloride).

Pharmacopoeias. In *Eur.* (see p. vii) and *US*, which permit the anhydrous and hemihydrate forms.

Ph. Eur. 8: (Paroxetine Hydrochloride, Anhydrous). A white or almost white, hygroscopic, crystalline powder. It exhibits polymorphism. Slightly soluble in water; sparingly soluble in dehydrated alcohol and in dichloromethane; freely soluble in methyl alcohol. Store in airtight containers at a temperature not exceeding 25 degrees.

Ph. Eur. 8: (Paroxetine Hydrochloride Hemihydrate). A white or almost white, crystalline powder. It exhibits pseudopolymorphism. Slightly soluble in water; sparingly soluble in alcohol and in dichloromethane; freely soluble in methyl alcohol. Protect from light.

USP 36: (Paroxetine Hydrochloride). It is anhydrous or contains one-half molecule of water of hydration. A white to off-white solid. Slightly soluble in water; soluble in alcohol and in methyl alcohol. Store the anhydrous form in airtight containers.

Paroxetine Mesilate *(BANM, rINNM)*

Mesilato de paroxetina; Paroxetina, mesilato de; Paroxétine, Mésilate de; Paroxetine Mesylate (USAN); Paroxetini Mesilas; Пароксетина Мезилат.

$C_{19}H_{20}FNO_3,CH_4O_3S$=425.5

CAS — 217797-14-3.

ATC — N06AB05.

ATC Vet — QN06AB05.
UNII — M711N184JE.

NOTE. The name Asimia has been used as a trade mark for paroxetine mesilate.

Uses and Administration

Paroxetine, a phenylpiperidine derivative, is an SSRI with actions and uses similar to those of fluoxetine (p. 417.1); it is also used for the treatment of vasomotor symptoms associated with the menopause (see Hot Flushes, under Fluoxetine, p. 418.2). It is given orally usually as paroxetine hydrochloride or the mesilate. Doses are expressed in terms of the base; paroxetine hydrochloride 22.8 mg or paroxetine mesilate 25.8 mg are each equivalent to about 20 mg of paroxetine.

The licensed doses for **psychiatric disorders** given below refer to preparations containing paroxetine hydrochloride; similar doses are also used when paroxetine is given as the mesilate. Doses of paroxetine are given as a single dose in the morning. They may be increased in steps of 10 mg at intervals of at least 1 week; however, the efficacy of maximum licensed doses has been questioned (for further details, see Administration, p. 443.1).

In the treatment of *depression*, the usual dose of paroxetine is 20 mg daily, increased gradually, if necessary, to a maximum of 50 mg daily.

In the treatment of *generalised anxiety disorder*, the initial dose is 20 mg daily; further increases to a maximum of 50 mg have been given.

The initial dose in *obsessive-compulsive disorder* is 20 mg daily increased gradually to a usual maintenance dose of 40 mg daily; some patients may require up to 60 mg daily.

In the treatment of *panic disorder* with or without agoraphobia, the initial dose is 10 mg daily increased gradually to the usual recommended maintenance dose of 40 mg daily; some patients may benefit from 60 mg daily.

The recommended starting dose for the treatment of *post-traumatic stress disorder* is 20 mg daily; if necessary this may be increased gradually to a maximum of 50 mg daily.

The initial dose for the treatment of *social anxiety disorder* is 20 mg daily increased gradually, if necessary, to a maximum of 50 or 60 mg daily.

A suggested maximum daily dose in elderly or debilitated patients is 40 mg; US licensed product information also recommends a starting dose of 10 mg daily in such patients. Reduced doses should be given to patients with hepatic or renal impairment, see p. 443.1.

A modified-release preparation (as the hydrochloride) is also available in the USA for the treatment of depression, panic disorder, and social anxiety disorder; the maximum doses with this preparation may be slightly greater than those recommended with the immediate-release preparation. The modified-release preparation may also be used in the treatment of *premenstrual dysphoric disorder*. The initial dose is 12.5 mg once daily, usually in the morning, which may be increased to 25 mg once daily, if necessary, after an interval of at least one week. Treatment may be given throughout the menstrual cycle or limited to the luteal phase.

When used for psychiatric disorders, paroxetine should be withdrawn gradually to reduce the risk of withdrawal symptoms; weekly decrements of 10 mg have been used (see also Withdrawal, under Precautions of Fluoxetine, p. 423.3).

Paroxetine mesilate is given for the treatment of moderate to severe **vasomotor symptoms associated with the menopause**; the usual dose is the equivalent of paroxetine 7.5 mg once daily at bedtime.

Reviews.
1. Wagstaff AJ, *et al.* Paroxetine: an update of its use in psychiatric disorders in adults. *Drugs* 2002; 62: 655–703. Correction. *ibid.*; 1461.
2. Pae CU, Patkar AA. Paroxetine: current status in psychiatry. *Expert Rev Neurother* 2007; 7: 107–20. Correction. *ibid.*; 313–14.
3. Tang SW, Helmeste D. Paroxetine. *Expert Opin Pharmacother* 2008; 9: 787–94.

Administration. Although paroxetine is licensed in the UK at higher doses for psychiatric disorders, the UK CSM considers that there is a lack of evidence from clinical studies of additional efficacy with paroxetine when given above the following daily doses:
- depression, generalised anxiety disorder, social anxiety disorder, post-traumatic stress disorder: 20 mg
- obsessive-compulsive disorder, panic disorder: 40 mg

1. CSM/MCA Paroxetine prescribing advice. *Current Problems* 2004; 30: 3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007448&RevisionSelectionMethod=LatestReleased (accessed 14/08/08)

Administration in hepatic or renal impairment. In the USA the recommended initial oral dose of paroxetine for psychiatric disorders in patients with severe renal or hepatic impairment is the equivalent of 10 mg daily, increased to a maximum of 40 mg daily as necessary. UK licensed product information recommends that doses in such patients are limited to the lower end of the range.

Anxiety disorders. Paroxetine is used in anxiety disorders including generalised anxiety disorder (p. 1028.1), obsessive-compulsive disorder (p. 1028.2), panic disorder (p. 1029.1), post-traumatic stress disorder (p. 1029.2), and social anxiety disorder (see under Phobic Disorders, p. 1029.1). It has also been tried for adult night terrors (see under Sleep-associated Movement Disorders, p. 1034.2).

References.
1. Oehrberg S, *et al.* Paroxetine in the treatment of panic disorder: a randomised, double-blind, placebo-controlled study. *Br J Psychiatry* 1995; 167: 374–9.
2. Zohar J, *et al.* Paroxetine versus clomipramine in the treatment of obsessive-compulsive disorder. *Br J Psychiatry* 1996; 169: 468–74.
3. Lecrubier Y, *et al.* Long-term evaluation of paroxetine, clomipramine and placebo in panic disorder. *Acta Psychiatr Scand* 1997; 95: 153–60.
4. Wilson SJ, *et al.* Adult night terrors and paroxetine. *Lancet* 1997; 350: 185.
5. Stein MB, *et al.* Paroxetine treatment of generalized social phobia (social anxiety disorder). *JAMA* 1998; 280: 708–13.
6. Baldwin D, *et al.* Paroxetine in social phobia/social anxiety disorder: randomised, double-blind, placebo-controlled study. *Br J Psychiatry* 1999; 175: 120–6.
7. Baldwin DS. Clinical experience with paroxetine in social anxiety disorder. *Int Clin Psychopharmacol* 2000; 15 (suppl): S19–24.
8. Marshall RD, *et al.* Efficacy and safety of paroxetine treatment for chronic PTSD: a fixed-dose, placebo-controlled study. *Am J Psychiatry* 2001; 158: 1982–8.
9. Tucker P, *et al.* Paroxetine in the treatment of chronic posttraumatic stress disorder: results of a placebo-controlled, flexible-dosage trial. *J Clin Psychiatry* 2001; 62: 860–8.
10. Liebowitz MR, *et al.* A randomized, double-blind, fixed-dose comparison of paroxetine and placebo in the treatment of generalized social anxiety disorder. *J Clin Psychiatry* 2002; 63: 66–74.
11. Stein DJ, *et al.* Efficacy of paroxetine for relapse prevention in social anxiety disorder: a 24-week study. *Arch Gen Psychiatry* 2002; 59: 1111–18.
12. Stocchi F, *et al.* Efficacy and tolerability of paroxetine for the long-term treatment of generalized anxiety disorder. *J Clin Psychiatry* 2003; 64: 250–8.
13. Hollander E, *et al.* Acute and long-term treatment and prevention of relapse of obsessive-compulsive disorder with paroxetine. *J Clin Psychiatry* 2003; 64: 1113–21.
14. Lepola U, *et al.* Controlled-release paroxetine in the treatment of patients with social anxiety disorder. *J Clin Psychiatry* 2004; 65: 222–9.
15. Sheehan DV, *et al.* Efficacy and tolerability of controlled-release paroxetine in the treatment of panic disorder. *J Clin Psychiatry* 2005; 66: 34–40.
16. Rickels K, *et al.* Remission of generalized anxiety disorder: a review of the paroxetine clinical trials database. *J Clin Psychiatry* 2006; 67: 41–7.

Depression. As discussed on p. 398.1, there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effect profile. SSRIs such as paroxetine are widely used as an alternative to the older tricyclics as they have fewer adverse effects and are safer in overdosage.

References.
1. Leyman S, *et al.* Paroxetine: post-marketing experience on 4024 depressed patients in Belgium. *Eur J Clin Res* 1995; 7: 287–96.
2. Rodríguez-Ramos P, *et al.* Effects of paroxetine in depressed adolescents. *Eur J Clin Res* 1996; 8: 49–61.
3. Franchini L, *et al.* Dose-response efficacy of paroxetine in preventing depressive recurrences: a randomized, double-blind study. *J Clin Psychiatry* 1998; 59: 229–32.
4. Williams JW, *et al.* Treatment of dysthymia and minor depression in primary care: a randomized controlled trial in older adults. *JAMA* 2000; 284: 1519–26.
5. Golden RN, *et al.* Efficacy and tolerability of controlled-release and immediate-release paroxetine in the treatment of depression. *J Clin Psychiatry* 2002; 63: 577–84.
6. Rapaport MH, *et al.* Efficacy of controlled-release paroxetine in the treatment of late-life depression. *J Clin Psychiatry* 2003; 64: 1065–74.
7. Misri S, *et al.* The use of paroxetine and cognitive-behavioral therapy in postpartum depression and anxiety: a randomized controlled trial. *J Clin Psychiatry* 2004; 65: 1236–41.
8. Trivedi MH, *et al.* Effectiveness of low doses of paroxetine controlled release in the treatment of major depressive disorder. *J Clin Psychiatry* 2004; 65: 1356–64.
9. Dunner DL, *et al.* Efficacy and tolerability of controlled-release paroxetine in the treatment of severe depression: post hoc analysis of pooled data from a subset of subjects in four double-blind clinical trials. *Clin Ther* 2005; 27: 1901–11.
10. Katzman MA, *et al.* Paroxetine versus placebo and other agents for depressive disorders: a systematic review and meta-analysis. *J Clin Psychiatry* 2007; 68: 1845–59.
11. Barbui C, *et al.* Effectiveness of paroxetine in the treatment of acute major depression in adults: a systematic re-examination of published and unpublished data from randomized trials. *CMAJ* 2008; 178: 296–305.

Hypochondriasis. For mention of the use of SSRIs, including paroxetine, in hypochondriasis, see under Fluoxetine, p. 418.2.

Premenstrual syndrome. Paroxetine (as a modified-release preparation) is used to control both the psychological and somatic symptoms of premenstrual syndrome (p. 2272.3).

References.
1. Cohen LS, *et al.* Paroxetine controlled release for premenstrual dysphoric disorder: a double-blind, placebo-controlled trial. *Psychosom Med* 2004; 66: 707–13.
2. Landén M, *et al.* Placebo-controlled trial comparing intermittent and continuous paroxetine in premenstrual dysphoric disorder. *Neuropsychopharmacology* 2007; 32: 153–61.
3. Steiner M, *et al.* Luteal phase administration of paroxetine for the treatment of premenstrual dysphoric disorder: a randomized, double-blind, placebo-controlled trial in Canadian women. *J Clin Psychiatry* 2008; 69: 991–8.

Pruritus. Paroxetine has produced some benefit in the relief of non-dermatological pruritus.[1]

1. Zylicz Z, *et al.* Paroxetine in the treatment of severe non-dermatological pruritus: a randomized, controlled trial. *J Pain Symptom Manage* 2003; 26: 1105–12.

Sexual dysfunction. Impotence or ejaculatory problems have been reported as adverse effects of SSRIs; for the potential use of these effects in the management of premature ejaculation see Fluoxetine, p. 419.1.

Adverse Effects, Treatment, and Precautions

As for SSRIs in general (see Fluoxetine, p. 419.1).

Extrapyramidal reactions (including orofacial dystonias) and withdrawal symptoms associated with paroxetine have been reported to the UK CSM more commonly than with other SSRIs. For further details, see Extrapyramidal Effects under Adverse Effects of Fluoxetine, p. 421.2 and Withdrawal under Precautions, p. 423.3.

Breast feeding. For comments on the use of SSRIs in breast-feeding patients, see under Precautions for Fluoxetine, p. 422.2.

Children. SSRIs are associated with an increased risk of potentially suicidal behaviour when used for the treatment of depression in children and adolescents under 18 years old; for further details, see under Effects on Mental State in Fluoxetine, p. 420.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies paroxetine as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Pregnancy. For discussion of the risks of SSRIs during pregnancy, and whether paroxetine is associated with a greater teratogenic risk than other SSRIs, see under Fluoxetine, p. 423.1.

Interactions

For interactions associated with SSRIs, see Fluoxetine, p. 424.1.

Pharmacokinetics

Paroxetine is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur within about 5 hours of ingestion. It undergoes extensive first-pass metabolism in the liver. The main metabolic pathway is oxidation followed by methylation and formation of glucuronide and sulfate conjugates. The cytochrome P450 isoenzyme CYP2D6 is partly responsible for the metabolism of paroxetine. Paroxetine is widely distributed throughout body tissues and is about 95% bound to plasma proteins. The elimination half-life of paroxetine is reported to be about 21 hours. Excretion is via the urine (about 64%) and the faeces (about 36%), mainly as metabolites in both cases. Paroxetine is distributed into breast milk (see Breast Feeding under Precautions in Fluoxetine, p. 422.2).

References.
1. Dalhoff K, *et al.* Pharmacokinetics of paroxetine in patients with cirrhosis. *Eur J Clin Pharmacol* 1991; 41: 351–4.
2. Hiemke C, Härtter S. Pharmacokinetics of selective serotonin reuptake inhibitors. *Pharmacol Ther* 2000; 85: 11–28.
3. Cristina Castelli M, *et al.* Pharmacokinetic properties of once-daily oral low-dose mesylate salt of paroxetine (LDMP 7.5 mg) following single and multiple doses in healthy postmenopausal women. *Clin Ther* 2013; 35: 862–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Afenexil; Aropax; Datevan; Meplar; Neurotrox; Olane; Pamoxet; Paxil; Psicoasten; Sicopax†; Sicotral; Sostel; Tiarix; Xilanic†; ***Austral.***: Aropax; Extine; Oxetine†; Paxtine; ***Austria***: Allenopar; Ennos; Parocetan; Paroxat; Seroxat; ***Belg.***: Aropax; Seroxat; ***Braz.***: Aropax; Arotin; Benepax; Cebrilin; Depaxan; Moratus; Parox; Paxan; Paxil; Paxtrat; Pondera; Roxetin; Sertero; Zyparox; ***Canad.***: Paxil; ***Chile***: Aroxat; Bectam; Pamax; Posivyl; Roxepar; Seretran; Traviata; ***China***: Le You (乐友); Seroxat (赛乐特); Cz.: Apo-Parox; Arketis; Parolex; Remood; Seroxat; ***Denm.***: Euplix; Optipar; Paroc; Paroxegen; Pasorex; Serorex; Seroxat; Seroxetabs; ***Fin.***: Optipar; Seroxat; ***Fr.***: Deroxat; Divarius; ***Ger.***: ParoLich†; Paroxalon; Paroxat†; Seroxat; Tagonis†; ***Gr.***: Noprilex; Parolet; Parosat; Paroxia; Paxinol; Prexat; Seroxat; Solben; Stilliden; Taberil; ***Hong Kong***: Parotin; Seroxat; ***Hung.***: Apodepi; Paretin; Parogen; Paroxat; Rexetin; Seroxat; Xetanor; ***India***: Cipar-CR; Deprox; Leparox; Oxitine; Panex; Paradise; Pari; Parotin; Xet; ***Indon.***: Seroxat†; ***Irl.***: Meloxat; Paroser; Parox; Paxt; Seroxat; ***Israel***: Parotin; Paxxet; Seroxat; ***Ital.***: Dapagut; Daparox; Dropaxin; Eutimil; Serestill; Sereupin; Seroxat; Stilliden; ***Jpn***: Paxil; ***Malaysia***: Seroxat; ***Mex.***: Apo-Oxpar; Aropax; Ixicrol; Ontracel;

The symbol † denotes a preparation no longer actively marketed

Paxil; Tamcere; Xetroran; ***Neth.***: Seroxat; ***Norw.***: Seroxat; ***NZ***: Aropax; Loxamine; ***Philipp.***: Panex; Seroxat; ***Pol.***: Arketis; Deprozel†; ParoGen; Paromerck; Paroxinor; Paxeratio†; Paxtin; Rexetin; Seroxat; Xetanor; ***Port.***: Denerval; Dropax; Paxetil; Paxpar; Ritlemi; Seroxat; Stiliden; Voltak; Zanoxina; ***Rus.***: Актапароксетин (Актапароксетин); Adepress (Адепресс); Paxil (Паксил); Plisil (Плизил); Rexetin (Рексетин); Serestill (Серестилл); ***S.Afr.***: Aropax; Deparoc; Parax; Paxil; Sedarin†; Serrapress; Xet; ***Singapore***: Seroxat; ***Spain***: Arapaxel; Casbol†; Daparox; Prosinor; Motivan; Paratonina†; Seroxat; Xetin; Zuria; ***Swed.***: Arketis; Paroxiflex; Seroxat; ***Switz.***: Deroxat; Parexat†; Paronex; Paroxetop†; ***Thai.***: Seroxat; ***Turk.***: Nokturn; Paroteva; Paxera; Paxil; Paxotin; Seroxat; Xetanor; Zoxapar; ***UK***: Seroxat; ***Ukr.***: Paroxin (Пароксин); Rexetin (Рексетин); ***USA***: Brisdelle; Paxil; Pexeva; ***Venez.***: Paxil.

Pharmacopoeial Preparations
BP 2014: Paroxetine Tablets;
USP 36: Paroxetine Tablets.

Phenelzine Sulfate *(BANM, pINNM)*

Fenelzina, sulfato de; Phénelzine, Sulfate de; Phenelzine Sulphate; Phenelzini Sulfas; Sulfato de fenelzina; Фенельзина Сульфат.

Phenethylhydrazine hydrogen sulphate.

$C_8H_{12}N_2,H_2SO_4$=234.3

CAS — 51-71-8 (phenelzine); 156-51-4 (phenelzine sulfate).

ATC — N06AF03.

ATC Vet — QN06AF03.

UNII — 2681D7P965.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Phenelzine Sulfate). A white powder or pearly platelets with a pungent odour. Freely soluble in water; practically insoluble in alcohol, in chloroform, and in ether. Protect from light.

USP 36: (Phenelzine Sulfate). A white to yellowish-white powder having a characteristic odour. Freely soluble in water; practically insoluble in alcohol, in chloroform, and in ether. pH of a 1% solution in water is between 1.4 and 1.9. Store in airtight containers. Protect from heat and light.

Uses and Administration

Monoamine oxidase inhibitors (MAOIs) inhibit the action of monoamine oxidase, the enzyme responsible for the metabolism of several biogenic amines. Monoamine oxidase exists in two forms, type A and type B. Monoamine oxidase type A preferentially de-aminates adrenaline, noradrenaline, and serotonin whereas monoamine oxidase type B preferentially metabolises benzylamine and phenylethylamine; dopamine and tyramine are de-aminated by both forms of the enzyme.

- The traditional MAOIs such as phenelzine, iproniazid, isocarboxazid, and tranylcypromine are inhibitors of both types; apart from tranylcypromine, which produces a less prolonged inhibition of the enzyme than phenelzine, all are hydrazine derivatives and bind irreversibly.
- Selective inhibitors include selegiline (p. 915.2), an irreversible inhibitor of monoamine oxidase type B used in the treatment of Parkinson's disease and depression. Clorgiline, an irreversible selective type A inhibitor, was investigated for use as an antidepressant.
- Reversible inhibitors of monoamine oxidase type A (RIMAs) are used in treatment of depression and include moclobemide.

Antidepressant activity appears to reside mainly with inhibition of monoamine oxidase type A although the mode of action of these drugs in depression is not fully understood. Selective inhibitors are claimed to have fewer or less severe adverse effects than non-selective inhibitors. As tyramine is de-aminated by both monoamine oxidase types A and B, inhibiting only one of the enzymes allows for continued, albeit reduced, de-amination. Thus the dietary precautions that need to be observed with non-selective inhibitors are less stringent with the selective inhibitors.

Phenelzine and other antidepressant MAOIs are used in the treatment of atypical depression, particularly where phobic features or associated anxiety are present, or in patients who have not responded to other antidepressants. However, the risks associated with irreversible non-selective MAOIs usually mean that other antidepressants are preferred. Up to a month may elapse before an antidepressant response is obtained with MAOIs. After a response has been obtained maintenance therapy may need to be continued for at least 6 months (12 months in the elderly) to avoid relapse on stopping therapy. Patients with a history of recurrent depression should continue to receive maintenance treatment for at least 2 years. Care should be taken in elderly patients because of an increased susceptibility to adverse effects. Moreover, therapy with the non-selective inhibitors is particularly unsuitable for patients considered unable to adhere to the strict dietary requirements necessary for safe usage. (For contra-indication in children, see under Precautions, p. 446.2).

Phenelzine is given orally as the sulfate although doses are expressed in terms of the base; phenelzine sulfate 25.8 mg is equivalent to about 15 mg of phenelzine. The usual initial dose is equivalent to phenelzine 15 mg three times daily; if no response has been obtained after 2 weeks the dosage may be increased to 15 mg four times daily; severely depressed patients in hospital may be given up to 30 mg three times daily. Once a response has been obtained the dosage may be gradually reduced for maintenance therapy; some patients may continue to respond to 15 mg on alternate days.

Phenelzine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Anxiety disorders. MAOIs have been used in the treatment of anxiety disorders. MAOIs appear to be effective in *panic disorder* (p. 1029.1). They also appear to be effective in *social anxiety disorder* (see under Phobic Disorders, p. 1029.1) and can improve anticipatory anxiety and functional disability. The main treatment for *post-traumatic stress disorder* (p. 1029.2) is psychotherapy but MAOIs are one of the alternatives that can help to reduce traumatic recollections and nightmares, and to repress flashbacks.

References.
1. Buigues J, Vallejo J. Therapeutic response to phenelzine in patients with panic disorder and agoraphobia with panic attacks. *J Clin Psychiatry* 1987; 48: 55–9.
2. Frank JB, *et al.* A randomized clinical trial of phenelzine and imipramine for posttraumatic stress disorder. *Am J Psychiatry* 1988; 145: 1289–91.
3. Heimberg RG, *et al.* Cognitive behavioural group therapy vs phenelzine therapy for social phobia: 12 week outcome. *Arch Gen Psychiatry* 1998; 55: 1133–41.
4. Aarre TF. Phenelzine efficacy in refractory social anxiety disorder: a case series. *Nord J Psychiatry* 2003; 57: 313–15.

Depression. As discussed on p. 398.1 there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effects. MAOIs are rarely used as first-choice antidepressants because of the dangers of dietary and drug interactions. Even in depressed patients with atypical, hypochondriacal, hysterical, or phobic features, for which MAOIs are particularly effective, it is often recommended that another antidepressant type should be tried first. Reversible inhibitors of monoamine oxidase type A (RIMAs) offer an alternative to the MAOIs and less strict dietary restrictions are necessary. They may be effective in depressive disorders, although their relative efficacy in atypical depression remains to be established.

Combination therapy with differing classes of antidepressants, including the MAOIs, has been used in the treatment of drug-resistant depression. However, such therapy may result in enhanced adverse reactions or interactions and requires expert supervision. For further details, see Antidepressants under Interactions, p. 447.2.

Hyperactivity. When drug therapy is required for attention deficit hyperactivity disorder (p. 2314.1), initial treatment is usually with a central stimulant. MAOIs have been used successfully but problems with dietary restriction and potential drug interactions have limited their use.

Migraine. Numerous drugs have been used for the prophylaxis of migraine (p. 670.3), although propranolol is generally preferred. Antidepressants such as the tricyclics can be useful alternatives when these drugs are ineffective or unsuitable. MAOIs are best reserved for severe cases refractory to other forms of prophylactic treatment.

Adverse Effects

Adverse effects commonly associated with phenelzine and other MAOIs include orthostatic hypotension and attacks of dizziness. Other common adverse effects include headache, dry mouth, constipation and other gastrointestinal disturbances (including nausea and vomiting), and oedema. Drowsiness, weakness, and fatigue are reported frequently although CNS stimulation may also occur and symptoms include agitation, nervousness, euphoria, restlessness, insomnia, and convulsions. Psychotic episodes, with hypomania or mania, confusion, hallucinations, or toxic delirium, may be induced in susceptible persons.

Sweating and muscle tremors, twitching, or hyperreflexia may occur, which in overdosage may present as extreme hyperpyrexia and neuromuscular irritability. Other reported reactions include blurred vision, nystagmus, urinary retention or difficulty in micturition, arrhythmias, rashes, leucopenia, sexual disturbances, and weight gain with inappropriate appetite. Jaundice has been reported with hydrazine MAOIs and, on rare occasions, fatal progressive hepatocellular necrosis. Peripheral neuropathies associated with the hydrazine derivatives may be caused by pyridoxine deficiency. Hyponatraemia, possibly due to inappropriate secretion of antidiuretic hormone, has been associated with the use of antidepressants, particularly in the elderly.

Symptoms of **overdosage** may be minor at first and progress over the ensuing 24 to 48 hours. After mild overdosage and symptomatic and supportive therapy, recovery may occur in 3 to 4 days, but after massive overdosage symptoms may persist for up to 2 weeks. CNS depression and drowsiness have been noted with overdosage, but CNS stimulation is more common, with irritability, hyperactivity, agitation, hallucinations, or convulsions. Respiratory depression and coma may ultimately occur. Cardiovascular effects include hypertension, sometimes with severe headache, although hypotension is more frequently reported; cardiac arrhythmias and peripheral collapse can also develop. Profuse sweating, hyperpyrexia, and neuromuscular excitation with hyperreflexia are also prominent features of overdosage.

MAOIs have been the most commonly implicated drugs in the serotonin syndrome (see p. 445.2). A severe hypertensive crisis, sometimes fatal, may occur if an MAOI is taken with some other drugs or certain foods (see Interactions, p. 447.1 and p. 446.3). These reactions are characterised by severe headache and a rapid and sometimes prolonged rise in blood pressure followed by intracranial haemorrhage or acute cardiac failure.

For the adverse effects of reversible inhibitors of monoamine oxidase type A (RIMAs), see Moclobemide, p. 437.3.

Incidence of adverse effects. A suspicion that the reported adverse effects of MAOIs were both exaggerated and overemphasised prompted a comparative study in patients receiving phenelzine or imipramine.[1] The report noted that the dosages of phenelzine used were at the upper end of the usual therapeutic range (mean 77 mg daily) while those of imipramine were in the middle of the usual therapeutic range (mean 139 mg daily). The profile of adverse effects in the two groups was very similar. With the exception of significantly increased incidence of drowsiness in the phenelzine group, the 2 groups did not differ in the frequency of autonomic, CNS, cardiovascular, or psychological adverse effects. However, a significantly greater number of patients given phenelzine had to stop their treatment because of the severity of the adverse effects. Nonetheless it was considered that phenelzine was reasonably well-tolerated when compared with imipramine.

Others have also studied the adverse effect profile of phenelzine and made comparisons with tranylcypromine and imipramine.[2,3] A retrospective review involving 198 patients concluded that although phenelzine was more likely than the other two drugs to induce adverse effects, drug withdrawal because of adverse effects was less likely to occur. This was probably because phenelzine showed clear-cut clinical efficacy resulting in prescribers being reluctant to stop therapy.

1. Evans DL, *et al.* Early and late side effects of phenelzine. *J Clin Psychopharmacol* 1982; 2: 208–10.
2. Rabkin J, *et al.* Adverse reactions to monoamine oxidase inhibitors. Part I: a comparative study. *J Clin Psychopharmacol* 1984; 4: 270–8.
3. Rabkin JG, *et al.* Adverse reactions to monoamine oxidase inhibitors Part II: treatment correlates and clinical management. *J Clin Psychopharmacol* 1985; 5: 2–9.

Effects on the cardiovascular system. MAOIs are generally considered to be relatively free of adverse cardiovascular effects. The hypertensive reaction that may follow interactions of MAOIs with foods or other drugs is well known (see Interactions, p. 446.3 and p. 447.1) but orthostatic hypotension may also occur when these drugs are used on their own.

In a study[1] involving 14 patients it was found that phenelzine produced both a significant decrease in systolic blood pressure while lying down, and significant orthostatic hypotension; in 2 patients these effects on blood pressure meant treatment had to be altered. Differences between the effects of phenelzine and those reported for the tricyclic antidepressants were noted. Tricyclics were not known to affect lying systolic blood pressure and although both tricyclics and phenelzine could cause orthostatic hypotension, with the tricyclics it typically reaches a maximum within the first week of treatment whereas with phenelzine the maximum effect was noted after 4 weeks. Additionally, the study provided some indication that the blood pressure effects of phenelzine may attenuate with time, a phenomenon that is not known to occur with the tricyclics.

1. Kronig MH, *et al.* Blood pressure effects of phenelzine. *J Clin Psychopharmacol* 1983; 3: 307–10.

Effects on the endocrine system. MAOIs may induce *hyperprolactinaemia*[1] and this has led to galactorrhoea in women.[2] Occasionally, MAOIs may cause *dilutional hyponatraemia* due to a reduction in the renal excretion of free water mediated by both enhanced vasopressin release and increased antidiuretic action on the renal tubule.[3] The UK CSM, commenting on reports[4] it had received of hyponatraemia with antidepressants (fluoxetine, paroxetine,

lofepramine, clomipramine, and imipramine), considered that it was likely to occur with any antidepressant and usually involved elderly patients.

1. *Slater SL, et al.* Elevation of plasma-prolactin by monoamine-oxidase inhibitors. *Lancet* 1977; ii: 275–6.
2. Segal M, Heys RF. Inappropriate lactation. *BMJ* 1969; 4: 236.
3. Baylis PH. Drug-induced endocrine disorders. *Adverse Drug React Bull* 1986; No 116: 432–5.
4. CSM/MCA. Antidepressant-induced hyponatraemia. *Current Problems* 1994; 20: 5–6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015616&RevisionSelectionMethod=LatestReleased (accessed 05/08/08)

Effects on the liver. Published case reports of hepatotoxic reactions to MAOIs have included jaundice in 4 patients[1] and hepatic failure progressing to encephalopathy in 2 patients;[2] this latter reaction was attributed to a hypersensitivity reaction.

Of 91 cases of hepatitis associated with antidepressants reported to French pharmacovigilance centres from 1977 to 1983, an MAOI (iproniazid) was implicated in 11. These 11 cases were associated with cytolytic reactions and 5 patients died.[3]

Two cases of fulminant hepatic failure have been reported[4] after use of phenelzine for 4 months; all other causes of acute liver damage were ruled out. Both patients recovered after emergency liver transplantation.

1. Holdsworth CD, *et al.* Hepatitis caused by the newer amine-oxidase-inhibiting drugs. *Lancet* 1961; ii: 621–3.
2. Wilkinson SP, *et al.* Frequency and type of renal and electrolyte disorders in fulminant hepatic failure. *BMJ* 1974; 1: 186–9.
3. Lefebure B, *et al.* Hépatites aux antidépresseurs. *Therapie* 1984; 39: 509–16.
4. Gómez-Gil E, *et al.* Phenelzine-induced fulminant hepatic failure. *Ann Intern Med* 1996; 124: 692–3.

Effects on the nervous system. MAOIs produce a variety of effects on the nervous system. Drowsiness is frequently reported but symptoms of CNS stimulation, including agitation, nervousness, and euphoria may also occur; psychotic episodes may be induced in susceptible individuals. Further adverse neurological reactions are described under Epileptogenic Effect, p. 445.1, and Extrapyramidal Effects, p. 445.2.

Peripheral neuropathies, sometimes associated with a documented pyridoxine deficiency, have been reported in patients receiving phenelzine.[1,2] In most of the patients the neuropathies developed 6 weeks to 4 months after starting phenelzine,[2] although in one case symptoms did not occur for 11 years.[1] The symptoms also generally disappeared when pyridoxine was given with continued phenelzine therapy.[2] The possibility that the dietary restrictions imposed on persons taking phenelzine might have contributed to a low pyridoxine intake was considered unlikely. The most probable mechanism for the induced pyridoxine deficiency was combination of the hydrazine moiety with the pyridoxal form of the vitamin to form an inactive compound.

Many drugs can inhibit transmission at the myoneural junction under experimental conditions and it has been said that phenelzine may cause postoperative respiratory depression, possibly through a combined action with neuromuscular blockers.[3] For further details, see Anaesthesia under Precautions, p. 446.1.

1. Heller CA, Friedman PA. Pyridoxine deficiency and peripheral neuropathy associated with long-term phenelzine therapy. *Am J Med* 1983; 75: 887–8.
2. Stewart JW, *et al.* Phenelzine-induced pyridoxine deficiency. *J Clin Psychopharmacol* 1984; 4: 225–6.
3. Lane RJM. Routledge PA. Drug-induced neurological disorders. *Drugs* 1983; 26: 124–47.

Effects on sexual function. MAOIs such as phenelzine and tranylcypromine have been implicated in producing both impotence and failure of ejaculation.[1,2] Priapism has been reported with phenelzine.[3] There have also been several reports of female anorgasmia attributed to MAOIs, an effect which appears to be dose-related.[4] Loss of libido and impotence are common symptoms of depression, often making the role of drugs in producing sexual dysfunction difficult to assess.

1. Simpson GM, *et al.* Effects of anti-depressants on genito-urinary function. *Dis Nerv Syst* 1965; 26: 787–9.
2. Wyatt RJ, *et al.* Treatment of intractable narcolepsy with a monoamine oxidase inhibitor. *N Engl J Med* 1971; 285: 987–91.
3. Yeraganí VK, Gershon S. Priapism related to phenelzine therapy. *N Engl J Med* 1987; 317: 117–18.
4. Shen WW, Sata LS. Inhibited female orgasm resulting from psychotropic drugs: a clinical review. *J Reprod Med* 1983; 28: 497–9.

Epileptogenic effect. Licensed product information indicates that convulsions represent one of the less common adverse effects of MAOIs; they may be a feature of overdosage.

A typical grand-mal seizure with tonic-clonic convulsions has been reported in a patient with no history of epilepsy or predisposing factors shortly after the start of phenelzine therapy.[1] The point was made that phenelzine-induced seizures had rarely been seen.

1. Bhugra DK, Kaye N. Phenelzine induced grand mal seizure. *Br J Clin Pract* 1986; 40: 173–4.

Extrapyramidal effects. A parkinsonian syndrome developed in a patient about 5 weeks after the start of therapy with phenelzine. Symptoms gradually resolved over 10 days after the withdrawal of phenelzine. The mechanisms by which phenelzine could have induced these effects were discussed.[1]

1. Gillman MA, Sandyk R. Parkinsonism induced by a monoamine oxidase inhibitor. *Postgrad Med J* 1986; 62: 235–6.

Hyponatraemia. See Effects on the Endocrine System, p. 442.3.

Lupus. A reversible lupus-like reaction has been reported in a patient who had been taking phenelzine sulfate for 8 months.[1]

1. Swartz C. Lupus-like reaction to phenelzine. *JAMA* 1978; 239: 2693.

Overdosage. MAOIs in overdose rarely produce severe hypertension; the blood pressure may be high or low, or may alternate between the two. More commonly the patient gradually develops widespread muscle spasms, trismus, and opisthotonus with widely dilated pupils and a hot and sweating skin. About 16 to 24 hours after ingestion potentially fatal hyperthermia may develop; temperatures of 42.1 to 43.8 degrees have been recorded immediately before death. Disseminated intravascular coagulation, rhabdomyolysis, and acute tubular necrosis can also occur.[1]

1. Henry JA. Specific problems of drug intoxication. *Br J Anaesth* 1986; 58: 223–33.

Serotonin syndrome. The serotonin syndrome is a drug-induced excess in serotonergic activity at central receptors.[1-10] It is characterised by the development of *at least three* of the following clinical features after a recent change in a treatment regimen involving serotonergic drugs:[1]

- agitation
- ataxia
- diaphoresis
- diarrhoea
- fever
- hyperreflexia
- myoclonus
- shivering
- changes in mental status

Strict application of these criteria may not identify early, mild, or subacute cases of serotonin syndrome and a simpler diagnostic approach focusing on neuromuscular features has also been suggested.[10] The syndrome should be distinguished from the hypertensive crises produced by the interaction between MAOIs and tyramine (see Interactions of MAOIs with Foods, p. 446.3), and from the neuroleptic malignant syndrome (see p. 1050.2).[3,8-10]

The onset of the syndrome is often within minutes of altering the regimen,[10] although some cases have occurred as much as several weeks later.[2] The occurrence and severity of the syndrome do not appear to be dose-related,[2] but to depend on the extent and duration of the rise in intrasynaptic serotonin.[5]

The serotonin syndrome is relatively uncommon and symptoms are usually mild. However, severe complications, including disseminated intravascular coagulation, severe hyperthermia, respiratory failure, and seizures have been reported; there have also been fatalities.

The serotonin syndrome may follow exposure to a single serotonergic drug or, more commonly, a combination of such drugs.[2,8-10] In the past, **MAOIs** have been the most commonly implicated drugs in this syndrome, particularly when taken with other antidepressants such as the tricyclics, SSRIs, serotonin and noradrenaline reuptake inhibitors (SNRIs) including venlafaxine, trazodone, lithium, and tryptophan. (The use of combination therapy with serotonergic antidepressant drugs is discussed under Interactions of MAOIs with other Drugs, p. 447.2.) MAOIs combined with the opioids dextromethorphan and pethidine have also produced the serotonin syndrome. The interaction can occur with both irreversible and reversible MAOIs, and with those selective for monoamine oxidase type A such as moclobemide as well as with non-selective MAOIs.[11] The selective inhibitor of monoamine oxidase type B, selegiline, may also pose problems at high doses as its selectivity starts to diminish.

As usage of the **SSRIs** has increased, so too has the number of reports of adverse reactions when these drugs have been combined with other serotonergic drugs, including the herbal preparation St John's wort.

Other drugs that may potentially cause serotonin syndrome in certain circumstances include antiemetics such as ondansetron, buspirone, carbamazepine, dihydroergotamine, methylenedioxyamfetamine, sibutramine, selective serotonin (5-HT_1) agonists such as sumatriptan, and tramadol.[3,8-10]

Serotonergic potentiation may also occur if one serotonergic drug is used after another without allowing a sufficient **drug-free interval** after stopping the first. This is a particular problem when the first drug is an irreversible MAOI or a drug with a long half-life such as the SSRI fluoxetine.

Most cases of serotonin syndrome resolve within 24 hours after withdrawal of the offending drugs and giving supportive **therapy**,[1-4,8-10] including appropriate management of fever and hyperthermia (p. 11.3). Benzodiazepines may be of value to control agitation, myoclonus, and seizures. The non-specific serotonin antagonist cyproheptadine may be useful in more severe cases although its efficacy has not been established;[8,10] methysergide has also been used with some success.[2,3,6] Other drugs that have been tried include propranolol, chlorpromazine, and dantrolene[2,3,6,8-10] although adverse effects may limit their usefulness.

1. Sternbach H. The serotonin syndrome. *Am J Psychiatry* 1991; 148: 705–13.
2. Sporer KA. The serotonin syndrome: implicated drugs, pathophysiology and management. *Drug Safety* 1995; 13: 94–104.
3. Corkeron MA. Serotonin syndrome—a potentially fatal complication of antidepressant therapy. *Med J Aust* 1995; 163: 481–2.
4. Brown TM, *et al.* Pathophysiology and management of the serotonin syndrome. *Ann Pharmacother* 1996; 30: 527–33.
5. Gillman PK. Serotonin syndrome: history and risk. *Fundam Clin Pharmacol* 1998; 12: 482–91.
6. *Gillman PK. The serotonin syndrome and its treatment. J Psychopharmacol* 1999; 13: 100–109.
7. Mason PJ, *et al.* Serotonin syndrome. Presentation of 2 cases and review of the literature. *Medicine (Baltimore)* 2000; 79: 201–9.
8. Birmes P, *et al.* Serotonin syndrome: a brief review. *Can Med Assoc J* 2003; 168: 1439–42.
9. Bilj D. The serotonin syndrome. *Neth J Med* 2004; 62: 309–13.
10. Boyer EW, Shannon M. The serotonin syndrome. *N Engl J Med* 2005; 352: 1112–20. Correction. *ibid.* 2007; 356: 2437.
11. Livingston MG. Interactions with selective MAOIs. *Lancet* 1995; 345: 533–4.

Treatment of Adverse Effects

In cases of overdosage with MAOIs the benefit of gastric decontamination is uncertain; however, in patients who present within 1 hour activated charcoal may be given orally, or, in potentially life-threatening cases, the stomach may be emptied by lavage. Management then largely involves intensive symptomatic and supportive therapy with particular attention being given to CNS effects, raised body temperature (which may develop into malignant hyperthermia), and cardiovascular effects. Delayed effects may develop some time after the overdose even in patients who are initially asymptomatic, and therefore prolonged monitoring for at least 12 hours is warranted. Other drugs taken with an overdose of MAOIs may complicate the features and result in the need for an even longer period of monitoring. Special care is needed with any drug therapy used in the management of MAOI overdosage in view of the many known interactions which occur with this class of drugs.

Muscle spasm, agitation, and convulsions should be treated with diazepam. Severe neuromuscular irritability may call for the use of a competitive neuromuscular blocker such as pancuronium and intubation with assisted ventilation. Hyperthermia may be a particular problem; if simple antipyretics such as paracetamol and external cooling measures fail a competitive neuromuscular blocker has often been advocated; dantrolene has also been suggested.

Hypotension, which is a fairly common feature, should be managed by intravenous fluid therapy and volume expansion; vasopressors should be avoided. Conversely, a hypertensive crisis may occasionally occur after an overdose with MAOIs and can be managed with phentolamine given by slow intravenous injection. Persistent hypertension may respond to intravenous nitrates.

Precautions

Phenelzine and other MAOIs should not be given to patients with liver disease or a history of abnormal liver function tests, or, because of their effects on blood pressure, to patients with congestive heart failure, cerebrovascular disease, or phaeochromocytoma. (Blood pressure should be monitored in all patients.) MAOIs should be avoided or only used with great caution in patients with blood disorders or cardiovascular disease, and in elderly or agitated patients who may be particularly susceptible to their adverse effects. They should be given with caution to epileptic patients. Caution has also been advised in diabetic patients because of conflicting evidence about whether glucose metabolism is altered or requirements for hypoglycaemics changed. MAOIs should be used with caution in patients with hyperthyroidism because of increased sensitivity to pressor amines.

Patients should be closely monitored during early antidepressant therapy until significant improvement in depression occurs because suicide is an inherent risk in depressed patients. For further details, see under Depression, p. 398.1. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when

treating patients with depression should therefore be observed when treating patients with other disorders.

Mania may be precipitated if MAOIs are used for the depressive component of bipolar disorder, and they are not usually indicated; similarly psychotic symptoms may be aggravated if they are used for a depressive component of schizophrenia.

MAOIs have a prolonged action so patients should not take any of the foods or drugs known to cause reactions (see Interactions, p. 446.3 and p. 447.1) for at least 14 days after stopping treatment. A similar drug-free period has been advised before any patient undergoes surgery since it may involve the use of drugs that can interact with MAOIs, although not all agree that this is necessary; caution has been advised in patients requiring MAOIs with ECT; for further details see under Anaesthesia, p. 446.1. Patients should carry cards giving details of their MAOI therapy; they and their relatives should be fully conversant with the implications of food and drug interactions and the precautions to be taken.

Patients liable to take charge of vehicles or other machinery should be warned that MAOIs may modify behaviour and state of alertness. Patients affected by drowsiness should not drive or operate machinery.

MAOIs should be withdrawn gradually to reduce the risk of withdrawal symptoms (see p. 446.2).

For the precautions to be observed with reversible inhibitors of monoamine oxidase A (RIMAs), see Moclobemide, p. 437.3.

Anaesthesia. The considerations given to patients taking tricyclic antidepressants before receiving anaesthesia for ECT or surgery (see Amitriptyline, p. 404.3) are also generally applicable to patients being treated with MAOIs; licensed product information for phenelzine also warns that transient respiratory and cardiovascular depression following ECT have been reported. The interactions of other drugs with MAOIs may be more numerous or more severe than those with tricyclics and the interaction with pethidine should not be forgotten.

A review[1] of the potential problems of anaesthesia in patients receiving MAOIs considered that stopping MAOIs about 2 weeks before anaesthesia was unreasonable, as there were safe and suitable anaesthetics available, although the dangers of sympathetic overactivity must always be remembered. This view, that it is safe to continue MAOIs throughout the period of anaesthesia, ECT, and surgery, is also held by others[2-4] although some disagree.[5]

Regardless of any decision, the anaesthetist should be informed of all drugs that the patient is or has been taking; this is particularly important when emergency surgery is required in a patient receiving MAOI therapy.

- It has been stated[1] that the interaction between MAOIs and *opioid analgesics* has two distinct forms: an excitatory form [serotonin syndrome—see p. 443.2]; and a depressive form consisting of respiratory depression, hypotension, and coma as a result of the inhibition of hepatic microsomal enzymes by the MAOI leading to accumulation of free opioid analgesic. *Pethidine* use during anaesthesia has elicited the excitatory response, which has frequently been severe and often fatal. For this reason, pethidine should never be given to patients receiving MAOIs. *Morphine* does not block neuronal serotonin uptake but its narcotic effects may be potentiated in the presence of MAOIs and a single case report of the depressive type of reaction has been described. Thus, morphine is the opioid analgesic of choice but must be given in reduced dosage and the dosage carefully titrated against clinical response. *Papaveretum* would appear to have no advantage over morphine. Although interactions of MAOIs with *pentazocine* have occurred in *animals*, it is not clear if this occurs in man. *Methadone* has been used in a patient without mishap and there is also anecdotal evidence to support the safety of *fentanyl*. A case report[6] described the successful use of *alfentanil* (with propofol and atracurium) mentioning that this was the first report of such use in patients receiving MAOIs. A further case report[7] has also described the safe use of alfentanil (with propofol and suxamethonium) for anaesthesia during ECT in 2 patients taking phenelzine. *Remifentanil* has also been used safely as part of an anaesthetic regimen (with sevoflurane, vecuronium, and isoflurane) in a patient also taking phenelzine.[8] In another case[9] a patient underwent successful anaesthesia with *sufentanil* (with thiopental, lidocaine, and vecuronium) while continuing to take an MAOI (tranylcypromine) as well as a tricyclic antidepressant (imipramine) and lorazepam.
- With regard to induction agents,[1] the use of *ketamine* in patients receiving MAOIs should be avoided on theoretical grounds, although no interactions have been reported. Potentiation of *barbiturates* may be expected.
- With neuromuscular blockers, phenelzine has been shown to decrease plasma cholinesterase concentrations and there have been case reports of a prolonged effect with *suxamethonium*; additionally this prolongation of the effect of suxamethonium may lead to apnoea and modification of the convulsion during ECT. However, a small case series of 4 patients taking tranylcypromine while undergoing ECT treatment (with suxamethonium as the neuromuscular blocker) found no difference in seizure length when compared with previous ECT courses when the patients were not taking an MAOI.[4] There may be a theoretical hazard with *pancuronium* since it releases stored adrenaline (although its use has been advocated in the treatment of symptoms of overdosage with MAOIs, see Treatment of Adverse Effects, p. 443.3), but *alcuronium*, *atracurium*, or *vecuronium* would all appear to be suitable alternatives.[1]
- *Enflurane*, *halothane*, *isoflurane*, and *nitrous oxide* are all safe in the presence of MAOIs, although there is a theoretical possibility of an increased risk of hepatic damage with halothane.
- *Indirect-acting sympathomimetics* pose the risk of a serious and possibly lethal hypertensive interaction but *direct-acting sympathomimetics*, such as *adrenaline*, *isoprenaline*, and *noradrenaline*, are reliable vasopressors in the presence of MAOIs although great care should be taken with their use because of enhanced receptor sensitivity.

1. Stack CG, *et al.* Monoamine oxidase inhibitors and anesthesia a review. *Br J Anaesth* 1988; 60: 222–7.
2. Hirshman CA, Lindeman K. MAO inhibitors: must they be discontinued before anesthesia? *JAMA* 1988; 260: 3507–8.
3. Hirshman CA, Lindeman KS. Anesthesia and monoamine oxidase inhibitors. *JAMA* 1989; 261: 3407–8.
4. Dolenc TJ, *et al.* Electroconvulsive therapy in patients taking monoamine oxidase inhibitors. *J ECT* 2004; 20: 258–61.
5. Gevirtz C. Anesthesia and monoamine oxidase inhibitors. *JAMA* 1989; 261: 3407.
6. Powell H. Use of alfentanil in a patient receiving monoamine oxidase inhibitor therapy. *Br J Anaesth* 1990; 64: 528.
7. Beresford BJ, *et al.* Combination propofol-alfentanil anesthesia for electroconvulsive therapy in patients receiving monoamine oxidase inhibitors. *J ECT* 2004; 20: 120–2.
8. Ure DS, *et al.* Safe use of remifentanil in a patient treated with the monoamine oxidase inhibitor phenelzine. *Br J Anaesth* 2000; 84: 414–16.
9. O'Hara JF, *et al.* Sufentanil-isoflurane-nitrous oxide anesthesia for a patient treated with monoamine oxidase inhibitor and tricyclic antidepressant. *J Clin Anesth* 1995; 7: 148–50.

Children. Phenelzine is not recommended for the treatment of depression in children and adolescents less than 16 years of age. In addition, other antidepressants have been shown to increase the risk of suicidal thoughts and behaviour in such patients (see Effects on Mental State, under Fluoxetine, p. 420.2).

Driving. While affective disorders probably impair driving skill,[1,2] treatment with antidepressant drugs may also be hazardous,[1] although patients may be safer drivers with medication than without.[2] Impairment of performance is largely related to sedative properties and some MAOIs can adversely affect psychomotor performance.[1,2]

In the UK, the Driver and Vehicle Licensing Authority (DVLA) considers that all drugs acting on the CNS can impair alertness, concentration, and driving performance, particularly at the start of treatment or when the dose is increased;[3] driving must cease if patients are adversely affected. Patients with severe depressive illnesses complicated by significant memory or concentration problems, agitation, behavioural disturbances, or suicidal thoughts should cease driving pending the outcome of medical enquiry.

1. Ashton H. Drugs and driving. *Adverse Drug React Bull* 1983; 98: 360–3.
2. Cremona A. Mad drivers: psychiatric illness and driving performance. *Br J Hosp Med* 1986; 35: 193–5.
3. Driver and Vehicle Licensing Agency. For medical practitioners: at a glance guide to the current medical standards of fitness to drive (issued November 2013). Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/258991/aagv1.pdf (accessed 20/11/13)

ECT. For comments concerning precautions in patients receiving ECT, see under Anaesthesia, above.

Surgery. For comments regarding precautions in patients undergoing surgery, see under Anaesthesia, above.

Withdrawal. Suddenly stopping antidepressant therapy after regular use for 8 weeks or more can precipitate withdrawal symptoms which may be very severe.

Symptoms associated with withdrawal of MAOIs[1,2] include gastrointestinal disturbances and generalised somatic symptoms such as nausea and vomiting, anorexia, chills, headache, and giddiness; sleep disturbances characterised by insomnia, severe nightmares, and somnolence; and CNS symptoms including panic, anxiety, restlessness, agitation, cognitive impairment, mood swings, depression and suicidal ideation, hypomania, delusions, and hallucinations. Some of the above may be controlled by restarting the MAOI in low doses, but the best management is considered to be prevention by gradually stopping the drug.[2] The *BNF* recommends reducing the dose over a period of 4 weeks, or as much as 6 months in patients who have been receiving long-term maintenance therapy.

The pathophysiology of the MAOI withdrawal syndrome is not fully known, although it has been hypothesised that some of the symptoms represent adrenergic hyperactivity produced by the release of excessive amounts of dopamine and noradrenaline.[2]

With the exception of tranylcypromine, the withdrawal syndrome of MAOIs is not a consequence of drug dependence.[1] Tranylcypromine has been reported to produce dependence and tolerance in patients receiving high doses irrespective of whether or not they had a history of substance abuse. Tranylcypromine is similar in structure to amfetamine, which may be responsible for its addictive properties.[1]

1. Anonymous. Problems when withdrawing antidepressives. *Drug Ther Bull* 1986; 24: 29–30.
2. Dilsaver SC. Withdrawal phenomena associated with antidepressant and antipsychotic agents. *Drug Safety* 1994; 10: 103–14.

Interactions of MAOIs with Foods

A major disadvantage of MAOIs such as phenelzine is that by inhibiting monoamine oxidase they cause an accumulation of amine neurotransmitters. This means that the pressor effects of *tyramine*, which occurs in several common foods and is also metabolised by monoamine oxidase, can be dangerously enhanced. Reactions to foods rich in pressor amines such as tyramine can therefore occur in patients being treated with MAOIs, producing hypertensive crises. Cheese, especially aged or matured cheeses, meat or yeast extracts, pickled herrings, sauerkraut, dry sausage, smoked foods, and broad bean pods have caused such reactions. Patients should be warned not to eat any of these foods while being treated with an MAOI and for at least 14 days after its discontinuation. Some foods will only cause a reaction if large amounts are eaten, and foods may vary in tyramine content depending upon methods of manufacture and storage. Any protein-containing food such as meat, fish, or game subject to hydrolysis, fermentation, pickling, smoking, or spoilage could contain tyramine derived from tyrosine as a result of these processes or of deterioration. Patients taking MAOIs should therefore be advised to eat protein-containing foods only if fresh.

Alcoholic beverages, including wines, beers, and drinks that are de-alcoholised or are low in alcohol, contain variable amounts of tyramine and are best avoided.

The above dietary restrictions that need to be followed with MAOIs may be less stringent for reversible inhibitors of monoamine oxidase type A (RIMAs) such as moclobemide (see p. 438.1), although licensed product information recommends that since some patients may be especially sensitive to tyramine, consumption of large amounts of tyramine-rich food should be avoided.

MAOIs can, when taken with certain foodstuffs, cause a potentially fatal hypertensive reaction. This effect is accepted and well documented and has led to the publication of many lists of prohibited foods and drinks. However, the dangers of the interaction may have been slightly overemphasised or exaggerated and published lists may have been overinclusive;[1-3] this may have led to reduced compliance in many patients.

A review and discussion[1] of the MAOI interaction with tyramine made the following observations and recommendations:

- the hyperadrenergic state resulting from this interaction consisted of three syndromes although significant overlap between them existed: paroxysmal headache of great severity; cardiovascular symptoms with paroxysmal hypertension; and intracerebral haemorrhage and death
- the most common offending drug reported had been tranylcypromine at doses of 20 to 50 mg daily although a few reports had involved phenelzine
- only 4 foodstuffs clearly warranted total prohibition: aged cheese, pickled herring or smoked fish, concentrated yeast extracts, and broad bean pods
- the ingestion of cheese was said to have been associated with 80% of all case reports and with virtually all fatalities. It was agreed that aged cheese should not be permitted, although cottage and cream cheese required no restriction. There was less agreement concerning dairy products such as yogurt and sour cream and it was suggested that limited amounts were permissible
- pickled herring or smoked fish were to be avoided because of several well-documented cases of hypertensive crisis as well as detection of high levels of tyramine. Any meat may become dangerous unless consumed while fresh as tyramine is formed from bacterial protein degradation
- concentrated yeast extracts have a significant tyramine content and yeast vitamin supplements may also constitute a hazard; baker's yeast was considered to be safe

- broad bean pods contain dopamine although the beans themselves were stated to have little pressor activity and carried no prohibition
- other foods which had been reported to have caused a hypertensive reaction but for which these authors considered that there was insufficient evidence to warrant dietary restriction were chocolate and caffeine-containing beverages, soy sauce, fresh fish, wild game, and fruits although caution was necessary with avocados and bananas.

Other reviews of foods[2,4,5] give broadly similar recommendations.

The consumption of alcoholic beverages, and in particular Chianti wine, has frequently been advised against. However, sources have differed on whether particular types of drink (white wine, red wine, spirits, or beer) are safe or not. A study[6] showed no significant differences in mean free tyramine concentration between white wine, red wine, Chianti, and beer although within each category of wine there could be up to a fiftyfold variation even if from the same grape stock. Mention has also been made[7,8] that alcohol-free or low-alcohol beers are likely to contain similar amounts of tyramine to alcoholic beers. The consumption of alcoholic drinks with MAOIs still appears to be controversial with some advocating total abstinence while others permit a modest intake.

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Interactions of MAOIs with other Drugs

MAOIs inhibit the metabolism of some *amine drugs* (notably indirect-acting sympathomimetics), which can lead to dangerous enhancement of their pressor effects. MAOIs also inhibit other drug-metabolising enzymes and are therefore responsible for a large number of *other drug interactions*. Moreover, they have an additive effect with serotonergic drugs which may result in the *serotonin syndrome* (see under Adverse Effects, p. 443.2). As in the case of foods, the danger of an interaction persists for at least 14 days after treatment with an MAOI has been stopped.

Severe hypertensive reactions due to enhancement of pressor activity have followed the use of sympathomimetics such as *amfetamines, dopamine, ephedrine, levodopa, phenylephrine, phenylpropanolamine,* and *pseudoephedrine*. Reactions may also follow the use of anorectics and stimulants with sympathomimetic activity such as *fenfluramine, methylphenidate, pemoline,* and *phentermine*. There have been case reports of fatalities in patients who took cough preparations containing *dextromethorphan*. There is no clinical evidence of dangerous interactions between *local anaesthetic preparations containing adrenaline* and MAOIs although they could occur if the preparation was accidentally given into a vein. Significant rises in blood pressure have been reported after the use of *buspirone* with MAOIs.

Inhibition of drug-metabolising enzymes by MAOIs may enhance the effects of *barbiturates* and possibly other *hypnotics, hypoglycaemics,* and possibly *antimuscarinics*. *Alcohol* metabolism may be altered and its effects enhanced; see also under Interactions of MAOIs with Foods, p. 444.3. Licensed product information suggests that the effects of various classes of *antihypertensives* may be enhanced by MAOIs, including *ACE inhibitors, beta blockers, calcium-channel blockers* and *thiazides*, with the potential for hypotension, although published evidence for most of these seems to be scanty. Some antihypertensives with direct actions on the sympathetic nervous system, such as *guanethidine, indoramin, methyldopa,* and, historically, *reserpine,* are suggested to be contra-indicated or used with great caution; both hypotensive and hypertensive reactions have been suggested.

Giving *pethidine* and possibly other *opioid analgesics* to patients taking an MAOI has also been associated with very severe and sometimes fatal reactions. When it is considered essential to use an opioid analgesic, one that does not inhibit serotonin reuptake should be chosen. The use of opioid analgesics and other drugs used during general anaesthesia in patients continuing to take MAOIs is discussed in Anaesthesia under Precautions, p. 444.1.

Clozapine may enhance the CNS effects of MAOIs.

Although different antidepressants have been used together under expert supervision in refractory cases of depression, severe adverse reactions may occur. MAOIs should not generally be given to patients receiving *tricyclic antidepressants, SSRIs, serotonin and noradrenaline reuptake inhibitors (SNRIs), bupropion, mirtazapine, nefazodone, reboxetine,* or *trazodone*. An appropriate drug-free interval should elapse between stopping one type of antidepressant and starting another. An MAOI should not be started until at least 1 or 2 weeks after stopping a tricyclic antidepressant. For the tricyclic antidepressants clomipramine and imipramine a drug-free interval of 3 weeks should be allowed. For an SSRI, an SNRI, reboxetine, nefazodone, trazodone, or any related antidepressant the drug-free interval should be at least one week; in the case of bupropion, mirtazapine, and the SSRI sertraline, the interval is extended to 2 weeks, and for fluoxetine, at least 5 weeks because of their longer half-lives. Conversely, 2 weeks should elapse between stopping MAOI therapy and starting patients on a tricyclic antidepressant (3 weeks in the case of clomipramine or imipramine), an SSRI, an SNRI, bupropion, mirtazapine, reboxetine, or any related antidepressant. For further warnings on the combined use of antidepressants, see p. 447.2. Interactions can also occur between MAOIs themselves.

For details of the less severe interactions associated with reversible inhibitors of monoamine oxidase A (RIMAs), see Interactions of Moclobemide, p. 438.1.

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Antidepressants. Combination therapy with differing classes of antidepressants may result in interactions or enhanced adverse reactions such as the serotonin syndrome (see under Adverse Effects, p. 443.2). Despite these drawbacks certain combinations of drugs have been found to be beneficial in the treatment of drug-resistant depression, although others are considered unsuitable; absence of information documenting unsuitability or hazard does not necessarily imply that the two drugs may be used safely together but may merely reflect an untried combination. Because combination therapy poses increased risks it should be used only under expert supervision.

- MAOIs have been used fairly frequently under expert supervision with tricyclics in refractory depression and it has been stated[1] that the risk of serious problems in combining *tricyclic antidepressant and MAOI* antidepressant therapy is almost exclusively limited to sequential prescribing, in particular the addition of a tricyclic to established treatment with an MAOI. The recommended procedure was said to be to allow a drug-free interval of at least one week and then to start both drugs together at a low dosage. The dosage of both drugs is then gradually increased to around half that normally prescribed for the drugs when given on their own. The dietary restrictions for MAOIs alone apply equally to the combined antidepressant regimen.
  Amitriptyline and trimipramine were considered to be the tricyclics least likely to produce adverse effects with MAOIs, while phenelzine and isocarboxazid were the safest MAOIs. In contrast, clomipramine (a tricyclic with serotonin reuptake inhibiting activity) and imipramine are unsuitable for such use.[2,3] The combination of clomipramine with tranylcypromine is particularly dangerous. Symptoms suggestive of the serotonin syndrome occurred in an elderly patient due to an interaction between clomipramine and moclobemide, a reversible inhibitor of monoamine oxidase type A (RIMA).[4] Two fatalities due to serotonin syndrome have been reported after overdosage with clomipramine and moclobemide.[5] The syndrome has also developed when a patient was switched from clomipramine to moclobemide with no suitable drug-free interval.[6] A 39-year-old woman developed the serotonin syndrome while taking imipramine with moclobemide, although it was suggested that an excessive dose of the tricyclic may have been ingested accidentally.[7]
- The UK CSM has warned[8] that enhanced serotonergic effects may result from using *SSRIs with MAOIs* or other antidepressants. Although such an enhancement may be beneficial in some instances it can produce a life-threatening serotonin syndrome. Such reactions were later reported in patients taking sertraline with MAOIs.[9-11] Three fatalities due to serotonin syndrome have been reported after overdosage with citalopram and moclobemide.[5] A case of serotonin syndrome has been reported after switching from fluoxetine to moclobemide with no suitable drug-free interval.[6] Some authors[12] have reported good efficacy and tolerability with combinations of moclobemide and SSRIs. However, others[13] reported a high rate of adverse events although, as significant improvement in depressive symptoms was seen in some patients, it was suggested that giving moclobemide with SSRIs deserved consideration as an option for the treatment of refractory depression.
- Combination therapy with a *tricyclic antidepressant and an SSRI* has sometimes been used to treat resistant depression. Fluvoxamine[14] and fluoxetine[15] have been reported to increase plasma concentrations of the tricyclic, although to varying degrees. Fluoxetine has been reported to produce three- to fourfold increases in plasma concentrations of desipramine and imipramine. Fluvoxamine has a minimal effect on desipramine plasma levels but produces a three- to fourfold increase in concentrations of imipramine.[16] Plasma-desipramine concentrations are elevated threefold by paroxetine but increases of only 30% are produced by sertraline.[16] However, an inadequate interval of one day between stopping desipramine and starting paroxetine resulted in a case of serotonin syndrome.[6] Serotonin syndrome has also been reported[17] in a patient who received paroxetine and imipramine and in another given sertraline and amitriptyline.[18] A threefold increase in concentrations of trimipramine resulting in sedation and orthostatic hypotension has been reported[19] in 2 patients also given paroxetine. Additionally, norfluoxetine, the active metabolite of fluoxetine, has a long half-life and is responsible for the continuing interaction with tricyclics for several days or weeks after fluoxetine has been withdrawn. Citalopram was reported to have no effect on plasma-tricyclic concentrations in a patient although antidepressant effects were augmented.[20]
- *Lithium* and *tryptophan* have been used to augment the effect of other antidepressants in refractory depression. Phenelzine has been used successfully with lithium and tryptophan[21] in patients with treatment-resistant chronic depression although such a regimen has probably been used less since the reports of the eosinophilia-myalgia syndrome associated with tryptophan (see p. 455.3). There have, however, been several case reports of reactions similar to the serotonin syndrome in patients receiving MAOIs with tryptophan.[22,23]
  Although lithium is often added to tricyclic antidepressant therapy in patients with refractory depression, epileptic seizures have been reported in a patient receiving amitriptyline when lithium was added.[24] Serotonin syndrome has been reported[25] in a patient given clomipramine and lithium. Severe neurotoxicity has been reported[26,27] in some patients receiving lithium and tricyclic or tetracyclic antidepressants; adverse effects included tremor, memory impairment, disorganised thinking, and auditory hallucinations. One manufacturer of lithium preparations also reports symptoms of nephrogenic diabetes in patients receiving these combinations.
  By 1989 the CSM had received 19 reports of adverse reactions in patients treated with fluvoxamine and lithium: 5 reports concerned convulsions and 1 hyperthermia.[8] Tremor has been reported when lithium was given with paroxetine,[28] and in general the risk of CNS toxicity is increased when lithium is given with fluoxetine, fluvoxamine, paroxetine, or sertraline. There has been a report[29] of a fatality when fluoxetine was replaced by tranylcypromine and tryptophan with no drug-free period; the patient was also receiving other drugs concurrently.
- Use of the serotonin and noradrenaline reuptake inhibitor (SNRI) *venlafaxine with tricyclic antidepressants* has been associated with increased antimuscarinic adverse effects.[30,31] Seizures have also been reported with venlafaxine and trimipramine[32] and serotonin syndrome developed in a patient given amitriptyline, venlafaxine, and pethidine.[33] Similar antimuscarinic adverse effects have occurred in patients given *venlafaxine and the SSRI* fluoxetine;[31] serotonin syndrome has been reported in a patient who received venlafaxine and paroxetine.[6] The use of *venlafaxine with MAOIs* is contra-indicated by the manufacturers of venlafaxine because of the risk of life-threatening adverse reactions. Serious adverse reactions have been reported when venlafaxine was combined with isocarboxazid,[34] moclobemide,[6] phenelzine,[35] or tranylcypromine.[36]
- *Trazodone* is chemically unrelated to other antidepressants but does have serotonergic actions. Serotonin syndrome has been reported when trazodone was combined with the SSRI *paroxetine*.[37]
- Serotonin syndrome has been reported[38] in a patient who took *nefazodone with fluoxetine*. There has been a similar report[39] in a patient who received *paroxetine* 2 days after finishing gradual withdrawal from over 6 months of treatment with nefazodone.
- Symptoms resembling serotonin syndrome have occurred in a patient taking the noradrenergic and specific serotonergic antidepressant, *mirtazapine* with *fluvoxamine*;[40] another report[41] suggests that the plasma concentrations of mirtazapine may be increased as much as fourfold by fluvoxamine.
- Raised *nortriptyline* levels were noted in a patient also taking *bupropion*; the effect recurred on rechallenge.[42]

- In a report[43] of an interaction between *St John's wort* and *paroxetine*, a 50-year-old woman was found incoherent, groggy, and slow-moving after self-administering a single dose of paroxetine while taking St John's wort; recovery was uneventful. Use of St John's wort with the SSRIs may potentiate their serotonergic effects and increase the incidence of adverse reactions. The CSM has advised that patients should stop taking St John's wort if treatment with an SSRI is necessary.[44] Symptoms of serotonin syndrome have also been reported when St John's wort and *nefazodone* were taken.[45]

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Antiepileptics. Antidepressants may antagonise the activity of antiepileptics by lowering the convulsive threshold.

UK licensed product information states that *carbamazepine* should be avoided with or within 2 weeks of a MAOI because of structural similarities with the tricyclic antidepressants; however, published evidence of adverse interactions is lacking. There is also a theoretical possibility of a similar interaction with *oxcarbazepine*.

Antimigraine drugs. For the effect of MAOIs on *serotonin (5-HT$_1$) agonists*, see under Sumatriptan, p. 681.3.

Antineoplastics. For the effect when MAOIs are used with *altretamine*, see p. 739.1.

Dopaminergics. For the effect of MAOIs with *amantadine*, see p. 893.2, with *levodopa*, see p. 908.2, and with *selegiline*, see p. 917.1.

General anaesthetics. The problems that may occur when patients receiving MAOIs are also given general anaesthetics are discussed under Anaesthesia in Precautions, p. 444.1.

Ginseng. There have been 2 reports[1,2] of adverse effects, including headaches, insomnia, tremulousness, and irritability when ginseng was taken with phenelzine.

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Histamine. For the effect of MAOIs on histamine given exogenously, see p. 2525.3.

Insulin. For the effect of MAOIs on insulin, see p. 488.3.

Neuromuscular blockers. For the effects of MAOIs on the action of *suxamethonium*, see p. 2040.1. Problems that may be encountered with MAOIs and neuromuscular blockers used during anaesthesia are discussed under Anaesthesia in Precautions, p. 444.1.

Opioid analgesics. The problems that may occur with MAOIs and opioid analgesics used during anaesthesia are discussed under Anaesthesia in Precautions, p. 444.1.

Respiratory stimulants. For the effect of MAOIs with *doxapram*, see p. 2322.1.

Pharmacokinetics

Phenelzine is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur 2 to 4 hours after ingestion. It is metabolised in the liver and is excreted in the urine almost entirely in the form of metabolites.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Nardil; *Belg.*: Nardelzine; *Canad.*: Nardil; *Irl.*: Nardil†; *Ital.*: Margyl; *NZ*: Nardil; *UK*: Nardil; *USA*: Nardil.

Pharmacopoeial Preparations
BP 2014: Phenelzine Tablets;
USP 36: Phenelzine Sulfate Tablets.

Pipofezine Hydrochloride *(rINNM)*

Hidrocloruro de pipofezina; Pipofézine, Chlorhydrate de; Pipofezine Dihydrochloride; Pipofezini Hydrochloridum; Пипофезина Гидрохлорид.

5-Methyl-3-(4-methyl-1-piperazinyl)-5*H*-pyridazino[3,4-*b*][1,4]benzoxazine dihydrochloride.

$C_{16}H_{19}N_5O,2HCl$=370.3

CAS — 24886-52-0 (pipofezine); 24853-80-3 (pipofezine hydrochloride).

Profile

Pipofezine is a tricyclic antidepressant (see Amitriptyline, p. 401.1).

In the treatment of depression (p. 398.1) pipofezine is usually given orally as the hydrochloride although doses are expressed in terms of the base; pipofezine hydrochloride 31.1 mg is equivalent to about 25 mg of pipofezine. An initial dose of 25 to 50 mg daily, given in 2 divided doses, is gradually increased as tolerated to a usual total daily dose of 150 to 200 mg given in 3 or 4 divided doses. If necessary, a maximum of 500 mg may be given daily in divided doses. For maintenance a modified-release preparation providing pipofezine 150 mg may be given once or twice daily.

Pipofezine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Rus.*: Azaphen (Азафен).

Pirlindole *(rINN)*

Pirlindol; Pirlindolum; Пирлиндол.

2,3,3a,4,5,6-Hexahydro-8-methyl-1*H*-pyrazino[3,2,1-*jk*]carbazole.

$C_{15}H_{18}N_2$=226.3

CAS — 60762-57-4.

UNII — V39YPH45FZ.

Profile

Pirlindole has been given orally in the treatment of depression.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Port.*: Implementor; *Rus.*: Normazidol (Нормазидол); Pyrazidol (Пиразидол); *Ukr.*: Normazidol (Нормазідол)†.

Protriptyline Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de protriptilina; MK-240; Protriptilina, hidrocloruro de; Protriptyline, chlorhydrate de; Protriptylini Hydrochloridum; Протриптилина Гидрохлорид.

3-(5*H*-Dibenzo[*a*,*d*]cyclohept-5-enyl)propyl(methyl)amine hydrochloride.

$C_{19}H_{21}N,HCl$=299.8

CAS — 438-60-8 (protriptyline); 1225-55-4 (protriptyline hydrochloride).

ATC — N06AA11.

ATC Vet — QN06AA11.

UNII — 44665V0008.

Pharmacopoeias

In *Br.* and *US.*

BP 2014: (Protriptyline Hydrochloride). A white to yellowish-white, odourless or almost odourless, powder. Freely soluble in water, in alcohol, and in chloroform; practically insoluble in ether. A 1% solution in water has a pH of 5.0 to 6.5.

USP 36: (Protriptyline Hydrochloride). A white to yellowish powder. Is odourless or has not more than a slight odour. Soluble 1 in 2 of water, 1 in 3.5 of alcohol, and 1 in 2.5 of chloroform; practically insoluble in ether. pH of a 1% solution in water is between 5.0 and 6.5.

Uses and Administration

Protriptyline is a dibenzocycloheptatriene tricyclic antidepressant with actions and uses similar to those of amitriptyline (p. 401.1). It is considerably less sedative than other tricyclics and may have a stimulant effect, thus making it particularly suitable for apathetic and withdrawn patients; its antimuscarinic effects are moderate.

In the treatment of depression, protriptyline hydrochloride is given in oral doses of 5 to 10 mg three or four times daily. It has been suggested that, because of its potential stimulant activity, any dosage increases should be added to the morning dose first and if insomnia occurs the last dose should be given no later than mid-afternoon. Higher doses of up to 60 mg daily may be required in severely depressed patients. A suitable initial dose for adolescents and the elderly is 5 mg three times daily; close monitoring of the cardiovascular system has been recommended if the dose exceeds a total of 20 mg daily in elderly subjects.

Protriptyline should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p. 402.3).

Since protriptyline may have some stimulant properties anxiety and agitation can occur more frequently; cardiovascular effects such as tachycardia and orthostatic hypotension may also be more frequent than with other tricyclics. Photosensitivity rashes have been noted more often with protriptyline than with other tricyclic antidepressants and patients taking it should avoid direct sunlight.

Interactions

For interactions associated with tricyclic antidepressants, see Amitriptyline, p. 406.1.

Pharmacokinetics

Protriptyline is well but slowly absorbed after oral doses: peak plasma concentrations occur only after 8 to 12 hours.

Paths of metabolism of protriptyline include *N*-oxidation and hydroxylation. Protriptyline is excreted in the urine, mainly in the form of its metabolites, either free or in conjugated form.

Protriptyline is widely distributed throughout the body and extensively bound to plasma and tissue protein. Protriptyline has been estimated to have a very prolonged elimination half-life ranging from 55 to 198 hours, which may be further prolonged in overdosage.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Vivactil.

Pharmacopoeial Preparations
BP 2014: Protriptyline Tablets;
USP 36: Protriptyline Hydrochloride Tablets.

Reboxetine Mesilate *(BANM, rINNM)*

FCE-20124 (reboxetine or reboxetine mesilate); Mesilato de reboxetina; PNU-155950E; Reboxetina, mesilato de; Réboxétine, Mésilate de; Reboxetine Mesylate (USAN); Reboxetine Mesylate; Reboxetini Mesilas; Ребоксетина Мезилат.

(±)-(2*RS*)-2-[(α*RS*)-α-(2-Ethoxyphenoxy)benzyl]morpholine methanesulphonate.

$C_{19}H_{23}NO_3.CH_4O_3S$=409.5

CAS — 71620-89-8; 98769-81-4 (both reboxetine); 98769-82-5; 98769-84-7 (both reboxetine mesilate).

ATC — N06AX18.

ATC Vet — QN06AX18.

UNII — L94J81YNNY.

Uses and Administration

Reboxetine is a selective and potent inhibitor of the reuptake of noradrenaline; it also has a weak effect on serotonin reuptake. Reboxetine has no significant affinity for muscarinic receptors. It is given orally as the mesilate for the treatment of depression with doses expressed as the base; reboxetine mesilate 5.2 mg is equivalent to about 4 mg of reboxetine. The dose of reboxetine is 4 mg twice daily, which may be increased after 3 to 4 weeks, if necessary, to 10 mg daily; the maximum daily dose should not exceed 12 mg. Reduced doses should be given in hepatic or renal impairment, see p. 449.1. Reboxetine is not recommended for use in elderly patients (see under Precautions, p. 449.3).

Antidepressants should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Administration in hepatic or renal impairment. Lower initial oral doses equivalent to 2 mg of reboxetine twice daily are recommended by UK licensed product information in hepatic or renal impairment; doses may be increased thereafter according to tolerance.

Anxiety disorders. Reboxetine has been tried with some benefit in panic disorder (p. 1029.1) although it may be less effective than the SSRIs.

References.

1. Versiani M, *et al.* Reboxetine, a selective norepinephrine reuptake inhibitor, is an effective and well-tolerated treatment for panic disorder. *J Clin Psychiatry* 2002; 63: 31–7.
2. Seedat S, *et al.* Reboxetine and citalopram in panic disorder: a single-blind, cross-over, flexible-dose pilot study. *Int Clin Psychopharmacol* 2003; 18: 279–84.
3. Bertani A, *et al.* Comparison of the treatment with paroxetine and reboxetine in panic disorder: a randomized, single-blind study. *Pharmacopsychiatry* 2004; 37: 206–10.

Depression. As discussed on p. 398.1, there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effect profile. Reboxetine, a selective inhibitor of noradrenaline reuptake, has a slightly different biochemical profile from both the tricyclics and the SSRIs; however, like the SSRIs, reboxetine appears to have fewer unpleasant adverse effects and to be safer in overdosage in comparison with the older tricyclics.

References.

1. Versiani M, *et al.* Reboxetine, a unique selective NRI, prevents relapse and recurrence in long-term treatment of major depressive disorder. *J Clin Psychiatry* 1999; 60: 400–406.
2. Holm KJ, Spencer CM. Reboxetine: a review of its use in depression. *CNS Drugs* 1999; 12: 65–83.
3. Scates AC, Doraiswamy PM. Reboxetine: a selective norepinephrine reuptake inhibitor for the treatment of depression. *Ann Pharmacother* 2000; 34: 1302–12.
4. Versiani M, *et al.* Double-blind, placebo-controlled study with reboxetine in inpatients with severe major depressive disorder. *J Clin Psychopharmacol* 2000; 20: 28–34.
5. Ferguson JM, *et al.* Effects of reboxetine on Hamilton Depression Rating Scale factors from randomized, placebo-controlled trials in major depression. *Int Clin Psychopharmacol* 2002; 17: 45–51.
6. Andreoli V, *et al.* Reboxetine, a new noradrenaline selective antidepressant, is at least as effective as fluoxetine in the treatment of depression. *J Clin Psychopharmacol* 2002; 22: 393–9.
7. Montgomery S, *et al.* The antidepressant efficacy of reboxetine in patients with severe depression. *J Clin Psychopharmacol* 2003; 23: 45–50.

Adverse Effects

Adverse effects most commonly seen with reboxetine include insomnia, dry mouth, constipation, and increased sweating. Disturbance of visual accommodation, loss of appetite, chills, vertigo, tachycardia, palpitations, vasodilatation, and orthostatic hypotension are reported as being common adverse reactions. Adverse urinary symptoms have also been reported as common and occur more frequently in men; effects include urinary hesitancy, frequency, and a sensation of incomplete bladder emptying. Erectile dysfunction, ejaculatory delay or pain, and testicular pain can also be common. There have been reports of allergic dermatitis, convulsions, agitation, anxiety, irritability, aggressive behaviour, hallucinations, cold extremities, paraesthesia, hypertension, and nausea and vomiting. Reduced plasma-potassium concentrations have been seen in elderly patients after prolonged use.

Hyponatraemia, possibly as a result of inappropriate secretion of antidiuretic hormone, has been associated with the use of antidepressants, particularly in the elderly.

Effects on body-weight. Body-weight fell from 55 to 43 kg over about 9 months in a woman given reboxetine.[1] She reported loss of appetite, without nausea or vomiting, although she continued eating three meals daily. High caloric dietary supplements did not reverse the weight loss. The effect started about 2 months after starting reboxetine, and weight was regained after stopping the drug. Weight loss occurred again when reboxetine was later restarted.

1. Lu TY-T, *et al.* Profound weight loss associated with reboxetine use in a 44-year-old woman. *Br J Clin Pharmacol* 2005; 60: 218–20.

Effects on the CNS. Episodes of sleepwalking (somnambulism) were seen in an 18-year-old woman several weeks after starting reboxetine (at an initial dose of 2 mg daily gradually increased to 8 mg daily).[1] The patient had a history of childhood somnambulism that had resolved spontaneously; these particular episodes ceased after the dose of reboxetine was reduced to 4 mg daily.

1. Künzel HE, *et al.* Sleepwalking associated with reboxetine in a young female patient with major depression: a case report. *Pharmacopsychiatry* 2004; 37: 307–8.

Effects on the endocrine system. Hyponatraemia thought to be associated with reboxetine therapy and to be due to the syndrome of inappropriate antidiuretic hormone secretion, has been reported in an elderly patient.[1]

1. Ranieri P, *et al.* Reboxetine and hyponatremia. *N Engl J Med* 2000; 342: 215–16.

Effects on sexual function. The Australian Adverse Drug Reactions Advisory Committee has received 130 reports of adverse reactions associated with reboxetine use;[1] of these, 22 described male sexual dysfunction including ejaculation disorder (7 reports), erectile dysfunction (4 reports), and testicular pain or swelling (10 reports). In addition there were 2 reports of increased libido in women.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Genitourinary symptoms with reboxetine. *Aust Adverse Drug React Bull* 2005; 24: 10. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0506.pdf (accessed 24/11/05)

Effects on the urinary system. The Australian Adverse Drug Reactions Advisory Committee has received 26 reports of urinary symptoms such as hesitancy, reduced urine flow, and retention in patients taking reboxetine.[1] Although the majority of cases occurred in male patients, 6 reports mentioned such symptoms in women.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Genitourinary symptoms with reboxetine. *Aust Adverse Drug React Bull* 2005; 24: 10. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0506.pdf (accessed 24/11/05)

Treatment of Adverse Effects

The benefit of gastric decontamination after reboxetine overdose is uncertain; however, activated charcoal may be considered in adults and children who have ingested more than 1 mg/kg if they present within 1 hour of ingestion. Management thereafter mainly involves symptomatic and supportive therapy as required. Cardiac rhythm, blood pressure, and pulse rate should be monitored.

Genito-urinary disorders. Tamsulosin has been used successfully in the treatment of urinary hesitancy and painful ejaculation associated with reboxetine (see p. 2369.2).

Precautions

Reboxetine should be used with caution in patients with renal or hepatic impairment. It should also be used under close supervision in patients with bipolar disorder, urinary retention, benign prostatic hyperplasia, glaucoma, or a history of epilepsy or cardiac disorders.

Patients should be closely monitored during early therapy until significant improvement in depression occurs because suicide is an inherent risk in depressed patients. For further details, see under Depression, p. 398.1. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be observed when treating patients with other disorders.

Ability to perform tasks requiring motor or cognitive skills or judgement may be impaired by reboxetine and patients, if affected, should not drive or operate machinery.

Breast feeding. Low concentrations of reboxetine were detected in the breast milk of 4 women being treated for post-natal depression.[1] There were also low concentrations in the plasma of 3 of the breast-fed infants, and the drug was not detected in the fourth. No adverse effects were seen in any of the 4 infants.

1. Hackett LP, *et al.* Transfer of reboxetine into breastmilk, its plasma concentrations and lack of adverse effects in the breastfed infant. *Eur J Clin Pharmacol* 2006; 62: 633–8.

Children. Reboxetine has not been studied for the treatment of depression in children and UK licensed product information recommends that it should not be used for this indication in children and adolescents under 18 years of age. In addition, other antidepressants have been shown to increase the risk of suicidal thoughts and behaviour in children and adolescents (see Effects on Mental State, under Fluoxetine, p. 420.2).

The elderly. Reboxetine is not recommended by UK licensed product information for use in elderly patients, because of a lack of experience in this patient group. However, reboxetine 2 mg orally twice daily was well tolerated in a study in 16 elderly patients (mean age 77.5 years) with post-stroke depression.[1]

1. Rampello L, *et al.* An evaluation of efficacy and safety of reboxetine in elderly patients affected by "retarded" post-stroke depression: a random, placebo-controlled study. *Arch Gerontol Geriatr* 2005; 40: 275–85.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies reboxetine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Pregnancy. A review of pregnancy outcomes in the Swedish Medical Birth Registry found data on 15 infants born to women who had taken reboxetine in early pregnancy.[1] There was 1 report of ventricular septum defect.

1. Lennestål R, Källén B. Delivery outcome in relation to maternal use of some recently introduced antidepressants. *J Clin Psychopharmacol* 2007; 27: 607–13.

Interactions

Reboxetine should not be taken with, or within 2 weeks of stopping, an MAOI; at least one week should elapse after stopping reboxetine therapy before starting any drug liable to provoke a serious reaction (e.g. phenelzine). Caution should be taken when reboxetine is given with other drugs that lower blood pressure because orthostatic hypotension has occurred with reboxetine. However, the use of reboxetine with ergot derivatives may cause an increase in blood pressure. The possibility of hypokalaemia if reboxetine is given with potassium-depleting diuretics should also be considered.

Reboxetine is mainly metabolised by the cytochrome P450 isoenzyme CYP3A4 and potent inhibitors of this isoenzyme may limit the elimination of reboxetine. Consequently, reboxetine should not be given with drugs known to inhibit CYP3A4 such as azole antifungals (e.g. ketoconazole), macrolide antibacterials (e.g. erythromycin) or fluvoxamine. Reboxetine in high concentrations has also been shown *in vitro* to inhibit CYP3A4 and CYP2D6; however, studies *in vivo* have suggested that interactions with drugs metabolised by these isoenzymes are unlikely.

Antifungals. Reboxetine's plasma concentrations were significantly increased when it was given with *ketoconazole*.[1]

The interaction was said to have involved the inhibition of the cytochrome P450 isoenzyme CYP3A4 by ketoconazole.

1. Herman BD, *et al.* Ketoconazole inhibits the clearance of the enantiomers of the antidepressant reboxetine in humans. *Clin Pharmacol Ther* 1999; 66: 374–9.

Pharmacokinetics

Reboxetine is well absorbed from the gastrointestinal tract and peak plasma concentrations occur after about 2 hours. Plasma protein binding is about 97% (92% in elderly subjects). *In-vitro* studies indicate that reboxetine is metabolised by the cytochrome P450 isoenzyme CYP3A4; the main metabolic pathways identified are dealkylation, hydroxylation, and oxidation followed by glucuronide or sulfate conjugation. Elimination is mainly via urine (78%) with 10% excreted as unchanged drug. The plasma elimination half-life is 13 hours. Data from *animal* studies indicate that reboxetine crosses the placenta. It is distributed into breast milk.

References.
1. Dostert P, *et al.* Review of the pharmacokinetics and metabolism of reboxetine, a selective noradrenaline reuptake inhibitor. *Eur Neuropsychopharmacol* 1997; 7 (suppl 1): S23–S35.
2. Fleishaker JC. Clinical pharmacokinetics of reboxetine, a selective norepinephrine reuptake inhibitor for the treatment of patients with depression. *Clin Pharmacokinet* 2000; 39: 413–27.
3. Coulomb F, *et al.* Pharmacokinetics of single-dose reboxetine in volunteers with renal insufficiency. *J Clin Pharmacol* 2000; 40: 482–7.
4. Poggesi I, *et al.* Pharmacokinetics of reboxetine in elderly patients with depressive disorders. *Int J Clin Pharmacol Ther* 2000; 38: 254–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Edronax; ***Austria***: Edronax; ***Belg.***: Edronax; ***Braz.***: Prolift; ***Chile***: Prolift; ***China***: Yeluoshu (叶洛抒); Zuolexin (佐乐辛); ***Denm.***: Edronax; ***Fin.***: Edronax; ***Ger.***: Edronax; Solvex; ***Hung.***: Edronax; ***India***: Narebox; ***Irl.***: Edronax; ***Israel***: Edronax; ***Ital.***: Davedax; Edronax; ***Mex.***: Edronax; ***Norw.***: Edronax; ***NZ***: Edronax; ***Pol.***: Edronax; ***Port.***: Edronax; ***Rus.***: Edronax (Эдронакс); ***S.Afr.***: Edronax; ***Spain***: Irenor; Norebox; ***Swed.***: Edronax; ***Switz.***: Edronax; ***Thal.***: Edronax; ***Turk.***: Edronax; ***UK***: Edronax.

Sertraline Hydrochloride

(BANM, USAN, rINNM)

CP-51974-01; CP-51974-1; Hidrocloruro de sertralina; Sertralina, hidrocloruro de; Sertraline, Chlorhydrate de; Sertralinhydrochlorid; Sertralini Hydrochloridum; Сертралина Гидрохлорид.

(1*S*,4*S*)-4-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthyl (methyl)amine hydrochloride.

$C_{17}H_{17}Cl_2N,HCl$=342.7

CAS — 79617-96-2 (sertraline); 79559-97-0 (sertraline hydrochloride).

ATC — N06AB06.

ATC Vet — QN06AB06.

UNII — UT18907Y6X.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of sertraline:

Z's; Zloft; Zoomers.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Sertraline Hydrochloride). A white or almost white, crystalline powder. It exhibits polymorphism. Slightly soluble in water; sparingly soluble or slightly soluble in anhydrous alcohol; slightly soluble in acetone and in isopropyl alcohol. Protect from light.

USP 36: (Sertraline Hydrochloride). White or off-white, crystalline powder. Slightly soluble in water, in acetone, and in isopropyl alcohol; freely soluble in absolute alcohol. Store in airtight containers at a temperature not exceeding 40 degrees. Protect from light.

Uses and Administration

Sertraline, a naphthaleneamine derivative, is an SSRI with actions and uses similar to those of fluoxetine (p. 417.1). It is given orally as sertraline hydrochloride as a single dose in the morning or evening. Doses are expressed in terms of the base; sertraline hydrochloride 56 mg is equivalent to about 50 mg of sertraline.

In the treatment of **depression**, the usual initial dose of sertraline is 50 mg daily increased, if necessary, in increments of 50 mg at intervals of at least a week to a maximum of 200 mg daily.

The usual initial dose of sertraline in **obsessive-compulsive disorder** is 50 mg daily. In the treatment of **panic disorder** with or without agoraphobia, **social anxiety disorder**, and **post-traumatic stress disorder**, the usual initial dose is 25 mg daily increased after one week to 50 mg daily. Thereafter, doses in all these disorders may be increased, if necessary, in increments of 50 mg at intervals of at least a week to a maximum of 200 mg daily.

In the treatment of **premenstrual dysphoric disorder**, sertraline is given in an initial dose of 50 mg daily either throughout the menstrual cycle or during the luteal phase only, as appropriate. Doses may be increased by 50 mg each menstrual cycle up to a maximum of 150 mg daily for continuous dosing or 100 mg daily when dosing during the luteal phase only. Those patients who require 100 mg daily during luteal phase-only dosing should initially be given 50 mg daily for the first 3 days of each luteal phase dosing period.

Once the optimal therapeutic response is obtained dosage should be reduced to the lowest effective level for maintenance.

For dosage adjustment in patients with hepatic impairment, and for doses used in children, see p. 450.2.

Sertraline should be withdrawn gradually to reduce the risk of withdrawal symptoms (see also Withdrawal, under Precautions of Fluoxetine, p. 423.3).

Administration in children. There are concerns about the use of SSRIs in children (see Effects on Mental State, under Adverse Effects of Fluoxetine, p. 420.2) and the use of sertraline for the treatment of **depression** in those under 18 years of age is unlicensed. Nevertheless, the *BNFC* suggests that it may be used by specialists for the treatment of major depression in those aged 12 years and over; the usual adult dose (see Uses and Administration, above) may be given.

Sertraline may be given for the treatment of **obsessive-compulsive disorder** in children and adolescents aged 6 years and over. In children aged 6 to 12 years the usual initial oral dose is 25 mg once daily; adolescents may be started on 50 mg once daily. Increases in doses, if necessary, are similar to those in adults (see above); however, the lower body-weights of children should be considered in order to avoid excessive doses.

Administration in hepatic impairment. The clearance of sertraline was reduced in patients with liver cirrhosis, in a single-dose pharmacokinetic study.[1] US licensed product information states that in a small group of patients with chronic mild impairment (Child-Pugh scores of 5 to 8), given 50 mg daily for 21 days, exposure to sertraline was about 3 times that found in subjects with normal hepatic function. It also states that the effects of sertraline have not been studied in moderate and severe impairment. If sertraline is to be used in patients with hepatic impairment, it suggests that the drug should be used with caution and given at a lower dose or less frequently. UK product information considers sertraline to be contra-indicated in significant hepatic impairment, because of insufficient clinical experience.

1. Démolis J-L, *et al.* Influence of liver cirrhosis on sertraline pharmacokinetics. *Br J Clin Pharmacol* 1996; 42: 394–7.

Anxiety disorders. Sertraline has been given in a variety of anxiety disorders (p. 1028.1) including obsessive-compulsive disorder (p. 1028.2), panic disorder (p. 1029.1), social anxiety disorder (see under Phobic Disorders, p. 1029.1), and post-traumatic stress disorder (p. 1029.2).

References.
1. March JS, *et al.* Sertraline in children and adolescents with obsessive-compulsive disorder: a multicenter randomized controlled trial. *JAMA* 1998; 280: 1752–6.
2. Londborg PD, *et al.* Sertraline in the treatment of panic disorder. A multisite, double-blind, placebo-controlled, fixed-dose investigation. *Br J Psychiatry* 1998; 173: 54–60.
3. Brady K, *et al.* Efficacy and safety of sertraline treatment of posttraumatic stress disorder: a randomized controlled trial. *JAMA* 2000; 283: 1837–44.
4. Walker JR, *et al.* Prevention of relapse in generalized social phobia: results of a 24-week study in responders to 20 weeks of sertraline treatment. *J Clin Psychopharmacol* 2000; 20: 636–44.
5. Rynn MA, *et al.* Placebo-controlled trial of sertraline in the treatment of children with generalized anxiety disorder. *Am J Psychiatry* 2001; 158: 2008–14.
6. Rapaport MH, *et al.* Sertraline treatment of panic disorder: results of a long-term study. *Acta Psychiatr Scand* 2001; 104: 289–98.
7. Rapaport MH, *et al.* Posttraumatic stress disorder and quality of life: results across 64 weeks of sertraline treatment. *J Clin Psychiatry* 2002; 63: 59–65.
8. Koran LM, *et al.* Efficacy of sertraline in the long-term treatment of obsessive-compulsive disorder. *Am J Psychiatry* 2002; 159: 88–95.
9. Zohar J, *et al.* Double-blind placebo-controlled pilot study of sertraline in military veterans with posttraumatic stress disorder. *J Clin Psychopharmacol* 2002; 22: 190–5.
10. Liebowitz MR, *et al.* Efficacy of sertraline in severe generalized social anxiety disorder: results of a double-blind, placebo-controlled study. *J Clin Psychiatry* 2003; 64: 785–92.
11. Allgulander C, *et al.* Efficacy of sertraline in a 12-week trial for generalized anxiety disorder. *Am J Psychiatry* 2004; 161: 1642–9.
12. Friedman MJ, *et al.* Randomized, double-blind comparison of sertraline and placebo for posttraumatic stress disorder in a Department of Veterans Affairs setting. *J Clin Psychiatry* 2007; 68: 711–20.

Depression. As discussed on p. 398.1, there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effect profile. SSRIs such as sertraline are widely used as an alternative to the older tricyclics as they have fewer adverse effects and are safer in overdosage.

References.
1. Stowe ZN, *et al.* Sertraline in the treatment of women with postpartum major depression. *Depression* 1995; 3: 49–55.
2. Keller MB, *et al.* Maintenance phase efficacy of sertraline for chronic depression: a randomized controlled trial. *JAMA* 1998; 280: 1665–72.
3. Baca E, *et al.* Sertraline is more effective than imipramine in the treatment of non-melancholic depression: results from a multicentre, randomized study. *Prog Neuropsychopharmacol Biol Psychiatry* 2003; 27: 493–500.
4. Lepine JP, *et al.* A randomized, placebo-controlled trial of sertraline for prophylactic treatment of highly recurrent major depressive disorder. *Am J Psychiatry* 2004; 161: 836–42.
5. Moscovitch A, *et al.* A placebo-controlled study of sertraline in the treatment of outpatients with seasonal affective disorder. *Psychopharmacology (Berl)* 2004; 171: 390–7.
6. Cipriani A, *et al.* Sertraline versus other antidepressive agents for depression. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2010 (accessed 02/08/10).

Premenstrual syndrome. Sertraline throughout the menstrual cycle has produced beneficial effects in controlling both the psychological and somatic symptoms of women with premenstrual syndrome (p. 2272.3).[1-3] Giving sertraline solely during the luteal phase was also of benefit.[3-7]

1. Yonkers KA, *et al.* Sertraline in the treatment of premenstrual dysphoric disorder. *Psychopharmacol Bull* 1996; 32: 41–6.
2. Yonkers KA, *et al.* Symptomatic improvement of premenstrual dysphoric disorder with sertraline treatment: a randomized controlled trial. *JAMA* 1997; 278: 983–8.
3. Freeman EW, *et al.* Continuous or intermittent dosing with sertraline for patients with severe premenstrual syndrome or premenstrual dysphoric disorder. *Am J Psychiatry* 2004; 161: 343–51.
4. Young SA, *et al.* Treatment of premenstrual dysphoric disorder with sertraline during the luteal phase: a randomized, double-blind, placebo-controlled crossover trial. *J Clin Psychiatry* 1998; 59: 76–80.
5. Jermain DM, *et al.* Luteal phase sertraline treatment for premenstrual dysphoric disorder: results of a double-blind, placebo-controlled, crossover study. *Arch Fam Med* 1999; 8: 328–32.
6. Halbreich U, *et al.* Efficacy of intermittent, luteal phase sertraline treatment of premenstrual dysphoric disorder. *Obstet Gynecol* 2002; 100: 1219–29.
7. Kornstein SG, *et al.* Low-dose sertraline in the treatment of moderate-to-severe premenstrual syndrome: efficacy of 3 dosing strategies. *J Clin Psychiatry* 2006; 67: 1624–32.

Sexual dysfunction. Impotence or ejaculatory problems have been reported as adverse effects of SSRIs; for the use of these effects as a potential form of management for premature ejaculation see Fluoxetine, p. 419.1.

Adverse Effects, Treatment, and Precautions

As for SSRIs in general (see Fluoxetine, p. 419.1). Menstrual irregularities and, rarely, erythema multiforme and pancreatitis have also been reported.

Sertraline should be used with caution in patients with hepatic or renal impairment; reduced doses should be considered in patients with hepatic impairment.

Breast feeding. For comments on the use of SSRIs in breast-feeding patients, see under Precautions for Fluoxetine, p. 422.2.

Children. SSRIs are associated with an increased risk of potentially suicidal behaviour when used for the treatment of depression in children and adolescents under 18 years old; for further details, see under Effects on Mental State in Fluoxetine, p. 420.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sertraline as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

For interactions associated with SSRIs, see Fluoxetine, p. 424.1.

Pharmacokinetics

Sertraline is slowly absorbed from the gastrointestinal tract and peak plasma concentrations occur about 4.5 to 8.4 hours after ingestion. It undergoes extensive first-pass metabolism in the liver. The main pathway is demethylation to inactive *N*-desmethylsertraline, a process that appears to involve multiple cytochrome P450 isoenzymes; further metabolism and glucuronide conjugation occurs. Sertraline is widely distributed throughout body tissues and is about 98% bound to plasma proteins. The plasma elimination half-life of sertraline is about 26 hours; steady-state concentrations occur after about one week with regular oral doses. Sertraline is excreted in about equal amounts in the urine and faeces, mainly as metabolites. Sertraline is distributed into breast milk (see Breast Feeding under Precautions in Fluoxetine, p. 422.2).

References.
1. Preskorn SH, ed. Sertraline: a pharmacokinetic profile. *Clin Pharmacokinet* 1997; 32 (suppl 1): 1–55.
2. Hiemke C, Härtter S. Pharmacokinetics of selective serotonin reuptake inhibitors. *Pharmacol Ther* 2000; 85: 11–28.
3. Wang J-R, *et al.* Pharmacokinetics of sertraline in relation to genetic polymorphism of CYP2C19. *Clin Pharmacol Ther* 2001; 70: 42–7.
4. DeVane CL, *et al.* Clinical pharmacokinetics of sertraline. *Clin Pharmacokinet* 2002; 41: 1247–66.
5. Obach RS, *et al.* Sertraline is metabolized by multiple cytochrome P450 enzymes, monoamine oxidases, and glucuronyl transferases in human: an in vitro study. *Drug Metab Dispos* 2005; 33: 262–70.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Anilar; Atenix; Bicromil; Celonfex; Cratular; Deprecalm; Insertec; Irradial; Serlina; Servantax; Vunot; Zoloft; Zoxx; *Austral.*: Concorz†; Eleva; Sertra; Sertracor; Setrona; Xydep; Zoloft; *Austria*: Adjuvin; Gladem; Tresleen; *Belg.*: Serlain; *Braz.*: Assert; Cefelic; Dieloft; Novativ; Sered; Serenata; Seronip; Teuloft; Tolrest; Zoloft; Zoltralina; Zysertin; *Canad.*: Zoloft; *Chile*: Altruline; Deprax; Eleval; Emergen; Implicane; Lowfin; Sedoran; Serivo; Seronex; Sertac; Tralinsert†; *China*: Bei Yu (贝玉); JinDeSi (津得斯); Kuai Wu You (快五优); Leyuan (乐元); Pi Mai Le (彼迈乐); Wei Ta Ting (唯他停); Xi Tong Jing (西同静); Xinya Quling (新亚曲灵); Yi Suo Ming (伊索明); Ying Si Tiao (应思调); Yu Lang (愈朗); Yu Luo Xin (都洛欣); Zoloft (左洛复); *Cz.*: Adjuvin; Apo-Sertral; Asentra; Serlift; Sertivan; Setaloft; Stimuloton; Zoloft; *Denm.*: Serlinan; Sertravis; Sertrix; Sertrone; Tralinan; Tralix; Zeelinax; Zeenix†; Zoloft; *Fin.*: Zoloft; *Fr.*: Zoloft; *Ger.*: Gladem†; Sertra-Isis†; Sertra†; Sertralon; Zoloft; *Gr.*: Certorun; Ditticone; Enidap; Epilyd; Mycinil; Neurosedine; Positiva; Serolux; Serotyp; Sertral; Zoloft; Zolotrin; Zortal; *Hong Kong*: Serdep; Stimuloton; Zoloft; *Hung.*: Asentra; Camidlin†; Gerotralin†; Serlift; Serlosane†; Sertadepi; Sertagen; Sertwin†; Setaloft; Stimuloton; Zoloft; *India*: Actiser; Aderta; Censir; Daxid; Dazolin; Deplin; Depsert; Episod; Inosert; Lindep; Line; Medisert; Mentolift; Obzin; Serdep; Serta; Xsert; *Indon.*: Anexin; Antipres; Deptral; Fatral; Fridep; Iglodep; Nudep; Serlof; Sernade; Zerlin; Zoloft; *Irl.*: Depreger; Lusert; Lustral; Seretral; Serimel; Serlan; Serlo; Sertraniche; *Israel*: Lustral; Serenada; *Ital.*: Tatig; Tralisen; Zoloft; *Malaysia*: Serlift; Setrof; Zoloft; *Mex.*: Acortral; Aleval; Altruline; Aluprex; Deptral; Equivac; Prosertin; Resteral; Serlift; Serolux; Sertex; *Neth.*: Asentra; Enore; Zoloft; *Norw.*: Zoloft; *NZ*: Setrona; Zoloft; *Philipp.*: Exulten; Serenata; Zolodin; Zoloft; Zotral; *Pol.*: Antideprimal; Apresia†; Asentra; Asertin; Luxeta; Miravil; Sertagen; Sertahexal†; Sertranorm; Setaloft; Setaratio†; Stimuloton; Zoloft; Zotral; Zotral; *Port.*: Aserin; Aserta; Deprilix; Eterim†; Gerlina; Luzina†; Psicotil; Serlin; Serpax; Sertabal; Sertralpharm†; Somidal; Tralin; Zoloft; *Rus.*: Aleval (Алевал); Asentra (Асентра); Deprefolt (Депрефолт); Seralin (Сералин); Serenata (Серената); Serlift (Сертифт); Stimuloton (Стимулотон); Torin (Торин); Zoloft (Золофт); *S.Afr.*: Adco-Zertra; Serdep; Serlife; Sermax; Sertra; Sertzol; Zolid; Zoloft; Zosert; Zylin; *Singapore*: Zoloft; *Spain*: Altisben; Aremis; Aserin; Besitran; Lustragen†; Lustramerck†; Sertrabrain†; Sertramerck†; *Swed.*: Oralin; Sertrone; Zoloft; *Switz.*: Seralin; Sertragen; Sertral†; Sertrin†; Zoloft; *Thai.*: Serlift; Sertra; Starin; Zoloft; Zotaline; *Turk.*: Lustec; Lustral; Misol; Selectra; Seralin; Serdep; Serotop; Serteva; Zeleft; *UK*: Lustral; *Ukr.*: Asentra (Асентра); Serlift (Сертифт); Sertraloft (Сертралофт)†; Stimuloton (Стимулотон); Zoloft (Золофт); *USA*: Zoloft; *Venez.*: Conexine; Lusedan; Satil; Serline; Serolux; Tialin; Zoloft.

Multi-ingredient Preparations. *India*: Alltop-S; Alprax Forte; Alprax Plus; Altalin; Alzex Forte; Alzex Plus; Anxit Forte; Anxit Plus; Azo-S; Censir Forte; L-Peez S; Manorest Forte; Manorest Plus; MCalm; Mentolift-Plus; Restyl Forte; Restyl Plus.

Pharmacopoeial Preparations
BP 2014: Sertraline Tablets;
USP 36: Sertraline Hydrochloride Oral Solution; Sertraline Tablets.

Setiptiline *(rINN)*

Setiptilina; Sétiptiline; Setiptilinum; Teciptiline; Сетиптилин

2,3,4,9-Tetrahydro-2-methyl-1*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*c*]pyridine.

$C_{19}H_{19}N$=261.4.

CAS — 57262-94-9 (setiptiline); 85650-57-3 (setiptiline maleate).

UNII — 7L38105Z6E.

Profile

Setiptiline is an antidepressant that has been used as the maleate in the treatment of depression.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Tecipul.

St John's Wort

Hierba de San Juan; Hipérico; Hiperikum; Hyperici Herba; Hypericum; Hypericum Perforatum; Johannesört; Johanniskraut; Jonažolių žolė; Mākikuisma; Millepertuis; Orbáncfű; Třezalková nať; Ziele dziurawca; Зверобой Продырявленный.

CAS — 548-04-9 (hypericin).

ATC Herb — HN06AW5001 (Hypericum perforatum: *flower*); *HM01AW5010* (Hypericum perforatum: *flower*); *HN06AW5002* (Hypericum perforatum: *germ*); *HM01AW5011* (Hypericum perforatum: *herb*); *HD03WX5008* (Hypericum perforatum: *herb*); *HN06AW5003* (Hypericum perforatum: *herb*).

UNII — UFH8805FKA (Hypericum perforatum *flowering top*); *XK4IUX8MNB* (Hypericum perforatum); *A6V4CUE7PV* (Hypericum perforatum *flower*).

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Eur. also includes the dry extract and a form for homoeopathic preparations.

Swiss also includes monographs for hypericum (fresh flowering tops) and hypericum oil.

Ph. Eur. 8: (St. John's Wort). The whole or fragmented, dried flowering tops of *Hypericum perforatum* gathered during flowering. It contains not less than 0.08% of total hypericins, expressed as hypericin ($C_{30}H_{16}O_8$ = 504.4) calculated with reference to the dried drug.

Ph. Eur. 8: (Hypericum for Homoeopathic Preparations; Hypericum Perforatum ad Praeparationes Homoeopathicas). The whole, fresh plant of *Hypericum perforatum*, at the beginning of the flowering period. Protect from light.

USP 36: (St. John's Wort). The dried flowering tops or aerial parts of *Hypericum perforatum* (Hypericaceae), gathered shortly before or during flowering. It contains not less than 0.04% of the combined total of hypericin ($C_{30}H_{16}O_8$ = 504.4) and pseudohypericin ($C_{30}H_{16}O_9$ = 520.4) and not less than 0.6% of hyperforin ($C_{35}H_{52}O_4$ = 536.8). Store in airtight containers. Protect from light.

Uses and Administration

Herbal preparations containing St John's wort are used, frequently for self-medication, in the treatment of depression. Such preparations are also promoted for the treatment of other nervous disorders such as insomnia and anxiety, particularly if associated with the menopause. St John's wort oil has also been used as an astringent.

The amount of active constituents can vary between different preparations and doses depend on the preparation being used.

Homoeopathy

St John's wort has been used in homoeopathic medicines under the following names: Hypericum; Hypericum perforatum; Hypericum perforatum ex herba; Hypericum, herba; Hyper.

References.
1. McIntyre M. A review of the benefits, adverse events, drug interactions, and safety of St John's Wort (Hypericum perforatum): the implications with regard to the regulation of herbal medicines. *J Altern Complement Med* 2000; 6: 115–24.

Depression. St John's wort extracts are widely used in some countries for the treatment of depression (p. 398.1).

A systematic review[1] of randomised controlled studies found St John's wort extracts to be more effective than placebo in the treatment of mild to moderate depressive disorders. A later, more focused, systematic review[2] included only studies in which patients met the diagnostic criteria for major depression (ranging in severity from mild to severe). St John's wort was found to be superior to placebo, and to be of similar efficacy to standard antidepressants but with fewer adverse effects. However, studies mostly included patients with mild to moderate symptoms, and it was considered that evidence for the treatment of severe depression was still insufficient to draw conclusions. The doses of standard antidepressants were also generally at the lower limit of the recommended range. It was also notable that findings from studies in German-speaking countries were generally more favourable for St John's wort versus placebo, compared with studies performed elsewhere, a difference that the authors felt needed more investigation.

The mechanism of action of St John's wort extracts in the treatment of depression remains unclear. Extracts contain at least 10 active principles. Hypericin, one of the major constituents of St John's wort, was first thought responsible for the antidepressant effect since it had an inhibitory action on monoamine oxidase *in vitro*. However, it was later shown that this action was, at best, weak and it is now generally believed that monoamine oxidase inhibition is not responsible for the antidepressant effect of St John's wort. More recent studies have suggested that hyperforin may be one of the major constituents responsible for the antidepressant effect.[3] Although the evidence is mainly from *in vitro* studies, hyperforin inhibits the reuptake of several major neurotransmitters including serotonin, dopamine, and noradrenaline.[4]

1. Stevinson C, Ernst E. Hypericum for depression: an update of the clinical evidence. *Eur Neuropsychopharmacol* 1999; 9: 501–5.
2. Linde K, *et al.* St John's wort for major depression. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 24/08/09).
3. Laakmann G, *et al.* St. John's Wort in mild to moderate depression: the relevance of hyperforin for the clinical efficacy. *Pharmacopsychiatry* 1998; 31 (suppl.): 54–9.
4. Chatterjee SS, *et al.* Hyperforin as a possible antidepressant component of hypericum extracts. *Life Sci* 1998; 63: 499–510.

Adverse Effects and Precautions

Adverse effects reported with St John's wort have included gastrointestinal symptoms, dizziness, headache, confusion, urinary frequency, allergic reactions, and fatigue. Photosensitivity has also been reported; hypericin and pseudohypericin are the constituents of St John's wort thought to be responsible for this reaction.

Effects on the nervous system. Subacute polyneuropathy after sun exposure developed in a woman who had taken St John's wort for mild depression; she improved after drug withdrawal.[1] Seizures and confusion occurred in a 16-year-old girl after an overdose of St John's wort.[2] She had taken large daily doses for 2 weeks and an overdose just before presentation.

1. Bove GM. Acute neuropathy after exposure to sun in a patient treated with St John's Wort. *Lancet* 1998; 352: 1121–2.
2. Karalapillai DC, Bellomo R. Convulsions associated with an overdose of St John's wort. *Med J Aust* 2007; 186: 213–14.

Effects on the skin. In addition to photosensitivity reactions associated with St John's wort use,[1] there has been a report of severe erythroderma in a patient who supplemented his regular antidepressant medication (dosulepin) with St John's wort.[2] The reaction was seen on both light-exposed and non-exposed areas, and was thought to be due to the St John's wort although there remained a possibility that it was due to an interaction between the 2 drugs.

1. Lane-Brown MM. Photosensitivity associated with herbal preparations of St John's wort (Hypericum perforatum). *Med J Aust* 2000; 172: 302.
2. Holme SA, Roberts DL. Erythroderma associated with St John's wort. *Br J Dermatol* 2000; 143: 1127–8.

Mania. Mania or hypomania has been associated with the use of St John's wort.[1-3]

1. Neirenberg AA, *et al.* Mania associated with St John's wort. *Biol Psychiatry* 1999; 46: 1707–8.
2. Fahmi M, *et al.* A case of mania induced by hypericum. *World J Biol Psychiatry* 2002; 3: 58–9.
3. Stevinson C, Ernst E. Can St John's wort trigger psychoses? *Int J Clin Pharmacol Ther* 2004; 42: 473–80.

Withdrawal. A 58-year-old woman developed symptoms such as nausea, anorexia, dizziness, dry mouth, thirst, chills, and fatigue the day after stopping St John's wort;[1] she had taken the drug for 32 days. The symptoms, which the authors considered suggestive of a withdrawal syndrome, resolved within 8 days.

1. Dean AJ, *et al.* Suspected withdrawal syndrome after cessation of St John's wort. *Ann Pharmacother* 2003; 37: 150.

Interactions

St John's wort has been shown to induce several drug metabolising enzymes including some cytochrome P450 isoenzymes (in particular CYP3A4) and the transport protein P-glycoprotein. Clinically important interactions resulting in decreased plasma concentrations of the interacting drug have been reported with ciclosporin, digoxin, HIV-protease inhibitors, NNRTIs, oral contraceptives, tacrolimus, theophylline, and warfarin. There is also a possibility of an interaction between St John's wort and antiepileptics. In addition, stopping St John's wort may result in increased, and possibly toxic, concentrations of the interacting drug.

In many countries, including the UK and USA, preparations of St John's wort are not required to be licensed as medicines, and the amount of active ingredient may vary widely between preparations. Changing preparations may therefore alter the degree of enzyme induction.

Use of St John's wort with drugs known to act on serotonergic neurotransmitters may result in synergistic interactions and an increased risk of adverse effects may also occur. Examples include the SSRIs and nefazodone (see Antidepressants, p. 445.2) and the selective serotonin (5-HT_1) agonists (see under Sumatriptan, p. 681.3) used to treat migraine.

References.
1. Roby CA, *et al.* St John's Wort: effect on CYP3A4 activity. *Clin Pharmacol Ther* 2000; 67: 451–7.
2. CSM/MCA. Reminder: St John's Wort (Hypericum perforatum) interactions. *Current Problems* 2000; 26: 6–7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 24/11/05)

3. Dürr D, *et al.* St John's Wort induces intestinal p-glycoprotein/MDR1 and intestinal and hepatic CYP3A4. *Clin Pharmacol Ther* 2000; **68**: 598–604.
4. Wang Z, *et al.* The effects of St John's wort (*Hypericum perforatum*) on human cytochrome P450 activity. *Clin Pharmacol Ther* 2001; **70**: 317–26.
5. Hennessy M, *et al.* St John's Wort increases expression of P-glycoprotein: implications for drug interactions. *Br J Clin Pharmacol* 2002; **53**: 75–82.
6. Henderson L, *et al.* St John's wort (*Hypericum perforatum*): drug interactions and clinical outcomes. *Br J Clin Pharmacol* 2002; **54**: 349–56.
7. Mills E, *et al.* Interaction of St John's wort with conventional drugs: systematic review of clinical trials. *BMJ* 2004; **329**: 27–30.
8. Mannel M. Drug interactions with St John's wort: mechanisms and clinical implications. *Drug Safety* 2004; **27**: 773–97.
9. Whitten DL, *et al.* The effect of St John's wort extracts on CYP3A: a systematic review of prospective clinical trials. *Br J Clin Pharmacol* 2006; **62**: 512–26.

Analgesics. For details of a possible interaction between St John's wort and the opioid analgesic *methadone*, see p. 90.3.

Anticoagulants. For mention of a possible interaction between St John's wort and *warfarin*, see p. 1535.2.

Antiepileptics. There is a possibility of an interaction between St John's wort and antiepileptics such as *carbamazepine* (see p. 516.2), *phenobarbital* (see p. 537.2), and *phenytoin* (see p. 543.1).

Antineoplastics. St John's wort may interact with some antineoplastics; examples include *aminolevulinic acid* (see p. 741.2), *imatinib* (see p. 809.2), and *irinotecan* (see p. 814.1).

Antivirals. For details of a possible interaction between St John's wort and *HIV-protease inhibitors* such as indinavir, see p. 989.3.

Anxiolytics. For mention of a possible interaction between St John's wort and *buspirone*, see p. 1043.2.

Cardiac glycosides. For details of a possible interaction between St John's wort and *digoxin*, see p. 1356.3.

Immunosuppressants. For details of possible interactions between St John's wort and *ciclosporin* or *tacrolimus*, see p. 1956.3 and p. 1977.3, respectively.

Oral contraceptives. For reports of a possible interaction between St John's wort and oral contraceptives, see p. 2243.2.

Verapamil. For details of a possible interaction between St John's wort and verapamil, see p. 1525.3.

Xanthines. For details of a possible interaction between St John's wort and *theophylline*, see p. 1234.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Amenicil; Hipax; Hiperinat; ***Austral.***: Remotiv; Stress-Relax†; ***Austria***: Esbericum; Hyperiforce; Jarsin; Johanicum; Kira; Laif; Perikan†; Psychotonin; Remotiv; ***Belg.***: Hyperiplant; Milperinol; Perika; Zibrine; ***Braz.***: Ciperico; Equilibrium; Felis†; Fiotan†; Fitovital†; Hiperex; Hipericin†; Hipérico†; Hipersac; Hyperigreen†; Iperisan; Motivent†; Prazen; Remotiv; Triativ; ***Canad.***: Hyperiforce†; Kira†; ***Chile***: Anxium; ***China***: Shuganjieyu Jiaonang (舒肝解郁); ***Cz.***: Felisio†; Helarium†; Hyperikan†; Jarsin; Laif; Nat Trezalky†; Remotiv†; Trezalka v Nalevovych Sacchich†; Trezalkova Nat; Trezalkovy Caj; ***Denm.***: Neurokan; ***Fin.***: Hyperiforce; ***Fr.***: Euphypertuis; Mildac; Procalmil; ***Ger.***: Cesradyston; Esbericum; Felis†; Hewepsychon uno†; Hyperforat; Jarsin; Kira; Laif; Neuroplant; Neurovegetalin; Psychotonin; Remotiv†; Spilan†; Texx; Tonizin†; ***Gr.***: Neukan†; ***Hung.***: Helarium†; Laif; Modigen; Myrall; Remotiv; ***India***: Depgard; J-Wort; Jovin; ***Indon.***: Preso†; ***Israel***: Laif; Remotiv; ***Ital.***: Nervaxon; Proserem†; Quiens; Remotive; ***Mex.***: Hiperikan; Remotiv†; ***Mon.***: Prosoft; ***Neth.***: Hyperiplant; Laif; ***Norw.***: Depasin†; Perika†; Velzina†; ***Pol.***: Apatinac; Deprim; Hypercaps; Hyperherba; Hyperosedat†; Perhip; Remotiv†; Silenil; ***Port.***: Alacre; Procalmil; ***Rus.***: Deprim (Деприм); Doppelherz Nervotonik (Доппельгерц Нервотоник); Helarium (Геларium); Negrustin (Негрустин); Novo-Passit (Ново-Пассит); ***Spain***: Animic†; Arkocapsulas Hipérico; Hipcedan; Hipérico†; Hyneurin; Livren†; Mediflor†; Perika†; Quetzal†; Vitalium†; ***Swed.***: Hypermin; Neurokan; ***Switz.***: Deprivita; Hyperiforce; HyperiMed; Hyperiplant; Hyperval; Jarsin; Lucilium; Mandal 425; ReBalance; Remotiv; Sanalum; Solevita; ***Thai.***: Hyperiforte; ***Turk.***: Felis†; ***UK***: Bettermood; Duchy Herbals Hyperi-Lift; Herbal Mood Relief; HRI Good Mood; HyperiCalm; Hypericon; Hyperidrine; Hyperiforce; Karma; Karmamood; Kira; Mood Boost; Moodeze; Neuropret; Ucalm; ***Ukr.***: Deprim (Деприм); Deprivit (Депривит); Helarium (Геларium); Herbion Hypericum (Гербион Гиперикум); Laif (Лайф); Neuroplant (Нейроплант); ***Venez.***: Hyperikan.

Multi-ingredient Preparations. ***Austral.***: 3B Beer Belly Buster†; Aloe Vera Gel; Cimicifuga Compound; Femi-Nan; Feminine Herbal Complex; Herbal Rest & Relax; Hernidisc; Irontona†; Joint & Muscle Cream; Lavandula Compound; Masculine Herbal Complex; Nappy Rash Relief Cream; Nevaton; Olf†; Vitatona†; Wild Yam Complex; ***Austria***: Magentee St Severin; Nerventee St Severin; Neurapas; Remifemin plus; Vulpuran; Wechseltee St Severin; ***Canad.***: Cystoforce†; Gallexier†; Salusan†; Trim-Fit†; ***Cz.***: Alvisan Neo; Cicaderma; Fytokliman Planta; Novo-Passit; Species Nervinae Planta; Stomaran; Zaludecni Cajova Smes; ***Ger.***: anabol-loges†; Dolo-cyl†; Gastritol; Hyperesa†; Neurapas; Psychotonin-sed†; Remifemin plus; Sedariston Konzentrat†; Sedariston plus†; ***Hung.***: Depsorin; Diabess; Gastrosol; Mensesyl; Remifemin Plus; Telma; ***Ital.***: Controller; Hiperogyn; Lenifren; Mithen; Skab 2†; Stressout; ***Malaysia***: Gyno-Plus; ***Mex.***: Nordimenty; ***Neth.***: Bioforce; ***Pol.***: Cholesol; Diges-Tonic; Doppelherz Energovital Tonik†; Fortestomachicae; Gastrobonisol; Guttae Stomachicae; Herbogastrin; Klosterfrau Aktiv; Krople Zoladkowe†; Krople Zoladkowe; Krople Zoladkowe; Melisal; Melissed; Nervomix; Perfocrat†; Prostapol; Psychotonisol†; Sedomix; Uroprost; ***Port.***: Cicaderma; ***Rus.***: Arfazetin-E (Арфазетин-Э); Brusniver (Брусниверр); Doppelherz Energotonik (Доппельгерц Энерготоник); Evalar (Эвалар); Polygemostat (Полигемостат); Prostanorm (Простанорм); Sibectan (Сибектан); ***Spain***: Neurapas; ***Switz.***: Huile de millepertuis A. Vogel (huile de St. Jean); Hyperiforce comp; Impuls a la consoude; Keppur; The d'avoine verte Vollmers†; Ziegella†; ***UK***: Botanova; DiaCalm; DiaMenoCalm; Menomood; Outlook; St Johnswort Compound; Tranquil; ***Ukr.***: Ambovit (Амбовит); Gastritol (Гастритол); Immuno-Ton (Іммуно-Тон); Novo-Passit (Ново-Пассит); Phytolyt (Фитолит); Sedavit (Седавит); Urochol (Урохол)†; Vitokan (Витокан); *USA*: Stinnie.

Homoeopathic Preparations. ***Austral.***: Arthritis Relief; Sports Ice Joint & Muscle; ***Austria***: Arnica Komplex†; Globuli gegen Sonnenallergie; Memoria; Repisan; Traumeel; Tropfen bei Verletzungen; Valerianaheel; Wirbelsaule- und Gelenkstropfen Nr 2†; ***Canad.***: Aches & Pains; Arnica + Pain Relief; Arnicaid; Bumps and Bruises; Calendula +; Calendula Ointment†; Capsicum + Arthri-Cream; Cicaderma†; Den 141†; Formula DM 210†; Herpes Soothing Cream; Kids' Teething; Loprax†; Traumeel; Valerianaheel Comp†; ***Chile***: Bioactiv Z; ***Cz.***: Traumeel; ***Fr.***: Arnica Complexe no 1; Cicaderma; Hypericum Complexe No 26; Zincum Cyanidum Complexe No 101†; ***Ger.***: Cefakliman N†; Hewepsychon Mono†; Hyperforat Nervo; Hyperforat Vita; Infi-China; Levisticum S; Naranofem†; Nervoject F; Nervoregin H; Phonix Urtica-Arsenicum spag; Roth's RKT Tropfen; Sedacalman; Sensiotin; Traumeel S; ***Hung.***: Traumeel; ***Neth.***: Achillite; Arnilite; Cephalite; Collite; Dermalite; Enulite; Gynaelite; Hepalite; Homeocare Nervo; Hyperilite; Mulimen H; Omnilite; Traumeel H; Traumeel S; ***Rus.***: Cicaderma (Цикадерма); Memoria (Мемория); Repisan (Реписан); Traumeel S (Траумель С); ***S.Afr.***: Berberis/Cantharis Comp†; Traumeel S; ***Switz.***: Nelsons Traumatica†; Regenaplex Nr. 12; Traumeel; ***UK***: Burns Cream; Hypercal; Pyrethrum Spray; ***Ukr.***: Memoria (Мемория); Traumeel S (Траумель С); *USA*: Preferred Remedies Aches & Pains; Traumeel; ***Venez.***: Traumeel.

Pharmacopoeial Preparations

Ph. Eur.: St John's Wort Dry Extract, Quantified.

Tianeptine Sodium *(rINNM)*

Natrii Tianeptinum; Taneptinum Natricum; Tianeptiininatrium; Tianeptin-Natrium; Tianeptin sodná sůl; Tianeptin Sodyum; Tianeptina sódica; Tianeptine sodique; Tianeptinnatrium; Tianeptin-nátrium; Tianeptino natrio druska; Tianeptinum Natricum; Натрий Тианептин.

The sodium salt of 7-[(3-chloro-6,11-dihydro-6-methyldibenzo[*c*,*f*][1,2]thiazepin-11-yl)amino]heptanoic acid *S,S*-dioxide.

$C_{21}H_{24}ClN_2NaO_4S$=458.9

CAS — 66981-73-5 (tianeptine).

ATC — N06AX14.

ATC Vet — QN06AX14.

UNII — YG0E19592I.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Tianeptine Sodium). A white or yellowish, very hygroscopic, powder. Freely soluble in water, in dichloromethane, and in methyl alcohol. Store in airtight containers.

Profile

Tianeptine sodium is an antidepressant reported to act by increasing (rather than inhibiting) the presynaptic reuptake of serotonin. It is given in oral doses of 12.5 mg three times daily in the treatment of depression (p. 398.1). Doses should be reduced to a total of 25 mg daily in elderly patients; for details of dosage in those with renal impairment, see p. 452.2.

Isolated cases of hepatitis have been reported during treatment with tianeptine.

Abuse. Reports of misuse of tianeptine.[1,2]

1. Leterme L, *et al.* Usage détourné de tianeptine: à propos de cinq cas de surconsommation. *Ann Med Interne (Paris)* 2003; **154**: 2558–2563.
2. Kisa C, *et al.* Is it possible to be dependent to tianeptine, an antidepressant? A case report. *Prog Neuropsychopharmacol Biol Psychiatry* 2007; **31**: 776–8.

Administration in renal impairment. Licensed product information recommends that oral doses of tianeptine sodium should not exceed a total of 25 mg daily in patients with renal impairment.

Asthma. Tianeptine has been reported to improve symptoms in patients with asthma.[1] It was thought that reduction of raised levels of free serotonin found in such patients contributed to the beneficial effect of tianeptine.

1. Lechin F, *et al.* The serotonin uptake-enhancing drug tianeptine suppresses asthmatic symptoms in children: a double-blind, crossover, placebo-controlled study. *J Clin Pharmacol* 1998; **38**: 918–25.

Depression. References to the use of tianeptine in patients with depression (p. 398.1) are given below.

1. Wilde MI, Benfield P. Tianeptine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in depression and coexisting anxiety and depression. *Drugs* 1995; **49**: 411–39.
2. Ginestet D. Efficacy of tianeptine in major depressive disorders with or without melancholia. *Eur Neuropsychopharmacol* 1997; **7** (suppl 3): S341–S345.
3. Wagstaff AJ, *et al.* Tianeptine: a review of its use in depressive disorders. *CNS Drugs* 2001; **15**: 231–59.
4. Kasper S, Olie JP. A meta-analysis of randomized controlled trials of tianeptine versus SSRI in the short-term treatment of depression. *Eur Psychiatry* 2002; **17** (suppl 3): 331–40.
5. Waintraub L, *et al.* Efficacy and safety of tianeptine in major depression: evidence from a 3-month controlled clinical trial versus paroxetine. *CNS Drugs* 2002; **16**: 65–75.
6. Nickel T, *et al.* Clinical and neurobiological effects of tianeptine and paroxetine in major depression. *J Clin Psychopharmacol* 2003; **23**: 155–68.

Pharmacokinetics. References.

1. Royer RJ, *et al.* Tianeptine and its main metabolite: pharmacokinetics in chronic alcoholism and cirrhosis. *Clin Pharmacokinet* 1989; **16**: 186–91.
2. Carlhant D, *et al.* Pharmacokinetics and bioavailability of tianeptine in the elderly. *Drug Invest* 1990; **2**: 167–72.
3. Demotes-Mainard F, *et al.* Pharmacokinetics of the antidepressant tianeptine at steady state in the elderly. *J Clin Pharmacol* 1991; **31**: 174–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Stablon; ***Austria***: Stablon; ***Braz.***: Stablon; ***China***: Tatinol (达体朗); ***Cz.***: Coaxil; ***Fr.***: Stablon; ***Hung.***: Coaxil; ***India***: Stablon; ***Indon.***: Stablon; ***Malaysia***: Stablon; ***Mex.***: Stablon; ***Philipp.***: Stablon†; ***Pol.***: Coaxil; ***Port.***: Stablon; ***Rus.***: Coaxil (Коаксил); ***Singapore***: Stablon; ***Thai.***: Stablon; ***Turk.***: Stablon; ***Ukr.***: Coaxil (Коаксил); ***Venez.***: Stablon.

Tranylcypromine Sulfate *(BANM, rINNM)*

SKF-385; Sulfato de tranilcipromina; Tranilcipromina, sulfato de; Transamine Sulphate; Tranylcypromine, Sulfate de; Tranylcypromine Sulphate; Tranylcypromini Sulfas; Транилципромина Сульфат.

(±)-*trans*-2-Phenylcyclopropylamine sulphate.

$(C_9H_{11}N)_2H_2SO_4$=364.5

CAS — 155-09-9 (tranylcypromine); 13492-01-8 (tranylcypromine sulfate).

ATC — N06AF04.

ATC Vet — QN06AF04.

UNII — 7ZAT6E5870.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Tranylcypromine Sulfate). A white or almost white crystalline powder; odourless or with a faint odour of cinnamaldehyde. Soluble in water; very slightly soluble in alcohol and in ether; insoluble in chloroform.

USP 36: (Tranylcypromine Sulfate). A white or almost white, crystalline powder. Freely soluble in water; very slightly soluble in alcohol and in ether; practically insoluble in chloroform.

Uses and Administration

Tranylcypromine, a cyclopropylamine derivative, is an MAOI with actions and uses similar to those of phenelzine (p. 442.1). It produces a less prolonged inhibition of the enzymes than phenelzine.

Tranylcypromine is used in the treatment of depression, but as discussed on p. 398.1 the risks associated with traditional non-selective MAOIs such as tranylcypromine usually mean that other antidepressants are preferred. It is given orally as the sulfate although doses are expressed in terms of the base. Tranylcypromine sulfate 13.7 mg is equivalent to about 10 mg of tranylcypromine.

The usual initial dose is equivalent to tranylcypromine 10 mg in the morning and 10 mg in the afternoon; if the response is inadequate after a week, the afternoon dose may be increased to 20 mg or alternatively, 10 mg may be given additionally at midday. A dosage of 30 mg daily should only be exceeded with caution, although in the USA a maximum dose of 60 mg daily is allowed. Once a satisfactory response has been obtained the dosage may be gradually reduced for maintenance; some patients may continue to respond to 10 mg daily.

Tranylcypromine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Adverse Effects, Treatment, and Precautions

As for MAOIs in general (see Phenelzine, p. 442.2).

Tranylcypromine has a stimulant action and insomnia is a common adverse effect if it is taken in the evening.

Hypertensive reactions are more likely to occur with tranylcypromine than with other MAOIs, but severe liver damage occurs less frequently.

Dependence. Dependence on tranylcypromine with tolerance has been reported in patients receiving high doses with or without a history of previous substance abuse. For further details, see Withdrawal under Precautions in Phenelzine, p. 444.2.

Effects on the cardiovascular system. Although orthostatic hypotension is more common, hypertension can occur with MAOIs. A hypertensive crisis has been described in 2 patients after only one dose of tranylcypromine.[1,2] In the first case it was thought possible that an autointeraction may have occurred between tranylcypromine and amfetamine to which it is partly metabolised. In the second case the provocation of hypertension led to the finding of a previously undiagnosed phaeochromocytoma and it was suggested this may have been a possibility in previous reports of hypertension induced by MAOIs.

1. Gunn J, *et al.* Hypertensive crisis and broad complex bradycardia after a single dose of monoamine oxidase inhibitor. *BMJ* 1989; **298:** 964.
2. Cook RF, Katritsis D. Hypertensive crisis precipitated by a monoamine oxidase inhibitor in a patient with phaeochromocytoma. *BMJ* 1990; **300:** 614.

Interactions

For interactions associated with MAOIs, see Phenelzine, p. 444.3 and p. 445.1.

The use of clomipramine with tranylcypromine is particularly hazardous.

Pharmacokinetics

Tranylcypromine is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur about 1 to 3 hours after ingestion. It is excreted in the urine mainly in the form of metabolites. Tranylcypromine has a reported plasma elimination half-life of about 2.5 hours.

In 9 depressed patients, tranylcypromine absorption was rapid after oral dosing.[1] Absorption was biphasic in 7. Elimination was also rapid, with an elimination half-life of 1.54 to 3.15 hours. From 2 to 7 hours after dosing, standing systolic and diastolic blood pressures were lowered, and standing pulse was raised. The onset of the effect on standing systolic blood pressure correlated with the time of peak plasma tranylcypromine concentration. Maximum orthostatic drop of blood pressure and rise in pulse rate occurred 2 hours after dosing. Mean plasma-tranylcypromine concentrations correlated with mean orthostatic drop of systolic blood pressure and rise of pulse rate. Patients having clinically significant hypotensive reactions to tranylcypromine may benefit from changes in their dose regimen aimed at minimising peak concentrations.

1. Mallinger AG, *et al.* Pharmacokinetics of tranylcypromine in patients who are depressed: relationship to cardiovascular effects. *Clin Pharmacol Ther* 1986; **40:** 444–50.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Parnate; *Braz.*: Parnate; *Canad.*: Parnate; *Ger.*: Jatrosom; *Irl.*: Parnate; *NZ*: Parnate; *S. Afr.*: Parnate; *Spain*: Parnate; *USA*: Parnate.

Multi-ingredient Preparations. *Arg.*: Cuait D; Stelapar; *Ital.*: Parmodalin.

Pharmacopoeial Preparations
BP 2014: Tranylcypromine Tablets;
USP 36: Tranylcypromine Tablets.

Trazodone Hydrochloride

(BANM, USAN, rINNM)

AF-1161; Hidrocloruro de trazodona; Trazodon Hidroklorür; Trazodona, hidrocloruro de; Trazodone, Chlorhydrate de; Trazodoni Hydrochloridum; Тразодона Гидрохлорид.

2-[3-(4-*m*-Chlorophenylpiperazin-1-yl)propyl]-1,2,4-triazolo[4,3-*a*]pyridin-3(2*H*)-one hydrochloride.

$C_{19}H_{22}ClN_5O,HCl$=408.3

CAS — 19794-93-5 (trazodone); 25332-39-2 (trazodone hydrochloride).

ATC — N06AX05.

ATC Vet — QN06AX05.

UNII — 6E8ZO8LRNM.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of trazodone hydrochloride:

Sleepeasy.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Trazodone Hydrochloride). A white or almost white crystalline powder. Soluble in water; sparingly soluble in alcohol; practically insoluble in ether. A 1% solution in water has a pH of 3.9 to 4.5. Store in airtight containers. Protect from light.

USP 36: (Trazodone Hydrochloride). A white to off-white crystalline powder. Sparingly soluble in water and in chloroform. Store in airtight containers. Protect from light.

Uses and Administration

Trazodone is a triazolopyridine antidepressant chemically unrelated to other classes of antidepressants. It blocks the reuptake of serotonin at presynaptic neurones and has an action at 5-HT_1 receptors. Trazodone is also an antagonist at 5-$HT_{2A/2C}$ receptors. Unlike the tricyclic antidepressants, trazodone does not inhibit the peripheral reuptake of noradrenaline, although it may indirectly facilitate neuronal release. Trazodone blocks central α_1-adrenoceptors and appears to have no effect on the central reuptake of dopamine. It does not appear to have very significant antimuscarinic properties, but has a marked sedative action.

For the treatment of **depression** trazodone hydrochloride is given in oral doses of 150 mg daily initially; total daily dosage may be increased by 50 mg every 3 or 4 days up to 300 to 400 mg daily if necessary. The daily dosage may be divided throughout the day after food or be given as a single dose at night. Divided daily dosages of up to 600 mg may be given in severe depression in hospitalised patients. A suggested initial dose in elderly and other susceptible patients is 100 mg daily, and total daily doses above 300 mg are unlikely to be needed in these patients. A modified-release preparation that is given once daily is also available; the maximum daily dose for this preparation is 375 mg as a single dose at bedtime.

In the treatment of **anxiety** (p. 1028.1), trazodone hydrochloride is given in an initial oral dose of 75 mg daily increasing to 300 mg daily if necessary.

As with other antidepressants, trazodone should be withdrawn gradually.

Depression. As discussed on p. 398.1, there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effect profile. Trazodone has a different biochemical profile from both the tricyclics and the SSRIs.

References.

1. Weisler RH, *et al.* Comparison of bupropion and trazodone for the treatment of major depression. *J Clin Psychopharmacol* 1994; **14:** 170–9.

Disturbed behaviour. Trazodone has produced beneficial results[1-3] when tried in various disorders for the control of symptoms such as agitation, aggression, and disruptive behaviour (see p. 1030.2). Some[4] also consider that, in the management of dementia, trazodone might be worth trying in nonpsychotic patients with disturbed behaviour, especially those with mild symptoms or those intolerant of or unresponsive to antipsychotics. However, the evidence for such use is poor; a systematic review on the use of trazodone in the treatment of behavioural and psychological symptoms of dementia found that the evidence from randomised, placebo-controlled studies was insufficient for any recommendations to be made.[5] The risk of adverse effects such as sedation and orthostatic hypotension, which may be particularly problematic in the elderly, should also be considered.[4]

1. Pasion RC, Kirby SG. Trazodone for screaming. *Lancet* 1993; **341:** 970.
2. Lebert F, *et al.* Behavioral effects of trazodone in Alzheimer's disease. *J Clin Psychiatry* 1994; **55:** 536–8.
3. Sultzer DL, *et al.* A double-blind comparison of trazodone and haloperidol for treatment of agitation in patients with dementia. *Am J Geriatr Psychiatry* 1997; **5:** 60–9.
4. Rabins PV, *et al.* APA Work Group on Alzheimer's Disease and other Dementias. Steering Committee on Practice Guidelines. American Psychiatric Association practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Second edition. *Am J Psychiatry* 2007; **164** (12 suppl): 5–56. Also available at: http://www.psychiatryonline.com/pracGuide/loadGuidelinePdf.aspx?file=AlzPG101007 (accessed 23/07/08)
5. Martinon-Torres G, *et al.* Trazodone for agitation in dementia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 24/11/05).

Sexual dysfunction. Priapism can occur as an adverse effect of trazodone (see Effects on Sexual Function in Adverse Effects, p. 454.1) and this has led to studies of oral trazodone for the treatment of erectile dysfunction (p. 2348.2). Positive responses have been reported, both with yohimbine[1] and alone.[2] However, there appear to have been few controlled studies and a systematic review[3] considered some of these to be either small, brief, or methodologically weak. Meta-analysis[3] of data from 6 studies did not find trazodone to be superior to placebo but subgroup analysis possibly suggested a better outcome in patients with psychogenic erectile dysfunction and in those given doses of 150 to 200 mg daily.

1. Montorsi F, *et al.* Effect of yohimbine-trazodone on psychogenic impotence: a randomized, double-blind, placebo-controlled study. *Urology* 1994; **44:** 732–6.
2. Lance R, *et al.* Oral trazodone as empirical therapy for erectile dysfunction: a retrospective review. *Urology* 1995; **46:** 117–20.
3. Fink HA, *et al.* Trazodone for erectile dysfunction: a systematic review and meta-analysis. *BJU Int* 2003; **92:** 441–6.

Substance dependence. The antidepressant, anxiolytic, and sedative properties of trazodone have been reported to have been useful when tried in patients having withdrawal syndromes from a variety of substances including alcohol (p. 1735.1),[1] cocaine (p. 1990.1),[2] and benzodiazepines (p. 1065.1).[3-5]

1. Le Bon O, *et al.* Double-blind, placebo-controlled study of the efficacy of trazodone in alcohol post-withdrawal syndrome: polysomnographic and clinical evaluations. *J Clin Psychopharmacol* 2003; **23:** 377–83.
2. Small GW, Purcell JJ. Trazodone and cocaine abuse. *Arch Gen Psychiatry* 1985; **42:** 524.
3. Ansseau M, De Roeck J. Trazodone in benzodiazepine dependence. *J Clin Psychiatry* 1993; **54:** 189–91.
4. Rickels K, *et al.* Trazodone and valproate in patients discontinuing long-term benzodiazepine therapy: effects on withdrawal symptoms and taper outcome. *Psychopharmacology (Berl)* 1999; **141:** 1–5.
5. Petrovic M, *et al.* A programme for short-term withdrawal from benzodiazepines in geriatric hospital inpatients: success rate and effect on subjective sleep quality. *Int J Geriatr Psychiatry* 1999; **14:** 754–60.

Adverse Effects and Treatment

Trazodone has sedative properties although drowsiness usually disappears on continuing treatment. Other adverse effects occasionally reported include dizziness, headache, nausea and vomiting, weakness, weight loss, tremor, dry mouth, bradycardia or tachycardia, orthostatic hypotension, oedema, constipation, diarrhoea, blurred vision, restlessness, confusional states, insomnia, and rash. Although some of these effects are typical of antimuscarinic activity it is reported that trazodone has little antimuscarinic activity compared with tricyclic antidepressants. *Animal* studies have also indicated that trazodone is less cardiotoxic than the tricyclics. Priapism has been reported.

Agranulocytosis, thrombocytopenia, and anaemia have been reported rarely. Adverse effects on hepatic function, including jaundice and hepatocellular damage, which may be severe, have also been reported rarely. There have been occasional reports of serotonin syndrome. Neuroleptic malignant syndrome has occurred rarely.

Hyponatraemia possibly due to inappropriate secretion of antidiuretic hormone has been associated with the use of antidepressants, particularly in the elderly.

Symptoms of overdosage include drowsiness, dizziness, vomiting, priapism, respiratory arrest, seizures, and ECG changes. The value of gastric decontamination after overdosage is uncertain; however, activated charcoal may be considered in adults and children who have taken more than 15 mg/kg and present within 1 hour. Thereafter, symptomatic and supportive therapy should be given as appropriate.

Effects on the cardiovascular system. Although trazodone is considered to cause fewer adverse cardiovascular reactions than the tricyclic antidepressants, they have, nevertheless, been reported in individual patients. In therapeutic doses it has been associated with heart block in a patient with pre-existing cardiovascular disease,[1] as well as in a patient with no ECG abnormalities.[2] Similarly, ventricular arrhythmias have been associated with therapeutic doses of trazodone both in patients with a history of cardiac problems,[3,4] and with no history of cardiac abnormalities.[5] Atrial fibrillation has been reported in a patient with ischaemic heart disease.[6]

1. Rausch JL, *et al.* Complete heart block following a single dose of trazodone. *Am J Psychiatry* 1984; **141:** 1472–3.
2. Lippmann S, *et al.* Trazodone cardiotoxicity. *Am J Psychiatry* 1983; **140:** 1383.
3. Janowsky D, *et al.* Ventricular arrhythmias possibly aggravated by trazodone. *Am J Psychiatry* 1983; **140:** 796–7.
4. Vlay SC, Friedling S. Trazodone exacerbation of VT. *Am Heart J* 1983; **106:** 604.
5. Johnson BA. Trazodone toxicity. *Br J Hosp Med* 1985; **33:** 298.
6. White WB, Wong SHY. Rapid atrial fibrillation associated with trazodone hydrochloride. *Arch Gen Psychiatry* 1985; **42:** 424.

Effects on the eyes. A patient receiving clomipramine and trazodone orally noted excessive blinking whenever the dose of trazodone exceeded or equalled that of clomipramine.[1] When trazodone, but not clomipramine, was withdrawn, blinking became normal within 3 weeks.

1. Cooper MA, Dening TR. Excessive blinking associated with combined antidepressants. *BMJ* 1986; **293:** 1243.

Effects on the liver. A mixed hepatocellular-cholestatic liver enzyme pattern has been reported in a patient after about 3 weeks of treatment with trazodone in doses of up to 500 mg daily.[1] The enzyme abnormalities returned to normal 4 weeks after trazodone was stopped but it was suggested that liver enzyme values should be monitored

during the first 4 weeks of therapy. A similar case apparently presenting as obstructive jaundice and hepatocellular inflammation, in which the patient had only been taking 50 mg daily for 2 weeks, has also been described.[2] It was believed that the patient had had an idiosyncratic drug reaction to trazodone. Further reports of trazodone-induced liver injury include an elderly patient who developed chronic active hepatitis after taking trazodone 150 mg daily for about 8 months.[3] Fatal hepatic necrosis in another elderly patient was considered to be due to treatment with trazodone and antipsychotics.[4] The authors of the report[4] noted that up to August 1991 the UK CSM had received 14 reports of adverse effects on the liver associated with trazodone including one case of fatal hepatic necrosis. In one of 2 later reports of trazodone-induced hepatotoxicity,[5] a female patient with rheumatoid arthritis developed jaundice 18 months after trazodone was added to her existing therapy. All drugs were stopped and the patient improved; however, an inadvertent rechallenge with trazodone alone led to a recurrence of her symptoms, which again resolved after trazodone withdrawal. The second case[6] involved a HIV-positive male who was started on methadone, clonidine, and trazodone as part of a detoxification programme; 4 days later acute hepatitis and cholestasis was noted and trazodone and clonidine were withdrawn with subsequent resolution of symptoms. The authors considered that trazodone was the probable cause.

1. Chu AG, *et al.* Trazodone and liver toxicity. *Ann Intern Med* 1983; **99:** 128–9.
2. Sheikh KH, Nies AS. Trazodone and intrahepatic cholestasis. *Ann Intern Med* 1983; **99:** 572.
3. Beck PL, *et al.* Chronic active hepatitis associated with trazodone therapy. *Ann Intern Med* 1993; **118:** 791–2.
4. Hull M, *et al.* Fatal hepatic necrosis associated with trazodone and neuroleptic drugs. *BMJ* 1994; **309:** 378.
5. Fernandes NF, *et al.* Trazodone-induced hepatotoxicity: a case report with comments on drug-induced hepatotoxicity. *Am J Gastroenterol* 2000; **95:** 532–5.
6. Rettman KS, McClintock C. Hepatotoxicity after short-term trazodone therapy. *Ann Pharmacother* 2001; **35:** 1559–61.

Effects on mental state. There have been reports of mania,[1,2] and psychosis with hallucinations[3,4] associated with the use of trazodone in depressed patients; delirium[5] in patients with bulimia nervosa and possible psychosis or hypomania[6] in a patient receiving trazodone-tryptophan treatment for aggression have also been reported.

1. Warren M, Bick PA. Two case reports of trazodone-induced mania. *Am J Psychiatry* 1984; **141:** 1103–4.
2. Arana GW, Kaplan GB. Trazodone-induced mania following desipramine-induced mania in major depressive disorders. *Am J Psychiatry* 1985; **142:** 386.
3. Kraft TB. Psychosis following trazodone administration. *Am J Psychiatry* 1983; **140:** 1383–4.
4. Mizoguchi Y, Monji A. Low-dose-trazodone-induced disorganized type psychosis. *J Neuropsychiatr Clin Neurosci* 2005; **17:** 253–4.
5. Damlouji NF, Ferguson JM. Trazodone-induced delirium in bulimic patients. *Am J Psychiatry* 1984; **141:** 434–5.
6. Patterson BD, Srisopark MM. Severe anorexia and possible psychosis or hypomania after trazodone-tryptophan treatment of aggression. *Lancet* 1989; **i:** 1017.

Effects on sexual function. Trazodone is notable for the number of reports of priapism associated with its use.[1,2] In most cases, priapism occurred during treatment with standard doses after 1 to 3 weeks of therapy. Several patients required surgery and recovery was not always complete.[1] A review[3] of priapism induced by psychotropic drugs proposed that the effect was related to blockade of alpha-adrenoceptors in the absence of sufficient antimuscarinic activity, criteria fulfilled by the pharmacological profile of trazodone.

Inhibition of ejaculation,[4] and an increase in libido in women[5] and men[6] have also been reported with trazodone therapy. There have also been reports of trazodone-associated priapism of the clitoris.[7,8]

1. CSM. Priapism and trazodone (Molipaxin). *Current Problems 13* 1984. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024205-RevisionSelectionMethod=LatestReleased (accessed 05/08/08)
2. Anonymous. Priapism with trazodone (Desyrel). *Med Lett Drugs Ther* 1984; **26:** 35.
3. Patel AG, *et al.* Priapism associated with psychotropic drugs. *Br J Hosp Med* 1996; **55:** 315–19.
4. Jones SD. Ejaculatory inhibition with trazodone. *J Clin Psychopharmacol* 1984; **4:** 279–81.
5. Gartrell N. Increased libido in women receiving trazodone. *Am J Psychiatry* 1986; **143:** 781–2.
6. Sullivan G. Increased libido in three men treated with trazodone. *J Clin Psychiatry* 1988; **49:** 202–3.
7. Pescatori ES, *et al.* Priapism of the clitoris: a case report following trazodone use. *J Urol (Baltimore)* 1993; **149:** 1557–9.
8. Medina CA. Clitoral priapism: a rare condition presenting as a cause of vulvar pain. *Obstet Gynecol* 2002; **100:** 1089–91.

Effects on the skin. Individual reports of adverse dermatological reactions to trazodone have included leucocytoclastic vasculitis,[1] erythema multiforme,[2] and exacerbation of psoriasis.[3]

1. Mann SC, *et al.* Leukocytoclastic vasculitis secondary to trazodone treatment. *J Am Acad Dermatol* 1984; **10:** 699–70.
2. Ford HE, Jenike MA. Erythema multiforme associated with trazodone therapy: case report. *J Clin Psychiatry* 1985; **46:** 294–5.
3. Barth JH, Baker H. Generalized pustular psoriasis precipitated by trazodone in the treatment of depression. *Br J Dermatol* 1986; **115:** 629–30.

Epileptogenic effect. Tonic-clonic seizures related to trazodone therapy have been reported in 2 patients[1,2] with no history of seizure disorders.

1. Bowdan ND. Seizure possibly caused by trazodone hydrochloride. *Am J Psychiatry* 1983; **140:** 642.
2. Lefkowitz D, *et al.* Seizures and trazodone therapy. *Arch Gen Psychiatry* 1985; **42:** 523.

Overdosage. Reviews have indicated that the incidence of serious toxicity from trazodone overdose alone was low compared with tricyclic antidepressant overdose.[1-4]

In a review of 149 such cases,[1] only 10 deaths had been reported and in only 1 case was trazodone the sole agent reported taken; in this case autopsy revealed an acute myocardial infarction after the patient was stable. The other 9 patients also had histories of taking unknown quantities of alcohol, benzodiazepines, or other sedative-hypnotics that may have contributed to their death. In the surviving 139 patients there were 2 cases of respiratory arrest, 2 cases of right bundle branch block, and one case each of priapism, seizure, atrioventricular block, and T-wave inversion. The remaining patients had minor CNS-depressant effects.

In another review[2] of overdose no fatalities occurred in 39 cases where trazodone was taken alone, but there were 9 deaths in 49 cases where trazodone was taken with other drugs or alcohol.

For a discussion of choice of antidepressant with respect to toxicity in overdosage, see under Depression, p. 398.1.

1. Hassan E, Miller DD. Toxicity and elimination of trazodone after overdose. *Clin Pharm* 1985; **4:** 97–100.
2. Gamble DE, Peterson LG. Trazodone overdose: four years of experience from voluntary reports. *J Clin Psychiatry* 1986; **47:** 544–6.
3. Crome P, Ali C. Clinical features and management of self-poisoning with newer antidepressants. *Med Toxicol* 1986; **1:** 411–20.
4. Gallant DM. Antidepressant overdose: symptoms and treatment. *Psychopathology* 1987; **20** (suppl 1): 75–81.

Precautions

Trazodone should be used with caution in patients with cardiovascular disorders, such as ischaemic heart disease, and its use is not recommended in the immediate recovery phase after myocardial infarction. Similarly, it should be used with caution in patients with epilepsy and severe hepatic or renal impairment. Trazodone should be stopped immediately if patients develop signs of hepatic dysfunction or blood dyscrasias. Patients developing inappropriate or prolonged penile erections should also stop trazodone immediately.

Patients should be closely monitored during early antidepressant therapy until significant improvement in depression occurs because suicide is an inherent risk in depressed patients. For further details, see under Depression, p. 398.1. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be observed when treating patients with other disorders.

Drowsiness often occurs at the start of trazodone therapy and patients, if affected, should not drive or operate machinery.

As with other antidepressants, trazodone therapy should be withdrawn gradually.

Breast feeding. The American Academy of Pediatrics[1] considers that, although the effect of trazodone on breast-fed infants is unknown, its use by mothers during breast feeding may be of concern since antidepressants do appear in breast milk and thus could conceivably alter infant CNS function both in the short and long term.

A study of 6 women each given a single 50-mg dose of trazodone concluded that the exposure of infants to trazodone via breast milk was very small.[2] However, trazodone has been reported to form an active metabolite and it was unknown to what extent this metabolite distributed into breast milk.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 24/11/05)
2. Verbeeck RK, *et al.* Excretion of trazodone in breast milk. *Br J Clin Pharmacol* 1986; **22:** 367–70.

Pregnancy. UK licensed product information states that trazodone should be avoided during pregnancy; that for the USA indicates that trazodone should only be used if the benefits to the mother outweigh the risks to the fetus.

For details of outcome in a multicentre study on the use of trazodone during pregnancy, see under Nefazodone, p. 439.2.

Interactions

Trazodone should not be given to patients receiving MAOIs or for at least 14 days afterwards. It has also been recommended that any drug liable to provoke a serious reaction (e.g. phenelzine) should not be given within one week of stopping trazodone therapy. For further details of combination antidepressant therapy, see Antidepressants under Interactions of Phenelzine, p. 445.2.

It is considered unlikely that trazodone will alter the effects of antihypertensives such as guanethidine; some interaction may, however, occur with clonidine. The dose of other antihypertensives may need to be reduced if used with trazodone.

The sedative effects of trazodone may be enhanced by alcohol or other CNS depressants. The potential for interaction between trazodone and general anaesthetics or muscle relaxants exists and some licensed product information recommends that trazodone should be stopped before elective surgery for as long as clinically feasible.

Trazodone may increase plasma concentrations of digoxin or phenytoin and some product information recommends monitoring their serum concentrations if used with trazodone.

Trazodone is metabolised by the cytochrome P450 isoenzyme CYP3A4 and inhibitors of this isoenzyme may limit the elimination of trazodone. Consequently, trazodone may need to be given in reduced doses with drugs known to be potent inhibitors of CYP3A4 such as the azole antifungals itraconazole and ketoconazole, and the HIV-protease inhibitors. CYP3A4 inducers such as carbamazepine may reduce the plasma concentrations of trazodone.

Anticoagulants. For the effect of trazodone on *warfarin* dose requirement, see p. 1531.3.

Antiepileptics. Antidepressants may antagonise the activity of antiepileptics by lowering the convulsive threshold.

Trazodone may increase plasma concentrations of *carbamazepine* (see p. 516.2) and *phenytoin* (see p. 543.1). Some licensed product information recommends monitoring concentrations of phenytoin if used with trazodone.

Antivirals. In a small study in 10 subjects, the use of low-dose *ritonavir* (200 mg twice daily for 2 days) with trazodone (50 mg once daily) more than halved the clearance of trazodone resulting in significant increases in its peak plasma concentrations.[1] Adverse reactions were noted in 3 subjects and included dizziness, nausea, hypotension, and syncope.

1. Greenblatt DJ, *et al.* Short-term exposure to low-dose ritonavir impairs clearance and enhances adverse effects of trazodone. *J Clin Pharmacol* 2003; **43:** 414–22.

Ginkgo biloba. Coma, reversible by flumazenil, developed in an 80-year-old woman with Alzheimer's disease 3 days after starting to take a preparation of ginkgo biloba with trazodone.[1]

1. Galluzzi S, *et al.* Coma in a patient with Alzheimer's disease taking low dose trazodone and gingko biloba. *J Neurol Neurosurg Psychiatry* 2000; **68:** 679–80.

Pharmacokinetics

Trazodone is readily absorbed from the gastrointestinal tract and when taken soon after a meal the amount absorbed may be increased. However, peak plasma concentrations, which may be reduced compared with the fasting state, occur about 1 hour after a dose taken on an empty stomach and after about 2 hours when taken with food. Protein binding is reported to be about 89 to 95%.

Trazodone is extensively metabolised in the liver and paths of metabolism include *N*-oxidation and hydroxylation. It is metabolised to its active metabolite *m*-chlorophenylpiperazine via the cytochrome P450 isoenzyme CYP3A4. Trazodone is excreted mainly in the urine almost entirely in the form of its metabolites, either in free or in conjugated form: some is excreted in the faeces via biliary elimination. The elimination of trazodone from the plasma is biphasic, with a terminal elimination half-life of 5 to 9 hours.

Small amounts of trazodone are distributed into breast milk.

References.

1. Bayer AJ, *et al.* Pharmacokinetic and pharmacodynamic characteristics of trazodone in the elderly. *Br J Clin Pharmacol* 1983; **16:** 371–6.
2. Nilsen OG, Dale O. Single dose pharmacokinetics of trazodone in healthy subjects. *Pharmacol Toxicol* 1992; **71:** 150–3.
3. Nilsen OG, *et al.* Pharmacokinetics of trazodone during multiple dosing to psychiatric patients. *Pharmacol Toxicol* 1993; **72:** 286–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Taxagon; *Austria*: Trittico; *Belg.*: Nestrolan; Trazolan; *Braz.*: Donaren; *Canad.*: Desyrel; Trazorel; *Chile*: Diapresan; Trant; Trittico; Tronsalan; *China*: Mei Su Yu (每素玉); Mesyrel (美抒玉); Shu Xu (舒绪); *Cz.*: Trit-

tico AC; *Fin.*: Azona; *Ger.*: Thombran†; *Gr.*: Trittico; *Hong Kong*: Trittico; *Hung.*: Trittico; *India*: Depryl; *Irl.*: Molipaxin; *Israel*: Trazodil; Trittico†; *Ital.*: Trittico; *Mex.*: Sideril; *Neth.*: Trazolan; *Pol.*: Trittico; *Port.*: Tranzelmi†; Trazone; Triticum; Zamegt; *Rus.*: Trittico (Триттико); *S.Afr.*: Molipaxin; *Singapore*: Trittico; *Spain*: Deprax; *Switz.*: Trittico; *Thai.*: Desirel; Trazo; Zodonrel; Zorel; *Turk.*: Desyrel; *UK*: Molipaxin; *Ukr.*: Trittico (Триттико); *USA*: Oleptro; *Venez.*: Trittico.

Pharmacopoeial Preparations
BP 2014: Trazodone Capsules; Trazodone Tablets;
USP 36: Trazodone Hydrochloride Tablets.

Trimipramine *(BAN, USAN, rINN)*

IL-6001; 7162-RP; Trimeprimine; Trimipramiini; Trimipramin; Trimipramina; Trimipraminum; Тримипрамин.
Dimethyl[3-(10,11-dihydro-5*H*-dibenz[*b*,*f*]azepin-5-yl-2-methyl)propyl]amine.
$C_{20}H_{26}N_2$=294.4
CAS — 739-71-9.
ATC — N06AA06.
ATC Vet — QN06AA06.
UNII — 6S082C9NDT.

Trimipramine Maleate *(BANM, USAN, rINNM)*

Maleato de trimipramina; Trimipramilnimaleaatti; Trimipramin maleinát; Trimipramina, maleato de; Trimipramine Hydrogen Maleate; Trimipramine, Maléate de; Trimipramini maleas; Trimipraminmaleat; Trimipramin-maleát; Trimipramino maleatas; Тримипрамина Малеат.
$C_{20}H_{26}N_2.C_4H_4O_4$=410.5
CAS — 521-78-8.
UNII — 269K6498LD.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Trimipramine Maleate). A white or almost white crystalline powder. Slightly soluble in water and in alcohol. Protect from light.

USP 36: (Trimipramine Maleate). A white to almost white crystalline powder. Slightly soluble in water and in alcohol. Store in airtight containers.

Uses and Administration

Trimipramine is a dibenzazepine tricyclic antidepressant with actions and uses similar to those of amitriptyline (p. 401.1). It has marked antimuscarinic and sedative properties.

Trimipramine is given orally as the maleate although doses are expressed in terms of the base. Trimipramine maleate 34.9 mg is equivalent to about 25 mg of trimipramine. In the treatment of depression, the usual initial dose is the equivalent of trimipramine 50 to 75 mg daily, gradually increased as necessary to 150 to 300 mg daily. The recommended initial dose for the elderly in the UK is 30 to 75 mg daily, gradually increased as necessary. In the USA, the elderly and adolescents may be given 50 mg daily initially followed by gradual increments as necessary up to a maximum of 100 mg daily. Trimipramine may be given in divided doses during the day, but since it has a prolonged half-life, once-daily dosage regimens are also suitable and usually given at night.

Trimipramine has also been given orally as the hydrochloride and the mesilate; the mesilate has also been given intramuscularly.

Trimipramine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p. 402.3).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies trimipramine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

For interactions associated with tricyclic antidepressants, see Amitriptyline, p. 406.1.

Pharmacokinetics

Trimipramine is readily absorbed after oral doses and peak plasma concentrations occur in 2 hours. It is metabolised in the liver to its major metabolite desmethyltrimipramine, which is active. Trimipramine is excreted in the urine mainly in the form of its metabolites. It is about 95% bound to plasma proteins. The plasma elimination half-life is reported to be about 23 hours.

References.
1. Maurer H. Metabolism of trimipramine in man. *Arzneimittelforschung* 1989; **39**: 101–3.
2. Musa MN. Nonlinear kinetics of trimipramine in depressed patients. *J Clin Pharmacol* 1989; **29**: 746–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Surmontil; *Canad.*: Apo-Trimip; Novo-Tripramine; *Denm.*: Surmontil†; *Fin.*: Surmontil; *Fr.*: Surmontil; *Ger.*: Herphonal; Stangyl; Trimineurin†; *Hong Kong*: Surmontil; *Hung.*: Sapilent; *India*: Surmontil; *Irl.*: Surmontil; *Israel*: Surmontil; *Ital.*: Surmontil; *Norw.*: Surmontil; *NZ*: Surmontil; Tripress†; *Philipp.*: Surmontil; *Port.*: Surmontil; *S.Afr.*: Surmontil†; Tydamine; *Singapore*: Apo-Trimip; *Spain*: Surmontil; *Switz.*: Surmontil; Trimine†; *UK*: Surmontil; *USA*: Surmontil.

Pharmacopoeial Preparations
BP 2014: Trimipramine Tablets.

Tryptophan *(BAN, USAN, rINN)*

Triptofán; Triptofanas; Triptófano; Tryptofaani; Tryptofan; L-Tryptophan; Tryptophane; Tryptophanum; W; Триптофан.
L-2-Amino-3-(indol-3-yl)propionic acid.
$C_{11}H_{12}N_2O_2$=204.2
CAS — 73-22-3.
ATC — N06AX02.
ATC Vet — QN06AX02.
UNII — 8DUH1N11BX.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Tryptophan). A white or almost white crystalline or amorphous powder. Sparingly soluble in water; slightly soluble in alcohol; dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides. Protect from light.

USP 36: (Tryptophan). White to slightly yellowish-white crystals or crystalline powder. Soluble in hot alcohol and in dilute hydrochloric acid. pH of a 1% solution in water is between 5.5 and 7.0.

Uses and Administration

Tryptophan is an amino acid that is an essential constituent of the diet. Tryptophan and DL-tryptophan have been used as dietary supplements.

Tryptophan is a precursor of serotonin. Because CNS depletion of serotonin is considered to be involved in depression, tryptophan has been used in its treatment. Although it has been given alone, evidence of efficacy is scant and tryptophan has generally been used as adjunctive therapy in depression. It has sometimes been given with pyridoxine and ascorbic acid, which are involved in its metabolism to serotonin (see Pharmacokinetics, p. 456.1).

In many countries preparations containing tryptophan have either been withdrawn from the market or their availability severely restricted or limited because of its association with the eosinophilia-myalgia syndrome. In the UK, tryptophan is restricted to use as an adjunct to other antidepressant medication or in patients who have failed to respond to an adequate trial of standard antidepressant drug treatment. Therapy should be started by hospital specialists; thereafter tryptophan may be prescribed in the community.

In the treatment of depression the usual oral dose of tryptophan is 1 g given three times daily, but some patients may require up to 6 g daily in divided doses. Lower doses may be required in the elderly especially those with renal or hepatic impairment.

Depression. Evidence of benefit for tryptophan when given alone for depression (p. 398.1) is lacking, though there is some suggestion of a weak antidepressant effect.[1] It has therefore mainly been used with other antidepressants in the belief that it would potentiate their effects. Although beneficial effects have been reported in some patients given tryptophan with SSRIs, tricyclic antidepressants, or MAOIs, either alone or with lithium, evidence of efficacy is mainly limited to case reports and small controlled studies.[2-4]

After the publication of reports linking the use of tryptophan with the eosinophilia-myalgia syndrome (see under Adverse Effects, p. 455.3) preparations containing tryptophan for depression were withdrawn from the market or their use restricted. For details of UK restrictions see Uses and Administration, above.

1. Shaw K, *et al.* Tryptophan and 5-hydroxytryptophan for depression. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2002 (accessed 24/11/05).
2. Barker WA, *et al.* The Newcastle chronic depression study: results of a treatment regime. *Int Clin Psychopharmacol* 1987; **2**: 261–72.
3. Smith S. Tryptophan in the treatment of resistant depression—a review. *Pharm J* 1998; **261**: 819–21.
4. Levitan RD, *et al.* Preliminary randomized double-blind placebo-controlled trial of tryptophan combined with fluoxetine to treat major depressive disorder: antidepressant and hypnotic effects. *J Psychiatry Neurosci* 2000; **25**: 337–46.

Dietary supplementation. The use of tryptophan as a dietary supplement has been reviewed.[1] However, because of its association with the eosinophilia-myalgia syndrome (see under Adverse Effects, p. 455.3), the addition of tryptophan to food intended for human consumption is prohibited in some countries.

1. Li Wan Po A, Maguire T. Tryptophan: useful dietary supplement or a health hazard? *Pharm J* 1990; **244**: 484–5.

Insomnia. Tryptophan, sometimes in the form of dietary supplements, has enjoyed some popularity for the treatment of insomnia (p. 1033.2). However, in comparison with other hypnotics such as the benzodiazepines, the effects of tryptophan have been difficult to substantiate, and enthusiasm for tryptophan has waned considerably amongst sleep researchers.[1] It should also be noted that since the publication of reports linking the use of tryptophan with the eosinophilia-myalgia syndrome (see under Adverse Effects, p. 455.3) preparations indicated for insomnia have been withdrawn from the market in many countries.

1. Lahmeyer HW. Tryptophan for insomnia. *JAMA* 1989; **262**: 2748.

Adverse Effects

Tryptophan-containing products have been associated with the eosinophilia-myalgia syndrome; for further details, see p. 455.3.

Other adverse effects that have been reported include nausea, headache, lightheadedness, and drowsiness.

An increased incidence of bladder tumours has been reported in *mice* given L-tryptophan orally as well as in cholesterol pellets embedded in the bladder lumen. However, there was no increase in tumour incidence when only high-dose, oral tryptophan was given.

Eosinophilia-myalgia syndrome. In late 1989 the first notification linking the eosinophilia-myalgia syndrome with the use of tryptophan-containing products was made in the USA.[1] There followed similar published case reports from the USA, Europe, and Japan. Reviews of tryptophan-associated eosinophilia-myalgia syndrome have noted that by early 1990 over 1500 cases were known in the USA.[2,3]

In early 1990 the CDC in the USA summarised the features and known reports concerning the syndrome.[4] As the name implies the characteristic features are an intense eosinophilia with disabling fatigue and muscle pain, although multisystem organ involvement and inflammatory disorders affecting the joints, skin, connective tissue, lungs, heart, and liver have also been recorded. Symptoms have generally developed over several weeks and the syndrome has occurred in patients who had been receiving tryptophan for many years previously with no untoward effect. In most patients slow and gradual improvement in the degree of eosinophilia and other clinical manifestations has followed the withdrawal of tryptophan, but in some patients the disease has progressed despite withdrawal and there have been fatalities.[5-7] The inflammatory condition has necessitated the use of corticosteroids in some patients.

The eosinophilia-myalgia syndrome has been reported in patients taking both tryptophan-containing prescription products for depression and non-prescription dietary supplements for disorders including insomnia, the premenstrual syndrome, and stress; it does not appear to have occurred in patients receiving amino-acid preparations containing tryptophan as part of total parenteral nutrition regimens. The recognition of this syndrome led to the withdrawal of tryptophan-containing products or severe restrictions being imposed upon their use in many countries during 1990.

Various theories were proposed as to the reason for the association of tryptophan with this syndrome. Confusion existed because the reports implicated a very wide range of products from different manufacturers. However, later evidence appeared to have confirmed that contaminated tryptophan had originated from a single manufacturer in Japan.[8-10] Bulk tryptophan was imported from Japan for manufacture into finished pharmaceutical dosage forms and it was noted in one of these reports[9] that a single product was often found to contain two or more lots of powdered tryptophan that were blended together during the production of tablets or capsules. Many trace contaminants have been found in batches of tryptophan associated with the syndrome.[11] One contaminant has been identified as 1,1'-ethylidenebis(tryptophan).[12] Its inclusion in bulk tryptophan powder appeared to coincide with alterations in the manufacturing conditions that involved a change in the strain of *Bacillus amyloliquefaciens* used in the fermentation process and a reduction in the amount of charcoal used for purification.[9] Other investigations indicated the presence of bacitracin-like peptides in batches

of the contaminated tryptophan.[13] However, further work[14] has provided only weak support for an association between the syndrome and any one particular contaminant and the causative agent remains to be confirmed. Nonetheless, since the syndrome only appeared to be associated with tryptophan from one manufacturer, tryptophan preparations were reintroduced in the UK in 1994 for restricted use under carefully monitored conditions.[15] In January 2005, the UK requirement for patient registration and monitoring was removed.

1. Anonymous. Eosinophilia-myalgia syndrome—New Mexico. *MMWR* 1989; 38: 765–7.
2. Troy JL. Eosinophilia-myalgia syndrome. *Mayo Clin Proc* 1991; 66: 535–8.
3. Milburn DS, Myers CW. Tryptophan toxicity: a pharmacoepidemiologic review of eosinophilia-myalgia syndrome. *DICP Ann Pharmacother* 1991; 25: 1259–62.
4. Kilbourne EM, *et al.* Interim guidance on the eosinophilia-myalgia syndrome. *Ann Intern Med* 1990; 112: 85–6.
5. Anonymous. Eosinophilia-myalgia syndrome associated with ingestion of L-tryptophan—United States, through August 24, 1990. *JAMA* 1990; 264: 1655.
6. Kaufman LD, *et al.* Clinical follow-up and immunogenetic studies of 32 patients with eosinophilia-myalgia syndrome. *Lancet* 1991; 337: 1071–4.
7. Hertzman PA, *et al.* The eosinophilia-myalgia syndrome: status of 205 patients and results of treatment 2 years after onset. *Ann Intern Med* 1995; 122: 851–5.
8. Slutsker L, *et al.* Eosinophilia-myalgia syndrome associated with exposure to tryptophan from a single manufacturer. *JAMA* 1990; 264: 213–17.
9. Belongia EA, *et al.* An investigation of the cause of the eosinophilia-myalgia syndrome associated with tryptophan use. *N Engl J Med* 1990; 323: 357–65.
10. Varga J, *et al.* The cause and pathogenesis of the eosinophilia-myalgia syndrome. *Ann Intern Med* 1992; 116: 140–7.
11. Hill RH, *et al.* Contaminants in L-tryptophan associated with eosinophilia myalgia syndrome. *Arch Environ Contam Toxicol* 1993; 25: 134–42.
12. Mayeno AN, *et al.* Characterization of "peak E", a novel amino acid associated with eosinophilia-myalgia syndrome. *Science* 1990; 250: 1707–8.
13. Barnhart ER, *et al.* Bacitracin-associated peptides and contaminated L-tryptophan. *Lancet* 1990; 336: 742.
14. Philen RM, *et al.* Tryptophan contaminants associated with eosinophilia-myalgia syndrome. *Am J Epidemiol* 1993; 138: 154–9.
15. CSM/MCA. L-Tryptophan (Optimax): limited availability for resistant depression. *Current Problems* 1994; 20: 2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024457&RevisionSelectionMethod=LatestReleased (accessed 05/08/08)

Precautions

Tryptophan has been associated with eosinophilia-myalgia syndrome (see p. 453.3); caution is advised in patients receiving the drug who develop some, but not all, of the symptoms of this syndrome. It should not be used in those with a history of eosinophilia-myalgia syndrome associated with tryptophan treatment.

Patients should be closely monitored during early antidepressant therapy until significant improvement in depression occurs because suicide is an inherent risk in depressed patients. For further details, see under Depression, p. 398.1. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be followed when treating patients with other disorders.

Patients taking tryptophan may experience drowsiness and, if affected, they should not drive or operate machinery. For further details of the effects of antidepressant therapy on driving see under Amitriptyline, p. 405.2.

Abnormal metabolism of tryptophan may occur in patients with pyridoxine deficiency and tryptophan is thus sometimes given with pyridoxine supplements.

Interactions

Although tryptophan has been given to patients receiving MAOIs in the belief that clinical efficacy may be improved, it should be noted that the adverse effects may also be potentiated. For further details, see Antidepressants under Interactions of Phenelzine, p. 445.2.

Use of tryptophan with drugs that inhibit the reuptake of serotonin may exacerbate the adverse effects of the latter and precipitate the serotonin syndrome (p. 443.2).

There have been occasional reports of sexual disinhibition in patients taking tryptophan with phenothiazines or benzodiazepines.

For a report of tryptophan reducing blood concentrations of levodopa, see Nutritional Agents under Interactions of Levodopa, p. 908.3.

Pharmacokinetics

Tryptophan is readily absorbed from the gastrointestinal tract. Tryptophan is extensively bound to plasma albumin. It is metabolised in the liver by tryptophan pyrrolase and tryptophan hydroxylase. Metabolites include hydroxytryptophan, which is then converted to serotonin, and kynurenine derivatives. Some tryptophan is converted to nicotinic acid and nicotinamide. Pyridoxine and ascorbic acid are cofactors in the decarboxylation and hydroxylation, respectively, of tryptophan; pyridoxine apparently prevents the accumulation of the kynurenine metabolites.

References.
1. Green AR, *et al.* The pharmacokinetics of L-tryptophan following its intravenous and oral administration. *Br J Clin Pharmacol* 1985; 20: 317–21.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Kalma; *Canad.*: Tryptan; *Ger.*: Ardeydorm; Ardeytropin; Kalma†; *UK*: Optimax†.

Multi-ingredient Preparations. *Braz.*: Organoneuro Optico; Profol; *Fr.*: Fibromyalgine Fort; Neurobiane; Phytozac; Seroxyl; Vita-Dermacide; *Ital.*: Brioplus; Pisioreve CM; Pineal; Promolax; Stressout; *Mex.*: Aminoyodarsencal; *Ukr.*: Gentaxan (Гентаксан); *USA*: PDP Liquid Protein.

Venlafaxine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de venlafaxina; Venlafaxina, hidrocloruro de; Venlafaxine, chlorhydrate de; Venlafaxinhydrochlorid; Venlafaxin-hydrochlorid; Venlafaxini Hydrochloridum; Venlafaxinum Hydrochloridum; Wenlafaksyny chlorowodorek; Wy-45030; Венлафаксина Гидрохлорид.

(*RS*)-1-(2-Dimethylamino-1-*p*-methoxyphenylethyl)cyclohexanol hydrochloride.

$C_{17}H_{27}NO_2,HCl$=313.9

CAS — 93413-69-5 (venlafaxine); 99300-78-4 (venlafaxine hydrochloride).

ATC — N06AX16.

ATC Vet — QN06AX16.

UNII — 7D7RXSA8MO.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Venlafaxine Hydrochloride). A white or almost white powder. It exhibits polymorphism. Freely soluble in water and in methyl alcohol; soluble in dehydrated alcohol; slightly soluble or practically insoluble in acetone.

USP 36: (Venlafaxine Hydrochloride). An off-white to white crystalline powder. Soluble in water and in methyl alcohol. Store at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Venlafaxine, a phenylethylamine derivative, is a serotonin and noradrenaline reuptake inhibitor (SNRI); it also weakly inhibits dopamine reuptake. It is reported to have little affinity for muscarinic, histaminergic, or α_1-adrenergic receptors *in vitro*. Venlafaxine is given orally as the hydrochloride although doses are expressed in terms of the base; venlafaxine hydrochloride 28.3 mg is equivalent to about 25 mg of venlafaxine. It should be taken with food.

Venlafaxine is used in the treatment of **depression**. The initial daily dose is equivalent to venlafaxine 75 mg in two or three divided doses. In the USA, it is suggested that some patients may be best started on 37.5 mg daily for the first 4 to 7 days before increasing the dose to 75 mg daily. The dose may be increased, if necessary, in steps of up to 75 mg and usually at intervals of 2 weeks or more. In some cases, because of disease severity, the dose may be increased more rapidly, but the interval between increases should be at least 4 days. Doses of up to 225 mg daily are usually effective for patients with moderate depression, but further increases up to a maximum daily dose of 375 mg, given in three divided doses, may be required in severely depressed patients. Modified-release preparations are available for once-daily dosing.

Venlafaxine is also used, as a modified-release preparation, in the treatment of **generalised anxiety disorder**. The recommended initial dose is 75 mg once daily. In the USA it is suggested that some patients may be best begun with 37.5 mg daily for 4 to 7 days initially, before increasing the dose to 75 mg daily. The dose may be subsequently increased, if necessary, in steps of up to 75 mg to a maximum of 225 mg daily. The interval between dose increases is usually 2 weeks or more, and should be at least 4 days.

Modified-release venlafaxine is licensed for the treatment of **social anxiety disorder** in doses similar to those used for generalised anxiety disorder (although licensed product information states that there is no evidence of additional benefit from doses above 75 mg daily). It is also licensed for **panic disorder** with or without agoraphobia in doses of 37.5 mg once daily for the first 7 days, then increasing to 75 mg daily. Subsequent increases in increments of up to 75 mg may be made to a maximum dose of 225 mg daily. The interval between dose increases is usually 2 weeks or more, and should be at least 7 days.

Reduced doses may need to be given in hepatic or renal impairment, see p. 456.3.

Venlafaxine should be withdrawn gradually to reduce the risk of withdrawal symptoms (see Precautions, p. 458.1).

Administration in hepatic impairment. In general, it is recommended that the usual dose of venlafaxine (see Uses and Administration, above) should be reduced by 50% in patients with mild to moderate hepatic impairment, and adjusted according to response. The drug should be used with caution, and even greater reductions in dose should be considered, for those with severe impairment or cirrhosis.

Administration in renal impairment. In the UK, licensed product information advises that patients with a glomerular filtration rate (GFR) of 30 mL/minute and above may be given the usual dose of venlafaxine (see Uses and Administration, above), although the drug should be used with caution. For patients with a GFR of less than 30 mL/minute, and those requiring haemodialysis, the usual dose should be reduced by 50%.

In the USA, it is suggested that the dose of venlafaxine should be reduced by 25% in patients with mild to moderate renal impairment, and by 50% in those requiring haemodialysis.

Anxiety disorders. Venlafaxine is used in the treatment of generalised anxiety disorder and social anxiety disorder (see under Phobic Disorders, p. 1029.1); it may also be of use in a variety of other types of anxiety disorders (p. 1028.1) including the treatment of obsessive-compulsive disorder (p. 1028.2), panic disorder (p. 1029.1), and post-traumatic stress disorder (p. 1029.2).

References.
1. Altamura AC, *et al.* Venlafaxine in social phobia: a study in selective serotonin reuptake inhibitor non-responders. *Int Clin Psychopharmacol* 1999; 14: 239–45.
2. Gelenberg AJ, *et al.* Efficacy of venlafaxine extended-release capsules in nondepressed outpatients with generalized anxiety disorder: a 6-month randomized controlled trial. *JAMA* 2000; 283: 3082–8.
3. Sheehan DV. Attaining remission in generalized anxiety disorder: venlafaxine extended release comparative data. *J Clin Psychiatry* 2001; 62 (suppl 19): 26–31.
4. Katz IR, *et al.* Venlafaxine ER as a treatment for generalized anxiety disorder in older adults: pooled analysis of five randomised placebo-controlled clinical trials. *J Am Geriatr Soc* 2002; 50: 18–25.
5. Hollander E, *et al.* Venlafaxine in treatment-resistant obsessive-compulsive disorder. *J Clin Psychiatry* 2003; 64: 546–50. Correction. *ibid.*; 972.
6. Lenox-Smith AJ, Reynolds A. A double-blind, randomised, placebo controlled study of venlafaxine XL in patients with generalised anxiety disorder in primary care. *Br J Gen Pract* 2003; 53: 772–7.
7. Boyer P, *et al.* Social adjustment in generalised anxiety disorder: a long-term placebo-controlled study of venlafaxine extended release. *Eur Psychiatry* 2004; 19: 272–9.
8. Denys D, *et al.* A double-blind switch study of paroxetine and venlafaxine in obsessive-compulsive disorder. *J Clin Psychiatry* 2004; 65: 37–43.
9. Liebowitz MR, *et al.* Venlafaxine extended release vs placebo and paroxetine in social anxiety disorder. *Arch Gen Psychiatry* 2005; 62: 190–8.
10. Liebowitz MR, *et al.* A randomized controlled trial of venlafaxine extended release in generalized social anxiety disorder. *J Clin Psychiatry* 2005; 66: 238–47.
11. Phelps NJ, Cates ME. The role of venlafaxine in the treatment of obsessive-compulsive disorder. *Ann Pharmacother* 2005; 39: 136–40.
12. Bradwejn J, *et al.* Venlafaxine extended-release capsules in panic disorder: flexible-dose, double-blind, placebo-controlled study. *Br J Psychiatry* 2005; 187: 352–9.
13. Davidson J, *et al.* Venlafaxine extended release in posttraumatic stress disorder: a sertraline- and placebo-controlled study. *J Clin Psychopharmacol* 2006; 26: 259–67. Correction. *ibid.*; 473. [dose]
14. Davidson J, *et al.* Treatment of posttraumatic stress disorder with venlafaxine extended release: a 6-month randomized controlled trial. *Arch Gen Psychiatry* 2006; 63: 1158–65.
15. Ferguson JM, *et al.* Relapse prevention of panic disorder in adult outpatient responders to treatment with venlafaxine extended release. *J Clin Psychiatry* 2007; 68: 58–68.

Depression. As discussed on p. 398.1, there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effect profile. In December 2004 the UK CSM recommended that, because of the risk of adverse cardiovascular effects and toxicity in overdosage (see Adverse Effects and Treatment, p. 457.1), venlafaxine treatment should be begun and maintained under specialist supervision only. After an assessment of further safety evidence, these restrictions were revised in May 2006 and specialist supervision was considered only necessary when starting venlafaxine treatment in severely depressed or hospitalised patients who require doses of 300 mg daily or above. However, it was also advised that venlafaxine should be considered a second-line treatment, after the SSRIs.

The *O*-desmethyl metabolite of venlafaxine, desvenlafaxine (p. 413.2), is also used in depression.

References.
1. Morton WA, *et al.* Venlafaxine: a structurally unique and novel antidepressant. *Ann Pharmacother* 1995; 29: 387–95.
2. Derivan A, *et al.* Venlafaxine: measuring the onset of antidepressant action. *Psychopharmacol Bull* 1995; 31: 439–47.
3. Wellington K, Perry CM. Venlafaxine extended-release: a review of its use in the management of major depression. *CNS Drugs* 2001; 15: 643–69.

4. Cohen LS, *et al.* Venlafaxine in the treatment of postpartum depression. *J Clin Psychiatry* 2001; 62: 592–6.
5. Montgomery SA, *et al.* Venlafaxine versus placebo in the preventive treatment of recurrent major depression. *J Clin Psychiatry* 2004; 65: 328–36.

Hot flushes. For the reference to the use of venlafaxine in the treatment of hot flushes, see under Fluoxetine, p. 418.2.

Hyperactivity. When drug therapy is indicated for attention deficit hyperactivity disorder (p. 2314.1) initial treatment is usually with a central stimulant. Antidepressants may be used for patients who fail to respond to, or who are intolerant of, central stimulants; in open studies venlafaxine has been reported to be effective in both adults[1-3] and children[4-6] although some individual patients had a worsening of symptoms.

1. Hedges D, *et al.* An open trial of venlafaxine in adult patients with attention deficit hyperactivity disorder. *Psychopharmacol Bull* 1995; 31: 779–83.
2. Adler LA, *et al.* Open-label trial of venlafaxine in adults with attention deficit disorder. *Psychopharmacol Bull* 1995; 31: 785–8.
3. Findling RL, *et al.* Venlafaxine in adults with attention-deficit/hyperactivity disorder: an open clinical trial. *J Clin Psychiatry* 1996; 57: 184–9.
4. Olvera RL, *et al.* An open trial of venlafaxine in the treatment of attention-deficit/hyperactivity disorder in children and adolescents. *J Child Adolesc Psychopharmacol* 1996; 6: 241–50.
5. Motavalli Mukaddes N, Abali O. Venlafaxine in children and adolescents with attention deficit hyperactivity disorder. *Psychiatry Clin Neurosci* 2004; 58: 92–5.
6. Findling RL, *et al.* Venlafaxine in the treatment of children and adolescents with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol* 2007; 17: 433–45.

Migraine. Retrospective analysis[1] in patients with tension-type headache (p. 671.3) or migraine (p. 670.3) indicated that venlafaxine, as a modified-release preparation, had potential for headache prophylaxis. A more recent randomised placebo-controlled study[2] also supports the use of modified-release venlafaxine in the prophylaxis of migraine.

1. Adelman LC, *et al.* Venlafaxine extended release (XR) for the prophylaxis of migraine and tension-type headache: a retrospective study in a clinical setting. *Headache* 2000; 40: 572–80.
2. Ozyalcin SN, *et al.* The efficacy and safety of venlafaxine in the prophylaxis of migraine. *Headache* 2005; 45: 144–52.

Pain. Venlafaxine may be of benefit in the treatment of neuropathic pain syndromes (p. 10.1)[1,2] including painful diabetic neuropathy (p. 8.2).[3-5] It has also shown some promise in the treatment of fibromyalgia (see Soft-tissue Rheumatism, p. 14.2).[6]

1. Sumpton JE, Moulin DE. Treatment of neuropathic pain with venlafaxine. *Ann Pharmacother* 2001; 35: 557–9.
2. Grothe DR, *et al.* Treatment of pain syndromes with venlafaxine. *Pharmacotherapy* 2004; 24: 621–9.
3. Davis JL, Smith RL. Painful peripheral diabetic neuropathy treated with venlafaxine HCl extended release capsules. *Diabetes Care* 1999; 22: 1909–10.
4. Kiayias JA, *et al.* Venlafaxine HCl in the treatment of painful peripheral diabetic neuropathy. *Diabetes Care* 2000; 23: 699.
5. Rowbotham MC, *et al.* Venlafaxine extended release in the treatment of painful diabetic neuropathy: a double-blind, placebo-controlled study. *Pain* 2004; 110: 697–706. Correction. *Ibid.* 2005; 113: 248.
6. Sayar K, *et al.* Venlafaxine treatment of fibromyalgia. *Ann Pharmacother* 2003; 37: 1561–5.

Adverse Effects and Treatment

Adverse effects that have been reported most frequently with venlafaxine include nausea, headache, insomnia, somnolence, dry mouth, dizziness, constipation, sexual dysfunction, asthenia, sweating, and nervousness. Other common adverse effects have included anorexia, diarrhoea, dyspepsia, abdominal pain, anxiety, urinary frequency, visual disturbances, mydriasis, vasodilatation, vomiting, tremor, paraesthesia, hypertonia, chills or fever, palpitations, weight gain or loss, increased serum-cholesterol, agitation, abnormal dreams, confusion, arthralgia, myalgia, tinnitus, pruritus, dyspnoea, yawning, and rashes. Dose-related increases in blood pressure have also been noted in some patients.

Less common effects have included reversible increases in liver enzymes, orthostatic hypotension, syncope, arrhythmias, tachycardia, mucous membrane bleeding, ecchymosis, hallucinations, bruxism, muscle spasm, myoclonus, alopecia, altered taste, urinary retention, menorrhagia, angioedema, and photosensitivity reactions.

Convulsions, galactorrhoea, haemorrhage including gastrointestinal bleeding, anaphylaxis, hepatitis, erythema multiforme, Stevens-Johnson syndrome, ataxia, dysarthria, extrapyramidal disorders including psychomotor restlessness and akathisia, and activation of mania or hypomania have been reported rarely. Other rare adverse effects include blood dyscrasias such as agranulocytosis, aplastic anaemia, neutropenia, pancytopenia, and thrombocytopenia, prolongation of the QT interval and torsade de pointes, ventricular tachycardia or fibrillation, rhabdomyolysis, delirium, pancreatitis, and pulmonary eosinophilia.

Aggressive behaviour has developed with venlafaxine treatment particularly at the start and when stopping therapy. Suicidal ideation has been reported, particularly in children (see under Effects on Mental State, p. 457.2).

Hyponatraemia possibly due to inappropriate secretion of antidiuretic hormone has been associated with the use of antidepressants, particularly in the elderly.

In overdosage, symptoms such as sweating, dizziness, somnolence, ECG changes, cardiac arrhythmias, and seizures may be noted. Treatment of overdosage includes consideration of the use of activated charcoal if 7 mg/kg or more has been ingested and the patient presents within 1 hour; this should be followed by symptomatic and supportive therapy. Dialysis, haemoperfusion, exchange perfusion, and measures to increase urine production are considered unlikely to be of benefit.

Effects on the endocrine system. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) with hyponatraemia may be more likely to occur with serotonergic antidepressants such as venlafaxine than with other antidepressants; for further details, see under Fluoxetine p. 419.3.

Effects on the eyes. Acute angle-closure glaucoma developed in a 45-year-old woman 3 days after starting venlafaxine;[1] she recovered after iridotomy. In another case, a 35-year-old man presented with bilateral acute angle-closure glaucoma 10 days after starting venlafaxine.[2] The patient had also had visual disturbances while on mirtazapine and sertraline.

1. Ng B, *et al.* Venlafaxine and bilateral acute angle closure glaucoma. *Med J Aust* 2002; 176: 241.
2. de Guzman MHP, *et al.* Bilateral acute angle closure caused by supraciliary effusions associated with venlafaxine intake. *Med J Aust* 2005; 182: 121–2.

Effects on the hair. Hair loss has been described in 3 women given venlafaxine. The effect was noticed by the patients within a few weeks[1] to 5 months[2] after starting treatment. One patient who noticed hair loss within 1 week of starting venlafaxine had the same problem during previous fluoxetine treatment.[3] In all 3 cases, hair loss abated soon after stopping venlafaxine. In 2 cases hair regrowth was reported within a few weeks,[2,3] but the third report was unclear as to whether regrowth occurred.[1]

1. Pitchot W, Ansseau M. Venlafaxine-induced hair loss. *Am J Psychiatry* 2001; 158: 1159–60.
2. Pereira CE, Goldman-Levine JD. Extended-release venlafaxine-induced alopecia. *Ann Pharmacother* 2007; 41: 1084.
3. O'Bryan EC, Albanese RP. A case report of fluoxetine- and venlafaxine-induced hair loss. *Prim Care Companion J Clin Psychiatry* 2004; 6: 181.

Effects on the liver. Acute hepatitis developed in a 44-year-old woman about 6 months after starting venlafaxine;[1] she recovered once venlafaxine was withdrawn. In another report,[2] acute hepatitis developed in a 78-year-old man about a month after venlafaxine was added to therapy. Again, symptoms resolved when the drug was stopped. Hepatitis was noted in a 60-year-old woman about a month after starting low-dose venlafaxine (75 mg daily); symptoms resolved when the drug was stopped and recurred on rechallenge.[3] Hepatitis has also been attributed to low-dose venlafaxine (37.5 mg daily) in a patient with chronic hepatitis B; other causes of hepatitis and relapse of viral hepatitis were excluded.[4]

For a report of hepatotoxicity in patients taking venlafaxine subsequent to an attempted overdose with sertraline, see p. 420.2.

1. Horsmans Y, *et al.* Venlaxafine-associated [sic] hepatitis. *Ann Intern Med* 1999; 130: 944.
2. Cardona X, *et al.* Venlafaxine-associated hepatitis. *Ann Intern Med* 2000; 132: 417.
3. Phillips BB, *et al.* Hepatitis associated with low-dose venlafaxine for postmenopausal vasomotor symptoms. *Ann Pharmacother* 2006; 40: 323–7.
4. Sencan I, *et al.* Low-dose venlafaxine-associated liver toxicity in chronic hepatitis. *Ann Pharmacother* 2004; 38: 352–3.

Effects on mental state. An expert working group was convened in May 2003 by the UK CSM to consider the ongoing safety concerns of the SSRIs and, in particular, the risk of suicidal behaviour in children; the safety of venlafaxine (another serotonergic antidepressant) was also considered. An interim report issued in September 2003 concluded that data from studies received by the CSM failed to show that venlafaxine was effective in the treatment of depressive illness in **children under 18 years** old and indicated that the risk of harmful outcome including self-harm and suicidal ideation was increased in those receiving venlafaxine when compared with placebo.[1] The CSM recommended that venlafaxine should not be used to treat depressive illness in children under 18 years old. Similar warnings have also been issued in Canada,[2] the EU,[3] and the USA. (The final report[4] of the CSM's expert working group was published in December 2004.)

The risk of suicide and suicide-related events with antidepressant treatment in **adults** including young adults is discussed under Fluoxetine, p. 420.2.

1. MHRA. Safety of venlafaxine in children and adolescents under 18 years in the treatment of depressive illness. Epinet message from Professor G Duff, Chairman of Committee on Safety of Medicines (issued 19th September, 2003). Available at: http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con019501.pdf (accessed 14/08/08)
2. Wyeth Canada. Important safety information regarding the use of Effexor (venlafaxine HCl) tablets and Effexor XR (venlafaxine HCl) capsules in children and adolescents (issued 10th September, 2003). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/effexor_hpc-cps-eng.pdf (accessed 14/08/08)
3. EMEA. European Medicines Agency finalises review of antidepressants in children and adolescents (issued 25th April, 2005). Available at: http://www.emea.europa.eu/docs/en_GB/document_library/Referrals_document/SSRI_31/WC500013082.pdf (accessed 02/08/10)
4. Weller IVD. *Report of the CSM expert working group on the safety of selective serotonin reuptake inhibitor antidepressants.* London: The Stationery Office, 2005. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON0194726&RevisionSelectionMethod=LatestReleased (accessed 14/08/08)

Effects on the skin. A patient developed Stevens-Johnson syndrome 12 days after starting therapy with venlafaxine for recurrent depression.[1] She had also been taking several other drugs for at least 6 months. Symptoms resolved on withdrawal of all medication and treatment with an intravenous corticosteroid. Other adverse dermatological effects that have been described in patients given venlafaxine include psoriasiform palmoplantar keratoderma with subungual hyperkeratosis,[2] and photodistributed eruptive telangiectasia.[3]

1. Weiss NT, *et al.* A possible case of venlafaxine-induced Stevens-Johnson syndrome. *J Clin Psychiatry* 2004; 65: 1431–3.
2. Dalle S, *et al.* Venlafaxine-associated psoriasiform palmoplantar keratoderma and subungual hyperkeratosis. *Br J Dermatol* 2006; 154: 999–1000.
3. Vaccaro M, *et al.* Photodistributed eruptive telangiectasia: an uncommon adverse drug reaction to venlafaxine. *Br J Dermatol* 2007; 157: 822–4.

Overdosage. Rare serious events including seizures and ECG changes[1-3] have occurred after venlafaxine overdoses; in some cases, death has ensued.[4,5] Symptoms suggestive of serotonin toxicity may also develop.[6,7]

Venlafaxine may not be as safe in overdose as some other serotonergic antidepressants. A review[8] of UK data recording the number of deaths due to acute poisoning by a single drug, with or without alcohol, found the number of fatalities per million prescriptions (the fatal toxicity index) was higher for venlafaxine than for other serotonergic antidepressants, and was similar to that for some of the less toxic tricyclic antidepressants.

1. White CM, *et al.* Seizure resulting from a venlafaxine overdose. *Ann Pharmacother* 1997; 31: 178–80.
2. Coorey AN, Wenck DJ. Venlafaxine overdose. *Med J Aust* 1998; 168: 523.
3. Blythe D, Hackett LP. Cardiovascular and neurological toxicity of venlafaxine. *Hum Exp Toxicol* 1999; 18: 309–13.
4. Banham NDG. Fatal venlafaxine overdose. *Med J Aust* 1998; 169: 445, 448.
5. Mazur JE, *et al.* Fatality related to a 30-g venlafaxine overdose. *Pharmacotherapy* 2003; 23: 1668–72.
6. Oliver JJ, *et al.* Venlafaxine poisoning complicated by a late rise in creatine kinase: two case reports. *Hum Exp Toxicol* 2002; 21: 463–6.
7. Whyte IM, *et al.* Relative toxicity of venlafaxine and selective serotonin reuptake inhibitors in overdose compared to tricyclic antidepressants. *Q J Med* 2003; 96: 369–74.
8. Buckley NA, McManus PR. Fatal toxicity of serotoninergic and other antidepressant drugs: analysis of United Kingdom mortality data. *BMJ* 2002; 325: 1332–3.

Serotonin syndrome. The serotonin syndrome (p. 443.2) is most often due to the additive adverse effects of two or more drugs that enhance serotonin activity at central receptors; rarely, a single serotonergic drug may cause the syndrome. One such case[1] was reported to have occurred in a 29-year-old woman who developed symptoms suggestive of serotonin syndrome 3 days after starting low-dose venlafaxine. However, this patient had been switched to venlafaxine the day after stopping imipramine treatment; it is usually recommended that at least 3 weeks should elapse after stopping imipramine before starting another drug with serotonergic properties.

1. Pan J-J, Shen WW. Serotonin syndrome induced by low-dose venlafaxine. *Ann Pharmacother* 2003; 37: 209–11.

Precautions

Venlafaxine should not be used in patients with an identified very high risk of a serious ventricular arrhythmia or uncontrolled hypertension. Caution is advised in those with a recent history of myocardial infarction or whose condition might be exacerbated by an increase in heart rate. Due to the risk of dose-related increases in blood pressure, blood pressure measurement should be performed regularly during therapy. Measurement of serum-cholesterol levels should also be considered with long-term treatment.

Venlafaxine should be used with caution in patients with moderate to severe hepatic or renal impairment and dosage adjustment may be necessary. It should also be used with caution in patients with a history of epilepsy and avoided in those with unstable disease; it should be stopped in any

patient developing a seizure or if there is an increase in seizure frequency. Caution is also advised in patients with a history of bleeding disorders or of hypomania or mania. Patients with raised intra-ocular pressure or at risk of angle-closure glaucoma should be monitored closely. Patients who develop a rash, urticaria, or related allergic reaction with venlafaxine should be advised to contact their doctor.

Patients should be closely monitored during early antidepressant therapy until a significant improvement in depression occurs because suicide is an inherent risk in depressed patients. For further details, see under Depression, p. 398.1. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be observed when treating patients with other disorders.

As with other antidepressants, venlafaxine may impair performance of skilled tasks and, if affected, patients should not drive or operate machinery. Patients, especially the elderly, should be warned of the risk of dizziness or unsteadiness due to orthostatic hypotension.

Symptoms reported on abrupt withdrawal or dose reduction of venlafaxine include fatigue, somnolence, headache, nausea, vomiting, anorexia, palpitations, dizziness, dry mouth, diarrhoea, insomnia, agitation, anxiety, nervousness, confusion, hypomania, paraesthesia, sweating, and vertigo. It is therefore recommended that venlafaxine should be withdrawn gradually and the patient monitored to minimise the risk of withdrawal reactions (see also Withdrawal, under Precautions of Fluoxetine, p. 423.3).

Abuse. A patient had an amfetamine-like "high" after taking crushed modified-release tablets of venlafaxine in doses of up to 3600 mg daily.[1] He continued to ingest increasing amounts of venlafaxine until a 4050-mg dose produced chest pain. On evaluation he had a raised pulse and blood pressure but these returned to normal within a few days.

1. Sattar SP, *et al.* A case of venlafaxine abuse. *N Engl J Med* 2003; 348: 764–5.

Breast feeding. Licensed product information recommends that venlafaxine should not be used in women who are breast feeding.

Venlafaxine and its metabolite *O*-desmethylvenlafaxine were both detected in breast milk in significant quantities in 3 women[1] and concentrations of desmethylvenlafaxine were measurable in their infants' plasma. In another study[2] by the same group the mean milk-to-plasma ratio in 6 breast-feeding women was calculated to be 2.5 for venlafaxine and 2.74 for *O*-desmethylvenlafaxine. Detectable plasma concentrations of venlafaxine were found only in 1 of 7 breast-fed infants while 4 had detectable *O*-desmethylvenlafaxine levels; no adverse effects were reported in the infants. Nonetheless, the authors recommended caution when giving venlafaxine to breast-feeding women particularly for those feeding premature or very young neonates. The distribution of venlafaxine into breast milk and the presence of *O*-desmethylvenlafaxine in the serum of a further 5 breast-fed infants has also been reported.[3,4] There were no detectable adverse effects in the infants, and the authors of 1 report[4] suggested that women being treated for postpartum depression should not be generally discouraged from breast feeding. A study[5] of a further 13 women and their breast-fed infants also found venlafaxine and desvenlafaxine in both breast milk and infant plasma. No adverse effects were seen in the infants.

It has been suggested that venlafaxine in breast milk might alleviate a withdrawal syndrome in the neonate (see Pregnancy, p. 458.2).

1. Ilett KF, *et al.* Distribution and excretion of venlafaxine and *O*-desmethylvenlafaxine in human milk. *Br J Clin Pharmacol* 1998; 45: 459–62.
2. Ilett KF, *et al.* Distribution of venlafaxine and its *O*-desmethyl metabolite in human milk and their effects in breastfed infants. *Br J Clin Pharmacol* 2002; 53: 17–22.
3. Hendrick V, *et al.* Venlafaxine and breast-feeding. *Am J Psychiatry* 2001; 158: 2089–90.
4. Berle JØ, *et al.* Breastfeeding during maternal antidepressant treatment with serotonin reuptake inhibitors: infant exposure, clinical symptoms, and cytochrome P450 genotypes. *J Clin Psychiatry* 2004; 65: 1228–34.
5. Newport DJ, *et al.* Venlafaxine in human breast milk and nursing infant plasma: determination of exposure. *J Clin Psychiatry* 2009; 70: 1304–10.

Children. Venlafaxine is associated with an increased risk of potentially suicidal behaviour when used for the treatment of depression in children and adolescents under 18 years old; for further details, see under Effects on Mental State, p. 455.2.

US licensed product information also refers to studies that suggest that venlafaxine may adversely affect weight and height changes in children. In particular, the difference between the real and the expected growth rate was larger for those children under 12 years of age than for older children.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies venlafaxine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Pregnancy. Licensed product information recommends that venlafaxine should not be used during pregnancy unless clearly necessary.

In a study of 150 women who took venlafaxine in the first trimester of pregnancy there were 125 live births, 18 spontaneous abortions, 7 therapeutic abortions, and 2 reports of major malformations (hypospadias and neural tube defect with club foot).[1] Although the rate of spontaneous abortions was non-significantly higher in the venlafaxine group than in historical controls, the rate of major malformations was not greater than the baseline rate of 1 to 3%.

A neonatal withdrawal syndrome developed in the infant of a mother who had taken venlafaxine throughout her pregnancy;[2] symptoms included restlessness, hypertonia, irritability, and poor feeding. The infant recovered within 8 days. Seizures have been described in 2 neonates whose mothers were taking venlafaxine.[3] Lip smacking and extensor limb posturing began at 30 minutes of age in 1 case, and multifocal myoclonic seizures occurred at 24 hours of age in the other; both recovered and were well at 1 year of age. Serum-venlafaxine concentrations had not been measured and the authors were unsure whether the adverse effects in the neonates were due to withdrawal or toxicity. In a retrospective study[4] of women who had taken SSRIs or venlafaxine during the third trimester (9 had taken venlafaxine), there were reports of adverse effects on the CNS and respiratory tract in the neonates, such as abnormal movements, tonus abnormalities, irritability, insomnia, indrawing, apnoea/bradycardia, and tachypnoea. The signs usually appeared on the first day of life and lasted for about 3 days in full-term neonates and about 5 days in those born prematurely.

Venlafaxine and its metabolite *O*-desmethylvenlafaxine are distributed into breast milk (see Breast Feeding, above), and it has been suggested that breast feeding might have helped to alleviate symptoms of a withdrawal syndrome in a neonate whose mother took venlafaxine throughout her pregnancy.[5]

1. Einarson A, *et al.* Pregnancy outcome following gestational exposure to venlafaxine: a multicenter prospective controlled study. *Am J Psychiatry* 2001; 158: 1728–30.
2. de Moor RA, *et al.* Withdrawal symptoms in a neonate following exposure to venlafaxine during pregnancy. *Ned Tijdschr Geneeskd* 2003; 147: 1370–2.
3. Pakalapati RK, *et al.* Neonatal seizures from in utero venlafaxine exposure. *J Paediatr Child Health* 2006; 42: 737–8.
4. Ferreira E, *et al.* Effects of selective serotonin reuptake inhibitors and venlafaxine during pregnancy in term and preterm neonates. *Pediatrics* 2007; 119: 52–9.
5. Koren G, *et al.* Can venlafaxine in breast milk attenuate the norepinephrine and serotonin reuptake neonatal withdrawal syndrome? *J Obstet Gynaecol Can* 2006; 28: 299–301.

Renal impairment. The mean terminal disposition half-life of venlafaxine was prolonged from a mean of 3.8 hours in 18 healthy subjects to 5.8 hours in 12 patients with mild to moderate renal impairment (creatinine clearance 10 to 70 mL/minute) and 10.6 hours in patients requiring haemodialysis;[1] corresponding values for *O*-desmethylvenlafaxine, the active major metabolite of venlafaxine, were 11.8, 16.8, and 28.5 hours, respectively. Because of the large intersubject variability, the change in disposition for venlafaxine and its active metabolite was evident only in patients with a creatinine clearance of less than 30 mL/minute; drug clearance in these patients was reduced by about 55% and half-life more than doubled. It was calculated that for these patients half the usual daily dose could be given once daily.

Similar recommendations are made in licensed product information, see under Uses and Administration, p. 454.3.

1. Troy SM, *et al.* The effect of renal disease on the disposition of venlafaxine. *Clin Pharmacol Ther* 1994; 56: 14–21.

Surgery. Serotonergic antidepressants such as venlafaxine may be associated with an increased risk of blood loss during surgery; for further details, see under Fluoxetine, p. 423.3.

Withdrawal. Withdrawal reactions may be more common with venlafaxine than with some other serotonergic antidepressants; for further details, see under Fluoxetine, p. 423.3. Withdrawal reactions may also be seen in neonates after maternal venlafaxine use, see under Pregnancy above.

Some cases[1-3] of withdrawal reactions to venlafaxine have been reported.

1. Anonymous. Venlafaxine withdrawal reactions. *Med J Aust* 1998; 169: 91–2.
2. Johnson H, *et al.* Withdrawal reaction associated with venlafaxine. *BMJ* 1998; 317: 787.
3. Khazaal Y. Mania after venlafaxine withdrawal in a patient with generalized anxiety disorder. *Ann Pharmacother* 2007; 41: 359–60.

Interactions

Although different antidepressants have been used together under expert supervision in refractory cases of depression, adverse reactions including the *serotonin syndrome* (see p. 443.2) may occur; in its more severe form, serotonin syndrome can resemble neuroleptic malignant syndrome. Sequential prescribing of different types of antidepressant may also produce adverse reactions, and an appropriate drug-free interval should elapse between stopping one type of antidepressant and starting another. Venlafaxine should not be used with MAOIs and at least 14 days should elapse between stopping an MAOI and starting treatment with venlafaxine. At least 7 days should elapse between stopping venlafaxine and starting any drug liable to provoke a serious reaction (e.g. phenelzine). For further details, see Antidepressants under Interactions of Phenelzine, p. 445.2. Adverse effects such as the serotonin syndrome may also occur when venlafaxine is given with other drugs known to act on the same neurotransmitter, a consequence of synergistic interaction.

Venlafaxine has occasionally been associated with bleeding disorders and other effects on the blood; caution is advised when giving venlafaxine with other drugs known to affect platelet function.

Although cimetidine inhibits the first-pass hepatic metabolism of venlafaxine, it has no effect on the active metabolite *O*-desmethylvenlafaxine, which is present in the plasma in much greater concentrations. Licensed product information therefore considers that when cimetidine and venlafaxine are used together, clinical monitoring may only be necessary in elderly patients and in those with hepatic impairment or pre-existing hypertension.

Conversion of venlafaxine to its equally active metabolite *O*-desmethylvenlafaxine is mediated by the cytochrome P450 isoenzyme CYP2D6. Therefore the potential exists for drugs that inhibit or act as a substrate for this enzyme to affect plasma concentrations of venlafaxine and its active metabolite. However, the US product information indicates that, as the total amount of active compounds is unaffected, no dosage adjustment is usually necessary for venlafaxine. Venlafaxine is also metabolised by CYP3A4 to the less active metabolite *N*-desmethylvenlafaxine. This is a relatively minor pathway and the potential for clinically significant interactions between venlafaxine and CYP3A4 inhibitors is considered to be small. However, potent inhibitors of CYP3A4 or drugs that inhibit both CYP2D6 and CYP3A4 could significantly increase venlafaxine concentrations in patients who are poor CYP2D6 metabolisers; such combinations should therefore be used with caution.

Venlafaxine itself is considered to be a relatively weak inhibitor of CYP2D6.

Antiarrhythmics. Psychosis with raised serum concentrations of venlafaxine and its metabolite *O*-desmethylvenlafaxine developed when *propafenone* therapy was started in a 67-year-old woman. There was improvement when venlafaxine was stopped and restarted at a reduced dose; 50 mg daily was sufficient to maintain therapeutic serum concentrations.[1]

1. Pfeffer F, Grube M. An organic psychosis due to a venlafaxine-propafenone interaction. *Int J Psychiatry Med* 2001; 31: 427–32.

Antibacterials. Tingling in the tip of the tongue, intense paraesthesia in the fingers, severe abdominal cramps, profuse diarrhoea, cold sweats, and uncontrolled shivering and tremor occurred when *co-amoxiclav* was started in a man taking venlafaxine.[1] The reaction lasted for about 6 hours. It occurred again 2 months later after a single dose of co-amoxiclav. The patient reported that he had taken co-amoxiclav in the past without any reaction at a time when he was not taking venlafaxine. The mechanism for an interaction between venlafaxine and co-amoxiclav causing this serotonin syndrome is unknown. The author also suggested that many patients must have taken this combination without adverse effect, and found no other reports.

Serotonin syndrome has been reported in an elderly patient taking venlafaxine, after 20 days of antibacterial treatment including *linezolid*.[2] In another report, serotonin syndrome developed 8 days after starting treatment with intravenous linezolid in a patient taking venlafaxine.[3] For advice regarding the use of linezolid with serotonergic antidepressants such as venlafaxine, see under Interactions of Fluoxetine, p. 424.1.

1. Connor H. Serotonin syndrome after single doses of co-amoxiclav during treatment with venlafaxine. *J R Soc Med* 2003; 96: 233–4.
2. Jones SL, *et al.* Serotonin syndrome due to co-administration of linezolid and venlafaxine. *J Antimicrob Chemother* 2004; 54: 289–90.
3. Bergeron L, *et al.* Serotonin toxicity associated with concomitant use of linezolid. *Ann Pharmacother* 2005; 39: 956–61.

Antimigraine drugs. There have been rare reports of serotonin syndrome associated with the use of serotonin and noradrenaline reuptake inhibitors (SNRIs) with serotonin (5-HT_1) agonists such as *sumatriptan* (see p. 681.3).

Antipsychotics. For mention of neuroleptic malignant syndrome developing in patients who received venlafaxine with antipsychotics see under Interactions in Chlorpromazine, p. 1052.1.

Gastrointestinal drugs. Signs suggestive of the serotonin syndrome that occurred after intravenous *metoclopramide* were attributed to an interaction with venlafaxine.[1] The 32-year-old woman experienced confusion, agitation, generalised shaking, myoclonus, facial twitching, diaphoresis, horizontal nystagmus, and dilated pupils, that resolved within 2 days after stopping both drugs and treatment with diazepam.

1. Fisher AA, Davis MW. Serotonin syndrome caused by selective serotonin reuptake-inhibitors–metoclopramide interaction. *Ann Pharmacother* 2002; 36: 67–71.

Selegiline. Although it is generally recommended that venlafaxine should not be started for at least 14 days after stopping an MAOI, there is a report[1] of serotonin syndrome developing when a patient began venlafaxine treatment 15 days after stopping selegiline, an MAO type B inhibitor.

1. Gitlin MJ. Venlafaxine, monoamine oxidase inhibitors, and the serotonin syndrome. *J Clin Psychopharmacol* 1997; 17: 66–7.

Pharmacokinetics

Venlafaxine is readily absorbed from the gastrointestinal tract. After oral doses it undergoes extensive first-pass metabolism in the liver mainly to the active metabolite *O*-desmethylvenlafaxine; formation of *O*-desmethylvenlafaxine is mediated by the cytochrome P450 isoenzyme CYP2D6. The isoenzyme CYP3A4 is also involved in the metabolism of venlafaxine. Other metabolites include *N*-desmethylvenlafaxine and *N,O*-didesmethylvenlafaxine. Peak plasma concentrations of venlafaxine and *O*-desmethylvenlafaxine occur about 2 and 4 hours after a dose, respectively. Venlafaxine is 27% and *O*-desmethylvenlafaxine 30% bound to plasma proteins. The mean elimination half-life of venlafaxine and *O*-desmethylvenlafaxine is about 5 and 11 hours, respectively. Venlafaxine is excreted mainly in the urine, mainly in the form of its metabolites, either free or in conjugated form; about 2% is excreted in the faeces. Venlafaxine and *O*-desmethylvenlafaxine have been detected in amniotic fluid and umbilical cord blood, and are distributed into breast milk.

References.

1. Troy SM, *et al.* The pharmacokinetics of venlafaxine when given in a twice-daily regimen. *J Clin Pharmacol* 1995; 35: 404–9.
2. Troy SM, *et al.* Pharmacokinetics and effect of food on the bioavailability of orally administered venlafaxine. *J Clin Pharmacol* 1997; 37: 954–61.
3. Ball SE, *et al.* Venlafaxine: in vitro inhibition of CYP2D6 dependent imipramine and desipramine metabolism; comparative studies with selected SSRIs, and effects on human hepatic CYP3A4, CYP2C9 and CYP1A2. *Br J Clin Pharmacol* 1997; 43: 619–26.
4. McAlpine DE, *et al.* Cytochrome P450 2D6 genotype variation and venlafaxine dosage. *Mayo Clin Proc* 2007; 82: 1065–8.

Pregnancy. Venlafaxine and its metabolite, *O*-desmethylvenlafaxine, have been detected in amniotic fluid[1,2] and umbilical cord blood.[1,3] For adverse effects that have occurred in neonates of women who were taking venlafaxine during the third trimester, see Pregnancy, under Precautions, p. 456.2.

1. Hostetter A, *et al.* Amniotic fluid and umbilical cord blood concentrations of antidepressants in three women. *Biol Psychiatry* 2000; 48: 1032–4.
2. Loughhead AM, *et al.* Antidepressants in amniotic fluid: another route of fetal exposure. *Am J Psychiatry* 2006; 163: 145–7.
3. Rampono J, *et al.* A pilot study of newer antidepressant concentrations in cord and maternal serum and possible effects in the neonate. *Int J Neuropsychopharmacol* 2004; 7: 329–34.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Alfaxin; Efexor; Elafax; Ganavax; Mezine; Pramina; Quilarex; Sesaren; Sunvex; Ventifax; ***Austral.***: Efexor; Elaxine; Venla; Venlexor; ***Austria***: Efectin; Venaxibene; Venlafab; ***Belg.***: Efexor; Vennaxa†; ***Braz.***: Alenthus; Efexor; Novidat; Venforin; Venlaxin; Venlift; ***Canad.***: Effexor; ***Chile***: Axone; Depurol; Efexor; Lafaxin†; Nervix; Norpilen; Senexon; Sentidol; Sesaren†; Subelan; Venlacross; Venlax; ***China***: Blossom (博乐欣); Efexor (怡诺思); ***Cz.***: Argofan; Convalemin; Depant; Efectin; Elify; Faxiprol; Lafaxon†; Mollome; Nisaxin†; Nopekar; Olwexya; Prefaxine†; Ranfaxiran†; Tifaxin; Velaxin; Venlafab†; Venlagamma†; ***Denm.***: Efexor; Effexor†; Lavenax†; Nopekar; Panofen; Velaxatin†; Venladima; Venlakato; Venlamed†; Venlapete; Venlapol; Venlathen; ***Fin.***: Efexor; ***Fr.***: Effexor; ***Ger.***: Trevilor; Venlagamma; Venlasan; ***Gr.***: Arvifax; Deprevix; Efaxin; Efetrin; Efexor; Elify; Melocin; Memomax-S; Norafexine; Norezor; Serosmine; Tudor; Velept; Velpine; Ven-Fax; Venaxol; Venlasan; Voxafen; Xadevil; Zacalen; ***Hong Kong***: Efexor; Velaxin; Venxor; ***Hung.***: Arixen; Efectin†; Falven; Faxiprol; Fobiven; Jarvis; Nopekar; Olwexya; Velaxin; Venlaxgen; Ventadepress; ***India***: Dalium; Envelaf; Faxiven; Flavix; Venlor; Vexor; ***Indon.***: Efexor; ***Irl.***: Efaxil; Efexor; Ireven; Tonpular; Vedixal; Velexor; Venex; Venixaf; Venlafex; Venlalic; Venlift†; Venlofex; Vensir; ***Israel***: Efexor; Venla; Viepax; ***Ital.***: Efexor; Faxine; Zarelis; ***Malaysia***: Efexor; Venxor; ***Mex.***: Benolaxe; Efexor; Lafaxven; Odven SBK; ***Neth.***: Efexor; Elbfaxin†; Hafaxin†; Jarvis; Kofaxin†; Symfaxin†; Tifaxin†; Vendep†; Venfalex; Venlabacher; Venlaburg†; Venladem†; Venladoz; Venlamyl; Venlanofi; Venlaraf†; Venlaran†; Venlasand; Venlatif; Venlatio†; Venlexor; ***Norw.***: Efexor; Venlix; ***NZ***: Efexor; ***Philipp.***: Efexor; Venlift; ***Pol.***: Alventa; Axyven; Efectin; Efevelon; Faxigen; Faxolet; Jarvis; Lafactin; Oriven; Prefaxine; Symfaxin; Tonpular; Velafax; Velaxin; Venlectine; ***Port.***: Afax; Bexalov; Desinax; Efexor; Genexin; Pracet; Tubernax; Vedixal; Velax; Venxin; Xapnev; Zarelix; ***Rus.***: Alventa (Алвента); Efectin (Эфектин); Efevelone (Эфевелон); Velafax (Велафакс); Velaxin (Велаксин); Venlaxor (Венлаксор); ***S.Afr.***: Efegen; Efexor; Illovex; Odiven; Venlor; ***Singapore***: Efexor; VicPax†; ***Spain***: Arafaxina; Conervin; Dislaven; Dobupal; Flaxen; Levest; Vandral; Venlabrain; Venlamylan; Venlapine; Zarelis; ***Swed.***: Efexor; ***Switz.***: Efexor; Venlax; ***Thai.***: Efexor; Valosine; ***Turk.***: Efexor; Venfecto; Veniba; ***UK***: Depefex; Efexor; Foraven; Politid; Tifaxin; Tonpular; Venaxx; Venlalic; Winfex; ***Ukr.***: Velaxin (Велаксин); Venlaxor (Венлаксор); ***USA***: Effexor; ***Venez.***: Efexor; Idoxen; Sesaren.

Pharmacopoeial Preparations

BP 2014: Prolonged-release Venlafaxine Capsules; Prolonged-release Venlafaxine Tablets; Venlafaxine Tablets;

USP 36: Venlafaxine Hydrochloride Extended-Release Capsules; Venlafaxine Tablets.

Vilazodone *(USAN, rINN)*

EMD-515259; Vilazodona; Vilazodonum; Вилазодон.

5-[4-[4-(5-Cyanoindol-3-yl)butyl]-1-piperazinyl]-2-benzofurancarboxamide.

$C_{26}H_{27}N_5O_2$=441.5

CAS — 163521-12-8.

UNII — 523902OOV3.

Vilazodone Hydrochloride *(USAN, rINNM)*

EMD-68843; Hidrocloruro de vilazodona; SB-659746A; Vilazodone, Chlorhydrate de; Vilazodoni Hydrochloridum; Вилазодона Гидрохлорид.

$C_{26}H_{27}N_5O_2$,HCl=478.0

CAS — 163521-08-2.

UNII — U8HTX2GK8J.

Profile

Vilazodone is a selective serotonin reuptake inhibitor (see Fluoxetine, p. 417.1) and a partial agonist at serotonin (hydroxytryptamine, 5-HT) receptors of the 5-HT_{1A} subtype. It is given orally as the hydrochloride in the treatment of depression (p. 398.1). The initial dose is 10 mg once daily for 7 days, followed by 20 mg once daily for another 7 days, then increased to the usual dose of 40 mg once daily; it should be taken with food.

Vilazodone is metabolised mainly by the cytochrome P450 isoenzyme CYP3A4; the usual dose should be reduced to 20 mg once daily in patients taking potent CYP3A4 inhibitors (e.g. ketoconazole), and in those taking moderate CYP3A4 inhibitors (e.g. erythromycin) who have intolerable adverse effects. CYP3A4 inducers may reduce the plasma concentrations of vilazodone although this has not been evaluated.

Vilazodone should be withdrawn gradually to reduce the risk of withdrawal symptoms (see also Withdrawal, under Precautions of Fluoxetine, p. 423.3).

References.

1. Rickels K, *et al.* Evidence for efficacy and tolerability of vilazodone in the treatment of major depressive disorder: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 2009; 70: 326–33.
2. Dawson LA, Watson JM. Vilazodone: a 5-HT_{1A} receptor agonist/serotonin transporter inhibitor for the treatment of affective disorders. *CNS Neurosci Ther* 2009; 15: 107–17.
3. Khan A. Vilazodone, a novel dual-acting serotonergic antidepressant for managing major depression. *Expert Opin Invest Drugs* 2009; 18: 1753–64.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Viibryd.

Viloxazine Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de viloxazina; ICI-58834; Viloxazina, hidrocloruro de; Viloxazine, Chlorhydrate de; Viloxazini Hydrochloridum; Вилоксазина Гидрохлорид.

2-(2-Ethoxyphenoxymethyl)morpholine hydrochloride.

$C_{13}H_{19}NO_3$,HCl=273.8

CAS — 46817-91-8 (viloxazine); 35604-67-2 (viloxazine hydrochloride).

ATC — N06AX09.

ATC Vet — QN06AX09.

UNII — OQW30I1332.

Profile

Viloxazine is a bicyclic antidepressant. Like the tricyclic antidepressants (see Amitriptyline, p. 401.1), viloxazine is an inhibitor of the reuptake of noradrenaline; it may also enhance the release of serotonin from neuronal stores. However, it does not have marked antimuscarinic, cardiotoxic, or sedative properties.

Viloxazine hydrochloride has been given for the treatment of depression. It should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Vortioxetine *(USAN, pINN)*

Lu-AA21004; Vortioxetina; Vortioxétine; Vortioxetinum; Вортиоксетин.

1-[2-[(2,4-Dimethylphenyl)sulfanyl]phenyl]piperazine.

$C_{18}H_{22}N_2S$=298.4

CAS — 508233-74-7.

UNII — 3O2K1S3WQV.

Vortioxetine Hydrobromide *(USAN, pINNM)*

Hidrobromuro de vortioxetina; Vortioxétine, Bromhydrate de; Vortioxetini Hydrobromidum; Вортиоксетина Гидробромид.

$C_{18}H_{22}N_2S$,HBr=379.4

CAS — 960203-27-4.

UNII — TKS641KOAY.

Profile

Vortioxetine inhibits the reuptake of serotonin (5-HT; see Fluoxetine, p. 417.1) and is an antagonist at 5-HT_3 and an agonist at 5-HT_{1A} receptors. It is given orally as the hydrobromide in the treatment of depression (p. 398.1). Doses are expressed in terms of the base; vortioxetine hydrobromide 12.7 mg is equivalent to about 10 mg of vortioxetine. The initial dose is the equivalent of 10 mg once daily, increased to 20 mg once daily if tolerated. A dose of 5 mg daily may be considered in patients who do not tolerate higher doses.

The metabolism of vortioxetine is mediated by the cytochrome P450 isoenzymes, mainly CYP2D6: the dose should be halved in patients taking potent CYP2D6 inhibitors, and should also not exceed 10 mg daily in known poor CYP2D6 metabolisers. Conversely, the dose of vortioxetine may be increased to a maximum of 3 times the original dose in those taking potent inducers of CYP isoenzymes for longer than 14 days.

Although vortioxetine may be stopped abruptly, transient withdrawal symptoms such as headache and muscle tension have been reported after abruptly stopping therapy. Patients taking 15 or 20 mg daily should reduce their dose of vortioxetine to 10 mg daily for 1 week before stopping.

References.

1. Bidzan L, *et al.* Vortioxetine (Lu AA21004) in generalized anxiety disorder: results of an 8-week, multinational, randomized, double-blind, placebo-controlled clinical trial. *Eur Neuropsychopharmacol* 2012; 22: 847–57.
2. Baldwin DS, *et al.* Vortioxetine (Lu AA21004) in the long-term open-label treatment of major depressive disorder. *Curr Med Res Opin* 2012; 28: 1717–24.
3. Chen G, *et al.* Pharmacokinetic drug interactions involving vortioxetine (Lu AA21004), a multimodal antidepressant. *Clin Drug Investig* 2013; 33: 727–36.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Brintellix.

Antidiabetics

Antidiabetic Drug Groups, p. 460
Alpha-glucosidase inhibitors, p. 460
Amylin analogues, p. 460
Biguanides, p. 460
Dipeptidylpeptidase-4 inhibitors, p. 460
Glucagon-like peptide 1 receptor agonists, p. 460
Insulin, p. 460
Meglitinides, p. 460
Sodium-glucose co-transporter 2 inhibitors, p. 460
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Management of diabetes mellitus, p. 461
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Gestational diabetes mellitus, p. 464
Diabetes mellitus in surgery or critical illness, p. 464
Diabetic complications, p. 464
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Diabetes-associated cardiovascular disease, p. 465
Diabetic diarrhoea, p. 466
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Diabetic nephropathy, p. 467
Diabetic neuropathy, p. 467
Diabetic emergencies, p. 467

This chapter describes diabetes mellitus (type 1, type 2, and gestational diabetes mellitus) and its management with antidiabetics, including oral antidiabetic drugs and insulin.

Antidiabetic Drug Groups

Alpha-glucosidase inhibitors

Alpha-glucosidase inhibitors act by delaying the absorption of glucose from the gastrointestinal tract. They are generally used in the management of type 2 diabetes mellitus.

Described in this chapter are
- Acarbose, p. 468.2
- Miglitol, p. 493.3
- Voglibose, p. 505.3

Amylin analogues

Amylin is a pancreatic peptide hormone, thought to play a role in the regulation of glucose homoeostasis. The amylin analogue, pramlintide, slows the rate of gastric emptying, prevents the postprandial rise in glucagon concentrations, and reduces appetite. It is used with insulin in the management of both type 1 and type 2 diabetes mellitus.

Described in this chapter are
- Pramlintide, p. 496.3

Biguanides

Biguanide antidiabetics may have several actions, but are considered to act mainly by decreasing hepatic gluconeogenesis and increasing peripheral utilisation of glucose. Metformin is commonly used in type 2 diabetes mellitus, especially in overweight patients. Biguanide antidiabetics are described in more detail on p. 469.3.

Described in this chapter are
- Buformin, p. 471.2
- Metformin, p. 491.1
- Phenformin, p. 495.1

Dipeptidylpeptidase-4 inhibitors

Dipeptidylpeptidase-4 inhibitors (gliptins) impair the degradation of incretin hormones, which play a role in glucose homoeostasis by increasing insulin synthesis and release, and reducing glucagon secretion. They are used in the management of type 2 diabetes mellitus.

Described in this chapter are
- Alogliptin, p. 469.2
- Linagliptin, p. 490.1
- Saxagliptin, p. 501.2
- Sitagliptin, p. 502.1
- Teneligliptin, p. 504.1
- Vildagliptin, p. 504.3

Glucagon-like peptide 1 receptor agonists

Glucagon-like peptide 1 receptor agonists (incretin mimetics) enhance insulin secretion in the presence of raised glucose concentrations; they also suppress inappropriate glucagon secretion, and slow gastric emptying. They are used in the management of type 2 diabetes mellitus.

Described in this chapter are
- Exenatide, p. 473.1
- Liraglutide, p. 490.2
- Lixisenatide, p. 491.1

Insulin

Insulin therapy is essential in the management of type 1 diabetes mellitus, and may be used in some patients with type 2 disease. Human insulin (produced by modification of porcine insulin or by recombinant DNA technology) has generally replaced bovine and unmodified porcine insulins. Insulin analogues are also in use.

Described in this chapter are
- Insulin, p. 479.3

Meglitinides

Meglitinide antidiabetics (glinides), like sulfonylureas (p. 460.2), stimulate the release of insulin from the pancreas by the inhibition of ATP-sensitive potassium channels. They are used in the management of type 2 diabetes mellitus.

Described in this chapter are
- Mitiglinide, p. 493.3
- Nateglinide, p. 494.1
- Repaglinide, p. 497.2

Sodium-glucose co-transporter 2 inhibitors

Sodium-glucose co-transporter 2 inhibitor antidiabetics enhance urinary excretion of glucose by suppressing renal glucose reabsorption. They are used in the management of type 2 diabetes mellitus.

Described in this chapter are
- Canagliflozin, p. 471.2
- Dapagliflozin, p. 472.2

Sulfonylureas

Sulfonylurea antidiabetics stimulate the release of insulin from the pancreas, by inhibition of ATP-sensitive potassium channels. They are used in the management of type 2 diabetes mellitus. Sulfonylurea antidiabetics are described in more detail on p. 502.3.

Described in this chapter are
- Acetohexamide, p. 469.2
- Carbutamide, p. 471.3
- Chlorpropamide, p. 472.1
- Glibenclamide, p. 474.1
- Glibornuride, p. 474.3
- Gliclazide, p. 474.3
- Glimepiride, p. 475.2
- Glipizide, p. 476.1
- Gliquidone, p. 476.3
- Glisentide, p. 476.3
- Glyclopyramide, p. 479.1
- Glycyclamide, p. 479.1
- Tolazamide, p. 504.1
- Tolbutamide, p. 504.2

Thiazolidinediones

Thiazolidinedione antidiabetics (glitazones) act as selective agonists at the peroxisome proliferator-activated receptor gamma (PPARγ) to improve insulin sensitivity in adipose tissue, skeletal muscle, and the liver. They are used in the management of type 2 diabetes mellitus.

Described in this chapter are
- Pioglitazone, p. 495.1
- Rosiglitazone, p. 498.3

Diabetes mellitus

Diabetes mellitus is a group of disorders of carbohydrate metabolism in which the action of insulin is diminished or absent through altered secretion, decreased insulin activity, or a combination of both factors. It is characterised by hyperglycaemia. As the disease progresses tissue or vascular damage ensues leading to severe complications such as retinopathy, nephropathy, neuropathy, cardiovascular disease, and foot ulceration.

Diabetes mellitus may be categorised into several types but the two major types are type 1 (insulin-dependent diabetes mellitus; IDDM) and type 2 (non-insulin-dependent diabetes mellitus; NIDDM). The term juvenile-onset diabetes has sometimes been used for type 1 and maturity-onset diabetes for type 2.

Type 1 diabetes mellitus is present in patients who have little or no endogenous insulin secretory capacity and who therefore require exogenous insulin therapy for survival. This form of the disease has an auto-immune basis in most cases, and usually develops before adulthood. The associated hypoinsulinaemia and hyperglucagonaemia put such patients at risk of ketosis and ketoacidosis.

In **type 2 diabetes mellitus**, insulin secretion may appear normal or even excessive (and type 2 patients are thus less prone to ketosis) but it is insufficient to compensate for insulin resistance (p. 489.1). Obesity is present in the majority of type 2 patients; non-obese patients tend to have low insulin secretory capacity (although not as low as in type 1 diabetes) rather than appreciable insulin resistance. Type 2 diabetes typically develops later in life; it is rare in adolescents and children but is becoming more prevalent, related in part to the increase in obesity occurring particularly in westernised countries. It is closely associated with cardiovascular disease, and the 2 may arise from a common antecedent described as the metabolic syndrome.

See below for information on:
- Diagnosis of Diabetes Mellitus, p. 460.3
- Management of Diabetes Mellitus, p. 461.1
- Prevention of Diabetes Mellitus, p. 462.3
- Monitoring of Therapy in Diabetes Mellitus, p. 463.1
- Diabetes Mellitus and Pregnancy, p. 463.3
- Gestational Diabetes Mellitus, p. 464.1
- Diabetes Mellitus in Surgery or Critical Illness p. 464.2

Diagnosis of diabetes mellitus

Diagnosis is based upon blood-glucose concentrations or glycated haemoglobin (HbA_{1c}) exceeding set values under specified conditions. Patients with abnormal blood-glucose concentrations that do not reach the defined threshold for overt diabetes may be considered to have *impaired glucose tolerance (IGT)* or *impaired fasting glucose (IFG)*, which are risk factors for developing diabetes and cardiovascular disease.[1,2] The term *pre-diabetes* has been applied to IGT and IFG, but its use is discouraged by WHO.[1] Venous plasma glucose measurement is advocated as the preferred method for diagnostic blood-glucose testing. Capillary plasma glucose may still be reported in areas where only capillary sampling is available; venous and capillary samples will give the same result in the fasting state, but non-fasting glucose concentrations are higher in capillary samples than venous samples. Glucose results in whole blood can differ from those in plasma, depending on various factors, and the conversion of figures from whole blood glucose to plasma glucose can therefore be problematic.[1] Diagnosis can be confirmed using the *oral glucose tolerance test* (OGTT).[1] This test consists of a 12-hour fast followed by measurement of the fasting plasma-glucose concentration 10 minutes before the administration of a 75-g oral glucose load (in children 1.75 g/kg up to a maximum of 75 g), and further measurement of the plasma-glucose concentration 2 hours later.[3] There has been some confusion at an international level as to whether the glucose load should be 75 g of the anhydrous form or the monohydrate. Sources at WHO have therefore suggested that the form should be standardised as 75 g of anhydrous glucose (anhydrous dextrose), which would be equivalent to 82.5 g of the monohydrate (Glucose BP; dextrose monohydrate).[4]

Measurement of HbA_{1c} had not been recommended for routine diagnosis because of a lack of global standardisation and uncertainty about diagnostic thresholds.[1] However, this situation has been reviewed because of the development of a new reference method for standardised measurements (see under Monitoring of Therapy, p. 463.1) and growing evidence of a relationship between HbA_{1c} and long-term complications of diabetes, particularly retinopathy. An international expert committee[5] suggested that in non-pregnant individuals, diabetes should be diagnosed when HbA_{1c} is ≥6.5%; diagnosis should be confirmed with a repeat HbA_{1c} test unless clinical symptoms and glucose concentrations above 11.1 mmol/litre are present. The committee also considered that individuals with measures of ≥6.0 to <6.5% were likely to be at high risk of progression to diabetes. The measurement of HbA_{1c} has therefore been incorporated into recommendations for diagnosis, but WHO points out that it is not available in many parts of the world and that results may be affected by a range of factors including haemoglobinopathies, certain anaemias, and disorders that affect red cell turnover such as malaria.[6]

The following diagnostic criteria have been recommended, although there are some slight differences between those of WHO[1,6] and the American Diabetes Association.[2]

Diabetes mellitus:
- classic symptoms of hyperglycaemia or hyperglycaemic crisis (including increased thirst and urine volume, and

unexplained weight loss), plus a random venous plasma glucose ≥ 11.1 mmol/litre[2]
or
- in the absence of symptoms and unequivocal hyperglycaemia, the following diagnostic results must be confirmed on a subsequent day:
  - fasting venous plasma glucose ≥ 7.0 mmol/litre[1,2] (the corresponding value for capillary plasma glucose is 7.0 mmol/litre[7])
  or
  - plasma glucose ≥ 11.1 mmol/litre after an OGTT[1,2] (the corresponding value for capillary plasma glucose is 12.2 mmol/litre[7])
  or
  - HbA_{1c} of ≥ 6.5%[2,6]

Impaired glucose tolerance (IGT):
- fasting venous plasma glucose < 7.0 mmol/litre *and* plasma glucose ≥ 7.8 mmol/litre to < 11.1 mmol/litre after an OGTT[1]
or
- venous plasma glucose 7.8 to 11.0 mmol/litre after an OGTT[2]

Impaired fasting glucose (IFG):
- fasting venous plasma glucose 6.1 to 6.9 mmol/litre *and* (if measured) < 7.8 mmol/litre after an OGTT[1]
or
- fasting venous plasma glucose 5.6 to 6.9 mmol/litre[2]

Raised HbA_{1c} indicating an increased risk of progression to diabetes:
- HbA_{1c} of 5.7 to 6.4%[2]

Other indicators, such as measurement of autoantibodies (to insulin or islet cells, for example) are not routinely used for diagnosis.

Once the presence of diabetes has been confirmed the distinction between type 1 and type 2 is made on clinical grounds.

1. WHO. International Diabetes Federation. *Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia*. Geneva: WHO, 2006. Available at: http://whqlibdoc.who.int/publications/2006/9241594934_eng.pdf (accessed 16/05/11)
2. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2011; 34 (suppl 1): S62–S69. Also available at: http://care.diabetesjournals.org/content/34/Supplement_1/S62.full.pdf (accessed 16/05/11)
3. WHO. *Laboratory diagnosis and monitoring of diabetes mellitus*. Geneva: WHO, 2002. Available at: http://whqlibdoc.who.int/hq/2002/9241590483.pdf (accessed 16/05/11)
4. WHO. *Definition, diagnosis and classification of diabetes mellitus and its complications*. Geneva: WHO, 1999.
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Management of diabetes mellitus

Diet, exercise, and the appropriate use of antidiabetic drugs including insulin, are all important aspects of the long-term management of diabetes mellitus. The main aims of management are to optimise glycaemic control and to reduce the risk of developing complications (see also Diabetic Complications, p. 464.2). For the management of diabetes mellitus in more specific groups, see also Diabetes Mellitus and Pregnancy, p. 463.3, Gestational Diabetes Mellitus, p. 464.1, and Diabetes Mellitus in Surgery or Critical Illness, p. 464.2.

DIETARY MODIFICATION. Dietary control is important in both type 1 and type 2 diabetes.[1-6] The goals of dietary modification are to maintain glucose concentrations in the normal range or as close to normal as possible, and a lipid and lipoprotein profile and blood pressure that reduce the risk of macrovascular disease. Correction of obesity is desirable in all patients, and weight loss in patients with type 2 diabetes can decrease insulin resistance, improve glycaemic and lipid measures, and reduce blood pressure. The influence of diet on diabetes is such that all diabetic patients need to be aware of the composition of foods and to be able to make adjustments to their diet, especially to counteract treatment-induced hypoglycaemia. However, neither protein restriction nor very low calorie diets are recommended.[4] A high fibre intake may lower blood-glucose concentrations and additional fibre is sometimes taken in the form of guar gum (see p. 479.2). Weight loss medication may be a useful adjunct to lifestyle changes in the management of overweight patients with type 2 diabetes.[4] There is some evidence that fluoxetine, orlistat, and sibutramine can achieve modest weight loss, and that fluoxetine and orlistat may contribute to a reduction in glycated haemoglobin, but long-term effects remain uncertain.[7] Some patients may be suitable candidates for bariatric surgery.[1,4]

EXERCISE. All diabetic patients should be encouraged to exercise, according to their age and physical capability.[1-3,5,6,8] Exercise improves carbohydrate metabolism, insulin sensitivity,[9] and cardiovascular function.[10] Small reductions in glycated haemoglobin (HbA_{1c}) can occur with exercise,[11,12] and a combination of aerobic and resistance training might be more effective than either alone.[13] It is also a useful component of any weight reduction programme although diet may be more effective in promoting weight loss and metabolic control.[10]

ORAL ANTIDIABETICS. For the majority of patients with *type 2* diabetes, diet and exercise are usually insufficient to control their disease in the long term, and the addition of an oral antidiabetic (oral hypoglycaemic) is needed to maintain glycaemic goals. Traditionally, patients with type 2 diabetes have been started on oral therapy after a suitable trial period of dietary modification and increased physical activity[2,6] (usually at least 3 months). The introduction and adjustment of drug therapy must be individualised, balancing the potential long-term benefits against other factors such as adverse effects and ease of use. The progressive nature of type 2 diabetes also means that many patients will eventually require combination oral therapy, and possibly the addition of insulin.[14] (The different antidiabetic drug groups are outlined p. 458.1.)

- Most patients with type 2 diabetes are overweight, and are preferably treated with the **biguanide** metformin.[5,6,14] It is generally well tolerated, does not cause hypoglycaemia on its own, and has either no effect on weight or promotes modest weight loss. However, it should not be used in patients with renal impairment in whom it has a rare tendency to cause lactic acidosis.[14] Although drug therapy is not normally not given in type 2 diabetes until diet and exercise have failed, a European/American consensus statement expressed the view that this generally occurred, and recommended that metformin be started, with lifestyle interventions, at diagnosis.[14]
- **A sulfonylurea** may be considered as an alternative for first-line oral monotherapy of type 2 diabetes. They are generally used in patients who are not overweight, when metformin is not tolerated or is contra-indicated, or if a rapid response is needed because of hyperglycaemic symptoms.[6] Sulfonylureas have a similar efficacy to metformin in terms of blood-glucose control, but can cause hypoglycaemia and are commonly associated with weight gain.[14] Chlorpropamide and glibenclamide have long half-lives and hence an increased tendency to cause hypoglycaemia, although a large study[15] reported that hypoglycaemic episodes were less frequent with chlorpropamide than glibenclamide. Nevertheless, shorter-acting sulfonylureas, such as gliclazide, glimepiride, and glipizide, are generally preferred.[14]
  A sulfonylurea may be added to therapy when glycaemic control is inadequate with metformin alone.[6,14] Alarming evidence[16] of an increased risk of death in patients enrolled in the UK Prospective Diabetes Study (UKPDS) given intensive therapy with metformin plus a sulfonylurea was not borne out by further analysis, and this combination is widely used (see also Metformin under Interactions of Sulfonylureas, p. 503.3).

Although other oral antidiabetics are often licensed for monotherapy of type 2 diabetes, their use is generally recommended when metformin and sulfonylureas are not sufficiently effective or cannot be used.

A thiazolidinedione may be added to either metformin or a sulfonylurea when a combination of these two is not feasible. Although initiation or intensification of insulin therapy is usually preferred to oral triple therapy,[14] adding a thiazolidinedione to both metformin and a sulfonylurea, may be considered when insulin would not be a suitable option.[6] Thiazolidinediones may cause weight gain, as well as fluid retention and exacerbation of heart failure, and they can increase the risk of bone fracture in women.[14,17] Although there is some evidence that pioglitazone may have beneficial effects on cardiovascular outcomes, risks may actually be increased with rosiglitazone (see Effects on the Cardiovascular System, p. 499.3) and the American Diabetes Association has advised against the use of this thiazolidinedione.[14]

- **Meglitinides** have a similar mechanism of action to sulfonylureas and are often used as alternatives. Repaglinide is almost as effective as metformin or the sulfonylureas, but nateglinide is considered to be somewhat less effective. The meglitinides are also associated with weight gain, but cause hypoglycaemia less frequently.[14] Their rapid onset and shorter duration of action may be advantageous in patients with erratic meal patterns.[6,17]
- The **dipeptidylpeptidase-4 (DPP-4) inhibitors** saxagliptin, sitagliptin, and vildagliptin, belong to a relatively new group of oral antidiabetics. They appear to be slightly less effective than other antidiabetics for glycaemic control,[18] but long-term comparative studies of efficacy and safety are lacking.[19] DPP-4 inhibitors may be added to either metformin or a sulfonylurea when a combination of these two is not appropriate.[6] Sitagliptin may be added to both metformin and a sulfonylurea when insulin would not be suitable. A DPP-4 inhibitor may be preferable to a thiazolidinedione if such therapy would be inappropriate.[6] DPP-4 inhibitors do not have a significant effect on weight, or cause hypoglycaemia when given alone.[14]
- The effects of **alpha-glucosidase inhibitors** are limited to reducing the rate of digestion and absorption of carbohydrates, and they are less effective than metformin and sulfonylureas.[14] They do not cause weight gain or hypoglycaemia, but adverse gastrointestinal effects can limit their use.[14,17] Acarbose may be considered as add-on therapy,[3] or for patients unable to use other oral antidiabetics.[6]

There is increasing interest in the use of oral antidiabetics as potential adjuncts to insulin therapy in children and adolescents with *type 1* diabetes. Drugs that have been tried include metformin and thiazolidinediones, which improve insulin sensitivity, and acarbose, as it alters carbohydrate absorption.[20] However, such therapy is not established and further research is needed.[3]

INSULIN THERAPY. In general, as *type 2* diabetes progresses, the majority of patients need multiple therapies to achieve glycaemic control.[21] Those who cannot be controlled adequately by oral drug therapy and diet need insulin either in addition to, or in place of, oral therapy. However, as insulin therapy is associated with more hypoglycaemic episodes and a greater tendency to weight gain, it remains reasonable to begin with oral therapy in type 2 diabetes before proceeding to insulin.[22] When insulin is added to oral treament, metformin is generally continued.[6] Although some suggest that sulfonylureas may be continued and reviewed if hypoglycaemia occurs,[6] others advise that both sulfonylureas and meglitinides should be stopped (or tapered then stopped) when insulin is started.[14] The combination of insulin with a thiazolidinedione is generally avoided because it increases the risk of fluid retention and heart failure; nevertheless, UK guidelines suggest that the combination of insulin with pioglitazone may be considered in patients who previously had a marked response to a thiazolidinedione, or whose blood glucose is inadequately controlled on high-dose insulin.[6] Acarbose may also be continued when insulin is started.[6] Therapy is often started with basal insulin, given as a long-acting insulin analogue (such as insulin detemir or glargine) or intermediate-acting isophane insulin.[2,6,14] Combination of a single isophane insulin injection at bedtime (morning injection is less effective) with oral hypoglycaemics (either a sulfonylurea, metformin, or both) is as effective as insulin alone, and if metformin is used, is associated with less weight gain.[23] If HbA_{1c} is particularly high a biphasic insulin may be given twice daily.[2,6] Alternatively, multiple-injection regimens (basal insulin plus mealtime injections) may be used where blood glucose control is suboptimal or mealtime flexibility is desired.[2,6,14]

While insulin may not be a necessary part of the management of type 2 diabetes, it is essential in the treatment of patients with *type 1*, since they have little or no endogenous insulin secretory capacity. The aim of insulin therapy is to achieve the best possible control of blood-glucose concentrations, in order to reduce long-term complications of diabetes, without the risk of the hypoglycaemia that can occur if too fine a degree of control is attempted. The choice of insulin regimen will be influenced by several factors including age, lifestyle, patient preference, and metabolic targets. Many patients with type 1 diabetes have a temporary improvement in pancreatic beta-cell function soon after starting insulin treatment. This produces a period of partial remission known as the honeymoon phase, during which a small dose of insulin (0.5 units/kg or less daily) is sufficient to maintain good control.[3,24,25] However, as beta-cell destruction continues the dose of insulin needs to be increased to avoid hyperglycaemia;[24] insulin requirements also increase with growth during childhood, particularly during puberty.[24,25] Insulin doses are adjusted according to food intake, exercise, blood glucose monitoring, hypoglycaemic episodes, and HbA_{1c} measures[3,24,25] (see also Monitoring of Therapy, p. 463.1). Dosage schedules make use of the varying durations of action of insulin and insulin analogues.[3,24,25] One, two, or three injections daily of biphasic insulin may be suitable. Increasingly, however, basal-bolus regimens are advocated to improve glycaemic control. These regimens combine an intermediate- or long-acting basal insulin (usually at bedtime or twice daily) with multiple doses of a short- or rapid-acting insulin given before meals and snacks. Continuous subcutaneous insulin infusion therapy with mealtime boluses is a suitable alternative to multiple daily injections for a growing number of patients (for further details, see Intensive Administration Regimens under Uses of Insulin, p. 482.3). A rapid-acting insulin analogue given shortly after meals may be useful in very young children, to better match insulin dosing with erratic food intake.

OTHER DRUG TREATMENTS. Other less well established drugs may also be tried in the management of diabetes mellitus,

particularly when conventional therapy has proved unsuccessful.

- Addition of the **amylin analogue** pramlintide to insulin therapy can reduce postprandial hyperglycaemia and improve glycaemic control in patients with type 1 and type 2 diabetes.[14,17,26] It also contributes to weight loss, in contrast to the weight gain that usually occurs in patients treated with insulin. Like insulin, pramlintide is given subcutaneously, and it can increase the risk of insulin-induced hypoglycaemia.
- The glucagon-like peptide 1 (GLP-1) receptor agonist and **incretin mimic** exenatide may be added to oral antidiabetic treatment of type 2 diabetes.[6,14] As well as improving glycaemic control, it can contribute to weight loss, but must be given subcutaneously.[14] Hypoglycaemia can occur, particularly when exenatide is used with a sulfonylurea.[17,18] Liraglutide[17,18] is another GLP-1 agonist licensed to treat type 2 diabetes mellitus with other oral antidiabetics.
- The **sodium-glucose co-transporter 2 inhibitor**, dapagliflozin, enhances the urinary excretion of glucose by suppressing renal glucose reabsorption and is used in type 2 diabetes. It improves glycaemic control and can contribute to weight loss, and may be used as monotherapy or with other oral antidiabetics or insulin.[27-29] Similarly, canagliflozin may be used for the management of diabetes.[30]
- Colesevelam, an oral **bile-acid sequestrant**, may be added to metformin, a sulfonylurea, or insulin therapy in type 2 diabetes and may be of additional benefit in patients who also have hyperlipidaemia. It can enhance the reduction in HbA_{1c}, although the mechanism by which it does this is still unclear. Colesevelam is reported to have little effect on weight gain in diabetic patients.[31]
- The **dopamine agonist** bromocriptine may improve glycaemic control when used as an adjunctive therapy in type 2 diabetes.[32]
- There is some evidence that adjunctive supplementation with the **trace element** chromium may improve glycaemic control in type 2 diabetes.[33,34] However, a systematic review[34] found the quality of many studies to be poor, and analysis was hampered by the differences among chromium formulations. Long-term safety and efficacy have not been established. There are some reports of improved insulin sensitivity after treatment with the **vanadium** salt, vanadyl sulfate, in type 2 diabetes.[35,36]

PANCREATIC TRANSPLANTATION. Transplantation of the whole pancreas in patients with type 1 diabetes poorly controlled by insulin therapy has led to insulin independence, and has usually been carried out with kidney transplantation (see also Pancreatic Transplantation, p. 1942.1).[37] Transplantation of pancreatic islet cells has been developed as an alternative. Since the introduction of the so-called 'Edmonton Protocol'[38] and related regimens for immunosuppression, and improvements in techniques for harvesting and preparing islet cells, more experienced centres are now reporting some success in achieving insulin independence.[37] However, at present successful patients exchange life-long insulin therapy for life-long immunosuppression. The induction of tolerance, less toxic immunosuppression, and enhanced islet engraftment remain the focus of investigation.[39,40] Results in *animals* have suggested that a reasonable degree of glycaemic control may be achievable long term without immunosuppression, using a vascularised 'artificial pancreas' containing allogeneic or even xenogeneic islet cells.[41] Islet cell replacement and regeneration is another area of research.[42] *Haematopoietic stem cell transplantation* is also under investigation, and insulin independence has been reported in a small number of patients.[43]

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Prevention of diabetes mellitus. Because overt diabetes is the culmination of a prolonged process, methods to delay or prevent its development are being investigated, either by modifying risk factors in populations or groups, or by targeting individuals thought to be at high risk. Various strategies are under investigation to prevent the onset or progression of **type 1 diabetes.**[1,2] Antigen-specific tolerance is being studied using oral or intranasal insulin in individuals at risk, such as first- and second-degree relatives of patients with type 1 diabetes, although some evidence suggests that such a strategy might be useful only in particular subgroups of subjects. The use of non-specific immunomodulators has also been tried, but studies using nicotinamide or BCG vaccine have failed to show benefit. The role of early exposure to cow's milk protein in the diet, as a risk factor in the development of type 1 diabetes in infants at risk, is also under investigation. In patients with recent-onset type 1 diabetes, similar approaches are being studied in an attempt to prevent further pancreatic beta cell loss. There have been some positive results in the stimulation of immune tolerance using treatments based on heat shock protein and glutamic acid decarboxylase. Results from studies of anti-CD3 monoclonal antibodies[1,2] and the anti-CD20 antibody rituximab[3] are also of interest. There has been some success with immunosuppressants such as ciclosporin, but their use is limited by concerns about toxicity.[1,2]

Preventive strategies for **insulin resistance and type 2 diabetes** have tended to focus on weight loss, dietary modification, and exercise.[4,5] Smoking is also a known risk factor for type 2 diabetes,[6,7] although smoking cessation may itself lead to a higher short-term risk of the condition and should be coupled with strategies for diabetes prevention and early detection.[7]

Prophylactic drug therapy may also be possible. A systematic review concluded that there was good evidence for a reduced incidence of diabetes in patients treated with metformin, acarbose, or orlistat, although the attrition rates were high with orlistat; evidence of benefit from statins, oestrogen, and various antihypertensive drugs was more equivocal. It was considered likely that some of the benefits were indirect, due to drug-induced weight loss, and in no case was the benefit definitive enough that the drug could be recommended for diabetes prevention.[8] Recommendations for the prevention or delay of type 2 diabetes in individuals with impaired glucose tolerance (IGT), impaired fasting glucose (IFG), or a raised glycated haemoglobin (HbA_{1c}) suggest that although drug therapy should not be routinely used, metformin may be considered for those at highest risk for developing diabetes especially if they demonstrate progression of hyperglycaemia despite life style intervention.[9]

There are limited data to support the use of other drugs. Some suggest that acarbose may also be worth considering, while orlistat might be useful in obese patients.[5] Thiazolidinediones have been studied and rosiglitazone was found to reduce the incidence of type 2 diabetes in patients with IGT or IFG,[10] but the benefit was not sustained after the drug was stopped.[11] Pioglitazone has also been reported to reduce the risk of progression to type 2 diabetes, but to cause significant weight gain and oedema.[12]

There has also been interest in the effects of ACE inhibitors and angiotensin II receptor antagonists. In large studies that had mainly measured cardiovascular outcomes in patients with cardiovascular disease, secondary analyses showed reduced rates of new-onset diabetes,[13,14] suggesting that these drugs might have a potential role in preventing the onset of diabetes in patients at risk. However, ramipril did not prevent diabetes when it was studied over a median of 3 years in patients with IGT or IFG, and no history of cardiovascular disease.[15] Another study found a small reduction in the incidence of diabetes with the use of valsartan in patients with IGT.[16]

Screening for IGT, IFG, raised HbA_{1c}, and diabetes has been encouraged, particularly for those patients with risk factors.[9,17]

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Monitoring of therapy in diabetes mellitus. Monitoring of therapy is an integral part of the management of all diabetic patients.

Many patients monitor their **blood-glucose** concentrations regularly at home, and this is essential for those on intensified insulin regimens when tight control is required. Self-monitoring facilitates the detection of hyper- and hypoglycaemia, and can be used to guide insulin dose adjustment relative to meals and exercise.[1-3]

The value of self-monitoring of blood-glucose concentrations in patients who are not using insulin is less clear, and the optimal frequency and timing of self-monitoring in these patients has not been established.[1] It may be useful for providing information on hypoglycaemia associated with oral antidiabetics, to assess changes in glucose control when medications and lifestyle are altered, and to monitor changes during intercurrent illness.[4] However, it may have only a modest influence on improving long-term glycaemic control.[5]

Patients use a blood glucose meter to measure glucose concentrations in capillary blood taken from a finger prick. Frequency and timing must be individualised, but several tests are usually spread throughout the day.[1,3] Continuous glucose monitoring uses a subcutaneous sensor to measure interstitial glucose, which correlates well with plasma glucose.[1] These monitors can alert the user to impending episodes of hyper- or hypoglycaemia and provide additional data on the patterns of glucose change over time, which can be used to guide insulin dose adjustment and improve long-term glycated haemoglobin (HbA_{1c}) control. However, self-testing of capillary blood is still necessary for calibrating these devices and making acute treatment decisions.[1,6,7] Non-invasive glucose sensors have been developed, based on a range of technologies, but various shortcomings mean that few, if any, are available for clinical use.[7] Detection of urinary glucose has generally been superseded by the monitoring of blood glucose. However, as long as results are interpreted correctly, and the limitations understood, urine glucose monitoring can be a useful alternative where blood glucose testing is not possible.[8] For further information on glucose tests, see p. 2516.3.

For adequate diabetic control, various recommendations have been made for capillary blood-glucose targets, usually measured preprandially (in a fasting state) and postprandially (at the usual glucose peak 1 to 2 hours after the start of a meal).

- In the UK,[2] recommended goals for *adults* are a preprandial concentration within the range of 4.0 to 7.0 mmol/litre, and a postprandial concentration of less than 9.0 mmol/litre.
  In the USA,[1] slightly higher concentrations are considered acceptable at 3.9 to 7.2 mmol/litre preprandially, and less than 10.0 mmol/litre postprandially.
  Tighter recommendations have been made by the International Diabetes Federation (IDF),[9] which advocates lowering glucose measures to as near as normal as is safely possible, suggesting targets of 5.5 mmol/litre preprandially and 7.8 mmol/litre postprandially.
- Goals for *children* differ from those for adults. Although it would be ideal to achieve glucose control as near to normal as possible, young children have limited hypoglycaemic awareness and are at risk of permanent cognitive impairment after episodes of severe hypoglycaemia.[1]
  In the UK[2] recommended goals are preprandial concentrations of 4.0 to 8.0 mmol/litre and less than 10.0 mmol/litre postprandially.
  Guidance in the USA[1] advocates age-specific preprandial goals of 5.6 to 10.0 mmol/litre for children up to 6 years of age, 5.0 to 10.0 mmol/litre for those aged 6 to 12 years, and 5.0 to 7.2 mmol/litre for those aged 13 to 19 years. US guidance also recommends bedtime or overnight blood-glucose goals of 6.1 to 11.1 mmol/litre, 5.6 to 10.0 mmol/litre, and 5.0 to 8.3 mmol/litre, respectively, for these same age groups. It also suggests that postprandial measures should be monitored when there is a discrepancy between preprandial results and HbA_{1c} values, and to help assess glycaemia in children and adolescents on basal-bolus insulin regimens.
  The International Society for Pediatric and Adolescent Diabetes (ISPAD)[3] recommends 5.0 to 8.0 mmol/litre preprandially and 5.0 to 10.0 mmol/litre postprandially, and suggests a bedtime target of 6.7 to 10.0 mmol/litre and a nocturnal target of 4.5 to 9.0 mmol/litre.

Diabetic clinics also measure the degree of haemoglobin glycation (HbA_{1c}) as an indicator of longer term blood-glucose control and hence the risk of complications. Testing is generally recommended at least twice each year in patients meeting treatment goals, and more frequently when glycaemic control is unstable.[1,2,4] HbA_{1c} is expressed as the percentage of haemoglobin that is glycated or in units of mmol/mol. For some time, an assay established by the National Glycohemoglobin Standardization Program (NGSP), which was based on that used in the Diabetes Control and Complications Trial (DCCT), has been used.[10] A new reference method with increased specificity has been developed by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) for the calibration of laboratory instruments, which provides percentage results that are lower than those arrived at by the NGSP method but that can be converted to the equivalent NGSP value. It was suggested in 2007 that in order to avoid confusion in the clinical setting, HbA_{1c} results should continue to be reported as the NGSP (or DCCT-derived) percentage result, as well as the metrologically correct units of mmol/mol (millimoles of HbA_{1c} per mole of total haemoglobin).[10,11] In addition, a study[12] showing correlation between HbA_{1c} and average glucose concentrations has provided evidence to support recommendations for HbA_{1c} results to also be reported as an estimated average glucose (eAG) in mmol/litre.[1,11]

Like blood glucose, goals for HbA_{1c} vary. The usual non-diabetic reference range is 4.0 to 6.0%.

- In *adults*, UK guidelines[4] recommend that a general target of 6.5 to 7.5% should be used for HbA_{1c} in patients with type 2 diabetes. For patients with type 1 diabetes,[2] HbA_{1c} lower than 7.5% is suggested, while a goal of 6.5% or lower may be of benefit in patients at increased risk of arterial disease.
  In the USA,[1] a target of below 7.0% has been recommended for diabetic patients in general, and possibly lower for those with a short duration of diabetes, long life expectancy, and no significant cardiovascular disease.
  The IDF[9] advocates lowering glucose measures to as near to normal as safely possible, suggesting a target HbA_{1c} of less than 6.5%.
- For *children*, a target HbA_{1c} of less than 7.5% has been recommended in the UK[2] and by ISPAD.[3]
  As for blood-glucose, guidance in the USA[1] advocates age-specific targets for HbA_{1c} (< 8.5% for children up to 6 years of age, < 8.0% for those aged 6 to 12 years, < 7.5% for those aged 13 to 19 years).

Less stringent HbA_{1c} targets may be appropriate for patients with a history of severe hypoglycaemia, limited life expectancy, advanced diabetic complications, extensive comorbid conditions, or where the general goal is difficult to attain in long-standing diabetes.[1,2] It has also been suggested, in the light of a retrospective cohort study involving almost 48 000 patients over 50 years old with type 2 diabetes which found that both low and high mean HbA_{1c} values were associated with increased all-cause mortality, that a minimum HbA_{1c} value might need to be specified.[13] Postprandial glucose may be targeted if HbA_{1c} goals are not met despite reaching preprandial glucose goals.[1,4]

Measurement of **glycated serum proteins**, particularly albumin, may be used to give an indication of glucose control, but covers a shorter period than haemoglobin. Such methods may be useful for measuring glycaemic control in patients with abnormal red cell survival-time.[3] Measurements of urinary or blood **ketones**, to detect impending ketoacidosis, should be monitored when there is uncontrolled hyperglycaemia, illness with fever and/or vomiting, episodes of drowsiness, abdominal pain, or rapid breathing. Blood ketone measurements are more accurate than urinary testing for diagnosing ketoacidosis.[3]

For more information on monitoring of diabetes mellitus in pregnancy, see p. 463.3, and in gestational diabetes mellitus, see p. 464.1.

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3. Rewers M, *et al.* ISPAD clinical practice consensus guidelines 2009 compendium: assessment and monitoring of glycemic control in children and adolescents with diabetes. *Pediatr Diabetes* 2009; 10 (suppl 12): 71–81. Also available at: http://www.ispad.org/FileCenter/ISPAD%20Guidelines%202009%20-%20Glycemic%20control%20with%20table%201.pdf (accessed 01/04/11)
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Diabetes mellitus and pregnancy

Adverse pregnancy outcomes, including spontaneous abortion, congenital malformation, and macrosomia, are more common in diabetic than in nondiabetic women. Improved management of the pregnant diabetic patient, particularly in early pregnancy, lessens the incidence of such events, but an increased risk still exists. Diabetic women are advised to plan their pregnancies so that glycaemic control can be improved before conception.[1-3] Recommendations for blood glucose and glycated haemoglobin (HbA_{1c}) are generally closer to normal than those recommended for nonpregnant patients (see below). Higher targets may be necessary for patients with hypoglycaemia unawareness or the inability to cope with intensified management.[3] Frequent self-monitoring is advised because of the increased potential for rapid-onset insulin-induced hypoglycaemia, and should be done both before and after meals, and at bedtime;[2,3] occasional measures taken between 2 and 4 a.m. have also been recommended.[3] (Pregnant diabetic patients are at risk of nocturnal hypoglycaemia owing to continued fetal glucose consumption while the mother is in a relatively fasting state.) Ketone testing is also advisable, particularly when there is persistent hyperglycaemia or the patient is unwell, as diabetic ketoacidosis can develop quickly and is associated with a high risk of fetal loss.[2,3]

- Preprandial capillary blood-glucose concentrations of between 3.5 and 5.9 mmol/litre, and 1-hour postprandial concentrations of below 7.8 mmol/litre, have been recommended in the UK.[2] In the USA,[1] a goal of 3.3 to 5.4 mmol/litre has been suggested for preprandial, bedtime, and overnight glucose, with a postprandial goal of 5.4 to 7.1 mmol/litre, and a mean daily glucose[3] of less than 6.2 mmol/litre. Tighter control (mean blood glucose less than 4.5 to 5.0 mmol/litre) should be avoided because of the risk of fetal growth restriction.[3]
- Suggested HbA_{1c} targets are below 6.1% in the UK[2] and below 6.0% in the USA.[3]

Insulin is the preferred treatment for both type 1 and type 2 diabetes mellitus in pregnancy. Insulin regimens are similar to those in non-pregnant patients, using a basal-bolus regimen or continuous subcutaneous insulin infusion.[3] As there is limited information about the safety of long-acting analogues, such as insulins detemir and glargine, isophane insulin should be used for the basal component. The rapid-acting insulin analogues, insulins aspart and lispro, are considered safe for use during pregnancy, and may produce better postprandial glucose control with less hypoglycaemia than regular insulin.[2,3] Insulin requirements may decrease during the first trimester, but then double or even triple during the course of the pregnancy.[3] Capillary blood-glucose concentrations should be monitored during labour and birth, and insulin doses will need to be reduced immediately after birth.[2]

Women with type 2 diabetes who have been taking oral antidiabetics are usually switched to insulin for the duration of the pregnancy.[3] However, there is increasing evidence to suggest that metformin might be used safely during pregnancy, and UK guidance[2] has suggested that it may be

used either as an adjunct or alternative to insulin if the likely benefits from improved glycaemic control outweigh the potential for harm. Nevertheless, the use of oral hypoglycaemics during pregnancy remains controversial; some argue that although there may be increasing evidence of fetal safety, oral treatments are not sufficiently effective to achieve the tight postprandial glycaemic control that is desirable during pregnancy.[4] Others suggest that oral treatments may have a role in poorly resourced settings where there is a lack of access to insulin.[5]

For information on gestational diabetes mellitus, see p. 464.1.

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Gestational diabetes mellitus. Gestational diabetes mellitus is defined as glucose intolerance with onset or first recognition during pregnancy, which generally resolves with delivery. However, increasing numbers of women with undiagnosed type 2 diabetes are being identified during screening for gestational diabetes.[1]

Initial screening is based on the assessment of risk factors such as age, body-mass index or body-weight, previous gestational diabetes, family history of diabetes, and ethnic origin with a high prevalence of diabetes. Various criteria have been used for gestational diabetes, but the American Diabetes Association suggests that those with risk factors should initially be screened for type 2 diabetes using standard diagnostic criteria (see Diagnosis of Diabetes Mellitus, p. 458.3). For women not found to have type 2 diabetes, a 75-g oral glucose tolerance test (OGTT) at 24 to 28 weeks of gestation is used to screen for gestational diabetes using criteria of:[1,2]

- fasting plasma glucose ⩾ 5.1 mmol/litre
  or
- plasma glucose ⩾ 10.0 mmol/litre at 1 hour after an OGTT
  or
- plasma glucose ⩾ 8.5 mmol/litre at 2 hours after an OGTT

As shown for women with pre-existing diabetes, good glycaemic control in gestational diabetes reduces the risk of fetal macrosomia and other complications.[3-5]

- Glycaemic goals in the UK[3] are preprandial capillary blood-glucose concentrations of between 3.5 and 5.9 mmol/litre, and a 1-hour postprandial concentration of below 7.8 mmol/litre.
  In the USA,[2,4] a preprandial goal of less than 5.3 mmol/litre has been suggested, with a postprandial goal of less than 7.8 mmol/litre at 1 hour or 6.7 mmol/litre at 2 hours.

However, mean concentrations maintained below 4.8 mmol/litre can increase the risk of fetal growth impairment.[4]

Most women with gestational diabetes can be managed by diet and exercise alone.[3,4] However, if these are insufficient, insulin therapy may be given as for pregnant women with pre-existing diabetes.[3,4] UK guidance[3] also states that there is adequate evidence of efficacy and safety to consider metformin or glibenclamide as an adjunct or alternative to insulin.

Antidiabetic treatment should be stopped immediately after birth.[3] Most women will return to normal glucose tolerance, although follow-up is recommended because of an increased risk of developing type 2 diabetes in the future;[6] however, some women will remain diabetic or have ongoing impaired glucose tolerance.[2-4]

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2011; 34 (suppl 1): S62–S69. Also available at: http://care.diabetesjournals.org/content/34/Supplement_1/S62.full.pdf (accessed 01/04/11)
2. American Diabetes Association. Standards of medical care in diabetes—2011. *Diabetes Care* 2011; 34 (suppl 1): S11–S61. Also available at: http://care.diabetesjournals.org/content/34/Supplement_1/S11.full.pdf (accessed 01/04/11)
3. National Collaborating Centre for Women's and Children's Health/NICE. Diabetes in pregnancy: management of diabetes and its complications from pre-conception to the postnatal period (issued March 2008, reissued July 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/CG63NICEGuideline.pdf (accessed 22/05/09)
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Diabetes mellitus in surgery or critical illness

Stress-induced hyperglycaemia is associated with surgery, trauma, and critical illness, and will increase insulin requirements. Insulin-dependent diabetics who require **surgery** usually need to be managed with a continuous intravenous insulin infusion, and various algorithms have been developed with the goal of avoiding both hypo- and hyperglycaemia. Different blood-glucose targets have been suggested, usually to keep perioperative blood glucose below 10.0 or 11.0 mmol/litre, and to aim for near normoglycaemia.[1-3]

- In general, *insulin-dependent patients* should be given their normal regimen the day before the operation. On the day of surgery, patients may be given half their usual subcutaneous basal insulin dose, or the full basal dose for those using insulin glargine or a continuous subcutaneous insulin infusion.[1,2] Perioperative intravenous insulin in saline is given as a variable rate infusion via a syringe pump, with a separate 5 or 10% glucose infusion. Potassium chloride may be included in the glucose infusion[2] or given separately.[1] Alternatively, insulin may be added to the glucose infusion,[3] or a combined insulin-glucose-potassium infusion may be suitable.[2]
- *Non-insulin-dependent patients* should have any oral antidiabetic treatment omitted on the day of surgery; metformin should be stopped at least 24 hours before the procedure.[1,2] An intravenous insulin infusion may be indicated during major surgery[1,2] or when glycaemic control is poor.[2] Subsequent conversion back to subcutaneous insulin or oral antidiabetics should be undertaken as soon as the patient is able to resume eating and drinking normally,[1,2] although metformin should be withheld for 48 to 72 hours after surgery or iodinated radiocontrast media, and until normal renal function has been confirmed.[2]

The treatment of hyperglycaemia is also desirable for **critically ill** patients, including diabetics. However, as well as the risks of insulin-induced hypoglycaemia, there is some evidence that tight glycaemic control might increase mortality in these patients (see also Critically Ill Patients, under Insulin, p. 483.2). Guidelines[4,5] recommend starting an intravenous insulin infusion at a blood-glucose threshold of 10 mmol/litre for the treatment of persistent hyperglycaemia in most critically ill patients in the intensive care setting, with a maintenance range of 7.8 to 10.0 mmol/litre.

1. Rhodes ET, *et al.* Perioperative management of pediatric surgical patients with diabetes mellitus. *Anesth Analg* 2005; 101: 986–99.
2. Smiley DD, Umpierrez GE. Perioperative glucose control in the diabetic or nondiabetic patient. *South Med J* 2006; 99: 580–9.
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Diabetic complications

Much of the increased mortality and morbidity seen in diabetic patients is the result of complications that develop with increasing duration of disease, particularly when glycaemic control is poor. Such complications may originate from increased glycation of proteins and other biological macromolecules in the hyperglycaemic environment, pathological activation of protein kinase C, or from increased accumulation of sorbitol and other polyols via the aldose reductase pathway,[1-3] but other factors play an important role in determining susceptibility. At the *macrovascular* level, diabetics are prone to hypertension and ischaemic heart disease, and heart disease is a major cause of death; control of blood pressure is now seen as being as important as glycaemic control in patients with type 2 diabetes. *Microvascular* tissue damage is an important factor in the development of diabetic nephropathy and retinopathy; it may also contribute to the other major complication, diabetic neuropathy. Collagen abnormalities are also seen. Diabetics with poor glycaemic control also have an increased liability to severe bacterial or fungal infection. Sometimes several factors may interact; thus neuropathy, infection, and impaired blood flow due to macro- or microvascular disease may all play a role in the development of diabetic foot disease, a complication which can ultimately lead to amputation.

For more information on these complications see under the headings Prevention of Diabetic Complications (p. 464.3), Diabetes-associated Cardiovascular Disease (p. 465.3), Diabetic Diarrhoea (p. 466.1), Diabetic Eye Disease (p. 466.2), Diabetic Foot Disease (p. 466.2), Diabetic Heart Disease (p. 466.3), Diabetic Nephropathy (p. 467.1), and Diabetic Neuropathy (p. 467.2).

1. Sheetz MJ, King GL. Molecular understanding of hyperglycemia's adverse effects for diabetic complications. *JAMA* 2002; 288: 2579–88.
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Prevention of diabetic complications. Much attention has been focused on whether strict or tight glycaemic control can modify the development or progression of diabetic complications. Tight glycaemic control has been shown to reduce microvascular complications of both type 1 and type 2 diabetes, but evidence for the prevention of macrovascular disease is less convincing.

The Diabetes Control and Complications Trial (DCCT)[1] compared the effects of conventional insulin therapy with those of continuous subcutaneous insulin infusion or multiple-injection regimens, on the development and progression of early complications in *type 1 diabetics*. The intensive treatment was aimed at keeping preprandial blood-glucose concentrations between 3.9 and 6.7 mmol/litre, postprandial concentrations at less than 10 mmol/litre, a weekly 3 a.m. measurement at greater than 3.6 mmol/litre, and the monthly glycated haemoglobin (HbA_{1c}) measurement at less than 6.05%. Intensive insulin therapy reduced the development and progression of retinopathy; it also reduced the occurrence of microalbuminuria, albuminuria, and clinical neuropathy. There was also a risk reduction for combined cardiovascular and peripheral vascular events, but it was based on a small number of events in a relatively young study population, and was not statistically significant. The major disadvantage of intensive insulin therapy was a threefold greater risk of hypoglycaemia; weight gain was also significantly greater.

While it is accepted that some patients will benefit from intensive insulin regimens, this approach requires caution in patients at risk of hypoglycaemia. Also such intensive treatment may not always be necessary, for example in patients known to maintain good control by conventional dosage schedules, or where improvement can be obtained by setting achievable targets and improving patient education.[2] However, intensive therapy can help sustain endogenous insulin secretion in type 1 diabetes, which is associated with improved metabolic control;[3] this would favour starting intensive insulin therapy at an early stage. After the DCCT finished the patients returned to their own healthcare providers for diabetes care, but were followed in a cohort study for a further 11 years.[4] Although more than 90% of all patients went on to use intensive therapy, and glycated haemoglobin values became very similar for both groups during this time, there were fewer cardiovascular events and less microalbuminuria and albuminuria in the group that had received intensive treatment during the original DCCT, showing that the beneficial effects of intensive therapy were maintained long term. Thirty-year observational follow-up of some of the patients in the DCCT study[5] has shown that proliferative retinopathy, nephropathy and cardiovascular disease were all significantly reduced in those who had intensive diabetes therapy.

The reports of the UK Prospective Diabetes Study (UKPDS) have provided similar evidence in patients with newly diagnosed *type 2 diabetes*. This study has examined the benefits of intensive therapy, using a variety of drugs with diet and exercise. Intensive therapy, which aimed at producing fasting plasma-glucose concentrations of below 6 mmol/litre, substantially decreased the risk of microvascular complications (particularly retinopathy). There was no difference in benefit between intensive therapy with sulfonylureas and with insulin.[6] Metformin also produced benefit in the overweight patients who received it.[7] The UKPDS did not provide unequivocal evidence of a reduction in macrovascular disease with improved glycaemic control, although there was some suggestion of a reduction in risk of myocardial infarction. However, it did show that vigorous control of blood pressure, using captopril or atenolol as the first-line drugs in hypertension, reduced the risk of both macrovascular and microvascular complications,[8,9] suggesting that this should have a high priority in the treatment of type 2 diabetes. Patients returned to their own healthcare providers after the UKPDS finished, but were followed up for a further 10 years. Within a year, the difference in HbA_{1c} between the intensively and conventionally treated groups had disappeared, but a reduction in microvascular risk persisted over the decade and was particularly evident in those who had received a sulfonylurea or insulin. In addition, the risk reductions for myocardial infarction and death from any cause became statistically significant during follow-up.[10] The blood pressure differences between the groups also disappeared within 2 years, and the associated risk reductions for both microvascular and macrovascular complications were not sustained after tight control of blood pressure was lost.[11]

The effect of tight glycaemic control has also been studied in type 2 diabetic patients with pre-existing diabetic complications. The intensive arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study[12] was stopped early, after a mean of 3.5 years of follow-up, when it became apparent that tight glycaemic control in patients with type 2 diabetes and a history of cardiovascular disease, or multiple cardiovascular risk factors, did not significantly reduce major cardiovascular events and was associated with increased death from any cause. The reason for this increased mortality rate was unclear, but possible factors included the low HbA_{1c} goal (targeted to below 6.0%; a median of 6.4% was achieved), or the magnitude or speed of reduction in HbA_{1c}. Five-year outcomes from the ACCORD study[13] confirmed that there was an increased mortality rate associated with intensive multidrug therapy to reduce HbA_{1c} below 6% in patients with sub-optimally controlled long-standing diabetes and a high risk of cardiovascular disease. Subgroup analysis[14] indicated that intensive therapy was most likely to increase risk in patients with HbA_{1c} ≥8.5%, aspirin use at study entry, or in particular, self-reported history of neuropathy. Intensive therapy did delay the onset of albuminuria, and, by some measures, eye complications and neuropathy.[15]

The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) included patients with type 2 diabetes and a history of, or risk factors for, vascular disease. Results from a median follow-up of 5 years provided further evidence for an association between intensive glucose control (HbA_{1c} 6.5%) and a reduction in microvascular risks, particularly nephropathy, but found no significant effect on major macrovascular events.[16] In a separate component of ADVANCE, a fixed combination of perindopril and indapamide reduced the risk of a major microvascular or macrovascular complication compared with placebo, regardless of initial blood pressure; significant reductions were seen in total coronary and renal events, but not cerebrovascular or diabetic eye events.[17] Further analysis of the ADVANCE study showed that combined blood pressure lowering and intensive glycaemic control resulted in substantial reductions in major renal events and all-cause death.[18]

Another study of glycaemic control, the Veterans Affairs Diabetes Trial (VADT), found that lowering HbA_{1c} to 6.9% in patients with poorly controlled, long-standing type 2 diabetes had no significant effect on either microvascular or macrovascular complications.[19]

Pioglitazone has also been studied in patients with extensive macrovascular disease, based on the suggestion that it might have beneficial effects in addition to its effect on glycaemic control. The Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) study targeted HbA_{1c} to below 6.5% and encouraged optimum lipid-lowering, antiplatelet, and antihypertensive therapy. Over 3 years it found no significant benefit in a broad composite end-point that included macrovascular outcomes as well as death from any cause, but did report significantly fewer events for a composite end-point that included only all-cause mortality, non-fatal myocardial infarction, and stroke.[20]

In an attempt to clarify the effects of intensive glycaemic control on cardiovascular outcomes in type 2 diabetes, a meta-analysis[21] combined data from UKPDS, PROactive, ADVANCE, VADT, and ACCORD, which included a total of more than 33 000 diabetic patients. Looking at separate end-points, there were significant reductions in non-fatal myocardial infarction and events of coronary heart disease, but the effects on stroke and all-cause mortality were not significant. Another meta-analysis[22] involving 13 studies and over 34 000 patients concluded that a benefit of intensive treatment on cardiovascular and all-cause mortality could not be shown, and although it was associated with modest improvements in the risk of non-fatal myocardial infarction and microalbuminuria, it also increased the risk of severe hypoglycaemia. A review of randomised controlled studies and meta-analyses of intensive versus conventional glycaemic control on microvascular and macrovascular complications in both type 1 and 2 diabetes[23] concluded that intensive therapy should be used at an early stage of diabetes and that for patients with long-standing well controlled diabetes it is more reasonable to use conventional glycaemic control.

The Bypass Angioplasty Revascularisation Investigation 2 Diabetes (BARI 2D) study[24] included type 2 diabetics who were candidates for elective coronary revascularisation. While receiving antidiabetic therapy targeted to HbA_{1c} less than 7.0%, the study examined the effects of various treatment options on cardiovascular outcomes. After an average follow-up of about 5 years, the rates of survival and major cardiovascular events did not differ overall between groups allocated to either medical therapy alone or prompt revascularisation (percutaneous coronary intervention or coronary-artery bypass grafting as appropriate) plus medical therapy. In subgroup analysis, there were fewer major cardiovascular events in candidates for bypass grafting who underwent prompt surgery compared with those allocated to medical therapy. However, there was no significant difference for those who were candidates for percutaneous intervention when compared with medical therapy. The type of medical therapy (insulin-sensitising or insulin-providing drugs) also had no apparent effect on outcome.

The relationship between postprandial glucose concentrations and the development of diabetic complications is under investigation. Epidemiological studies in general populations have shown an association between macrovascular disease and hyperglycaemia after a glucose challenge. However, there are limited data about this relationship in diabetic patients. There is also some evidence that postprandial hyperglycaemia is associated with accelerated atherosclerosis. Whether targeting postprandial glucose concentrations can reduce or prevent cardiovascular complications is yet to be established.[25] The American Diabetes Association[26] has suggested that for patients with a raised HbA_{1c} despite preprandial glucose values within the target range, a postprandial target of lower than 10.0 mmol/litre (measured 1 to 2 hours after the start of the meal) may help to reduce HbA_{1c}. The International Diabetes Federation[27] has suggested a 2-hour postprandial goal closer to normal, at less than 7.8 mmol/litre. For details on recommended preprandial and HbA_{1c} goals, see Monitoring of Therapy, under Diabetes Mellitus, p. 459.1.

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Diabetes-associated cardiovascular disease. Diabetic patients are at increased risk of cardiovascular disease, and it is apparent that tight glycaemic control alone is not sufficient to avoid complications.[1] Diet and exercise are important components of cardiovascular risk reduction for diabetics, as well as the control of blood pressure and serum lipids, use of antiplatelet therapy, and the avoidance of smoking. For broader discussions about the management of cardiovascular disease, see Cardiovascular Risk Reduction (p. 1246.1), Hyperlipidaemias (p. 1248.1), and Hypertension (p. 1251.1). Peripheral arterial disease is more common in diabetics, is associated with an increased risk of cardiovascular and cerebrovascular events, and is a contributing factor to diabetic foot disease (see p. 466.2); cardiovascular risk reduction is therefore strongly advocated in diabetic patients with peripheral arterial disease.[2,3] The management of peripheral arterial disease is discussed on p. 1272.3. Diabetics are also prone to cardiomyopathy, see under Diabetic Heart Disease (p. 466.3).

Hypertension should be treated aggressively to prevent both microvascular and macrovascular complications of diabetes, and blood pressure is generally targeted to below 130/80 mmHg.[4-8] However, this may be unnecessarily stringent: evidence from the ACCORD study[9] suggested that a systolic blood-pressure target below 120 mmHg did not reduce rates of fatal and non-fatal cardiovascular events any further than one of 140 mmHg, and a subgroup analysis of the INVEST study indicated that no improved cardiovascular outcomes were seen from systolic blood pressure control below the range of 130 to 139 mmHg.[10] Although diet and exercise are recommended in the management of hypertension, most diabetics will require multidrug therapy. All of the main groups of antihypertensive drugs may be used, although an ACE inhibitor or angiotensin II receptor antagonist is usually recommended for first-line therapy. Calcium-channel blockers, diuretics, or beta blockers may be added as necessary.

Patients with diabetes are prone to develop elevated triglycerides and a serum-cholesterol profile associated with increased cardiovascular risk, and the management of ***dyslipidaemia*** is therefore advocated.[5,8] The American Diabetes Association[4] recommends a low-density-lipoprotein (LDL)-cholesterol target below 2.6 mmol/litre in patients without overt cardiovascular disease, and a lower goal of less than 1.8 mmol/litre in those with overt disease. Triglycerides of less than 1.7 mmol/litre are also suggested, with high-density-lipoprotein (HDL)-cholesterol above 1.0 mmol/litre in men and above 1.3 mmol/litre in women. Statins are the lipid lowering drugs of choice for LDL-cholesterol.[4,6,11] If statins are not tolerated or maximal doses do not achieve treatment goals, other drugs such as ezetimibe, bile-acid binding resins, or nicotinic acid may be tried; they are less effective than statins as monotherapy for lowering LDL-cholesterol, but may be added to statin therapy.[11] Fibrates, such as gemfibrozil, or nicotinic acid may be used for management of HDL-cholesterol and triglycerides. High doses of nicotinic acid can affect glycaemic control, but modest doses (0.75 to 2 g daily) may improve lipid profiles with manageable increases in blood-glucose concentrations.[4] Statins are also recommended regardless of baseline lipid levels for diabetics with overt cardiovascular disease, and for those without overt disease who are over the age of 40 years and have one or more other risk factors for cardiovascular disease.[4] A meta-analysis[12] of statin studies has shown cardiovascular benefits for diabetics similar to those seen in patients without diabetes, regardless of lipid profile and whether vascular disease was already present.[12] A possible beneficial effect from fibrates has also been suggested, and was studied in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study[13] in patients with type 2 diabetes, with or without cardiovascular disease and without dyslipidaemia requiring treatment. After about 5 years of therapy, fenofibrate was not associated with a significant reduction in major coronary events, although there were reductions in non-fatal myocardial infarction and coronary revascularisations. However, follow-up of the FIELD study showed that fenofibrate may reduce the risk of both first myocardial infarction and further cardiovascular events after silent myocardial infarction.[14] A meta-analysis[15] that was dominated by the FIELD study concluded that fibrates reduced the incidence of cardiovascular events in type 2 diabetics, but the effect on mortality was not significant.

Antiplatelet therapy has also been recommended for cardiovascular risk reduction in diabetics. Aspirin is recommended for secondary prevention in diabetic patients with cardiovascular disease,[4,8] although some data suggest that there may be less benefit than in patients without diabetes.[6,7] It has also been recommended as primary

prevention in patients at increased risk, but the strength of evidence for this recommendation had been challenged because of extrapolation from studies of other high-risk groups, and limited benefit in diabetic subgroups within primary prevention studies.[16] Subsequent primary prevention studies specifically undertaken in diabetic patients have not definitively shown that low-dose aspirin reduced the risk of cardiovascular events,[17,18] although the Fremantle Diabetes Study in type 2 diabetics showed reduced cardiovascular and all-cause mortality in a primary prevention setting.[19] Despite a lack of conclusive evidence the American Diabetes Association, the American Heart Association, and the American College of Cardiology Foundation recommend that primary prevention be considered in most diabetic men over 50 years of age and women over 60 who have at least one additional major risk factor (a family history of cardiovascular disease, hypertension, smoking, dyslipidaemia, or albuminuria).[4,20] Clopidogrel is generally reserved for patients who are unable to take aspirin,[4,8] and the combination of aspirin and clopidogrel may be used for up to a year after an acute coronary syndrome.[4]

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Diabetic diarrhoea. Diabetic patients may develop intermittent bouts of watery diarrhoea, sometimes alternating with constipation; autonomic neuropathy and abnormalities of digestion and bowel flora may play a role.[1] Clonidine has been suggested for severe cases,[2] and octreotide has been used successfully,[3,4] but otherwise conventional management with antidiarrhoeal drugs (p. 1808.2) is advocated; a broad spectrum antibacterial (especially tetracycline[5]) may also be effective. The mechanism of action of tetracycline in diabetic diarrhoea is uncertain, but it has been suggested that 2 or 3 doses of tetracycline 250 mg can be tried at the start of an attack.

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Diabetic eye disease. Diabetic patients are prone to potentially blinding eye disease, usually in the form of cataract or diabetic retinopathy. Cataract generally requires surgical extraction, particular care being taken to avoid infection. Diabetic retinopathy may take a 'background', non-proliferative form, or become a more serious proliferative retinopathy associated with neovascularisation, vitreous haemorrhage and retinal detachment. Macular oedema, characterised by retinal thickening from leaky blood vessels, can develop at any stage of retinopathy.[1]

Aggressive glycaemic and blood pressure control is used to reduce the onset and progression of diabetic retinopathy.[1-3] Transient early worsening may occur in patients transferred to more intensive glycaemic regimens, which may be related to higher baseline HbA_{1c} values and a more rapid reduction of HbA_{1c}.[1] Although dyslipidaemia appears to increase the risk of retinopathy, it is still unclear whether lipid lowering therapy would be useful for prevention of diabetic retinopathy.[1] However, the ACCORD Eye Study Group showed that fenofibrate, when added to a statin, slowed the progression of diabetic retinopathy in type 2 diabetes.[3] The FIELD study[4] reported that fenofibrate reduced the need for laser treatment, but suggested that the mechanism of effect did not seem to be related to plasma-lipid concentrations.

Once severe nonproliferative or proliferative retinopathy has developed, pan-retinal laser photocoagulation is effective in limiting progression, while focal laser therapy may be used in macular oedema.[1,2] Surgical vitrectomy may be helpful for vitreous haemorrhage and areas of traction involving or threatening the macula in advanced proliferative retinopathy, and in widespread or diffuse macular oedema that has not responded to laser treatment.[1] Intravitreal injection of the corticosteroid triamcinolone acetonide may be useful for persistent diabetic macular oedema;[1,5,6] intravitreal implants that release fluocinolone acetonide or dexamethasone have also been studied.[1,6] However, cataract formation and raised intra-ocular pressure have been associated with intravitreal corticosteroids. Intravitreal ranibizumab, an inhibitor of vascular endothelial growth factor (VEGF), can improve visual acuity and appears to be more effective than laser therapy,[7,8] but the combination may be no better than ranibizumab alone.[8] It may be used alone or with laser therapy, but long-term efficacy is not yet proven. Other VEGF inhibitors that have been studied include bevacizumab and pegaptanib.[7]

Many drugs have been tried for the prevention or retardation of diabetic eye disease but mostly with indifferent results; these included aspirin, ticlopidine, aldose reductase inhibitors, ruboxistaurin, and octreotide.[1,9] There is some evidence that blockade of the renin-angiotensin system with an ACE inhibitor or angiotensin II receptor antagonist may be of benefit in retarding progression of early disease.[10]

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Diabetic foot disease. Peripheral arterial disease, neuropathy, collagen changes, and increased susceptibility to infection may contribute to the foot lesions to which diabetics are prone. Ulceration and tissue necrosis at pressure-points may be followed by tissue and bone infection, gangrene, and sepsis.

Management involves drainage and debridement of dead and infected tissue, pain care, and the use of antibacterials if necessary.[1,2] Surgical debridement of necrotic wound tissue has been shown to improve wound healing, and needs to be repeated if new necrotic tissue continues to form. Other, less well proven, methods include enzymatic debridement using collagenase, and larval (maggot) therapy.[3] While oral antibacterials with Gram-positive coverage may be adequate for mild to moderate infections, broad spectrum cover should be started intravenously if there is severe, limb-threatening infection; treatment should be adapted once the results of bacteriological culture are available.[1,3-6]

Various other adjunctive therapies that may be considered in the management of diabetic foot ulcers include becaplermin, bioengineered skin substitutes, hyperbaric oxygen therapy, and negative pressure wound therapy, although supporting evidence for these may be limited.[3,5,7,8] Granulocyte colony-stimulating factors given as adjunctive therapy with antibacterials may not accelerate wound healing or resolution of infection, but could reduce rates of amputation and other surgical procedures.[9] A retrospective cohort study[10] of over 2500 patients treated with advanced biological therapies has shown that wounds first treated with a bioengineered human skin equivalent (*Apligraf*) were more likely to heal than those treated with becaplermin or an autologous platelet-derived growth factor (platelet-rich plasma; platelet releasate *Procuren*).

Diabetic neuropathic osteoarthropathy (Charcot foot), characterised by joint dislocation, fracture, and destruction of the structures of the foot, is managed with immobilisation, stress reduction, and surgery; improvements in markers of bone turnover have been reported in small studies using bisphosphonates.[3]

Strict control of blood glucose is important and insulin should be given as required. Reduction of pressure to the ulcer (off-loading) should be offered to prevent further trauma and promote healing;[1] effective pain relief and bed rest may be needed, and surgical reconstruction to improve blood supply may be helpful in some cases.[3]

Ultimately, some patients require amputation of all or part of the foot.[3] Preventive care, with regular visits to a chiropodist, is therefore particularly important. The possibility that fenofibrate might reduce the risk of amputation in type 2 diabetics has been raised by results from the FIELD study.[11] Although lower limb vascular status was not routinely measured at baseline or in those who did not have an amputation, fenofibrate was associated with a reduction in the risk of first minor amputation in patients without documented large vessel (atherosclerotic) disease; the risk of either minor or major amputation was not reduced in those with large vessel disease.

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Diabetic heart disease. Diabetics may develop a form of cardiomyopathy, characterised by left ventricular hypertrophy with diastolic and systolic dysfunction in the absence of ischaemic heart disease and hypertension.[1,2] Tight glycaemic control might prevent or limit the development of heart disease, although data to confirm this are limited. Until more specific data become available, management strategies for associated heart failure (p. 1262.3) are based on those for non-diabetic patients, using ACE inhibitors, angiotensin II receptor antagonists, and beta blockers. Other conditions affecting the heart in diabetic patients include cardiovascular disease (see p. 463.3) and cardiac autonomic neuropathy (see Diabetic Neuropathy, p. 467.2)

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Diabetic nephropathy. Nephropathic changes associated with microvascular disease develop in up to 30% of patients with type 1 diabetes and up to 40% of those with type 2 disease; diabetic nephropathy, of which the first clinical sign is albuminuria, is one of the major causes of end-stage renal disease (see Chronic Renal Failure, p. 1781.1).

Results from the DCCT indicate that strict glycaemic control reduces the incidence of microalbuminuria in type 1 diabetes[1] (with long-term renal benefits[2]), and smaller reductions were seen in the UKPDS[3] and ADVANCE[4] studies in patients with type 2 diabetes. It is also evident from the DCCT[1] and ADVANCE[4] that strict glycaemic control can slow the progression of nephropathy in patients who are already microalbuminuric.

An important approach to the management of diabetic nephropathy is optimal blood pressure control, because the treatment of hypertension can reduce the risk of developing microalbuminuria and delay progression.[5-7] The UKPDS[8] found atenolol and captopril to have similar effects on the progression of albuminuria in type 2 diabetics with hypertension. However, ACE inhibitors may have renoprotective effects independent of the patient's blood pressure[9,10] or the type of diabetes,[10] probably by inhibition of the renin-angiotensin system. Reduced progression to macroalbuminuria has been also found in normotensive patients with type 1 diabetes given ACE inhibitors.[11] As well as slowing progression, ACE inhibitors can normalise albumin excretion in patients with microalbuminuria.[10,11] There is also evidence for the efficacy of ACE inhibitors in the primary prevention of diabetic kidney disease,[12] although a 5-year study that measured structural changes in the kidney failed to find evidence that use of enalapril or losartan prevented development and progression of nephropathy.[13] For these reasons, ACE inhibitors are generally recommended as first-line therapy in diabetic patients with hypertension and albuminuria.[6]

Angiotensin II receptor antagonists have also been shown to reduce the progression of renal disease in type 2 patients with both microalbuminuria and macroalbuminuria,[7,10] and US recommendations consider them an equal first choice with ACE inhibitors;[6] UK guidelines suggest they may be used in those unable to tolerate ACE inhibitors.[14] Although direct comparisons are limited to small studies, the effects of ACE inhibitors and angiotensin II receptor antagonists on renal outcomes appear to be equivalent.[10] The combination of an ACE inhibitor with an angiotensin II receptor antagonist has been reported to reduce proteinuria more than an ACE inhibitor alone; however, most studies have been small and short-term, and there have been associated falls in glomerular filtration rate and raised serum potassium;[15] a larger multicentre study[16] suggested that combination therapy with telmisartan and ramipril, although it reduced proteinuria more than either drug alone, was associated with a higher incidence of renal events.

The renin inhibitor aliskiren has also been investigated as an addition to angiotensin II inhibitors, and improvements in albuminuria have been reported.[17] However, the combination of aliskiren with angiotensin II receptor inhibitors or ACE inhibitors has been contra-indicated because of an increased risk of adverse effects (see Diabetes Mellitus, under Precautions of Aliskiren Fumarate, p. 1296.1).

Addition of paricalcitol to treatment with ACE inhibitors or angiotensin II receptor antagonists also appears to lower residual albuminuria in patients with diabetic nephropathy,[18] and has been suggested as a possible novel approach to improve renal outcomes.

There has also been interest in the effects of fibrates on diabetic nephropathy. Tertiary outcome results from the FIELD study showed a reduced onset or progression of albuminuria in patients with type 2 diabetes given fenofibrate; there was also more regression of albuminuria in the fenofibrate group.[19] A substudy of the FIELD research[20] did not show a benefit on albumin excretion from using fenofibrate and noted increases in creatinine and cystatin-C measurements in patients, indicative of a negative effect on renal function However, further analysis of data from the main study[21] suggested that the effects of fenofibrate on plasma creatinine were reversible, and confirmed a reduction in albuminuria and a slowing of estimated decline in renal function over 5 years.

Dietary protein restriction (see Renal Failure, p. 2043.3) appears from several small studies to have a beneficial, although small, effect on disease progression.[22] It has been recommended for consideration particularly when nephropathy is progressing despite optimal glycaemic and blood pressure control and the use of an ACE inhibitor and/or angiotensin II receptor antagonist.[6]

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Diabetic neuropathy. Peripheral neuropathies are common complications of diabetes mellitus. The intensity and extent of neurological abnormalities are proportional to the degree and duration of hyperglycaemia. The manifestations of sensorimotor neuropathy (distal symmetrical polyneuropathy) classically progress from the fingers and toes in a symmetrical pattern. The most common symptom is sensory loss, which is a significant risk factor for the development of diabetic foot disease; neuropathic pain and paraesthesia can also occur. Autonomic neuropathy affecting the cardiovascular system can cause tachycardia and orthostatic hypotension, and may increase the risk of silent myocardial infarction. Other manifestations of autonomic neuropathy include gastroparesis, diarrhoea, bladder atony, and erectile dysfunction.[1,2] Focal neuropathies are less common, but may cause unilateral cranial nerve palsies, truncal pain or dysaesthesia, or proximal pain, sensory loss, muscle weakness, and atrophy of the thigh. Multifocal neuropathy affecting the lower limbs, trunk, and upper extremities is also less common.[2]

Results from the DCCT indicated that strict glycaemic control could substantially reduce the occurrence of clinical neuropathy in patients with type 1 diabetes,[3-5] a result which was not duplicated in the UKPDS in patients with type 2 diabetes.[6] Long-term follow-up studies from the DCCT/EDIC group showed that the benefits of intensive diabetes control on development of peripheral neuropathy still persisted 14 years later,[7] and that intensive therapy benefited type 1 patients with cardiac autonomic neuropathy over a similar period of time.[8]

Other treatments have also been studied in an attempt to prevent, treat, or slow the progression of diabetic neuropathy. Aldose reductase inhibitors such as epalrestat have been investigated, but a meta-analysis of 32 studies found no convincing evidence of benefit,[9] and serious adverse effects have halted development of several drugs in this class. The antioxidant thioctic acid has been studied in the treatment of diabetic neuropathy, and is promoted in some countries as a dietary supplement. Symptomatic improvements in sensorimotor neuropathy have been reported in some short-term studies using intravenous or high oral doses, but evidence of long-term efficacy and safety are lacking.[10,11] Results from another short-term study[12] have suggested slight improvement in cardiac autonomic neuropathy.

Other management of diabetic neuropathy is essentially symptomatic.[1,13,14] The management of diabetic neuropathic pain is discussed on p. 8.2. Tachycardia may require the use of beta blockers while orthostatic hypotension should be managed conventionally[1,15] (see under Fludrocortisone, p. 1634.3), although care may be required in the use of elastic stockings in patients with impaired blood flow to the feet. Diabetic gastroparesis may respond to prokinetic drugs such as metoclopramide, cisapride, domperidone, or erythromycin,[1,14,16,17] but their effects can be variable and long-term use may be limited by tachyphylaxis and adverse effects. Antiemetics may be used as adjuncts to prokinetic therapy, and endoscopic or surgical interventions may be needed when symptoms cannot be controlled. Management of diabetic diarrhoea is discussed p. 464.1. For the management of erectile dysfunction, see p. 2348.2.

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Diabetic emergencies

The most frequent complication of insulin therapy is **hypoglycaemia** and patients taking insulin need to be educated about its cause, symptoms, and treatment. Most patients can recognise the early warning signs of hypoglycaemia and by taking sugar immediately can prevent more serious symptoms developing. Comatose patients need to be given intravenous glucose or, if this is not practicable, subcutaneous, intramuscular, or intravenous glucagon (although glucose is still required if there is no response within 10 minutes). Hypoglycaemia can also develop in patients taking oral antidiabetics, notably the sulfonylureas.

Some patients report loss of the warning signs of hypoglycaemia after transferring from animal to human insulin and these patients, if appropriate, may need to be transferred back to animal insulin. However, the most significant factor in the loss of warning signs is exposure to hypoglycaemia itself, and loss of awareness is liable to be a particular problem in patients receiving intensive therapy. Hypoglycaemic unawareness can be reversed by avoiding

hypoglycaemia for 2 to 3 weeks, and there is limited evidence to suggest that caffeine can improve awareness of hypoglycaemia.[1,2]

Further details on drug-induced hypoglycaemia can be found in Hypoglycaemia under Insulin (p. 486.2) and Sulfonylurea Antidiabetics (p. 504.1), while management is discussed under Treatment of Insulin-Induced Hypoglycaemia (p. 486.3) and Treatment of Adverse Effects (p. 504.1), respectively.

Diabetic ketoacidosis is caused by an absolute or relative lack of insulin, with an increase in counter-regulatory hormones such as glucagon, catecholamines, cortisol, and growth hormone. The condition is characterised by hyperglycaemia, hyperketonaemia, metabolic acidosis, and glycosuria causing osmotic diuresis with subsequent dehydration and electrolyte abnormalities; death may result in up to 1% of cases overall.[3,4] Presenting symptoms include thirst, polyuria, weight loss, nausea, vomiting, diffuse abdominal pain, dehydration, weakness, and impaired mental status ranging from lethargy to coma.[4] Young children are also at increased risk of cerebral oedema.[3,5] Symptoms of poorly controlled diabetes may be present for several days before metabolic acidosis, which tends to develop quickly, typically over less than 24 hours.[4] Diabetic ketoacidosis is commonly precipitated by a failure to adjust insulin dosage in the presence of infection. Other precipitating factors include discontinuation of or inadequate insulin therapy, failure of a continuous subcutaneous insulin infusion pump, drugs that affect carbohydrate metabolism, and medical conditions such as pancreatitis, myocardial infarction, and stroke.[4] Diabetic ketoacidosis is often present when type 1 diabetes mellitus is diagnosed, particularly in younger children.[3] Pregnant diabetic women are also prone to the development of diabetic ketoacidosis, particularly in the second and third trimesters because of insulin resistance that increases insulin requirements.[6]

Diabetic ketoacidosis is a medical emergency. The basic principles of treatment are fluid replacement, insulin therapy, and correction of electrolyte imbalances.[3-5,7-9]

- Fluid requirements depend on individual needs, but treatment is generally started with sodium chloride 0.9% infusion, which is subsequently adjusted according to the hydration state, serum-electrolyte concentrations, and urinary output. Care should be taken to avoid overvigorous fluid replacement;[4] in children this can particularly exacerbate the risk of cerebral oedema.[3]
- Soluble regular insulin should be given once hypokalaemia (see below) has been excluded or treated, with doses adjusted to achieve a steady decline in plasma-glucose concentrations.[8,9] For details of insulin dosing recommendations, see Diabetic Emergencies under Insulin, p. 483.3. Large doses were formerly thought necessary, but lower dose regimens accompanied by adequate hydration and correction of hyperosmolarity have proven to be adequate and are now recommended.[3,4]

  Continuous intravenous infusion is the preferred method of insulin delivery for managing diabetic ketoacidosis. In the USA an initial intravenous bolus dose has been recommended in some regimens for adults;[4] it is considered unnecessary in children and may increase the risk of cerebral oedema.[3] Frequent subcutaneous injection is another option for giving regular insulin, but it has a delayed onset of action and prolonged half-life compared with intravenous infusion.[4] In the management of mild to moderate, uncomplicated diabetic ketoacidosis, the use of a subcutaneous rapid-acting insulin analogue may be considered.[3,4]

  Ketonaemia typically takes longer to clear than hyperglycaemia, and once plasma glucose has fallen to a suitable value, the dose of insulin is reduced and infusion of glucose is begun simultaneously,[4] allowing insulin to be continued in order to clear ketone bodies without inducing hypoglycaemia. Once glucose concentrations have been controlled and acidosis has completely cleared, transition to a maintenance subcutaneous dosage regimen of insulin can begin. However, intravenous insulin should not be stopped until this has taken effect, which may be 1 to 2 hours after starting subcutaneous regular insulin.[3,4] Any established therapy with a long-acting insulin analogue (insulin detemir or insulin glargine) should be continued during treatment for ketoacidosis.[8]
- Although total body stores of potassium are depleted in diabetic ketoacidosis, mainly from the intracellular pool, patients may present with serum concentrations that are normal, increased, or decreased.[3,4] Giving insulin and correcting acidosis will drive potassium back into the cells and lower the serum-potassium concentration; patients will generally need potassium replacement regardless of their serum concentration at presentation. Potassium is given by infusion and may be started after adequate renal function has been confirmed. In hyperkalaemic patients, potassium is given once serum concentrations have fallen to within normal limits.[4] For normokalaemic patients, it should be started when insulin therapy begins, after initial fluid expansion.[3] In the rare patient presenting with hypokalaemia, potassium replacement should begin with fluid replacement and insulin withheld until potassium concentrations have risen to normal values.[4]

  Intravenous bicarbonate is now generally reserved for patients with severe acidaemia despite fluid replacement and insulin therapy. Some[3,4] have suggested that bicarbonate may be given to those with a pH of less than 6.9, aiming to achieve a pH above 7.0. Bicarbonate treatment can increase the risk of hypokalaemia, and potassium may be added to the infusion.

  Phosphate concentrations are affected in a similar manner to potassium concentrations in the ketoacidotic state, but there is less agreement on the need for routine doses of phosphate. Phosphate concentrations should be monitored and phosphate given if clinically significant hypophosphataemia occurs.[3,4]

The precipitating cause of diabetic ketoacidosis should also be identified and managed appropriately.

Hyperosmolar hyperglycaemic state (HHS) or hyperosmolar hyperglycaemic nonketotic coma (HONK) occurs mainly in elderly patients with type 2 diabetes and though much less common than diabetic ketoacidosis it carries a higher mortality.[10] HHS is an emerging problem in children and adolescents with type 2 diabetes.[11] Adult patients may present in coma with severe hyperglycaemia but with minimal ketosis; dehydration and renal impairment are common. Treatment is similar to that of diabetic ketoacidosis using intravenous insulin (see above), although the insulin dose should be reduced and glucose started once the plasma-glucose concentration has fallen to about 17 mmol/litre. A concentration of about 11 to 17 mmol/litre should be maintained until the patient is mentally alert and HHS resolves.[4] Features of HHS, such as dehydration and contracted vascular volume, low cardiac output, increased blood viscosity, and very high osmolarity may predispose the patient to thrombosis. Although prophylactic heparin may be considered in patients at high risk of thrombosis, there is a lack of evidence to confirm its safety or efficacy in this situation.[10] Treatment aims in children are similar to those for adults and although no definitive regimen is yet available suggested guidelines have been proposed.[12]

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Acarbose *(BAN, USAN, rINN)*

Acarbosa; Acarbosio; Acarbosum; AG-5421; Akarboosi; Akarbos; Akarbosa; Akarboz; Akarbozé; Akarboza; Bay-g-5421; Акарбоза.

O-[4-Amino-4,6-dideoxy-*N*-[(1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-hydroxymethylcyclohex-2-enyl]-α-D-glucopyranosyl]-(1→4)-*O*-α-D-glucopyranosyl-(1→4)-D-glucopyranose.

$C_{25}H_{43}NO_{18}$=645.6

CAS — 56180-94-0.

ATC — A10BF01.

ATC Vet — QA10BF01.

UNII — T58MSI464G.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Acarbose). A white or yellowish, amorphous, hygroscopic powder. Very soluble in water; practically insoluble in dichloromethane; soluble in methyl alcohol. A 5% solution in water has a pH of 5.5 to 7.5. Store in airtight containers.

USP 36: (Acarbose). Produced by certain strains of *Actinoplanes utahensis.* Store in airtight containers.

Uses and Administration

Acarbose is an inhibitor of alpha glucosidases, especially sucrase. This slows the digestion and absorption of carbohydrates in the small intestine and hence reduces the increase in blood-glucose concentrations after a carbohydrate load. It is given in the treatment of type 2 diabetes mellitus (p. 459.1) either alone or with a sulfonylurea, biguanide, or insulin. Acarbose treatment may be started with a low oral dose of 25 or 50 mg daily to minimise gastrointestinal disturbance. It is then gradually increased to a usual dose of 25 or 50 mg three times daily immediately before food. After 4 to 8 weeks, the dose may be increased further if necessary, and doses up to 100 to 200 mg three times daily may be given. Licensed US product information recommends a maximum dose of 50 mg three times daily for patients weighing up to 60 kg, and a maximum of 100 mg three times daily for those weighing more. Some benefit has also been found when acarbose is used to supplement insulin therapy in type 1 diabetes mellitus.

Acarbose has also been studied for the treatment of reactive hypoglycaemia, the dumping syndrome, certain types of hyperlipoproteinaemia, and polycystic ovary syndrome.

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Impaired glucose tolerance. A prospective study of patients with impaired glucose tolerance concluded that acarbose delayed the development of type 2 diabetes[1] and significantly reduced the incidence of cardiovascular disease and hypertension.[2] However, a systematic review,[3] which included this study, found that data were limited and that the quality of the other 4 included studies was poor. The authors of the review concluded that there was evidence that acarbose reduced the incidence of type 2 diabetes, but the effects on glycaemic control were limited and it was unclear whether the effect should be seen as prevention, delay, or masking of diabetes. They also felt that more study was needed to confirm whether acarbose prevented cardiovascular events in these patients.

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Adverse Effects

Acarbose often causes gastrointestinal disturbances, particularly flatulence due to bacterial action on non-absorbed carbohydrate in the colon. Abdominal distension, diarrhoea, and pain may occur. A decrease in dosage and improved dietary habits may reduce these adverse effects, and they generally diminish with time. Ileus has been rarely reported. Transient and reversible increases in liver enzyme values can occur, and acarbose should be withdrawn if the elevations persist; there have also been rare reports of jaundice and hepatitis including fatal fulminant hepatitis. Thrombocytopenia and pneumatosis cystoides intestinalis

have been reported. Skin reactions and oedema have been reported rarely.

Incidence of adverse effects. The manufacturers reported that adverse effects of acarbose were rarer in postmarketing surveillance studies than in previous clinical studies;[1,2] this was held to represent better tailoring of individual doses to patient tolerability.

1. Spengler M, Cagatay M. The use of acarbose in the primary-care setting: evaluation of efficacy and tolerability of acarbose by postmarketing surveillance study. *Clin Invest Med* 1995; 18: 325–31.
2. Mertes G. Safety and efficacy of acarbose in the treatment of type 2 diabetes: data from a 5-year surveillance study. *Diabetes Res Clin Pract* 2001; 52: 193–204.

Effects on the gastrointestinal tract. Pneumatosis cystoides intestinalis has been reported after the use of alpha-glucosidase inhibitors including acarbose, miglitol, and voglibose.[1,2] The most common symptoms were abdominal distension and pain; haematochezia (blood in the stool) was also reported. The interval between starting therapy and onset of pneumatosis varied greatly, ranging from 7 days to 11 years.

1. Tsujimoto T, *et al.* Pneumatosis cystoides intestinalis following alpha-glucosidase inhibitor treatment: a case report and review of the literature. *World J Gastroenterol* 2008; 14: 6087–92.
2. Kojima K, *et al.* Pneumatosis cystoides intestinalis induced by the alpha-glucosidase inhibitor miglitol. *Intern Med* 2010; 49: 1545–8.

Effects on the liver. Hepatocellular liver damage and elevated serum aminotransferases, with or without jaundice, have been reported in patients receiving acarbose.[1-4] In these cases, symptoms resolved on stopping the drug; however, licensed product information states that there have been cases of fatal fulminant hepatitis.

1. Andrade RJ, *et al.* Hepatic injury caused by acarbose. *Ann Intern Med* 1996; 124: 931.
2. Carrascosa M, *et al.* Acarbose-induced acute severe hepatotoxicity. *Lancet* 1997; 349: 698–9.
3. Fujimoto Y, *et al.* Acarbose-induced hepatic injury. *Lancet* 1998; 351: 340.
4. Hsiao S-H, *et al.* Hepatotoxicity associated with acarbose therapy. *Ann Pharmacother* 2006; 40: 151–4.

Effects on the skin. Generalised erythema multiforme and eosinophilia occurred in a male diabetic patient 13 days after starting acarbose.[1] The hypersensitivity reaction was confirmed by rechallenge.

1. Kono T, *et al.* Acarbose-induced generalised erythema multiforme. *Lancet* 1999; 354: 396–7.

Precautions

Acarbose is contra-indicated in inflammatory bowel disease, particularly where there is associated ulceration, and in gastrointestinal obstruction or patients predisposed to it. It should be avoided in patients with chronic intestinal diseases that significantly affect digestion or absorption, and in conditions which may deteriorate as a result of increased gas formation, such as hernia.

Acarbose is also contra-indicated in patients with hepatic impairment and liver enzyme values should be monitored, particularly during the first 6 to 12 months of therapy and at high doses.

Acarbose given alone should not cause hypoglycaemia, but may potentiate the effects of sulfonylureas and insulin. If hypoglycaemia doses develop in a patient receiving acarbose it needs to be treated with glucose, since the action of acarbose inhibits the hydrolysis of disaccharides.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies acarbose as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Interactions

Acarbose may enhance the effects of other antidiabetics, including insulin, and a reduction in their dosage may be needed. Use with gastrointestinal adsorbents and digestive enzyme preparations can diminish the effects of acarbose and should be avoided. Neomycin and colestyramine may enhance the effects of acarbose and a reduction in its dosage may be required. Acarbose may inhibit the absorption of digoxin (see Antidiabetics, under Interactions of Digoxin, p. 1356.3).

Pharmacokinetics

After ingestion of acarbose, the majority of active unchanged drug remains in the lumen of the gastrointestinal tract to exert its pharmacological activity and is metabolised by intestinal enzymes and by the microbial flora. Less than 2% of a dose is absorbed unchanged, but about 35% is absorbed in the form of metabolites. Acarbose is excreted in the urine and faeces.

Renal impairment. Increased peak plasma concentrations of acarbose and areas under the concentration-time curve (of about 5 and 6 times normal, respectively) have been found in pharmacokinetic studies of patients with severe renal impairment (creatinine clearance less than 25 mL/min per 1.73 m^2). The clinical significance of these effects is unknown.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Glucobay; ***Austral.***: Glucobay; ***Austria***: Glucobay; ***Belg.***: Glucobay; ***Braz.***: Aglucose; Glucobay; ***Canad.***: Glucobay; Prandase†; ***Chile***: Glucobay; ***China***: Beixi (贝希); Glucobay (拜唐苹); Kaboping (卡博平); ***Cz.***: Glucobay; ***Denm.***: Glucobay; ***Fin.***: Glucobay; ***Fr.***: Glucor; ***Ger.***: Glucobay; ***Gr.***: Glucobay; ***Hong Kong***: Glucobay; ***Hung.***: Glucobay; ***India***: Abacus; Acarb; Acarbay; Acarex; Acarwin; Asucrose; Diabose; Diadose; Glubose; Glucar; Glucobay; Glucobose; Gludase; K-Carb; ***Indon.***: Eclid; Glucobay; ***Irl.***: Glucobay; ***Israel***: Acrose; Prandase; ***Ital.***: Glicobase; Glucobay; ***Malaysia***: Dibose; Garbose; Glucar; Glucobay; Glucorid; Precarbay; Precose†; ***Mex.***: Glemisal; Glucobay; Incardel; Sincrosa; ***Neth.***: Glucobay; ***Norw.***: Glucobay; ***NZ***: Glucobay; ***Philipp.***: Glucobay; Gluconase; ***Pol.***: Glucobay; ***Port.***: Alsucril; Bluecose; Establix; Glucobay; Linacal; ***Rus.***: Glucobay (Глюкобай); ***S.Afr.***: Glucobay; ***Singapore***: Glucobay; ***Spain***: Glucobay; Glumida; ***Swed.***: Glucobay; ***Switz.***: Glucobay; ***Thai.***: Glucobay; ***Turk.***: Acaris; Arokan; Glucar; Glucobay; Glynose; ***UK***: Glucobay; ***Ukr.***: Glucobay (Глюкобай)†; ***USA***: Precose; ***Venez.***: Glucobay.

Acetohexamide *(BAN, USAN, rINN)*

Acetohexamid; Acetohexamida; Acétohexamide; Acetohexamidum; Asetoheksamidi; Compound 33006; Ацетогексамид.

1-(4-Acetylbenzenesulphonyl)-3-cyclohexylurea.

$C_{15}H_{20}N_2O_4S$=324.4

CAS — 968-81-0.

ATC — A10BB31.

ATC Vet — QA10BB31.

UNII — QGC8W08I6I.

Pharmacopoeias. In *Jpn* and *US*.

USP 36: (Acetohexamide). A white, practically odourless, crystalline powder. Practically insoluble in water and in ether; soluble 1 in 230 of alcohol and 1 in 210 of chloroform; soluble in pyridine and in dilute solutions of alkali hydroxides.

Profile

Acetohexamide is a sulfonylurea antidiabetic (p. 502.3). It has been given in the treatment of type 2 diabetes mellitus.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Dimelin.

Pharmacopoeial Preparations
USP 36: Acetohexamide Tablets.

Alogliptin Benzoate *(USAN, rINNM)*

Alogliptine, Benzoate de; Alogliptini Benzoas; Benzoato de alogliptina; SYR-322; Альоглиптина Бензоат.

6-[(3*R*)-3-Aminopiperidin-1-yl]-1-(2-cyanobenzyl)-3-methylpyrimidin-2,4(1*H*,3*H*)-dione monobenzoate.

$C_{18}H_{21}N_5O_2.C_7H_6O_2$=461.5

CAS — 850649-61-5 (alogliptin); 850649-62-6 (alogliptin benzoate).

ATC — A10BH04.

ATC Vet — QA10BH04.

UNII — EEN99869SC.

Uses and Administration

Like sitagliptin (p. 502.1), alogliptin benzoate is an inhibitor of dipeptidylpeptidase-4 and is used in the treatment of type 2 diabetes mellitus (p. 459.1).

Alogliptin is given as the benzoate, but doses are expressed in terms of the base; 34 mg of alogliptin benzoate is equivalent to about 25 mg of alogliptin. The usual oral dose is the equivalent of alogliptin 25 mg once daily with or without food. When given with metformin, alogliptin may be given in 2 divided doses. The dose of sulfonylurea or insulin may need to be lowered when used with alogliptin. Dosage should be adjusted in patients with renal impairment (see p. 469.3).

References.

1. Scott LJ. Alogliptin: a review of its use in the management of type 2 diabetes mellitus. *Drugs* 2010; 70: 2051–72. Correction. *ibid.*; 2475.
2. Baetta R, Corsini A. Pharmacology of dipeptidyl peptidase-4 inhibitors: similarities and differences. *Drugs* 2011; 71: 1441–67.

Administration in renal impairment. Licensed product information suggests the following oral doses of alogliptin in patients with renal impairment, based on creatinine clearance (CC):

- mild impairment (CC 60 mL/min or more): no adjustment necessary, 25 mg once daily
- moderate impairment (CC 30 to less than 60 mL/min): 12.5 mg once daily
- severe impairment (CC 15 to less than 30 mL/min) or end-stage renal disease (CC less than 15 mL/min or requiring haemodialysis): 6.25 mg once daily. Alogliptin may be given without regard to the timing of haemodialysis but it has not been studied in peritoneal dialysis

Adverse Effects, Treatment, and Precautions

As for Sitagliptin Phosphate, p. 502.1.

There have been reports of fatal and non-fatal hepatic failure in patients taking alogliptin. It should be used with caution in patients with abnormal liver test results, and treatment interrupted in those who develop symptoms of liver injury and persistently elevated liver enzyme concentrations.

Interactions

The efficacy of alogliptin may be affected by other drugs that have an independent effect on blood glucose. For more details and examples of drugs that can increase or decrease blood-glucose concentrations, see Interactions under Sulfonylureas, p. 504.3.

Pharmacokinetics

Alogliptin is absorbed from the gastrointestinal tract, with a peak plasma concentration occurring about 1 to 2 hours after a single oral dose, and a bioavailability of almost 100%. Alogliptin is not extensively metabolised; about 76% is excreted in the urine and 13% in the faeces. Its terminal half-life is about 21 hours.

References.

1. Scheen AJ. Pharmacokinetics of dipeptidylpeptidase-4 inhibitors. *Diabetes Obes Metab* 2010; 12: 648–58.
2. Golightly LK, *et al.* Comparative clinical pharmacokinetics of dipeptidyl peptidase-4 inhibitors. *Clin Pharmacokinet* 2012; 51: 501–14. Correction. *ibid.*; 831.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Nesina; ***UK***: Vipidia; ***USA***: Nesina.

Multi-ingredient Preparations. ***Jpn***: Liovel; ***UK***: Vipdomet; ***USA***: Kazano; Oseni.

Biguanide Antidiabetics

Antidiabéticos biguanídicos; Бигуаниды Антидиабетические.

Uses and Administration

The biguanide antidiabetics are a class of oral antidiabetic drugs used in the treatment of type 2 diabetes mellitus (p. 459.1). They are given to supplement treatment by diet modification when such modification has not proved effective on its own. In addition, because biguanides are not associated with weight gain, they are preferred in obese patients. In non-obese patients sulfonylureas (p. 502.3) may be preferred, although a biguanide is often added or given instead to patients who are not responding to a sulfonylurea.

The mode of action of biguanides is not clear. They do not stimulate insulin release but require that some insulin be present in order to exert their antidiabetic effect. Possible mechanisms of action include delay in the absorption of glucose from the gastrointestinal tract, an increase in insulin sensitivity and glucose uptake into cells, and inhibition of hepatic gluconeogenesis. Biguanides do not usually lower blood-glucose concentrations in non-diabetic subjects.

Hyperlipidaemias. The effect of biguanides on lipid metabolism is unclear, although some beneficial effects on serum-lipid profiles have been described. Study results in patients with type 2 diabetes have been reviewed.[1] Reductions in concentrations of total cholesterol and low-density-lipoprotein cholesterol can occur, an effect which may not necessarily depend on glycaemic control. Increases in high-density-lipoprotein cholesterol have not been significant. There is evidence for a reduction in serum-triglyceride levels, which may be related to glycaemic control and metformin dose. However, the review found that effects

The symbol † denotes a preparation no longer actively marketed

on lipids were generally limited and not expected to result in major reductions in cardiovascular end-points.

1. Wulffelé MG, *et al.* The effect of metformin on blood pressure, plasma cholesterol and triglycerides in type 2 diabetes mellitus: a systematic review. *J Intern Med* 2004; 256: 1–14.

Polycystic ovary syndrome. For discussion of the potential of metformin in polycystic ovary syndrome, see p. 492.2.

Adverse Effects

Gastrointestinal adverse effects including anorexia, nausea, vomiting, and diarrhoea may occur with biguanides, often at the start of treatment. The effects generally resolve spontaneously, but can be minimised by introducing the drug gradually. Patients may have taste disturbance and there may be weight loss. Absorption of various substances including vitamin B_{12} may be impaired. Skin reactions have been reported rarely.

Hypoglycaemia is rare with a biguanide given alone, although it may occur if other contributing factors or drugs are present.

Lactic acidosis, sometimes fatal, has occurred with biguanides, mainly with phenformin. When it has occurred with metformin most cases have been in patients whose condition contra-indicated the use of the drug, particularly those with renal impairment.

Phenformin has been implicated in the controversial reports of excessive cardiovascular mortality associated with oral hypoglycaemic therapy (see under Sulfonylureas, Effects on the Cardiovascular System, p. 503.2).

Reviews.

1. Paterson KR, *et al.* Undesired effects of biguanide therapy. *Adverse Drug React Acute Poisoning Rev* 1984; 3: 173–82.
2. Howlett-HCS, Bailey CJ. A risk-benefit assessment of metformin in type 2 diabetes mellitus. *Drug Safety* 1999; 20: 489–503.

Effects on the blood. Megaloblastic anaemia has occurred with biguanide therapy (see Malabsorption, under Effects on the Gastrointestinal Tract, p. 470.1). A few cases of metformin-induced haemolysis resulting in hyperbilirubinaemia and jaundice have also been described,[1-3] including a case that progressed to massive haemolysis, shock, and death.[4]

1. Lin K-D, *et al.* Metformin-induced hemolysis with jaundice. *N Engl J Med* 1998; 339: 1860–1.
2. Kashyap AS, Kashyap S. Haemolytic anaemia due to metformin. *Postgrad Med J* 2000; 76: 125–6.
3. Meir A, *et al.* Metformin-induced hemolytic anemia in a patient with glucose-6-phosphate dehydrogenase deficiency. *Diabetes Care* 2003; 26: 956–7.
4. Packer CD, *et al.* Fatal hemolytic anemia associated with metformin: a case report. *J Med Case Reports* 2008; 2: 300.

Effects on the gastrointestinal tract. *DIARRHOEA.* Diarrhoea is a well-known adverse effect of metformin.[1] It often occurs when treatment is started, but generally subsides with continued use; it can also be minimised by taking metformin with meals, starting with a low dose and increasing gradually. Chronic diarrhoea described as watery, often explosive, and frequently causing faecal incontinence, has been reported as an adverse effect of late onset in patients receiving metformin. Some patients had been on stable metformin therapy for several years before the onset of diarrhoea. Symptoms ceased upon withdrawal of metformin, and recurred in cases of rechallenge.[2,3]

1. Bytzer P, *et al.* Oral hypoglycaemic drugs and gastrointestinal symptoms in diabetes mellitus. *Aliment Pharmacol Ther* 2001; 15: 137–42.
2. Raju B, *et al.* Metformin and late gastrointestinal complications. *Am J Med* 2000; 109: 260–1.
3. Foss MT, Clement KD. Metformin as a cause of late-onset chronic diarrhea. *Pharmacotherapy* 2001; 21: 1422–4.

MALABSORPTION. Megaloblastic anaemia due to vitamin B_{12} malabsorption in a 58-year-old woman was associated with long-term use of metformin.[1] Metformin also appeared to precipitate a fall in serum concentrations of vitamin B_{12} with megaloblastic anaemia, within 10 months of starting therapy, in a woman who had previously undergone gastrectomy.[2] She was successfully managed with mecobalamin supplementation and the use of nateglinide for the management of her diabetes.

In a survey of diabetic patients receiving biguanide therapy,[3] malabsorption of vitamin B_{12} was seen in 14 of 46 diabetics taking metformin or phenformin; metformin was more commonly to blame. Withdrawal of the drug resulted in normal absorption in only 7 of the 14. A placebo-controlled study[4] in 353 patients also found reduced vitamin B_{12} concentrations after 16 weeks of metformin, with associated decreases in serum-folate and increases in homocysteine. A study[5] in 390 patients has confirmed the effects of metformin on vitamin B_{12} and homocysteine concentrations. In a series of 10 patients[6] with vitamin B_{12} deficiency associated with metformin, vitamin B_{12} concentrations and blood count abnormalities were reported to have been corrected within 3 months of starting treatment with intramuscular or oral cyanocobalamin; 2 patients were transferred to treatment with other antidiabetic agents. Dietary advice on vitamin B_{12} intake has also been suggested as an intervention.[7]

1. Callaghan TS, *et al.* Megaloblastic anaemia due to vitamin B_{12} malabsorption associated with long-term metformin treatment. *BMJ* 1980; 280: 1214–15.
2. Fujita H, *et al.* A case of megaloblastic anemia due to vitamin B_{12} deficiency precipitated in a totally gastrectomized type II diabetic patient following the introduction of metformin therapy. *Endocr J* 2003; 50: 483–4.
3. Adams JF, *et al.* Malabsorption of vitamin B_{12} and intrinsic factor secretion during biguanide therapy. *Diabetologia* 1983; 24: 16–18.
4. Wulffelé MG, *et al.* Effects of short-term treatment with metformin on serum concentrations of homocysteine, folate and vitamin B12 in type 2 diabetes mellitus: a randomized, placebo-controlled trial. *J Intern Med* 2003; 254: 455–63.
5. de Jager J, *et al.* Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. *BMJ* 2010; 340: c2181.
6. Andrès E, *et al.* Metformin-associated vitamin B_{12} deficiency. *Arch Intern Med* 2002; 162: 2251–2.
7. Vidal-Alaball J, Butler CC. Reduced serum vitamin B-12 in patients taking metformin. *BMJ* 2010; 340: 1147–8.

Effects on the liver. Hepatotoxic reactions to metformin are rare, but several cases of cholestatic hepatitis have been described.[1-8] Generally, the reaction occurred less than 2 months after starting metformin, and resolved within about 3 months after stopping the drug.

1. Babich MM, *et al.* Metformin-induced acute hepatitis. *Am J Med* 1998; 104: 490–2.
2. Desilets DJ, *et al.* Cholestatic jaundice associated with the use of metformin. *Am J Gastroenterol* 2001; 96: 2257–8.
3. Nammour FE, *et al.* Metformin-induced cholestatic hepatitis. *Endocr Pract* 2003; 9: 307–9.
4. Deutsch M, *et al.* Metformin hepatotoxicity. *Ann Intern Med* 2004; 140: W25. Available at: http://www.annals.org/cgi/reprint/140/5/W-25.pdf (accessed 05/10/09)
5. Kutoh E. Possible metformin-induced hepatotoxicity. *Am J Geriatr Pharmacother* 2005; 3: 270–3.
6. Barquero Romero J, Pérez Miranda M. Hepatitis colestásica inducida por metformina. *Gastroenterol Hepatol* 2005; 28: 257–8.
7. Cone CJ, *et al.* Hepatotoxicity associated with metformin therapy in treatment of type 2 diabetes mellitus with nonalcoholic fatty liver disease. *Ann Pharmacother* 2010; 44: 1655–9.
8. Miralles-Linares F, *et al.* Metformin-induced hepatotoxicity. *Diabetes Care* 2012; 35: e21.

Effects on the pancreas. Although acute pancreatitis is more commonly associated with phenformin[1,2] there have also been a few cases of pancreatitis associated with metformin, in which renal failure may have precipitated metformin toxicity.[3,4] Pancreatitis has also occurred in a patient without renal impairment, about 48 hours after starting metformin for polycystic ovary syndrome.[5]

1. Wilde H. Pancreatitis and phenformin. *Ann Intern Med* 1972; 77: 324.
2. Chase RS, Mogan GR. Phenformin-associated pancreatitis. *Ann Intern Med* 1977; 87: 314–15.
3. Mallick S. Metformin induced acute pancreatitis precipitated by renal failure. *Postgrad Med J* 2004; 80: 239–40.
4. Fimognari FL, *et al.* Metformin-induced pancreatitis: a possible adverse drug effect during acute renal failure. *Diabetes Care* 2006; 29: 1183.
5. Molina Infante J, *et al.* Pancreatitis aguda tóxica por metformina sin insuficiencia renal. *Med Clin (Barc)* 2008; 131: 519.

Hypersensitivity. Vasculitis and pneumonitis in a 59-year-old woman was associated with use of metformin.[1] Symptoms improved on withdrawal of metformin, but reappeared on its reintroduction. Cutaneous vasculitis in a 33-year-old woman also resolved on withdrawal of metformin and recurred with its reintroduction.[2]

1. Klapholz L, *et al.* Leucocytoclastic vasculitis and pneumonitis induced by metformin. *BMJ* 1986; 293: 483.
2. Salem CB, *et al.* Rare case of metformin-induced leukocytoclastic vasculitis. *Ann Pharmacother* 2006; 40: 1685–7.

Hypoglycaemia. Licensed product information for metformin states that hypoglycaemia does not occur with metformin alone, even in overdosage, although it may occur if given with alcohol or other hypoglycaemics. Interim 3-year results from the UK Prospective Diabetes Study[1] indicated that metformin therapy was associated with fewer hypoglycaemic episodes than sulfonylurea or insulin treatment, but more than with diet alone. In a follow-up study of 290 patients who were treated with metformin for at least 6 years, the annual percentage of patients reporting at least one hypoglycaemic episode was 1.7%, compared with 0.8% of 756 patients managed on diet alone.[2]

1. United Kingdom Prospective Diabetes Study Group. United Kingdom prospective diabetes study (UKPDS) 13: relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for 3 years. *BMJ* 1995; 310: 83–8.
2. Wright AD, *et al.* for the UKPDS Group. Hypoglycemia in type 2 diabetic patients randomized to and maintained on monotherapy with diet, sulfonylurea, metformin, or insulin for 6 years from diagnosis: UKPDS73. *J Diabetes Complications* 2006; 20: 395–401.

Lactic acidosis. There is a small but definite risk of lactic acidosis associated with use of biguanide antidiabetics. Most early reports involved phenformin, which was consequently removed from the market in many countries although cases of phenformin-associated lactic acidosis still occur.[1-5] There has therefore been concern about the risks of lactic acidosis with metformin, which is still in wide use. However, lactic acidosis with metformin appears to be much less common:[6] a review suggested that the incidence was of the order of 3 cases per 100 000 patient years, which was 20 times less frequent than with phenformin.[7] This concurs with the findings of the FDA after the introduction of metformin to the US market: in the year after the marketing of metformin in the USA, the FDA had received reports of metformin-associated lactic acidosis in 66 patients,[8] the diagnosis being confirmed in 47. This represented a rate of about 5 cases per 100 000. Most patients who do develop lactic acidosis with metformin have one or more precipitating risk factors such as renal impairment, congestive heart failure, or other conditions predisposing to hypoxaemia or acute renal failure, including septicaemia, acute hepatic decompensation, alcohol abuse, acute myocardial infarction, and shock.[6,7] Dehydration might also be a contributing factor.[9-11] See also Heart Failure, p. 471.1, for further discussion on the risks of using metformin in patients with that condition. A systematic review,[12] which considered study results comprising over 70 000 patient years of treatment with metformin, concluded that provided metformin was prescribed taking into account the proper contra-indications, there was no evidence of an increased risk of lactic acidosis. The relationship between metformin and lactic acidosis has also been directly questioned in a review of 47 case reports.[13] The authors asserted that these patients had other risk factors that could account for the development of lactic acidosis, and that no relationship could be established between lactate concentration, metformin concentration, and mortality. They suggested, therefore, that the association between metformin use and lactic acidosis in these cases could have been coincidental rather than causal. Nonetheless, there have been a few reports of lactic acidosis developing in metformin-treated patients without apparent risk factors.[7,14,15]

1. Rosand J, *et al.* Fatal phenformin-associated lactic acidosis. *Ann Intern Med* 1997; 127: 170.
2. Enia G, *et al.* Lactic acidosis induced by phenformin is still a public health problem in Italy. *BMJ* 1997; 315: 1466–7.
3. Kwong SC, Brubacher J. Phenformin and lactic acidosis: a case report and review. *J Emerg Med* 1998; 16: 881–6.
4. Kumar A, *et al.* Severe acidosis in a patient with type 2 diabetes mellitus, hypertension, and renal failure. *Chest* 2003; 123: 1726–9.
5. Fimognari FL, *et al.* Phenformin-induced lactic acidosis in an older diabetic patient: a recurrent drama (phenformin and lactic acidosis). *Diabetes Care* 2006; 29: 930–1.
6. Lalau J-D. Lactic acidosis induced by metformin: incidence, management and prevention. *Drug Safety* 2010; 33: 727–40.
7. Chan NN, *et al.* Metformin-associated lactic acidosis: a rare or very rare clinical entity? *Diabet Med* 1999; 16: 273–81.
8. Misbin RI, *et al.* Lactic acidosis in patients with diabetes treated with metformin. *N Engl J Med* 1998; 338: 265–6.
9. Adverse Drug Reactions Advisory Committee (ADRAC). Metformin, dehydration and lactic acidosis. *Aust Adverse Drug React Bull* 2009; 28: 11–12. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0906.pdf (accessed 11/02/11)
10. Fitzgerald E, *et al.* Metformin associated lactic acidosis. *BMJ* 2009; 339: 1254–6.
11. Preiss DJ, Sattar N. Metformin and lactic acidosis. Metformin: framed again? *BMJ* 2010; 340: 8–9.
12. Salpeter SR, *et al.* Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2010 (accessed 11/08/10).
13. Stades AME, *et al.* Metformin and lactic acidosis: cause or coincidence? A review of case reports. *J Intern Med* 2004; 255: 179–87.
14. Silvestre J, *et al.* Metformin-induced lactic acidosis: a case series. *J Med Case Reports* 2007; 1: 126.
15. Bruijstens LA, *et al.* Reality of severe metformin-induced lactic acidosis in the absence of chronic renal impairment. *Neth J Med* 2008; 66: 185–90.

Treatment of Adverse Effects

Acute poisoning with biguanides may lead to the development of lactic acidosis (see Metabolic Acidosis, p. 1777.2) and calls for intensive supportive therapy. Glucose or glucagon may be required for hypoglycaemia, the general management of which is outlined in Insulin, p. 486.3. Activated charcoal may be given orally within 1 hour of overdose, provided the airway can be protected.

Overdosage. References.

1. Spiller HA, *et al.* Multicenter case series of pediatric metformin ingestion. *Ann Pharmacother* 2000; 34: 1385–8.
2. Forrester MB. Adult metformin ingestions reported to Texas poison control centers, 2000—2006. *Hum Exp Toxicol* 2008; 27: 575–83.

Precautions

Biguanides are inappropriate for patients with diabetic coma and ketoacidosis, or for those with severe infection, trauma, or other severe conditions where the biguanide is unlikely to control the hyperglycaemia; insulin should be used in such situations. Biguanides are generally avoided in patients with renal impairment, as it may predispose patients to lactic acidosis, and renal function should be monitored throughout therapy (see also Renal Impairment under Precautions of Metformin, p. 493.1). Dehydration may contribute to renal impairment. Conditions associated with hypoxia, such as acute heart failure, recent myocardial infarction, or shock, may increase the risk of lactic acidosis. Other conditions that may also predispose to lactic acidosis

in a patient taking a biguanide include excessive alcohol intake and hepatic impairment. Biguanides should be discontinued in patients undergoing surgery and only restarted once normal renal function has been established. They may also need to be temporarily stopped for examinations using contrast media in some patients (see under Interactions, p. 471.1).

Insulin is preferred for the treatment of diabetes in pregnancy (but see also p. 493.1 for reports of metformin use during pregnancy).

Owing to the possibility of decreased vitamin B_{12} absorption, annual monitoring of vitamin B_{12} concentrations is advisable during long-term treatment.

Driving. Diabetes mellitus, its complications, and the medications used to treat it, may affect a patient's ability to drive safely—see under Insulin (p. 487.2) for restrictions applied to diabetic patients in the UK.

Heart failure. Metformin has been contra-indicated in diabetic patients with heart failure, because of an increased risk of lactic acidosis. However, there is evidence from observational studies that although this contra-indication has been increasingly ignored, lactic acidosis in these patients is still rare.[1] A causal role for metformin in cases of lactic acidosis has also been questioned (see Lactic Acidosis, p. 468.2). Although heart failure is a common comorbidity in diabetics, controlled studies of metformin in these patients are lacking. Data from observational and retrospective studies, and a small prospective study, have shown no increase in risk of lactic acidosis with metformin, and have actually suggested that metformin may be associated with lower rates of morbidity and mortality, of any cause, in patients with heart failure.[1-4] It has therefore been suggested that metformin may be used, with caution, in diabetic patients with compensated, stable heart failure.[5] However, it is still contra-indicated in those with acute or unstable symptoms,[5] and in those with coexisting risk factors such as renal impairment.[1,3]

1. Tahrani AA, *et al.* Metformin, heart failure, and lactic acidosis: is metformin absolutely contraindicated? *BMJ* 2007; 335: 508–12.
2. Eurich DT, *et al.* Benefits and harms of antidiabetic agents in patients with diabetes and heart failure: systematic review. Abridged version: *BMJ* 2007; 335: 497–501. Full version: http://www.bmj.com/cgi/reprint/335/7618/497 (accessed 23/02/09)
3. Roberts F, Ryan GJ. The safety of metformin in heart failure. *Ann Pharmacother* 2007; 41: 642–6.
4. Khurana R, Malik IS. Metformin: safety in cardiac patients. *Heart* 2010; 96: 99–102.
5. Inzucchi SE, *et al.* Metformin therapy in patients with type 2 diabetes complicated by heart failure. *Am Heart J* 2007; 154: e45. Also published in: *Diabetes Care* 2007; 30: e129.

Interactions

Use of a biguanide with other drugs that lower blood-glucose concentrations increases the risk of hypoglycaemia, while drugs that increase blood glucose may reduce the effect of biguanide therapy.

In general fewer drug interactions have been reported with biguanides than with sulfonylureas. Alcohol may increase the risk of lactic acidosis as well as of hypoglycaemia. Care should be taken if biguanides are given with drugs that may impair renal function.

Anticoagulants. For the effect of metformin on *phenprocoumon* activity, see Antidiabetics, p. 1531.3.

Antivirals. Fatal lactic acidosis has been reported[1] in a patient given metformin with *didanosine, stavudine,* and *tenofovir.*

1. Worth L, *et al.* A cautionary tale: fatal lactic acidosis complicating nucleoside analogue and metformin therapy. *Clin Infect Dis* 2003; 37: 315–16.

Cimetidine. Cimetidine increased plasma-metformin concentrations in 7 healthy subjects.[1] The renal clearance of metformin was reduced; competition for proximal tubular secretion was considered responsible. A reduction in metformin dosage may be required in patients taking metformin and cimetidine, in order to reduce the risk of lactic acidosis. For a report of lactic acidosis in a patient given metformin, cimetidine, and orlistat, see Orlistat, p. 471.2.

1. Somogyi A, *et al.* Reduction of metformin renal tubular secretion by cimetidine in man. *Br J Clin Pharmacol* 1987; 23: 545–51.

Contrast media. Caution is required when using iodinated contrast media in those receiving biguanides because of the risk of patients developing lactic acidosis. Licensed product information for some contrast media preparations warns that biguanides should be temporarily stopped 48 hours before the examination, and withheld until normal renal function is confirmed. However, several guidelines[1-4] that give advice on the use of iodinated contrast media in patients taking metformin, do not support such general restrictions for patients with normal serum creatinine and/or a glomerular filtration rate above 60 mL/minute. In general they recommend that for patients with:

- no comorbidities and normal renal function: there is no need to discontinue metformin before use of an iodinated contrast medium and no need to check serum creatinine afterwards
- multiple comorbidities and normal renal function: metformin should be discontinued at the time of the procedure and withheld for 48 hours. A repeat serum creatinine measurement is not mandatory before restarting metformin in such patients unless there are risk factors for renal damage
- renal dysfunction: metformin should be discontinued at the time of the procedure and should be restarted after at least 48 hours and then only if renal function remains stable

Canadian guidelines[1] also consider that metformin should be withheld in all patients for 48 hours if the volume of contrast medium is greater than 100 mL.

1. Benko A, *et al.* Canadian Association of Radiologists: consensus guidelines for the prevention of contrast-induced nephropathy. *Can Assoc Radiol J* 2007; 58: 79–87. Correction available at: http://www.car.ca/Files%5CNephropathy.pdf (accessed 22/05/09) [correct version]
2. European Society of Urogenital Radiology. ESUR guidelines on contrast media (version 7.0, issued August 2008). Available at: http://www.esur.org/ESUR_Guidelines_NEW.6.0.html (accessed 22/05/09)
3. Committee on Drugs and Contrast Media. American College of Radiology manual on contrast media (version 7, issued 2010). Available at: http://www.acr.org/SecondaryMainMenuCategories/quality_safety/contrast_manual/FullManual.aspx (accessed 24/08/10)
4. Board of the Faculty of Clinical Radiology; The Royal College of Radiologists. Standards for intravascular contrast agent administration to adult patients, second edition (issued April 2010). Available at: http://www.rcr.ac.uk/docs/radiology/pdf/BFCR%2810%294_Stand_contrast.pdf (accessed 24/08/10)

Ketotifen. Platelet counts in 10 diabetic patients receiving biguanides fell (markedly in 3 patients) when they were also given ketotifen.[1] Counts returned to normal a few days after the end of ketotifen therapy. However, the investigators did not consider the effect clinically significant.

1. Doleček R. Ketotifen in the treatment of diabetics with various allergic conditions. *Pharmatherapeutica* 1981; 2: 568–74.

Orlistat. A study in healthy subjects found no significant interaction between orlistat and metformin.[1] However, lactic acidosis developed in a woman with diabetes mellitus given metformin, orlistat, and cimetidine.[2] The authors postulated that diarrhoea caused by orlistat may have led to renal impairment, and a subsequent impairment of metformin excretion. Alternatively, orlistat may have enhanced the absorption of metformin or increased the metformin-induced conversion of glucose to lactate in the gut. These possible interactions may have then been exacerbated by cimetidine, which may reduce renal clearance of metformin (see Cimetidine, above).

1. Zhi J, *et al.* Pharmacokinetic evaluation of the possible interaction between selected concomitant medications and orlistat at steady state in healthy subjects. *J Clin Pharmacol* 2002; 42: 1011–19.
2. Dawson D, Conlon C. Case study: metformin-associated lactic acidosis: could orlistat be relevant? *Diabetes Care* 2003; 26: 2471–2.

Sulfonylureas. For reference to an apparent increase in mortality with an intensive regimen of metformin plus a sulfonylurea, see p. 503.3.

Buformin *(USAN, pINN)*

Buformina; Buformine; Buforminum; DBV; W-37; Буформин.

1-Butylbiguanide.

$C_6H_{15}N_5$=157.2

CAS — 692-13-7 (buformin); 1190-53-0 (buformin hydrochloride).

ATC — A10BA03.

ATC Vet — QA10BA03.

UNII — W2115E9C7B.

Profile

Buformin is a biguanide antidiabetic (p. 467.3). It has been given orally in the treatment of type 2 diabetes mellitus (p. 459.1) in doses of up to 300 mg daily. Buformin is also used as the hydrochloride.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Hung.*: Adebit.

Canagliflozin *(USAN, rINN)*

Canagliflozina; Canagliflozine; Canagliflozinum; JNJ-24831754ZAE; JNJ-28431754; JNJ-28431754AAA; TA-7284; Канаглифлозин.

(1*S*)-1,5-Anhydro-1-*C*-(3-{[5-(4-fluorophenyl)thiophen-2-yl]methyl}-4-methylphenyl)-D-glucitol hemihydrate

$C_{24}H_{25}FO_5S,½H_2O$=453.5

CAS — 842133-18-0 (anhydrous canagliflozin); 928672-86-0 (canagliflozin hemihydrate).

UNII — 0SAC974Z85.

NOTE. Canagliflozin (*INN*) is anhydrous, while Canagliflozin (*USAN*) refers to the hemihydrate.

Uses and Administration

Canagliflozin is a sodium-glucose co-transporter 2 inhibitor. It has similar actions to dapagliflozin (p. 472.2) and is used in the management of type 2 diabetes mellitus (p. 459.1).

Canagliflozin is given as the hemihydrate, but doses are expressed in terms of the anhydrous form; 102 mg of canagliflozin hemihydrate is equivalent to about 100 mg of anhydrous canagliflozin. An oral dose of 100 mg once daily is given before the first meal of the day. The dose may be increased to 300 mg once daily if necessary. In particular, patients taking inducers of uridine diphosphate glucuronosyltransferase (UGT), such as rifampicin, may need a daily dose of 300 mg. Doses of insulin, sulfonylurea, or other insulin secretagogues may need to be lowered when used with canagliflozin.

For the use of canagliflozin in renal impairment, see p. 471.3.

References.

1. Nisly SA, *et al.* Canagliflozin, a new sodium-glucose cotransporter 2 inhibitor, in the treatment of diabetes. *Am J Health-Syst Pharm* 2013; 70: 311–19.

Administration in renal impairment. A canagliflozin dose of 100 mg orally once daily should not be exceeded in patients with moderate renal impairment (estimated GFR 45 to less than 60 mL/min per 1.73 m^2). It should not be used when estimated GFR is less than 45 mL/min per 1.73 m^2.

Adverse Effects and Precautions

As for Dapagliflozin, p. 472.3. Electrolyte disturbances associated with canagliflozin include increases in serum concentrations of potassium, magnesium, and phosphate. Hypersensitivity reactions have been reported.

Interactions

Rifampicin can decrease canagliflozin exposure by induction of uridine diphosphate glucuronosyltransferase (UGT) enzymes, including UGT1A9 and UGT2B4. See Uses and Administration, above, for canagliflozin dose adjustment in patients also given UGT inducers.

Canagliflozin may affect digoxin exposure (see Antidiabetics under Interactions of Digoxin, p. 1356.3).

Pharmacokinetics

Canagliflozin is absorbed from the gastrointestinal tract, with peak plasma concentrations occurring within 1 to 2 hours after a dose and an absolute bioavailability of about 65%. It is extensively bound to plasma proteins. Canagliflozin undergoes glucuronidation, mainly by the uridine diphosphate glucuronosyltransferases UGT1A9 and UGT2B4. There is minimal oxidative metabolism via the cytochrome P450 isoenzyme CYP3A4. About 52% of a dose is excreted in the faeces, mainly as unchanged canagliflozin; about 33% is found in the urine, mainly as *O*-glucuronide metabolites. It has a terminal half-life of about 10 to 13 hours. Removal of canagliflozin by haemodialysis is negligible.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *UK*: Invokana; *USA*: Invokana.

Carbutamide *(BAN, rINN)*

BZ-55; Ca-1022; Carbutamida; Carbutamidum; Glybutamide; Karbutamid; Karbutamidi; U-6987; Карбутамид.

1-Butyl-3-sulphanilylurea.

$C_{11}H_{17}N_3O_3S$=271.3

CAS — 339-43-5.

ATC — A10BB06.

ATC Vet — QA10BB06.

UNII — E3K8P4869P.

Profile

Carbutamide is a sulfonylurea antidiabetic (p. 502.3). It is given orally in the treatment of type 2 diabetes mellitus (p. 459.1) in single daily doses of 0.5 to 1 g, but is more toxic than chlorpropamide.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Glucidoral†.

Chlorpropamide *(BAN, rINN)*

Chloropropamid; Chlorpropamid; Chlorpropamidas; Chlorpropamidum; Clorpropamida; Kloorlpropamidi; Klorpropamid; Klórpropamid; Хлорпропамид.
1-(4-Chlorobenzenesulphonyl)-3-propylurea.
$C_{10}H_{13}ClN_2O_3S$=276.7
CAS — 94-20-2.
ATC — A10BB02.
ATC Vet — QA10BB02.
UNII — WTM2C3IL2X.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Chlorpropamide). A white or almost white, crystalline powder. It exhibits polymorphism. Practically insoluble in water; soluble in alcohol; freely soluble in acetone and in dichloromethane; dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 36: (Chlorpropamide). A white crystalline powder having a slight odour. Practically insoluble in water; soluble in alcohol; sparingly soluble in chloroform.

Uses and Administration

Chlorpropamide is a sulfonylurea antidiabetic (p. 502.3). It has a duration of action of at least 24 hours, and is given orally in the treatment of type 2 **diabetes mellitus** (p. 459.1) in an initial daily dose of 250 mg as a single dose with breakfast. After 5 to 7 days the dose may be adjusted, in steps of 50 to 125 mg at intervals of 3 to 5 days, to achieve an optimum maintenance dose which is usually in the range 100 to 500 mg daily. Increasing the dose above 500 mg daily is unlikely to produce further benefit, and doses above 750 mg daily should be avoided. Although a reduced dose range has been proposed for the elderly, use of chlorpropamide is inadvisable in this group.

Chlorpropamide, though not the other sulfonylureas, is also sometimes used in cranial **diabetes insipidus** (p. 2348.2). It has been reported to act by sensitising the renal tubules to antidiuretic hormone. The dose has to be carefully adjusted to minimise the risk of hypoglycaemia. An initial oral dose of 100 mg daily, adjusted if necessary to a maximum of 350 mg daily has been recommended, although doses of up to 500 mg daily have been used.

Diabetes mellitus. Patients with type 2 diabetes whose blood glucose is adequately controlled at first by sulfonylureas often eventually have treatment failure and loss of diabetic control. Results from the UK Prospective Diabetes Study[1] have suggested that the 6-year failure rate was higher in patients treated with glibenclamide (48%) than in those given chlorpropamide (40%). This difference was equivalent to delaying the requirement for additional therapy for a year in chlorpropamide-treated patients.

1. Matthews DR, *et al.* UKPDS 26: sulphonylurea failure in non-insulin-dependent diabetic patients over six years. *Diabet Med* 1998; 15: 297–303.

Adverse Effects and Treatment

As for sulfonylureas in general, p. 503.1 and p. 504.1.

Chlorpropamide may be more likely than other sulfonylureas to induce a syndrome of inappropriate secretion of antidiuretic hormone characterised by water retention, hyponatraemia, and CNS effects. Patients receiving chlorpropamide may develop facial flushing after drinking alcohol.

Precautions

As for sulfonylureas in general, p. 504.2.

Chlorpropamide should be avoided in the elderly and in renal or hepatic impairment because its long half-life increases the risk of hypoglycaemia. The antidiuretic effect of chlorpropamide may cause problems in patients with conditions associated with fluid retention.

Fasting. For the view that although some sulfonylurea antidiabetics may be able to be used with caution in fasting Muslim patients during Ramadan, chlorpropamide is contra-indicated, see under Precautions of Insulin, p. 487.3.

Thyroid disorders. Some manufacturers have recommended that chlorpropamide should not be used in patients with impaired thyroid function, but see under Sulfonylureas, p. 504.3.

Interactions

As for sulfonylureas in general, p. 504.3.

Chlorpropamide may produce profound facial flushing associated with alcohol ingestion.

Pharmacokinetics

Chlorpropamide is readily absorbed from the gastrointestinal tract and is extensively bound to plasma proteins. The half-life is about 35 hours. About 80% of a dose is metabolised in the liver; metabolites and unchanged drug are excreted in the urine. Chlorpropamide crosses the placenta and has been detected in breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Diabinese; Idle; Trane; *Braz.*: Diabecontrol; Diabinese; Glicoben; Glicorp; Pramidalin; *Canad.*: Novo-Propamide†; *Chile*: Diabinese; *Gr.*: Diabinese; *Hong Kong*: Diabinese; *India*: Copamide; *Indon.*: Diabinese; *Israel*: Diabitex†; *Ital.*: Diabemide; *Malaysia*: Propamide; *Mex.*: Apoprod; Bioness; Diabiclor†; Diabinese; Insogen; *Philipp.*: Diabinese†; *S.Afr.*: Diabinese†; Diabitex; Hypomide; *Singapore*: Anti-D: Propamide; *Spain*: Diabinese†; *Thai.*: Decose; Diabeedol†; Diabetese†; Diabinese; Dibecon; Dibemide; Glycemin†; Propamide; *Turk.*: Diabinese; *Venez.*: Dabinese.

Multi-ingredient Preparations. *India*: Chlorformin; *Ital.*: Bidiabe; Pleiamide; *Mex.*: Apometoclor; Insogen Plus; Mellitron; Obinese; *Switz.*: Diabiformine†.

Pharmacopoeial Preparations
BP 2014: Chlorpropamide Tablets;
USP 36: Chlorpropamide Tablets.

Dapagliflozin *(rINN)*

BMS-512148; Dapagliflozina; Dapagliflozine; Dapagliflozinum; Дапаглифлозин.
(1S)-1,5-Anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-D-glucitol.
$C_{21}H_{25}ClO_6$=408.9
CAS — 461432-26-8.
ATC — A10BX09.
ATC Vet — QA10BX09.
UNII — 1ULL0QJ8UC.

NOTE. Dapagliflozin (*USAN*) is the monohydrate of a compound of dapagliflozin with propanediol (see p. 472.2).

Dapagliflozin Propanediol *(rINNM)*

BMS-512148-05; Dapagliflozin (USAN).
(1S)-1,5-Anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-D-glucitol compound with (2S)-propane-1,2-diol (1:1) monohydrate.
$C_{21}H_{25}ClO_6.C_3H_8O_2.H_2O$=503.0
CAS — 960404-48-2.
ATC — A10BX09.
ATC Vet — QA10BX09.
UNII — 887K2391VH.

Uses and Administration

Dapagliflozin is a sodium-glucose co-transporter 2 inhibitor that enhances urinary excretion of glucose by suppressing renal glucose reabsorption. It is used as monotherapy or with other antidiabetic treatment, including insulin, in the management of type 2 diabetes mellitus (p. 459.1).

It is given as the monohydrate of a compound of dapagliflozin with propanediol, but doses are expressed in terms of dapagliflozin; 12.3 mg of dapagliflozin propanediol monohydrate is equivalent to about 10 mg of dapagliflozin. The usual oral dose is 10 mg once daily. Doses of insulin, sulfonylurea, and other insulin secretagogues may need to be lowered when used with dapagliflozin. The dose of dapagliflozin should be reduced in hepatic impairment (see p. 472.2).

References.
1. Anderson SL, Marrs JC. Dapagliflozin for the treatment of type 2 diabetes. *Ann Pharmacother* 2012; 46: 590–8.
2. Kim Y, Babu AR. Clinical potential of sodium-glucose cotransporter 2 inhibitors in the management of type 2 diabetes. *Diabetes Metab Syndr Obes* 2012; 5: 313–27.
3. Clar C, *et al.* Systematic review of SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes. *BMJ Open* 2012; 2: e001007.

Administration in hepatic impairment. A starting oral dose of dapagliflozin 5 mg once daily is recommended in patients with severe hepatic impairment, which may be increased to 10 mg once daily if well tolerated. No dose adjustment is needed in mild and moderate impairment.

Adverse Effects and Precautions

The most common adverse effects of dapagliflozin are dysuria, polyuria, and genital and urinary-tract infections including vulvovaginitis and balanitis; the increase in rates of infection may be related to raised concentrations of urinary glucose. Dyslipidaemia and increased haematocrit are also common, and increases in blood concentrations of creatinine and urea have been reported. Other effects include back pain, hyperhidrosis, constipation, nausea, dizziness, and rash. Dapagliflozin increases diuresis, which can cause volume depletion and a fall in blood pressure; the effect may be greater in patients with very high blood-glucose concentrations. Dapagliflozin itself is unlikely to cause hypoglycaemia, but it may contribute to hypoglycaemia caused by other antidiabetics such as sulfonylureas and insulin.

Higher incidences of bladder, breast, and prostate cancers were recorded during clinical studies of dapagliflozin. However, risk factors and clinical characteristics of the cases were typical for these types of cancers, the duration of exposure to dapagliflozin before tumour diagnosis was short, and the small number of cases limited the assessment for statistical analysis of causality.

Dapaglillozin is less effective in patients with renal impairment; in addition the risk of adverse effects may also be greater in such patients. Although no dose adjustment is recommended in those with mild renal impairment, its use is not recommended in moderate to severe impairment (creatinine clearance < 60 mL/min). Renal function should be checked before starting dapagliflozin and monitored during treatment.

The dose of dapagliflozin should be reduced in hepatic impairment.

Pharmacokinetics

Peak plasma concentrations of dapagliflozin occur with in 2 to 3 hours after an oral dose, with a bioavailability of about 78%. It is about 91% bound to plasma proteins. Dapagliflozin is extensively metabolised to inactive metabolites via uridine diphosphate glucuronosyltransferase UGT1A9 in the liver and kidney. It has a plasma terminal half-life of about 13 hours; about 75% of the dose is excreted in the urine and 21% in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Denm.*: Forxiga; *Neth.*: Forxiga; *UK*: Forxiga; *USA*: Farxiga.

Epalrestat *(rINN)*

Épalrestat; Epalrestatum; ONO-2235; Эпалрестат.
5-[(*Z*,*E*)-β-Methylcinnamylidene]-4-oxo-2-thioxo-3-thiazolidineacetic acid.
$C_{15}H_{13}NO_3S_2$=319.4
CAS — 82159-09-9.
UNII — 424DV0807X.

NOTE. The name Aldonil has been used as a trade mark for epalrestat.

Profile

Epalrestat inhibits the enzyme aldose reductase which catalyses the conversion of glucose to sorbitol. It has been suggested that accumulation of sorbitol in certain cells, occurring only in conditions of hyperglycaemia and resulting in a hyperosmotic effect, may be involved in the pathogenesis of some diabetic complications. Aldose reductase inhibitors have no influence on blood-glucose concentrations. Epalrestat is given orally for the treatment of diabetic peripheral neuropathy (see p. 465.2), in a usual dose of 50 mg three times daily before meals.

References.
1. Goto Y, *et al.* A placebo-controlled double-blind study of epalrestat (ONO-2235) in patients with diabetic neuropathy. *Diabet Med* 1993; 10 (suppl 2): 39S–43S.
2. Uchida K, *et al.* Effect of 24 weeks of treatment with epalrestat, an aldose reductase inhibitor, on peripheral neuropathy in patients with non-insulin-dependent diabetes mellitus. *Clin Ther* 1995; 17: 460–4.
3. Hotta N, *et al.* Clinical investigation of epalrestat, an aldose reductase inhibitor, on diabetic neuropathy in Japan: multicenter study. *J Diabetes Complications* 1996; 10: 168–72.
4. Ikeda T, *et al.* Long-term effect of epalrestat on cardiac autonomic neuropathy in subjects with non-insulin dependent diabetes mellitus. *Diabetes Res Clin Pract* 1999; 43: 193–8.
5. Iso K, *et al.* Long-term effect of epalrestat, an aldose reductase inhibitor, on the development of incipient diabetic nephropathy in type 2 diabetic patients. *J Diabetes Complications* 2001; 15: 241–4.
6. Hotta N, *et al.* Long-term clinical effects of epalrestat, an aldose reductase inhibitor, on diabetic peripheral neuropathy: the 3-year, multicenter, comparative Aldose Reductase Inhibitor-Diabetes Complications Trial. *Diabetes Care* 2006; 29: 1538–44.
7. Ramírez MA, Borja NL. Epalrestat: an aldose reductase inhibitor for the treatment of diabetic neuropathy. *Pharmacotherapy* 2008; 28: 646–55.

8. Maladkar M, *et al.* Efficacy, safety, and tolerability of epalrestat compared to methylcobalamine in patients with diabetic neuropathy. *Int J Diabetes Dev Ctries* 2009; 29: 28–34.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Tang Lin (唐林); YiHeng (伊衡); *Jpn*: Kinedak.

Exenatide *(BAN, USAN, rINN)*

AC-002993; AC-2993; AC-2993A; Eksenatyd; Exenatid; Exenatida; Exénatide; Exenatidum; LY-2148568; Synthetic Exendin-4; Эксенатид.

$C_{184}H_{282}N_{50}O_{60}S$=4186.6

CAS — 141758-74-9 (exenatide); 141732-76-5 (exendin-4).

ATC — A10BX04.

ATC Vet — QA10BX04.

UNII — 9P1872D4OL.

Uses and Administration

Exenatide is a synthetic form of exendin-4, a 39-amino acid peptide isolated from the venom of the Gila monster lizard (*Heloderma suspectum*, Helodermatidae). The drug is an incretin mimic that acts as an agonist at the glucagon-like peptide 1 receptor to enhance insulin secretion in the presence of raised glucose concentrations; it also suppresses inappropriate glucagon secretion and slows gastric emptying. Exenatide is used as adjunctive therapy in type 2 diabetes mellitus (p. 459.1) in patients who do not have adequate glycaemic control with metformin, a sulfonylurea, a thiazolidinedione, or dual therapy (metformin plus a sulfonylurea or thiazolidinedione). It is also used as adjunctive therapy to basal insulin with or without metformin and/or a thiazolidinedione. Exenatide is given by subcutáneous injection in an initial dose of 5 micrograms twice daily up to 60 minutes before the main morning and evening meals, which should be at least 6 hours apart. It should not be administered after a meal and if a dose is missed treatment should continue at the next scheduled dose. The dose of exenatide may be increased after 1 month to 10 micrograms twice daily if required.

A long-acting formulation of exenatide, for once-weekly dosing, is also available. A dose of 2 mg is given by subcutaneous injection on the same day each week (which can be changed if necessary provided the next dose is given at least 24 hours later) at any time of day, irrespective of meals.

For the use of exenatide in renal impairment, see p. 473.2.

References.
1. Gallwitz B. Benefit-risk assessment of exenatide in the therapy of type 2 diabetes mellitus. *Drug Safety* 2010; 33: 87–100.
2. Shyangdan DS, *et al.* Glucagon-like peptide analogues for type 2 diabetes mellitus: systematic review and meta-analysis. *BMC Endocr Disord* 2010; 10: 20. Available at: http://www.biomedcentral.com/1472-6823/10/20 (accessed 27/09/11)
3. Ratner R, *et al.* Cardiovascular safety of exenatide BID: an integrated analysis from controlled clinical trials in participants with type 2 diabetes. *Cardiovasc Diabetol* 2011; 10: 22. Available at: http://www.cardiab.com/content/10/1/22 (accessed 27/09/11)
4. Garber AJ. Long-acting glucagon-like peptide 1 receptor agonists: a review of their efficacy and tolerability. *Diabetes Care* 2011; 34 (suppl 2): S279–S284.
5. Esposito K, *et al.* GLP-1 receptor agonists and HBA1c target of < 7% in type 2 diabetes: meta-analysis of randomized controlled trials. *Curr Med Res Opin* 2011; 27: 1519–28.
6. Pinelli NR, Hurren KM. Efficacy and safety of long-acting glucagon-like peptide-1 receptor agonists compared with exenatide twice daily and sitagliptin in type 2 diabetes mellitus: a systematic review and meta-analysis. *Ann Pharmacother* 2011; 45: 850–60.
7. Best JH, *et al.* Risk of cardiovascular disease events in patients with type 2 diabetes prescribed the glucagon-like peptide 1 (GLP-1) receptor agonist exenatide twice daily or other glucose-lowering therapies: a retrospective analysis of the LifeLink database. *Diabetes Care* 2011; 34: 90–5.
8. Monami M, *et al.* Glucagon-like peptide-1 receptor agonists and cardiovascular events: a meta-analysis of randomized clinical trials. *Exp Diabetes Res* 2011; 2011: 215764.
9. Gallwitz B. Glucagon-like peptide-1 analogues for type 2 diabetes mellitus: current and emerging agents. *Drugs* 2011; 71: 1675–88.
10. Vilsbøll T, *et al.* Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. *BMJ* 2012; 344: d7771. Available at: http://www.bmj.com/content/344/bmj.d7771?view=long&pmid=22236411 (accessed 13/08/12)
11. Bertle H, *et al.* Glucagon-like peptide-1 receptor agonists as add-on therapy to basal insulin in patients with type 2 diabetes: a systematic review. *Diabetes Metab Syndr Obes* 2012; 5: 165–74.

Action. Orally ingested glucose triggers a much greater secretion of insulin from the pancreas than when given intravenously, a phenomenon known as the 'incretin effect'. Two peptide hormones associated with the incretin effect are glucose-dependent insulin releasing polypeptide (GIP; formerly called gastric inhibitory peptide) and glucagon-like peptide 1 (GLP-1), which are both secreted by gastrointestinal cells in response to food ingestion, and act at specific receptors expressed on pancreatic and other tissue cells. Both stimulate insulin secretion and promote beta cell proliferation; GLP-1 also inhibits glucagon secretion, stimulates the biosynthesis of insulin, slows gastrointestinal transit, decreases the secretion of digestive enzymes, and enhances satiety to reduce food intake. Both GIP and GLP-1 are rapidly degraded by the cell-surface enzyme dipeptidylpeptidase-4 (DPP-4), which is found throughout the body.

In patients with type 2 diabetes the circulating levels of GIP are normal or slightly increased; however, its insulinotropic actions are reduced. Levels of GLP-1 appear to be reduced but response to its action is maintained. Consequently, research has focused on GLP-1 and two groups of drugs have been developed for use in type 2 diabetics: GLP-1 analogues (incretin mimetics), such as exenatide, have a prolonged agonist effect at GLP-1 receptors, while DPP-4 inhibitors, such as sitagliptin (p. 502.1), prevent the degradation of endogenous incretins.

Reviews.
1. Gautier JF, *et al.* Biological actions of the incretins GIP and GLP-1 and therapeutic perspectives in patients with type 2 diabetes. *Diabetes Metab* 2005; 31: 233–42.
2. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet* 2006; 368: 1696–1705.
3. Nauck MA. Unraveling the science of incretin biology. *Am J Med* 2009; 122 (6 suppl): S3–S10.

Administration in renal impairment. Exenatide should not be used in patients with severe renal impairment (creatinine clearance less than 30 mL/min) or end-stage renal disease, in whom clearance is reduced and risk of adverse gastrointestinal effects increased; it should be used with caution in patients with a renal transplant. Immediate-release exenatide may be used with caution in patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min); data on the use of a long-acting formulation of exenatide in such patients are very limited. Patients with mild impairment (creatinine clearance 50 to 80 mL/min) may take the recommended doses of either formulation (see Uses and Administration, above).

Nausea and vomiting with transient hypovolaemia that is caused by exenatide may worsen renal function.

Adverse Effects and Precautions

Hypoglycaemia can occur in patients given exenatide, particularly when given with a sulfonylurea (see also Interactions, p. 473.3). Exenatide commonly causes mild to moderate nausea, which is dose-dependent and tends to decrease with continued therapy in most patients. Other adverse effects include vomiting, diarrhoea, nervousness, dizziness, headache, and dyspepsia. Less frequent reports include asthenia, decreased appetite, gastro-oesophageal reflux, abdominal distension or pain, and hyperhidrosis. Mild injection site reactions may be common. Rashes and hypersensitivity reactions have occurred, and alopecia has also been reported. Acute pancreatitis has been reported, and in such cases exenatide should be stopped permanently.

There have been rare reports of altered renal function in patients given exenatide, including increased serum-creatinine concentrations, renal impairment, worsened chronic renal failure, and acute renal failure (sometimes requiring haemodialysis). Some of these patients also had nausea, vomiting, and/or diarrhoea, which may have affected hydration status, or were taking drugs known to affect renal function or hydration status.

Patients may develop antibodies to exenatide, but this does not usually affect glycaemic control and the antibody titres diminish with time. A small proportion of patients may develop high titres of antibodies, which may impair the efficacy of exenatide.

Exenatide should not be used in type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Use is not recommended in patients with severe renal impairment (creatinine clearance less than 30 mL/min) or end-stage renal disease, in whom clearance is reduced and risk of adverse gastrointestinal effects increased. It should be used with caution in moderate renal impairment (creatinine clearance 30 to 50 mL/min) and in patients with a renal transplant. Although exenatide has not been studied in patients with severe gastrointestinal disease, such as gastroparesis, the drug should probably be avoided in such cases because of the gastrointestinal adverse effects commonly associated with its use.

Transient increases in blood-glucose concentrations, that generally improve within the first 2 weeks of treatment, may occur in patients switching from the standard to the once-weekly formulation of exenatide.

Driving. Diabetes mellitus, its complications, and the medications used to treat it, may affect a patient's ability to drive safely—see under Insulin (p. 487.2) for restrictions applied to diabetic patients in the UK.

Effects on the pancreas. A 69-year-old man developed pancreatitis within a few days of starting exenatide therapy. Serum-lipase concentrations returned to normal and abdominal pain resolved rapidly when exenatide was stopped.[1] The FDA has also reviewed 30 reports of acute pancreatitis in patients treated with exenatide.[2,3] In 27 cases there was at least one other risk factor for acute pancreatitis such as gallstones, severe hypertriglyceridaemia, and alcohol use. Improvement after stopping exenatide was confirmed in 22 reports, and in 3 cases of rechallenge there was a return of symptoms of acute pancreatitis. The FDA subsequently reported[4] in August 2008 that they had received reports of 6 cases of haemorrhagic or necrotising pancreatitis associated with exenatide; all patients required hospitalisation and 2 died. It was recommended that exenatide therapy should be stopped if signs or symptoms of pancreatitis develop and should not be restarted if pancreatitis is confirmed; other antidiabetic drugs should be considered for those with a history of pancreatitis. However, patients with type 2 diabetes may have a greater incidence of pancreatitis when compared with non-diabetic subjects,[5] and large cohort studies have not found a further increase in risk with exenatide itself.[6,7]

1. Denker PS, Dimarco PE. Exenatide (exendin-4)-induced pancreatitis: a case report. *Diabetes Care* 2006; 29: 471.
2. FDA. Information for healthcare professionals: exenatide (marketed as Byetta) (issued October 2007). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124712.htm (accessed 24/08/10)
3. Ahmad SR, Swann J. Exenatide and rare adverse events. *N Engl J Med* 2008; 358: 1970–1.
4. FDA. Information for healthcare professionals: exenatide (marketed as Byetta) (issued August 2008). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124713.htm (accessed 24/08/10)
5. Garg R, *et al.* Acute pancreatitis in type 2 diabetes treated with exenatide or sitagliptin: a retrospective observational pharmacy claims analysis. *Diabetes Care* 2010; 33: 2349–54.
6. Dore DD, *et al.* Use of a claims-based active drug safety surveillance system to assess the risk of acute pancreatitis with exenatide or sitagliptin compared to metformin or glyburide. *Curr Med Res Opin* 2009; 25: 1019–27.
7. Dore DD, *et al.* A cohort study of acute pancreatitis in relation to exenatide use. *Diabetes Obes Metab* 2011; 13: 559–66.

Interactions

A reduction in the sulfonylurea dose may be required when exenatide is added to therapy, because of an increased risk of hypoglycaemia with this combination. No increase in hypoglycaemia occurs when exenatide is used with metformin or a thiazolidinedione. The extent and rate of absorption of oral drugs may be reduced by exenatide. Where such an interaction would be undesirable, the oral medication should be given at least 1 hour before exenatide. If the oral medication must be taken with food, it should, where possible, be with a meal or snack when exenatide is not used. There may be an interaction between exenatide and warfarin (see Antidiabetics, under Interactions of Warfarin, p. 1531.3).

Pharmacokinetics

After subcutaneous injection, peak plasma concentrations of exenatide occur in about 2 hours. It is eliminated through the kidneys by glomerular filtration followed by proteolytic degradation, with a terminal half-life of about 2.4 hours. Clearance is reduced in patients receiving dialysis for end-stage renal disease.

References.
1. Kolterman OG, *et al.* Pharmacokinetics, pharmacodynamics, and safety of exenatide in patients with type 2 diabetes mellitus. *Am J Health-Syst Pharm* 2005; 62: 173–81.
2. Linnebjerg H, *et al.* Effect of renal impairment on the pharmacokinetics of exenatide. *Br J Clin Pharmacol* 2007; 64: 317–27.
3. Kothare PA, *et al.* Pharmacokinetics, pharmacodynamics, tolerability, and safety of exenatide in Japanese patients with type 2 diabetes mellitus. *J Clin Pharmacol* 2008; 48: 1389–99.
4. Iwamoto K, *et al.* Safety, tolerability, pharmacokinetics, and pharmacodynamics of exenatide once weekly in Japanese patients with type 2 diabetes. *Endocr J* 2009; 56: 951–62.
5. Fineman M, *et al.* Pharmacokinetics and pharmacodynamics of exenatide extended-release after single and multiple dosing. *Clin Pharmacokinet* 2011; 50: 65–74.
6. Linnebjerg H, *et al.* Exenatide—pharmacokinetics, pharmacodynamics, safety and tolerability in patients ≥ 75 years of age with type 2 diabetes. *Int J Clin Pharmacol Ther* 2011; 49: 99–108.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Byetta; *Austral.*: Byetta; *Austria*: Byetta; *Belg.*: Byetta; *Braz.*: Byetta; *Canad.*: Byetta; *Chile*: Byetta; *China*: Byetta (百泌达); *Cz.*: Byetta; *Denm.*: Bydureon; Byetta; *Fr.*: Byetta; *Ger.*: Bydureon; Byetta; *Gr.*: Byetta; *Hong Kong*: Byetta; *Hung.*: Byetta; *Irl.*: Bydureon; Byetta; *Israel*: Bydureon; Byetta; *Ital.*: Byetta; *Jpn*: Bydureon; Byetta; *Malaysia*: Byetta; *Mex.*: Baletta; *Neth.*: Bydureon; Byetta; *Norw.*: Bydureon; Byetta; *NZ*: Byetta; *Philipp.*: Byetta; *Pol.*: Byetta; *Port.*: Byetta; *Rus.*: Byetta (Баета); *Singapore*: Byetta; *Spain*: Byetta; *Swed.*: Bydureon; Byetta; *Switz.*: Bydureon; Byetta; *Thal.*: Byetta; *Turk.*: Byetta; *UK*: Bydureon; Byetta; *USA*: Bydureon; Byetta.

Glibenclamide *(BAN, rINN)*

Glibenclamid; Glibenclamida; Glibenclamidum; Glibenklamid; Glibenklamidas; Glibenklamidi; Glybenclamide; Glybenzcyclamide; Glyburide (USAN); HB-419; U-26452; Глибенкламид.

1-[4-[2-(5-Chloro-2-methoxybenzamido)ethyl]benzenesulphonyl]-3-cyclohexylurea.

$C_{23}H_{28}ClN_3O_5S$=494.0

CAS — 10238-21-8.

ATC — A10BB01.

ATC Vet — QA10BB01.

UNII — SX6K58TVWC.

NOTE. The name glibornuride has frequently but erroneously been applied to glibenclamide.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Glibenclamide). A white or almost white, crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in methyl alcohol; sparingly soluble in dichloromethane. It shows polymorphism.

USP 36: (Glyburide). Store in airtight containers.

Uses and Administration

Glibenclamide is a sulfonylurea antidiabetic (p. 502.3). It is given orally in the treatment of type 2 diabetes mellitus (p. 459.1) and has a duration of action of up to 24 hours.

The usual initial dose of conventional formulations in type 2 diabetes mellitus is 2.5 to 5 mg daily with breakfast, adjusted every 7 days in steps of 2.5 mg daily up to 15 mg daily. Although increasing the dose above 15 mg is unlikely to produce further benefit, doses of up to 20 mg daily have been given. Doses greater than 10 mg daily may be given in 2 divided doses. Because of the relatively long duration of action of glibenclamide, it is best avoided in the elderly. For doses used in adolescents, see p. 474.1.

In some countries micronised preparations of glibenclamide are available, in which the drug is formulated with a smaller particle size, and which have enhanced bioavailability. The usual initial dose of one such preparation (*Glynase PresTab; Pharmacia Upjohn, USA*) is 1.5 to 3 mg daily, adjusted every 7 days in steps of 1.5 mg, up to a usual maximum of 12 mg daily. Doses greater than 6 mg daily may be given in 2 divided doses.

Action. References.

1. Gavin JR, ed. Glyburide: new insights into its effects on the beta cell and beyond. *Am J Med* 1990; **89** (suppl 2A): 1–53S.
2. Luzi L, Pozza G. Glibenclamide: an old drug with a novel mechanism of action? *Acta Diabetol* 1997; **34**: 239–44.

Administration in children. There is limited experience with the use of sulfonylureas in children with type 2 diabetes mellitus, and the biguanide, metformin, is generally preferred. The *BNFC* suggests that oral treatment should only be started under specialist supervision, and that shorter-acting alternatives, such as tolbutamide, may be preferred to longer-acting sulfonylureas, such as glibenclamide, that have a greater risk of hypoglycaemia. Although not licensed for use in children in the UK, the *BNFC* suggests that glibenclamide may be given to adolescents, aged 12 to 18 years, in the management of type 2 diabetes mellitus and maturity-onset diabetes of the young. An initial oral dose of 2.5 mg daily, given with breakfast, may be adjusted according to response to a maximum of 15 mg daily.

For details of the use of glibenclamide in neonatal diabetes, see Diabetes Mellitus under Sulfonylureas, p. 503.1.

Adverse Effects, Treatment, and Precautions

As for sulfonylureas in general, p. 503.1, p. 504.1, and p. 504.2.

For a suggestion that the failure rate in type 2 diabetics treated with glibenclamide may be higher than that for those treated with chlorpropamide, see Diabetes Mellitus under Uses and Administration of Chlorpropamide, p. 470.1.

Hypoglycaemia. Severe hypoglycaemia may occur in any patient given any sulfonylurea (see p. 504.1); glibenclamide which has a relatively prolonged duration of action, may cause severe hypoglycaemia more often than shorter-acting sulfonylureas.

In a 1983 review[1] of 57 instances of hypoglycaemia associated with glibenclamide the median age of patients affected was 70 years; only one was less than 60 years old. Median daily dosage was 10 mg. Coma or disturbed consciousness was seen in 46 patients. Ten of these remained comatose despite alleviation of their hypoglycaemia and died up to 20 days after presentation. The authors noted that, including their series of 57 cases, there had been published reports on 101 cases of severe hypoglycaemia with glibenclamide, 14 with a fatal outcome.

There has been a report[2] of hypoglycaemic coma associated with the inhalation of glibenclamide by a worker at a pharmaceutical plant.

1. Asplund K, *et al.* Glibenclamide-associated hypoglycaemia: a report on 57 cases. *Diabetologia* 1983; **24**: 412–17.
2. Albert P, *et al.* Hypoglycaemia by inhalation. *Lancet* 1993; **342**: 47–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies glibenclamide as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Pregnancy. Sulfonylurea antidiabetics are generally avoided in the treatment of diabetes mellitus during pregnancy. However, glibenclamide may have a role in the management of gestational diabetes (see under Sulfonylureas, p. 504.3).

Interactions

As for sulfonylureas in general, p. 504.3.

Pharmacokinetics

Glibenclamide is readily absorbed from the gastrointestinal tract and peak plasma concentrations usually occur within 2 to 4 hours. It is extensively bound to plasma proteins. Absorption may be slower in hyperglycaemic patients and may differ according to the particle size of the preparation used. It is metabolised, almost completely, in the liver, the principal metabolite being only very weakly active. About 50% of a dose is excreted in the urine and 50% via the bile into the faeces.

References.

1. Coppack SW, *et al.* Pharmacokinetic and pharmacodynamic studies of glibenclamide in non-insulin dependent diabetes mellitus. *Br J Clin Pharmacol* 1990; **29**: 673–84.
2. Jaber LA, *et al.* The pharmacokinetics and pharmacodynamics of 12 weeks of glyburide therapy in obese diabetics. *Eur J Clin Pharmacol* 1993; **45**: 459–63.
3. Hoffman A, *et al.* The effect of hyperglycaemia on the absorption of glibenclamide in patients with non-insulin-dependent diabetes mellitus. *Eur J Clin Pharmacol* 1994; **47**: 53–5.
4. Rydberg T, *et al.* Concentration-effect relations of glibenclamide and its active metabolites in man: modelling of pharmacokinetics and pharmacodynamics. *Br J Clin Pharmacol* 1997; **43**: 373–81.
5. Jönsson A, *et al.* Pharmacokinetics of glibenclamide and its metabolites in diabetic patients with impaired renal function. *Eur J Clin Pharmacol* 1998; **53**: 429–35.
6. Zhou L, *et al.* Contributions of human cytochrome P450 enzymes to glyburide metabolism. *Biopharm Drug Dispos* 2010; **31**: 228–42.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Agobilina; Benclamid; Broi; Daonil; Diabe Pass; Diabemin; Dismiben; Euglucon; Gardoton; Glaturin; Glentor; Glibemida; Glidanil; Gliptid; Glitral; GON; Pira; Siruc; ***Austral.***: Daonil; Glimel; Semi-Daonil†; ***Austria***: Daonil; Euglucon†; Glucobene; Normoglucon; ***Belg.***: Bevoren†; Daonil; Euglucon; ***Braz.***: Aglucil†; Benclamin; Clamiben; Daonil; Diabenil†; Diabexil†; Euglucon†; Glibenclamon; Glibendiab; Glibexil; Glicamin; Glimil; Glionil; Lisaglucon; Nilclamida; ***Canad.***: DiaBeta; Euglucon; Gen-Glybe†; Med Glybe†; Mylan-Glybe; ***Chile***: Daonil; Euglusid†; Hipexal; Mezalit; ***China***: Pu Le Kang Ni (普乐康尼); ***Cz.***: Glucobene; Maninil; ***Denm.***: Daonil†; Hexaglucon; ***Fin.***: Euglamin; Euglucon†; Origlucon†; ***Fr.***: Daonil; Euglucan†; Hemi-Daonil; Miglucan†; ***Ger.***: Euglucon N; Glib-ratiopharm; Gliben†; Glibenbeta†; Glibendoc†; Glibenhexal†; Maninil; Semi-Euglucon N; ***Gr.***: Asugrin; Daonil; Derocryl; Diabefar; Euglykon; Ozepal; ***Hong Kong***: Clamide; CP-Gliben†; Daonil; Euglucon†; Gliben†; Gliboral; Glimel; Glitisol; Marglucon†; Semi-Euglucon†; Xeltic; ***Hung.***: Gilemal; Glucobene; ***India***: Afdiex; Aviglen; Betanase; C-Mide; Codica; D-Con; Daonil; Diabetnil; Diolin; Euglucon; G-Nil; GLCO; Glibet; Glinil; Gluconil; Glucosafe; Glutril; Glyboral; Glybovin; Semi-Daonil; Semi-Euglucon; ***Indon.***: Condiabet; Daonil; Glidanil; Glimel; Gluconic; Glulo; Glyamid†; Libronil†; Padonil; Prodiabet†; Prodiamel; Renabetic; Semi-Daonil; Tiabet†; Trodeb; ***Irl.***: Daonil; Semi-Daonil; ***Israel***: Glibetic; Gluben; ***Ital.***: Daonil; Euglucon; Gliben; Gliboral; ***Jpn***: Euglucon; ***Malaysia***: Daonil; Dibelet; Euglucon; Gliben; Glibesyn; Glimide; ***Mex.***: Abuglib†; Apogly; Biojara; Biostin; Daonil; Dibetid; Diglexol; Euglucon; Gadinor; Glemicid†; Glibenil; Glibenval; Glicavin; Glicoxem; Glifarcal; Glihexal; Glipar; Glucal; Glucoven; Insusym; Mibeclag; Norboral; Ocrix; Reglusan; ***NZ***: Daonil; Gliben†; ***Philipp.***: Amecladin; Bendix; Benglycon; Daonil; Diabitor; Euglodin; Euglotab; Euglucon; Eundin; Gluban; Glymod†; Insol†; Lodulce; Orabetic; Semi-Euglucon; Sentionyl; Sucron†; ***Pol.***: Euclamin†; ***Port.***: Daonil; Semi-Daonil; ***Rus.***: Betanase (Бетаназ)†; Glibamide (Глибамид); Glibex (Глибекс); Glidanil (Глидания); Glimidstada (Глимидстада); Maniglid (Маниглид); Maninil (Маниинл); ***S.Afr.***: Daonil; Diacare; Glycomin; ***Singapore***: Benil; Clamide; Daonil; Dibelet; Glibesyn†; Glimel; Glimide; SP-Diatab; TO Nil; ***Spain***: Daonil; Euglucon; Glucolon; Norglicem; ***Swed.***: Daonil; Euglucon†; ***Switz.***: Daonil; Euglucon†; Glibenorm; Glibesifar; Melix; Semi-Daonil; ***Thai.***: Benclamin; BNIL†; Daonil; Daono; Debtan; Diabenol; Dibelet†; Dibesin; Diclanil†; Euglucon†; Glamide; Glibetic; Glibic; Gliclamin; Glicon; Glimide; Gluconil; Gluzo; Locose; Manoglucon; Semi-Dibenol; Sugril; TO Nil; Unil†; Xeltic; ***Turk.***: Dianorm; Diyaben†; Gliben; ***UAE***: Glynase; Mini-Glynase; ***UK***: Daonil; ***Ukr.***: Maninil (Маниинл); ***USA***: DiaBeta; Glynase; Micronase†; ***Venez.***: Daonil; Euglucon; Glicliron.

Multi-ingredient Preparations. ***Arg.***: DBI Duo; Glucovance; Islaglib; Medobis G; Metformin Duo; Metglucon Duo; ***Austria***: Glucovance; ***Belg.***: Glucovance; ***Braz.***: Glucovance; ***Chile***: Bi-Euglucon M; Diabetyl-G†; Diaglitab Plus; Fintaxim G; Glicenex Duo; Glidanil-G; Glifortex-G; Glimet†; Glucovance; Glukat; Hipoglucin DA; ***China***: AnHe (安禾); Bai Kang (拜康); Gan Ke Fu (甘利可夫); Ge Shuang (格爽); Ge Wan Si (格万斯); Hao Luo Ping (惠络平); Jiang Xi (绛兮); Jin Ping Tang (金平唐); Jun Fu Le (君复乐); Ke Mai Ning (可麦宁); KeRuiTe (可瑞特); Jiang (立将); Li Li Le (利力乐); Li Li Nuo (利力诺); Li Sheng Yuan (立生源); Lian He Tang Ding (联合唐定); Lian Jiang (联将); Mei Jia Te (美佳特); Na Xun (拿迅); Qi Ting (齐亭); Rui Lian (瑞联); Shi Ke Yi (适可一); Shuang Ge Ning (双格宁); Shuang Li (双利); Shuang Ping Le (双平乐); Si Yi (思宜); Tai Bi (泰比); Tang Bei Kang (唐贝康); Tang Ke Jie (唐可捷); Tang He Ning (唐柯宁); Tang Li Ke (唐立克); Tang Ping (唐平); Tang Rui Ping (唐瑞平); Wan Su Qi (万苏琪); Wei Neng (威能); Wei Yi (维宜); Yi Fu Yun (一孚芸); Yi Ke Fu (乙可夫); Yi Sha Ning (伊沙宁); Zhao Wei (兆威); ***Cz.***: Formaglyben; Glibomet; Glucovance; ***Fr.***: Glucovance; ***Gr.***: Daopar; Normell; ***Hong Kong***: Glyconorm; Glucovance; Mydiatab; ***India***: Aviglen-Forte; Avigler-MF; Ben-Q-Met; Benclamet; Benformin; C-Mide Plus; Clamet; Combidos; Daocon-M; Daonil M; Diabetrol-3D; Diabetrol; Diforte; Diolin-M; Dior Plus; Duotrol; Eumet-D; G-Formin; Glibact-M; Glibomet; Glifil M; Glinil M; Glitrac-M; Glucomin-Plus; Gluconil-M; Glucored; Glucotrac Plus; Glutowin Forte; Glucurb; Iscept-P; Iscept; Melitus; Metclam; Metica-G; ***Indon.***: Glucovance; ***Ital.***: Bi-Euglucon M; Diaglimet; Dialinax; Gliben; Glibomet; Gliconorm; Glicorest; Glucomide; Suguan M; ***Malaysia***: Diamide; Glucovance; GlyMet; ***Mex.***: Apometglu; Bi-Dizlon†; Bi-Euglucon M; Bi-Pradia; Dibenmin; Dimefor-G; Duanglucid; Glinorboral; Glucotec; Glucovance; Glunovag; Gluxson; Imalet; Insusym-Forte; Kontroger; Maviglin; Metixor G; Midapharma; Mifelar-C; Nadib-M; Natisfar; Norfaben M; Sibet-C; Sil-Norboral; Wadil; ***Neth.***: Glucovance; ***Philipp.***: Euglo Plus; Glucovance; ***Pol.***: Glucovance; ***Port.***: Glucovance; ***Rus.***: Bagomet Plus (Багомет Плюс); Glibomet (Глибомет); Gluconorm (Глюконорм); Glucovance (Глюкован); ***S.Afr.***: Glucovance; ***Singapore***: Glucovance; ***Switz.***: Glucovance; ***Thai.***: Glucovance; ***Turk.***: Duplax; Glibomet; Glucovance; ***Ukr.***: Duotrol (Дуотрол); Glibofor (Глибофор); Glibomet (Глибомет); Glucovance (Глюкованс); ***USA***: Diofen; Glucovance; Glybofen; ***Venez.***: Bi-Euglucon; Diaformina Plus; Glucovance.

Pharmacopoeial Preparations

BP 2014: Glibenclamide Tablets;

USP 36: Glyburide and Metformin Hydrochloride Tablets; Glyburide Tablets.

Glibornuride *(BAN, USAN, rINN)*

Glibornurid; Glibornurida; Glibornuridi; Glibornuridum; Ro-6-4563; Глибornурид.

1-[(2*S*,3*R*)-2-Hydroxyborn-3-yl]-3-tosylurea; 1-[(2*S*,3*R*)-2-Hydroxyborn-3-yl]-3-*p*-tolylsulphonylurea.

$C_{18}H_{26}N_2O_4S$=366.5

CAS — 26944-48-9.

ATC — A10BB04.

ATC Vet — QA10BB04.

UNII — VP83E7434R.

NOTE. The name glibornuride has frequently but erroneously been applied to glibenclamide.

Profile

Glibornuride is a sulfonylurea antidiabetic (p. 502.3). It is given orally in the treatment of type 2 diabetes mellitus (p. 459.1) in doses of 12.5 to 75 mg daily. Daily doses of 50 mg or more are given in 2 divided doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Glutril†; ***Fr.***: Glutril; ***Switz.***: Glutril; ***Turk.***: Glutril.

Gliclazide *(BAN, rINN)*

Gliclazid; Gliclazida; Gliclazidum; Gliklatsidi; Gliklazid Gliklazidas; Gliklazyd; Glyclazide; SE-1702; Гликлазид.

1-(3-Azabicyclo[3.3.0]oct-3-yl)-3-tosylurea; 1-(3-Azabicyclo[3.3.0]oct-3-yl)-3-*p*-tolylsulphonylurea.

$C_{15}H_{21}N_3O_3S$=323.4

CAS — 21187-98-4.

ATC — A10BB09.

ATC Vet — QA10BB09.

UNII — G4PX8C4HKV.

NOTE. The names Crawnart, Diaglico, Glimiran, and Glutameal have been used as trade marks for gliclazide.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Ph. Eur. 8: (Gliclazide). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in acetone; freely soluble in dichloromethane.

Uses and Administration

Gliclazide is a sulfonylurea antidiabetic (p. 502.3). It is given orally in the treatment of type 2 diabetes mellitus (p. 459.1) and has a duration of action of 12 to 24 hours. Because its effects are less prolonged than those of chlorpropamide or glibenclamide it may be more suitable for elderly patients, who are prone to hypoglycaemia with longer-acting sulfonylureas. The usual initial dose is 40 to 80 mg daily with breakfast, gradually increased, if necessary, up to 320 mg daily. Doses of more than 160 mg daily are given in 2 divided doses. For doses used in adolescents, see p. 475.1. A modified-release tablet is also available: the usual initial dose is 30 mg once daily, increased if necessary in steps of 30 mg up to a maximum of 120 mg daily. The interval between dose increases of the modified-release preparation should be at least 1 month, but the dose may be increased after just 2 weeks in those patients who have not responded.

References.
1. Palmer KJ, Brogden RN. Gliclazide: an update of its pharmacological properties and therapeutic efficacy in non-insulin-dependent diabetes mellitus. *Drugs* 1993; 46: 92–125.
2. Mailhot J. Efficacy and safety of gliclazide in the treatment of non-insulin-dependent diabetes mellitus: a Canadian multicenter study. *Clin Ther* 1993; 15: 1060–8.
3. Ziegler O, Drouin P. Hemobiological properties of gliclazide. *J Diabetes Complications* 1994; 8: 235–9.
4. Jennings PE. Vascular benefits of gliclazide beyond glycemic control. *Metabolism* 2000; 49 (suppl 2): 17–20.
5. Crepaldi G, Fioretto P. Gliclazide modified release: its place in the therapeutic armamentarium. *Metabolism* 2000; 49 (suppl 2): 21–5.
6. McGavin JK, *et al.* Gliclazide modified release. *Drugs* 2002; 62: 1357–64.
7. Drouin P, Standl E. Diamicron MR Study Group. Gliclazide modified release: results of a 2-year study in patients with type 2 diabetes. *Diabetes Obes Metab* 2004; 6: 414–21.
8. Ceriello A. Effects of gliclazide beyond metabolic control. *Metabolism* 2006; 55 (suppl 1): S10–S15.
9. Brown N. Is it time to re-assess the role of gliclazide? Targeting insulin resistance in type 2 diabetes patients suboptimally controlled with insulin. *Postgrad Med J* 2006; 82: 471–5.
10. Zoungas S, *et al.* The efficacy of lowering glycated haemoglobin with a gliclazide modified release-based intensive glucose lowering regimen in the ADVANCE trial. *Diabetes Res Clin Pract* 2010; 89: 126–33.

Administration in children. There is limited experience with the use of sulfonylureas in children with type 2 diabetes mellitus, and the biguanide, metformin, is generally preferred. The *BNFC* suggests that oral treatment should only be started under specialist supervision and that shorter-acting alternatives may be preferred to longer-acting sulfonylureas that have a greater risk of hypoglycaemia. Although not licensed for use in children in the UK, the *BNFC* suggests that gliclazide may be given to adolescents, aged 12 to 18 years, in the management of type 2 diabetes mellitus and maturity-onset diabetes of the young. An initial oral dose of 20 mg once daily, given with breakfast, may be adjusted according to response to a maximum of 320 mg daily. Doses of more than 160 mg daily are given in 2 divided doses.

Adverse Effects, Treatment, and Precautions

As for sulfonylureas in general, p. 503.1, p. 504.1, and p. 504.2.

The *BNF* suggests that gliclazide may be suitable for use in patients with renal impairment, but that careful monitoring of blood-glucose concentration is essential and that the smallest possible dose for adequate control should be used. UK licensed product information recommends that it should not be used in patients with severe renal impairment.

Interactions

As for sulfonylureas in general, p. 504.3.

Pharmacokinetics

Gliclazide is readily absorbed from the gastrointestinal tract. It is extensively bound to plasma proteins. The half-life is about 10 to 12 hours. Gliclazide is extensively metabolised in the liver to metabolites that have no significant hypoglycaemic activity. Metabolites and a small amount of unchanged drug are excreted in the urine.

References.
1. Kobayashi K, *et al.* Pharmacokinetics of gliclazide in healthy and diabetic subjects. *J Pharm Sci* 1984; 73: 1684–7.
2. Davis TME, *et al.* Pharmacokinetics and pharmacodynamics of gliclazide in Caucasians and Australian Aborigines with type 2 diabetes. *Br J Clin Pharmacol* 2000; 49: 223–30.
3. Elliot DJ, *et al.* Identification of the human cytochromes P450 catalysing the rate-limiting pathways of gliclazide elimination. *Br J Clin Pharmacol* 2007; 64: 450–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Aglucide; Diamicron; Unava; *Austral.*: Diamicron; Glyade; Mellihexal; Nidem; Oziclide; *Austria*: Diabreziде; Diamicron; Gliclada; *Belg.*: Diamicron; Uni Diamicron; *Braz.*: Azukon; Diamicron; Erowgliz; Glicaron; *Canad.*: Diamicron: *Chile*: Dianormax; *China*: Da Er De (达尔得); Diamicron (达美康); Hong Xu Yang (弘旭阳); Li Ning Ge (利宁格); Ruimai (瑞迈); *Cz.*: Diadeon; Diaprel; Glyclada; Normodiab; Zeglydia; *Denm.*: Altermicron†; Diamicron; Gliclinoz†; Glizamed; Glucostabil; Glydium; Normodiab; Uni Diamicron; Zeglidia; *Fr.*: Diamicron; Glydium; *Ger.*: Diamicron; *Gr.*: Diabezid; Diamicron; *Hong Kong*: CP-Gliz; Diamicron; Diamitex†; Dianorm†; Efton†; Gliclada; Glimicron; Gluconox†; Glucozide; Glupozide†; Glyade†; Glyzyl; Licla; Marclazide†; Melicron†; Nidem; Pharlinde†; Qualizide; Suclear; Sun-Glizide; Vickamicron†; *Hung.*: Diaprel; Gliclada; Gluctam; Normadiab; Zeglidia; *India*: Alglid; Aviglic; Azukon; CGCron; Claz; Comzid; D-Clic; Debgone; Diabend; Diabic; Diagli; Diamicron; Dianorm; Diaob; Diatrol; Diazide; Dizide; Euclide; Fordib; Glatix; Glic; Glican; Glicla; Gliclafin; Gliclan; Gliclatan; Gliclaz; Glicron; Gliden; Glidiet; Glisafe; Glital; Glityx; Glix; Gliza; Glizid; Glucoact; Glucofit; Glucozid; Glurib; Glutide; Glyca; Glychek; Glycigon; Glycinorm; Glycor; Glycozide; Glygard; Glyloc; Glyneed; Glyred; Glysiss; Glyzee; GLZ; Intragly; Jozide; Kampex; Liz; Lo-G; Lycazid; Meglyde; Novozid; Nuzide; Semi-Glycigon; *Indon.*: Diamicron; Fredam; Glicab; Glidabet; Glikamel; Glucodex; Glucored; Glukolos; Glycafor†; Linodiab†; Meltika; Nufamicron; Pedab; Tiaglib†; Xepabet; Zumadiac; *Irl.*: Diabrezide; Diaclide; Diaglyc; Diamicron; Glydium; Myglyc; Vitile; *Ital.*: Diabrezide; Diamicron; Dramion; Galtes; Glucobloc; *Malaysia*: Diamicron; Diamitex; Dianid; Glimicron; Glucozide; Glyade; Medoclazide; Opglucon; Reclide; Remicron; Sun-Glizide; *Mex.*: Diamicron; *Neth.*: Diamicron; Glicacon; Glidabore; Gliclalane; Gliclareze; Gliclatab; Glydium; *NZ*: Diamicron; Glizon; *Philipp.*: Clibite; Clizid; Diaclid; Diamicron; Dianorm; Glubitor; Gluconil; Glucoprime†; Succedin; Zebet; *Pol.*: Diabezidum†; Diabrezide; Diagen; Diaprel; Diazidan; Glazide; Gliclada; Glinormax†; Glisan; Gluctam; Glydium; Normodiab; Norsulin†; *Port.*: Diadeon; Diamicron; *Rus.*: Diabefarm (Диабефарм); Diabest (Диабест)†; Diabeton (Диабетон); Diabinax (Диабинакс); Diabrezide (Диабрезид); Diatica (Диатика); Gliclada (Гликлада); Glucostabil (Глюкостабил); Glydiab (Глидиаб); Reclide (Реклид)†; *S.Afr.*: Adco-Glucomed; Diaglucide; Diamicron; Diaran; Glycron; Glygard; Ziclin†; *Singapore*: Diamicron; Dianorm; Diapro; Glimicron; Glizide; Glucozide; Glyade; Medoclazide; Melicron; Mexan; Nidem; SP-Glimed; Sun-Glizide; *Spain*: Diamicron; Uni Diamicron†; *Switz.*: Diamicron; *Thai.*: Beclazide; Cadicon; Clazide; Diabeside; Diabetab; Diacose; Diamexon; Diamicron; Dianid; Diatica; Dicaron; Dicron; Diglucron; Dimetus; Gliclabit; Glicron†; Glucid; Glucocron; Gluconox; Glucozide†; Glycinorm; Glycon; Medoclazide; Ranclazide; Serviclazide†; *Turk.*: Betanorm; Diamicron; Efikas; Glazid†; Glikron; Glumikron; Hipoglis; Oramikron; *UAE*: Glyzide; *UK*: Diaglyk; Diamicron; Laaglyda; Vitile; Zicron; *Ukr.*: Diabeton (Диабетон); Diaglizide (Диаглизид); Glioral (Глиорал)†; Oziklid (Озиклид); *Venez.*: Diamicron; Glidan.

Multi-ingredient Preparations. *China*: Du He (度和); He Wei Yi (合维伊); Qi Zhi Ping (齐致平); *India*: Alglid-M; Alnamet-G; Aviglic-MF; Azukon M; Best-M; Bigan-GC; Claformin; Claz-M; Comzid-M; Dabby; Debgone-M; Diabend-M; Diabic-M; Dianorm-M; Dianosis-MF; Diaob-M; Diatrol-M; Dizide-M; Elmet-G; Euclide-M; Evermet-G; Exermet Gz; Fordib MF; Gefor; Glatix-M; Glicamet; Glican-M; Glicas-M; Glicina-GM; Gliclafin-M; Gliclan M; Gliclastar M; Glidaz-M; Glicmet; Glideu-MF; Glidiet-M; Glikare-M; Glim-C; Glim; Glisafe M; Glital-M; Glityx-M; Glitz-MF; Glix-M; Gliza-MF; Glizid-M; Glormin; Glucoact-M; Glucofit-M; Glucozid-M; Glurib-M; Glycard-M; Glycasia-MF; Glychek-M; Glydcon Mod; Glycigon-M; Glycinorm M; Glyclamin; Glycor-C; Glygard M; Glyhil; Glykind-M; Glyloc-M; Glymin; Glyneed-M; Glyni-M; Glyori; Glyred-M; Glyroz; Glysiss-M; Glyvik-M; Glyzee-M; GLZ Plus; Intragly-M; Jozide-M; K-Gem; Liz-M; Lodia; Lycazid-M; Melfor-G; Metfor-G; Mildim; Mintide Plus; Mintide; Nuzide-M; Obax; *Rus.*: Glimekomb (Глимекомб); *Thai.*: Glizid-M; *Ukr.*: Dianorm-M (Діанорм-М).

Pharmacopoeial Preparations
BP 2014: Gliclazide Tablets.

Glimepiride *(BAN, USAN, rINN)*

Glimepirid; Glimepirida; Glimépiride; Glimepiridi; Glimepiridum; Glimepiryd; Hoe-490; Глимепирид.

1-[*p*-[2-(3-Ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl]sulfonyl)-3-(*trans*-4-methylcyclohexyl)urea.

$C_{24}H_{34}N_4O_5S$=490.6

CAS — 93479-97-1.

ATC — A10BB12.

ATC Vet — QA10BB12.

UNII — 6KY687524K.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Glimepiride). A white to almost white powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in dichloromethane; soluble in dimethylformamide; very slightly soluble in methyl alcohol.

USP 36: (Glimepiride). A white to almost white powder. Practically insoluble in water; sparingly soluble in dichloromethane; soluble in dimethylformamide; slightly soluble in methyl alcohol. It dissolves in dilute alkali hydroxides and in dilute acids. Store at a temperature not exceeding 25 degrees.

Uses and Administration

Glimepiride is a sulfonylurea antidiabetic (p. 502.3). It is given orally for the treatment of type 2 diabetes mellitus (p. 459.1) and has a duration of action of up to 24 hours. Initial doses of 1 to 2 mg daily may be increased if necessary, in steps of 1 to 2 mg at intervals of 1 to 2 weeks, to 4 mg daily for maintenance. The maximum recommended dose is 6 mg in the UK and 8 mg in the USA. Glimepiride is generally taken as a single dose with breakfast or the first main meal of the day. For the use of glimepiride in children, see p. 475.3.

References.
1. Massi-Benedetti M. Glimepiride in type 2 diabetes mellitus: a review of the worldwide therapeutic experience. *Clin Ther* 2003; 25: 799–816.
2. Weitgasser R, *et al.* Effects of glimepiride on HbA(1c) and body weight in type 2 diabetes: results of a 1.5-year follow-up study. *Diabetes Res Clin Pract* 2003; 61: 13–19.
3. Feinbock C, *et al.* Prospective multicentre trial comparing the efficacy of, and compliance with, glimepiride or acarbose treatment in patients with type 2 diabetes not controlled with diet alone. *Diabetes Nutr Metab* 2003; 16: 214–21.
4. Briscoe VJ, *et al.* The role of glimepiride in the treatment of type 2 diabetes mellitus. *Expert Opin Drug Metab Toxicol* 2010; 6: 225–35.

Administration in children. There is limited experience with the use of sulfonylureas in children, and the biguanide, metformin, is generally preferred. For further details on sulfonylurea use in children, see p. 502.3. Glimepiride was found to be safe and effective in children with type 2 diabetes (mean age 13.8 years), but associated with more weight gain than metformin.[1]

1. Gottschalk M, *et al.* Glimepiride versus metformin as monotherapy in pediatric patients with type 2 diabetes: a randomized, single-blind comparative study. *Diabetes Care* 2007; 30: 790–4.

Adverse Effects, Treatment, and Precautions

As for sulfonylureas in general, p. 503.1, p. 504.1, and p. 504.2. In some countries hepatic and haematological monitoring is recommended in patients receiving glimepiride; in the UK the *BNF* considers there is limited evidence of the clinical value of such monitoring.

Fasting. Glimepiride, given in unchanged doses but with the time of the single daily dose switched from morning to just before breaking fast after sunset, was used in Muslim patients during Ramadan without causing an increased incidence of hypoglycaemic episodes.[1]

For further advice on the management of diabetes mellitus in fasting Muslim patients during Ramadan see under Precautions of Insulin, p. 487.3.

1. The Glimepiride in Ramadan (GLIRA) Study Group. The efficacy and safety of glimepiride in the management of type 2 diabetes in Muslim patients during Ramadan. *Diabetes Care* 2005; 28: 421–2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies glimepiride as possibly porphyrinogenic: it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Interactions

As for sulfonylureas in general, p. 504.3.

Pharmacokinetics

Glimepiride is completely absorbed from the gastrointestinal tract. Peak plasma concentrations occur in 2 to 3 hours, and it is highly protein bound. The drug is extensively metabolised in the liver to two main metabolites. The cytochrome P450 isoenzyme CYP2C9 is involved in the formation of a hydroxy derivative, which is further metabolised to a carboxy derivative by cytosolic enzymes. The half-life after multiple doses is about 9 hours. About 60% of a dose is eliminated in the urine and 40% in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Adiuvan; Amaryl; Diabutil; Endial; Glemaz; Glimeplic; Gluceride; Glucopirida; Gretilab†; Hipoglut; Islopir; Lomet; Next Step; *Austral.*: Amaryl; Aylide; Diapride; Dimirel; *Austria*: Amaryl; Glimestad; *Belg.*: Amarylle; *Braz.*: Amapirida; Amaryl; Azulix; Bioglic; Diabemed; Diamellitis; Gliansor; Glimepibal; Glimepil; Glimeran; Glycopirida; Hipomeril; *Canad.*: Amaryl; *Chile*: Amaryl; Glemaz; Glix; Glucomet; Taboss; *China*: Amaryl (亚莫利); Amoli (阿莱立); An Duo Mei (安多美); An Ni Ping (安尼平); Di Bei (迪北); Jia He Luo (佳和洛); Ke De Ping (科德平); Li Yi Ping (力勤平); Pu Ren Ping (普仁平); Rui Ping (瑞平); Sheng Ping (圣平); Tang Fu (唐弗); Wan Su Ping (万苏平); Yi Rui (伊瑞); You Su (佑苏); *Cz.*: Amarwin†; Amaryl; Amyx; Apo-Glimep†; Eglymad; Glemid; Glimegamma; GlimTek†; Glymexan; Medopirid; Melyd; Metist†; Oltar; *Denm.*: Amaryl; Dibiglim; Glimeprisan; Glivasol; Limepisil†; Limezapine; Stapiride; Tineril; *Fin.*: Amaryl; Dialosa; Gli-

mendin†; Glimespes; Oltar; Pirtad†; Priglide; *Fr.*: Amarel; *Ger.*: Amaryl†; Glimegamma; Magna†; *Gr.*: Adinsulin-S; Anovis; Dia-Ban; Dialosa; Glidil; Glimepiron; Glimerid; Glimespes; Glimexin; Glimosa; Glincil; Gliperin; Glirid; Idesal; Mepirid; Nicordilen†; Penoza; Pharlecon; Raltone; Saccharofar; Solosa; Sucryl; Tetig; Tipo II; Toremol; Zutra; *Hong Kong*: Amaryl; Diapride; Glimaryl; Glimeryl; *Hung.*: Amagen; Amaryl; Dialosa; Diamitus; Glempid; Glibezid; Glimegamma; GlimeWin†; Glindia; Gliprex; Limeral; Melyd; Sintecal; *India*: Adride; Amaryl; Asoride; Azulix; Bepride; Betaglim; Blisto; Capril; CGRyl; Chempride; Conpride; Daoride; Daoryl; Diaglim; Diapride; Diaset; Diaswich; Diazero; Dibiglim; Dipride; Elim; Emperide; Euglim; Euroglip; Flexiglim; Gadz; Gepride; Gimip; Gitae; Givov; Glador; Glamor; Gleam; Gli; Glimcare; Glimchek; Glimcip; Glimcom; Glimecure; Glimer; Glimestar; Glimetop; Glimfit; Glimid; Glimidot; Glimifix; Glimikare; Glimiprex; Glimiriv; Glimisave; Glimitab; Glimitan; Glimkap; Glimpax; Glimpid; Glimpil; Glimser; Glimsite; Glimtide; Glimulin; Glimy; Glimz; Glinidd; Glinorm; Glista-OD; Glisu; GLP; Glucoryl; Glucut; Glycirid; Glyfix; Glypride; Glyree M; Glyree; GMR; GP; Gride; Idapride; Ilet; Isryl; K-Glim; Karmelitus; Leride; Mepusulin; Mypride; Nabal; Novaride; Odiglim; *Indon.*: Amadiab; Amaryl; Anpiride; Diaglime; Friladar; Glamarol; Glimexal; Gliperid; Glucoryl; Gluvas; Mapryl; Mepirilid; Metrix; Norizec; Paride; Relide; Simryl; *Irl.*: Amaryl; *Israel*: Amaryl; *Ital.*: Amaryl; Diamel; Solosa; *Malaysia*: Amaryl; Ameride; Diapride; Glenix; Glimaryl; Glimin; Glimpid; Glimulin; Miaryl; *Mex.*: Amaryl; Diaglim; Diapride; Glimal; Glipiran†; Glupropan; Mepiritev; Redu-ST; Zukedib; *Neth.*: Amaryl; Fertin; *Norw.*: Amaryl; *NZ*: Amaryl†; *Philipp.*: Acotril; Aforglim; Arya; Azulix; Climeril; Diaberid; Diaglim; Diameride; Diamex; Diapride; Euglim; Geopride; Getryl; Glimarex; Glimaryl; Glimauno; Glimec; Glimed; Glimesyn; Gliperide; Glipiren; Glycobate; Glyper; Imerid; Mira; Neoglim; Norizec; Solodiab; Solosa; Sulfast; Syngly; *Pol.*: Amaryl; Amyx; Apo-Glim; Avaron; Betaglid†; Diaril; Glemid†; Glibetic; Glibezid†; Glidiamid; Glimehexal; Glimesan†; GlimTeva†; Glindia†; Glipid; Limeral; Melyd; Oltar†; Pemidal; Symglic; *Port.*: Amaryl; Andissa; Diapiride; Glimial; Gludon; Zopide; *Rus.*: Amaryl (Амарил); Glemaz (Глемаз); Gliamal (Глиамал); Glumedex (Глюмедекс); Meglimid (Меглимид); *S.Afr.*: Amaryl; Diaglim; Euglim; Glamaryl; Sulphonur; *Singapore*: Amaryl; Dialosa; Diapride; *Spain*: Amaryl; Roname; *Swed.*: Amaryl; *Switz.*: Amaryl; Glimerax†; Glimeryle; *Thai.*: Amaryl; Diaglip; Dibiglim; *Turk.*: Amaryl; Diaglin; Diameprid; Glimax; Glirid; Mepiriks; Sanprid; Tideca; *UAE*: Glypride; *UK*: Amaryl; Niddaryl; *Ukr.*: Amapirid (Амапирид); Amaryl (Амарил); Diameprid (Диамеприд)†; Diapirid (Диапирид); Glianov (Глианов); Glibetic (Глибетик)†; Glipomar (Глипомар)†; Glirid (Глирид); Oltar (Олтар); *USA*: Amaryl; *Venez.*: Amaryl; Dimavyl; Glimerid.

Multi-ingredient Preparations. *Arg.*: Amaryl M; Avandaryl; Endial Met; Hipoglut Met; *Austria*: Avaglim†; Tandemact; *Braz.*: Amaryl Flex; Meritor; *Canad.*: Avandaryl†; *Chile*: Amaryl M; Avandaryl; *Cz.*: Avaglim†; Tandemact; *Denm.*: Avaglim†; *Fr.*: Tandemact†; *Ger.*: Avaglim†; Tandemact; *Gr.*: Avaglim†; *Hung.*: Avaglim†; *India*: Adride-M; Adride-P; Alnamet-GSR; Amaryl-M; Aroglim-M2; Azulix MF; Bepride-MF; Bepride-SF; Betaglim M; Betagrim-M; Bigan-GM; Bigonyl; Blisto-MF; Conpride M; Daoride-M; Daoride-PM; Daoryl-M; Deralin-M; Diakit-3; Diakit-4; Dianosis-P3; Diapex-M; Diaprid-M; Diapride Forte; Diapride Plus; Diaset-M; Diaswich M; Diazero-M; Diazero-PM; Dibiglim-P; Dipride-M; Euglim-M; Euglim-MP; Euglim-P; Euroglip Forte; Euroglip-M2; Evermet-GSR; Exermet GM; Forme; G-Tase G; Gemer P; Gemer; Gepride-M; Gimip-M; Gimip-PM; Gitae-M; Gitar; Glamor-M; Glamor-P; Glamor-PM; Glicon-M; Glicosi-M; Glimaday; Glimcare Forte; Glimcare Plus; Glimchek M; Glimestar PM; Glimestar-M; Glimi DM; Glimid-M; Glimidot-M; Glimifix-M; Glimikare-MSR; Gliminprex MF; Glimisave-M; Glimizide-M; Glimizide-PG; Glimkap M2; Glimpax-M; Glimpil-MP; Glimsite-M; Glimsite-MP; Glimtide Forte; Glimtide Plus; Glimulin-MF; Glimy-M; Glimy-MP; Glimy-P; Glinidd-M; Glinorm-M; Glip-MF; Glista; GLM; GLP-M; GLP-PM; Gluconorm-G; Glucut-GMP; Glucut-MT; Gluformin G; Glyciphage PG; Glyciphage-G; Glycomet-GP; GM; GMR-M; GMT; GPM; Gride-M; Idapride-M; Idapride-PM; Ilet-B; Ioglime; Isryl-M; K-Glim M; K-Pio-G; Matce-G; Matce-PG; Mepride-M; Metanorm G; Metapride; Metgli; Metride Plus; Metride; Minsugar-G; Obimet-GX; Odiglim-M; One Dia; *Indon.*: Amaryl M; Avandaryl; *Irl.*: Avaglim†; Tandemact; *Ital.*: Avaglim†; Tandemact; *Jpn*: Sonias; *Malaysia*: Amaryl M; *Mex.*: Amaryl M; Glimetal; Pime; Rangimet G; *Neth.*: Avaglim†; Tandemact; *Norw.*: Avaglim†; *Philipp.*: Asenza Plus; Avandaryl†; Solosamet; *Pol.*: Tandemact; *Port.*: Avaglim†; Tandemact; *Rus.*: Avandaglim (Авандаглим); *Spain*: Avaglim†; Tandemact; *Swed.*: Avaglim†; *Thai.*: Amaryl M; Avandaryl†; *Ukr.*: Amaryl M (Амарил М); Tripride (Трипрайд); *USA*: Avandaryl; Duetact.

Pharmacopoeial Preparations
BP 2014: Glimepiride Tablets;
USP 36: Glimepiride Tablets; Pioglitazone and Glimepiride Tablets.

Glipizide *(BAN, USAN, pINN)*

CP-28720; Glipitsidi; Glipizid; Glipizida; Glipizidas; Glipizidum; Glipizyd; Glydiazinamide; K-4024; Глипизид.
1-Cyclohexyl-3-[4-[2-(5-methylpyrazine-2-carboxamido)ethyl]benzenesulphonyl]urea.
$C_{21}H_{27}N_5O_4S$=445.5
CAS — 29094-61-9.
ATC — A10BB07.
ATC Vet — QA10BB07.
UNII — X7WDT95N5C.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Glipizide). A white or almost white crystalline powder. Practically insoluble in water and in alcohol; very slightly soluble in acetone and in dichloromethane. It dissolves in dilute solutions of alkali hydroxides.

USP 36: (Glipizide). Store in airtight containers. Protect from light.

Uses and Administration

Glipizide is a sulfonylurea antidiabetic (p. 502.3). It is given orally in the treatment of type 2 diabetes mellitus (p. 459.1) and has a duration of action of up to 24 hours. The usual initial dose is 2.5 to 5 mg daily given as a single dose about 30 minutes before breakfast. Dosage may be adjusted at intervals of several days by amounts of 2.5 to 5 mg daily, to a maximum of 20 mg daily. Doses up to 40 mg daily have been used, but see p. 476.2. Doses larger than 15 mg daily are given in two divided doses before meals. Modified-release formulations of glipizide are available in some countries; one such preparation (*Glucotrol XL; Pfizer, USA*) is given in usual doses of 5 to 10 mg daily as a single dose with breakfast.

Administration. Although glipizide may be given in doses up to a maximum of 40 mg daily, evidence for the benefits of high doses is scanty. A small study in patients with type 2 diabetes mellitus found that not only did increases in glipizide doses to more than 10 mg daily produce little or no benefit, but that the higher doses were associated with reduced rises in plasma-insulin concentrations and a lesser reduction in plasma-glucose concentrations.[1] There is, however, some evidence that glycaemic control and insulin sensitivity can be improved by the use of a modified-release rather than a conventional formulation of glipizide.[2,3]

1. Stenman S, *et al.* What is the benefit of increasing the sulfonylurea dose? *Ann Intern Med* 1993; 118: 169–72.
2. Berelowitz M, *et al.* Comparative efficacy of once-daily controlled-release formulation of glipizide and immediate-release glipizide in patients with NIDDM. *Diabetes Care* 1994; 17: 1460–4.
3. Leaf E, King JO. Patient outcomes after formulary conversion from immediate-release to extended-release glipizide tablets. *Am J Health-Syst Pharm* 1999; 56: 454–6.

Adverse Effects, Treatment, and Precautions

As for sulfonylureas in general, p. 503.1, p. 504.1, and p. 504.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies glipizide as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Interactions

As for sulfonylureas in general, p. 504.3.

Pharmacokinetics

Glipizide is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur 1 to 3 hours after a single dose. It is extensively bound to plasma proteins and has a half-life of about 2 to 4 hours. It is metabolised mainly in the liver and excreted chiefly in the urine, largely as inactive metabolites.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Minodiab; *Austral.*: Melizide; Minidiab; *Austria*: Glibenese; Minidiab; *Belg.*: Glibenese; Minidiab; *Braz.*: Minidiab; *Chile*: Minidiab; Xiprine; *China*: Ge Di (格迪); Glucotrol (瑞易宁); Glutrol (安吉); Jie Bei (捷贝); Li Da Mei (力达美); Meibida (美呲达); Mieteni (灭特尼); Minidiab (垦迪宝); Qin Su (秦苏); Si Le Ke (思乐克); Tonbac (唐贝克); Xiboge (西博格); Yi Ping (怡平); Yibida (依必达); Youdaling (优哒灵); Yuan Tan (元坦); Yuelai (悦来); *Cz.*: Minidiab; *Denm.*: Glibenese†; Mindiab; Minodiab; *Fin.*: Mindiab; *Fr.*: Glibenese; Minidiab; Ozidia; *Gr.*: Glibenese; Minodiab; *Hong Kong*: Diaset; Glucotrol; Melizide†; Minidiab; Sunglucon; *Hung.*: Minidiab; *India*: Bimode-M; Bimode; D-Glip; Diacon; Diaglip; Dibizide; G-Trol; Glez; Glibetic; Glide; Glip; Glipiriv; Glipy; Glucolip; Glucotrol; Glylin; Glynase; Glytop; Glyzip; Godde; Lipi; *Indon.*: Aldiab†; Glucotrol; Glyzid†; *Irl.*: Glibenese; *Israel*: Gluco-Rite; *Ital.*: Minidiab; *Malaysia*: Dipazide†; Glix; Melizide†; Minidiab; *Mex.*: Luditec†; Minodiab; Pigloss; Prugal; Singloben; *Norw.*: Mindiab; *NZ*: Minidiab; *Philipp.*: Brilizid; Glimax; Glix; Minidiab; *Pol.*: Antidiab†; Glibenese; *Port.*: Minidiab; *Rus.*: Glibenese (Глибенез); Glynase (Глинез); *S.Afr.*: Minidiab; *Singapore*: Beapizide; Diaset; Dibizide; Glucotrol; Glynase; Melizide; Minidiab; Sunglucon; *Spain*: Minodiab; *Swed.*: Mindiab *Switz.*: Glibenese†; *Thai.*: Depizide; Diabemin†; Diaset; Dipazide; Gipzide; Glibenil; Glimax†; Glipimed; Glipizon; Glizide Glucodiab; Glucotrol; Glycediab; Glygen; GP-Zide; Manpizide Melizide†; Minibit; Minidiab; Namedia; Neodiab†; Pezide; Pharmdiab; Topizide; Tozide; *Turk.*: Glucotrol; Minidiab; *UK* Glibenese†; Minodiab; *Ukr.*: Glynase (Глинез); *USA*: Glucotrol *Venez.*: Minidiab.

Multi-ingredient Preparations. *India*: Actizide-M; Bigan-GP; Diacon M; Diaglip M; Dibimet Plus; Dibizide-M; Glibetic-MF; Glicept; Gliformin; Glimet; Glipimet; Glipmet; Glucotrol MF; Glynase MF; Godde-M; Grip-M; Lipi-M; Metaglez; Metglib; *Mex.* Metdual; *Philipp.*: Norsulin; *Ukr.*: Dibizide-M (Дибизид-М) *USA*: Metaglip†.

Pharmacopoeial Preparations
BP 2014: Glipizide Tablets;
USP 36: Glipizide and Metformin Hydrochloride Tablets Glipizide Tablets.

Gliquidone *(BAN, rINN)*

ARDF-26; Glikidon; Glikidoni; Gliquidona; Gliquidonum; Гликвидон.
1-Cyclohexyl-3-(4-[2-(3,4-dihydro-7-methoxy-4,4-dimethyl-1,3-dioxo-2(1*H*)-isoquinolyl)ethyl]benzenesulphonyl)urea.
$C_{27}H_{33}N_3O_6S$=527.6
CAS — 33342-05-1.
ATC — A10BB08.
ATC Vet — QA10BB08.
UNII — C7C2QDD75P.

Pharmacopoeias. In *Br.* and *Chin.*

BP 2014: (Gliquidone). A white or almost white powder Practically insoluble in water; slightly soluble in alcohol and in methyl alcohol; soluble in acetone; freely soluble in dimethylformamide.

Profile

Gliquidone is a sulfonylurea antidiabetic (p. 502.3). It is given orally in the treatment of type 2 diabetes mellitus (p. 459.1) in a usual initial dosage of 15 mg daily given as a single dose up to 30 minutes before breakfast. Dosage may be adjusted by increments of 15 mg to a usual dose of 45 to 60 mg daily in 2 or 3 unequally divided doses, the largest dose being taken in the morning with breakfast. Single doses above 60 mg and daily doses above 120 mg are not recommended.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Glurenorm; *Belg.*: Glurenorm; *China*: Jie Shi (捷适); Ka Rui Lin (卡瑞林); Pu Yi (普怡); Tangshiping (糖适平); *Cz.*: Glurenorm; *Ger.*: Glurenorm; *Gr.*: Devotan; *Hung.*: Glurenorm; *Indon.*: Fordiab; Glidiab; Glurenorm; Lodem; *Ital.*: Glurenor; *Pol.*: Glurenorm; *Rus.*: Glurenorm (Глюренорм); *Spain*: Glurenor; *Thai.*: Glurenor; *Turk.*: Glurenorm; *Ukr.*: Glurenorm (Глюренорм).

Pharmacopoeial Preparations
BP 2014: Gliquidone Tablets.

Glisentide *(rINN)*

Glipentide; Glisentida; Glisentidum; Глизентид.
1-Cyclopentyl-3-[*p*-(2-*o*-anisamidoethyl)benzenesulphonyl]urea.
$C_{22}H_{27}N_3O_5S$=445.5
CAS — 32797-92-5.
UNII — 392TQL1E2Z.

Profile

Glisentide is a sulfonylurea antidiabetic (p. 502.3). It is given orally in the treatment of type 2 diabetes mellitus (p. 459.1) in doses of 2.5 to 20 mg daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Spain*: Staticum.

Glybuzole *(rINN)*

AN-1324; Désaglybuzole; Glibuzol; Glybuzolum; RP-7891; Глибузол.
N-(5-*tert*-Butyl-1,3,4-thiadiazol-2-yl)benzenesulphonamide.
$C_{12}H_{15}N_3O_2S_2$=297.4
CAS — 1492-02-0.
UNII — 1DJ2B68M2C.

Profile

Glybuzole is an oral antidiabetic with a structure distinct from that of the sulfonylureas, biguanides, or sulfonamidopyrimidines.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Gludiase†.

Glyclopyramide *(rINN)*

Glidiopiramida; Glyclopyramidum; Гликлопирамид.
1-(4-Chlorobenzenesulphonyl)-3-(pyrrolidin-1-yl)urea.
$C_{13}H_{14}ClN_3O_3S$=303.8
CAS — 631-27-6.
UNII — KE474IKG1W.

Profile

Glyclopyramide is a sulfonylurea antidiabetic (p. 502.3). It is given orally in the treatment of type 2 diabetes mellitus (p. 459.1) in doses of between 125 to 500 mg daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Deamelin.

Glycyclamide *(rINN)*

Gliciclamida; Gliciclamide; Glycyclamidum; K-38; K-386; Tolcyclamide; Глициламид.
1-Cyclohexyl-3-tosylurea; 1-Cyclohexyl-3-*p*-tolylsulphonylurea.
$C_{14}H_{20}N_2O_3S$=296.4
CAS — 664-95-9.
UNII — C40N4EJY68.

Profile

Glycyclamide is a sulfonylurea antidiabetic (p. 502.3). It has been given orally in the treatment of type 2 diabetes mellitus.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Diaborale.

Guar Gum

Cyamopsidis seminis pulvis; E412; Goma guar; Gomma di guar; Gomme de guar; Guar; Guar Flour; Guar Galactomannan; Guar, galactomannane du; Guar Galactomannanum; Guar galaktomanan; Guar galaktomannan; Guaran; Guaras; Guárbab galaktomannán; Guárbabmag-por; Guarbloem; Guargalactomannan; Guargalaktomannaani; Guargalaktomannan; Guargom; Gúargúmmí; Guarkämmjöl; Guarkernmehl; Guarkumi; Guarmehl; Guarmjöl; Guaro galaktomananas; Guarpitmeel; Guma guar; Jaguar Gum; Гуаровая Смола; Гуаровая Камедь; Гуарова Гума.
CAS — 9000-30-0.
ATC — A10BX01.
ATC Vet — QA10BX01.
ATC Herb — HA10BX5001 (Cyamopsis tetragonoloba: *gum*); *HC10AW5005* (Cyamopsis tetragonoloba: *gum*); *HA06AC5003* (Cyamopsis tetragonoloba: *gum*).
UNII — E89I1637KE.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Guar). Guar is obtained by grinding the endosperms of the seeds of *Cyamopsis tetragonolobus*. It consists mainly of guar galactomannan. Guar is a white or almost white powder, yielding a mucilage of variable viscosity when dissolved in water. Practically insoluble in alcohol.

Ph. Eur. 8: (Guar Galactomannan). A yellowish-white powder. It is soluble in cold and hot water; practically insoluble in organic solvents. Its main components are polysaccharides composed of D-galactose and D-mannose at molar ratios of 1:1.4 to 1:2. The molecules consist of a linear main chain of β-(1→4)-glycosidically linked mannopyranoses and single α-(1→6)-glycosidically linked galactopyranoses.

USNF 31: (Guar Gum). A gum obtained from the ground endosperms of *Cyamopsis tetragonolobus* (Leguminosae). It consists chiefly of a high-molecular-weight hydrocolloidal polysaccharide, a galactomannan, composed of galactan and mannan units combined through glycosidic linkages. It is a white to yellowish-white, practically odourless, powder. Dispersible in hot or cold water forming a colloidal solution.

Uses and Administration

Guar gum is used in diabetes mellitus (see p. 479.2) as an adjunct to treatment with diet, insulin, or oral antidiabetics since it results in some reduction in both postprandial and fasting blood-glucose concentrations. It is given with or immediately before meals in doses of 5 g usually 3 times daily. Adverse gastrointestinal effects may be reduced by using a lower initial dose of 5 g once daily before breakfast for 1 week, then increasing to 5 g twice daily, then 3 times daily, as required. Each dose of guar gum granules should be taken stirred in about 200 mL of a cold drink.

Guar gum is also used as an adjunct in the treatment of hyperlipidaemias (see p. 479.2). It may be used to slow gastric emptying in some patients with the dumping syndrome (p. 1809.2).

Guar gum is used as a thickening and suspending agent, and as a tablet binder and disintegrant. It has been incorporated into processed foods.

Guar gum is an example of a soluble fibre.[1] On contact with water it forms a highly viscous gel, the viscosity of which varies with such factors as its plant source or the form in which it is given.[2]

Fibres such as guar gum reduce postprandial and fasting blood-glucose concentrations as well as plasma-insulin concentrations in healthy subjects and diabetic patients.[1,3,4] Such reductions in blood-glucose concentrations and in glycated haemoglobin have been found in both type 1 and type 2 **diabetes mellitus** (p. 459.1), but they have generally been small.[3] Possible mechanisms for these effects of guar gum include a delay in gastric emptying,[1,3-5] decreased small-bowel motility,[1,4] decreased glucose absorption resulting from increased viscosity of the contents of the gastrointestinal tract,[1,3] or inhibition of gastrointestinal hormones.[3]

Guar gum also lowers serum total cholesterol and low-density-lipoprotein (LDL) cholesterol concentrations; high-density-lipoprotein (HDL) cholesterol and triglyceride concentrations appear to be unaffected.[4] The most likely mechanism is binding of bile acids, reducing their enterohepatic circulation in a similar way to bile-acid sequestrants.[3,4] It might also interfere with absorption of dietary cholesterol.[4,6] When used alone in patients with **hypercholesterolaemia** guar gum has generally produced a modest reduction in plasma-cholesterol and LDL-cholesterol concentrations although some studies have been unable to find an effect. A few studies have suggested that the cholesterol-lowering effect is attenuated after 8 to 12 weeks of treatment but a long-term study saw a 17% decrease in total serum cholesterol that was maintained for 24 months.[7] Some studies have shown further reductions in cholesterol and LDL-cholesterol concentrations on addition of guar gum to therapy with other lipid regulating drugs.[4] The usual treatment of hyperlipidaemias is discussed on p. 1248.1.

There have been suggestions that guar gum reduces appetite by promoting a feeling of fullness, but a meta-analysis has indicated that it is not effective for reducing body-weight.[8] Products containing guar gum have, however, been promoted as **slimming aids**. Their use cannot be advocated because of the risk of tablets swelling before reaching the stomach and causing oesophageal obstruction.

1. Hockaday TDR. Fibre in the management of diabetes 1: natural fibre useful as part of total dietary prescription. *BMJ* 1990; 300: 1334–6.
2. Ellis PR. *et al.* Guar gum: the importance of reporting data on its physicochemical properties. *Diabet Med* 1986; 3: 490–1.
3. Anonymous. Guar gum: of help to diabetics? *Drug Ther Bull* 1987; 25: 65–7.
4. Todd PA. *et al.* Guar gum: a review of its pharmacological properties, and use as a dietary adjunct in hypercholesterolaemia. *Drugs* 1990; 39: 917–28.
5. Tattersall R, Mansell P. Fibre in the management of diabetes 2: benefits of fibre itself are uncertain. *BMJ* 1990; 300: 1336–7.
6. Rideout TC. *et al.* Guar gum and similar soluble fibers in the regulation of cholesterol metabolism: current understandings and future research priorities. *Vasc Health Risk Manag* 2008; 4: 1023–33.
7. Salenius J-P. *et al.* Long term effects of guar gum on lipid metabolism after carotid endarterectomy. *BMJ* 1995; 310: 95–6.
8. Pittler MH, Ernst E. Guar gum for body weight reduction: meta-analysis of randomized trials. *Am J Med* 2001; 110: 724–30.

Adverse Effects and Precautions

Guar gum can cause gastrointestinal disturbance with flatulence, diarrhoea, or nausea, particularly at the start of treatment.

Because guar gum swells on contact with liquid it should always be washed down carefully with water and should not be taken immediately before going to bed. It should not be used in patients with dysphagia, oesophageal disease, or intestinal obstruction.

Interactions

Guar gum may retard the absorption of other drugs; where this is likely to pose a problem the other drug should be taken at least an hour before guar gum.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Chile*: Benefibra; *Cz.*: Benefibra; *Fin.*: Guarem; *Ger.*: Figur-Verlan; Guar Verlan; Urgo Hydrogel; *India*: Nosulin; *Ital.*: Benefibra; Novafibra†; *NZ*: Guarcol; *Spain*: Fibraguar; *Switz.*: Leiguar; Vitaguarin; *UK*: Resource OptiFibre; *Ukr.*: Guarem (Гуарем).

Multi-ingredient Preparations. *Arg.*: Desgras Complex; Desgras; Green Diet; *Fr.*: Cyamox; Cyamox; Moxydar; Mucipulgite†; Mulkine†; Seroxydar†; *Hung.*: Lipolest; *India*: Fibrotin; *Ital.*: Cruscasohn; Fibrovit; Resource Gellificata†; *Singapore*: Bios Life; Chitosano; *Switz.*: Mucipulgite†.

Insulin ⊗

B28-Asp-Insulin (insulin aspart); HMR-1964 (insulin glulisine); Hoe-71GT (insulin glargine); Hoe-901 (insulin glargine); INA-X14 (insulin aspart); Insiln; Insulien; Insulilin; Insulilini; Insülin; Insúlin; Insulinã; Insulin X14 (insulin aspart); Insulina; Insulinas; Insuline; Insulinin; Insulinum; Insulins; Inzulin; Inzulín; NN-304 (insulin detemir); NN-1250 (insulin degludec); Инсулин.
CAS — 9004-10-8 (insulin, neutral insulin); 11070-73-8 (bovine insulin); 12584-58-6 (porcine insulin); 11061-68-0 (human insulin); 8063-29-4 (biphasic insulin); 9004-21-1 (globin zinc insulin); 68859-20-1 (insulin argine); 8049-62-5 (insulin zinc suspension); 53027-39-7 (isophane insulin); 9004-17-5 (protamine zinc insulin); 9004-12-0 (dalanated insulin); 51798-72-2 (bovine insulin defalan); 11091-62-6 (porcine insulin defalan); 116094-23-6 (insulin aspart); 844439-96-9 (insulin degludec); 169148-63-4 (insulin detemir); 160337-95-1 (insulin glargine); 207748-29-6 (insulin glulisine); 133107-64-9 (insulin lispro); 1200440-65-8 (insulin peglispro); 874442-57-6 (insulin tregopil).
ATC — A10AB01 (human); A10AB02 (beef); A10AB03 (pork); A10AB04 (lispro); A10AB05 (aspart); A10AB06 (glulisine); A10AC01 (human); A10AC02 (beef); A10AC03 (pork); A10AC04 (lispro); A10AE01 (human); A10AE02 (beef); A10AE03 (pork); A10AE04 (glargine); A10AE05 (detemir).
ATC Vet — QA10AB01 (human); QA10AB02 (beef); QA10AB03 (pork); QA10AB04 (lispro); QA10AB05 (aspart); QA10AB06 (glulisine); QA10AC01 (human); QA10AC02 (beef); QA10AC03 (pork); QA10AC04 (lispro); QA10AD01 (human); QA10AD02 (beef); QA10AD03 (pork); QA10AD04 (lispro); QA10AD05 (aspart); QA10AE01 (human); QA10AE02 (beef); QA10AE03 (pork); QA10AE04 (glargine); QA10AE05 (detemir); QA10AF01 (human).
UNII — D933668QVX (aspart); 576O9IZ534 (beef); 54Q18076QB (degludec); 4FT78T86XV (detemir); 2ZM8CX04RZ (glargine); 7XIY785AZD (glulisine); 1Y17CTI5SR (human); GFX7QIS1I (lispro); AVT68QJB39 (pork).

Pharmacopoeias. Most pharmacopoeias have monographs for insulin and a variety of insulin preparations.

Ph. Eur. 8: (Insulin, Bovine). The natural antidiabetic principle obtained from beef pancreas and purified. A white or almost white powder. Practically insoluble in water and in dehydrated alcohol. It dissolves in dilute mineral acids and, with decomposition, in dilute solutions of alkali hydroxides. Store in airtight containers. Protect from light. It should be stored at -20 degrees until released by the manufacturer. When thawed, insulin may be stored at 2 degrees to 8 degrees and used for manufacturing purposes within a short period of time. To avoid absorption of humidity from the air during weighing, the insulin must be at room temperature.

Ph. Eur. 8: (Insulin, Porcine). The natural antidiabetic principle obtained from pork pancreas and purified. A white or almost white powder. Practically insoluble in water and in dehydrated alcohol. It dissolves in dilute mineral acids and, with decomposition, in dilute solutions of alkali hydroxides. Store in airtight containers. Protect from light. It should be stored at -20 degrees until released by the manufacturer. When thawed, insulin may be stored at 2 degrees to 8 degrees and used for manufacturing purposes within a short period of time. To avoid absorption of humidity from the air during weighing, the insulin must be at room temperature.

Ph. Eur. 8: (Insulin, Human). A protein having the structure of the antidiabetic hormone produced by the human pancreas. It is produced either by enzymatic modification and suitable purification of insulin obtained from the pancreas of the pig or by a method based on recombinant DNA (rDNA) technology. A white or almost white powder. Practically insoluble in water and in alcohol. It dissolves in dilute mineral acids and, with decomposition,

in dilute solutions of alkali hydroxides. Store in airtight containers. Protect from light. It should be stored at or below -18 degrees or below until released by the manufacturer. When thawed, insulin is stored at 2 degrees to 8 degrees and used for manufacturing preparations within a short period of time. To avoid absorption of humidity from the air during weighing, the insulin must be at room temperature.

Ph. Eur. 8: (Insulin Aspart; Insulinum Aspartum). It is a 2-chain peptide containing 51 amino acids. The A-chain is composed of 21 amino acids and the B-chain is composed of 30 amino acids. It is identical in primary structure to human insulin, except that it has aspartic acid instead of proline at position 28 of the B-chain. As in human insulin, insulin aspart contains 2 interchain disulfide bonds and 1 intrachain disulfide bond. It is produced by a method based on recombinant DNA (rDNA) technology. A white or almost white powder. Practically insoluble in aqueous solutions with a pH around 5.1. In aqueous solutions below pH 3.5 or above pH 6.5, the solubility is greater than or equal to 25 mg/mL. Store in airtight containers. Protect from light. It should be stored at or below -18 degrees until released by the manufacturer. When thawed, insulin aspart may be stored at 2 degrees to 8 degrees and used for manufacturing purposes within a short period of time. To avoid absorption of humidity from the air during weighing, insulin aspart must be at room temperature before opening the container.

Ph. Eur. 8: (Insulin Glargine; Insulinum Glarginum). It is a 2-chain peptide containing 53 amino acids. The A-chain is composed of 21 amino acids and the B-chain is composed of 32 amino acids. It is identical in primary structure to human insulin, only differing in amino acid sequence at position 21 in the A-chain and at the C-terminal end of the B-chain where it contains 2 additional amino acids. Human insulin is Asn(A21), whereas insulin glargine is Gly(A21), Arg(B31), Arg(B32). As in human insulin, insulin glargine contains 2 interchain disulfide bonds and 1 intrachain disulfide bond. It is produced by a method based on recombinant DNA (rDNA) technology. A white or almost white, hygroscopic powder. Practically insoluble in water and in anhydrous alcohol; soluble in dilute mineral acids. Store in airtight containers at a temperature of -20 degrees, excursions permitted between -15 degrees and -25 degrees. Protect from light.

Ph. Eur. 8: (Insulin Lispro; Insulinum Lisprum). It is a 2-chain peptide containing 51 amino acids. The A-chain is composed of 21 amino acids and the B-chain is composed of 30 amino acids. It is identical in primary structure to human insulin, only differing in amino acid sequence at positions 28 and 29 of the B-chain. Human insulin is Pro(B28), Lys (B29), whereas insulin lispro is Lys(B28), Pro(B29). As in human insulin, insulin lispro contains 2 interchain disulfide bonds and 1 intrachain disulfide bond. It is produced by a method based on recombinant DNA (rDNA) technology. A white or almost white powder. Practically insoluble in water and in alcohol. It dissolves in dilute mineral acids and with decomposition in dilute solutions of alkali hydroxides. Store in airtight containers. Protect from light. It should be stored at or below -18 degrees. When thawed, insulin lispro is used for manufacturing purposes within a short period of time. To avoid absorption of humidity from the air during weighing, insulin aspart must be at room temperature before opening the container.

USP 36: (Insulin). A protein that affects the metabolism of glucose obtained from the pancreas of healthy bovine or porcine animals, or both, used for food by humans. White or practically white crystals. Soluble in solutions of dilute acids and alkalis. Store in airtight containers. Protect from light. It should be stored at -10 degrees to -25 degrees.

USP 36: (Insulin Human). A protein corresponding to the active principle elaborated in the human pancreas that affects the metabolism of carbohydrate (particularly glucose), fat, and protein. It is derived by enzymatic modification of insulin from pork pancreas in order to change its amino acid sequence appropriately, or produced by microbial synthesis via a recombinant DNA process. Store in airtight containers. Protect from light. It should be stored at -10 degrees to -25 degrees.

USP 36: (Insulin Lispro). Insulin Lispro is identical in structure to Insulin Human, except that it has lysine and proline at positions 28 and 29, respectively, of chain B, whereas this sequence is reversed in Insulin Human. It is produced by microbial synthesis via a recombinant DNA process. White or practically white crystals. Soluble in solutions of dilute acids and alkalis. Store in airtight containers. Protect from light. It should be stored at -10 degrees to -25 degrees.

Definitions and Terminology

Insulin is a hormone produced by the beta cells of the islets of Langerhans of the pancreas and consists of 2 chains of amino acids, the A and B chains, connected by 2 disulfide bridges. Insulin produced by different species conforms to the same basic structure but has different sequences of amino acids in the chains. **Porcine insulin** ($C_{256}H_{381}N_{65}O_{76}S_6$ = 5777.6) differs from **human insulin** ($C_{257}H_{383}N_{65}O_{77}S_6$ = 5807.6) in only one amino acid in the B chain, whereas **bovine insulin** ($C_{254}H_{377}N_{65}O_{75}S_6$ = 5733.6) differs from human insulin not only in this same amino acid in the B chain but also in 2 amino acids in the A chain.

The precursor of insulin in the pancreas is proinsulin which is a single polypeptide chain incorporating both the A and B chains of insulin connected by a peptide termed the C-peptide (or connecting-peptide). Although the insulins of various species may be similar in composition the proinsulins are not, in that the sequence and number of amino acids in the C-peptide may vary considerably.

Early commercial insulins were obtained by extraction from bovine or porcine or mixed bovine and porcine pancreases and were purified by recrystallisation only. Insulins obtained by such methods were often termed **'conventional insulins'** to distinguish them from insulins which have undergone further purification processes. An extract which has been recrystallised only once can be separated into 3 components or fractions termed the 'a', 'b', and 'c' components. The 'a' component consists of high molecular weight substances and is only usually found in very impure preparations since repeated recrystallisation will remove most of it. The 'b' component consists largely of proinsulin and insulin dimers, and the 'c' component consists of insulin, insulin esters, arginine insulin, and desamidoinsulin. Other pancreatic peptides such as glucagon, pancreatic polypeptide, somatostatin, and vasoactive intestinal peptide are also usually found in products which have not undergone further purification. Gel filtration will substantially reduce the content of proinsulin but will not significantly reduce the content of insulin derivatives or pancreatic peptides; products purified by gel filtration are often termed **'single-peak insulins'**. Addition of ion-exchange chromatography to the purification methods will further reduce the proinsulin content and also reduce the contamination by insulin derivatives and pancreatic peptides. In the UK **'highly purified insulins'** and **'monocomponent insulins'** are terms sometimes applied to insulins that have undergone both gel filtration and ion-exchange chromatography. In the USA the FDA has designated the term **'purified insulins'** for preparations similarly prepared and containing less than 10 ppm of proinsulin.

Much of the insulin now produced has an amino-acid sequence identical to that of human insulin. **Human insulin (emp)** is produced by the enzymatic modification of insulin obtained from the porcine pancreas; it is also sometimes called **semisynthetic human insulin.** The term **human insulin (crb)** is used for insulin produced by the chemical combination of A and B chains which have been obtained from bacteria genetically modified by recombinant DNA technology. **Human insulin (prb)** is produced from proinsulin obtained from bacteria genetically modified by recombinant DNA technology. **Human insulin (pyr)** is insulin produced from a precursor obtained from a yeast genetically modified by recombinant DNA technology. Human insulin obtained by recombinant DNA technology is sometimes termed **biosynthetic human insulin.**

Insulin or human insulin is supplied in a variety of forms in solution or suspension for injection (see Table 1, p. 477). Crystalline insulin may be prepared for therapeutic use merely by making a solution, either of acidic or neutral pH. **Soluble insulin** or **'neutral insulin'** is a short-acting preparation that can be given intravenously if necessary to cover emergencies. Soluble formulations are sometimes referred to as **'regular insulin'** or **'unmodified insulin'**; these names reflect the fact that the preparation has not been formulated to prolong its duration of action.

In order to prolong the duration of action of insulin, preparations may be formulated as suspensions in 2 general ways. The first involves complexing insulin with a protein from which it is slowly released; examples are **protamine zinc insulin**, which contains an excess of protamine, and **isophane insulin** (NPH insulin), which contains equimolecular amounts of insulin and protamine. The second method of prolonging the action of insulin is to modify the particle size and the various **insulin zinc suspensions** are in this category.

Biphasic insulins are mixtures providing for both immediate and prolonged action.

Chemical modification of the insulin molecule has resulted in insulins such as **dalanated insulin** (prepared by the removal of the C-terminal alanine from the B chain of insulin), **insulin defalan** (prepared by the removal of the terminal phenylalanine), and **sulfated insulin**, but these insulins have not been widely used.

More recently, recombinant DNA technology has enabled production of *insulin analogues* with altered pharmacokinetic profiles. **Insulin lispro** and **insulin aspart** are available as rapidly acting alternatives to soluble insulin and as intermediate-acting complexes with protamine. **Insulin glulisine** is another rapidly acting analogue. **Insulin glargine** is a long-acting form for once-daily use, and **insulin detemir** is used once or twice daily. **Insulin degludec** is described as an ultra-long acting analogue, which is used once daily. Further information on these can be found under the heading Insulin Analogues, in Uses, p. 482.1.

Stability and Storage

Both the Ph. Eur. 8 and the USP 36 recommend that insulin preparations be stored in a refrigerator at 2 degrees to 8 degrees and not be allowed to freeze. The Ph. Eur. 8 directs that insulin preparations should be protected from light, and the USP 36 that they should be protected from sunlight. It is recognised that patients may not follow such stringent storage guidelines and most manufacturers of commercial insulin preparations consider that storage by the patient at a temperature of up to 25 degrees would be acceptable for up to one month (individual product information should be consulted). Patients should still be advised not to expose their vials or cartridges to excessive heat or sunlight.

It is advisable to shake suspensions gently before a dose is withdrawn.

Insulin in powder form should be stored in airtight containers and protected from light. Storage at a low temperature is also recommended. The Ph. Eur. 8 advises storage at a temperature of -20 degrees for bovine and porcine insulin and Insulin Glargine and at -18 degrees or below for Human Insulin, and for Insulin Aspart and Insulin Lispro; the USP 36 requires storage at -10 degrees to -25 degrees for all types of insulin. It is stressed that this temperature is for the powder and not for the preparations; preparations should not be subjected to storage conditions that lead to freezing.

Adsorption. Insulin can be adsorbed onto glass and plastics used in giving sets, reducing the amount of insulin delivered by infusion before binding sites are saturated.[1,2] The tubing of giving sets are often primed using, for example, 50 mL of infusion containing insulin 1 unit/mL, but a smaller volume of 20 mL may be adequate.[1] In the past, albumin or polygeline were added to insulin solutions but this practice is no longer recommended.[3,4]

Variations in insulin dose delivery may be particularly problematic with the relatively dilute solutions and low flow rates used in neonatal hyperglycaemia.[5] Various methods have been investigated and found to reduce the amount of insulin lost by adsorption to the giving set, including flushing[6] or priming[7] the system with the insulin infusion, or using a concentrated insulin solution to prime the tubing.[5] A study[8] that compared different methods found wide variation in insulin delivery depending on solution concentration, flow rate, addition of albumin, catheter type, and priming or flushing of the system.

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Aggregation. For discussion of the problems of insulin aggregation, see Intensive Administration Regimens under Uses, p. 482.3.

Compatibility. The compatibility of insulin combinations is discussed in Mixing of Insulins under Uses, p. 483.1.

Units

One unit of *bovine insulin* is contained in 0.03891 mg of the first International Standard (1986). One unit of *porcine insulin* is contained in 0.03846 mg of the first International Standard (1986). One unit of *human insulin* is contained in 0.03846 mg of the first International Standard (1986).

Uses and Administration

Insulin is a hormone that plays a key role in regulating carbohydrate, protein, and fat metabolism. The main stimulus for its secretion is glucose, although many other factors including amino acids, catecholamines, glucagon, and somatostatin, are involved in its regulation. The secretion of insulin is not constant and peaks occur in response to the intake of food.

Table 1. Ph. Eur., BP, and USP insulin preparations.

Type	Ph. Eur./BP/USP Title	Synonyms	Description	pH	Common classification	Approximate action profile after subcutaneous administration		
						Onset	Time to peak	Duration
Soluble insulins (also known as regular or unmodified insulin)	Soluble Insulin Injection (Ph. Eur. 8)	Neutral Insulin Neutral Insulin Injection Soluble Insulin Insulin Injection	Solution of bovine, porcine, or human insulin	6.9 to 7.8				
	Insulin Injection (USP 36)		Solution of bovine or porcine, or a mixture of bovine and porcine, insulin	7.0 to 7.8	Short-acting	30 minutes to 1 hour	2 to 5 hours	6 to 8 hours
	Insulin Human Injection (USP 36)		Solution of human insulin	7.0 to 7.8				
Insulin analogues, rapid	Insulin Aspart Injection (BP 2014)		Solution of insulin aspart	6.9 to 7.8				
	Insulin Lispro Injection (BP 2014)		Solution of insulin lispro	6.9 to 7.8	Short-acting	5 to 20 minutes	1 to 3 hours	2 to 5 hours
	Insulin Lispro Injection (USP 36)		Solution of insulin lispro	7.0 to 7.8				
Biphasic insulins	Biphasic Insulin Injection (Ph. Eur. 8)	Biphasic Insulin	Suspension of crystals containing bovine insulin in a solution of porcine insulin	6.6 to 7.2				
	Biphasic Isophane Insulin Injection (Ph. Eur. 8)	Biphasic Isophane Insulin	Buffered suspension of porcine insulin or human insulin complexed with protamine sulfate or other suitable protamine, in a solution of porcine insulin or human insulin respectively.	6.9 to 7.8				
	Human Insulin Isophane Suspension and Human Insulin Injection (USP 36)		Buffered suspension of human insulin complexed with protamine sulfate, in a solution of human insulin	7.0 to 7.8				
Insulin suspensions	Isophane Insulin Injection (Ph. Eur. 8)	Isophane Insulin Isophane Insulin (NPH) Isophane Protamine Insulin Injection	Suspension of bovine, porcine, or human insulin complexed with protamine sulfate or another suitable protamine. Contains 300 to 600 micrograms of protamine sulfate per 100 units of insulin	6.9 to 7.8				
	Isophane Insulin Suspension (USP 36)		Buffered aqueous suspension of zinc-insulin (bovine or porcine) crystals and protamine sulfate, combined in a manner such that the solid phase of the suspension consists of crystals composed of insulin, protamine, and zinc	7.0 to 7.8	Intermediate-acting	Within 2 hours	4 to 12 hours	Up to 24 hours
	Isophane Insulin Human Suspension (USP 36)		Buffered aqueous suspension of zinc-insulin human crystals and protamine sulfate, combined in such a manner that the solid phase of the suspension consists of crystals composed of insulin human, protamine, and zinc	7.0 to 7.5				
	Insulin Zinc Injectable Suspension (Amorphous) (Ph. Eur. 8)	Amorph. I.Z.S. Insulin Semilente Insulin Zinc Suspension (Amorphous)	Suspension of bovine, porcine, or human insulin complexed with a suitable zinc salt; the insulin is in a form practically insoluble in water	6.9 to 7.8				

Table 1. Ph. Eur., BP, and USP insulin preparations.

Type	Ph. Eur./BP/USP Title	Synonyms	Description	pH	Common classification	Approximate action profile after subcutaneous administration		
						Onset	Time to peak	Duration
Insulin suspensions *cont*	Prompt Insulin Zinc Suspension (USP 36)		Buffered aqueous suspension of bovine or porcine, or a mixture of bovine and porcine, insulin modified by the addition of a suitable zinc salt in a manner such that the solid phase is amorphous	7.0 to 7.8				
	Insulin Zinc Injectable Suspension (Ph. Eur. 8)	Insulin Lente I.Z.S. I.Z.S. (Mixed) Insulin Zinc Suspension (Mixed) Insulin Zinc Suspension	Suspension of bovine or porcine, or a mixture of bovine and porcine, or human insulin with a suitable zinc salt; the insulin is in a form practically insoluble in water. It may be produced by mixing Insulin Zinc Injectable Suspension (Amorphous) (Ph. Eur. 8) and Insulin Zinc Injectable Suspension (Crystalline) (Ph. Eur. 8) in a ratio of 3 to 7	6.9 to 7.8				
	Insulin Zinc Suspension (USP 36)	Insulin Zinc	Buffered aqueous suspension of bovine or porcine, or a mixture of bovine and porcine, insulin modified by the addition of a suitable zinc salt in a manner such that the solid phase of the suspension consists of a mixture of approximately 3 parts of amorphous insulin to 7 parts of crystalline insulin	7.0 to 7.8	Intermediate or long-acting	2 to 3 hours	6 to 15 hours	Up to 30 hours
	Insulin Human Zinc Suspension (USP 36)		Buffered aqueous suspension of human insulin modified by the addition of a suitable zinc salt in a manner such that the solid phase of the suspension consists of a mixture of approximately 3 parts of amorphous insulin to 7 parts of crystalline insulin	7.0 to 7.8				
	Insulin Zinc Injectable Suspension (Crystalline) (Ph. Eur. 8)	Cryst. I.Z.S. Insulin Ultralente Insulin Zinc Suspension (Crystalline)	Suspension of bovine, porcine, or human insulin complexed with a suitable zinc salt; the insulin is in a form practically insoluble in water	6.9 to 7.8				
	Protamine Zinc Insulin Injection (BP 2014)	Protamine Zinc Insulin	Buffered suspension of bovine, porcine, or human insulin complexed with protamine sulfate or another suitable protamine and zinc chloride or another suitable zinc salt	6.9 to 7.8				
	Extended Insulin Zinc Suspension (USP 36)		Buffered aqueous suspension of bovine or porcine, or a mixture of bovine and porcine, insulin modified by the addition of a suitable zinc salt in a manner such that the solid phase is predominantly crystalline	7.0 to 7.8	Long-acting	4 hours	10 to 20 hours	Up to 36 hours
	Extended Insulin Human Zinc Suspension (USP 36)		Buffered aqueous suspension of human insulin modified by the addition of a suitable zinc salt in a manner such that the solid phase of the suspension is predominantly crystalline	7.0 to 7.8				

The major effects of insulin on carbohydrate homoeostasis follow its binding to specific cell-surface receptors on insulin-sensitive tissues, notably the liver, muscles, and adipose tissue. It inhibits hepatic glucose production and enhances peripheral glucose disposal thereby reducing blood-glucose concentration. It also inhibits lipolysis thereby preventing the formation of ketone bodies.

Therapy with insulin is essential for the long-term survival of all patients with type 1 diabetes mellitus. It may also be necessary in some patients with type 2 disease. The role of insulin is discussed further in the Management of Diabetes Mellitus (p. 459.1), Diabetes Mellitus and Pregnancy (p. 461.3), Gestational Diabetes Mellitus (p. 462.1), and Diabetes Mellitus in Surgery or Critical Care (p. 462.2).

Choice of insulin. The different types of insulin and their formulations are described under Definitions and Terminology, p. 476.1. In some countries including the UK the commercially available preparations have been standardised to a single **strength** containing 100 units/mL; a strength of 40 units/mL is still available in some other countries, and in others concentrated injections (500 units/mL) are available to enable high doses to be given subcutaneously in a small volume. The analogue insulin degludec may be available in strengths of 100 units/mL and 200 units/mL. All formulations can be given by subcutaneous injection, most by intramuscular injection, but only some soluble insulins and short-acting analogues can be given by the intravenous **route**. The long-term management of diabetic patients usually involves the subcutaneous route. Single-use syringes and needles, which are calibrated for the particular concentration of insulin being given, should preferably be used. Pen-injector devices which hold the insulin in cartridge form and meter the required dose are becoming increasingly popular. Soluble insulin is often given by the intraperitoneal route to patients on continuous ambulatory peritoneal dialysis. A product supplying short-acting insulin by inhalation (*Exubera; Pfizer*) was withdrawn from the market in late 2007, but the development of alternative inhaler products is continuing.

The various formulations of insulin are classified, according to their **duration of action** after subcutaneous injection, as short-, intermediate-, or long-acting. The exact duration of action for any particular preparation, however, is variable and may depend upon factors such as interindividual variation, the patient's antibody status, whether the insulin is identical to human insulin or of animal origin, the dose, and the site of injection.

- *Short-acting* insulins are the soluble insulins, which have an onset after about 30 minutes to 1 hour, a peak activity at about 2 to 5 hours, and a duration of about 6 to 8 hours. Some analogues, such as insulins lispro and aspart, are also short-acting, with a faster onset and shorter duration of action than soluble insulin and are often known as rapid-acting insulins.
- *Intermediate-acting* insulins include biphasic insulins, isophane insulins, and amorphous insulin zinc suspensions. In general these have an onset within about 2 hours, peak activity after about 4 to 12 hours, and a duration of up to 24 hours. Commercially available mixtures of soluble insulins and isophane insulins have activities which would normally place them within the intermediate-acting category.
- Mixed insulin zinc suspensions may be classified as either *intermediate- or long-acting* as the duration of action may be up to 30 hours; the onset of action is generally 2 to 3 hours and the time to peak activity 6 to 15 hours.
- *Long-acting* insulins include crystalline insulin zinc suspensions and protamine zinc insulins. These generally have an onset after about 4 hours, a peak activity at about 10 to 20 hours, and a duration of up to 36 hours. The insulin analogues insulin glargine and insulin detemir are also long-acting, but these show a more consistent absorption profile with little or no pronounced peak of activity. Insulin degludec is described as an ultra-long acting analogue.

After intramuscular injection, the onset of action of all insulins is generally more rapid and the duration of action shorter.

The type of formulation, its dose, and the frequency of administration are chosen to suit the needs of the individual patient. Whatever the formulation, human insulin or insulin analogues are generally used for all newly diagnosed diabetics.

Control. The **dosage** of insulin must be determined for each patient and although a precise dose range cannot be given, total daily subcutaneous doses up to about 1 unit/kg may be appropriate. Insulin requirements can be altered by various factors (see Precautions, p. 487.1) and very high doses may be necessary in patients with insulin resistance (p. 489.1). The dose should be adjusted as necessary according to the results of regular monitoring of blood concentrations (or occasionally urine concentrations) of glucose by the patient. In practice, the *BNF* suggests that it is generally acceptable for patients to aim for blood-glucose concentrations between 4 and 9 mmol/litre (4 to 7 mmol/litre preprandially, and less than 9 mmol/litre postprandially) with the understanding that occasional variations outside this range may occur. Long-term control is determined by monitoring glycated haemoglobin (HbA_{1c}) concentrations; ideally the aim is an HbA_{1c} level of 6.5 to 7.5% (48 to 59 mmol/mol) or less. However, recommendations vary between authorities, and may depend on factors such as age and comorbidities; for further details see Monitoring of Therapy in Diabetes Mellitus, p. 461.1.

The aim of any **regimen** should be to achieve the best possible control of blood glucose by attempting to mimic as closely as possible the pattern of optimum endogenous insulin secretion. Many regimens involve the use of a short-acting soluble insulin with an intermediate-acting insulin, such as isophane insulin or insulin zinc suspension, often given twice daily. Basal-bolus regimens, using multiple daily injections to improve glycaemic control, typically combine an intermediate- or long-acting basal insulin (in the evening or twice daily) with a dose of short-acting insulin before each meal. A continuous subcutaneous insulin infusion (CSII) can be a suitable alternative for intensive therapy in some patients. CSII delivers a constant basal infusion of insulin, with patient-activated bolus doses before each meal. A short-acting soluble insulin or insulin analogue is used, although some formulations of soluble insulin are unsuitable because of the risk of catheter obstruction; insulin suspensions and long-acting analogues are also unsuitable. Patients using CSII need to be well-motivated, able to monitor their own blood glucose, and have access to expert advice at all times. A once-daily injection of an intermediate-or long-acting insulin is now generally considered to be acceptable only for those patients with type 2 diabetes mellitus who still retain some endogenous insulin secretion but nevertheless require insulin therapy.

Ketoacidosis. Insulin is also an essential part of the emergency management of diabetic ketoacidosis. Only short-acting soluble insulins should be used. Treatment includes adequate fluid replacement, usually by infusing sodium chloride 0.9% initially, and the use of potassium salts to prevent or correct hypokalaemia. Insulin should be given by continuous intravenous infusion if possible, although other routes have also been used. Since insulin normally corrects hyperglycaemia before ketosis it is usually necessary to continue giving insulin once normoglycaemia has been achieved but to change the rehydration fluid to a glucose infusion so that the additional glucose prevents the development of hypoglycaemia. For details of regimens see Diabetic Emergencies, under Diabetes Mellitus, p. 483.3.

General reviews of insulin and its use.[1-6] It has been suggested that the plethora of insulin preparations available might sensibly be reduced,[2] although others dispute this.[7]

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Administration. *ADMINISTRATION ROUTES.* The long-term management of diabetic patients usually involves insulin injection by the **subcutaneous** route, using a syringe or insulin pen device. The *depth* of injection is important since insulin is absorbed more rapidly after intramuscular than subcutaneous injection; inadvertent intramuscular injection may therefore lead to greater day-to-day variability in blood-glucose control.[1] Full-depth vertical injection can increase the chance of intramuscular injection, particularly in lean patients. Techniques for minimising intramuscular administration include injecting into a raised skin fold, injecting at a 45 degree angle instead of perpendicular to the skin surface, and the use of a shorter needle.[2,3] Inconsistency in the time lapse before withdrawing the needle, and the possible reflux of insulin from the subcutaneous tissue if the needle is withdrawn too quickly, might also contribute to variability in the absorbed insulin dose.[1]

The anatomic *site* of subcutaneous insulin injection is usually rotated in an attempt to decrease local adverse effects (see Adverse Effects, p. 485.2). However, the rate of absorption varies between sites and such a practice may also contribute to day-to-day variability in blood-glucose concentrations.[4] For example, large variations in blood-glucose concentrations have been reported on subcutaneous injection into the thigh.[5] Some have suggested rotation of injection sites within an anatomic region, or possibly use of the same anatomic region for injections given at a specific time of day.[1,4]

Jet injectors deliver insulin at high pressure across the skin into the subcutaneous tissue without use of a needle.[6,7] The greater dispersion obtained gives more rapid absorption of short- and intermediate-acting insulins and consequently reduces the total duration of action.[6] Mild pain, bruising, and bleeding may be a problem.[6-8] Despite having been available for some years, there is little information about their benefits and risks and they are not widely used.[7] However, results in a small study in women with gestational diabetes have suggested that jet injection may be associated with less variation in postprandial blood-glucose concentration and a lower incidence of insulin antibodies.[9]

Insulin preparations may also be given by **intramuscular** injection. Absorption is more rapid than from a subcutaneous injection. However, exercise may produce considerable variations in insulin absorption after intramuscular injection.[10] Soluble insulins and rapid-acting soluble insulin analogues may be given **intravenously**; this route is used in diabetic ketoacidosis, and also in surgery and labour.

The subcutaneous and intravenous routes, and, rarely, the intramuscular route have all been used for the continuous administration of insulin (see Intensive Administration Regimens, p. 482.3).

Formulations of insulin for **intranasal** use are under investigation.[8,11-13] They have been tried in both type 1 and type 2 diabetes, but bioavailability is low and variable. Absorption enhancers have been used to facilitate uptake of insulin from the nasal mucosa and local adverse effects are dependent, in part, on their irritancy. Similarly, **buccal** formulations are under investigation[8,13,14] and have become available in some countries for use as short-acting prandial doses of insulin (*Oral-lyn; Generex*).

Devices for delivering insulin to the lungs via oral **inhalation** have been developed.[8,15-18] Inhaled insulin is effective in maintaining glycaemic control in both type 1 and type 2 diabetes.[19-22] Although there is some evidence from longer-term studies that it is slightly less effective than subcutaneous injection, patient acceptability is higher with inhaled insulin.[19] It is given before meals as a short-acting insulin in patients also receiving intermediate or long-acting subcutaneous insulins or oral antidiabetics; in type 2 diabetes it has also been used alone. Data regarding the long-term safety of inhaled insulin need to be collected, given reports of pulmonary effects and higher levels of insulin antibodies in people with type 1 diabetes. A few cases of primary lung malignancies have occurred in clinical studies of inhaled insulin, at a higher incidence than in comparator-treated patients. However, the number of cases was too small to determine whether these events were related to inhaled insulin, and all affected patients had a history of cigarette smoking. The first licensed product for inhalation (*Exubera; Pfizer*) was withdrawn from the market in late 2007, although other products are still in development.

Endogenous insulin is delivered into the portal venous system, and then passes immediately to the liver where a large fraction of the insulin is extracted. The above routes of administration all deliver insulin into the peripheral circulation, with the risk of peripheral hyperinsulinaemia which has been considered a risk factor for atherosclerotic complications.[23] Giving insulin via the **intraperitoneal** or **oral** routes may overcome this problem to some extent. Peritoneal insulin is used routinely in diabetics undergoing chronic ambulatory peritoneal dialysis,[24,25] but has also been used for continuous administration (see Intensive Administration Regimens, p. 482.3). Various formulations of insulin for oral delivery are also under investigation.[8,12-14,26] **Transdermal**[8,13,27] insulin has also been tried.

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INSULIN ANALOGUES. Most of the insulin in pharmaceutical preparations is in the form of hexamers, which take time to dissociate into dimers and monomers that can be absorbed from a subcutaneous site. Substitution of amino-acid residues in the insulin molecule, using recombinant DNA technology, has produced insulin analogues such as insulin aspart and insulin lispro that form less stable hexamers and are therefore absorbed more rapidly. Similarly, structural changes have been made to develop long-acting basal analogues, such as insulin detemir and insulin glargine, as described below.

In the ***short-acting*** analogue **insulin lispro**, the B28 and B29 residues are replaced with lysine and proline, respectively. Compared with human regular insulin, it has a faster onset of action (within 15 minutes), peaks earlier, and has a shorter duration of action (2 to 5 hours). As a result, insulin lispro is given shortly before meals, but can alternatively be given immediately after eating if necessary. In diabetic patients, it controls postprandial glucose concentrations and glycated haemoglobin (HbA_{1c}) at least as well as regular insulin, without an increased risk of hypoglycaemia.[1] As well as adults, insulin lispro may be used in children and has been given during pregnancy. It is suitable for use in a continuous subcutaneous insulin infusion (CSII) and may be given intravenously in the treatment of ketoacidosis or during surgery.[1] Insulin lispro has also been complexed with protamine to produce an intermediate-acting form, which is available as a biphasic preparation.[1,2] A few cases of response to insulin lispro in patients with severe insulin resistance have been reported.[3,4]

Insulin aspart is another short-acting insulin analogue, with aspartic acid replacing proline at position B28.[5,6] It is also used immediately before meals and controls postprandial blood-glucose concentrations at least as well as regular human insulin, and may cause fewer hypoglycaemic episodes. Like insulin lispro, insulin aspart may be given to adults, children, and pregnant women, used in CSII, or given intravenously. It has also been formulated with protamine to create a biphasic preparation.[2,7]

Insulin glulisine is another insulin analogue, with asparagine at position B3 replaced by lysine, and lysine at B29 replaced by glutamic acid.[8] It also has a rapid onset (about 20 minutes) and short duration of action (4 hours), and is given about 15 to 20 minutes before meals or within 20 minutes after starting the meal.[9,10] Insulin glulisine has proven effective in the control of blood glucose in diabetic adults, but there is limited information about its use in young children and pregnant women. It may also be given by CSII or intravenously.

A systematic review[11] of studies comparing short-acting insulin analogues (aspart, glulisine, or lispro) with regular insulin found evidence of a minor benefit from analogues in improving HbA_{1c} values in adults with type 1 diabetes. The effect was more pronounced in studies using CSII and in studies with an intervention period of more than 3 months. No superiority could be shown in type 2 diabetics. Overall hypoglycaemia was similar, but severe episodes occurred less often in the analogue group. However, the effects of long-term analogue therapy on microvascular complications of diabetes remain to be studied. Another review[12] that included studies of biphasic insulin analogues in adults with type 2 diabetes concluded that they were similar to biphasic human insulin in controlling fasting glucose and HbA_{1c}, but more effective in lowering postprandial glucose concentrations. Premixed analogues may also provide better glycaemic control than long-acting insulin analogues and non-insulin antidiabetics.

Recombinant DNA technology has also been used to produce a ***long-acting*** basal insulin analogue, **insulin glargine**, in which glycine replaces asparagine at position A21 and two arginine molecules are added to the C-terminus of the B chain.[13-15] It is available as a solution at pH 4; on subcutaneous injection and neutralisation by tissue buffering processes, microprecipitates are formed that slowly release insulin glargine over 24 hours with no pronounced peak in concentration or in metabolic activity. As a result, insulin glargine is given once daily at any time, but should be given at the same time each day. The prolonged effects of insulin glargine may be advantageous in the management of patients who are susceptible to morning hyperglycaemia (see p. 488.1). Controlled studies have reported insulin glargine to be more effective than human isophane insulin in producing glycaemic control as part of a basal-bolus regimen, and to be associated with fewer hypoglycaemic episodes.[15] However, a systematic review[16] of studies in adults with type 2 diabetes did not find a significant advantage over human isophane insulin in glycaemic control. Insulin glargine was associated with fewer hypoglycaemic events reported by study participants, but confirmed and severe hypoglycaemia were not significantly different; there was slightly less weight gain with isophane insulin. Insulin glargine may be used in children over 2 years of age.

Insulin detemir is another long-acting insulin analogue. It is a neutral soluble human insulin analogue in which the terminal amino acid at B30 has been replaced by myristic acid, a 14-carbon fatty acid chain. This allows insulin detemir to bind reversibly to albumin, producing slow absorption and a prolonged and consistent metabolic effect for up to 24 hours, permitting once or twice daily dosing. It appears to be at least as effective as isophane insulin in maintaining overall glycaemic control but with less intrapatient variability, a similar or lower risk of hypoglycaemia, and less body-weight gain.[17] A systematic review[18] found no clinically relevant differences in efficacy between insulin glargine and insulin detemir although the former was associated with fewer injection-site reactions, and the latter with less weight gain. Insulin detemir may be used in children aged 2 years and older, and considered for use in pregnant women.

A systematic review[19] of studies in type 2 diabetics found that long-acting insulin analogues (detemir or glargine) had a similar effect to isophane insulin on glycaemic control, although they may be associated with less hypoglycaemia, including nocturnal events. The authors suggested a cautious approach to the use of these analogues until further efficacy and safety data become available.

Insulin degludec is an ultra-long-acting neutral soluble insulin analogue, in which the amino acid at position B30 is deleted and hexadecanoic acid is attached to the lysine at B29 via a glutamic acid spacer. After subcutaneous injection, molecules self-associate into multi-hexameric chains to form a depot, which slowly dissociates to release active monomers that are absorbed into the circulation. It has a duration of action of more than 42 hours, and is reported to have a flat, stable glucose-lowering effect; steady state occurs after 2 to 3 days of administration. Insulin degludec is used as a once daily injection, and although it should be given at the same time each day its long duration of action allows for some flexibility in dosing. It achieves similar glycaemic control to insulin glargine, but with less risk of nocturnal hypoglycaemia.[20-22] Insulin degludec has also been investigated in three times a week regimens.[22]

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INTENSIVE ADMINISTRATION REGIMENS. Intensive insulin regimens aim to mimic more closely the physiological insulin pattern in which a basal insulin concentration is supplemented by a preprandial boost of insulin. Such intensive regimens are used to provide tight control in an attempt to avoid long-term complications (see p. 462.3).

Intensified insulin regimens have the advantage of improving the patient's lifestyle and allowing flexibility in timing of meals. However, careful dietary control must still be maintained and regular monitoring of blood-glucose concentrations is an important component of such regimens. Therefore patients must be well-motivated, reliable, and able to monitor their own blood glucose, and should have access to expert 24-hour help.

In **multiple daily injection** regimens, the basal insulin is provided by injection of an intermediate- or long-acting insulin or insulin analogue, given usually at night, and soluble insulin or a short-acting analogue given before each main meal. Systems for **continuous administration** may be designed on an open-loop or closed-loop delivery system. *Open-loop systems* comprise an infusion pump with the infusion rate programmed or controlled manually according to blood-glucose monitoring carried out manually or continuously by a subcutaneous glucose sensor. *Closed-loop systems* (the 'artificial pancreas') consist of an insulin pump, a glucose sensor, and a computer for analysis of blood-glucose data and adjustment of insulin delivery. Systems for continuous administration have most commonly used the subcutaneous route, but intraperitoneal, intravenous, or intramuscular infusion have also been used.

The most extensively used **open-loop** systems are *continuous subcutaneous insulin infusion* (CSII) using an external pump. A battery-powered pump infuses soluble insulin or a short-acting analogue via a subcutaneous catheter which is resited every 2 to 3 days. A background infusion is given at a predetermined rate, and preprandial bolus doses given using an override switch or manually drive.[1] CSII appears to provide better glycaemic control than conventional injection therapy.[2] It may be only slightly more effective than optimised multiple daily injection therapy in type 1 diabetics,[2-6] although the use of a continuous subcutaneous glucose sensor might further improve glycaemic control with pump therapy.[7] CSII may be used in all age groups including children,[3,4,6,8,9] and might be particularly useful in very young children because of their erratic food intake and reduced ability to convey symptoms of hypoglycaemia.[10]

Intensive regimens are associated with decreased hypoglycaemic awareness and more severe hypoglycaemic episodes compared with conventional therapy.[11] Although study results have been mixed as to whether CSII reduces the risk of severe hypoglycaemia compared with multiple daily injection therapy,[6,7,12] disabling hypoglycaemia associated with multiple daily injections may be an indication for changing to CSII.[6] Other complications include erythema, abscess, or cellulitis at the injection site and, rarely, contact dermatitis to components of the giving set, pump malfunction, or precipitation of insulin and catheter obstruction.[1] Pump therapy increases the risk of ketoacidosis if the pump fails or there is an acute increase in insulin requirements; the onset of ketoacidosis may be more rapid and more likely to be associated with dangerous hyperkalaemia than with conventional regimens because there is no depot of insulin.[1,13]

Further development of open-loop delivery systems has been in the design of *implantable insulin pumps* that deliver insulin intraperitoneally. Specially formulated insulin preparations have been developed to cope with the physical conditions of implanted pump therapy; for example Hoe 21PH is a highly concentrated insulin solution containing a stabilising agent. Some studies have shown improved glycaemic control, and fewer episodes of hypoglycaemia compared with intensive subcutaneous delivery. The main associated problems are pump slow-down or catheter

obstruction due to aggregation of insulin within the device; these can normally be corrected by procedures to flush the pump and catheter. Problems at the implantation site can include infection, fluid accumulation, or skin thickening. The bulkiness of current pumps makes them unsuitable for children and adolescents who have not yet reached adult size.[14]

Closed-loop continuous infusion systems are generally confined to research and experimental work, although several prototypes have been studied in patients with type 1 diabetes.[15,16] Systems in development have been based on subcutaneous glucose monitoring and insulin delivery, or intravenous glucose monitoring with intraperitoneal insulin delivery from an implanted pump. Semiclosed-loop systems are also being considered, in which there is some manual input into prandial dose adjustment.[17,18]

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MIXING OF INSULINS. Mixtures of insulin with differing durations of action may be used in order to produce a more normal pattern of blood glucose variation than can be achieved with a single insulin. However, physicochemical changes in the mixture may occur, either immediately on mixing or over time, and the physiological response to the mixture may therefore be different than if the components were given separately. An early review[1] suggested that insulins from different manufacturers should not be mixed, since formulation differences might render them incompatible. It is important that a consistent routine is followed in preparing and using such mixtures, and manufacturers advise that the shorter-acting insulin should be drawn into the syringe first, to avoid contamination of the vial with the longer-acting component. Pre-prepared mixtures are available from many manufacturers and may be preferable provided that the proportions are suited to the patient's needs.

The American Diabetes Association has issued guidelines[2] for mixing of insulins, including:

- patients well controlled on a particular mixed regimen should maintain their standard procedure for preparing doses
- no other medication or diluent should be mixed with insulin unless approved by the prescriber
- insulin glargine should not be mixed with other forms of insulin because of the low pH of its diluent
- currently available isophane and short-acting insulin formulations when mixed may be used immediately or stored for future use
- rapid-acting insulins (insulin aspart, insulin lispro) can be mixed with isophane, lente, and ultralente insulins. Ultralente insulins do not affect the onset of action of the rapid-acting component; a slight decrease in absorption rate but not bioavailability is seen if rapid-acting insulins are mixed with isophane insulin but postprandial blood-glucose response is similar to that seen with mixtures of rapid-acting and ultralente insulin
- mixtures of rapid-acting insulin with an intermediate- or long-acting insulin should be injected within 15 minutes before a meal
- mixing of short-acting (soluble) and lente or ultralente insulin is not recommended, as zinc ions present in the lente insulin may bind with the short-acting insulin and delay its effects. The degree and rate of binding vary with the insulins used, and may not reach equilibrium for 24 hours; if such mixtures are used the patient should standardise the interval between mixing and injection
- phosphate-buffered insulins (*e.g.* isophane insulin) should not be mixed with zinc-containing (lente or ultralente) insulins, as zinc phosphate may be precipitated, and the longer acting insulin may be partially and unpredictably converted to a short-acting form

Insulin formulations may change and the manufacturers should be consulted if their recommendations differ from those in the guidelines.

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Administration in children. Insulin is used for the management of type 1 diabetes mellitus in children, as it is in adults (see Uses, p. 476.3) and doses are adjusted similarly to achieve the desired control of blood sugar. The *BNFC* notes that most pre-pubertal children require insulin doses of around 0.6 to 0.8 units/kg daily once the initial temporary remission phase has ended. Unless the child has a very sedentary lifestyle a requirement for higher doses may indicate poor compliance or absorption, or the beginning of puberty. During puberty up to 1.5 to 2 units/kg daily may be required, especially during growth spurts; doses may subsequently require some adjustment to avoid excessive weight gain. There is less experience with insulin analogues in young children. Although type 2 diabetes is rare in children the incidence is rising, and insulin may be needed to maintain glycaemic control in some of these patients also.

Further details on the use of insulin in children can also be found in Diabetic Emergencies, p. 483.3, and Neonatal Hyperglycaemia, p. 485.1. See p. 486.3 for the treatment of insulin-induced hypoglycaemia in children.

Critically ill patients. Strict glycaemic control has been advocated for the management of stress-induced hyperglycaemia in critically ill patients, whether they are diabetic or not. However, a meta-analysis[1] of 29 studies, which included more than 8000 critically ill adult medical and surgical patients, did not confirm the beneficial results of an earlier influential study.[2] It found that using an insulin infusion to maintain tight control of glucose below 8.3 mmol/litre was not associated with reduced hospital mortality, but did increase hypoglycaemia. Another meta-analysis[3] that included only studies of the perioperative use of insulin (with or without glucose targets) found that it reduced mortality, but also increased hypoglycaemia. However, most of the effect was accounted for by the influential study[2] that had been stopped early because of an unexpectedly large treatment effect; when this study was removed from the meta-analysis, the beneficial effect of insulin on mortality was no longer statistically significant.

Subsequent to these analyses, a large randomised study (NICE-SUGAR)[4] compared the outcome of more than 6000 critically ill medical and surgical patients maintained in a target glucose range of either 4.5 to 6.0 mmol/litre, or up to 10.0 mmol/litre. In this study, intensive glucose control in the lower target range was actually associated with an increased risk of death in the 90 days after randomisation, as well as more hypoglycaemia. A further meta-analysis,[5] which incorporated the NICE-SUGAR results, found that intensive insulin therapy had no effect on the overall risk of death. Subgroup analysis showed a benefit for patients treated in a surgical intensive care unit, but the authors urged caution in the interpretation of this result because of low event rates in this group. The meta-analysis also confirmed an increased risk of hypoglycaemia from intensive insulin therapy. In another study[6] of 509 patients with septic shock who were given corticosteroid treatment, which can induce or exacerbate hyperglycaemia, the addition of intensive insulin therapy did not improve inpatient mortality when compared with conventional insulin therapy.

Although hyperglycaemia is known to be harmful in critically ill patients, there is uncertainty about which subgroups, if any, might benefit from the routine use of tight glycaemic control.[7,8] There is still controversy regarding the most appropriate blood-glucose target, how and when to measure blood-glucose concentrations, and the best method of insulin administration. The risks associated with insulin-induced hypoglycaemia also need to be considered. The effects of different feeding regimens might also be important.[5,9] Nevertheless, guidelines have been issued on the management of hyperglycaemia in critically ill patients. Some[10] have recommended starting insulin infusion therapy for persistent hyperglycaemia at a blood-glucose concentration threshold of no greater than 10.0 mmol/litre, with a target range of 7.8 to 10.0 mmol/litre, while others[11] have suggested a target range of 7.8 to 11.1 mmol/litre.

For a discussion of the management of hyperglycaemia in non-critically ill hospitalised patients, see Inpatient Hyperglycaemia, p. 484.3.

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Diabetes mellitus. Insulin is the mainstay of the treatment of **type 1 diabetes mellitus**. For a discussion of the treatment of diabetes mellitus, including the contexts in which insulin is used, see p. 459.1. The possible role of tight glycaemic control with insulin to prevent the development of microvascular and macrovascular complications in patients with type 1 diabetes is discussed on p. 462.3, while further discussion of specific regimens and approaches to insulin therapy is given under Administration, p. 479.2.

DIABETIC EMERGENCIES. As discussed on p. 465.3, **diabetic ketoacidosis** and hyperosmolar hyperglycaemic state (HHS) are medical emergencies and should be treated immediately with fluid replacement and insulin. Potassium, and possibly phosphate, replacement may also be required, but bicarbonate should not be given unless acidaemia is very severe. In addition, potassium replacement, given by infusion, is generally necessary during insulin treatment to prevent insulin-induced hypokalaemia.

In the *UK* the *BNF* recommends that insulin be given by intravenous infusion for diabetic ketoacidosis, as a solution of soluble insulin 1 unit/mL in sodium chloride 0.9%. A fixed infusion rate of 0.1 units/kg per hour is recommended initially, with the rate adjusted so that the blood-ketone concentration falls by at least 0.5 mmol/litre per hour and the blood-glucose concentration falls by at least 3.0 mmol/litre per hour. When the blood-glucose concentration has fallen below 14 mmol/litre, glucose 10% infusion is started at a rate of 125 mL/hour in addition to the sodium chloride 0.9% infusion. The insulin infusion is continued until the blood-ketone concentration is below 0.3 mmol/litre and the blood pH is above 7.3. When the patient is able to eat and drink, subcutaneous fast-acting insulin should be given with a meal, and the insulin infusion may be stopped 1 hour later. Any established therapy with a long-acting insulin analogue (insulin detemir or insulin glargine) should be continued during treatment for ketoacidosis.

The *BNFC* gives some guidance on management of children with diabetic ketoacidosis. Children with mild ketoacidosis and less than 5% dehydration may be managed with oral rehydration and subcutaneous insulin. Those who do not respond, or are clinically unwell or more severely dehydrated are best managed with intravenous fluids and insulin. Rehydration should be with sodium chloride 0.9%,

at a rate that replaces deficit and provides maintenance over 48 hours; for those in shock an initial bolus of 10 mL/kg repeated up to twice, may be given. Fluid replacement may be changed to sodium chloride 0.45% with glucose 5% after 12 hours if response is adequate and plasma-sodium concentration stable. Potassium chloride should be included in rehydration fluids unless anuria is suspected. Insulin infusion should not be started until at least 1 hour after starting rehydration; soluble insulin 1 unit/mL in sodium chloride 0.9% is infused at a rate of 0.1 units/kg per hour. Once blood-glucose falls to 14.0 mmol/litre (and provided the blood pH is over 7.3) this rate can be reduced to 0.05 units/kg per hour; at the same time, glucose 5 or 10% should be added to the infusion fluids. This is continued until the patient is ready to take food orally. The insulin infusion should not be stopped until 1 hour after starting subcutaneous insulin or 10 minutes after starting a short-acting analogue.

Similar recommendations have been made in other UK guidelines on the management of diabetic ketoacidosis in adults and children.[1,2]

Intravenous insulin is also recommended in the *USA*. One set of recommendations[3] for diabetic ketoacidosis in adults suggests that once hypokalaemia has been excluded, treatment begins with an intravenous bolus of soluble regular insulin 0.1 units/kg, which is followed by infusion of 0.1 units/kg per hour. Alternatively, an infusion may be started (without a preceding bolus) at 0.14 units/kg per hour. The blood-glucose concentration should usually fall by about 2.5 to 4.0 mmol/litre per hour, but if it has not done so in the first hour then the intravenous infusion rate may be increased. (These intravenous insulin regimens may also be used in patients with **HHS**.) Treatment is continued until a blood-glucose concentration of about 11.0 mmol/litre is reached (or about 17.0 mmol/litre for HHS), when the insulin infusion rate may be reduced to 0.02 to 0.05 units/kg per hour; alternatively, a rapid-acting subcutaneous insulin analogue may be given at 0.1 units/kg every 2 hours in mild to moderate diabetic ketoacidosis. An infusion of glucose 5% should also be started. The blood-glucose concentration should be maintained between 8.3 and 11.0 mmol/litre (or between 11.0 and 17.0 mmol/litre for HHS) until the metabolic disturbance has resolved. When the patient is able to eat, intravenous insulin should still be continued for 1 to 2 hours after a maintenance subcutaneous insulin regimen has begun.

Children in the *USA*[4] with diabetic ketoacidosis may be started on insulin treatment after initial fluid replacement (usually after about 1 to 2 hours), using an intravenous infusion of 0.1 units/kg per hour. An initial insulin bolus dose is considered unnecessary and may increase the risk of cerebral oedema. After a rapid decline in plasma glucose during the initial volume expansion, it usually decreases at a rate of about 3.0 to 5.0 mmol/litre per hour. The dose of insulin may be reduced to 0.05 units/kg per hour in patients who have a marked sensitivity to insulin. Glucose 5% infusion should be started when the blood-glucose concentration reaches about 17.0 mmol/litre, but may need to be started sooner if the concentration falls more rapidly than 5.0 mmol/litre per hour. Higher concentrations of 10 or 12.5% glucose may be needed to prevent hypoglycaemia while continuing the insulin infusion required to correct the metabolic acidosis. If intravenous administration is not possible, hourly or 2-hourly doses of a subcutaneous or intramuscular rapid-acting insulin analogue may be considered.

1. **Savage MW *et al.*** Joint British Diabetes Societies Inpatient Care Group. The management of diabetic ketoacidosis in adults. (Issued March 2010). Available at: http://www.diabetes.nhs.uk/document.php?o=1336 (accessed 10/08/11)
2. **Edge JA.** British Society of Paediatric Endocrinology and Diabetes. Guidelines for the management of diabetic ketoacidosis (issued November 2009). Available at: http://www.bsped.org.uk/professional/guidelines/docs/DKAGuideline.pdf (accessed 17/03/11)
3. **Kitabchi AE, *et al.*** Hyperglycemic crises in adult patients with diabetes. *Diabetes Care* 2009; 32: 1335–43.
4. **Wolfsdorf J, *et al.*** Diabetic ketoacidosis in infants, children, and adolescents: a consensus statement from the American Diabetes Association. *Diabetes Care* 2006; 29: 1150–9. Also available at: http://care.diabetesjournals.org/content/29/5/1150.full.pdf (accessed 25/06/09)

TYPE 2 DIABETES MELLITUS. Traditionally the use of insulin in patients with type 2 diabetes has tended to be reserved for those who cannot be controlled by diet and oral antidiabetics alone.[1,2] Given the possible association between circulating insulin and atherosclerotic cardiovascular symptoms[3] there had been some concern about the use of exogenous insulin in insulin-resistant patients who are already hyperinsulinaemic, but evidence of harm is lacking.[4] Furthermore, patients switched to insulin tend to gain weight[2] which is undesirable in a frequently obese patient group.

Insulin is nonetheless being used more frequently in type 2 patients. This is largely because of a trend toward more intensive regimens designed to produce tighter glycaemic control, on the hypothesis that, as in patients with type 1 disease, this will reduce the development and progression of diabetic complications. Results from the UK Prospective Diabetes Study,[5-7] show that insulin is an effective option in type 2 diabetes, and confirm both the value of intensive therapy in retarding microvascular complications,[7,8] and that oral therapy should be used before insulin in patients with primary diet failure.[9]

Insulin is usually started when combination oral antidiabetic therapy does not achieve adequate glycaemic control. Some advocate the early initiation of insulin therapy to slow the rate of disease progression by minimising hyperglycaemia.[4,10] Which insulin regimen is most appropriate for a patient with type 2 diabetes will be influenced by baseline hyperglycaemia and other measures of glycaemic control, as well as lifestyle and patient preference. Suitable regimens might include a single injection of basal insulin at night, a premixed biphasic insulin, or a multiple injection basal-bolus regimen.[4,10-12] Insulin sensitisers, such as thiazolidinediones and in particular, metformin, are generally continued;[10,11] however, the combination of a thiazolidinedione with insulin is associated with an increased risk of fluid retention and heart failure.[4,11] The combination of insulin secretagogues, such as sulfonylureas, with insulin may reduce the required insulin dose. However, the effect may be transient because these drugs require some residual beta cell function, which diminishes as the disease progresses.[11] The combination of bedtime isophane insulin with oral antidiabetics provides similar glycaemic control to insulin monotherapy, and is associated with less weight gain if metformin is used.[13] See Insulin Analogues, p. 480.1, for further information on their use in type 2 diabetics.

Several studies[14-16] have investigated the use of short-term intensive insulin therapy in newly diagnosed type 2 diabetes. These studies suggest that early intensive insulin therapy for 2 to 3 weeks to correct hyperglycaemia may provide a foundation for good glycaemic control through diet.

For further discussion of the management of type 2 diabetes mellitus see p. 459.1.

1. Tattersall RB, Scott AR. When to use insulin in the maturity onset diabetic. *Postgrad Med J* 1987; 63: 859–64.
2. Taylor R. Insulin for the non-insulin dependent? *BMJ* 1988; 296: 1015–16.
3. Stern MP. Do non-insulin-dependent diabetes mellitus and cardiovascular disease share common antecedents? *Ann Intern Med* 1996; 124 (suppl): 110–16.
4. Wyne KL, Mora PF. Insulin therapy in type 2 diabetes. *Endocr Res* 2007; 32: 71–107.
5. United Kingdom Prospective Diabetes Study Group. United Kingdom prospective diabetes study (UKPDS) 13: relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin-dependent diabetes followed for three years. *BMJ* 1995; 310: 83–8.
6. Turner R, *et al.* United Kingdom Prospective Diabetes Study 17: a 9-year update of a randomized, controlled trial on the effect of improved metabolic control on complications in non-insulin-dependent diabetes mellitus. *Ann Intern Med* 1996; 124 (suppl): 136–45.
7. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; 352: 837–53. Correction. *ibid.* 1999; 354: 602.
8. Holman RR, *et al.* 10-Year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008; 359: 1577–89.
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10. Tibaldi J, Rakel RE. Why, when and how to initiate insulin therapy in patients with type 2 diabetes. *Int J Clin Pract* 2007; 61: 633–44.
11. Raskin P. Why insulin sensitizers but not secretagogues should be retained when initiating insulin in type 2 diabetes. *Diabetes Metab Res Rev* 2008; 24: 3–13.
12. Holman RR, *et al.* 4-T Study Group. Three-year efficacy of complex insulin regimens in type 2 diabetes. *N Engl J Med* 2009; 361: 1736–47. Correction. *ibid.* 2010; 363: 2078.
13. Goudswaard AN, *et al.* Insulin monotherapy versus combinations of insulin with oral hypoglycaemic agents in patients with type 2 diabetes mellitus. Available in The Cochrane Database of Systematic Reviews: Issue 4. Chichester: John Wiley; 2004 (accessed 27/08/09).
14. Ryan EA, *et al.* Short-term intensive insulin therapy in newly diagnosed type 2 diabetes. *Diabetes Care* 2004; 27: 1028–32.
15. Li Y, *et al.* Induction of long-term glycemic control in newly diagnosed type 2 diabetic patients is associated with improvement of β-cell function. *Diabetes Care* 2004; 27: 2597–2602.
16. Weng J, *et al.* Effect of intensive insulin therapy on β-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial. *Lancet* 2008; 371: 1753–60.

Diagnosis and testing. *PITUITARY FUNCTION.* Insulin-induced hypoglycaemia has been used to provide a stressful stimulus in order to assess hypothalamic-pituitary function.[1] The insulin stress or insulin-tolerance test has been used as a standard test for assessment of growth hormone or corticotropin deficiency. However, it is unpleasant and not without risk, and is contra-indicated in patients with ischaemic heart disease or a history of seizures, and in the elderly. Testing should only be performed in specialist units under strict surveillance.[2-4]

1. Petersenn S, *et al.* The rational use of pituitary stimulation tests. *Dtsch Arztebl Int* 2010; 107: 437–43.
2. Lange M, *et al.* An audit of the insulin-tolerance test in 255 patients with pituitary disease. *Eur J Endocrinol* 2002; 147: 41–7.
3. Galloway PJ, *et al.* Safety of the insulin tolerance test. *Arch Dis Child* 2002; 87: 354–6.
4. Wright D, *et al.* The insulin stress test performed by an experienced endocrine specialist nurse: a safe and reliable procedure. *Clin Endocrinol (Oxf)* 2007; 66: 755–6.

Hyperkalaemia. Insulin promotes the intracellular uptake of potassium. It is therefore used in the management of moderate to severe hyperkalaemia, when it is given with glucose (see p. 1779.1).

Inpatient hyperglycaemia. Although few randomised controlled studies have been carried out to establish specific guidelines, recommendations have been made[1,2] for preventing hyperglycaemia in non-critically ill inpatients. These suggest that blood-glucose monitoring should be carried out and pre-meal blood-glucose targets should be less than 7.8 mmol/litre, with random blood-glucose values of less than 10.0 mmol/litre. To avoid hypoglycaemia, insulin regimens should be reassessed if blood-glucose falls below 5.6 mmol/litre and modified if blood-glucose falls below 3.9 mmol/litre (unless explained by factors such as a missed meal). Historically sliding scale insulin (SSI) has been the method of calculating the insulin dose required, based on urinary glucose measurement or blood-glucose concentrations. In SSI, subcutaneous insulin is given with no reference to the timing of meals consumed or to basal glucose production. SSI is not supported by evidence of improved glycaemic control or clinical outcome and its use is now discouraged.[3,4] Instead, the recommended method is to use a subcutaneous basal-bolus regimen. This method involves monitoring blood glucose and using basal, nutritional, and correction insulin doses to achieve and maintain glucose control. The basal insulin dose covers endogenous glucose production, the bolus (nutritional) dose covers carbohydrates consumed with a meal, and a corrective or supplemental dose can be added if blood glucose is above the target range.[1,2,5-7] The treatment of hyperglycaemia in critically ill patients is discussed p. 481.2.

1. Moghissi ES, *et al.* American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. *Diabetes Care* 2009; 32: 1119–31. Also available at: http://care.diabetesjournals.org/content/32/6/1119.full.pdf (accessed 11/03/11) Also published in: *Endocr Pract* 2009; 15: 353–69. Also available at: https://www.aace.com/sites/default/files/InpatientGlycemicControlConsensusStatement.pdf (accessed 10/08/11)
2. Umpierrez GE, *et al.* Management of hyperglycemia in hospitalized patients in non-critical care setting: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2012; 97: 16–38.
3. Umpierrez GE, *et al.* Sliding scale insulin use: myth or insanity? *Am J Med* 2007; 120: 563–7.
4. Hirsch IB. Sliding scale insulin—time to stop sliding. *JAMA* 2009; 301: 213–14.
5. Umpierrez GE, *et al.* Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes (RABBIT 2 trial). *Diabetes Care* 2007; 30: 2181–6.
6. Juneja R, *et al.* The nuts and bolts of subcutaneous insulin therapy in non-critical care hospital settings. *Postgrad Med* 2010; 122: 153–62.
7. Umpierrez GE, *et al.* Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes undergoing general surgery (RABBIT 2 surgery). *Diabetes Care* 2011; 34: 256–61.

Myocardial infarction. Discussions on the effects of insulin with glucose and potassium in the ischaemic heart, including its effect in reducing blood free fatty acids, have emphasised its potential benefits in left ventricular failure and cardiogenic shock.[1,2] A meta-analysis[3] of randomised controlled studies performed before the widespread use of thrombolytics found a reduction in mortality in recipients of glucose-insulin-potassium solutions. However, although a pilot study[4] that included patients undergoing reperfusion (thrombolysis or percutaneous coronary intervention) reported benefit, this was not confirmed in larger randomised studies using standard glucose-insulin-potassium infusions.[5,6] A further study[7] found that routine use of such infusions in patients undergoing reperfusion had no effect on myocardial salvage, although some improvement was reported in diabetics. Reviews have concluded that glucose-insulin-potassium infusions do not reduce mortality in patients with acute myocardial infarction,[8,9] and cannot be recommended as standard adjunctive treatment with reperfusion.[10]

Intensive glucose control, with insulin-glucose infusion followed by multiple daily subcutaneous insulin injections has been reported to reduce mortality in diabetics who suffered a myocardial infarction.[11,12] A similar study[11] of treatment after myocardial infarction included only patients with type 2 diabetes mellitus who were treated with routine care, or insulin-glucose infusion followed by either long-term subcutaneous insulin or standard glucose control. The study was stopped early due to slow patient recruitment, but results did suggest that although glucose concentration was a strong independent predictor of long-term mortality, the use of long-term insulin treatment did not improve survival compared with conventional treatment at similar levels of glucose control. Further analysis[14] of the results of this study found an increase in non-fatal re-infarction and stroke associated with ongoing insulin therapy, although the reason for this was not clear. An observational study[15] in non-diabetics with hyperglycaemia suggested that intensive glucose control also improved outcomes in this population,

but another study[16] found no benefit. However, the glucose control achieved in this study was similar in both the intensive and the conventional treatment groups and an analysis based on blood-glucose concentrations suggested that strict glucose control was beneficial.[16]

For the conventional management of myocardial infarction, see p. 1257.1.

1. Opie LH. Glucose and the metabolism of ischaemic myocardium. *Lancet* 1995; 345: 1520–1.
2. Taegtmeyer H, *et al.* Metabolic support for the postischaemic heart. *Lancet* 1995; 345: 1552–5.
3. Fath-Ordoubadi F, Beatt KJ. Glucose-insulin-potassium therapy for treatment of acute myocardial infarction: an overview of randomized placebo-controlled trials. *Circulation* 1997; 96: 1152–6.
4. Díaz R, *et al.* Metabolic modulation of acute myocardial infarction: the ECLA Glucose-Irisulin-Potassium Pilot Trial. *Circulation* 1998; 98: 2227–34.
5. Mehta SR, *et al.* Effect of glucose-insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction: the CREATE-ECLA randomized controlled trial. *JAMA* 2005; 293: 437–46.
6. Díaz R, *et al.* Glucose-insulin-potassium therapy in patients with ST-segment elevation myocardial infarction. *JAMA* 2007; 298: 2399–2405.
7. Pache J, *et al.* A randomized evaluation of the effects of glucose-insulin-potassium infusion on myocardial salvage in patients with acute myocardial infarction treated with reperfusion therapy. *Am Heart J* 2004; 148: e3.
8. Puskarich MA, *et al.* Effect of glucose-insulin-potassium infusion on mortality in critical care settings: a systematic review and meta-analysis. *J Clin Pharmacol* 2009; 49: 758–67.
9. Zhao Y-T, *et al.* Comparison of glucose-insulin-potassium and insulin-glucose as adjunctive therapy in acute myocardial infarction: a contemporary meta-analysis of randomised controlled trials. *Heart* 2010; 96: 1622–6.
10. Kloner RA, Nesto RW. Glucose-insulin-potassium for acute myocardial infarction: continuing controversy over cardioprotection. *Circulation* 2008; 117: 2523–33.
11. Malmberg K, *et al.* Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI Study): effects on mortality at 1 year. *J Am Coll Cardiol* 1995; 26: 57–65.
12. Malmberg K, *et al.* Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. *BMJ* 1997; 314: 1512–15.
13. Malmberg K, *et al.* Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur Heart J* 2005; 26: 650–61.
14. Mellbin LG, *et al.* DIGAMI 2 Investigators. The impact of glucose lowering treatment on long-term prognosis in patients with type 2 diabetes and myocardial infarction: a report from the DIGAMI 2 trial. *Eur Heart J* 2008; 29: 166–76.
15. Weston C, *et al.* Early impact of insulin treatment on mortality for hyperglycaemic patients without known diabetes who present with an acute coronary syndrome. *Heart* 2007; 93: 1542–6.
16. Cheung NW, *et al.* The Hyperglycemia: Intensive Insulin Infusion in Infarction (HI-5) study: a randomized controlled trial of insulin infusion therapy for myocardial infarction. *Diabetes Care* 2006; 29: 765–70.

Neonatal hyperglycaemia. Hyperglycaemia is common in very immature neonates because of delayed or reduced insulin production. It can be treated by glucose restriction until glucose tolerance improves. However, this may not provide enough glucose to meet basal metabolic needs, and the use of an insulin infusion can allow sufficient glucose to be given. It has been suggested that insulin is best given intravenously in a separate, easily titratable solution because of the frequent fluctuations of requirement in these infants.[1] However, evidence from large, randomised, controlled studies to weigh up the risks and benefits of treating hyperglycaemia is lacking.[2] In addition, a controlled study of preventive early insulin therapy, using a fixed-dose continuous insulin infusion with intravenous glucose adjusted to maintain euglycaemia, was stopped early.[3] Although glycaemic control was better compared with standard care, there were more episodes of hypoglycaemia in infants given early insulin therapy and mortality before 28 days after birth was increased.

1. Ditzenberger GR, *et al.* Continuous insulin intravenous infusion therapy for VLBW infants. *J Perinat Neonatal Nurs* 1999; 13: 70–82.
2. Bottino M, *et al.* Interventions for treatment of neonatal hyperglycemia in very low birth weight infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 07/04/09).
3. Beardsall K, *et al.* Early insulin therapy in very-low-birth-weight infants. *N Engl J Med* 2008; 359: 1873–84.

Overdosage with calcium-channel blockers. High-dose insulin, with glucose and potassium as required to maintain normal plasma concentrations of these, has been reported to be of value in the treatment of overdosage with calcium-channel blockers[1] that has not been adequately managed with conventional therapy (which is described under Treatment of Adverse Effects under Nifedipine, p. 1452.3). A review[2] of 13 reported cases found that various dosage regimens had been tried. These included bolus doses of insulin 10 to 20 units, and continuous infusions of 0.1 to 1 unit/kg per hour. The authors of one report[3] proposed a regimen that includes an initial intravenous bolus dose of insulin 1 unit/kg, followed by a continuous infusion of 0.5 units/kg per hour; this may be increased to 1 unit/kg per hour if necessary. A prospective study[4] of 7 further cases permitted up to 2 units/kg per hour for the infusion dose. Others[5] have also suggested that because the onset of action may be delayed by about 30 to 45 minutes, the earlier use of a high-dose insulin regimen combined with supportive measures may be justified, and may reduce the need for more invasive circulatory support.

1. Engebretsen KM, *et al.* High-dose insulin therapy in beta-blocker and calcium channel-blocker poisoning. *Clin Toxicol* 2011; 49: 277–83.
2. Shepherd G, Klein-Schwartz W. High-dose insulin therapy for calcium-channel blocker overdose. *Ann Pharmacother* 2005; 39: 923–30.
3. Boyer EW, *et al.* Hyperinsulinemia/euglycemia therapy for calcium channel blocker poisoning. *Pediatr Emerg Care* 2002; 18: 36–7.
4. Greene SL, *et al.* Relative safety of hyperinsulinaemia/euglycaemia therapy in the management of calcium channel blocker overdose: a prospective observational study. *Intensive Care Med* 2007; 33: 2019–24.
5. Lheureux PER, *et al.* Bench-to-bedside review: hyperinsulinaemia/euglycaemia therapy in the management of overdose of calcium-channel blockers. *Crit Care* 2006; 10: 212. Available at: http://ccforum.com/content/pdf/cc4938.pdf (accessed 31/07/09)

Adverse Effects

The most frequent complication of insulin therapy is hypoglycaemia, the speed of onset and duration of which may vary according to the type of preparation and the route used. It is usually associated with an excessive dosage of insulin, the omission of a meal by the patient, or increased physical activity. Patients, especially the elderly or those with tightly controlled diabetes or diabetes of long standing, may not have the typical early warning symptoms of a hypoglycaemic attack. There have been reports of hypoglycaemia, sometimes with decreased warning symptoms, in patients changing from animal (especially bovine) to human insulin (see under Hypoglycaemia, p. 486.2). Symptoms of hypoglycaemia resulting from increased sympathetic activity include hunger, pallor, sweating, palpitations, anxiety, and tremulousness. Other symptoms include headache, visual disturbances such as blurred or double vision, slurred speech, paraesthesia of the mouth and fingers, alterations in behaviour, and impaired mental or intellectual ability. If untreated, hypoglycaemia may lead to convulsions and coma which should not be confused with hyperglycaemic coma. Excessive doses of insulin can also cause electrolyte disturbances. Insulin stimulates a shift of potassium to the intracellular space and hypokalaemia may be particularly associated with intravenous use in the management of diabetic ketoacidosis (see Diabetic Emergencies, p. 465.3).

Insulin, given subcutaneously, may cause either lipoatrophy or lipohypertrophy. Lipoatrophy appears to occur less frequently with purified insulins than with conventional insulins; if it has occurred, it may be reversed by the injection of a purer animal insulin or human insulin into and around the atrophied site. Lipohypertrophy is usually associated with repeated injections at the same site and may usually be overcome by rotating the site of injection, although absorption of insulin may vary from different anatomical areas. Weight gain is often associated with insulin treatment, particularly intensive therapy regimens. Transient blurred vision and peripheral oedema may occur in the first few weeks of therapy.

Insulin occasionally causes local or systemic hypersensitivity reactions. Local reactions, characterised by erythema and pruritus at the injection site, usually disappear with continued use. Generalised hypersensitivity may produce urticaria, angioedema, and very rarely anaphylactic reactions; if continued therapy with insulin is essential hyposensitisation may be needed. Again, hypersensitivity reactions occur less frequently with purified than with conventional insulins and porcine insulin is less immunogenic than bovine insulin; human insulins and insulin analogues are less immunogenic again, but reactions may still occur.

Many patients treated with insulin, either animal or human insulin, develop antibodies but the clinical significance of this is not entirely clear.

Of patients given intensive insulin therapy for type 1 diabetes as part of the Diabetes Control and Complications Trial, those who had the greatest weight gain also had increased blood concentrations of triglycerides and low-density-lipoprotein cholesterol, and lowered high-density-lipoprotein cholesterol.[1] These lipid changes, with higher blood pressure, increased waist-to-hip ratio, and greater insulin requirements, were held to be similar to the symptoms of insulin resistance and to indicate a possible increased risk of macrovascular disease. Results from the UK Prospective Diabetes Study indicated that type 2 diabetic patients treated with insulin had greater weight gain than those managed with other therapies,[2] but found no evidence of harmful cardiovascular effects.

For discussion of some of the specific problems associated with continuous infusion of insulin, see Intensive Administration Regimens under Uses, p. 480.3.

1. Purnell JQ, *et al.* Effect of excessive weight gain with intensive therapy of type 1 diabetes on lipid levels and blood pressure: results from the DCCT. *JAMA* 1998; 280: 140–6. Correction. *ibid.*; 1484.
2. UK Prospective Diabetics Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; 352: 837–53. Correction. *ibid.* 1999; 354: 602.

Carcinogenicity. *Colorectal* cancer occurs more commonly in patients with type 2 diabetes mellitus than in the general population, and most studies estimate a 30 to 40% risk increase.[1] Results from a large retrospective cohort study with a nested case-control study, using data from the UK General Practice Research Database, suggested an increased risk of colorectal cancer associated with long-term insulin use in type 2 diabetics.[2] It has been hypothesised that hyperinsulinaemia is a risk factor, and that insulin therapy in patients with type 2 diabetes might increase the risk further.[1] Some have suggested colorectal cancer screening for patients with type 2 diabetes, particularly those treated with insulin,[1,2] but others have cautioned that further information would be needed before widespread screening is advocated.[3]

Primary *lung* malignancies have been found in a few patients receiving inhaled insulin; for further details, see Administration Routes, p. 479.2. A case-control study[4] of over 900 patients with *pancreatic* cancer also suggested an increase in risk in patients using insulin or insulin secretagogues.

There has been concern that insulin glargine, which has shown a greater affinity for the IGF-I receptor than human insulin, might also be linked with an increased risk of carcinogenicity.[5] Several cohort studies have reported differing results with a number of confounding factors affecting conclusions. An increase in malignancy was seen with increased human insulin dose[5] with a higher risk for the glargine analogue. An increase in the risk of breast cancer in users of insulin glargine alone in Sweden[6] was seen, but it was suggested that this might be due to random fluctuation. Furthermore a Scottish study[7] showed no overall increase in cancer risk; an increase in breast cancer with insulin glargine monotherapy was thought to be attributable to allocation bias. A retrospective cohort study of over 62 000 patients with type 2 diabetes[8] concluded that insulin glargine was not associated with an increased cancer risk compared with human insulin. A commentary on these cohort studies[9] concluded that the current epidemiological evidence was insufficient to confirm or refute a carcinogenic effect of specific insulins or specific cancers. Regulators in Europe and the USA[10,11] also concluded that study limitations did not allow a relationship between insulin glargine and cancer to be confirmed or excluded but continue to monitor the situation.

1. Berster JM, Göke B. Type 2 diabetes mellitus as risk factor for colorectal cancer. *Arch Physiol Biochem* 2008; 114: 84–98.
2. Yang Y-X, *et al.* Insulin therapy and colorectal cancer risk among type 2 diabetes mellitus patients. *Gastroenterology* 2004; 127: 1044–50.
3. Renehan AG, Shalet SM. Diabetes, insulin therapy, and colorectal cancer. *BMJ* 2005; 330: 551–2.
4. Li D, *et al.* Antidiabetic therapies affect risk of pancreatic cancer. *Gastroenterology* 2009; 137: 482–8.
5. Hemkens LG, *et al.* Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study. *Diabetologia* 2009; 52: 1732–44.
6. Jonasson JM, *et al.* Insulin glargine use and short-term incidence of malignancies—a population-based follow-up study in Sweden. *Diabetologia* 2009; 52: 1745–54.
7. Colhoun HM. SDRN Epidemiology Group. Use of insulin glargine and cancer incidence in Scotland: a study from the Scottish Diabetes Research Network Epidemiology Group. *Diabetologia* 2009; 52: 1755–65.
8. Currie CJ, *et al.* The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. *Diabetologia* 2009; 52: 1766–77.
9. Hernández-Díaz S, Adami H-O. Diabetes therapy and cancer risk: causal effects and other plausible explanations. *Diabetologia* 2010; 53: 802–8.
10. EMEA. European Medicines Agency update on safety of insulin glargine (Issued 23rd July, 2009). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500010016.pdf (accessed 23/02/11)
11. FDA. FDA Drug Safety Communication: update to ongoing safety review of Lantus (insulin glargine) and possible risk of cancer (issued 12th January, 2011). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm239376.htm (accessed 23/02/11)

Effects on the liver. For a report of hepatomegaly occurring after insulin overdosage, see under Abuse, in Precautions, p. 487.2.

Effects on the skin. Skin reactions to insulin therapy include lipodystrophies and allergic skin reactions (see Hypersensitivity, p. 486.1). Although the incidence of some reactions have decreased considerably with the purification of conventional insulins and the development of recombinant human insulin, they continue to be reported with human insulin and have been associated with insulin analogues.

Lipohypertrophy is the most commonly reported cutaneous complication of insulin therapy. It usually presents as soft dermal nodules containing adipocytes, and is a consequence of repeated injection at the same site.[1,2] Patients have been found to preferentially inject into these sites because of their relative anaesthesia,[1] but insulin absorption from these nodules can be impaired,[1,3] resulting in poor glycaemic control.[4] Lipohypertrophy can be avoided or limited by rotation of injection sites, and avoidance of affected areas can bring about regression. The use of a rapidly absorbed short-acting insulin analogue might also have a less stimulatory effect on lipohypertrophy

development. Liposuction has been used when other measures have failed, but experience is limited.[1,2]

It is thought that *lipoatrophy*, a loss of fat at injection sites, might be caused by an immune reaction. The condition has become rare with the use of recombinant human insulin.[1,2] Insulin analogues, both short- and long-acting, have also been reported to cause lipoatrophy.[2,5-8] Patients are advised to avoid further injection into affected areas, but spontaneous resolution is rare.[1] The successful use of a corticosteroid injected into lipoatrophic areas has been described.[9]

The growth of *amyloid nodules* at insulin injection sites has been reported;[10] they may be mistaken for lipohypertrophy, but are usually harder.

1. Richardson T, Kerr D. Skin-related complications of insulin therapy: epidemiology and emerging management strategies. *Am J Clin Dermatol* 2003; 4: 661–7.
2. Radermecker RP, *et al.* Lipodystrophy reactions to insulin: effects of continuous insulin infusion and new insulin analogs. *Am J Clin Dermatol* 2007; 8: 21–8.
3. Johansson U-B, *et al.* Impaired absorption of insulin aspart from lipohypertrophic injection sites. *Diabetes Care* 2005; 28: 2025–7.
4. Chowdhury TA, Escudier V. Poor glycaemic control caused by insulin induced lipohypertrophy. *BMJ* 2003; 327: 383–4.
5. Arranz A, *et al.* A case of lipoatrophy with lispro insulin without insulin pump therapy. *Diabetes Care* 2004; 27: 625–6.
6. Ampudia-Blasco FJ, *et al.* A case of lipoatrophy with insulin glargine: long-acting insulin analogs are not exempt from this complication. *Diabetes Care* 2005; 28: 2983.
7. Al-Khenaizan S, *et al.* Lispro insulin-induced lipoatrophy: a new case. *Pediatr Diabetes* 2007; 8: 393–6.
8. del Olmo MI, *et al.* A case of lipoatrophy with insulin detemir. *Diabetes Res Clin Pract* 2008; 80: e20–e21.
9. Ramos AJS, Farias MA. Human insulin-induced lipoatrophy: a successful treatment with glucocorticoid. *Diabetes Care* 2006; 29: 926–7.
10. Nagase T, *et al.* The insulin ball. *Lancet* 2009; 373: 184.

Hypersensitivity. The most common hypersensitivity reactions to subcutaneous insulin are localised urticarial reactions that start within 10 to 20 minutes of injection; late reactions of diffuse swelling and erythema may begin 2 to 3 hours after injection, peak at 6 to 12 hours, and resolve within 12 to 24 hours. Generalised reactions, including anaphylaxis, have also occurred.[1,2] Although the prevalence of insulin allergy decreased significantly with the introduction of highly purified and human insulins, such reactions may still occur.[1,3] Delayed pressure urticaria, in the form of large wheals occurring 4 to 6 hours after prolonged pressure, and lasting for up to 24 hours, was seen in a patient with type 1 diabetes within 6 months of changing from animal to human insulin.[4] The condition improved after a switch back to insulin of animal origin, and grew worse again after a second attempt to use human insulin. Intermittent urticaria simultaneously affecting previous injection sites was reported in a child receiving human insulin, who had never received animal insulin.[5] There are also reports of both local and generalised reactions to insulin analogues;[2,6-8] however, they have also been used successfully in patients with a history of hypersensitivity to human insulin.[9-11]

Substitution of a different insulin preparation or analogue may be tried in the management of allergy, and continuous subcutaneous insulin infusion using short-acting analogues has been successful. Treatment with an antihistamine and/or corticosteroid may be required for symptomatic relief, and a course of insulin desensitisation may be necessary in some cases.[1,2] Omalizumab was reported to improve symptoms in a case of severe, refractory insulin allergy; the patient first received a course of rituximab to reduce the total IgE level before omalizumab was given.[12]

The development of painful subcutaneous nodules at the injection site of insulin detemir has been reported.[13-16] The reactions generally started a few hours after injection and resolved spontaneously after a few days; in some cases the reaction started after the first injection of insulin detemir.

Hypersensitivity reactions to insulin preparations may be caused not only by the insulin itself, but also by other components of the formulation such as zinc,[17-19] protamine[2,20-25] (see also Hypersensitivity to Protamine under Precautions, p. 487.3), and *m*-cresol.[2]

1. Hoffman AG, *et al.* Type I allergy to insulin: case report and review of localized and systemic reactions to insulin. *Dermatitis* 2008; 19: 52–8.
2. Ghazavi MK, Johnston GA. Insulin allergy. *Clin Dermatol* 2011; 29: 300–5.
3. Schernthaner G. Immunogenicity and allergenic potential of animal and human insulins. *Diabetes Care* 1993; 16 (suppl 3): 155–65.
4. Payne CMER, *et al.* True delayed pressure urticaria induced by human Monotard insulin. *Br J Dermatol* 1996; 134: 184.
5. Sackey AH. Recurrent generalised urticaria at insulin injection sites. *BMJ* 2000; 321: 1449.
6. Takata H, *et al.* The human insulin analogue aspart is not the almighty solution for insulin allergy. *Diabetes Care* 2003; 26: 253–4.
7. Durand-Gonzalez K-N, *et al.* Glargine insulin is not an alternative in insulin allergy. *Diabetes Care* 2003; 26: 2216.
8. JiXiong X, *et al.* The human insulin analog aspart can induce insulin allergy. *Diabetes Care* 2004; 27: 2084–5.
9. Airaghi L, *et al.* The insulin analog aspart: a safe alternative in insulin allergy. *Diabetes Care* 2001; 24: 2000.
10. Yasuda H, *et al.* Human insulin analog insulin aspart does not cause insulin allergy. *Diabetes Care* 2001; 24: 2008–9.
11. Kara C, *et al.* Successful treatment of insulin allergy in a 1-year-old infant with neonatal diabetes by lispro and glargine insulin. *Diabetes Care* 2005; 28: 983–4.
12. Yong PFK, *et al.* Rituximab and omalizumab in severe, refractory insulin allergy. *N Engl J Med* 2009; 360: 1045–7.
13. Darmon P, *et al.* Type III allergy to insulin detemir. *Diabetes Care* 2005; 28: 2980.
14. Blumer IR. Severe injection site reaction to insulin detemir. *Diabetes Care* 2006; 29: 946.
15. Stechemesser L, *et al.* Type III allergy to insulin detemir: response to Darmon et al. *Diabetes Care* 2006; 29: 2758.
16. Sola-Gazagnes A, *et al.* Type I and type IV allergy to the insulin analogue detemir. *Lancet* 2007; 369: 637–8.
17. Feinglos MN, Jegasothy BV. "Insulin" allergy due to zinc. *Lancet* 1979; i: 122–4.
18. Bruni B, *et al.* Case of generalized allergy due to zinc and protamine in insulin preparation. *Diabetes Care* 1986; 9: 552.
19. Gin H, Aubertin J. Generalized allergy due to zinc and protamine in insulin preparation treated with insulin pump. *Diabetes Care* 1987; 10: 789–90.
20. Sánchez MB, *et al.* Protamine as a cause of generalised allergic reactions to NPH insulin. *Lancet* 1982; i: 1243.
21. Hulshof MM, *et al.* Granulomatous hypersensitivity to protamine as a complication of insulin therapy. *Br J Dermatol* 1992; 127: 286–8.
22. Kim R. Anaphylaxis to protamine masquerading as an insulin allergy. *Del Med J* 1993; 65: 17–23.
23. Dykewicz MS, *et al.* Immunologic analysis of anaphylaxis to protamine component in neutral protamine Hagedorn human insulin. *J Allergy Clin Immunol* 1994; 93: 117–25
24. Blanco C, *et al.* Anaphylaxis to subcutaneous neutral protamine Hagedorn insulin with simultaneous sensitization to protamine and insulin. *Allergy* 1996; 51: 421–4.
25. Bollinger ME, *et al.* Protamine allergy as a complication of insulin hypersensitivity: a case report. *J Allergy Clin Immunol* 1999; 104: 462–5.

HYPOSENSITISATION. After failure of standard hyposensitisation measures in a patient with cutaneous hypersensitivity to insulin, hyposensitisation was attempted by giving insulin orally.[1] Oral aspirin (1.3 g three times daily) was also given to antagonise vascular mediators of the reaction. After one week subsequent hyposensitisation using insulin by injection was successful. When the patient stopped taking aspirin after 6 months the original hypersensitivity reactions recurred; aspirin was then given permanently in a dose of 1.3 g twice daily.

1. Holdaway IM, Wilson JD. Cutaneous insulin allergy responsive to oral desensitisation and aspirin. *BMJ* 1984; 289: 1565–6.

Hypoglycaemia. Hypoglycaemia is the major adverse effect of insulin treatment, with severe hypoglycaemic episodes occurring in up to a third of all insulin-treated patients at some point in their lives. Moves towards more intensive insulin therapy, in order to reduce the development of diabetic complications, increase the risk of hypoglycaemic episodes.[1,2] Patients maintaining strict glycaemic control are prone to 'hypoglycaemia unawareness' in which the normal adrenergic response to hypoglycaemia (characterised by symptoms such as pallor, sweating, and tremor) is reduced or lost.[3,4] The development of hypoglycaemic unawareness is linked to previous episodes of hypoglycaemia and increased duration of diabetes. In addition, the normal counter-regulatory hormonal response to hypoglycaemia becomes defective in diabetic patients. These factors predispose to the development of hypoglycaemia and neuroglycopenic symptoms (including irritability, blurred vision, lethargy, seizure, and coma) without warning. Nocturnal hypoglycaemia has also been implicated in the sudden nocturnal death of young, otherwise healthy, patients with type 1 diabetes;[4,5] this is a rare condition in which hypoglycaemia might contribute to cardiac arrhythmia.

Avoidance of hypoglycaemia for 2 to 3 weeks helps restore awareness. Patient education is an important strategy in avoiding hypoglycaemia, with particular attention paid to diet, exercise, and self-monitoring of blood-glucose concentrations. Adjustment of insulin regimens might include the use of rapid-acting insulin analogues at mealtimes to avoid hypoglycaemia between meals, long-acting (relatively peakless) analogues to reduce nocturnal hypoglycaemia, or use of a continuous subcutaneous insulin infusion (CSII).[3,4]

When recombinant human insulin became generally available in the late 1980s some patients complained of a loss of awareness of impending hypoglycaemia after transfer to human insulin,[6,7] and there were reports of severe or even fatal hypoglycaemia occurring in patients who had been well stabilised on animal insulins.[6-8]

This was, and remains, a somewhat controversial area. Despite some small studies suggesting a problem, others failed to find evidence of a difference between animal and human insulins, and a systematic review[9] concluded that the available evidence did not support the suggestion that human insulin increased the frequency or severity of hypoglycaemia, or affected the symptoms of hypoglycaemia, compared with animal insulins. However, most commentators appeared to consider that patients should continue to have access to animal insulins if desired, and that those well maintained on animal insulin should not be transferred to human insulin without appropriate clinical grounds,[8,10-13] and then only with careful monitoring.

There has also been concern about possible long-term sequelae of hypoglycaemic episodes on the CNS. However, a report on patients participating in the Diabetes Control and Complications Trial (DCCT) suggested that the increased risk of hypoglycaemia seen with intensive therapy was not associated with neuropsychological impairment.[14] Nevertheless, there is some evidence of an association between episodes of severe hypoglycaemia and cognitive impairment in young children (diagnosed before 5 or 6 years of age) [3]

For the treatment of insulin-induced hypoglycaemia, see p. 486.3.

1. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; 329: 977–86.
2. Egger M, *et al.* Risk of adverse effects of intensified treatment in insulin-dependent diabetes mellitus: a meta-analysis. *Diabet Med* 1997; 14: 9–28.
3. Dagogo-Jack S. Hypoglycemia in type 1 diabetes mellitus: pathophysiology and prevention. *Treat Endocrinol* 2004; 3: 91–103.
4. de Galan BE, *et al.* Pathophysiology and management of recurrent hypoglycaemia and hypoglycaemia unawareness in diabetes. *Neth J Med* 2006; 64: 269–79.
5. Clarke W, *et al.* International Society for Pediatric and Adolescent Diabetes. ISPAD Clinical Practice Consensus Guidelines 2009 Compendium: assessment and management of hypoglycemia in children and adolescents with diabetes. *Pediatr Diabetes* 2009; 10 (suppl 12): 134–45. Also available at: http://www.ispad.org/FileCenter/ISPAD%20Guidelines%202009%20-%20Hypoglycemia.pdf (accessed 14/02/11)
6. Teuscher A, Berger WG. Hypoglycaemia unawareness in diabetics transferred from beef/porcine insulin to human insulin. *Lancet* 1987; ii: 382–3.
7. Pickup J. Human insulin: problems with hypoglycaemia in a few patients. *BMJ* 1989; 299: 991–3.
8. Gale EAM. Hypoglycaemia and human insulin. *Lancet* 1989; ii: 1264–6.
9. Airey CM, *et al.* Hypoglycaemia induced by exogenous insulin - 'human' and animal insulin compared. *Diabet Med* 2000; 17: 416–32.
10. Everett J, Kerr D. Changing from porcine to human insulin. *Drugs* 1994; 47: 286–96.
11. Gerich JE. Unawareness of hypoglycaemia and human insulin. *Br J* 1992; 305: 324–5.
12. Williams G, Patrick AW. Human insulin and hypoglycaemia: burning issue or hot air? *BMJ* 1992; 305: 355–7
13. Teuscher A, Kiln MR. Patient-empowerment and free insulin market. *Lancet* 1994; 344: 1299–1300.
14. The Diabetes Control and Complications Trial Research Group. Effects of intensive diabetes therapy on neuropsychological function in adults in the Diabetes Control and Complications Trial. *Ann Intern Med* 1996; 124: 379–88.

Oedema. Severe, acute oedema is a rare adverse effect of insulin treatment, occurring most often when starting therapy.[1-7] It should be distinguished from chronic and subacute forms of oedema which may be complications of the diabetic disease process.[2,3] Possible mechanisms of acute oedema are sodium retention resulting from a direct action of insulin on the renal tubule or an effect of insulin on vascular permeability.[5] The oedema is usually self-limiting,[2,4] but does respond to a decrease in insulin dosage, or diuretic therapy.[1,3,5-7]

1. Bleach NR, *et al.* Insulin oedema. *BMJ* 1979; 2: 177–8.
2. Lawrence JR, Dunnigan MG. Diabetic (insulin) oedema. *BMJ* 1979; 2: 445.
3. Evans DJ, *et al.* Insulin oedema. *Postgrad Med J* 1986; 62: 665–8.
4. Hirshberg B, *et al.* Natural course of insulin edema. *J Endocrinol Invest* 2000; 23: 187–8.
5. Kalambokis GN, *et al.* The edematogenic properties of insulin. *Am J Kidney Dis* 2004; 44: 575–90.
6. Mamoulakis D, *et al.* Insulin-induced oedema in children and adolescents. *J Paediatr Child Health* 2006; 42: 655–7.
7. Kawashima S, *et al.* Acute progression of severe insulin edema accompanied by pericardial and pleural effusion in a patient with type 1 diabetes. *Diabetes Res Clin Pract* 2008; 81: e18–e19.

Treatment of Insulin-induced Hypoglycaemia

In the conscious and cooperative patient hypoglycaemia is treated by eating a readily absorbable form of carbohydrate such as sugar lumps or a glucose-based drink; all diabetics should always carry a suitable sugar source by way of precaution.

If the patient is drowsy or unconscious, then glucose must be given parenterally. Doses of 50 mL of a 20% solution of glucose or 25 to 50 mL of glucose 50% can be given intravenously; the higher concentration is more viscous and irritant to the veins. Lower concentrations are equally effective, and carry less risk of irritant effects, but larger volumes are required (e.g. up to 250 mL of 10%, titrated to patient response). Smaller quantities (e.g. 5 mL/kg of a 10% solution) are required in children. Bolus doses may need to be repeated, or a maintenance infusion started, to prevent persistent hypoglycaemia. If the patient has not regained consciousness within a few minutes after a bolus dose of glucose, the possibility of cerebral oedema should be considered.

In situations where giving intravenous glucose is impractical or not feasible, glucagon may be used to arouse the patient sufficiently to allow oral glucose to be given. Glucagon may be given intravenously, but is generally given by subcutaneous or intramuscular injection in a dose of 1 mg for adults and children weighing more than 25 kg, or 500 micrograms for children below 25 kg. The *BNFC* suggests that neonates requiring glucagon may be given 20 micrograms/kg. If the patient fails to respond to glucagon within about 10 to 15 minutes, then glucose has to be given intravenously despite any impracticalities. The effect of

glucagon relies upon the patient having adequate liver glycogen stores, which may not always be the case (as in starvation, adrenal insufficiency, alcohol-induced hypoglycaemia, or chronic hypoglycaemia).

After a return to consciousness, oral carbohydrates may need to be given until the action of insulin has ceased. For preparations with a relatively long duration of action such as isophane insulin, some insulin zinc suspensions, protamine zinc insulin, and long-acting insulin analogues, this may be several hours or possibly days.

Carbohydrate. A comparative study[1] of 7 different preparations of oral carbohydrate for the treatment of hypoglycaemia in the conscious patient found no significant difference in efficacy between glucose or sucrose in solution or tablet form; a hydrolysed polysaccharide solution containing glucose, maltose, and various more complex saccharides (*Glucidex 19*) was also roughly comparable. However, a glucose gel and orange juice were each less effective than the other formulations in treating hypoglycaemia.

1. Slama G, *et al.* The search for an optimized treatment of hypoglycemia: carbohydrates in tablets, solution, or gel for the correction of insulin reactions. *Arch Intern Med* 1990; **150**: 589–93.

Glucagon. Although intravenous glucose is the treatment of choice in drowsy or unconscious patients with insulin-induced hypoglycaemia, parenteral glucagon is a suitable alternative when glucose is impractical or not feasible (see p. 484.3). Subcutaneous or intramuscular glucagon can be particularly useful in non-hospital settings when it may have to be given by a relative or friend.[1,2]

Low doses of subcutaneous glucagon (so-called 'mini-dose' glucagon) have been successfully used in the management of impending or mild hypoglycaemia in children and adolescents with type 1 diabetes mellitus and gastroenteritis or poor oral carbohydrate intake. Two studies have described a protocol based on a dose of 10 micrograms per year of age, ranging from 20 micrograms for children under 2 years of age up to 150 micrograms for those aged 15 years.[3,4]

1. Gibbins RL. Treating hypoglycaemia in general practice. *BMJ* 1993; **306**: 600–601.
2. Pearson T. Glucagon as a treatment of severe hypoglycemia: safe and efficacious but underutilized. *Diabetes Educ* 2008; **34**: 128–34.
3. Haymond MW, Schreiner B. Mini-dose glucagon rescue for hypoglycemia in children with type 1 diabetes. *Diabetes Care* 2001; **24**: 643–5.
4. Hartley M, *et al.* Mini-dose glucagon rescue for mild hypoglycaemia in children with type 1 diabetes: the Brisbane experience. *J Paediatr Child Health* 2006; **42**: 108–11.

Overdose. The requirements for glucose are greater and more prolonged when hypoglycaemia is caused by insulin or insulin analogue overdosage rather than therapeutic doses.[1-4] Correction of insulin-induced hypokalaemia may also be required. Surgical excision of tissue at the site of injection has been used for massive overdose of a long-acting insulin.[5,6]

1. Roberge RJ, *et al.* Intentional massive insulin overdosage: recognition and management. *Ann Emerg Med* 1993; **22**: 228–34.
2. Bivar M, *et al.* Prolonged hypoglycaemia after insulin lispro overdose. *Eur J Emerg Med* 2005; **12**: 234–5.
3. Promont L, *et al.* Prolonged glucose requirements after intentional glargine and aspart overdose. *Diabetes Metab* 2007; **33**: 390–2.
4. Ashawesh K, *et al.* Intentional overdose with insulin glargine. *Am J Health-Syst Pharm* 2009; **66**: 534.
5. Campbell IW, Ratcliffe JG. Suicidal insulin overdose managed by excision of insulin injection site. *BMJ* 1982; **285**: 408–9.
6. Levine DF, Bulstrode C. Managing suicidal insulin overdose. *BMJ* 1982; **285**: 974–5.

Precautions

Dosage requirements of insulin may be altered by many factors.

- Increased doses are usually necessary during infection, emotional stress, accidental or surgical trauma, puberty, and the last two trimesters of pregnancy.
- Decreased doses are usually necessary in patients with impaired renal or hepatic function or during the first trimester of pregnancy.

On first stabilising therapy in newly diagnosed diabetic patients, a temporary decrease in requirements may also occur (the so-called honeymoon period).

Because of the possibility of differing responses to insulins from different species, inadvertent change from insulin of one species to another should be avoided. Reduction in insulin dosage may be required on transfer from animal (especially bovine) to human insulin. Hypoglycaemic problems associated with a change to human insulin are discussed under Hypoglycaemia, p. 484.2. Care is also necessary during exercise, when insulin dosage and carbohydrate intake should be adjusted according to the intensity and duration of exercise. Insulin levels that are too low may not be sufficient to respond to the rising glucose concentrations stimulated by exercise, while insulin levels that are too high can attenuate the release of glucose and lead to hypoglycaemia; exercise might also increase insulin absorption.

The use of insulin requires monitoring of therapy, such as testing blood or urine for glucose concentrations and the urine for ketones, by the patient.

Drugs that have an effect on blood-glucose concentrations may alter glycaemic control with consequent need for a change in insulin dose (see Interactions, p. 488.3).

CAUTION. *Biphasic insulin, insulin zinc suspensions, isophane insulin, protamine zinc insulin, insulin detemir, and insulin glargine should never be given intravenously and they are not suitable for the emergency treatment of diabetic ketoacidosis.*

Abuse. Transient recurrent hepatomegaly associated with hypoglycaemia was associated with the surreptitious injection of additional insulin doses in an insulin-dependent diabetic. Increased storage of glycogen in the liver resulting from insulin excess was considered responsible for the hepatomegaly.[1]

Decreased plasma C-peptide concentrations or the presence of anti-insulin antibodies may be used to confirm insulin abuse as a cause of hypoglycaemia in patients who have never been treated with insulin medically.[2] Insulin has been abused by bodybuilders and other sportspersons;[3-5] severe brain damage after prolonged neuroglycopenia has resulted.[3] There are rare reports of the misuse of insulin to induce mind-altering effects of hypoglycaemia.[6]

1. Asherov J, *et al.* Hepatomegaly due to self-induced hyperinsulinism. *Arch Dis Child* 1979; **54**: 148–9.
2. Grunberger G, *et al.* Factitious hypoglycemia due to surreptitious administration of insulin: diagnosis, treatment, and long-term follow-up. *Ann Intern Med* 1988; **108**: 252–7.
3. Elkin SL, *et al.* Bodybuilders find it easy to obtain insulin to help them in training. *BMJ* 1997; **314**: 1280.
4. Honour JW. Misuse of natural hormones in sport. *Lancet* 1997; **349**: 1786.
5. Evans PJ, Lynch RM. Insulin as a drug of abuse in body building. *Br J Sports Med* 2003; **37**: 356–7.
6. Cassidy EM, *et al.* Insulin as a substance of misuse in a patient with insulin dependent diabetes mellitus. *BMJ* 1999; **319**: 1417–18.

Accelerated absorption. Factors such as a hot bath, sauna, or use of a sunbed have been reported to accelerate the absorption of subcutaneous injection, presumably by an increase in skin blood flow.[1-4] There may, therefore, be a risk of hypoglycaemia.[4]

1. Koivisto VA. Sauna-induced acceleration in insulin absorption from subcutaneous injection site. *BMJ* 1980; **280**: 1411–13.
2. Cüppers HJ, *et al.* Sauna-induced acceleration in insulin absorption? *BMJ* 1980; **281**: 307.
3. Koivisto VA. Sauna-induced acceleration in insulin absorption. *BMJ* 1980; **281**: 621–2.
4. Husband DJ, Gill GV. "Sunbed seizures": a hypoglycaemic hazard for insulin-dependent diabetics. *Lancet* 1984; **ii**: 1477.

Adrenocortical insufficiency. Recurrent severe hypoglycaemia, which occurred in 2 patients with type 1 diabetes, persisted despite a reduction in insulin doses and proved to be due to Addison's disease.[1] Insulin requirements rose again in both patients after replacement therapy with fludrocortisone and hydrocortisone.

1. Armstrong L, Bell PM. Addison's disease presenting as reduced insulin requirement in insulin dependent diabetes. *BMJ* 1996; **312**: 1601–2.

Driving. In the UK, all patients with diabetes mellitus treated with insulin are required to notify their condition to the Driver and Vehicle Licensing Agency (DVLA), who then assess their fitness to drive. Those applying for an ordinary driving licence, who are treated with oral hypoglycaemics or non-insulin injectable medication, are only required to notify the DVLA if they have associated problems that may affect driving, such as impaired eyesight, impaired circulation or sensation in the legs or feet, episodes of disabling hypoglycaemia, or impaired hypoglycaemic awareness. Regardless of the type of diabetes or treatment, patients are required to notify the DVLA if such complications develop. Patients treated with oral hypoglycaemics or non-insulin injectable medication are generally allowed to retain ordinary driving licences; those treated with insulin receive restricted licences which must be renewed (with appropriate checks) every 1 to 3 years.[1] Patients should be warned of the dangers of hypoglycaemic attacks while driving, and should be counselled in appropriate management of the situation (stopping driving as soon as it is safe to do so, taking carbohydrate immediately, and quitting the driving seat and removing the ignition key from the car) should such an event occur.[2] Patients who have lost hypoglycaemic awareness, or have frequent hypoglycaemic episodes, should not drive. In addition, eyesight must be adequate (including field of vision of at least 120 degrees) for a licence to be valid.[1]

Patients treated with diet, oral hypoglycaemics, or non-insulin injectable medication are normally allowed to hold vocational driving licences for heavy goods or public service vehicles, unless they develop relevant disabilities. However, those treated with drugs that carry a risk of hypoglycaemia, such as sulfonylureas and glinides, must inform the DVLA and satisfy the criteria of well-controlled blood-glucose concentrations and full hypoglycaemic awareness; licences are issued for 1 to 3 years. Those treated with insulin may apply for a restricted 1 year licence provided they have not suffered from an episode of severe hypoglycaemia in the preceding 12 months and do not suffer from any other complication that may impair their ability to drive. Patients must undergo yearly medical assessments to satisfy the criteria of well-controlled blood-glucose concentrations and full hypoglycaemic awareness. Blood glucose must be monitored regularly and the risks of hypoglycaemia understood.[1]

Regulations in other countries differ widely.[3]

1. Driver and Vehicle Licensing Agency. For medical practitioners: at a glance guide to the current medical standards of fitness to drive (issued November 2013) Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/258991/aagv1.pdf (accessed 20/11/13)
2. Diabetes UK. Information sheet: driving and diabetes: May 2012. Available at: https://shop.diabetes.org.uk/usr/downloads/Driving%20infosheet%202012.pdf (accessed 20/11/13)
3. DiaMond Project Group on Social Issues. Global regulations on diabetics treated with insulin and their operation of commercial motor vehicles. *BMJ* 1993; **307**: 250–3.

Exercise. Discussions[1-3] of the metabolic effects of exercise, and precautions to be taken by exercising diabetic patients using insulin.

1. Robertson K, *et al.* ISPAD Clinical Practice Consensus Guidelines 2009 Compendium. Exercise in children and adolescents with diabetes. *Pediatr Diabetes* 2009; **10** (suppl 12): 154–68. Also available at: http://www.ispad.org/FileCenter/ISPAD%20Guidelines%202009%20-%20Exercise.pdf (accessed 14/02/11)
2. Draznin MB. Managing the adolescent athlete with type 1 diabetes mellitus. *Pediatr Clin North Am* 2010; **57**: 829–37.
3. American College of Sports Medicine, American Diabetes Association. Joint position statement: exercise and type 2 diabetes. *Med Sci Sports Exerc* 2010; **42**: 2282–2303. Also available at: http://journals.lww.com/acsm-msse/Fulltext/2010/12000/Exercise_and_Type_2_Diabetes__American_College_of.18.aspx (accessed 10/08/11)

Fasting. Reduction in food intake or alteration in the pattern of meal times may affect insulin requirements and predispose to the development of hypoglycaemia (p. 484.2). Muslim patients who are receiving antidiabetic therapy and who fast during Ramadan have been shown to be at increased risk of severe hypoglycaemic episodes during this month.[1] Only a few small studies have reported on the adjustment of insulin regimens in patients with type 1 diabetes. Possible regimens[2] include once or twice daily injections of an intermediate- or long-acting insulin, given before the predawn and sunset meals, with a short-acting insulin at the meal itself. It has also been suggested that between 70 and 85% of the non-fasting daily insulin dose is used.[3] Most patients using insulin infusion pumps will need to reduce their basal infusion rate while increasing bolus doses to cover predawn and sunset meals.[2]

Patients with type 2 diabetes maintained on insulin may be managed similarly, by judicious use of intermediate or long-acting insulin plus a short-acting insulin given before meals, particularly at the sunset meal to cover the longer caloric load.[2] Studies have suggested that insulin lispro may produce good blood glucose control in fasting patients with type 2 diabetes during Ramadan.[4,5]

Care is also required in patients with type 2 diabetes being treated with oral antidiabetic drugs. Patients being treated with metformin or insulin sensitisers such as the glitazones have a low risk of hypoglycaemia, although it has been suggested that the timing of metformin doses be altered so that two-thirds of the daily dose is taken just before the sunset meal and the other third before the predawn meal. Short-acting secretagogues such as repaglinide or nateglinide can also be taken twice daily before the sunset and predawn meals. However, sulfonylureas should be used with caution, and the use of chlorpropamide may be contra-indicated because of the high risk of prolonged and unpredictable hypoglycaemia. Patients taking once-daily sulfonylureas may take the dose before the sunset meal, adjusting the dose based on glycaemic control and the risk of hypoglycaemia. Those taking a twice-daily dose of sulfonylurea may take half the normal morning dose with the predawn meal and the usual dose with the sunset meal.[2] For patients taking alpha-glucosidase inhibitors or incretin-based therapies it has been suggested that no dosage adjustments are required.[2]

1. Salti I, *et al.* A population-based study of diabetes and its characteristics during the fasting month of Ramadan in 13 countries: results of the epidemiology of diabetes and Ramadan 1422/2001 (EPIDIAR) study. *Diabetes Care* 2004; **27**: 2306–11.
2. Al-Arouj M, *et al.* Recommendations for management of diabetes during Ramadan: update 2010. *Diabetes Care* 2010; **33**: 1895–1902.
3. Kobeissy A, *et al.* Suggested insulin regimens for patients with type 1 diabetes mellitus who wish to fast during the month of Ramadan. *Clin Ther* 2008; **30**: 1408–15.
4. Akram J, De Verga V. Ramadan Study Group. Insulin lispro (Lys(B28), Pro(B29)) in the treatment of diabetes during the fasting month of Ramadan. *Diabet Med* 1999; **16**: 861–6.
5. Mattoo V, *et al.* A comparison of insulin lispro Mix25 and human insulin 30/70 in the treatment of type 2 diabetes during Ramadan. *Diabetes Res Clin Pract* 2003; **59**: 137–43.

Hypersensitivity to protamine. Retrospective surveys have indicated that patients receiving isophane insulin, which contains protamine, have an increased risk of severe anaphylactoid reactions when protamine is used to reverse

systemic heparinisation after cardiac catheterisation or cardiac surgery. The degree of increase in risk is unclear, however, as it has been reported as both large[1] and small.[2,3] A review of the literature suggested that surgical patients may be at greater risk because of a higher rate of prior sensitisation to protamine and the larger doses used.[3] A mechanism involving IgE and IgG antibodies to protamine has been proposed.[4]

See also Hypersensitivity under Adverse Effects, p. 484.1.

1. Stewart WJ, *et al.* Increased risk of severe protamine reactions in NPH insulin-dependent diabetics undergoing cardiac catheterization. *Circulation* 1984; 70: 788–92.
2. Levy JH, *et al.* Evaluation of patients at risk for protamine reactions. *J Thorac Cardiovasc Surg* 1989; 98: 200–204.
3. Vincent GM, *et al.* Protamine allergy reactions during cardiac catheterization and cardiac surgery: risk in patients taking protamine-insulin preparations. *Cathet Cardiovasc Diagn* 1991; 23: 164–8.
4. Weiss ME, *et al.* Association of protamine IgE and IgG antibodies with life-threatening reactions to intravenous protamine. *N Engl J Med* 1989; 320: 886–92.

Infections. Decreased requirements of insulin, added to the dialysate, occurred in 6 diabetic patients undergoing continuous ambulatory peritoneal dialysis for chronic renal failure during episodes of severe bacterial peritonitis.[1] This was contrary to the increased insulin requirements of most diabetic patients during severe infections and probably resulted from increased absorption of insulin due to mesothelial damage.

1. Henderson IS, *et al.* Decreased intraperitoneal insulin requirements during peritonitis on continuous ambulatory peritoneal dialysis. *BMJ* 1985; 290: 1474.

Menstruation. Changes in glycaemic control associated with the menstrual cycle have been recorded in women with type 1 diabetes mellitus. In a retrospective review of 124 women,[1] 61% reported perimenstrual changes in glucose concentrations and 36% made adjustments to their insulin dose, usually a small increase in the premenstrual insulin dose followed by a small decrease at the onset of menstruation. Based on mean glycated haemoglobin measurements, there was no evidence of improved glycaemic control in women adjusting their insulin dose compared with those leaving it unchanged despite changes in capillary glucose measurements. Changes in appetite and food consumption associated with the menstrual cycle may affect variations in glucose concentrations and insulin requirements.

1. Lunt H, Brown LJ. Self-reported changes in capillary glucose and insulin requirements during the menstrual cycle. *Diabet Med* 1996; 13: 525–30.

Morning hyperglycaemia. Patients with diabetes lack the normal circadian cycle of insulin release that occurs in response to the surge of glucose produced by the liver during the dawn hours. In insulin-treated diabetics, morning hyperglycaemia may therefore be the result of mere waning of insulin injected subcutaneously the evening before. Conversely, it may be rebound hyperglycaemia occurring after an episode of nocturnal hypoglycaemia, usually resulting from an excessive dose of insulin that peaks in the middle of the night (post-hypoglycaemic hyperglycaemia or the Somogyi phenomenon). However, morning hyperglycaemia commonly occurs without preceding hypoglycaemia and is referred to as the dawn phenomenon.[1,2] Clinically, it is important to distinguish between these 3 effects because their treatment differs.

Management of the dawn phenomenon and insulin waning is generally based on optimising basal insulin to provide adequate coverage between 4 a.m. and 8 a.m. Treatment must be individualised, but options include giving a long-acting insulin, or insulin analogue such as insulin glargine, or the use of a continuous subcutaneous insulin infusion. Overall improvement of glycaemic control can also reduce the dawn phenomenon.[2] The addition of a bedtime dose of basal insulin may also be considered for type 2 diabetics when adjustment of diet and oral therapy has not been sufficient to manage the dawn phenomenon.[1,2] Management of rebound hyperglycaemia is aimed at avoiding nocturnal hypoglycaemia, by improving basal insulin control with a peakless long-acting insulin such as insulin glargine, or providing additional late-evening carbohydrate. If an intermediate-acting insulin is being used, hypoglycaemia may be reduced by giving it at bedtime rather than before the evening meal, and injecting into the lower buttock to slow absorption.[1] Mistaking rebound hyperglycaemia for the dawn phenomenon or mere waning of injected insulin could result in more serious nocturnal hypoglycaemia, if evening doses of insulin were increased.

1. Sheehan JP. Fasting hyperglycemia: etiology, diagnosis, and treatment. *Diabetes Technol Ther* 2004; 6: 525–33.
2. Carroll MF, Schade DS. The dawn phenomenon revisited: implications for diabetes therapy. *Endocr Pract* 2005; 11: 55–64.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies human insulin and the analogues insulin aspart and insulin lispro as not porphyrinogenic; they may be used as drugs of first choice and no precautions are needed.[1] Other forms of insulin have not yet been classified by NAPOS.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Pregnancy. For discussion of the precautions necessary in the management of diabetes mellitus during pregnancy, see p. 461.3.

There has been a report of 2 cases of fetal malformation in the offspring of well-controlled diabetic women who received *insulin lispro*.[1] However, the incidence of fetal malformation is increased in infants of women with diabetes. At that time the manufacturers were aware of 19 live births among women treated with insulin lispro, 1 of which had a congenital abnormality.[2] Since then, several retrospective studies[3-8] and a prospective observational study[9] have looked at the rates of fetal malformations in the offspring of women treated with insulin lispro, for either pre-existing diabetes mellitus or gestational diabetes. These have included groups ranging in size from 27 to 496 women, and none have found any evidence of an increase in the incidence of abnormalities with insulin lispro compared with rates for women treated with other insulins.

A single-dose study has reported[10] that *insulin aspart* was effective in reducing postprandial glucose concentration in gestational diabetes. Randomised studies in women with type 1 diabetes[11] or gestational diabetes[12] have also found no indication of an increase in congenital malformations with insulin aspart compared with human insulin.

The possible effects on the fetus of *insulin glargine* have also been examined in women with pre-existing or gestational diabetes. Several retrospective studies,[13-16] and a prospective observational study of 115 women with type 1 diabetes,[17] found no indication of an increased rate of fetal malformations in women given this long-acting insulin analogue at any stage during pregnancy. One retrospective case-control study[18] of women with type 1 diabetes did find a higher incidence of fetal femoral length < 50th centile associated with insulin glargine use in the second and third trimesters, compared with healthy controls, although the final neonatal length was not affected. This finding was the opposite of what might be expected because of insulin glargine's affinity for the insulin-like growth factor I (IGF-1) receptor, and the authors stated that further studies would be needed to confirm an effect. A subsequent meta-analysis,[19] which included the retrospective studies above, did not find any significant increase in adverse fetal outcomes with insulin glargine compared with standard insulin therapy.

1. Diamond T, Kormas N. Possible adverse fetal effect of insulin lispro. *N Engl J Med* 1997; 337: 1009.
2. Anderson JH, *et al.* Possible adverse fetal effect of insulin lispro. *N Engl J Med* 1997; 337: 1010.
3. Bhattacharyya A, *et al.* Insulin lispro and regular insulin in pregnancy. *Q J Med* 2001; 94: 255–60.
4. Garg SK, *et al.* Insulin lispro therapy in pregnancies complicated by type 1 diabetes: glycemic control and maternal and fetal outcomes. *Endocr Pract* 2003; 9: 187–93.
5. Masson EA, *et al.* Pregnancy outcome in type 1 diabetes mellitus treated with insulin lispro (Humalog). *Diabet Med* 2003; 20: 46–50.
6. Wyatt JW, *et al.* Congenital anomaly rate in offspring of mothers with diabetes treated with insulin lispro during pregnancy. *Diabet Med* 2005; 22: 803–7.
7. Lapolla A, *et al.* Outcome of pregnancy in type 1 diabetic patients treated with insulin lispro or regular insulin: an Italian experience. *Acta Diabetol* 2008; 45: 61–6.
8. Aydin Y, *et al.* Is insulin lispro safe in pregnant women: does it cause any adverse outcomes on infants or mothers? *Diabetes Res Clin Pract* 2008; 80: 444–8.
9. Durnwald CP, Landon MB. A comparison of lispro and regular insulin for the management of type 1 and type 2 diabetes in pregnancy. *J Matern Fetal Neonatal Med* 2008; 21: 309–13.
10. Pettitt DJ, *et al.* Comparison of an insulin analog, insulin aspart, and regular human insulin with no insulin in gestational diabetes mellitus. *Diabetes Care* 2003; 26: 183–6.
11. Hod M, *et al.* Fetal and perinatal outcomes in type 1 diabetes pregnancy: a randomized study comparing insulin aspart with human insulin in 322 subjects. *Am J Obstet Gynecol* 2008; 198: 186.e1–186.e7.
12. Pettitt DJ, *et al.* Efficacy, safety and lack of immunogenicity of insulin aspart compared with regular human insulin for women with gestational diabetes mellitus. *Diabet Med* 2007; 24: 1129–35.
13. Price N, *et al.* Use of insulin glargine during pregnancy: a case-control pilot study. *BJOG* 2007; 114: 453–7.
14. Di Cianni G, *et al.* Perinatal outcomes associated with the use of glargine during pregnancy. *Diabet Med* 2008; 25: 993–6.
15. Smith JG, *et al.* Insulin glargine versus neutral protamine Hagedorn insulin for treatment of diabetes in pregnancy. *Am J Perinatol* 2009; 26: 57–62.
16. Fang YMV, *et al.* Insulin glargine compared with neutral protamine Hagedorn insulin in the treatment of pregnant diabetics. *J Matern Fetal Neonatal Med* 2009; 22: 249–53.
17. Gallen IW, *et al.* Survey of glargine use in 115 pregnant women with type 1 diabetes. *Diabet Med* 2008; 25: 165–9.
18. Imbergamo MP, *et al.* Use of glargine in pregnant women with type 1 diabetes mellitus: a case-control study. *Clin Ther* 2008; 30: 1476–84.
19. Pollex E, *et al.* Safety of insulin glargine use in pregnancy: a systematic review and meta-analysis. *Ann Pharmacother* 2011; 45: 9–16.

Renal impairment. See under Infections, above.

Smoking. Smoking has been reported to decrease the absorption of insulin and dosage adjustment may be necessary, although glycaemic control does not seem to be significantly affected.[1]

1. Zevin S, Benowitz NL. Drug interactions with tobacco smoking: an update. *Clin Pharmacokinet* 1999; 36: 425–38.

Surgery. For a discussion of the management of diabetes mellitus during surgery, see p. 462.2. The use of insulin for the management of stress-induced hyperglycaemia is discussed under Critically Ill Patients, p. 481.2, and Inpatient Hyperglycaemia, p. 482.3.

Travelling. Advice for the diabetic patient when travelling, including adjustment of insulin dosage when crossing time zones, is available.[1-3] Since insulin solution or suspension must not be frozen, it should not be carried in the luggage hold of an aircraft.

1. Barry M, Bia F. Advice for the traveling diabetic. *JAMA* 1989; 261: 1719.
2. Sane T, *et al.* Adjustment of insulin doses of diabetic patients during long distance flights. *BMJ* 1990; 301: 421–2.
3. Dewey CM, Riley WJ. Have diabetes, will travel. *Postgrad Med* 1999; 105: 111–13, 117–18, 124–6.

Interactions

Many drugs have an effect on blood-glucose concentrations and may alter insulin requirements. Drugs with hypoglycaemic activity or which may decrease insulin requirements include ACE inhibitors, alcohol, anabolic steroids, aspirin, beta blockers (which may also mask the warning signs of hypoglycaemia), disopyramide, fenfluramine, fluoxetine, guanethidine, some MAOIs, mebendazole, high-dose sulfonamide antibacterials, some tetracyclines, and the tricyclic antidepressant amitriptyline.

On the other hand, increased requirements of insulin may possibly be seen with atypical antipsychotics, chlordiazepoxide, chlorpromazine, some calcium-channel blockers such as diltiazem or nifedipine, corticosteroids, diazoxide, lithium, thiazide diuretics, and thyroid hormones.

Both increased and decreased requirements may occur with cyclophosphamide, isoniazid, and oral contraceptives. Octreotide may increase or decrease insulin requirements, but most patients with type 1 diabetes are likely to require a reduction in insulin dose. Lanreotide may similarly alter blood-glucose concentrations, which should be checked to determine whether antidiabetic treatment needs to be adjusted.

Mealtime doses of insulin need to be reduced when pramlintide is added to therapy, to avoid hypoglycaemia (see Adverse Effects and Precautions of Pramlintide, p. 497.1).

ACE inhibitors. Although ACE inhibitors are favoured for use in diabetic patients with hypertension or evidence of incipient nephropathy or both, they may increase insulin sensitivity and thus decrease insulin requirements.[1,2] A study[3] of hospital admissions found that ACE inhibitors increased the risk of severe hypoglycaemia in patients receiving insulin. However, an analysis of pharmacovigilance data[4] and a case-control study[5] have both found no such increase in risk.

1. Ferriere M, *et al.* Captopril and insulin sensitivity. *Ann Intern Med* 1985; 102: 134–5.
2. McMurray J, Fraser DM. Captopril, enalapril, and blood glucose. *Lancet* 1986; I: 1035.
3. Morris AD, *et al.* ACE inhibitor use is associated with hospitalization for severe hypoglycemia in patients with diabetes. *Diabetes Care* 1997; 20: 1363–7.
4. Moore N, *et al.* Reports of hypoglycaemia associated with the use of ACE inhibitors and other drugs: a case/non-case study in the French pharmacovigilance system database. *Br J Clin Pharmacol* 1997; 44: 513–8.
5. Thamer M, *et al.* Association between antihypertensive drug use and hypoglycemia: a case-control study of diabetic users of insulin or sulfonylureas. *Clin Ther* 1999; 21: 1387–1400.

Alcohol. Severe hypoglycaemic episodes have been reported in type 1 diabetics after heavy drinking episodes.[1,2] Alcohol inhibits gluconeogenesis, and its effects are therefore likely to be greatest if taken without food however, it seems to be generally agreed that diabetics need not abstain from a moderate alcohol intake with meals.

1. Arky RA, *et al.* Irreversible hypoglycemia. *JAMA* 1968; 206: 575–8.
2. Potter J, *et al.* Insulin-induced hypoglycaemia in an accident and emergency department: the tip of an iceberg. *BMJ* 1982; 285: 1180–2.

Aspirin. Aspirin produces a modest decrease in blood-glucose concentrations but a significant interaction at conventional analgesic doses appears to be unlikely. A study in children with type 1 diabetes found an average 15% decrease in blood glucose values following treatment with aspirin 1.2 or 2.4 g daily for 3 days, but there were no significant changes in insulin requirements.[1] However, high doses of aspirin (3.5 to 7.5 g daily) can reduce or even replace the insulin dose required.[2] Other salicylates might be expected to have similar properties.

1. Kaye R, *et al.* Antipyretics in patients with juvenile diabetes mellitus. *Am J Dis Child* 1966; 112: 52–5.
2. Reid J, Lightbody TD. The insulin equivalence of salicylate. *BMJ* 1959; 1: 897.

Beta blockers. There are a few reports of severe hypoglycaemia in patients, including insulin-treated diabetics, who were given *propranolol* or *pindolol*;[1-3] there is also a report of an interaction with *timolol* given as eye drops.[4] Some evidence exists of an interaction with *metoprolol*,[5] but little evidence for some of the more selective beta blockers. Because of the effects of beta blockers on the sympathetic nervous system the usual premonitory signs of hypoglycaemia may not occur, allowing a severe episode to develop before the patient is aware and able to counter it.

1. Kotler MN, *et al.* Hypoglycaemia precipitated by propranolol. *Lancet* 1966; II: 1389–90.
2. McMurtry RJ. Propranolol, hypoglycemia, and hypertensive crisis. *Ann Intern Med* 1974; 80: 669–70.
3. Samii K, *et al.* Severe hypoglycaemia due to beta-blocking drugs in haemodialysis patients. *Lancet* 1976; i: 545–6.
4. Angelo-Nielsen K. Timolol topically and diabetes mellitus. *JAMA* 1980; 244: 2263.
5. Newman RJ. Comparison of propranolol, metoprolol, and acebutolol on insulin-induced hypoglycaemia. *BMJ* 1976; 2: 447–9.

Calcium-channel blockers. Diabetes worsened in an insulin-treated diabetic when given *diltiazem*.[1] The resultant intractable hyperglycaemia improved when the drug was withdrawn, and recurred, although at a more manageable level, when diltiazem was restarted at a lower dose. There are also reports of a diabetogenic effect of *nifedipine*.[2,3] However, reports of significant disturbances of metabolic control appear to be uncommon.

1. Pershadsingh HA, *et al.* Association of diltiazem therapy with increased insulin resistance in a patient with type I diabetes mellitus. *JAMA* 1987; 257: 930–1.
2. Bharnagar SK, *et al.* Diabetogenic effects of nifedipine. *BMJ* 1984; 289: 19.
3. Heyman SN, *et al.* Diabetogenic effect of nifedipine. *DICP Ann Pharmacother* 1989; 23: 236–7.

Interferons. Markedly increased insulin requirements developed in a previously well controlled diabetic after treatment with *interferon alfa 2a*.[1] Insulin requirements rapidly fell once interferon therapy was stopped.

1. Campbell S, *et al.* Rapidly reversible increase in insulin requirement with interferon. *BMJ* 1996; 313: 92.

Oral contraceptives. Both increases and decreases (mainly the former) in insulin requirements have been reported in insulin-dependent diabetics given various oral contraceptives.[1] However, it appears that in most cases the effects of a hormonal contraceptive on diabetic control are modest or insignificant: limited data suggest that progestogen-only and combined oral contraceptives in general have little effect.[2,3]

1. Zeller WJ, *et al.* Verträglichkeit von hormonalen Ovulationskemmern bei Diabetikerinnen. *Arzneimittelforschung* 1974; 24: 351–7.
2. Rådberg T, *et al.* Oral contraception in diabetic women: diabetes control, serum and high density lipoprotein lipids during low-dose progestogen, combined oestrogen/progestogen and non-hormonal contraception. *Acta Endocrinol (Copenh)* 1981; 98: 246–51.
3. Lunt H, Brown LJ. Self-reported changes in capillary glucose and insulin requirements during the menstrual cycle. *Diabet Med* 1996; 13: 525–30.

Pharmacokinetics

Insulin has no hypoglycaemic effect when given orally since it is inactivated in the gastrointestinal tract.

It is fairly rapidly absorbed from subcutaneous tissue on injection and although the half-life of unmodified insulin in blood is very short (being only a matter of minutes), the duration of action of most preparations is considerably longer because of their formulation (for further details see Uses and Administration, p. 476.3). The rate of absorption from different anatomical sites depends on local blood flow, with absorption from the abdomen being faster than that from the arm, and that from the arm faster than from buttock or thigh. Absorption may also be increased by exercise. The absorption of insulin after intramuscular injection is more rapid than that after subcutaneous doses. Human insulin may be absorbed slightly faster from subcutaneous tissue than porcine or bovine insulin.

Insulin is rapidly metabolised, mainly in the liver but also in the kidneys and muscle tissue. In the kidneys it is reabsorbed in the proximal tubule and either returned to venous blood or metabolised, with only a small amount excreted unchanged in the urine.

For discussion of factors which may affect the absorption of insulin, see under Precautions, Accelerated Absorption, p. 485.2, and Uses, Administration Routes, p. 479.2.

Resistance to Insulin

The term insulin resistance has traditionally been used to describe a state in which diabetic patients have considerably increased insulin requirements. It is now used in a much wider sense, and is for instance also applied to patients in whom a subnormal biological response to insulin can be shown, although many of these patients do not apparently present difficulties in their clinical management. Insulin resistance is found particularly in obese patients; resistance to endogenous insulin is thought to be linked to the development of type 2 diabetes in such patients. Insulin resistance is frequently associated with lipid disorders, hypertension, and ischaemic heart disease, a complex sometimes described as the metabolic syndrome. In women, it may also be linked to polycystic ovary syndrome.

Insulin resistance of the type manifested by greatly increased insulin requirements may be due to factors including antibody formation and inadequate absorption of insulin from subcutaneous sites. A few patients with severe insulin resistance have responded to insulin lispro (see Insulin Analogues under Uses, p. 480.1).

Mecasermin (insulin-like growth factor I) has been seen to improve insulin sensitivity in insulin resistance (see p. 1932.3).

References.

1. Moller DE, Flier JS. Insulin resistance—mechanisms, syndromes, and implications. *N Engl J Med* 1991; 325: 938–48.
2. Eckel RH. Insulin resistance: an adaptation for weight maintenance. *Lancet* 1992; 340: 1452–3.
3. Clausen JO, *et al.* Insulin resistance: interactions between obesity and a common variant of insulin receptor substrate-1. *Lancet* 1995; 346: 397–402.
4. Davidson MB. Clinical implications of insulin resistance syndromes. *Am J Med* 1995; 99: 420–6.
5. Krentz AJ. Insulin resistance. *BMJ* 1996; 313: 1385–9. Correction. *ibid.* 1997; 314: 134.
6. Cochran E, *et al.* The use of U-500 in patients with extreme insulin resistance. *Diabetes Care* 2005; 28: 1240–4. Correction. *ibid.* 2007; 30: 1035.
7. Kurtz TW. New treatment strategies for patients with hypertension and insulin resistance. *Am J Med* 2006; 119 (suppl 1): S24–S30.
8. Ballani P, *et al.* Clinical experience with U-500 regular insulin in obese, markedly insulin-resistant type 2 diabetic patients. *Diabetes Care* 2006; 29: 2504–5. Correction. *ibid.* 2007; 30: 455.
9. Lane WS, *et al.* High-dose insulin therapy: is it time for U-500 insulin? *Endocr Pract* 2009; 15: 71–9.
10. Davidson MB, *et al.* U-500 regular insulin: clinical experience and pharmacokinetics in obese, severely insulin-resistant type 2 diabetic patients. *Diabetes Care* 2010; 33: 281–3.
11. Samuel VT, *et al.* Lipid-induced insulin resistance: unravelling the mechanism. *Lancet* 2010; 375: 2267–77.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Actrapid HM; Apidra; Betalin Lenta†; Betalin Mix; Betalin NPH†; Betalin; Betasint; Biohulin C; Biohulin N; Densulin; Humalog Mix 25 and 50; Humalog; Humulin 70/30; Humulin NPH; Humulin R; Insulatard HM; Insuman N; Insuman R; Lantus; Levemir; Mixtard 30 HM†; Novolin N; Novolin R; NovoMix 30; NovoRapid; ***Austral.***: Actrapid; Apidra; Humalog Mix 25 and 50; Humalog; Humulin 30/70; Humulin NPH; Humulin R; Hypurin Isophane; Hypurin Neutral; Lantus; Levemir; Mixtard 30/70, 50/50; NovoMix 30; NovoRapid; Protaphane; ***Austria***: Actrapid; Apidra; Humalog Mix 25 and 50; Humalog; Huminsulin Basal; Huminsulin Normal; Huminsulin Profil III; Insulatard; Insuman Basal; Insuman Comb 15, 25, and 50; Insuman Infusat; Insuman Rapid; Lantus; Levemir; Mixtard 30 and 50; NovoMix 30 or 70; NovoRapid; ***Belg.***: Actrapid; Apidra; Humalog Mix 25 and 50; Humalog; Humuline 30/70; Humuline NPH; Humuline Regular; Insulatard; Insuman Basal; Insuman Rapid; Lantus; Levemir; Mixtard 30; NovoMix 30, 50, 70; NovoRapid; ***Braz.***: Apidra; Biohulin NPH†; Biohulin Regular†; Exubera†; Humalog Mix 25; Humalog; Humulin 70/30; Humulin Lenta; Humulin NPH; Humulin Regular; Insuman Comb 85N/15R and 75N/25R; Insuman N; Insuman R; Insuneo N; Lantus; Levemir; Novolin 70/30; Novolin N; Novolin R; NovoMix; NovoRapid; ***Canad.***: Apidra; Humalog Mix 25 and 50; Humalog; Humulin 30/70; Humulin L†; Humulin N; Humulin R; Hypurin NPH; Hypurin Regular; Iletin II Pork Lente†; Iletin II Pork NPH†; Iletin II Pork Regular†; *Lantus; Levemir; Novolin 30/70, 40/60, 50/50;* Novolin NPH; Novolin Toronto; NovoMix 30; NovoRapid; ***Chile***: Actrapid HM; Apidra; Bioinsugen-30/70; Bioinsugen-N; Bioinsugen-R; Humalog Mix 25; Humalog; Humulin 70/30; Humulin L; Humulin N; Humulin R; Insulatard HM; Insuman N; Insuman R; Lantus; Levemir; Mixtard 30 HM; NovoMix 30; NovoRapid; Wosulin 30/70†; Wosulin-N†; Wosulin-R†; ***China***: Apidra (艾倍得); Chang Xiu Lin (长秀霖); GanShuLin N (甘舒霖N); GanShuLin R (甘舒霖R); Humalog (优泌乐); Humalog Mix 25 and 50; Humulin 70/30 (优泌林 70/30); Humulin NPH (优泌林 NPH); Humulin R (优泌林 R); Lantus (来得时); Levemir (诺和平); Novolin 30R, 50R (诺和灵); Novolin N (诺和灵 N); Novolin R (诺和灵 R); NovoMix 30 (诺和锐30); NovoRapid (诺和锐); SciLin M30 (重和林M30); SciLin N (重和林N); SciLin R (重和林R); Su Bi Lin (苏泌啉); Su Mi Lin En (苏泌啉恩); Uslin (优思灵); Wan Bang Lin (万邦林); Wan Bang Lin N (万邦林N); Wan Bang Lin R (万邦林R); Wan Su Lin (万苏林); ***Cz.***: Actraphane 30, 40, 50; Actrapid; Apidra; Exubera†; Humalog Basal; Humalog Mix 25 and 50; Humalog NPL†; Humalog; Humulin M3; Humulin N; Humulin R; Insulatard; Insuman Basal; Insuman Comb 15, 25, 30, 50; Insuman Infusat; Insuman Rapid; Lantus; Levemir; Liprolog Basal; Liprolog Mix 25 and 50; Liprolog; Mixtard 30, 40, and 50; NovoMix 30, 50, 70; NovoRapid; Optisulin; Protaphane; Velosulin†; ***Denm.***: Actrapid; Apidra; Humalog Mix 25 and 50; Humalog; *Humulin NPH; Humulin Regular; Insulatard;* Insuman Basal†; Insuman Rapid; Lantus; Levemir; Mixtard 30; NovoMix 30, 50, 70; NovoRapid; Tresiba; ***Fin.***: Actrapid; Humalog Mix 25 and 50; Humalog; Humulin NPH; Humulin Regular; Insuman Basal; Insuman Comb 25; Insuman Infusat; Insuman Rapid; Lantus; Levemir; NovoMix 30; NovoRapid; Protaphane; ***Fr.***: Actrapid; Apidra; Humalog Mix 25 and 50; Humalog; Insulatard; Insuman Basal; Insuman Comb 15, 25, and 50; Insuman Infusat; Insuman Rapid; Insuplant†; Lantus; Levemir; Mixtard 30; NovoMix 30, 50, 70; NovoRapid; Umuline NPH; Umuline Profil 30; Umuline Rapide; ***Ger.***: Actraphane 30, 50; Actrapid; Apidra; Berlinsulin H 30/70; Berlinsulin H Basal; Berlinsulin H Normal; Humalog Mix 25 and 50; Humalog; Huminsulin Basal; Huminsulin Normal; Huminsulin Profil III; Insulin Basal; Insulin Comb 30/70; Insulin Rapid; Insuman Basal; Insuman Comb 15, 25, and 50; Insuman Infusat; Insuman Rapid; Lantus; Levemir; Liprolog Mix 25 and 50; Liprolog; NovoMix 30; NovoRapid; Protaphane; ***Gr.***: Actraphane 30; Actrapid; Apidra; Exubera; Humalog Basal; Humalog Mix 25 and 50; Humalog NPL; Humalog; Humulin L; Humulin M1, M2, M3, M4, M5; Humulin NPH; Humulin Regular; Humulin UL; Insuman Basal; Insuman Comb 15, 25, and 50; Insuman Infusat; Insuman Rapid; Lantus; Levemir; Mixtard 10, 20, 30, 40, and 50; Monotard; NovoMix 30; NovoRapid; Protaphane; Ultratard; Velosulin; ***Hong Kong***: Actrapid HM; Humalog; Humulin 70/30; Humulin L†; Humulin N; Humulin R; Hypurin Isophane†; Hypurin Lente†; Hypurin Neutral†; Hypurin Protamine Zinc†; Lantus; Levemir; Mixtard 30 HM; Monotard HM†; NovoMix 30; NovoRapid; Protaphane HM; SciLin M30; SciLin N; SciLin R; Ultratard HM†; ***Hung.***: Actrapid; Apidra; Humalog Mix25 and Mix50; Humalog; Humulin M3; Humulin N; Humulin R; Insulatard; Insuman Basal; Insuman Comb 15, 25, and 50; Insuman Rapid; Lantus; Levemir; Mixtard 10, 20, 30, 40, and 50; NovoMix 30; NovoRapid; ***India***: Actrapid HM; Actrapid†; Apidra; Bovine Fastact; Bovine Longact; Bovine-Mixact; FlexPen; Humalog Mix 25 and 50; Humalog; Human Fastact; Human Insunorm; Human Longact; Human Monotard; Human Prodica; Human Rapidica; Human Rapimix; Human Zinulin; Human-Mixact; Humanext N; Humapen; Huminsulin L; Huminsulin N; Huminsulin R; Huminsulin 30/70 and 50/50; Humstard; Iletin N; Iletin R; Insucare-N; Insugen-N; Insugen-R; Insugen 30/70 and 50/50; Insulatard HM; Insuman Basal; Insuman Rapid; Insuman 25/75 and 50/50; Lantus; Lentard; Lentisulin-CPI; Lentisulin-HPI-400; Lentisulin-HPI; Levemir; Lupisulin-N; Mixtard 30 and 50; Mixulin; NovoMix 30; NovoRapid; Rapidica; Rapimix; Wosulin N; Wosulin R; Wosulin 30/70 and 50/50; Zinulin; ***Indon.***: Actrapid; Apidra; Humalog Mix 25; Humalog; Humulin 30/70; Humulin N; Humulin R; Insulatard HM; Lantus; Levemir; Mixtard 30; Monotard HM; NovoMix 30; NovoRapid; Sansulin; ***Irl.***: Actraphane; Actrapid; Apidra; Humalog Mix 25 and 50; Humalog NPL; Humalog; Humulin I; Humulin M3; Humulin S; Insulatard; Insuman Basal; Insuman Comb 15, 25, and 50; Insuman Infusat; Insuman Rapid; Lantus; Levemir; Liprolog Mix 25 and 50; Liprolog; Mixtard 10, 20, 30, 40, and 50; NovoMix 30, 50, 70; NovoRapid; Optisulin; Protaphane; ***Israel***: Actrapid; Apidra; Humalog Mix 25 and 50; Humalog NPL; Humalog; Humulin 70/30; Humulin N; Humulin R; Insulatard; Lantus; Levemir; Mixtard HM 30, 40, and 50; NovoMix 30, 50, 70; NovoRapid; ***Ital.***: Actraphane 30, 50; Actrapid; Apidra; Humalog Mix 25 and 50; Humalog NPL; Humalog; Humulin 30/70; Humulin I; Humulin R; Insuman Rapid; Lantus; Levemir; NovoMix 30, 50, 70; NovoRapid; Protaphane; ***Jpn***: Humacart 3/7†; InnoLet 10R, 20R, 30R, 40R, and 50R; InnoLet N; InnoLet R; Levemir; Novolin 30R, 40R, and 50R; Novolin N; Novolin R; NovoRapid 30 Mix; NovoRapid; Penfill N†; Penfill R†; Penfill 10R, 20R, 30R, 40R, 50R†; Tresiba; Velosulin†; ***Malaysia***: Actrapid HM; Humalog Mix 25; Humalog; Humulin 30/70; Humulin N; Humulin R; Insulatard; Lantus; Levemir; Mixtard 30 HM; NovoMix; NovoRapid; ***Mex.***: Bonglixan; Glinux 70/30; Glinux-N; Humalog Mix 25; Humalog; Humanilusin; Humulin 70/30; Humulin L†; Humulin N; Humulin R; Insulex 70/30; Insulex N; Insulex R; Insuman 100N; Insuman R; Insuman 15R/85N, 25R/75N, 50R/50N; Lantus; Levemir; Novolin 30/70; Novolin N; Novolin R; NovoMix 30; NovoRapid; Prodiabin-N; Shorant; ***Neth.***: Actraphane 10, 20, 30, 40, 50; Actrapid; Apidra; Exubera†; Humalog Mix 25 and 50; Humalog NPL; Humalog; Humuline 30/70; Humuline NPH; Humuline Regular; Insulatard; Insuman Basal; Insuman Comb 15, 25, 30, and 50; Insuman Infusat; Insuman Rapid; Lantus; Levemir; Liprolog Mix 25 and 50; Liprolog; Mixtard 10, 20, 30, 40, and 50; NovoMix 30, 50, 70; NovoRapid; Optisulin; Protaphane; Ryzodeg; Tresiba; Velosulin†; ***Norw.***: Actrapid; Apidra; Humalog Mix 25; Humalog; Humulin NPH; Insulatard; Insuman Basal; Insuman Comb 25†; Insuman Infusat†; Insuman Rapid; Lantus; Levemir; NovoMix 30; NovoRapid; ***NZ***: Actrapid; Apidra; Humalog Mix 25 and 50; Humalog; Humulin 70/30; Humulin NPH; Humulin R; Insulatard MC; Lantus; Levemir; Mixtard 30; Monotard; NovoMix 30; NovoRapid; PenMix 10, 20, 30, 40, or 50; Protaphane; Ultratard; Velosulin HM; Velosulin MC; ***Philipp.***: Actrapid HM; Apidra; Biosulidd L; Humalog; Humulin 70/30; Humulin N (NPH); Humulin R (Regular); Insuget 70/30: Insuget-N; Insuget-R; Insulatard HM; Lantus; Levemir; Mixtard 30 HM; NovoMix 30; NovoRapid; Ransulin 70/30; Ransulin-N; Ransulin-R; *SciLin M30; SciLin N;* SciLin R; Wosulin 30/70; Wosulin-N; Wosulin-R; ***Pol.***: Actraphane 10, 20, 30, 40, 50; Actrapid; Apidra; Gensulin N; Gensulin R; Gensulin M30, M40, or M50; Humalog Mix 25 and 50; Humalog NPL; Humalog; Humulin M3 (30/70); Humulin N; Humulin R; Insulatard; Insulinum Lente; Insulinum Maxirapid; Insulinum Semilente†; Insulinum Ultralente†; Insuman Basal; Insuman Comb 15, 25, 50; Insuman Infusat; Insuman Rapid; Lantus; Levemir; Liprolog; Mixtard 10, 20, 30, 40, and 50; NovoMix 30, 50, or 70; NovoRapid; Optisulin; Polhumin Mix -2, -3, -4, -5; Polhumin N; Polhumin R; Protaphane; Ultratard HM†; ***Port.***: Actraphane 10, 20, 30, 40, 50; Actrapid; Apidra; Humalog Basal; Humalog Mix 25 and 50; Humalog; Humulin M3; Humulin NPH; Humulin Regular; Insulatard; Insuman Basal; Insuman Comb 15, 25, 30, 50; Insuman Infusat; Insuman Rapid; Lantus; Levemir; Liprolog Basal; Liprolog Mix 25 and 50; Liprolog; Mixtard 10, 20, 30, 40, and

50 HM; NovoMix 30, 50, 70; NovoRapid; Optisulin; Protaphane; Velosulin†; ***Rus.***: Actrapid HM (Актрапид НМ); Actrapid MC (Актрапид МС)†; Apidra (Апидра); Biosulin N (Биосулин Н); Biosulin R (Биосулин Р); Humalog (Хумалог); Humalog Mix 25 (Хумалог Микс 25); Humodar B (Хумодар Б); Humodar K25-100 (Хумодар К25-100); Humulin M3 (Хумулин М3); Humulin NPH (Хумулин НПХ); Humulin Regular (Хумулин Регуляр); Insulidd L (Инсулидд Л)†; Insulin Lt (Инсулин Лт)†; Insulin Maxirapid (Инсулин Максирапид)†; Insuman Basal (Инсуман Базал); Insuman Comb 25 (Инсуман Комб 25); Insuman Rapid (Инсуман Рапид); Insuran NPH (Инсуран НПХ); Insuran R (Инсуран Р); Lantus (Лантус); Levemir (Левемир); Levulin L (Левулин Л)†; Mixtard 30 HM (Микстард 30 НМ); Monosuinsulin MK (Моносуинсулин МК); Monotard MC (Монотард МС)†; NovoMix 30, 50, 70 (НовоМикс 30); NovoRapid (Новорапид); Protaphane HM (Протафан НМ); Rinsulin NPH (Ринсулин НПХ); Rinsulin R (Ринсулин Р); Rosinsuline R (Росинсулин Р); Rosinsuline S (Росинсулин С); ***S.Afr.***: Actraphane HM; Actrapid HM; Apidra; Biosulin 30/70; Biosulin L; Biosulin N; Biosulin R; Humalog Mix 25 and 50; Humalog; Humulin 30/70; Humulin N; Humulin R; Insuman Comb; Lantus; Levemir; NovoMix 30; NovoRapid; Protaphane HM; ***Singapore***: Actrapid; Apidra; Humalog Mix 25; Humalog; Humulin 30/70; Humulin N; Humulin R; Insulatard; Lantus; Levemir; Mixtard 30 and 50; NovoMix 30; NovoRapid; Ultratard HM; ***Spain***: Actrapid; Apidra; Humalog Mix 25 and 50; Humalog NPL†; Humalog; Humulina 30:70; Humulina NPH; Humulina Regular; Insulatard; Insuman Basal†; Insuman Comb 15, 25, 30, 50†; Insuman Infusat†; Insuman Rapid†; Lantus; Levemir; Mixtard 30; NovoMix 30, 50, 70; NovoRapid; ***Swed.***: Actrapid; Apidra; Humalog Mix 25 and 50; Humalog; Humulin Mix 30/70†; Humulin NPH; Humulin Regular; Insulatard; Insuman Basal; Insuman Comb 25; Insuman Infusat; Insuman Rapid; Lantus; Levemir; NovoMix 30; NovoRapid; ***Switz.***: Actrapid HM; Apidra; Humalog; Huminsulin Basal (NPH); Huminsulin Normal†; Huminsulin Profil III†; Hypurin 30/70 Mix; Hypurin Isophane;, Hypurin Neutral; Insulatard HM; Insuman Basal; Insuman Comb 25; Insuman Infusat; Insuman Rapid; Lantus; Levemir; Mixtard HM 30; NovoMix 30; NovoRapid; Tresiba; ***Thai.***: Actrapid HM; Apidra; Basalin; Gensulin N; Gensulin R; Gensulin M30, M50; Humalog Mix 25; Humalog; Humulin 70/30; Humulin N; Humulin R; Insugen-30/70; Insugen-N; Insugen-R; Insulatard; Lantus; Levemir; Mixtard HM; NovoMix 30; NovoRapid; ***Turk.***: Actrapid; Apidra; Humalog Mix 25 and 50; Humalog; Humulin M 70/30 and 80/20; Humulin N; Humulin R; Insulatard; Lantus; Levemir; Mixtard 20, 30, and 40; NovoMix 30, 50, 70; NovoRapid; Orgasulin Mix 30/70†; Orgasulin NPH; ***UAE***: Jusline 30/70; Jusline N; Jusline R; ***UK***: Actrapid; Apidra; Humalog Mix 25 and 50; Humalog; Humulin I; Humulin M3; Humulin S; Hypurin 30/70; Hypurin Isophane; Hypurin Lente; Hypurin Neutral; Hypurin Protamine Zinc; Insulatard; Insuman Basal; Insuman Comb 15, 25, and 50; Insuman Rapid; Lantus; Levemir; Mixtard 30†; NovoMix 30; NovoRapid; Tresiba; ***Ukr.***: Apidra (Эпайдра)†; Farmasulin H (Фармасулин Н); Farmasulin N 30/70 (Фармасулин Н 30/70); Farmasulin N NP (Фармасулин Н NP); Humodar B100 (Хумодар Б100Р); Humodar C25 100 (Хумодар К25 100Р); Humodar R100 (Хумодар Р100Р); Lantus (Лантус); Levemir (Левемир); NovoMix 30 (Новомикс 30); NovoRapid (Новорапид); Wosulin 30/70 (Восулин)†; Wosulin-N (Восулин-Н)†; Wosulin-R (Восулин-Н-Р)†; ***USA***: Apidra; Humalog Mix 75/25 and 50/50; Humalog; Humulin 70/30; Humulin N; Humulin R; Lantus; Lente Iletin II†; Lente; Levemir; Novolin 70/30; Novolin N; Novolin R; NovoLog; Regular Iletin II†; Ultralente; ***Venez.***: Humalog Mix 25; Humalog; Humulin 70/30; Humulin N; Humulin R; Insuman N; Insuman R; Lantus.

Pharmacopoeial Preparations

BP 2014: Insulin Aspart Injection; Insulin Lispro Injection; Protamine Zinc Insulin Injection;

Ph. Eur.: Biphasic Insulin Injection; Biphasic Isophane Insulin Injection; Insulin Zinc Injectable Suspension (Amorphous); Insulin Zinc Injectable Suspension (Crystalline); Insulin Zinc Injectable Suspension; Isophane Insulin Injection; Soluble Insulin Injection;

USP 36: Extended Insulin Human Zinc Suspension; Extended Insulin Zinc Suspension; Human Insulin Isophane Suspension and Human Insulin Injection; Insulin Human Injection; Insulin Human Zinc Suspension; Insulin Injection; Insulin Lispro Injection; Insulin Zinc Suspension; Isophane Insulin Human Suspension; Isophane Insulin Suspension; Prompt Insulin Zinc Suspension.

Linagliptin *(USAN, rINN)*

BI-1356; BI-1356-BS; Linagliptina; Linagliptine; Linagliptinum; Линаглиптин.

8-[(3*R*)-3-Aminopiperidin-1-yl]-7-(but-2-yn-1-yl)-3-methyl-1-[(4-methylquinazolin-2-yl)methyl]-3,7-dihydro-1*H*-purine-2,6-dione.

$C_{25}H_{28}N_8O_2$=472.6

CAS — 668270-12-0.

ATC — A10BH05.

ATC Vet — QA10BH05.

UNII — 3X29ZE4R2.

NOTE. The name Ondero has been used as a trade mark for linagliptin.

Uses and Administration

Like sitagliptin (p. 502.1), linagliptin is an inhibitor of dipeptidylpeptidase-4 and is used in the treatment of type 2 diabetes mellitus (p. 459.1). The usual oral dose of linagliptin is 5 mg once daily, with or without food. When given with metformin, linagliptin may be given in 2 divided doses.The dose of sulfonylurea or insulin may need to be lowered when used with linagliptin.

References.

1. Baetta R, Corsini A. Pharmacology of dipeptidyl peptidase-4 inhibitors: similarities and differences. *Drugs* 2011; 71: 1441–67.
2. Neumiller JJ. Pharmacology, efficacy, and safety of linagliptin for the treatment of type 2 diabetes mellitus. *Ann Pharmacother* 2012; 46: 358–67.
3. Deeks ED. Linagliptin: a review of its use in the management of type 2 diabetes mellitus. *Drugs* 2012; 72: 1793–1824.
4. Forst T, Pfützner A. Linagliptin, a dipeptidyl peptidase-4 inhibitor with a unique pharmacological profile, and efficacy in a broad range of patients with type 2 diabetes. *Expert Opin Pharmacother* 2012; 13: 101–10.
5. Neumiller JJ, Setter SM. Review of linagliptin for the treatment of type 2 diabetes mellitus. *Clin Ther* 2012; 34: 993–1005.
6. Brown DX, *et al.* Linagliptin as add-on therapy for type 2 diabetes - an overview. *Drugs Today* 2012; 48: 645–54.

Adverse Effects, Treatment, and Precautions

As for Sitagliptin Phosphate, p. 502.1.

Interactions

The efficacy of linagliptin may be affected by other drugs that have an independent effect on blood glucose. For more details and examples of drugs that can increase or decrease blood-glucose concentrations, see Interactions under Sulfonylureas, p. 504.3.

Linagliptin is a P-glycoprotein substrate; strong inducers of P-glycoprotein, such as rifampicin, may decrease plasma concentrations of linagliptin and reduce its efficacy.

Pharmacokinetics

Linagliptin has nonlinear pharmacokinetics because of high-affinity saturable binding to dipeptidylpeptidase-4 (DPP-4) in plasma and tissue.It is rapidly absorbed from the gastrointestinal tract, and peak plasma concentrations occur within about 1.5 hours. The absolute bioavailability of linagliptin is about 30%. The mean apparent volume of distribution after an intravenous dose is about 1110 litres indicating that linagliptin is extensively distributed to the tissues. Plasma protein binding of linagliptin is concentration-dependent; at low concentrations it is 99% bound, but at high concentrations when DPP-4 is fully saturated, 70 to 80% is bound to other plasma proteins and 20 to 30% is unbound.

After multiple oral doses, linagliptin has an accumulation half-life of about 12 hours. Linagliptin is not extensively metabolised. It undergoes biphasic (or possibly triphasic) elimination and at steady state has a terminal half-life of more than 100 hours. About 80% is eliminated in the faeces and 5% in the urine.

References.

1. Scheen AJ. Linagliptin for the treatment of type 2 diabetes (pharmacokinetic evaluation). *Expert Opin Drug Metab Toxicol* 2011; 7: 1561–76.
2. Graefe-Mody U, *et al.* Clinical pharmacokinetics and pharmacodynamics of linagliptin. *Clin Pharmacokinet* 2012; 51: 411–27.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Trajenta; ***Belg.***: Trajenta; ***Canad.***: Trajenta; ***Denm.***: Trajenta; ***Fr.***: Trajenta; ***Irl.***: Trajenta; ***Jpn***: Trazenta; ***Neth.***: Trajenta; ***Norw.***: Trajenta; ***Singapore***: Trajenta; ***Spain***: Trajenta; ***UK***: Trajenta; ***USA***: Tradjenta.

Multi-ingredient Preparations. ***Denm.***: Jentadueto; ***Neth.***: Jentadueto; ***Spain***: Jentadueto; ***Switz.***: Jentadueto; ***UK***: Jentadueto; ***USA***: Jentadueto.

Liraglutide *(BAN, USAN, rINN)*

Liraglutida; Liraglutidum; NN-2211; NNC-901170; Лираглутид.

N^{26}-(Hexadecanoyl-L-γ-glutamyl)-(34-L-arginine)GLP-1-(7-37)-peptide.

$C_{172}H_{265}N_{43}O_{51}$=3751.3

CAS — 204656-20-2.

ATC — A10BX07.

ATC Vet — QA10BX07.

UNII — 839I73S42A.

Uses and Administration

Liraglutide is an analogue of the incretin hormone, glucagon-like peptide 1 (GLP-1), and by acting as an agonist at the glucagon-like peptide 1 receptor has actions similar to those of exenatide (p. 471.1). Liraglutide is used as adjunctive therapy in type 2 diabetes mellitus (p. 459.1) in patients who do not have adequate glycaemic control with metformin, a sulfonylurea, or with dual therapy of metformin plus either a sulfonylurea or a thiazolidinedione. It is given once daily by subcutaneous injection, which may be independent of meal times but should preferably be at the same time each day. A low starting dose of 600 micrograms daily is used to reduce gastrointestinal adverse effects, and is not effective for glycaemic control. After at least 1 week, the dose is increased to 1.2 mg daily. Some patients may benefit from a further increase to 1.8 mg once daily, but the interval between dose increases should be at least 1 week.

References.

1. Croom KF, McCormack PL. Liraglutide: a review of its use in type 2 diabetes mellitus. *Drugs* 2009; 69: 1985–2004.
2. Joffe D. Liraglutide: a once-daily human glucagon-like peptide-1 analogue for type 2 diabetes mellitus. *Am J Health-Syst Pharm* 2010; 67: 1326–36.
3. NICE. Liraglutide for the treatment of type 2 diabetes mellitus: Technology Appraisal 203 (issued October 2010). Available at: http://www.nice.org.uk/nicemedia/live/13248/51259/51259.pdf (accessed 12/09/11)
4. Shyangdan DS, *et al.* Glucagon-like peptide analogues for type 2 diabetes mellitus: systematic review and meta-analysis. *BMC Endocr Disord* 2010; 10: 20. Available at: http://www.biomedcentral.com/1472-6823/10/20 (accessed 27/09/11)
5. Garber AJ. Long-acting glucagon-like peptide 1 receptor agonists: a review of their efficacy and tolerability. *Diabetes Care* 2011; 34 (suppl 2): S279–S284.
6. Pinelli NR, Hurren KM. Efficacy and safety of long-acting glucagon-like peptide-1 receptor agonists compared with exenatide twice daily and sitagliptin in type 2 diabetes mellitus: a systematic review and meta-analysis. *Ann Pharmacother* 2011; 45: 850–60.
7. Ryan GJ, *et al.* Review of the therapeutic uses of liraglutide. *Clin Ther* 2011; 33: 793–811.

Administration in renal impairment. No dose adjustment is considered necessary for liraglutide in patients with mild renal impairment (creatinine clearance 60 to 90 mL/min); however, it should be used with caution, if at all, in those with moderate or severe impairment due to limited data.

Obesity. Liraglutide is under investigation in the management of obesity[1,2] (p. 2315.1).

1. Astrup A, *et al.* Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. *Lancet* 2009; 374: 1606–16. Correction. *ibid.* 2010; 375: 984.
2. Astrup A, *et al.* Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. *Int J Obes (Lond)* 2011; doi: 10.1038/ijo.2011.158. Also available at: http://www.nature.com/ijo/journal/vaop/ncurrent/pdf/ijo2011158a.pdf (accessed 02/11/11)

Adverse Effects and Precautions

As for Exenatide, p. 471.2. Adverse thyroid effects have occurred with liraglutide treatment, particularly in patients with pre-existing thyroid disease; reports have included increased blood calcitonin, goitre, and thyroid neoplasms. Liraglutide is contra-indicated in patients with a history, or family history, of medullary thyroid cancer, and in patients with multiple endocrine neoplasia syndrome type 2.

Interactions

A reduction in the sulfonylurea dose may be required when liraglutide is added to therapy, because of an increased risk of hypoglycaemia with this combination. Doses of metformin and thiazolidinediones do not generally need adjustment when liraglutide is added. Liraglutide's effects on the gastrointestinal tract, such as a small delay in gastric emptying or diarrhoea, may affect the absorption of orally administered drugs.

Pharmacokinetics

Liraglutide is absorbed slowly after subcutaneous injection, reaching a maximum concentration after 8 to 12 hours. It has a bioavailability of about 55%, and is more than 98% bound to plasma proteins. Although a specific organ has not been identified as the major route for its removal, liraglutide is metabolised and has an elimination half-life of about 13 hours after a single subcutaneous dose.

References.

1. Meece J. Pharmacokinetics and pharmacodynamics of liraglutide, a long-acting, potent glucagon-like peptide-1 analog. *Pharmacotherapy* 2009; 29: 335–425.
2. Watson E, *et al.* Population pharmacokinetics of liraglutide, a once-daily human glucagon-like peptide-1 analog, in healthy volunteers and subjects with type 2 diabetes, and comparison to twice-daily exenatide. *J Clin Pharmacol* 2010; 50: 886–94.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Victoza; ***Austria***: Victoza; ***Belg.***: Victoza; ***Braz.***: Victoza; ***Canad.***: Victoza; ***China***: Victoza (诺和力); ***Cz.***: Victoza; ***Denm.***: Victoza; ***Fr.***: Victoza; ***Ger.***: Victoza; ***Gr.***: Victoza; ***Irl.***: Victoza; ***Israel***: Victoza; ***Jpn***: Victoza; ***Neth.***: Victoza; ***Norw.***: Victoza; ***Pol.***: Victoza; ***Port.***: Victoza; ***Rus.***: Victoza (Виктоза); ***Singapore***: Victoza; ***Spain***: Victoza; ***Swed.***: Victoza; ***Switz.***: Victoza; ***Thai.***: Victoza; ***UK***: Victoza; ***Ukr.***: Victoza (Виктоза); ***USA***: Victoza.

Lixisenatide *(rINN)*

AVE-0010; Lixisenatida; Lixisénatide; Lixisenatidum; ZP-10; Ликсисенатид.

Des-38-proline-exendine-4 (*Heloderma suspectum*)-(1-39)-peptidylpenta-Lysyl-L-lysinamide.

$C_{215}H_{347}N_{61}O_{65}S$=4858.6

CAS — 320367-13-3.

UNII — 74O62B801U.

Uses and Administration

Lixisenatide is an analogue of the incretin hormone, glucagon-like peptide 1 (GLP-1), and by acting as an agonist at the GLP-1 receptor has actions similar to those of exenatide (p. 471.1). It is used as adjunctive therapy in type 2 diabetes mellitus (p. 459.1) in patients who do not have adequate glycaemic control with oral antidiabetics or basal insulin. It is given once daily by subcutaneous injection, within the hour before the first meal of the day or the evening meal. If a dose is missed it should be injected within the hour before the next meal. A starting dose of 10 micrograms daily is used for 14 days; the maintenance dose of 20 micrograms daily is started on day 15. If lixisenatide is added to either a sulfonylurea or basal insulin, the dose of sulfonylurea or insulin may need to be adjusted to reduce the risk of hypoglycaemia. Lixisenatide should not be given with a combination of sulfonylurea and basal insulin.

For administration in renal impairment, see p. 491.1.

References.

1. Christensen M, *et al.* Lixisenatide for type 2 diabetes mellitus. *Expert Opin Invest Drugs* 2011; 20: 549–57.
2. Elkinson S, Keating GM. Lixisenatide: first global approval. *Drugs* 2013; 73: 383–91.
3. Rosenstock J, *et al.* Efficacy and safety of lixisenatide once daily versus exenatide twice daily in type 2 diabetes inadequately controlled on metformin: a 24-week, randomized, open-label, active-controlled study (GetGoal-X). *Diabetes Care* 2013;

Administration in renal impairment. No dose adjustment is considered necessary for lixisenatide in patients with mild renal impairment (creatinine clearance 50 to 80 mL/min); however, it should be used with caution in those with moderate impairment and is not recommended in those with severe impairment or end-stage renal disease due to lack of data.

Adverse Effects and Precautions

As for Exenatide, p. 471.2.

Interactions

As for Exenatide, p. 471.3.

Pharmacokinetics

Lixisenatide is absorbed rapidly after subcutaneous injection reaching a maximum concentration after about 1 to 3.5 hours; it is about 55% bound to plasma proteins. Lixisenatide is eliminated through glomerular filtration, followed by tubular reabsorption and subsequent metabolic degradation into smaller peptides and amino acids. It has a mean terminal half-life of about 3 hours after multiple-dose subcutaneous administration.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Lyxumia; *UK*: Lyxumia.

Metformin Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de metformina; LA-6023 (metformin or metformin hydrochloride); Metformilinihydrokloridi; Metformin Hidroklorür; Metformin hydrochlorid; Metformina, hidrocloruro de; Metformine, Chlorhydrate de; Metforminhidroklorid; Metforminhydrochlorid; Metforminhydroklorid; Metformini Hydrochloridum; Metformino hidrochloridas; Метформина Гидрохлорид.

1,1-Dimethylbiguanide hydrochloride.

$C_4H_{11}N_5$,HCl=165.6

CAS — 657-24-9 (metformin); 1115-70-4 (metformin hydrochloride).

ATC — A10BA02.

ATC Vet — QA10BA02.

UNII — 786Z46389E.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Metformin Hydrochloride). White or almost white crystals. Freely soluble in water; slightly soluble in alcohol; practically insoluble in acetone and in dichloromethane.

USP 36: (Metformin Hydrochloride). A white crystalline powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in acetone and in dichloromethane.

Uses and Administration

Metformin hydrochloride is a biguanide antidiabetic (p. 467.3). It is given orally in the treatment of type 2 diabetes mellitus (p. 491.3), and is the drug of first choice in overweight patients. Initial dosage is 500 mg two or three times daily or 850 mg once or twice daily with or after meals, gradually increased if necessary, at intervals of at least 1 week, to 2 to 3 g daily; doses of 3 g daily are associated with an increased incidence of gastrointestinal adverse effects. Gastrointestinal effects are also common on beginning therapy, and the *BNF* recommends starting therapy more gradually with 500 mg at breakfast for at least 1 week, then increasing to 500 mg twice daily with the morning and evening meals for at least 1 week, then 500 mg three times daily; the usual maximum is 2 g daily in divided doses.

A modified-release preparation is also available, which is given in an initial dose of 500 mg once daily and may be increased in increments of 500 mg, at intervals of at least 1 week, to a maximum of 2 g once daily with the evening meal. If glycaemic control is not adequate the dose may be divided to give 1 g twice daily with meals. If doses above 2 g daily are required, they should be given as the standard preparation.

For doses used in children and adolescents, see p. 491.2.

Metformin is also used as the chlorophenoxyacetate and as the embonate.

General references.

1. Dunn CJ, Peters DH. Metformin: a review of its pharmacological properties and therapeutic use in non-insulin-dependent diabetes mellitus. *Drugs* 1995; 49: 721–49.
2. Davidson MB, Peters AL. An overview of metformin in the treatment of type 2 diabetes mellitus. *Am J Med* 1997; 102: 99–110.
3. Klepser TB, Kelly MW. Metformin hydrochloride: an antihyperglycemic agent. *Am J Health-Syst Pharm* 1997; 54: 893–903. Correction. *ibid.*; 1335.
4. Kirpichnikov D, *et al.* Metformin: an update. *Ann Intern Med* 2002; 137: 25–33.
5. Hundal RS, Inzucchi SE. Metformin: new understandings, new uses. *Drugs* 2003; 63: 1879–94.
6. Goodarzi MO, Bryer-Ash M. Metformin revisited: re-evaluation of its properties and role in the pharmacopoeia of modern antidiabetic agents. *Diabetes Obes Metab* 2005; 7: 654–65.
7. Stumvoll M, *et al.* Metformin. *Endocr Res* 2007; 32: 39–57.
8. Scarpello JHB, Howlett HCS. Metformin therapy and clinical uses. *Diab Vasc Dis Res* 2008; 5: 157–67.

Action. The mechanisms by which metformin increases insulin sensitivity and glucose uptake into cells, and inhibits hepatic gluconeogenesis, are unclear. One reviewer[1] considered that metformin acts mainly at the level of the cell membrane. In insulin-resistant cells it is thought to correct defects in insulin signaling, which then normalises glucose transport and glycogen synthesis. In the presence of hyperglycaemia, metformin is also reported to improve the activity of membrane-inserted glucose transporters. There is also some evidence that metformin can inhibit the formation of advanced glycation end-products, which are associated with the development of diabetic complications.[2]

1. Wiernsperger NF. Membrane physiology as a basis for the cellular effects of metformin in insulin resistance and diabetes. *Diabetes Metab* 1999; 25: 110–27.
2. Beisswenger P, Ruggiero-Lopez D. Metformin inhibition of glycation processes. *Diabetes Metab* 2003; 29: 6S95–6S103.

Administration in children. In children aged 10 years and older with type 2 diabetes mellitus, oral metformin hydrochloride may be used in a starting dose of 500 mg or 850 mg once daily, or 500 mg twice daily, given with or after a meal. It may be gradually increased if needed, at intervals of at least 1 week, to a maximum of 2 g daily given in 2 or 3 divided doses. Gastrointestinal effects are common on starting therapy, and the *BNFC* suggests that the initial dose should be 500 mg once daily; it also suggests that children who are 8 to 10 years of age may be started on a dose of 200 mg once daily, although such use is unlicensed in the UK. Modified-release preparations are generally not licensed for use in children.

Although rare, the incidence of type 2 diabetes is increasing in children and adolescents, related in part to the increase in obesity occurring particularly in westernised countries. A small placebo-controlled study[1] of patients aged 10 to 17 years with type 2 diabetes found that metformin improved glycaemic control and that adverse effects were similar to those in adults. It was also found to be safe and effective in 131 children with a mean age of 13.8 years, in a comparison with glimepiride.[2] In obese children and adolescents with hyperinsulinaemia, who are at risk of developing type 2 diabetes, small studies[3-7] of metformin use have reported improvements in body composition and fasting insulin concentrations.

Insulin resistance and a deterioration in metabolic control can occur during puberty in adolescent type 1 diabetics. There has, therefore, been some interest in the use of metformin as an adjunct to insulin therapy in these patients, and small studies have reported improvements in glycaemic control[8-10] and reductions in insulin requirements.[8,10]

Metformin has also been studied in small groups of adolescents with polycystic ovary syndrome. There are reports of a reduction in testosterone and improvements in menstrual cycle regularity,[11-13] as well as improved insulin sensitivity in those with hyperinsulinism.[11] Some, but not all, studies have also reported beneficial effects on body-mass index[11,13] and hirsutism.[13]

1. Jones KL, *et al.* Effect of metformin in pediatric patients with type 2 diabetes: a randomized controlled trial. *Diabetes Care* 2002; 25: 89–94.
2. Gottschalk M, *et al.* Glimepiride versus metformin as monotherapy in pediatric patients with type 2 diabetes: a randomized, single-blind comparative study. *Diabetes Care* 2007; 30: 790–4.
3. Freemark M, Bursey D. The effects of metformin on body mass index and glucose tolerance in obese adolescents with fasting hyperinsulinemia and a family history of type 2 diabetes. Abstract: *Pediatrics* 2001; 107: 763–4. Full version: http://pediatrics.aappublications.org/cgi/content/full/107/4/e55 (accessed 25/06/07)
4. Srinivasan S, *et al.* Randomized, controlled trial of metformin for obesity and insulin resistance in children and adolescents: improvement in body composition and fasting insulin. *J Clin Endocrinol Metab* 2006; 91: 2074–80.
5. Atabek ME, Pirgon O. Use of metformin in obese adolescents with hyperinsulinemia: a 6-month, randomized, double-blind, placebo-controlled clinical trial. *J Pediatr Endocrinol Metab* 2008; 21: 339–48.
6. Park MH, *et al.* Metformin for obesity in children and adolescents: a systematic review. *Diabetes Care* 2009; 32: 1743–5.
7. Yanovski JA, *et al.* Effects of metformin on body weight and body composition in obese insulin-resistant children: a randomized clinical trial. *Diabetes* 2011; 60: 477–85.
8. Hamilton J, *et al.* Metformin as an adjunct therapy in adolescents with type 1 diabetes and insulin resistance: a randomized controlled trial. *Diabetes Care* 2003; 26: 138–43.
9. Särnblad S, *et al.* Metformin as additional therapy in adolescents with poorly controlled type 1 diabetes: randomised placebo-controlled trial with aspects on insulin sensitivity. *Eur J Endocrinol* 2003; 149: 323–9.
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11. Allen HF, *et al.* Randomized controlled trial evaluating response to metformin versus standard therapy in the treatment of adolescents with polycystic ovary syndrome. *J Pediatr Endocrinol Metab* 2005; 18: 761–8.
12. Bridger T, *et al.* Randomized placebo-controlled trial of metformin for adolescents with polycystic ovary syndrome. *Arch Pediatr Adolesc Med* 2006; 160: 241–6.
13. De Leo V, *et al.* Metformin treatment is effective in obese teenage girls with PCOS. *Hum Reprod* 2006; 21: 2252–6.

Diabetes mellitus. Results of the UK Prospective Diabetes Study (UKPDS) showed that intensive blood glucose control with metformin reduces the risk of diabetic complications (p. 462.3) and death in overweight patients with type 2 diabetes.[1,2] The study also generated some concern regarding intensive therapy with metformin plus a sulfonylurea (see under Interactions, p. 503.3) but this was not borne out on further analysis and such combinations are widely used in the management of type 2 diabetes mellitus (p. 459.1). Metformin is also used with other antidiabetic drugs in patients requiring combined or more intensive therapy. A systematic review[3] found only a limited number of controlled studies comparing various combinations of metformin with another oral antidiabetic (acarbose, exenatide, meglitinides, sulfonylureas, and thiazolidinediones) or insulin, and concluded that no particular combination provided better glycaemic control.

Metformin has also been investigated for the *prevention* of type 2 diabetes in patients at high risk. Although metformin treatment for an average 2.8 years reduced the incidence of type 2 diabetes by 31% in a placebo-controlled study[4] of patients with impaired glucose tolerance, intensive lifestyle modification was actually more effective (58% reduction). Lifestyle modification was also more effective than metformin in reducing cardiovascular risk factors[5] and the development of the metabolic syndrome.[6] After completion of this study all patients were offered lifestyle interventions and, in addition, those previously in the metformin group were continued on the drug.[7] Follow up of these patients found that there was no significant difference in incidence of diabetes between the groups which was attributed to a fall in the number of new cases in the metformin and placebo groups to similar rates to those seen in the lifestyle group. Cardiovascular risk factors also improved in all 3 groups. The cumulative incidence of diabetes in the 10 years since initial randomisation was reduced by 34% in the lifestyle group and by 18% in the metformin group when compared with placebo. A meta-analysis[8] also found that metformin improved body-weight, lipid profiles, and insulin resistance, and reduced the onset of type 2 diabetes in patients at risk, but concluded that diet and exercise remained the basis of diabetes prevention.

Insulin is generally preferred for the treatment of **diabetes during pregnancy**. However, there is increasing evidence to suggest that metformin might be used safely in pregnant women with type 2 diabetes (see Pregnancy under Precautions, p. 493.1), and UK guidance[9] has suggested that it may be used either as an adjunct or alternative to insulin if the likely benefits from improved glycaemic control outweigh the potential for harm. Nevertheless, the use of oral hypoglycaemics during pregnancy remains controver-

sial; see Diabetes Mellitus, p. 459.1 for further details. Metformin has also been tried in women who develop gestational diabetes[10] and UK guidance[9] states that there is sufficient evidence of efficacy and safety to consider metformin as an adjunct or alternative to insulin. Following the birth, glucose tolerance returns to normal in most women; however, the risk of developing type 2 diabetes in the future is increased. Metformin use in women with a history of gestational diabetes has been shown to reduce the incidence of type 2 diabetes by about 50% when compared with placebo.[11] A similar reduction was seen in women managed through lifestyle interventions.

There is some interest in using oral metformin as an adjunct to insulin therapy in patients with **type 1 diabetes**,[12] particularly those who are overweight or have poor glycaemic control. Studies have consistently reported that total daily insulin requirements were reduced in patients given metformin.[13-17] Although results from small short-term studies have suggested that metformin may improve glycaemic control,[14-16] larger studies lasting 6 months[13] and 12 months[17] found no significant changes in glycated haemoglobin (HbA_{1c}). Reductions in body-weight[17] and body-mass index[16] were only significant in groups of patients given metformin for at least 1 year. Overall, the addition of metformin did not affect the frequency of hypoglycaemic events, but results from one study[17] suggested that major events were potentially more serious.

Metformin has also been studied in adolescents with type 1 diabetes and pubertal insulin resistance, and type 2 diabetes (see Administration in Children, p. 489.2).

1. UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998; **352**: 854–65.
2. Holman RR, *et al.* 10-Year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008; **359**: 1577–89.
3. Monami M, *et al.* Comparison of different drugs as add-on treatments to metformin in type 2 diabetes: a meta-analysis. *Diabetes Res Clin Pract* 2008; **79**: 196–203.
4. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; **346**: 393–403.
5. Diabetes Prevention Program Research Group. Impact of intensive lifestyle and metformin therapy on cardiovascular disease risk factors in the Diabetes Prevention Program. *Diabetes Care* 2005; **28**: 888–94.
6. Orchard TJ, *et al.* The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. *Ann Intern Med* 2005; **142**: 611–19.
7. Diabetes Prevention Program Research Group. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet* 2009; **374**: 1677–86.
8. Salpeter SR, *et al.* Meta-analysis: metformin treatment in persons at risk for diabetes mellitus. *Am J Med* 2008; **121**: 149–57.
9. National Collaborating Centre for Women's and Children's Health/NICE. Diabetes in pregnancy: management of diabetes and its complications from pre-conception to the postnatal period (issued March 2008, reissued July 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/CG63NICEGuideline.pdf (accessed 21/02/11)
10. Wensel TM. Role of metformin in the treatment of gestational diabetes. *Ann Pharmacother* 2009; **43**: 939–43.
11. Ratner RE, *et al.* Diabetes Prevention Program Research Group. Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. *J Clin Endocrinol Metab* 2008; **93**: 4774–9.
12. Vella S, *et al.* The use of metformin in type 1 diabetes: a systematic review of efficacy. *Diabetologia* 2010; **53**: 809–20.
13. Meyer L, *et al.* The benefits of metformin therapy during continuous subcutaneous insulin infusion treatment of type 1 diabetic patients. *Diabetes Care* 2002; **25**: 2153–8.
14. Gunton JE, Twigg SM. Metformin use as an adjunct to insulin treatment in selected patients with type 1 diabetes mellitus. *Med J Aust* 2003; **178**: 591–2.
15. Khan ASA, *et al.* The effect of metformin on blood glucose control in overweight patients with type 1 diabetes. *Diabet Med* 2006; **23**: 1079–84.
16. Moon RJ, *et al.* The addition of metformin in type 1 diabetes improves insulin sensitivity, diabetic control, body composition and patient well-being. *Diabetes Obes Metab* 2007; **9**: 143–5.
17. Lund SS, *et al.* Effect of adjunct metformin treatment in patients with type-1 diabetes and persistent inadequate glycaemic control: a randomized study. *PLoS One* 2008; **3**: e3363. Available at: http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0003363 (accessed 17/08/09)

Malignant neoplasms. There is some evidence to suggest that the incidence of, or mortality from, malignant neoplasms may be reduced in patients taking metformin,[1-4] and there has been considerable interest in the potential of metformin as a prophylactic agent or as an adjuvant in the management of malignant neoplasms.[5-13]

1. Libby G, *et al.* New users of metformin are at low risk of incident cancer: a cohort study among people with type 2 diabetes. *Diabetes Care* 2009; **32**: 1620–5.
2. Landman GW, *et al.* Metformin associated with lower cancer mortality in type 2 diabetes: ZODIAC-16. *Diabetes Care* 2010; **33**: 322–6.
3. Bodmer M, *et al.* Long-term metformin use is associated with decreased risk of breast cancer. *Diabetes Care* 2010; **33**: 1304–8.
4. Donadon V, *et al.* Metformin and reduced risk of hepatocellular carcinoma in diabetic patients with chronic liver disease. *Liver Int* 2010; **30**: 750–8.
5. Jiralerspong S, *et al.* Metformin and pathologic complete responses to neoadjuvant chemotherapy in diabetic patients with breast cancer. *J Clin Oncol* 2009; **27**: 3297–3302.
6. Martin-Castillo B, *et al.* Incorporating the antidiabetic drug metformin in HER2-positive breast cancer treated with neo-adjuvant chemotherapy and trastuzumab: an ongoing clinical-translational research experience at the Catalan Institute of Oncology. *Ann Oncol* 2010; **21**: 187–9.
7. Gonzalez-Angulo AM, Meric-Bernstam F. Metformin: a therapeutic opportunity in breast cancer. *Clin Cancer Res* 2010; **16**: 1695–1700.
8. Martin-Castillo B, *et al.* Metformin and cancer: doses, mechanisms and the dandelion and hormetic phenomena. *Cell Cycle* 2010; **9**: 1057–64.
9. Ben Sahra I, *et al.* Metformin in cancer therapy: a new perspective for an old antidiabetic drug? *Mol Cancer Ther* 2010; **9**: 1092–9.
10. Wysocki PJ, Wierusz-Wysocka B. Obesity, hyperinsulinemia and breast cancer: novel targets and a novel role for metformin. *Expert Rev Mol Diagn* 2010; **10**: 509–19.
11. Papanas N, *et al.* Metformin and cancer: licence to heal? *Expert Opin Invest Drugs* 2010; **19**: 913–17.
12. Li D, *et al.* Antidiabetic therapies affect risk of pancreatic cancer. *Gastroenterology* 2009; **137**: 482–8.
13. DeCensi A, *et al.* Metformin and cancer risk in diabetic patients: a systematic review and meta-analysis. *Cancer Prev Res (Phila)* 2010; **3**: 1451–61.

Nutritional and metabolic disorders. In addition to its use in diabetes mellitus (p. 489.3), metformin has also been tried in a diverse range of nutritional and metabolic disorders that may involve weight gain, hyperinsulinaemia and insulin resistance, glucose intolerance, and lipodystrophies. These include obesity in patients without diabetes,[1-3] obesity-related acanthosis nigricans,[4] antipsychotic-induced weight gain,[5,6] HIV-associated lipodystrophy,[7,8] and precocious puberty.[9]

1. Desilets AR, *et al.* Role of metformin for weight management in patients without type 2 diabetes. *Ann Pharmacother* 2008; **42**: 817–26.
2. Park MH, *et al.* Metformin for obesity in children and adolescents: a systematic review. *Diabetes Care* 2009; **32**: 1743–5.
3. Glaser Pediatric Research Network Obesity Study Group. Metformin extended release treatment of adolescent obesity: a 48-week randomized, double-blind, placebo-controlled trial with 48-week follow-up. *Arch Pediatr Adolesc Med* 2010; **164**: 116–23.
4. Romo A, Benavides S. Treatment options in insulin resistance obesity-related acanthosis nigricans. *Ann Pharmacother* 2008; **42**: 1090–4.
5. Wu R-R, *et al.* Lifestyle intervention and metformin for treatment of antipsychotic-induced weight gain: a randomized controlled trial. *JAMA* 2008; **299**: 185–93.
6. Ehret M, *et al.* The effect of metformin on anthropometrics and insulin resistance in patients receiving atypical antipsychotic agents: a meta-analysis. *J Clin Psychiatry* 2010; **71**: 1286–92.
7. Driscoll SD, *et al.* Differential effects of metformin and exercise on muscle adiposity and metabolic indices in human immunodeficiency virus-infected patients. *J Clin Endocrinol Metab* 2004; **89**: 2171–8.
8. van Wijk JPH, *et al.* Comparison of rosiglitazone and metformin for treating HIV lipodystrophy: a randomized trial. *Ann Intern Med* 2005; **143**: 337–46.
9. Ibáñez L, *et al.* Pubertal metformin therapy to reduce total, visceral, and hepatic adiposity. *J Pediatr* 2010; **156**: 98–102.

Polycystic ovary syndrome. It has been suggested that hyperinsulinism may play a pathogenetic role in stimulating the abnormal androgen production from the ovary seen in women with polycystic ovary syndrome (PCOS, p. 2253.3). Most early studies of metformin in PCOS were small, observational, and of short duration, with mixed results. Although there were reports of reduced insulin levels, increased insulin sensitivity, and improved androgen concentrations, other studies failed to confirm these effects.[1] Later randomised studies were also small, but some were of longer duration. These reported weight reductions in obese patients,[2] reductions in insulin levels[2-4] and increased sensitivity,[5] improved androgen and other hormonal measures,[2,3,5] and improved menstrual patterns,[2,4,5] but again, not consistently. Metformin has also been reported to reduce hirsutism in women with PCOS, but it appears to have only a modest effect similar to that of hormonal contraceptives, and is less effective than anti-androgen therapy.[6,7]

The effect of metformin on infertility in PCOS has also been investigated. Early small studies suggested that it could improve ovulation when used alone or with clomifene citrate; pregnancy rates were also improved when metformin was used with clomifene.[8] However, 2 large, placebo-controlled studies later found that metformin, either alone or with clomifene, did not improve the rate of ovulation, pregnancy, or live births in women with polycystic ovary syndrome.[9,10] A meta-analysis[11] that included these 2 large studies concluded that metformin did not improve live birth rates when given alone or with clomifene in clomifene therapy-naive women, but there was evidence of better rates when metformin was added to clomifene therapy in clomifene-resistant women. Based on limited data, it also appeared that there was no benefit from the addition of metformin to laparoscopic ovarian drilling or follicle-stimulating hormone. A systematic review[12] of studies using assisted reproduction (IVF or intra-cytoplasmic sperm injection) found that addition of metformin did not improve rates of live birth, clinical pregnancy, or miscarriage. Metformin was associated with a reduced risk of ovarian hyperstimulation syndrome, but the possible mechanism for this was unclear. It has also been suggested that pre-pregnancy metformin may decrease the rate of first-trimester miscarriage, which is common in women with PCOS; however, a meta-analysis[13] found no evidence of significant benefit with metformin use, when given alone or with other fertility drugs before pregnancy. Although it is usual to stop treatment with metformin after conception, some women have continued treatment throughout their pregnancies and there is growing evidence to suggest that this may have a beneficial effect on pregnancy outcome.[14,15]

Women with PCOS are at increased risk of developing impaired glucose tolerance, type 2 diabetes mellitus, and other features of the metabolic syndrome. In the USA, metformin has been recommended for consideration in most women with PCOS, particularly in those who are overweight or obese.[16] Although metformin may have beneficial effects on these risk factors for cardiovascular disease, prospective long-term studies are lacking.[7]

1. Norman RJ, *et al.* Metformin and intervention in polycystic ovary syndrome. *Med J Aust* 2001; **174**: 580–3.
2. Pasquali R, *et al.* Effect of long-term treatment with metformin added to hypocaloric diet on body composition, fat distribution, and androgen and insulin levels in abdominally obese women with and without the polycystic ovary syndrome. *J Clin Endocrinol Metab* 2000; **85**: 2767–74.
3. Nestler JE, Jakubowicz DJ. Decreases in ovarian cytochrome P450c17 α activity and serum free testosterone after reduction of insulin secretion in polycystic ovary syndrome. *N Engl J Med* 1996; **335**: 617–23.
4. Morin-Papunen LC, *et al.* Endocrine and metabolic effects of metformin versus ethinyl estradiol-cyproterone acetate in obese women with polycystic ovary syndrome: a randomized study. *J Clin Endocrinol Metab* 2000; **85**: 3161–8.
5. Moghetti P, *et al.* Metformin effects on clinical features, endocrine and metabolic profiles, and insulin sensitivity in polycystic ovary syndrome: a randomized, double-blind, placebo-controlled 6-month trial, followed by open, long-term clinical evaluation. *J Clin Endocrinol Metab* 2000; **85**: 139–46.
6. Cosma M, *et al.* Insulin sensitizers for the treatment of hirsutism: a systematic review and metaanalyses of randomized controlled trials. *J Clin Endocrinol Metab* 2008; **93**: 1135–42.
7. Mathur R, *et al.* Use of metformin in polycystic ovary syndrome. *Am J Obstet Gynecol* 2008; **199**: 596–609.
8. Lord JM, *et al.* Metformin in polycystic ovary syndrome: systematic review and meta-analysis. *BMJ* 2003; **327**: 951–3.
9. Moll E, *et al.* Effect of clomifene citrate plus metformin and clomifene citrate plus placebo on induction of ovulation in women with newly diagnosed polycystic ovary syndrome: randomised double blind clinical trial. Abridged version: *BMJ* 2006; **332**: 1485–8. Full version: http://www.bmj.com/cgi/reprint/332/7556/1485 (accessed 17/06/08) Correction available at: http://www.bmj.com/cgi/content/full/336/7643/0-b (accessed 17/06/08)
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11. Moll E, *et al.* The role of metformin in polycystic ovary syndrome: a systematic review. *Hum Reprod Update* 2007; **13**: 527–37.
12. Tso LO, *et al.* Metformin treatment before and during IVF or ICSI in women with polycystic ovary syndrome. Available in The Cochrane Database of Systematic Reviews: Issue 2. Chichester: John Wiley; 2009 (accessed 30/06/09).
13. Palomba S, *et al.* Effect of preconceptional metformin on abortion risk in polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials. *Fertil Steril* 2009; **92**: 1646–58.
14. Glueck CJ, *et al.* Pregnancy outcomes among women with polycystic ovary syndrome treated with metformin. *Hum Reprod* 2002; **17**: 2858–64.
15. Nawaz FH, *et al.* Does continuous use of metformin throughout pregnancy improve pregnancy outcomes in women with polycystic ovarian syndrome? *J Obstet Gynaecol Res* 2008; **34**: 832–7.
16. AACE Polycystic Ovary Syndrome Writing Committee. American Association of Clinical Endocrinologists position statement on metabolic and cardiovascular consequences of polycystic ovary syndrome. *Endocr Pract* 2005; **11**: 126–34. Also available at: http://www.aace.com/pub/pdf/guidelines/PCOSpositionstatement.pdf (accessed 30/06/09)

Adverse Effects, Treatment, and Precautions

As for biguanides in general, p. 468.1.

Breast feeding. Based on *animal* studies, UK and US licensed product information warns that metformin may be distributed into breast milk, and that the possible effects on the infant should be considered if women wish to breast feed while receiving the drug. However, a study in 7 breast-feeding women receiving metformin at a median dose of 1.5 g daily found the concentrations in milk to be about a third of those in maternal plasma, resulting in a mean calculated dose to the infants of 40 micrograms/kg daily. Blood samples were taken from 4 of the infants: metformin concentrations were undetectable in 2, and were very low (10 to 15% of maternal values) in the others. Given these results the authors considered that women receiving metformin need not be discouraged from breast feeding.[1] Similar results from 3 other studies[2,3] that included 13 women have provided further evidence that metformin is distributed into breast milk, that concentrations in milk are less than those in maternal plasma, and that breast-fed infants would be exposed to a very small percentage of the maternal dose. Six infants were breast-fed with no adverse effects that could be attributed to metformin. A prospective study[4] of weight, height, and motor-social development over 6 months, in infants of women taking metformin (1.5 to 2.55 g daily) for polycystic ovary syndrome, found no difference between 61 infants who were breast-fed and 50 who were formula-fed.

1. Hale TW, *et al.* Transfer of metformin into human milk. *Diabetologia* 2002; **45**: 1509–14.
2. Gardiner SJ, *et al.* Transfer of metformin into human milk. *Clin Pharmacol Ther* 2003; **73**: 71–7.
3. Briggs GG, *et al.* Excretion of metformin into breast milk and the effect on nursing infants. *Obstet Gynecol* 2005; **105**: 1437–41.
4. Glueck CJ, *et al.* Growth, motor, and social development in breast- and formula-fed infants of metformin-treated women with polycystic ovary syndrome. *J Pediatr* 2006; **148**: 628–32.

Fasting. For the view that metformin could be used with little risk of hypoglycaemia in fasting Muslim patients during Ramadan, and suggestions for modifying the timing of doses, see under Precautions of Insulin, p. 485.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies metformin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 29/07/11)

Pregnancy. Insulin is generally preferred for treatment of diabetes during pregnancy. However, there are limited data to suggest that metformin does not increase the risk of congenital abnormalities[1,2] and does not adversely affect pregnancy outcome in diabetic women.[2] In gestational diabetes, a controlled study[3] in more than 700 women found that metformin, either alone or with insulin, did not increase adverse maternal or neonatal complications, compared with insulin therapy alone. Although the rate of preterm birth (before 37 weeks) was higher in the metformin group, this was not associated with a higher rate of other complications. For the use of metformin in the management of diabetes during pregnancy, see Diabetes Mellitus under Uses, p. 489.3.

The use of metformin to improve ovulation in polycystic ovary syndrome is increasing (see under Uses, p. 490.2) and there is evidence to suggest that metformin used before and during pregnancy in these women does not increase the risk of congenital abnormalities.[1,4-7]

1. Gilbert C, *et al.* Pregnancy outcome after first-trimester exposure to metformin: a meta-analysis. *Fertil Steril* 2006; **86:** 658–63.
2. Hughes RCE, Rowan JA. Pregnancy in women with type 2 diabetes: who takes metformin and what is the outcome? *Diabet Med* 2006; **23:** 318–22.
3. Rowan JA, *et al.* MiG Trial Investigators. Metformin versus insulin for the treatment of gestational diabetes. *N Engl J Med* 2008; **358:** 2003–15. Correction. *ibid.*; **359:** 106.
4. Glueck CJ, *et al.* Pregnancy outcomes among women with polycystic ovary syndrome treated with metformin. *Hum Reprod* 2002; **17:** 2858–64.
5. Glueck CJ, *et al.* Height, weight, and motor-social development during the first 18 months of life in 126 infants born to 109 mothers with polycystic ovary syndrome who conceived on and continued metformin through pregnancy. *Hum Reprod* 2004; **19:** 1323–30.
6. Thatcher SS, Jackson EM. Pregnancy outcome in infertile patients with polycystic ovary syndrome who were treated with metformin. *Fertil Steril* 2006; **85:** 1002–9.
7. Nawaz FH, *et al.* Does continuous use of metformin throughout pregnancy improve pregnancy outcomes in women with polycystic ovarian syndrome? *J Obstet Gynaecol Res* 2008; **34:** 832–7.

Renal impairment. Biguanides are generally avoided in patients with renal impairment because of the risk of lactic acidosis, and US licensed product information advises that metformin should not be given if serum-creatinine concentrations are above the upper limit of normal for age, or there is any other evidence of renal impairment. In the UK, licensed product information suggests that metformin should not be used when creatinine clearance is less than 60 mL/min. However, some authors consider that the risk of lactic acidosis with metformin in patients with renal impairment has been overstated.[1,2] Indeed, guidelines from NICE[3] advise that the dose of metformin should be reviewed if serum creatinine exceeds 130 micromoles/litre or the estimated glomerular filtration rate is below 45 mL/min per 1.73 m^2, and that the drug should be stopped if serum creatinine exceeds 150 micromoles/litre or the estimated glomerular filtration rate falls below 30 mL/min per 1.73 m^2.

1. Philbrick AM, *et al.* Metformin use in renal dysfunction: is a serum creatinine threshold appropriate? *Am J Health-Syst Pharm* 2009; **66:** 2017–23.
2. Pilmore HL. Review: metformin: potential benefits and use in chronic kidney disease. *Nephrology (Carlton)* 2010; **15:** 412–18.
3. National Collaborating Centre for Chronic Conditions/NICE. Type 2 diabetes: the management of type 2 diabetes (issued May 2009). Available at: http://www.nice.org.uk/nicemedia/pdf/CG87NICEGuideline.pdf (accessed 16/06/09)

Interactions

As for biguanides in general, p. 469.1.

Pharmacokinetics

Metformin hydrochloride is slowly and incompletely absorbed from the gastrointestinal tract; the absolute bioavailability of a single 500-mg dose is reported to be about 50 to 60%, although this is reduced somewhat if taken with food. Protein binding in plasma is negligible. Metformin is excreted unchanged in the urine. The plasma elimination half-life is reported to range from about 2 to 6 hours. Metformin crosses the placenta and is distributed into breast milk in small amounts.

References.

1. Sambol NC, *et al.* Pharmacokinetics and pharmacodynamics of metformin in healthy subjects and patients with noninsulin-dependent diabetes mellitus. *J Clin Pharmacol* 1996; **36:** 1012–21.
2. Charles B, *et al.* Population pharmacokinetics of metformin in late pregnancy. *Ther Drug Monit* 2006; **28:** 67–72.
3. Zolk O. Current understanding of the pharmacogenomics of metformin. *Clin Pharmacol Ther* 2009; **86:** 595–8.
4. Eyal S, *et al.* Pharmacokinetics of metformin during pregnancy. *Drug Metab Dispos* 2010; **38:** 833–40.
5. Graham GG, *et al.* Clinical pharmacokinetics of metformin. *Clin Pharmacokinet* 2011; **50:** 81–98.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Baligluc; DBI AP; Diab Dos; Diabesil; Duburina; Glucaminol; Glucogood; Glucophage; Islotin; Mectin; Medobis; Melgib; Metforal; Metglucon; MTF; Oxemet; Quexel; Redugluc; ***Austral.***: Diabex; *Diaformin*; Formet; Glucohexal†; Glucomet; Glucophage; Metex; Novomet†; ***Austria***: Diabetex; Glucophage; Meglucon; ***Belg.***: Glucophage; Metformax; ***Braz.***: Diaformin; Dimefor; Formyn; Glicefor; Glifage; Gliformil; Glucoformin; Meguanin; Metform; Metformed; Metformix; Metta; Teutoformin; ***Canad.***: Glucophage; Glumetza; Glycon; ***Chile***: Diabetyl; Diaglitab; Fintaxim; Glaformil; Glicenex; Glidanil; Glifortex; Glucophage; Hipoglucin; Oxemet; ***China***: Bai Si Ping (佰思平); Bei Shun (倍顺); Bo Ke (卜可); De Ai Xin (德艾欣); Diaformin (迪化唐锭); Du Le Ning (都乐宁); Glucophage (格华止); Hong Fei Kang (弘飞康); Jiang Li Shu (降力舒); JinZhenXing (津真型); Jun Li Da (君力达); Jun Shi Da Xin (君士达新); Li Le Er (力乐尔); Ming Nuo (名诺); Pu Le Kang Ni (普乐康尼); Qi Ji (齐信); Qing Kuang (清旷); Ren Xin (仁欣); Rui Nuo Shu (瑞诺舒); Ruijiu (瑞久); San Xiao Ping (三肖平); Shan Mu Shi (山姆士); Sheng Bang Jie (圣邦杰); Tai Bai (泰白); Tang Bi Fu (唐必呋); Tang Ge (唐格); Tang Luo (唐落); Tang Tan (唐坦); Wei Er Tang (维尔唐); Xin Shu Shi Ning (欣舒施宁); Xin Tang Ping (欣唐屏); Yi Heng (亿恒); Yue Da Ning (悦达宁); Zhong Shi De (众氏得); ***Cz.***: Adimet; Diaphage†; Glucomerck†; Glucophage; Gluformin†; Glumetsan†; Langerin; Metfirex; Metfogamma; Metfogen; Normaglyc; Siofor; Stadamet; ***Denm.***: Glucophage†; Mitforgen; Orabet; ***Fin.***: Diformin; Glucophage; Metforem; Metgol†; Oramet; ***Fr.***: Diabamyl; Glucophage; Stagid; ***Ger.***: Biocos†; Diabesin†; Diabetase†; Glucobon†; Glucophage; Juformin†; Mediabet†; Meglucon†; Mescorit†; Met; Metfogamma; Metformdoc†; Siofor; ***Gr.***: Glucofree; Glucophage; Glucoplus; Metforil; Sukontrol; ***Hong Kong***: CP-Metform; Deson; Diabesafe†; Diabetmin; Diaformin; Glucodown; Glucomet; Glucomin†; Glucophage; Glumet; Guamet; Melbin; ***Hung.***: Adimet; Metforal; Meglucon; Merckformin; Metfogamma; Metrivin; Stadamet; ***India***: Alnamet; Atformin; Avimet; Bigan; Bigomet; Bigsens; Bimode-M; C-Mine; Cetapin; Conformin; D-Bay; D-Met; Daomet; Diafer; Diamet; Dibeta; Dibimet; Diform; Emfor; Emnorm; Etformin; Eumet; Exermet; Formet; Formin; Forminal; Frame; G Reg; G-Met; G-Reg; Glinate-MF; Gluconorm; Gluformin; Glumet; Glyciphage; Glycomet; Glycotan; Glyree M; Glyrep; Insumet; K-Met; M-Forlin; Matce; Medformin; Melmet; Mesite; Metadoze-IPR; Metafor; Metanorm; Metcalf; Metchek; Metco; Metfor; Metica; Metkap; Metkor; Metlife; Metlong; Metmin; Metneed; Metsafe; Metsar; Metswift; MF; Minimet; MR-Met; Obimet; Okamet; Omet; Oriphage; Walaphage; Xmet; ***Indon.***: Adecco; Benofomin; Diabex; Diafac; Efomet; Eraphage; Forbetes; Formell; Gliformin; Glikos; Glucofor; Glucophage; Glucotika; Gludepatic; Glufor; Glumin; Glunor; Gradiab; Methormyl; Methpica; Metphar; Nevox; Pionix-M; Reglus; Tudiab; Zendiab; Zumamet; ***Irl.***: Bellformin†; Gerformin; Glucophage; Metophage; ***Israel***: Glucomin; Glucophage; Glufor; ***Ital.***: Glucophage; Metbay; Metespina; Metfonorm; Metforal; Zuglimet; ***Jpn***: Glycoran; Melbin†; ***Malaysia***: Diabetmin; Glucomet; Glucon; Glucophage; Glumet; Riomet; Xmet; ***Mex.***: Aglumet; Anglucid; Apozemia; Dabex; Debeone; Dimefor; Dinamel; Ficonax; Forlucyl; Glucophage; Glucotec S; Glunovag; Harbamind; Ifor; Meglubet; Melbexa; Metbax†; Metixor; Mifelar; Minatozil; Minraam; Pharmafet; Pre-Dial; Sibet; ***Neth.***: Diabex†; Glucophage†; Metnova; Niformina†; ***Norw.***: Glucophage; ***NZ***: Glucomet; Metchek; Metomin†; ***Philipp.***: Ansures; Briform; Diafat; Diazen; Euform; Formet; Formidd; Glucare†; Glucoform; Glucomed; Glucophage; Glucopres; Gludin; Glumet; Glyformin; Horsulin†; Humamet; I-Max; Insunex; Marphage; Mellinix; Metanorm; Neoform; Neomet; Nidcor; Panfor; Sucranorm†; Vimetrol†; Xmet; ***Pol.***: Avamina; Etform; Formetic; Glucophage; Gluformin; Metfogamma; Metformax; Metifor; Metral; Mylformet; Siofor; ***Port.***: Diabex; Glucophage; Mekoll; Risidon; Romac; Stagid; ***Rus.***: Bagomet (Багомет); Dianormet (Дианормет); Formetin (Форметин); Formin (Формин Плив); Gliformin (Глиформин); Gliminfor (Глимининфор); Glucophage (Глюкофаж); Lanagerin (Ланжерин); Metadien (Метадиен); Metfogamma (Метфогамма); Metospanin (Метоспанин); NovoFormin (НовоФормин); Siofor (Сиофор); ***S. Afr.***: Bigsens; Diabetmin; Diaformin; Forminal; Gluconorm; Glucophage; Mengen; Metforal; Metored; Metphage; ***Singapore***: Diabetmin; Diaformin; Formet; Glucomet; Glucophage; Glycomet; Glyformin; Metforal; SP-Glucomet; ***Spain***: Dianben; ***Swed.***: Glucophage; ***Switz.***: Glucophage; Metfin; ***Thail.***: Ammiformin; Buformin; Deglucos; Deson; Diamet; Diaslim; Formin; Glucino; Gluco; Glucoles; Glucolyte; Glucono; Glucophage; Gluformin†; Glugenmin; Glugon; Glustress; Glutabloc; Gluzolyte; Maformin; ME-F; Meformed; Metfor†; Metforex; Metfron; Metica; Miformin; Pocophage; Poli-Formin; Prophage; Serformin†; Siamformet; ***Turk.***: Diaformin; Glifor; Glucophage; Gluformin; Glukofen; Matofin; ***UAE***: Dialon; ***UK***: Bolamyn; Glucophage; Metabet; Metsol; ***Ukr.***: Diaformin (Диаформин); Dianormet (Дианормет); Glucophage (Глюкофаж); Glycomet (Гликомет); Metfogamma (Метфогамма); Panfor (Панфор)†; Siofor (Сиофор); Tefor (Тефор)†; ***USA***: Fortamet; Glucophage; Glumetza; Riomet; ***Venez.***: Diaformina; Glaformil; Glucaminol; Glucofage.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

BP 2014: Metformin Oral Solution; Metformin Tablets;
USP 36: Glipizide and Metformin Hydrochloride Tablets; Glyburide and Metformin Hydrochloride Tablets; Metformin Hydrochloride Extended-Release Tablets; Metformin Hydrochloride Tablets; Pioglitazone and Metformin Hydrochloride Tablets.

Miglitol *(BAN, USAN, pINN)*

Bay-m-1099; Miglitoli; Miglitolum; Миглитол.

(2*R*,3*R*,4*R*,5*S*)-1-(2-Hydroxyethyl)-2-(hydroxymethyl)piperidine-3,4,5-triol.

$C_8H_{17}NO_5$=207.2

CAS — 72432-03-2.

ATC — A10BF02.

ATC Vet — QA10BF02.

UNII — 0V5436JAQW.

Uses and Administration

Miglitol is an alpha-glucosidase inhibitor similar in action to acarbose (p. 466.3). It is given orally in the management of type 2 diabetes mellitus (p. 459.1), alone or with a sulfonylurea. Usual initial doses are 25 mg three times daily with meals, although a lower dose may be used to minimise gastrointestinal disturbances, starting at 25 mg once daily and gradually increasing to three times daily. After 4 to 8 weeks of a regimen of 25 mg three times daily, the dose may be increased to 50 mg three times daily, then adjusted after a further 3 months, if necessary. The maximum recommended dose of miglitol is 100 mg three times daily.

References.

1. Scott LJ, Spencer CM. Miglitol: a review of its therapeutic potential in type 2 diabetes mellitus. *Drugs* 2000; **59:** 521–49.
2. Aoki K, *et al.* Comparison of pre- vs. postmeal administration of miglitol for 3 months in type 2 diabetic patients. *Diabetes Obes Metab* 2008; **10:** 970–2.
3. Nemoto M, *et al.* Efficacy of combined use of miglitol in type 2 diabetes patients receiving insulin therapy-placebo-controlled double-blind comparative study. *Acta Diabetol* 2011; **48:** 15–20.

Adverse Effects and Precautions

As for alpha-glucosidase inhibitors in general (see Acarbose, p. 466.3 and p. 467.1).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies miglitol as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Interactions

As for alpha-glucosidase inhibitors in general (see Acarbose, p. 467.1). Miglitol may reduce the bioavailability of propranolol and ranitidine.

Pharmacokinetics

Miglitol is completely absorbed at a dose of 25 mg, but only 50 to 70% of a 100 mg-dose is absorbed. It is not metabolised, and is excreted unchanged in the urine with a plasma elimination half-life of about 2 hours. Increased plasma concentrations of miglitol have been found in patients with renal impairment (creatinine clearance less than 25 mL/min), but the clinical significance of this effect is unknown. A small amount of miglitol is distributed into breast milk, and the estimated exposure to a breastfed infant is about 0.4% of the maternal dose.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Diastabol; ***China***: Diastabol (德赛天); Laiping (来平); ***Cz.***: Diastabol†; ***Fin.***: Diastabol†; ***Fr.***: Diastabol; ***Ger.***: Diastabol†; ***Gr.***: Diastabol; ***Hung.***: Diastabol; ***India***: Diamig; Elitox; Euglitol; Miglit; Mignar; Migset; Migtor; Minerva; Misobit; ***Irl.***: Diastabol†; ***Mex.***: Diastabol; ***Neth.***: Diastabol; ***Pol.***: Diastabol†; ***Port.***: Diastabol; *Limarcan*; ***Spain***: Diastabol; Plumarol; ***Switz.***: Diastabol†; ***USA***: Glyset.

Mitiglinide *(pINN)*

Mitiglinida; Mitiglinidum; Митиглинид.

(-)-(2*S*,3a,7a-*cis*)-α-Benzylhexahydro-γ-oxo-2-isoindolinebutyric acid.

$C_{19}H_{25}NO_3$=315.4

CAS — 145375-43-5.

ATC — A10BX08.

ATC Vet — QA10BX08.

UNII — D86I0XLB13.

Mitiglinide Calcium *(rINNM)*

Calcii Mitiglinidum; KAD-1229; Mitiglinida cálcica; Mitiglinide Calcique; Mitiglinide Calcium Hydrate; S-21403; Кальций Митиглинид.

$C_{38}H_{46}CaN_2O_6.2H_2O$=704.9

CAS — 145525-41-3 (anhydrous mitiglinide calcium); 207844-01-7 (mitiglinide calcium).

ATC — A10BX08.

ATC Vet — QA10BX08.

UNII — 9651C21W3Z.

Profile

Mitiglinide is a meglitinide antidiabetic (see Repaglinide, p. 497.2) that is used in the treatment of type 2 diabetes mellitus (p. 459.1). Mitiglinide calcium is given in usual oral doses of 10 mg three time daily, immediately before meals.

References.
1. Yoshihara T, *et al.* Therapeutic efficacy of mitiglinide combined with once daily insulin glargine after switching from multiple daily insulin regimen of aspart insulin and glargine in patients with type 2 diabetes mellitus. *Endocr J* 2006; 53: 67–72.
2. Kumashiro N, *et al.* Long-term effect of combination therapy with mitiglinide and once daily insulin glargine in patients who were successfully switched from intensive insulin therapy in short-term study. *Endocr J* 2007; 54: 163–6.
3. Yamada S, *et al.* Effect of combination therapy of a rapid-acting insulin secretagogue (glinide) with premixed insulin in type 2 diabetes mellitus. *Intern Med* 2007; 46: 1893–7.
4. Malaisse WJ. Mitiglinide: a rapid- and short-acting non-sulfonylurea insulinotropic agent for the treatment of type 2 diabetic patients. *Expert Opin Pharmacother* 2008; 9: 2691–8.
5. Kaku K, *et al.* Effect of mitiglinide on glycemic control over 52 weeks in Japanese type 2 diabetic patients insufficiently controlled with pioglitazone monotherapy. *Endocr J* 2009; 56: 739–46.
6. Gao X. Multicentre, double-blind, randomized study of mitiglinide compared with nateglinide in type 2 diabetes mellitus patients in China. *J Int Med Res* 2009; 37: 812–21.
7. Abe M, *et al.* Efficacy and safety of mitiglinide in diabetic patients on maintenance hemodialysis. *Endocr J* 2010; 57: 579–86.
8. Phillippe HM, Wargo KA. Mitiglinide: a novel agent for the treatment of type 2 diabetes mellitus. *Ann Pharmacother* 2010; 44: 1615–23.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Fa Ai Si (法艾斯); Fadi (法迪); Glufast (快如妥); *Jpn*: Glufast; *Thai.*: Glufast.

Multi-ingredient Preparations. *Jpn*: Glubes.

Nateglinide *(USAN, rINN)*

A-4166; AY-4166; DJN-608; Nateglinid; Nateglinida; Natéglinide; Nateglinidi; Nateglinidum; SDZ-DJN-608; Senaglinide; YM-026; Нателинид.

(-)-*N*-[(*trans*-4-Isopropylcyclohexyl)carbonyl]-D-phenylalanine.

$C_{19}H_{27}NO_3$=317.4

CAS — 105816-04-4.

ATC — A10BX03.

ATC Vet — QA10BX03.

UNII — 41X3PWK4O2.

Pharmacopoeias. In *Eur.* see (p. vii) and *US.*

Ph. Eur. 8: (Nateglinide). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; freely soluble in methyl alcohol and in dichloromethane.

USP 36: (Nateglinide). A white powder. Practically insoluble in water; freely soluble in alcohol and methyl alcohol; soluble in ether; sparingly soluble in acetonitrile and octanol. Store in airtight containers.

Uses and Administration

Nateglinide, like repaglinide (p. 497.2), is a meglitinide antidiabetic used in the treatment of type 2 diabetes mellitus (p. 459.1). It is given within the 30 minutes before meals in oral doses of 60 or 120 mg three times daily. This may be increased to 180 mg three times daily if necessary. Nateglinide is also given in similar doses with metformin or a thiazolidinedione in type 2 diabetes not adequately controlled by these drugs alone.

Although dose adjustment is not generally required in renal impairment, serious hypoglycaemia has occurred in patients with chronic renal failure (see p. 494.2).

References.
1. Dunn CJ, Faulds D. Nateglinide. *Drugs* 2000; 60: 607–15.
2. Hanefeld M, *et al.* Rapid and short-acting mealtime insulin secretion with nateglinide controls both prandial and mean glycemia. *Diabetes Care* 2000; 23: 202–7.
3. Levien TL, *et al.* Nateglinide therapy for type 2 diabetes mellitus. *Ann Pharmacother* 2001; 35: 1426–34.
4. Black C, *et al.* Meglitinide analogues for type 2 diabetes mellitus. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 03/04/09).
5. Holman RR, *et al.* NAVIGATOR Study Group. Effect of nateglinide on the incidence of diabetes and cardiovascular events. *N Engl J Med* 2010; 362: 1463–76. Correction. *ibid.*; 1748.
6. Grunberger G. Quo vadis nateglinide? Ten-year perspective. *Expert Opin Pharmacother* 2011; 12: 2097–2106.

Adverse Effects and Precautions

As for Repaglinide, p. 497.2.

Incidence of adverse effects. A postmarketing cohort study collected adverse effect data for the first 6 months after starting nateglinide in 4557 patients.[1] Of these, 336 (7.4%) used nateglinide alone, but the majority (76%) were treated with nateglinide plus metformin. There were 80 adverse event reports attributed to nateglinide. Gastrointestinal disturbances were most common, particularly diarrhoea. There were 4 reports of hypersensitivity reactions, presenting as pruritus or rash. Of the 45 reports of hypoglycaemia involving nateglinide, 5 patients were on monotherapy, while the rest were also taking other antidiabetics. Isolated reports that were assessed as probably related to nateglinide included palpitations, Raynaud's phenomenon, and oedema and fluid retention.

1. Twaites B, *et al.* Safety of nateglinide as used in general practice in England: results of a prescription-event monitoring study. *Acta Diabetol* 2007; 44: 233–9.

Overdosage. A blood-glucose concentration of 2.0 mmol/litre was measured 1 hour after ingestion of nateglinide 3.42 g in a 30-year-old woman.[1] She was able to walk unaided, but seemed drowsy. The hypoglycaemic effect of nateglinide lasted for 6 hours and was treated with intravenous glucose (total dose 100 g).

1. Nakayama S, *et al.* Hypoglycemia following a nateglinide overdose in a suicide attempt. *Diabetes Care* 2005; 28: 227–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nateglinide as possibly porphyrinogenic: it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Pregnancy. Insulin is generally preferred to oral antidiabetics in the treatment of diabetes mellitus during pregnancy. An analysis of postmarketing data found 2 reports of nateglinide use during pregnancy.[1] In both cases the drug was given in the first trimester only, with metformin. One pregnancy resulted in a live birth with no reported congenital abnormalities. In the other, nateglinide was stopped 3 months after the last menstrual period and replaced with metformin for the rest of the pregnancy; the baby was reported to have polycystic kidneys.

1. Twaites B, *et al.* Safety of nateglinide as used in general practice in England: results of a prescription-event monitoring study. *Acta Diabetol* 2007; 44: 233–9.

Renal impairment. A single-dose pharmacokinetic study[1] found that moderate to severe renal impairment (creatinine clearance 15 to 50 mL/minute per 1.73 m^2) and haemodialysis did not significantly affect the pharmacokinetics of nateglinide. However, the metabolite M1 has been found to accumulate after repeated doses of nateglinide in patients with renal impairment requiring haemodialysis, although haemodialysis removes it.[2] M1 is a major metabolite that has modest hypoglycaemic activity compared with nateglinide. An analysis[3] of pooled study data found that efficacy and tolerability of nateglinide in elderly diabetic patients were not significantly affected by renal impairment (mean creatinine clearance 50.9 mL/minute per 1.73 m^2). Nevertheless, a 56-year-old diabetic woman whose renal failure was managed with haemodialysis developed severe hypoglycaemia with nateglinide; the reaction was attributed to the accumulation of M1.[4] Severe hypoglycaemia, attributed to therapeutic doses of nateglinide, also occurred in a 73-year-old diabetic woman with chronic renal failure managed with haemodialysis.[5] In this case, octreotide (100 micrograms subcutaneously) was given as well as parenteral glucose treatment. Licensed product information in the UK and USA suggest that no dosage adjustment is necessary in renal impairment, although UK information suggests that dose adjustment might be required in patients on haemodialysis.

1. Devineni D, *et al.* Pharmacokinetics of nateglinide in renally impaired diabetic patients. *J Clin Pharmacol* 2003; 43: 163–70.
2. Inoue T, *et al.* Pharmacokinetics of nateglinide and its metabolites in subjects with type 2 diabetes mellitus and renal failure. *Clin Nephrol* 2003; 60: 90–5.
3. Del Prato S, *et al.* Treatment of patients over 64 years of age with type 2 diabetes: experience from nateglinide pooled database retrospective analysis. *Diabetes Care* 2003; 26: 2075–80.
4. Nagai T, *et al.* Hypoglycemia due to nateglinide administration in diabetic patient with chronic renal failure. *Diabetes Res Clin Pract* 2003; 59: 191–4.
5. Sherk DK, Bryant SM. Octreotide therapy for nateglinide-induced hypoglycemia. *Ann Emerg Med* 2007; 50: 745–6.

Interactions

The efficacy of nateglinide may be affected by other drugs that have an independent effect on blood glucose. For more details and examples of drugs that can increase or decrease blood-glucose concentrations, see Interactions under Sulfonylureas, p. 504.3.

Reviews.
1. Scheen AJ. Drug-drug and food-drug pharmacokinetic interactions with new insulinotropic agents repaglinide and nateglinide. *Clin Pharmacokinet* 2007; 46: 93–108.

Antibacterials. *Rifampicin* reduced the plasma concentrations and half-life of nateglinide in healthy subjects, probably by induction of the cytochrome P450 isoenzyme CYP2C9.[1] The glucose-lowering effect of nateglinide was not affected, but there was a marked interindividual variation in the pharmacokinetic changes, and the authors suggested that some diabetic patients could be affected.

1. Niemi M, *et al.* Effect of rifampicin on the pharmacokinetics and pharmacodynamics of nateglinide in healthy subjects. *Br J Clin Pharmacol* 2003; 56: 427–32.

Antifungals. *Fluconazole* raised the plasma concentrations and prolonged the half-life of nateglinide in healthy subjects, probably by inhibition of its metabolism by the cytochrome P450 isoenzyme CYP2C9.[1] The glucose-lowering effect of nateglinide was not affected, but a low dose of nateglinide had been used and the authors suggested that in diabetic patients fluconazole may enhance and prolong the effects of nateglinide.

1. Niemi M, *et al.* Effect of fluconazole on the pharmacokinetics and pharmacodynamics of nateglinide. *Clin Pharmacol Ther* 2003; 74: 25–31.

Lipid regulating drugs. A study[1] investigating the effects of the *gemfibrozil* and *itraconazole* combination on the pharmacokinetics of nateglinide showed only a limited interaction. Nateglinide plasma concentrations were raised moderately and the blood glucose response to nateglinide was not significantly changed. This is in contrast to the substantial interaction of gemfibrozil with repaglinide (p. 498.2).

1. Niemi M, *et al.* Coadministration of gemfibrozil and itraconazole has only a minor effect on the pharmacokinetics of the CYP2C9 and CYP3A4 substrate nateglinide. *Br J Clin Pharmacol* 2005; 60: 208–17.

Pharmacokinetics

Nateglinide is rapidly absorbed after oral doses and peak plasma concentrations occur within one hour. It has an absolute bioavailability of 73% and is 98% bound to plasma proteins. Nateglinide is mainly metabolised by cytochrome P450 isoenzyme CYP2C9, and to a lesser extent by CYP3A4. The major metabolites are less potent than nateglinide. The parent drug and metabolites are mainly excreted in the urine but about 10% is eliminated in the faeces. The elimination half-life is about 1.5 hours.

References.
1. Choudhury S, *et al.* Single-dose pharmacokinetics of nateglinide in subjects with hepatic cirrhosis. *J Clin Pharmacol* 2000; 40: 634–40.
2. Devineni D, *et al.* Pharmacokinetics of nateglinide in renally impaired diabetic patients. *J Clin Pharmacol* 2003; 43: 163–70.
3. McLeod JF. Clinical pharmacokinetics of nateglinide: a rapidly-absorbed, short-acting insulinotropic agent. *Clin Pharmacokinet* 2004; 43: 97–120.
4. Kirchheiner J, *et al.* Influence of CYP2C9 and CYP2D6 polymorphisms on the pharmacokinetics of nateglinide in genotyped healthy volunteers. *Clin Pharmacokinet* 2004; 43: 267–78.
5. Zhang W, *et al.* Effect of SLCO1B1 genetic polymorphism on the pharmacokinetics of nateglinide. *Br J Clin Pharmacol* 2006; 62: 567–72.
6. Kalliokoski A, *et al.* Different effects of SLCO1B1 polymorphism on the pharmacokinetics and pharmacodynamics of repaglinide and nateglinide. *J Clin Pharmacol* 2008; 48: 311–21.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Nateglin†; Starlix: *Braz.*: Starlix; *Canad.*: Starlix; *Chile*: Gluconol; Starlix; *China*: Antangping (安唐平); Bei Jia (贝加); Cankexin (参可欣); ChangTai (常泰); Danping (丹平); Di Fang (迪方); Fei Ge Na (菲戈纳); Fu Ge Qing (芙格清); Kai Shu (凯舒); Ke Bin (可宾); La Mu (拉姆); Luoyu (罗愉); Qi Fu (齐复); Starlix (唐力); Tang Ling (唐苓); Tang Na (唐那); Tang Rui (唐瑞); Tang Yi (唐易); Wan Su Xin (万苏欣); Xi Rui (锡瑞); Ya Li Ding (亚立订); Yi Ke Xian (逸可仙); Yi Ke Ya Xin (易克亚欣); Yi You Li An (易优利安); *Cz.*: Starlix; Trazec†; *Fin.*: Starlix†; *Ger.*: Starlix; *Gr.*: Starlix; *Hung.*: Starlix; *India*: Glinate-MF; Glinate; Natelide; *Indon.*: Starlix; *Irl.*: Starlix; *Jpn*: Starsis; *Malaysia*: Starlix; *Mex.*: Starlix; *Neth.*: Starlix; *Norw.*: Starlix; *Philipp.*: Starlix; *Pol.*: Starlix; *Port.*: Starlix; *Rus.*: Starlix (Старликс); *S.Afr.*: Starlix; *Singapore*: Starlix; *Spain*: Starlix; *Swed.*: Starlix; *Switz.*: Starlix; *Turk.*: Incuria; Mecosyn; Starlix; Teglix; *UK*: Starlix; *USA*: Starlix; *Venez.*: Starlix.

Multi-ingredient Preparations. *Braz.*: Starform; *Venez.*: Starform.

Pharmacopoeial Preparations

USP 36: Nateglinide Tablets.

Phenformin Hydrochloride *(BANM, pINNM)*

Fenformin-Hidroklorid; Fenformina Cloridrato; Fenformina, hidrocloruro de; Hidrocloruro de fenformina; Phenformine, Chlorhydrate de; Phenformini Hydrochloridum; Фенформина Гидрохлорид.

1-Phenethylbiguanide hydrochloride.

$C_{10}H_{15}N_5$,HCl=241.7

CAS — 114-86-3 (phenformin); 834-28-6 (phenformin hydrochloride).

ATC — A10BA01.

ATC Vet — QA10BA01.

UNII — 91XC93EU03.

Pharmacopoeias. In *Chin.*

Profile

Phenformin hydrochloride is a biguanide antidiabetic (p. 467.3). Although it is generally considered to be associated with an unacceptably high incidence of lactic acidosis, often fatal, it is still available in some countries for the treatment of type 2 diabetes mellitus.

Phenformin was implicated in the controversial reports of excess cardiovascular mortality associated with oral hypoglycaemic therapy (see under Sulfonylureas, Effects on the Cardiovascular System, p. 503.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Informin; *India*: DBI.

Multi-ingredient Preparations. *Gr.*: Daopar; *India*: Chlorformin; *Ital.*: Bidiabe; Gliben F; *Mex.*: Glinorboral.

Pioglitazone Hydrochloride

(BANM, USAN, rINNM)

AD-4833 (pioglitazone); Hidrocloruro de pioglitazona; Pioglitazona, hidrocloruro de; Pioglitazone, Chlorhydrate de; Pioglitazoni Hydrochloridum; U-72107A; U-72107E (pioglitazone); Пиоглитазона Гидрохлорид.

(±)-5-[*p*-[2-(5-Ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione hydrochloride.

$C_{19}H_{20}N_2O_3S$,HCl=392.9

CAS — 111025-46-8 (pioglitazone); 112529-15-4 (pioglitazone hydrochloride).

ATC — A10BG03.

ATC Vet — QA10BG03.

UNII — JQT35NPK6C.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Pioglitazone Hydrochloride). White or almost white crystals or crystalline powder. Practically insoluble in water; slightly soluble to soluble in methyl alcohol; very slightly soluble in dichloromethane.

USP 36: (Pioglitazone Hydrochloride). White crystals or crystalline powder. Practically insoluble in water; slightly soluble in dehydrated alcohol; very slightly soluble in acetone and in acetonitrile; insoluble in ether; soluble in dimethylformamide.

Uses and Administration

Pioglitazone is a thiazolidinedione antidiabetic with actions similar to those of rosiglitazone (p. 498.3). It is used in the management of type 2 diabetes mellitus (p. 459.1). It is given as pioglitazone hydrochloride but doses are expressed in terms of the base; pioglitazone hydrochloride 1.1 mg is equivalent to about 1 mg of pioglitazone. It is given orally as monotherapy, particularly in patients who are overweight and for whom metformin is contra-indicated or not tolerated. Pioglitazone may also be added to metformin or a sulfonylurea or both, or to insulin, when such therapy is inadequate (but see Administration, p. 495.1). The usual dose is 15 or 30 mg once daily. This may be increased to a maximum of 45 mg once daily if necessary. Pioglitazone may be taken with or without food.

References.

1. Waugh J, *et al.* Pioglitazone: a review of its use in type 2 diabetes mellitus. *Drugs* 2006; 66: 85–109. Correction. *ibid.*; 340–1.
2. Richter B, *et al.* Pioglitazone for type 2 diabetes mellitus. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 21/03/07).
3. Deeks ED, Scott LJ. Pioglitazone/metformin. *Drugs* 2006; 66: 1863–77.
4. Derosa G. Efficacy and tolerability of pioglitazone in patients with type 2 diabetes mellitus: comparison with other oral antihyperglycaemic agents. *Drugs* 2010; 70: 1945–61.

Administration. Although pioglitazone is licensed for use with other antidiabetic drugs, the specifics of licensing and use may vary from country to country. In both the UK and USA, pioglitazone (*Actos; Takeda*) is licensed for monotherapy, and for use with metformin or a sulfonylurea when single agent therapy is inadequate. In the UK, pioglitazone may also be used with both if necessary. However, UK[1] and combined European/US guidelines[2] do not endorse the use of thiazolidinedione monotherapy. In the UK, NICE only recommends dual therapy that includes a thiazolidinedione in patients who cannot be given a combination of metformin plus a sulfonylurea (because of drug intolerance or contra-indication, or where the risk or consequences of hypoglycaemia would be unacceptable). NICE also suggests that a thiazolidinedione only be added to metformin plus a sulfonylurea if insulin is likely to be unacceptable or inappropriate.[1] The European/US guidelines suggest that pioglitazone may be considered for addition to metformin, or metformin plus a sulfonylurea, only when hypoglycaemia is particularly undesirable.[2]

The addition of pioglitazone to insulin is licensed for use in the USA, and in the UK when the addition of metformin is inappropriate. However, there is an associated increased risk of fluid retention and heart failure for which patients should be monitored (see also Effects on the Heart, under Rosiglitazone, p. 500.2). The European/US guidelines[2] do not include a combination of thiazolidinedione with insulin, and NICE[1] only recommends pioglitazone with insulin when a thiazolidinedione has previously had a marked glucose-lowering effect, or when blood glucose is not adequately controlled on high-dose insulin therapy.

1. National Collaborating Centre for Chronic Conditions/NICE. Type 2 diabetes: the management of type 2 diabetes: partial update (issued March 2010). Available at: http://www.nice.org.uk/nicemedia/pdf/CG87NICEGuideline.pdf (accessed 11/10/11)
2. Nathan DM, *et al.* Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2009; 32: 193–203.

Diabetic complications. It has been suggested that, in addition to their hypoglycaemic effect, thiazolidinediones may have beneficial effects in the prevention of macrovascular diabetic complications (p. 462.2). Studies[1,2] in patients with type 2 diabetes mellitus have shown that pioglitazone may slow the progression of carotid intima-media thickness, an indicator for cardiovascular risk. It may also slow the progression of coronary atherosclerosis in patients with coronary artery disease.[3] The PROactive study[4] of secondary prevention found that, compared with placebo (in addition to usual medications for glucose control), pioglitazone reduced the secondary composite endpoint of death from any cause, myocardial infarction, and stroke. There was also a reduced need to add insulin for glucose control. However, there was no significant difference between the groups for the broader primary endpoint that also included acute coronary syndrome, leg amputation, and coronary or leg revascularisation. Subgroup analysis[5] also found that pioglitazone reduced the risk of fatal and non-fatal myocardial infarction and acute coronary syndrome in patients with a history of myocardial infarction. There was also a suggestion that pioglitazone reduced the risk of recurrent stroke, but there was no effect on first strokes.[6] It was unclear, however, whether this apparent effect of pioglitazone was applicable to all types of stroke, as data on stroke pathology were not available. A meta-analysis[7] that included the results of PROactive with cardiovascular outcome data from studies of glycaemic control found that pioglitazone significantly reduced the risk of death, myocardial infarction, and stroke in a diverse population of patients with type 2 diabetes. However, the risk of serious heart failure was increased (see also Effects on the Heart, p. 500.2).

It is unclear whether other thiazolidinediones might have similar effects and whether patients at lower risk might benefit.[8] Rosiglitazone and pioglitazone are known to have different effects on lipids (p. 496.1) and there is evidence that rosiglitazone may have adverse cardiovascular effects (p. 499.3).

1. Langenfeld MR, *et al.* Pioglitazone decreases carotid intima-media thickness independently of glycemic control in patients with type 2 diabetes mellitus: results from a controlled randomized study. *Circulation* 2005; 111: 2525–31.
2. Mazzone T, *et al.* Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: a randomized trial. *JAMA* 2006; 296: 2572–81.
3. Nissen SE, *et al.* PERISCOPE Investigators. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. *JAMA* 2008; 299: 1561–73.
4. Dormandy JA, *et al.* Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 2005; 366: 1279–89.
5. Erdmann E, *et al.* The effect of pioglitazone on recurrent myocardial infarction in 2,445 patients with type 2 diabetes and previous myocardial infarction: results from the PROactive (PROactive 05) Study. *J Am Coll Cardiol* 2007; 49: 1772–80.
6. Wilcox R, *et al.* PROactive Investigators. Effects of pioglitazone in patients with type 2 diabetes with or without previous stroke: results from PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events 04). *Stroke* 2007; 38: 865–73.
7. Lincoff AM, *et al.* Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. *JAMA* 2007; 298: 1180–8.
8. Rizza R, *et al.* Commentary on the results and clinical implications of the PROactive study. *Diabetes Care* 2005; 28: 2965–7.

Liver disorders. Small studies using pioglitazone in patients with nonalcoholic steatohepatitis have reported improvements in insulin sensitivity, liver function, and histology.[1-4] However, weight gain was common[1-4] and benefits were not maintained after treatment was stopped.[4,5]

1. Promrat K, *et al.* A pilot study of pioglitazone treatment for nonalcoholic steatohepatitis. *Hepatology* 2004; 39: 188–96.
2. Belfort R, *et al.* A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. *N Engl J Med* 2006; 355: 2297–2307.
3. Aithal GP, *et al.* Randomized, placebo-controlled trial of pioglitazone in nondiabetic subjects with nonalcoholic steatohepatitis. *Gastroenterology* 2008; 135: 1176–84.
4. Sanyal AJ, *et al.* Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. *N Engl J Med* 2010; 362: 1675–85.
5. Lutchman G, *et al.* The effects of discontinuing pioglitazone in patients with nonalcoholic steatohepatitis. *Hepatology* 2007; 46: 424–9.

Malignant neoplasms. For references to the experimental use of pioglitazone with rofecoxib and trofosfamide as anti-angiogenic therapy for malignant neoplasms see Trofosfamide, p. 878.1.

Psoriasis. It has been suggested that by binding to peroxisome proliferator-activated receptor gamma (PPARγ), pioglitazone may have an anti-inflammatory effect in conditions such as chronic plaque psoriasis (p. 1688.1) and psoriatic arthritis (see Spondyloarthropathies, p. 14.3). In a small open-label study,[1] oral doses of 30 mg daily were reported to improve moderate chronic plaque psoriasis in 4 of 5 patients, with definite improvement seen 1 to 3 months after starting therapy. Treatment was stopped in 1 other patient because of fluid retention. In a double-blind study,[2] 70 patients with moderate to severe disease were treated for 10 weeks with daily doses of pioglitazone 15 mg, 30 mg, or placebo. Greater improvements were reported with pioglitazone than with placebo, and the dose of 30 mg appeared to be slightly more effective than 15 mg. A 12-week randomised placebo-controlled study[3] in 41 patients also with moderate to severe disease found that those who were given pioglitazone 15 mg daily plus acitretin 25 mg daily showed more improvement than patients given acitretin plus placebo. There has also been a report[4] of improvements in tender and swollen joints in a small group of patients with psoriatic arthritis who were given a high dose of pioglitazone (30 mg twice daily) for 12 weeks. Fluid retention was reported.

The effect of rosiglitazone has also been studied in moderate to severe chronic plaque psoriasis. Two large studies that included more than 2500 patients found that rosiglitazone, in oral doses of 2 mg, 4 mg, or 8 mg daily, was no more effective than placebo over a treatment period of 12 months. Similar results were also found in patients who continued in 44-week blinded extension studies. Interestingly, improvement occurred in all groups, and there was evidence of a large placebo response.[5]

1. Robertshaw H, Friedmann PS. Pioglitazone: a promising therapy for psoriasis. *Br J Dermatol* 2005; 152: 189–91.
2. Shafiq N, *et al.* Pilot trial: pioglitazone versus placebo in patients with plaque psoriasis (the PPP). *Int J Dermatol* 2005; 44: 328–33.
3. Mittal R, *et al.* Efficacy and safety of combination acitretin and pioglitazone therapy in patients with moderate to severe chronic plaque-type psoriasis: a randomized, double-blind, placebo-controlled clinical trial. *Arch Dermatol* 2009; 145: 387–93.
4. Bongartz T, *et al.* Treatment of active psoriatic arthritis with the PPAR γ ligand pioglitazone: an open-label pilot study. *Rheumatology (Oxford)* 2005; 44: 126–9.
5. Ellis CN, *et al.* Avandia Psoriasis Study Group. Placebo response in two long-term randomized psoriasis studies that were negative for rosiglitazone. *Am J Clin Dermatol* 2007; 8: 93–102.

Reperfusion and revascularisation procedures. Thiazolidinediones are under investigation in the prevention of restenosis after percutaneous coronary revascularisation procedures—see under Rosiglitazone, p. 499.2.

Adverse Effects and Precautions

As for Rosiglitazone, p. 499.2. The effects of pioglitazone on serum lipid concentrations appear to differ from those of rosiglitazone, see p. 496.1. Other adverse effects reported include upper respiratory-tract infections, haematuria, and visual disturbances. For precautions and contra-indications to the use of thiazolidinediones in heart failure see Effects on the Heart, under Rosiglitazone, p. 500.2. Liver function should be monitored periodically as there have been isolated reports of liver dysfunction, and the drug should be used with caution in patients with hepatic impairment (see p. 496.2).

An increased risk of bladder cancer has been reported for pioglitazone (see p. 496.1).

Incidence of adverse effects. The placebo-controlled PROactive study[1] of pioglitazone for secondary prevention of cardiovascular events in patients with type 2 diabetes recorded oedema in 26.4% of 2605 patients given pioglitazone, compared with 15.1% in 2633 given placebo; heart failure occurred in 10.8% and 7.5%, respectively, but rates of death from heart failure were similar for the 2 groups. The study also found an increased rate of fracture

in women given pioglitazone. Average weight gain was 3.8 kg (after 30 months or at the final visit) compared with a loss of 0.6 kg for placebo. Hypoglycaemia occurred in 27.2% of patients treated with pioglitazone, compared with 18.8% in the placebo group, but was highly dependent on the use of other antidiabetic drugs, particularly insulin and sulfonylureas.

A study of postmarketing events used data from more than 12 000 patients started on pioglitazone treatment, almost all of whom were also taking at least one other oral antidiabetic.[2] The suspected adverse effects most commonly attributed to pioglitazone were malaise or lassitude, nausea or vomiting, dizziness, headache, diarrhoea, oedema, visual disturbances, joint pain, and weight gain.

1. Dormandy J, *et al.* PROactive investigators. Safety and tolerability of pioglitazone in high-risk patients with type 2 diabetes: an overview of data from PROactive. *Drug Safety* 2009; 32: 187–202.
2. Kasliwal R, *et al.* Monitoring the safety of pioglitazone: results of a prescription-event monitoring study of 12 772 patients in England. *Drug Safety* 2008; 31: 839–50.

Carcinogenicity. An interim report of a longitudinal cohort study[1] concluded that pioglitazone use for more than 2 years was weakly associated with an increased risk of bladder cancer. This prompted the FDA to recommend that pioglitazone should not be used in patients with active bladder cancer, and used with caution in those with a history of the disease.[2] However, based on this and other epidemiological studies, the EMEA concluded that pioglitazone should be avoided in patients with either a history of bladder cancer or current disease.[3]

1. Lewis JD, *et al.* Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study. *Diabetes Care* 2011; 34: 916–22.
2. FDA. Update to ongoing safety review of Actos (pioglitazone) and increased risk of bladder cancer (issued 15th June, 2011). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm259150.htm (accessed 01/08/11)
3. EMEA. European Medicines Agency recommends new contra-indications and warnings for pioglitazone to reduce small increased risk of bladder cancer: benefit-risk balance remains positive in a limited population of type 2 diabetics (issued 21st July, 2011). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2011/07/WC500109176.pdf (accessed 01/08/11)

Effects on lipids. Thiazolidinediones are reported to affect serum concentrations of lipids. Compared with placebo in short-term studies,[1,2] pioglitazone has been found to reduce triglycerides, increase high-density lipoprotein (HDL)-cholesterol, and have little or no effect on low-density lipoprotein (LDL)- and total cholesterol. Pooled data from 4 studies of pioglitazone given for a year, used alone or with metformin or a sulfonylurea, also found that pioglitazone reduced triglycerides and increased HDL-cholesterol.[3] There were also reductions in free fatty acid concentrations and in the ratio of total to HDL-cholesterol.

In studies of patients transferred from troglitazone to another thiazolidinedione, lipid profiles have improved in those given pioglitazone,[4,5] but significant increases in total and LDL-cholesterol, and triglycerides, have occurred in some patients transferred to rosiglitazone.[4] A controlled study[6] in more than 800 patients with type 2 diabetes and dyslipidaemia has also directly compared the effects of two thiazolidinediones, finding again a more desirable response to pioglitazone than to rosiglitazone. Triglycerides significantly decreased with pioglitazone but increased with rosiglitazone, greater rises in HDL-cholesterol occurred with pioglitazone than rosiglitazone, and although both increased LDL-cholesterol the effect was less significant with pioglitazone.[6] The study also found that these drugs had different effects on lipoprotein particle concentrations and size.[6,7]

Whether these effects of pioglitazone reduce cardiovascular risk in patients with type 2 diabetes is yet to be fully established, but the large prospective PROactive study did suggest that it could reduce the risk of macrovascular events in patients with evidence of macrovascular disease, although the risk of heart failure appears to be *increased* (see Diabetic Complications, p. 493.2, and Effects on the Heart, under Rosiglitazone, p. 500.2).

1. Kipnes MS, *et al.* Pioglitazone hydrochloride in combination with sulfonylurea therapy improves glycemic control in patients with type 2 diabetes mellitus: a randomized, placebo-controlled study. *Am J Med* 2001; 111: 10–17.
2. Rosenblatt S, *et al.* The impact of pioglitazone on glycemic control and atherogenic dyslipidemia in patients with type 2 diabetes mellitus. *Coron Artery Dis* 2001; 12: 413–23.
3. Khan M, *et al.* Effects of pioglitazone on the components of diabetic dyslipidaemia: results of double-blind, multicentre, randomised studies. *Int J Clin Pract* 2004; 58: 907–12.
4. Gegick CG, Altheimer MD. Comparison of effects of thiazolidinediones on cardiovascular risk factors: observations from a clinical practice. *Endocr Pract* 2001; 7: 162–9.
5. Khan MA, *et al.* A prospective, randomized comparison of the metabolic effects of pioglitazone or rosiglitazone in patients with type 2 diabetes who were previously treated with troglitazone. *Diabetes Care* 2002; 25: 708–11.
6. Goldberg RB, *et al.* GLAI Study Investigators. A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. *Diabetes Care* 2005; 28: 1547–54.
7. Deeg MA, *et al.* GLAI Study Investigators. Pioglitazone and rosiglitazone have different effects on serum lipoprotein particle concentrations and sizes in patients with type 2 diabetes and dyslipidemia. *Diabetes Care* 2007; 30: 2458–64.

Effects on the liver. There have been isolated reports of hepatocellular injury including fatalities, in patients receiving pioglitazone.[1-6] However, retrospective analysis of a medical and pharmacy claims database found no evidence of an increased risk of liver failure or hepatitis for pioglitazone, compared with rosiglitazone, sulfonylureas, or metformin.[7] Additionally, a 3-year randomised study of liver safety in type 2 diabetics using pioglitazone[8] showed no serious drug-induced liver injury.

UK and US licensed product information recommends that liver enzymes should be checked before starting therapy with pioglitazone; patients with aminotransferase (ALT) concentrations more than 2.5 times the upper limit of normal should not be given pioglitazone. ALT concentrations should then be monitored periodically during treatment. If ALT concentrations rise to more than 3 times the upper limit of normal and remain so after retesting then treatment with pioglitazone should be stopped; treatment should also be stopped if jaundice develops.

1. Maeda K. Hepatocellular injury in a patient receiving pioglitazone. *Ann Intern Med* 2001; 135: 306.
2. May LD, *et al.* Mixed hepatocellular-cholestatic liver injury after pioglitazone therapy. *Ann Intern Med* 2002; 136: 449–52.
3. Pinto AG, *et al.* Severe but reversible cholestatic liver injury after pioglitazone therapy. *Ann Intern Med* 2002; 137: 857.
4. Chase MP, Yarze JC. Pioglitazone-associated fulminant hepatic failure. *Am J Gastroenterol* 2002; 97: 502–3.
5. Farley-Hills E, *et al.* Fatal liver failure associated with pioglitazone. *BMJ* 2004; 329: 429.
6. Floyd JS, *et al.* Case series of liver failure associated with rosiglitazone and pioglitazone. *Pharmacoepidemiol Drug Safety* 2009; 18: 1238–43.
7. Rajagopalan R, *et al.* Comparison of pioglitazone with other antidiabetic drugs for associated incidence of liver failure: no evidence of increased risk of liver failure with pioglitazone. *Diabetes Obes Metab* 2005; 7: 161–9.
8. Tolman KG, *et al.* Liver safety in patients with type 2 diabetes treated with pioglitazone: results from a 3-year, randomized, comparator-controlled study in the US. *Drug Safety* 2009; 32: 787–800.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pioglitazone as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Interactions

Pioglitazone is extensively metabolised, mainly by the cytochrome P450 isoenzyme CYP2C8. When given with gemfibrozil, an inhibitor of CYP2C8, there may be a threefold increase in the AUC of pioglitazone; a decrease in pioglitazone dose may be needed if it is given with gemfibrozil or similar CYP2C8 inhibitors. Conversely, rifampicin, a potent inducer of cytochrome P450, halves the AUC of pioglitazone when both are given, and the pioglitazone dose may need to be increased.

Use of insulin with pioglitazone may increase the risk of oedema and heart failure (see also Effects on the Heart, under Rosiglitazone, p. 500.2, and Administration, p. 493.1).

Antibacterials. See under Rosiglitazone, p. 501.1, for a reference to the interaction between pioglitazone and *rifampicin*. For a report of hypoglycaemia when *gatifloxacin* was given to a patient already receiving oral hypoglycaemics including pioglitazone, see p. 304.1.

Lipid regulating drugs. For references to the interaction between pioglitazone and *gemfibrozil*, see under Rosiglitazone, p. 501.1.

Pharmacokinetics

Pioglitazone is rapidly absorbed after oral doses. Peak plasma concentrations occur within 2 hours and bioavailability exceeds 80%. Pioglitazone is more than 99% bound to plasma proteins. It is extensively metabolised, mainly by the cytochrome P450 isoenzyme CYP2C8 to both active and inactive metabolites. It is excreted in urine and faeces and has a plasma half-life of up to 7 hours. The active metabolites have a half-life of up to 24 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Actos; Cerelug; Higlucem; Miglen; Pioglit; Piotamax; Zatium; *Austral.*: Acpio; Actos; Vexazone; *Austria*: Actos; *Belg.*: Actos; *Braz.*: Actos; Aglitil; Piotaz; *Canad.*: Actos; *Chile*: Actos; Tiaza; Zatium; *China*: Actins (艾汀); Actos (艾可拓); An Ke Tuo (安可妥); An Long Ping (安龙平); Beitangning (贝唐宁); Dun Ling (顿灵); Jia Pu Xi (佳普喜); Jiang Shuang (绛爽); Kai Bao Wei Yuan (凯宝维元); Kasiping (卡司平); Kecheng (可成); Lie Luo (列洛); Ou Di Bei (欧迪贝); Qian Er (倩尔); Rui Ge Lin (瑞格临); Rui Tong (瑞彤); Tai Luo Ping (泰洛平); Wan Su Min (万苏敏); Wei Yuan (维元); Yi You (爽友); *Cz.*: Actos; Glustin; *Denm.*: Actos; *Fin.*: Actos; *Fr.* Actos†; *Ger.*: Actos; *Gr.*: Actos; *Hong Kong*: Actos; *Hung.* Actos; *India*: Betapride; Depel; Diaglit; Diavista; G-Tase; Glita; Glito; Glitter; Glizone; Glufit; K-Pio; Lita; Logit; Oglo; Opam; P-Glitz; Pepar; Piomed; Piosafe; Piozulin; *Indon.*: Actos; Deculin; Pionix-M; Pionix; *Irl.*: Actos; Glustin; *Ital.*: Actos; *Jpn*: Actos; *Malaysia*: Actos; *Mex.*: Zactos; *Neth.*: Actos; Glustin; Paglitaz; Sepioglin†; Sympion; *Norw.*: Actos; *NZ*: Actos; Pizaccord; *Philipp.*: Actos; Diabetone; Glitaz; Glitter; Glizone; Glucozone; Insulact; Piotaz; Piouno; Piozar; Piozone; Ppar; Prialta; Pyoglit; Zolid; Zypl; *Pol.*: Actos; Glustin; *Port.*: Actos; Glustin; *Rus.*: Actos (Актос); Amalvia (Амальвиа); Astrozone (Астрозон); Diab-Norm (Диаб-Норм); Diaglitazon (Диаглитазон); Pioglar (Пиоглар); Pioglit (Пиоглит); *S.Afr.*: Actos; *Singapore*: Actos; *Spain*: Actos; Glustin; *Swed.*: Actos; *Switz.*: Actos; *Thai.*: Actos; Gitazone; Glubosil; Piozone; Senzulin; Utmos; *Turk.*: Actos; Dropia; Glifix; Pioforce; Piogtan; Piondia; *UK*: Actos; Glidipion; *Ukr.*: Nilgar (Нилгар)†; Pioglar (Пиоглар); Pioz (Пиоз); *USA*: Actos; *Venez.*: Actos.

Multi-ingredient Preparations. *Austria*: Competact; Tandemact; *Chile*: Actos Met; *China*: Furuitong (复瑞彤); *Cz.*: Competact; Glubrava; Tandemact; *Fr.*: Competact†; Tandemact†; *Ger.*: Competact; Tandemact; *Gr.*: Competact; *Hong Kong*: Actosmet; *Hung.*: Competact; *India*: Adride-P; Bigan-P; Cetapin P; Daoride-PM; Diamet PG; Dianosis-P3; Diavista-M; Diazero-PM; Dibiglim-P; Euglim-MP; Euglim-P; Euroglip Forte; Exermet P; G-Tase G; G-Tase M; Gemer P; Gimip-PM; Gitar; Glamor-P; Glamor-PM; Glimestar PM; Glimizide-PG; Glimsite-MP; Glimy-MP; Glimy-P; Glita-M; Glitafor; Glitter-M; Glizone-M; GLP-PM; Gluconorm-P; Glucut-GMP; Glyciphage PG; Glyciphage-P; GPM; Idapride-PM; Ioglime; Iscept-P; K-Pio-G; K-Pio-M; Lita-M; Matce-P; Matce-PG; Metanorm P; Metride Plus; Mopaday; One Dia; P&M; P-Glitz M; Piomed M; Piosafe MF; *Irl.*: Competact; Glubrava; Tandemact; *Ital.*: Competact; Tandemact; *Jpn*: Liovel; Sonias; *Mex.*: Competact; Diabamet; *Neth.*: Competact; Glubrava; Tandemact; *Norw.*: Competact; *Philipp.*: Actosmet; Asenza Plus; Prialta-Met; *Pol.*: Competact; Glubrava; Tandemact; *Port.*: Competact; Glubrava; Tandemact; *Spain*: Competact; Glubrava; Tandemact; *Swed.*: Competact; *Switz.*: Competact; *Thai.*: Actosmet; *Turk.*: Dropia-Met; Preko; *UK*: Competact; *Ukr.*: Tripride (Трипрайд); *USA*: Actoplus Met; Duetact; Oseni.

Pharmacopoeial Preparations

USP 36: Pioglitazone and Glimepiride Tablets; Pioglitazone and Metformin Hydrochloride Tablets; Pioglitazone Tablets.

Pramlintide *(BAN, USAN, rINN)*

AC-0137 (pramlintide or pramlintide acetate); AC-137; Pramlintida; Pramlintidum; Pramlintyd; Tripro-amylin; Прамлинтид.

$C_{171}H_{267}N_{51}O_{53}S_2$=3949.4

CAS — 151126-32-8.

ATC — A10BX05.

ATC Vet — QA10BX05.

UNII — D3FM8FA78T.

Pramlintide Acetate *(BANM, USAN, rINNM)*

AC-0137 (pramlintide or pramlintide acetate); Acetato de pramlintida; Pramlintide, Acétate de; Pramlintidi Acetas; Прамлинтида Ацетат.

25-L-Proline-28-L-proline-29-L-prolineamylin (human) acetate hydrate.

$C_{171}H_{267}N_{51}O_{53}S_2$, $xC_2H_4O_2$, yH_2O

CAS — 196078-30-5.

ATC — A10BX05.

ATC Vet — QA10BX05.

UNII — 726I6TE06G.

Incompatibility. The possible effect of mixing pramlintide with insulin (regular or isophane) in the same syringe has been studied.[1] Patients with type 1 diabetes were given the study treatments, either separately or as a combination mixed within 5 minutes before injection, on single occasions in a crossover study. Although there were minor changes in the pharmacokinetics of pramlintide, they were considered to be clinically insignificant. However, the authors cautioned that the study did not cover the full range of insulin formulations available, the long-term use of such combinations, or the range of doses used in clinical practice. Licensed product information for pramlintide warns that it should not be mixed in the same syringe with insulin because of reported changes in the pharmacokinetic parameters of pramlintide.

1. Weyer C, *et al.* Properties of pramlintide and insulin upon mixing. *Am J Health-Syst Pharm* 2005; 62: 816–22.

Uses and Administration

Pramlintide is a synthetic analogue of amylin, a pancreatic peptide hormone thought to play a role in the regulation of glucose homoeostasis. It differs from amylin by replacement with proline at positions 25 (alanine), 28 (serine), and 29 (serine). Pramlintide slows the rate of gastric emptying,

prevents the postprandial rise in glucagon concentrations, and reduces appetite. It is used in the management of diabetes mellitus (p. 459.1) that is not adequately controlled by mealtime insulin therapy. Pramlintide is given as the acetate, but doses are expressed in terms of the base.

In patients with type 1 diabetes mellitus, an initial dose of pramlintide 15 micrograms is given subcutaneously immediately before major meals. The dose of any rapid-acting or short-acting insulins, including premixed insulins, given before meals should be halved. The pramlintide dose may be increased in increments of 15 micrograms to a maintenance dose of 30 or 60 micrograms when no clinically significant nausea has occurred for at least 3 days. Once the maintenance dose of pramlintide has been achieved, the dose of insulin should be further adjusted for optimum glycaemic control.

In patients with type 2 diabetes mellitus who are using insulin, the initial dose of pramlintide is 60 micrograms, subcutaneously, immediately before major meals. The dose may be increased to 120 micrograms when no nausea has occurred for 3 to 7 days. The dose of insulin therapy should be adjusted as described for patients with type 1 diabetes mellitus (above).

References.
1. Hollander PA, *et al.* Pramlintide as an adjunct to insulin therapy improves long-term glycemic and weight control in patients with type 2 diabetes: a 1-year randomized controlled trial. *Diabetes Care* 2003; 26: 784–90.
2. Kruger DF, Gloster MA. Pramlintide for the treatment of insulin-requiring diabetes mellitus: rationale and review of clinical data. *Drugs* 2004; 64: 1419–32.
3. Ratner RE, *et al.* Amylin replacement with pramlintide as an adjunct to insulin therapy improves long-term glycaemic and weight control in type 1 diabetes mellitus: a 1-year, randomized controlled trial. *Diabet Med* 2004; 21: 1204–12.
4. Riddle M, *et al.* Pramlintide improved glycemic control and reduced weight in patients with type 2 diabetes using basal insulin. *Diabetes Care* 2007; 30: 2794–9.
5. Singh-Franco D, *et al.* Pramlintide acetate injection for the treatment of type 1 and type 2 diabetes mellitus. *Clin Ther* 2007; 29: 535–62.
6. Ryan G, *et al.* Review of pramlintide as adjunctive therapy in treatment of type 1 and type 2 diabetes. *Drug Des Devel Ther* 2009; 2: 203–14.
7. Pencek R, *et al.* Safety of pramlintide added to mealtime insulin in patients with type 1 or type 2 diabetes: a large observational study. *Diabetes Obes Metab* 2010; 12: 548–51.
8. Lee NJ, *et al.* Efficacy and harms of the hypoglycemic agent pramlintide in diabetes mellitus. *Ann Fam Med* 2010; 8: 542–9.
9. Singh-Franco D, *et al.* The effect of pramlintide acetate on glycemic control and weight in patients with type 2 diabetes mellitus and in obese patients without diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab* 2011; 13: 169–80.
10. Younk LM, *et al.* Pramlintide and the treatment of diabetes: a review of the data since its introduction. *Expert Opin Pharmacother* 2011; 12: 1439–51.

Obesity. Pramlintide is under investigation in the management of obesity[1-4] (p. 2315.1).

1. Smith SR, *et al.* Pramlintide treatment reduces 24-h caloric intake and meal sizes and improves control of eating in obese subjects: a 6-wk translational research study. *Am J Physiol Endocrinol Metab* 2007; 293: E620–E627.
2. Smith SR, *et al.* Sustained weight loss following 12-month pramlintide treatment as an adjunct to lifestyle intervention in obesity. *Diabetes Care* 2008; 31: 1816–23.
3. Dunican KC, *et al.* The role of pramlintide for weight loss. *Ann Pharmacother* 2010; 44: 538–45.
4. Singh-Franco D, *et al.* The effect of pramlintide acetate on glycemic control and weight in patients with type 2 diabetes mellitus and in obese patients without diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab* 2011; 13: 169–80.

Adverse Effects and Precautions

Pramlintide alone does not cause hypoglycaemia, but increases the risk associated with insulin use, particularly in type 1 diabetes mellitus; severe hypoglycaemia may occur within 3 hours of pramlintide injection. Blood-glucose concentrations must be closely monitored, both before and after meals, and the dose of insulin should be halved when pramlintide therapy is started (see Uses and Administration, p. 494.3).

Other adverse effects of pramlintide include nausea, vomiting, anorexia, headache, reactions at the injection site, and hypersensitivity. Nausea commonly occurs at the beginning of therapy and decreases with time; incidence and severity are reduced if pramlintide is gradually titrated to the maintenance dose. Pramlintide is contra-indicated in patients with gastroparesis.

Interactions

Pramlintide has the potential to delay the absorption of oral medication; in cases where the rapid onset of action from an oral drug is critical, it should be given at least 1 hour before or 2 hours after pramlintide. Also, pramlintide may interfere with drugs given to alter gastrointestinal motility or absorption.

Pramlintide increases the risk of insulin-induced hypoglycaemia (see Adverse Effects and Precautions, above).

Pharmacokinetics

The bioavailability of pramlintide is about 30 to 40% from a subcutaneous injection, and peak plasma concentrations are reached after about 20 minutes. It is metabolised by the kidneys and has a half-life of about 48 minutes in healthy subjects.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Symlin.

Repaglinide *(BAN, USAN, rINN)*

AG-EE-6232W; AG-EE-623-ZW; Repaglinid; Repaglinida; Repaglinidas; Répaglinide; Repaglinidi; Repaglinidum; Репаглинид.

(+)-2-Ethoxy-α-[[(*S*)-α-isobutyl-*o*-piperidinobenzyl]carbamoyl]-*p*-toluic acid; (*S*)-2-Ethoxy-4-[[1-(*o*-piperidinophenyl)-3-methylbutyl]carbamoylmethyl]benzoic acid.

$C_{27}H_{36}N_2O_4$=452.6

CAS — 135062-02-1.

ATC — A10BX02.

ATC Vet — QA10BX02.

UNII — 668Z8C33LU.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Repaglinide). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; freely soluble in dichloromethane and in methyl alcohol. Protect from light.

USP 36: (Repaglinide). A white to off-white solid. Soluble in methyl alcohol. Store in airtight containers.

Uses and Administration

Repaglinide is a meglitinide antidiabetic used for the treatment of type 2 diabetes mellitus (p. 459.1). It has a chemical structure different from that of the sulfonylureas, but appears to have a similar mode of action and is also described as an insulin secretagogue.

Repaglinide is given up to 30 minutes before meals, and usually within 15 minutes, in initial oral doses of 500 micrograms; initial doses of 1 or 2 mg are given to patients who have had previous hypoglycaemic treatment. The dose may be adjusted, at intervals of 1 to 2 weeks, up to a maximum of 4 mg before meals; a total of 16 mg daily should not be exceeded. Repaglinide is also given with metformin or a thiazolidinedione in type 2 diabetes not adequately controlled by monotherapy. When given with metformin in a combination preparation, the maximum recommended daily dose of repaglinide is 10 mg.

References.
1. Moses RG, *et al.* Flexible meal-related dosing with repaglinide facilitates glycemic control in therapy-naive type 2 diabetes. *Diabetes Care* 2001; 24: 11–15.
2. Culy CR, Jarvis B. Repaglinide: a review of its therapeutic use in type 2 diabetes mellitus. *Drugs* 2001; 61: 1625–60.
3. Black C, *et al.* Meglitinide analogues for type 2 diabetes mellitus. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 13/03/09).
4. Johansen OE, Birkeland KI. Defining the role of repaglinide in the management of type 2 diabetes mellitus: a review. *Am J Cardiovasc Drugs* 2007; 7: 319–35.

Administration in renal impairment. Although repaglinide is cleared mainly by hepatic metabolism, small pharmacokinetic studies have reported that exposure to repaglinide may be increased in patients with renal impairment.[1,2] A larger open-label study[3] that included 151 patients with normal renal function and 130 patients with varying degrees of renal impairment found that the incidence of adverse effects was not influenced by renal function. However, at the end of the 3-month maintenance treatment period, there was a trend towards lower effective doses of repaglinide with increasing degree of renal impairment. US licensed product information suggests that the usual initial oral dose of repaglinide 500 micrograms before meals may be used in severe renal impairment, and adjusted with care.

1. Marbury TC, *et al.* Pharmacokinetics of repaglinide in subjects with renal impairment. *Clin Pharmacol Ther* 2000; 67: 7–15.
2. Schumacher S, *et al.* Single- and multiple-dose pharmacokinetics of repaglinide in patients with type 2 diabetes and renal impairment. *Eur J Clin Pharmacol* 2001; 57: 147–52.
3. Hasslacher C. Safety and efficacy of repaglinide in type 2 diabetic patients with and without impaired renal function. *Diabetes Care* 2003; 26: 886–91.

Adverse Effects and Precautions

Repaglinide may cause gastrointestinal adverse effects including abdominal pain, diarrhoea, constipation, nausea, and vomiting. Hypoglycaemia may be common, but is usually mild. Back and joint pain have also been reported. Rare effects have included hypersensitivity reactions, vasculitis, pruritus, rashes, urticaria, Stevens-Johnson syndrome, elevated liver enzyme values, severe hepatic dysfunction, pancreatitis, haemolytic anaemia, leucopenia, and thrombocytopenia. There have also been rare cases of transient visual disturbances attributed to changes in blood-glucose concentrations associated with starting repaglinide treatment. Myocardial ischaemia has been reported in patients who were treated with repaglinide and isophane insulin; the combination is not recommended.

Precautions are similar to those which apply with the shorter-acting sulfonylurea hypoglycaemics (p. 504.2). Repaglinide should be given with caution to patients with hepatic impairment (consideration should be given to extending the interval between dose adjustments), and possibly avoided in severe impairment.

Incidence of adverse effects. Diarrhoea, abdominal pain, and nausea were found to be the adverse effects most commonly reported during the first 6 months of repaglinide therapy in an analysis of postmarketing data relating to 5731 patients. The effects that occurred more often in the first month of treatment, compared with months 2 to 6, included diarrhoea, nausea or vomiting, abdominal pain or distension, malaise or lassitude, headache or migraine, dizziness, and hypoglycaemia. There were also reports of rash, visual disturbance, palpitations, and abnormal liver function values.[1]

1. Marshall V, *et al.* Safety profile of repaglinide as used in general practice in England: results of a prescription-event monitoring study. *Acta Diabetol* 2006; 43: 6–13.

Abuse. Several episodes of serious hypoglycaemia, once accompanied by seizures, occurred in a young man who covertly took repaglinide.[1]

1. Hirshberg B, *et al.* Repaglinide-induced factitious hypoglycemia. *J Clin Endocrinol Metab* 2001; 86: 475–7.

Driving. Diabetes mellitus, its complications, and the medications used to treat it, may affect a patient's ability to drive safely—see under Insulin (p. 485.2) for restrictions applied to diabetic patients in the UK.

Effects on the liver. Hepatotoxic reactions have been reported for repaglinide[1,2] including cholestatic hepatitis and jaundice with pruritus.

1. Nan DN, *et al.* Acute hepatotoxicity caused by repaglinide. *Ann Intern Med* 2004; 141: 823.
2. López-García F, *et al.* Cholestatic hepatitis associated with repaglinide. *Diabetes Care* 2005; 28: 752–3.

Fasting. For mention that nateglinide or repaglinide can probably be used with low risk of hypoglycaemia in fasting Muslim patients during Ramadan see under Precautions of Insulin, p. 485.3.

Hypoglycaemia. Mild hypoglycaemia has been reported in patients receiving repaglinide,[1] although in a study comparing flexible repaglinide dosing with fixed glibenclamide dosing, all hypoglycaemic events recorded were in the glibenclamide group.[2] Other studies have found rates of hypoglycaemia in patients receiving repaglinide to be less than, or similar to, sulfonylureas.[3] The risk of hypoglycaemia may be reduced as patients can omit a dose of repaglinide if a meal is missed. Serious hypoglycaemia resulting in a seizure has been reported[4] in a patient who took a missed dose of repaglinide 3 hours after his evening meal. The risk was probably further increased because of hepatic impairment. An observational study[5] based on prescription-event monitoring data in the UK suggested that hypoglycaemic events were most likely shortly after starting treatment with repaglinide. For a report of factitious hypoglycaemia, see Abuse, above.

1. Moses RG, *et al.* Flexible meal-related dosing with repaglinide facilitates glycemic control in therapy-naive type 2 diabetes. *Diabetes Care* 2001; 24: 11–15.
2. Damsbo P, *et al.* A double-blind randomized comparison of meal-related glycemic control by repaglinide and glyburide in well-controlled type 2 diabetic patients. *Diabetes Care* 1999; 22: 789–94.
3. Culy CR, Jarvis B. Repaglinide: a review of its therapeutic use in type 2 diabetes mellitus. *Drugs* 2001; 61: 1625–60.
4. Flood TM. Serious hypoglycemia associated with misuse of repaglinide. *Endocr Pract* 1999; 5: 137–8.
5. Vickova V, *et al.* Hypoglycaemia with oral antidiabetic drugs: results from prescription-event monitoring cohorts of rosiglitazone, pioglitazone, nateglinide and repaglinide. *Drug Safety* 2009; 32: 409–18.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies repaglinide as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Pregnancy. Insulin is generally preferred to oral antidiabetics in the treatment of diabetes mellitus during pregnancy. Repaglinide has been used in 3 women during the first 6 to 7 weeks of gestation;[1,2] treatment was then changed to insulin for the rest of the pregnancy. Their babies were delivered at term, with adequate weight for birth age and no congenital malformations. An analysis of postmarketing data found 5 reports of repaglinide use dur-

ing pregnancy.[3] Three babies were born with no abnormalities reported, the outcome of one pregnancy was unknown, and in one case Fraser syndrome was diagnosed and the baby stillborn at 26 weeks.

1. Napoli A, *et al.* Use of repaglinide during the first weeks of pregnancy in two type 2 diabetic women. *Diabetes Care* 2006; **29:** 2326–7.
2. Mollar-Puchades MA, *et al.* Use of repaglinide on a pregnant woman during embryogenesis. *Diabetes Obes Metab* 2007; **9:** 146–7.
3. Marshall V, *et al.* Safety profile of repaglinide as used in general practice in England: results of a prescription-event monitoring study. *Acta Diabetol* 2006; **43:** 6–13.

Interactions

The efficacy of repaglinide may be affected by other drugs that have an independent effect on blood glucose. For more details and examples of drugs that can increase or decrease blood-glucose concentrations, see Interactions under Sulfonylureas, p. 504.3.

Drugs that affect the cytochrome P450 isoenzymes CYP2C8 and CYP3A4 may alter the metabolism of repaglinide. Use of repaglinide with the CYP2C8 inhibitor gemfibrozil has resulted in marked reduction in repaglinide clearance, and severe hypoglycaemia; licensed product information contra-indicates concomitant use. Repaglinide also appears to be a substrate for active hepatic uptake by the organic anion transporting protein OATP1B1, and may be affected by drugs that have the potential for its inhibition.

References.

1. Hatorp V, Thomsen MS. Drug interaction studies with repaglinide: repaglinide on digoxin or theophylline pharmacokinetics and cimetidine on repaglinide pharmacokinetics. *J Clin Pharmacol* 2000; **40:** 184–92.
2. Hatorp V, *et al.* Influence of drugs interacting with CYP3A4 on the pharmacokinetics, pharmacodynamics, and safety of the prandial glucose regulator repaglinide. *J Clin Pharmacol* 2003; **43:** 649–60.
3. Scheen AJ. Drug-drug and food-drug pharmacokinetic interactions with new insulinotropic agents repaglinide and nateglinide. *Clin Pharmacokinet* 2007; **46:** 93–108.

Antibacterials. A study[1] in healthy subjects found that the plasma concentration of a single dose of repaglinide was reduced, and its half-life shortened, when it was given 12.5 hours after the last dose of a 5-day course of *rifampicin*. This effect was attributed to the induction of the cytochrome P450 isoenzyme CYP3A4 by rifampicin. In another study[2] repaglinide was given either with the last dose of a 7-day course of rifampicin or 24 hours later, and the effects on repaglinide were found to be greater on day 8 than day 7. The authors suggested that rifampicin acted as both an inducer and an inhibitor of CYP3A4 and possibly CYP2C8, and that after rifampicin was stopped its inductive effect lasted longer, thereby having a greater effect 24 hours later.

A study[3] in healthy subjects reported that *clarithromycin* can increase the plasma concentrations and prolong the elimination half-life of repaglinide, probably by inhibition of CYP3A4. An 80-year-old man stabilised on repaglinide therapy suffered severe hypoglycaemia about 48 hours after starting clarithromycin.[4] *Telithromycin*, another inhibitor of CYP3A4, also increased plasma concentrations of repaglinide in a study of healthy subjects, although the elimination half-life of repaglinide was not significantly affected.[5] *Trimethoprim*[6,7] can have a similar effect by the inhibition of CYP2C8.

For a report of hypoglycaemia when *gatifloxacin* was given to a patient already receiving repaglinide, see p. 304.1.

1. Niemi M, *et al.* Rifampin decreases the plasma concentrations and effects of repaglinide. *Clin Pharmacol Ther* 2000; **68:** 495–500.
2. Bidstrup TB, *et al.* Rifampicin seems to act as both an inducer and an inhibitor of the metabolism of repaglinide. *Eur J Clin Pharmacol* 2004; **60:** 109–14.
3. Niemi M, *et al.* The cytochrome P4503A4 inhibitor clarithromycin increases the plasma concentrations and effects of repaglinide. *Clin Pharmacol Ther* 2001; **70:** 58–65.
4. Khamaisi M, Leitersdorf E. Severe hypoglycemia from clarithromycin-repaglinide drug interaction. *Pharmacotherapy* 2008; **28:** 682–4.
5. Kajosaari LI, *et al.* Telithromycin, but not montelukast, increases the plasma concentrations and effects of the cytochrome P450 3A4 and 2C8 substrate repaglinide. *Clin Pharmacol Ther* 2006; **79:** 231–42.
6. Niemi M, *et al.* The CYP2C8 inhibitor trimethoprim increases the plasma concentrations of repaglinide in healthy subjects. *Br J Clin Pharmacol* 2004; **57:** 441–7.
7. Roustit M, *et al.* Symptomatic hypoglycemia associated with trimethoprim/sulfamethoxazole and repaglinide in a diabetic patient. *Ann Pharmacother* 2010; **44:** 764–7.

Ciclosporin. Ciclosporin markedly increased plasma concentrations of repaglinide in healthy subjects, probably by inhibiting both its metabolism by the cytochrome P450 isoenzyme CYP3A4 and hepatic uptake by the organic anion transporting polypeptide OATP1B1.[1] However, there was a large variation in the effect, which may have been partly related to genetic factors. Although there is, therefore, a possibility of increased risk of hypoglycaemia if these 2 drugs are taken together, repaglinide has been used successfully, in usual doses, for diabetes mellitus following renal transplantation in patients receiving immunosuppression regimens that included ciclosporin.[2] Hypoglycaemia was reported,[2] but it was mild and occurred at a similar rate in patients given repaglinide with either ciclosporin (1 of 7 patients) or with tacrolimus (2 of 14).[3] Nevertheless, the authors stated that in these patients, oral antidiabetics in general should be started at a low dose and adjusted gradually with close monitoring of blood-glucose concentrations.[3]

1. Kajosaari LI, *et al.* Cyclosporine markedly raises the plasma concentrations of repaglinide. *Clin Pharmacol Ther* 2005; **78:** 388–99.
2. Türk T, *et al.* Repaglinide in the management of new-onset diabetes mellitus after renal transplantation. *Am J Transplant* 2006; **6:** 842–6.
3. Türk T, Witzke O. Pharmacological interaction between cyclosporine A and repaglinide. Is it clinically relevant? *Am J Transplant* 2006; **6:** 2223.

Deferasirox. In a single-dose study[1] in healthy subjects, deferasirox, an inhibitor of the cytochrome P450 isoenzyme CYP2C8, increased plasma-repaglinide concentrations about twofold but with little change in blood glucose. The authors recommended monitoring blood-glucose concentrations when these drugs are taken together.

1. Skerjanec A, *et al.* Investigation of the pharmacokinetic interactions of deferasirox, a once-daily oral iron chelator, with midazolam, rifampin, and repaglinide in healthy volunteers. *J Clin Pharmacol* 2010; **50:** 205–13.

Grapefruit juice. Grapefruit juice increased the bioavailability of repaglinide in a study of healthy subjects.[1] The half-life of repaglinide was not affected, suggesting that grapefruit juice inhibited its presystemic metabolism by the cytochrome P450 isoenzyme CYP3A4 in the gut wall. Blood-glucose concentrations were not affected.

1. Bidstrup TB, *et al.* The impact of CYP2C8 polymorphism and grapefruit juice on the pharmacokinetics of repaglinide. *Br J Clin Pharmacol* 2006; **61:** 49–57.

Lipid regulating drugs. A study[1] in healthy subjects found that *gemfibrozil* significantly increased the plasma concentrations of repaglinide and enhanced and prolonged its glucose-lowering effect. This interaction can persist for at least 12 hours after a gemfibrozil dose; it might be caused by accumulation in the liver of the metabolite gemfibrozil glucuronide and subsequent prolonged inhibition of the cytochrome P450 isoenzyme CYP2C8.[2] To a lesser extent, gemfibrozil may inhibit the hepatic uptake of repaglinide by the organic anion transporting protein 1B1, and the extent of this effect might be influenced by OATP1B1-related genotype.[3] An *in-vitro* study[4] found that gemfibrozil inhibited uridine diphosphate glucuronosyltransferase (UGT) enzymes, particularly UGT1A1, and suggested that inhibition of repaglinide glucuronidation by gemfibrozil may also contribute to the mechanism of this interaction. In 2003, the EMEA stated that it had received 5 reports of serious hypoglycaemia in patients given repaglinide and gemfibrozil, and contra-indicated the combination.[5] Other studies in healthy subjects found, however, that repaglinide was not affected by *bezafibrate*,[6] *colesevelam*,[7] or *fenofibrate*.[6]

1. Niemi M, *et al.* Effects of gemfibrozil, itraconazole, and their combination on the pharmacokinetics and pharmacodynamics of repaglinide: potentially hazardous interaction between gemfibrozil and repaglinide. *Diabetologia* 2003; **46:** 347–51.
2. Tornio A, *et al.* The effect of gemfibrozil on repaglinide pharmacokinetics persists for at least 12h after the dose: evidence for mechanism-based inhibition of CYP2C8 in vivo. *Clin Pharmacol Ther* 2008; **84:** 403–11.
3. Kalliokoski A, *et al.* Effects of gemfibrozil and atorvastatin on the pharmacokinetics of repaglinide in relation to SLCO1B1 polymorphism. *Clin Pharmacol Ther* 2008; **84:** 488–96.
4. Gan J, *et al.* Repaglinide-gemfibrozil drug interaction: inhibition of repaglinide glucuronidation as a potential additional contributing mechanism. *Br J Clin Pharmacol* 2010; **70:** 870–80.
5. EMEA. EMEA public statement on repaglinide (NovoNorm/Prandin) contraindication of concomitant use of repaglinide and gemfibrozil (issued 21st May, 2003). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2010/08/WC500095476.pdf (accessed 24/08/10)
6. Kajosaari LI, *et al.* Lack of effect of bezafibrate and fenofibrate on the pharmacokinetics and pharmacodynamics of repaglinide. *Br J Clin Pharmacol* 2004; **58:** 390–6.
7. Brown KS, *et al.* Effect of the bile acid sequestrant colesevelam on the pharmacokinetics of pioglitazone, repaglinide, estrogen estradiol, norethindrone, levothyroxine, and glyburide. *J Clin Pharmacol* 2010; **50:** 554–65.

Pharmacokinetics

Repaglinide is rapidly absorbed from the gastrointestinal tract and peak plasma concentrations occur within 1 hour. The mean bioavailability is about 60%. Repaglinide is highly bound to plasma proteins, and has a plasma elimination half-life of about 1 hour. It appears to be a substrate for active hepatic uptake by the organic anion transporting protein OATP1B1, and undergoes almost complete hepatic metabolism involving the cytochrome P450 isoenzymes CYP2C8 and CYP3A4. The glucuronidation of repaglinide is thought to involve uridine diphosphate glucuronosyltransferase (UGT) enzymes, particularly UGT1A1. The metabolites, which are inactive, are excreted in the bile. Higher plasma concentrations and prolonged half-life of repaglinide may occur in patients with renal impairment (creatinine clearance less than 40 mL/min) or chronic liver disease.

References.

1. Hatorp V, *et al.* Single-dose pharmacokinetics of repaglinide in subjects with chronic liver disease. *J Clin Pharmacol* 2000; **40:** 142–52.
2. Hatorp V. Clinical pharmacokinetics and pharmacodynamics of repaglinide. *Clin Pharmacokinet* 2002; **41:** 471–83.
3. Bidstrup TB, *et al.* CYP2C8 and CYP3A4 are the principal enzymes involved in the human in vitro biotransformation of the insulin secretagogue repaglinide. *Br J Clin Pharmacol* 2003; **56:** 305–14.
4. Niemi M, *et al.* Polymorphism in CYP2C8 is associated with reduced plasma concentrations of repaglinide. *Clin Pharmacol Ther* 2003; **74:** 380–7.
5. Niemi M, *et al.* Polymorphic organic anion transporting polypeptide 1B1 is a major determinant of repaglinide pharmacokinetics. *Clin Pharmacol Ther* 2005; **77:** 468–78.
6. Kalliokoski A, *et al.* Different effects of SLCO1B1 polymorphism on the pharmacokinetics and pharmacodynamics of repaglinide and nateglinide. *J Clin Pharmacol* 2008; **48:** 311–21.
7. Kalliokoski A, *et al.* The effect of SLCO1B1 polymorphism on repaglinide pharmacokinetics persists over a wide dose range. *Br J Clin Pharmacol* 2008; **66:** 818–25.
8. Ruzilawati AB, Gan SH. CYP3A4 genetic polymorphism influences repaglinide's pharmacokinetics. *Pharmacology* 2010; **85:** 357–64.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Cravenorm; Glukenil; NovoNorm; Sestrine; *Austral.*: NovoNorm; *Austria*: NovoNorm; *Belg.*: NovoNorm; *Braz.*: Gluconorm†; NovoNorm; Posprand; Prandin; *Canad.*: Gluconorm; *Chile*: Hipover; NovoNorm; *China*: Fulaidi (孚来迪); NovoNorm (诺和龙); *Cz.*: Enyglid; NovoNorm; Prandin; Reneos; *Denm.*: NovoNorm; *Fin.*: NovoNorm; *Fr.*: NovoNorm; *Ger.*: Enyglid; NovoNorm; *Gr.*: NovoNorm; *Hong Kong*: NovoNorm; *Hung.*: NovoNorm; *India*: Eurepa; NovoNorm: Page; Rapilin; *Indon.*: Dexanorm; *Irl.*: Enyglid; NovoNorm: Prandin: *Israel*: NovoNorm; *Ital.*: NovoNorm; *Jpn*: Surepost; *Malaysia*: NovoNorm; *Mex.*: NovoNorm; Prandin: *Neth.*: Enyglid; NovoNorm; Prandin; *Norw.*: NovoNorm; *NZ*: NovoNorm; *Philipp.*: NovoNorm; *Pol.*: Enyglid; Ilgaper; NovoNorm; Prandin; *Port.*: Enyglid; NovoNorm; Prandin; *Rus.*: NovoNorm (НовоНорм); *S.Afr.*: NovoNorm; *Singapore*: NovoNorm; *Spain*: NovoNorm; Prandin; *Swed.*: NovoNorm: *Switz.*: NovoNorm; *Thai.*: NovoNorm; *Turk.*: Diafree; Novade; NovoNorm; *UK*: Prandin; *Ukr.*: NovoNorm (Новонорм); *USA*: Prandin.

Multi-ingredient Preparations. *Israel*: Novogard; *USA*: Prandi-Met.

Pharmacopoeial Preparations
USP 36: Repaglinide Tablets.

Rosiglitazone *(BAN, rINN)*

Rosiglitatsoni; Rosiglitazon; Rosiglitazona; Rosiglitazonum; Rozyglitazon; Розиглитазон.

(±)-5-[*p*-[2-(Methyl-2-pyridylamino)ethoxy]benzyl]-2,4-thiazolidinedione.

$C_{18}H_{19}N_3O_3S$=357.4

CAS — 122320-73-4.

ATC — A10BG02.

ATC Vet — QA10BG02.

UNII — 05V02F2KDG.

Rosiglitazone Maleate *(BANM, USAN, rINNM)*

BRL-49653-C; Maleato de rosiglitazona; Rosiglitazona, maleato de; Rosiglitazone, Maléate de; Rosiglitazoni Maleas; Roziglitazon Maleat; Розиглитазона Малеат.

$C_{18}H_{19}N_3O_3S.C_4H_4O_4$=473.5

CAS — 155141-29-0.

ATC — A10BG02.

ATC Vet — QA10BG02.

UNII — KX2339DP44.

Pharmacopoeias. In *US.*

USP 36: (Rosiglitazone Maleate). A white to off-white solid. Practically insoluble to very slightly soluble in water; sparingly soluble in alcohol; slightly soluble in dichloromethane. Store in airtight containers.

Rosiglitazone Potassium *(BANM, rINNM)*

Kalii Rosiglitazonum; Rosiglitazona potásica; Rosiglitazone Potassique; Калия Розиглитазон.

$C_{18}H_{19}N_3O_3SK$=396.5

CAS — 316371-84-3.

ATC — A10BG02.

ATC Vet — QA10BG02.

Uses and Administration

Rosiglitazone is a thiazolidinedione antidiabetic that acts as a selective agonist at the peroxisome proliferator-activated receptor gamma (PPARγ). It improves insulin sensitivity in adipose tissue, skeletal muscle, and the liver, and is therefore used for the treatment of type 2 diabetes mellitus (p. 459.1), although its use is limited because of possible increased cardiovascular risks. It is usually given as rosiglitazone maleate, and the potassium salt is used in some countries, but doses are expressed in terms of the base; rosiglitazone maleate 1.32 mg and rosiglitazone potassium 1.11 mg are both equivalent to about 1 mg of rosiglitazone.

The hydrochloride has also been used. Rosiglitazone is given orally as monotherapy, particularly in patients who do not achieve adequate glycaemic control with other antidiabetics or in whom other antidiabetics are contra-indicated or not tolerated. It may also be added to metformin, a sulfonylurea, or a combination of the two. The combination of insulin and rosiglitazone is generally avoided (see Administration, p. 499.1). The usual initial dose is 4 mg daily, given in a single dose or two divided doses. The dose may be increased to a maximum of 8 mg daily if necessary after 8 to 12 weeks. Rosiglitazone may be taken with or without food.

References.
1. Czoski-Murray C, *et al.* Clinical effectiveness and cost-effectiveness of pioglitazone and rosiglitazone in the treatment of type 2 diabetes: a systematic review and economic evaluation. *Health Technol Assess* 2004; 8: 1–91.
2. Wellington K. Rosiglitazone/metformin. *Drugs* 2005; 65: 1581–92.
3. Deeks ED, Keam SJ. Rosiglitazone: a review of its use in type 2 diabetes mellitus. *Drugs* 2007; 67: 2747–79.
4. Richter B, *et al.* Rosiglitazone for type 2 diabetes mellitus. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 06/07/09).
5. Anonymous. Glitazones in type 2 diabetes: an update. *Drug Ther Bull* 2008; 46: 25–9.

Administration. Although rosiglitazone was licensed for use with other antidiabetic drugs the specifics of licensing and use have varied from country to country. In both the UK and USA, rosiglitazone (*Avandia; GSK*) was licensed for monotherapy, and for use with metformin or a sulfonylurea, or both if necessary, in patients in whom single or dual agent therapy is inadequate. However, UK[1] and combined European/US guidelines[2] do not endorse the use of thiazolidinedione monotherapy. In the UK, NICE only recommends dual therapy that includes a thiazolidinedione in patients who cannot be given a combination of metformin plus a sulfonylurea (because of drug intolerance or contra-indication, or where the risk or consequences of hypoglycaemia would be unacceptable). NICE also suggests that a thiazolidinedione only be added to metformin plus a sulfonylurea if insulin is likely to be unacceptable or ineffective.[1] The European/US guidelines discourage the use of rosiglitazone altogether, but do suggest a role for pioglitazone.[2] In September 2010 the EMEA suspended the marketing authorisation of rosiglitazone and the FDA restricted its use; in 2013 the FDA removed its restrictions (for details, see Effects on the Cardiovascular System, p. 499.3).

The combination of rosiglitazone with insulin is now generally avoided because of an increased risk of heart failure and other cardiac adverse events (see also Effects on the Heart, p. 500.2), and licensed product information recommends against such use. The European/US guidelines[2] do not include a combination of thiazolidinedione with insulin, and NICE[1] only recommends pioglitazone with insulin in particular circumstances.

1. National Collaborating Centre for Chronic Conditions/NICE. Type 2 diabetes: the management of type 2 diabetes: partial update (issued March 2010). Available at: http://www.nice.org.uk/nicemedia/pdf/CG87NICEGuideline.pdf (accessed 10/10/11)
2. Nathan DM, *et al.* Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2009; 32: 193–203.

Inflammatory bowel disease. There is some evidence[1] to suggest that drugs such as rosiglitazone that act as ligands to peroxisome proliferator-activated receptor gamma (PPARγ) may offer a novel therapeutic approach to management of inflammatory bowel disease (p. 1811.3).

1. Lewis JD, *et al.* Rosiglitazone for Ulcerative Colitis Study Group. Rosiglitazone for active ulcerative colitis: a randomized placebo-controlled trial. *Gastroenterology* 2008; 134: 688–95.

Liver disorders. Small studies using rosiglitazone in nonalcoholic steatohepatitis have reported improvements in insulin sensitivity, liver function, and histology.[1-4] However, weight gain was common[1-3] and benefits were not maintained after treatment was stopped.[1] Furthermore, no additional improvement in histology was shown beyond 1 year of treatment despite a maintained effect on insulin sensitivity and transaminase levels.[4]

1. Neuschwander-Tetri BA, *et al.* Improved nonalcoholic steatohepatitis after 48 weeks of treatment with the PPAR-γ ligand rosiglitazone. *Hepatology* 2003; 38: 1008–17.
2. Wang C-H, *et al.* Safety and effectiveness of rosiglitazone in type 2 diabetes patients with nonalcoholic fatty liver disease. *J Formos Med Assoc* 2006; 105: 743–52.
3. Ratziu V, *et al.* LIDO Study Group. Rosiglitazone for nonalcoholic steatohepatitis: one-year results of the randomized placebo-controlled Fatty Liver Improvement with Rosiglitazone Therapy (FLIRT) Trial. *Gastroenterology* 2008; 135: 100–10.
4. Ratziu V, *et al.* LIDO Study Group. Long-term efficacy of rosiglitazone in nonalcoholic steatohepatitis: results of the fatty liver improvement by rosiglitazone therapy (FLIRT 2) extension trial. *Hepatology* 2010; 51: 445–53.

Polycystic ovary syndrome. Insulin resistance is a feature of polycystic ovary syndrome (PCOS; p. 2253.3) and the use of rosiglitazone has been investigated. Rosiglitazone has been reported to improve insulin resistance in women with PCOS, as well as reduce androgen concentrations and normalise sex-hormone binding globulin. There have been reports of reduced hirsutism, a return to regular menstrual cycles, and improved ovulation rates. Many women with PCOS are overweight or obese and there has been concern that thiazolidinediones might exacerbate this, but some studies have reported improvements in measures of PCOS without significant weight gain. Improvements in PCOS have also been found in lean women without insulin resistance. Overall, however, studies have been small and short-term, and further research is needed.[1]

1. Elkind-Hirsch KE. Thiazolidinediones for the therapeutic management of polycystic ovary syndrome: impact on metabolic and reproductive abnormalities. *Treat Endocrinol* 2006; 5: 171–187.

Psoriasis. Rosiglitazone has been studied in the treatment of chronic plaque psoriasis (see under Pioglitazone, p. 493.3).

Reperfusion and revascularisation procedures. Restenosis is a particular problem after percutaneous coronary revascularisation procedures (p. 1259.2) and various drugs have been tried for its prevention. Oral thiazolidinediones have been reported to reduce the risk of repeat revascularisation in patients with and without diabetes, but studies have been small and have not always documented the type of stent used.[1]

1. Riche DM, *et al.* Thiazolidinediones and risk of repeat target vessel revascularization following percutaneous coronary intervention: a meta-analysis. *Diabetes Care* 2007; 30: 384–8.

Adverse Effects and Precautions

Hypoglycaemia is uncommon during rosiglitazone monotherapy, but it may be common when the drug is given with other oral antidiabetics, particularly a sulfonylurea, or insulin. Weight gain appears to be dose-related, and may be caused by a combination of fat accumulation and fluid retention. Other common adverse effects of rosiglitazone include increased appetite, gastrointestinal disturbances, and headache. Reductions in haemoglobin and haematocrit can occur and appear to be related to both rosiglitazone dose and increased plasma volume; patients with low haemoglobin concentrations before starting therapy may be at risk of developing anaemia. Changes in serum lipids may also occur, including hypertriglyceridaemia and mild to moderate hypercholesterolaemia. Other adverse effects that have been reported include dizziness, palpitations, muscle cramps, back pain, arthralgia, paraesthesia, and alopecia. There have also been very rare reports of anaphylactic reactions, angioedema, and skin reactions such as urticaria, pruritus, and rashes. Rosiglitazone can also increase the risk of bone fracture in women.

Rosiglitazone can cause fluid retention, which may worsen or precipitate heart failure; rapid weight gain and dyspnoea may be indicative of fluid retention. It should therefore be used with caution in patients with oedema, and should not be used in those with a history of heart failure (see also Effects on the Heart, p. 500.2). Renal impairment may increase the risk of fluid retention and heart failure. Rosiglitazone should also be avoided in patients having an acute coronary event because this condition has the potential to precipitate heart failure. There have been very rare reports of new onset and worsening diabetic macular oedema with decreased visual acuity (see also Effects on the Eyes, p. 500.1). There is evidence of a possible increased cardiovascular risk with the use of rosiglitazone, and it is not recommended in patients with ischaemic heart disease or peripheral arterial disease (see also Effects on the Cardiovascular System, p. 499.3). Liver function should be monitored periodically as there have been isolated reports of liver dysfunction, and the drug should be used with caution in patients with hepatic impairment (see Effects on the Liver, p. 500.3).

Rosiglitazone is not appropriate for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis.

In women who are anovulatory because of insulin resistance, rosiglitazone therapy may result in a resumption of ovulation.

Driving. Diabetes mellitus, its complications, and the medications used to treat it, may affect a patient's ability to drive safely—see under Insulin (p. 485.2) for restrictions applied to diabetic patients in the UK.

Effects on the blood. Leucopenia and thrombocytopenia developed in a 50-year-old woman treated with rosiglitazone. The effect resolved after the drug was stopped, but recurred when pioglitazone was later given. The patient again recovered after pioglitazone treatment was withdrawn.[1] A case of rosiglitazone-induced immune thrombocytopenia, with recovery after drug withdrawal, has also been described.[2]

1. Digman C, *et al.* Leukopenia and thrombocytopenia caused by thiazolidinediones. *Ann Intern Med* 2005; 143: 465–6.
2. Liu X, *et al.* Rosiglitazone-induced immune thrombocytopenia. *Platelets* 2006; 17: 143–8.

Effects on the bones. Use of thiazolidinediones such as pioglitazone or rosiglitazone has been associated with decreases in bone mineral density and increased risk of fractures in female patients. Analysis of data from a comparative study (ADOPT)[1] of glycaemic control with rosiglitazone, metformin, or glibenclamide involving 4360 randomised patients found that the risk of fracture in female patients in these 3 groups was 9.3%, 5.1%, and 3.5% respectively;[2] the risk in male patients was not significantly different in the 3 groups at around 3.4 to 3.95%. Analysis of data from another large ongoing study was also consistent with an increased fracture risk with rosiglitazone,[2] and data from the manufacturer of pioglitazone involving over 8100 treated patients also revealed an increased risk of fracture in women given the drug;[3] the excess risk was calculated to be 0.8 per 100 patient years of use. Following on from these reports, a meta-analysis of fracture data from 10 studies of thiazolidinediones in diabetes was undertaken, although none were prospectively designed to measure fracture risk.[4] The analysis confirmed an increased risk of fracture overall with thiazolidinedione use. Based on the 5 studies providing data by sex, the risk of fracture was found to be doubled in women, but not significantly increased in men.

The pattern of fractures seemed to differ from that associated with postmenopausal osteoporosis, being mainly in the upper arm, hand, or foot, rather than hip or spine.[2] However, this may be because many affected patients were relatively younger (mean age 56 years),[1] and there is some evidence that hip and femur fractures in older women are significantly associated with thiazolidinediones.[4] An observational study has suggested that thiazolidinedione use is associated with ongoing loss of whole-body bone mineral density in women but not men.[5] Further analysis of the ADOPT results found that the increased risk of fracture only became apparent after 1 year of rosiglitazone treatment, but identified no particular risk factors in affected women.[6]

This adverse effect has been reviewed[7,8] and attributed to the selective agonist action of rosiglitazone at the peroxisome proliferator-activated receptor (PPAR)-γ; *animal* studies have shown that the activation of PPAR-γ decreases bone formation and increases bone resorption.

1. Kahn SE, *et al.* ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med* 2006; 355: 2427–43. Correction. *ibid.* 2007; 356: 1387–8.
2. GSK, Canada. Increased incidence of fractures in female patients who received long-term treatment with Avandia (rosiglitazone maleate) tablets for type 2 diabetes mellitus (issued 23rd February, 2007). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/medeff/advisories-avis/prof/2007/avandia_hpc-cps_3-eng.pdf (accessed 01/11/11)
3. Takeda, USA. Re observation of an increased incidence of fractures in female patients who received long-term treatment with Actos (pioglitazone HCl) tablets for type 2 diabetes mellitus (issued March 2007). Available at: http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM153896.pdf (accessed 01/11/11)
4. Loke YK, *et al.* Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis. *CMAJ* 2009; 180: 32–9.
5. Schwartz AV, *et al.* Thiazolidinedione use and bone loss in older diabetic adults. *J Clin Endocrinol Metab* 2006; 91: 3349–54.
6. Kahn SE, *et al.* Rosiglitazone-associated fractures in type 2 diabetes: an analysis from A Diabetes Outcome Progression Trial (ADOPT). *Diabetes Care* 2008; 31: 845–51.
7. Bodmer M, *et al.* Risk of fractures with glitazones: a critical review of the evidence to date. *Drug Safety* 2009; 32: 539–47.
8. Lecka-Czernik B. Bone loss in diabetes: use of antidiabetic thiazolidinediones and secondary osteoporosis. *Curr Osteoporos Rep* 2010; 8: 178–84.

Effects on the cardiovascular system. It had been suggested that, in addition to their hypoglycaemic effect, thiazolidinediones may have beneficial effects in the prevention of macrovascular diabetic complications, and there is some evidence that pioglitazone may improve some cardiovascular outcomes (see Diabetic Complications, p. 493.2). However, a meta-analysis[1] of 42 studies found that, compared with either placebo or other antidiabetic drugs, rosiglitazone was associated with a significant increase in the risk of myocardial infarction, and an increase of borderline significance in death from cardiovascular causes. There were limitations to this analysis as the studies were not primarily intended to examine cardiovascular outcomes, and many were small and short-term. Studies with no recorded cardiovascular events were excluded from the meta-analysis,[1] and this has been questioned. An alternative analysis[2] that accounted for these excluded studies, with appropriate analysis adjustment, found odds ratios for myocardial infarction and cardiovascular death that were not statistically significant, and concluded that neither increased nor decreased risk could be established.

In response to concerns raised by the initial meta-analysis, an unplanned interim analysis of an ongoing open-label study (RECORD) designed to assess cardiovascular outcomes was published (rosiglitazone added to either metformin or a sulfonylurea compared with metformin plus

a sulfonylurea).[3] The data, however, were insufficient to determine whether there was an increased risk of myocardial infarction, and the findings were inconclusive regarding any effect on overall risks of hospitalisation or death from cardiovascular causes. A subsequent meta-analysis[4] was restricted to 4 long-term studies (at least 12 months of treatment) that had specified an intention to evaluate cardiovascular adverse effects, including the interim RECORD results. It found an increased risk of myocardial infarction with rosiglitazone use, without a significant increase in the risk of cardiovascular mortality. The final results of RECORD[5] showed that after 5 to 7 years of follow-up, rosiglitazone did not increase overall cardiovascular morbidity or mortality, but the data could not rule out a small increased risk in myocardial infarction. The strength of these findings were weakened by a substantially lower than expected rate of cardiovascular events. A later meta-analysis considered that the risk-benefit ratio for rosiglitazone was unfavourable.[6] Concerns about the cardiovascular safety of rosiglitazone contributed to recommendations that its use should be limited, and in September 2010 the FDA restricted rosiglitazone to patients with diabetes that could not be controlled by other medications,[7] and the marketing of rosiglitazone was suspended in the EU.[8] The FDA also requested an independent review of the RECORD results because of questions about potential bias in the identification of cardiovascular events. Based on this, the FDA concluded that it was not clear whether the risk of death, heart attack, and stroke were truly different between rosiglitazone and metformin plus sulfonylurea, and in 2013 lifted restrictions on its prescription.[9] (See also Administration, p. 497.1.)

For the risks of heart failure associated with thiazolidinediones, see Effects on the Heart, p. 500.2.

1. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007; 356: 2457–71. Correction. *ibid.*; 357: 100.
2. Diamond GA, *et al.* Uncertain effects of rosiglitazone on the risk for myocardial infarction and cardiovascular death. *Ann Intern Med* 2007; 147: 578–81.
3. Home PD, *et al.* RECORD Study Group. Rosiglitazone evaluated for cardiovascular outcomes—an interim analysis. *N Engl J Med* 2007; 357: 28–38.
4. Singh S, *et al.* Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. *JAMA* 2007; 298: 1189–95.
5. Home PD, *et al.* RECORD Study Team. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet* 2009; 373: 2125–35.
6. Nissen SE, Wolski K. Rosiglitazone revisited: an updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. *Arch Intern Med* 2010; 170: 1191–1201.
7. FDA. Avandia (rosiglitazone): REMS - risk of cardiovascular events (issued 23rd September, 2010). Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm226994.htm (accessed 24/09/10)
8. EMEA. European Medicines Agency recommends suspension of Avandia, Avandamet and Avaglim: anti-diabetes medication to be taken off the market (issued 23rd September, 2010). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/09/WC500096996.pdf (accessed 24/09/10)
9. FDA. FDA requires removal of some prescribing and dispensing restrictions for rosiglitazone-containing diabetes medicines (issued 25th November, 2013). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm376389.htm (accessed 26/11/13)

Effects on the eyes. The manufacturers in the USA and Canada (*GSK*) have received postmarketing reports of the development or worsening of **diabetic macular oedema** in patients treated with rosiglitazone-containing products; in most cases the patients also reported peripheral oedema or fluid retention.[1,2] In some cases visual impairment improved or resolved after stopping the drug. A later observational study[3] in 170 000 diabetic patients showed that treatment with a thiazolidinedione was modestly associated with an increased 1-year incidence of diabetic macular oedema after adjusting for age, glycaemic control, and insulin use. More recently, however, a cross-sectional analysis[4] of data from a substudy of a large multicentre randomised controlled study in diabetic patients did not find any association, although this study did not adjust for duration of exposure, past exposure, and type of thiazolidinedione used.

A retrospective review[5] of 30 patients with lower extremity oedema, and clinically significant diabetic macular oedema, assessed the changes that were recorded after rosiglitazone or pioglitazone had been stopped. Although weight loss and improvement in peripheral oedema were generally rapid (usually within 2 months), the resolution of macular oedema was often very slow. Most patients underwent macular laser treatment, and in some cases visual acuity remained poor because of macular scarring from chronic oedema.

The manufacturers advise that rosiglitazone should be used with caution in patients with pre-existing diabetic retinopathy or macular oedema, and should be stopped, and ophthalmological consultation sought, if visual impairment develops while using the drug.[2] This adverse effect has also been reviewed.[6]

There have been reports of the exacerbation of **thyroid eye disease**, particularly proptosis associated expansion of the orbital fat compartment, in euthyroid patients given thiazolidinediones.[7,8] Proptosis, with normal orbital fat and extra-ocular muscles, has also been reported with rosiglitazone in the absence of thyroid disease.[9] A small study in 36 patients measured eye protrusion before and after 6 months of pioglitazone therapy.[10] Overall there was a small increase, but none of the patients noted any changes in the appearance of their eyes. Previous or current thyroid disturbances, a low adiponectin level, and higher pioglitazone dose, were found more frequently in patients with the greatest increase in protrusion.

1. GSK, USA. Avandia (rosiglitazone maleate), Avandamet (rosiglitazone maleate/metformin HCl): letter to healthcare professionals (issued December 2005). Available at: http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM153072.pdf (accessed 24/08/10)
2. GSK, Canada. Association of Avandia and Avandamet with new onset and/or worsening of macular edema (issued 19th December, 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/medeff/advisories-avis/prof/2005/avandia_avandamet_hpc-cps-eng.pdf (accessed 02/11/11)
3. Pong DS, Contreras R. Glitazone use associated with diabetic macular edema. *Am J Ophthalmol* 2009; 147: 583–586.e1.
4. Ambrosius WT, *et al.* ACCORD Study Group. Lack of association between thiazolidinediones and macular edema in type 2 diabetes: the ACCORD eye study. *Arch Ophthalmol* 2010; 128: 312–18.
5. Ryan EH, *et al.* Diabetic macular edema associated with glitazone use. *Retina* 2006; 26: 562–70.
6. Merante D, *et al.* Diabetic macular edema: correlations with available diabetes therapies—evidence across a qualitative review of published literature from MEDLINE and EMBASE. *Drug Safety* 2010; 33: 643–52.
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8. Lee S, *et al.* Thiazolidinedione induced thyroid associated orbitopathy. *BMC Ophthalmol* 2007; 7: 8.
9. Levin F, *et al.* Rosiglitazone-induced proptosis. *Arch Ophthalmol* 2005; 123: 119–21.
10. Dorkhan M, *et al.* Treatment with a thiazolidinedione increases eye protrusion in a subgroup of patients with type 2 diabetes. *Clin Endocrinol (Oxf)* 2006; 65: 55–9.

Effects on the heart. Both pioglitazone and rosiglitazone can cause peripheral and pulmonary oedema, which can worsen or precipitate heart failure; several cases have been described.[1-4] A large retrospective cohort study[7] also found that the use of thiazolidinediones increased the risk of heart failure. The incidence of peripheral oedema with monotherapy has been reported[8] to range from 3 to 5%, and this increases slightly when a thiazolidinedione is used with another oral antidiabetic. The incidence is about 15% when a thiazolidinedione is used with insulin. The incidence of heart failure is generally lower, but has been reported to be 2 to 3% when a thiazolidinedione is used with insulin; however, a large prospective study,[9] which was intended to examine the cardiovascular benefits of pioglitazone in preventing secondary macrovascular events in diabetic patients with pre-existing macrovascular disease, reported a 6% incidence of heart failure, compared with 4% in the placebo group. Mortality rates from heart failure did not differ between groups. These figures were confirmed on re-analysis.[10,11] Subsequent reviews have also concluded that thiazolidinediones increase the risk of heart failure,[12,13] but without an associated increase in the risk of cardiovascular death.[13]

The American Heart Association and American Diabetes Association have recommended[8] that patients with risk factors for heart disease or a depressed ejection fraction but without symptoms, and patients with NYHA class I or II heart failure, should start with a low dose of a thiazolidinedione that is only increased gradually as necessary and with careful monitoring. Patients with more severe heart failure (class III and IV) should not receive these drugs. These recommendations are reflected in US licensed product information. Licensed product information in other countries may contra-indicate the use of pioglitazone or rosiglitazone in patients with heart failure or any history of heart failure, even of class I or II.

For restrictions on combination therapy see Administration, p. 497.1.

1. Page RL, *et al.* Possible heart failure exacerbation associated with rosiglitazone: case report and literature review. *Pharmacotherapy* 2003; 23: 945–54.
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4. Shah M, *et al.* Pioglitazone-induced heart failure despite normal left ventricular function. *Am J Med* 2004; 117: 973–4.
5. CSM/MHRA. Reminder: thiazolidinediones (glitazones) contraindications. *Current Problems* 2004; 30: 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007448&RevisionSelectionMethod=LatestReleased (accessed 02/06/06)
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8. Nesto RW, *et al.* Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. *Circulation* 2003; 108: 2941–8. Also available at: http://circ.ahajournals.org/cgi/reprint/108/23/2941.pdf (accessed 26/03/07) Also published in *Diabetes Care* 2004; 27: 256–63. Also available at: http://care.diabetesjournals.org/content/27/1/256.full.pdf (accessed 06/07/09)
9. Dormandy JA, *et al.* Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 2005; 366: 1279–89.
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11. Erdmann E, *et al.* PROactive investigators. Pioglitazone use and heart failure in patients with type 2 diabetes and preexisting cardiovascular disease: data from the PROactive study (PROactive 08). *Diabetes Care* 2007; 30: 2773–8.
12. Singh S, *et al.* Thiazolidinediones and heart failure: a teleo-analysis. *Diabetes Care* 2007; 30: 2148–53.
13. Lago RM, *et al.* Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials. *Lancet* 2007; 370: 1129–36

Effects on lipids. Rosiglitazone and pioglitazone have different effects on serum lipids—see p. 494.1.

Effects on the liver. Several cases of hepatotoxicity, including fatalities, have been described in patients receiving rosiglitazone. Most of these occurred within a few weeks or months of starting rosiglitazone therapy,[1-3] but some patients had been taking the drug for about a year or more.[6-8] However, the causality of some of these cases has been debated[9,10] because of coexisting disease and concomitant medication.

Licensed product information recommends that liver enzymes should be checked before starting therapy with rosiglitazone. Patients with aminotransferase (ALT) concentrations more than 2.5 times the upper limit of normal should not be given rosiglitazone, and it should be used with caution, if at all, in patients with milder elevations of liver enzyme values. ALT concentrations should be monitored periodically in all patients given rosiglitazone. If ALT concentrations rise to more than 3 times the upper limit of normal and remain so after retesting then treatment with rosiglitazone should be stopped; treatment should also be stopped if jaundice develops.

1. Forman LM, *et al.* Hepatic failure in a patient taking rosiglitazone. *Ann Intern Med* 2000; 132: 118–21.
2. Al-Salman J, *et al.* Hepatocellular injury in a patient receiving rosiglitazone: a case report. *Ann Intern Med* 2000; 132: 121–4.
3. Ravinuthala RS, Nori U. Rosiglitazone toxicity. *Ann Intern Med* 2000; 133: 658.
4. Hachey DM, *et al.* Isolated elevation of alkaline phosphatase level associated with rosiglitazone. *Ann Intern Med* 2000; 133: 752.
5. Floyd JS, *et al.* Case series of liver failure associated with rosiglitazone and pioglitazone. *Pharmacoepidemiol Drug Safety* 2009; 18: 1238–43.
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7. Su D-H, *et al.* Liver failure in a patient receiving rosiglitazone therapy *Diabet Med* 2006; 23: 105–6.
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10. Isley WL, Oki JC. Rosiglitazone and liver failure. *Ann Intern Med* 2000; 133: 393.

Fasting. For mention that glitazones can probably be used with low risk of hypoglycaemia in fasting Muslim patients during Ramadan see under Precautions of Insulin, p. 485.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies rosiglitazone as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Pregnancy. Insulin is generally preferred for treatment of diabetes mellitus during pregnancy. Rosiglitazone crosses the placenta and is detectable in fetal tissue, but there is some evidence that the fetus may be able to metabolise the drug.[1] Data on the clinical use of rosiglitazone during pregnancy are limited. There was no evidence of congenital abnormalities or delayed development in the infants of a series of 8 women with polycystic ovary syndrome who had been given rosiglitazone for ovulation induction and during the first 12 weeks of gestation.[2] There has also been a report of rosiglitazone use during weeks 13 to 17 of gestation in a woman with diabetes mellitus, with no malformations detected in the baby.[3]

1. Chan LY-S, *et al.* Placental transfer of rosiglitazone in the first trimester of human pregnancy. *Fertil Steril* 2005; 83: 955–8.
2. Haddad GF, *et al.* Case series of rosiglitazone used during the first trimester of pregnancy. *Reprod Toxicol* 2008; 26: 183–4.
3. Kalyoncu NI, *et al.* A case of rosiglitazone exposure in the second trimester of pregnancy. *Reprod Toxicol* 2005; 19: 563–4.

Interactions

Rosiglitazone is mainly metabolised by the cytochrome P450 isoenzyme CYP2C8. Use with CYP2C8 inhibitors such as gemfibrozil, ketoconazole, and trimethoprim, can increase plasma concentrations of rosiglitazone. Conversely, rifampicin, a potent inducer of cytochrome P450, can

reduce rosiglitazone concentrations. These drugs should be given with caution to patients taking rosiglitazone, and glycaemic control should be monitored.

Use of NSAIDs or insulin with rosiglitazone may increase the risk of oedema and heart failure (see also Effects on the Heart, p. 498.2, and Administration, p. 497.1).

Reviews.
1. Scheen AJ. Pharmacokinetic interactions with thiazolidinediones. *Clin Pharmacokinet* 2007; **46:** 1–12.

Antibacterials. *Rifampicin* significantly reduced the plasma concentration and elimination half-life of rosiglitazone[1,2] and pioglitazone[3] in studies of healthy subjects, probably by induction of the cytochrome P450 isoenzyme CYP2C8. Conversely, *trimethoprim* can inhibit CYP2C8, and was found to modestly increase the concentration and half-life of rosiglitazone.[2,4]

1. Park J-Y, *et al.* Effect of rifampin on the pharmacokinetics of rosiglitazone in healthy subjects. *Clin Pharmacol Ther* 2004; **75:** 157–62.
2. Niemi M, *et al.* Effects of trimethoprim and rifampin on the pharmacokinetics of the cytochrome P450 2C8 substrate rosiglitazone. *Clin Pharmacol Ther* 2004; **76:** 239–49.
3. Jaakkola T, *et al.* Effect of rifampicin on the pharmacokinetics of pioglitazone. *Br J Clin Pharmacol* 2006; **61:** 70–8.
4. Hruska MW, *et al.* The effect of trimethoprim on CYP2C8 mediated rosiglitazone metabolism in human liver microsomes and healthy subjects. *Br J Clin Pharmacol* 2005; **59:** 70–9.

Antifungals. In healthy subjects,[1] *ketoconazole* increased the plasma concentration and elimination half-life of rosiglitazone, probably by inhibition of the cytochrome P450 isoenzyme CYP2C8 and to a lesser extent CYP2C9.

1. Park J-Y, *et al.* Effect of ketoconazole on the pharmacokinetics of rosiglitazone in healthy subjects. *Br J Clin Pharmacol* 2004; **58:** 397–402.

Lipid regulating drugs. *Gemfibrozil* significantly increased the plasma concentration and about doubled the half-life of rosiglitazone in healthy subjects,[1] probably by inhibiting its metabolism. The authors suggested that these drugs should not be used together, or that the dose of rosiglitazone should be at least halved if gemfibrozil treatment is started. Marked increases in the plasma concentration and half-life of pioglitazone have also been found in healthy subjects given gemfibrozil.[2,3]

For reports of a paradoxical decrease in plasma high-density-lipoprotein cholesterol in patients taking thiazolidinediones with fibrates, see p. 1325.2.

1. Niemi M, *et al.* Gemfibrozil considerably increases the plasma concentrations of rosiglitazone. *Diabetologia* 2003; **46:** 1319–23.
2. Jaakkola T, *et al.* Effects of gemfibrozil, itraconazole, and their combination on the pharmacokinetics of pioglitazone. *Clin Pharmacol Ther* 2005; **77:** 404–14.
3. Deng L-J, *et al.* Effect of gemfibrozil on the pharmacokinetics of pioglitazone. *Eur J Clin Pharmacol* 2005; **61:** 831–6.

Pharmacokinetics

Rosiglitazone is well absorbed from the gastrointestinal tract after oral dosing. Peak plasma concentrations occur about 1 hour after a dose and the bioavailability is 99%. It is 99.8% bound to plasma proteins. Rosiglitazone is extensively metabolised, mainly by the cytochrome P450 isoenzyme CYP2C8. It is excreted in the urine and faeces, and has a half-life of 3 to 4 hours. Rosiglitazone crosses the placenta and has been found in fetal tissue.

References.
1. Baldwin SJ, *et al.* Characterization of the cytochrome P450 enzymes involved in the in vitro metabolism of rosiglitazone. *Br J Clin Pharmacol* 1999; **48:** 424–32.
2. Chapelsky MC, *et al.* Pharmacokinetics of rosiglitazone in patients with varying degrees of renal insufficiency. *J Clin Pharmacol* 2003; **43:** 252–9.
3. Kirchheiner J, *et al.* Pharmacokinetics and pharmacodynamics of rosiglitazone in relation to CYP2C8 genotype. *Clin Pharmacol Ther* 2006; **80:** 657–67.
4. Aramwit P, *et al.* Pharmacokinetics of single-dose rosiglitazone in chronic ambulatory peritoneal dialysis patients. *J Clin Pharm Ther* 2008; **33:** 685–90.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Avandia; Diaben; Gaudil; Glimide; Glixinina; Gludex; Rosiglit; ***Austral.***: Avandia; ***Austria***: Avandia†; ***Belg.***: Avandia†; ***Braz.***: Avandia†; ***Canad.***: Avandia; ***Chile***: Avandia; Rosivan; ***China***: Ai Neng (爱能); Ao Luo Hua (奥洛华); Avandia (文迪雅)†; Naidi (耐迪); Sheng Ao (圣奥); Sheng Min (圣敏); Weigeluo (维戈洛); Yi Li Xi (宜力喜); ***Cz.***: Avandia†; ***Denm.***: Avandia†; ***Fin.***: Avandia†; ***Fr.***: Avandia†; ***Ger.***: Avandia†; ***Gr.***: Avandia†; ***Hong Kong***: Avandia; ***Hung.***: Avandia†; ***India***: Rezult; Roglin; Rosicon; ***Indon.***: Avandia; ***Irl.***: Avandia†; ***Israel***: Avandia; Rosi; Rossini†; ***Ital.***: Avandia†; ***Malaysia***: Avandia; ***Mex.***: Avandia; ***Neth.***: Avandia†; ***Norw.***: Avandia†; ***NZ***: Avandia; ***Philipp.***: Avandia†; ***Pol.***: Avandia†; ***Port.***: Avandia†; ***Rus.***: Avandia (Авандия); Roglit (Роглит); ***S.Afr.***: Avandia†; ***Singapore***: Avandia; ***Spain***: Avandia†; ***Swed.***: Avandia†; ***Switz.***: Avandia†; ***Thai.***: Avandia†; ***Turk.***: Avandia; Rosenda; Rosette; Rositaz; Rosvel; ***UK***: Avandia†; ***Ukr.***: Diaglytason (Диаглитазон)†; Roglit (Роглит); ***USA***: Avandia; ***Venez.***: Avandia.

Multi-ingredient Preparations. *Arg.*: Avandamet; Avandaryl; Gludex Plus; Rosiglit-Met; ***Austral.***: Avandamet; ***Austria***: Avaglim†; Avandamet†; ***Belg.***: Avandamet†; ***Braz.***: Avandamet†; ***Canad.***: Avandamet; Avandaryl†; ***Chile***: Avandamet; Avandaryl; ***China***: Avandamet (文达敏)†; ***Cz.***: Avaglim†; Avandamet†; ***Denm.***: Avaglim†; Avandamet†; ***Fin.***: Avandamet†; ***Fr.***: Avandamet†; ***Ger.***: Avaglim†; Avandamet†; ***Gr.***: Avaglim†; Avandamet†; ***Hong Kong***: Avandamet; ***Hung.***: Avaglim†; Avandamet†; ***India***: Diabetrol-3D; Glyroz; Roglin-M; Rosicon MF; ***Indon.***: Avandamet; Avandaryl; ***Irl.***: Avaglim†; Avandamet†; ***Israel***: Avandamet; ***Ital.***: Avaglim†; Avandamet†; ***Malaysia***: Avandamet; ***Mex.***: Avandamet; ***Neth.***: Avaglim†: Avandamet†; ***Norw.***: Avaglim†; Avandamet†; ***Philipp.***: Avandamet†; Avandaryl†; ***Pol.***: Avandamet†; ***Port.***: Avaglim†; Avandamet†; ***Rus.***: Avandaglim (Авандаглим); Avandamet (Авандамет); ***Singapore***: Avandamet; ***Spain***: Avaglim†; Avandamet†; ***Swed.***: Avaglim†; Avandamet†; ***Switz.***: Avandamet†; ***Thai.***: Avandamet†; Avandaryl†; ***Turk.***: Avandamet; ***UK***: Avandamet†; ***Ukr.***: Avandamet (Авандамет)†; ***USA***: Avandamet; Avandaryl; ***Venez.***: Avandamet.

Ruboxistaurin *(rINN)*

LY-333531; LY-341684 (ruboxistaurin mesilate); Ruboxistaurina; Ruboxistaurine; Ruboxistaurinum; Рубоксистаурин.

(9*S*)-9-[(Dimethylamino)methyl]-6,7,10,11-tetrahydro-9*H*,19*H*-5,21:12,17-dimethenodibenzo[*e*,*k*]pyrrolo[3,4-*h*][1,4,13]oxadiazacyclohexadecene-18,20-dione.

$C_{28}H_{28}N_4O_3$=468.6

CAS — 169939-94-0 (ruboxistaurin); 169939-93-9 (ruboxistaurin hydrochloride); 202260-21-7 (ruboxistaurin mesilate).

UNII — 721809WQCP.

NOTE. The name Arxxant has been used as a trade mark for ruboxistaurin.

Profile

Ruboxistaurin is an oral inhibitor of the β-isoform of the enzyme protein kinase C, which is thought to play a role in the development of diabetic microvascular complications. It is under investigation as an adjunct in the treatment of diabetic retinopathy (p. 464.2).

References.
1. Joy SV, *et al.* Ruboxistaurin, a protein kinase C β inhibitor, as an emerging treatment for diabetes microvascular complications. *Ann Pharmacother* 2005; **39:** 1693–9.
2. Vinik A. The protein kinase C-β inhibitor, ruboxistaurin, for the treatment of diabetic microvascular complications. *Expert Opin Invest Drugs* 2005; **14:** 1547–59.
3. The PKC-DRS Study Group. The effect of ruboxistaurin on visual loss in patients with moderately severe to very severe nonproliferative diabetic retinopathy: initial results of the Protein Kinase C β Inhibitor Diabetic Retinopathy Study (PKC-DRS) multicenter randomized clinical trial. *Diabetes* 2005; **54:** 2188–97.
4. Vinik AI, *et al.* The MBBQ Study Group. Treatment of symptomatic diabetic peripheral neuropathy with the protein kinase C β-inhibitor ruboxistaurin mesylate during a 1-year, randomized, placebo-controlled, double-blind clinical trial. *Clin Ther* 2005; **27:** 1164–80.
5. Aiello LP, *et al.* PKC-DRS 2 Group. Effect of ruboxistaurin on visual loss in patients with diabetic retinopathy. *Ophthalmology* 2006; **113:** 2221–30.
6. The PKC-DMES Study Group. Effect of ruboxistaurin in patients with diabetic macular edema: thirty-month results of the randomized PKC-DMES clinical trial. *Arch Ophthalmol* 2007; **125:** 318–24.
7. Tuttle KR, *et al.* PKC-DRS, PKC-DMES, and PKC-DRS 2 Study Groups. Kidney outcomes in long-term studies of ruboxistaurin for diabetic eye disease. *Clin J Am Soc Nephrol* 2007; **2:** 631–6.
8. Danis RP, Sheetz MJ. Ruboxistaurin: PKC-beta inhibition for complications of diabetes. *Expert Opin Pharmacother* 2009; **10:** 2913–25.
9. Sheetz MJ, *et al.* The Mbdv Study Group. Effect of ruboxistaurin (RBX) on visual acuity decline over a 6-year period with cessation and reinstitution of therapy: results of an open-label extension of the Protein Kinase C Diabetic Retinopathy Study 2 (PKC-DRS2). *Retina* 2011; **31:** 1053–9.
10. Aiello LP, *et al.* The PKC-DRS and PKC-DRS2 Study Groups. Oral protein kinase C β inhibition using ruboxistaurin: efficacy, safety, and causes of vision loss among 813 patients (1,392 eyes) with diabetic retinopathy in the Protein Kinase C β Inhibitor-Diabetic Retinopathy Study and the Protein kinase C β Inhibitor-Diabetic Retinopathy Study 2. *Retina* 2011; **31:** 2084–94.

Saxagliptin *(BAN, USAN, rINN)*

BMS-477118-11 (saxagliptin monohydrate); BMS-477118; Saksagliptyna; Saxagliptina; Saxagliptine; Saxagliptinum; Саксаглиптин.

(1*S*,3*S*,5*S*)-2-[(2*S*)-2-Amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile.

$C_{18}H_{25}N_3O_2$=315.4

CAS — 361442-04-8 (saxagliptin); 945667-22-1 (saxagliptin monohydrate); 709031-78-7 (saxagliptin hydrochloride).

ATC — A10BH03.

ATC Vet — QA10BH03.

UNII — 8I7KO46IVQ (saxagliptin); 9GB927LAJW (saxagliptin monohydrate).

NOTE. Saxagliptin (*INN*) is anhydrous, while Saxagliptin (*USAN*) refers to the monohydrate.

Saxagliptin Hydrochloride *(BANM, rINNM)*

Hidrocloruro de saxagliptina; Saxagliptine, Chlorhydrate de; Saxagliptini Hydrochloridum; Саксаглиптина Гидрохлорид.

$C_{18}H_{25}N_3O_2$,HCl=351.9

CAS — 709031-78-7.

ATC — A10BH03.

ATC Vet — QA10BH03.

UNII — Z8J84YIX6L.

Uses and Administration

Like sitagliptin (p. 502.1), saxagliptin is an inhibitor of dipeptidylpeptidase-4 and is used in the treatment of type 2 diabetes mellitus (p. 459.1). Saxagliptin is given as the hydrochloride, but doses are expressed in terms of the anhydrous base; 2.79 mg of saxagliptin hydrochloride is equivalent to about 2.5 mg of saxagliptin. The usual oral dose is 2.5 or 5 mg once daily, given with or without food. When saxagliptin is given with strong inhibitors of the cytochrome P450 isoenzymes CYP3A4 and CYP3A5, the dose of saxagliptin is usually 2.5 mg once daily.

For the dose of saxagliptin used in renal impairment, see p. 501.3.

References.
1. Neumiller JJ, Campbell RK. Saxagliptin: a dipeptidyl peptidase-4 inhibitor for the treatment of type 2 diabetes mellitus. *Am J Health-Syst Pharm* 2010; **67:** 1515–25.
2. Baetta R, Corsini A. Pharmacology of dipeptidyl peptidase-4 inhibitors: similarities and differences. *Drugs* 2011; **71:** 1441–67.
3. Scheen AJ. Metformin + saxagliptin for type 2 diabetes. *Expert Opin Pharmacother* 2012; **13:** 139–46.
4. Yang LP. Saxagliptin: a review of its use as combination therapy in the management of type 2 diabetes mellitus in the EU. *Drugs* 2012; **72:** 229–48.
5. Barnett AH, *et al.* Effect of saxagliptin as add-on therapy in patients with poorly controlled type 2 diabetes on insulin alone or insulin combined with metformin. *Curr Med Res Opin* 2012; **28:** 513–23.

Administration in renal impairment. UK and US licensed product information state that no dose adjustment for saxagliptin is needed in patients with mild renal impairment. A maximum oral dose of 2.5 mg once daily has been recommended for patients with moderate or severe impairment (creatinine clearance less than or equal to 50 mL/min), including those with end-stage renal disease requiring haemodialysis (although UK product information recommends against use altogether in the last patient group). Saxagliptin should be given after haemodialysis.

Adverse Effects and Precautions

As for Sitagliptin Phosphate, p. 502.1. Small decreases in lymphocyte counts have been seen in patients given saxagliptin, but clinically relevant adverse effects did not occur.

Interactions

The efficacy of saxagliptin may be affected by other drugs that have an independent effect on blood glucose. For more details and examples of drugs that can increase or decrease blood-glucose concentrations, see Interactions under Sulfonylureas, p. 504.3. Drugs that alter the activity of the cytochrome P450 isoenzymes CYP3A4 and CYP3A5 could affect the metabolism of saxagliptin. Although dosage adjustment of saxagliptin is not thought necessary with moderate inhibitors of these enzymes, such as diltiazem, low doses of saxagliptin should be used when strong inhibitors, such as ketoconazole, are given with saxagliptin (see above). The enzyme inducer rifampicin can significantly decrease exposure to saxagliptin, but exposure to its active metabolite (5-hydroxy saxagliptin) and plasma dipeptidylpeptidase-4 inhibition are not affected.

Pharmacokinetics

Saxagliptin is rapidly absorbed from the gastrointestinal tract, and peak plasma concentrations occur within about 2 hours. It is metabolised mainly by the cytochrome P450 isoenzymes CYP3A4 and CYP3A5, and its major metabolite, 5-hydroxy saxagliptin, has half the potency of saxagliptin. Peak plasma concentrations of this metabolite occur within about 4 hours. The terminal plasma elimination half-lives of saxagliptin and its metabolite are about 2.5 and 3.1 hours, respectively. Both saxagliptin and 5-hydroxy saxagliptin are excreted in the urine; there may be some active renal excretion of unchanged saxagliptin. There is also some elimination of a dose in the faeces.

References.
1. Boulton DW, *et al.* Influence of renal or hepatic impairment on the pharmacokinetics of saxagliptin. *Clin Pharmacokinet* 2011; **50:** 253–65.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Onglyza; ***Austral.***: Onglyza; ***Austria***: Onglyza; ***Belg.***: Onglyza; ***Braz.***: Onglyza; ***Canad.***: Onglyza; ***Chile***: Onglyza; ***China***: Onglyza (安立泽); ***Cz.***: Onglyza; ***Denm.***: Onglyza; ***Fr.***: Onglyza; ***Ger.***: Onglyza; ***Gr.***: Onglyza; ***Hong Kong***: Onglyza; ***Hung.***: Onglyza; ***India***: Onglyza; ***Israel***: Onglyza; ***Ital.***: Onglyza; ***Jpn***: Onglyza; ***Malaysia***: Onglyza; ***Mex.***: Onglyza; ***Neth.***: Onglyza; ***Norw.***: Onglyza; ***NZ***: Onglyza; ***Philipp.***: Onglyza; ***Pol.***: Onglyza; ***Port.***: Onglyza; ***Rus.***: Onglyza (Онглиза); ***Singapore***: Onglyza; ***Spain***: Onglyza; ***Swed.***: Ongly-

za; *Switz.*: Onglyza; *Thai.*: Onglyza; *Turk.*: Onglyza; *UK*: Onglyza; *Ukr.*: Ongliza (Онглиза); *USA*: Onglyza.

Multi-ingredient Preparations. *Belg.*: Kombiglyze; *Neth.*: Komboglyze; *Spain*: Komboglyze; *Switz.*: Duoglyze; Kombiglyze; *UK*: Komboglyze; *USA*: Kombiglyze.

Sitagliptin Phosphate

(BANM, USAN, rINNM)

Fosfato de sitagliptina; MK-0431; MK-431; Ono-5435; Sitagliptine Phosphate de; Sitagliptini Phosphas; Ситаглиптина Фосфат.

7-[(3*R*)-3-Amino-4-(2,4,5-trifluorophenyl)butanoyl]-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazinemonophosphate monohydrate.

$C_{16}H_{15}F_6N_5O.H_3O_4P.H_2O$=523.3

CAS — 486460-32-6 (sitagliptin); 654671-78-0 (sitagliptin phosphate); 654671-77-9 (sitagliptin phosphate monohydrate). UNII — TS63EW8X6F.

Uses and Administration

Sitagliptin inhibits dipeptidylpeptidase-4, an enzyme responsible for degradation of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) (see Action, under Exenatide, p. 471.1, for more detail on the role of incretin hormones in glucose homoeostasis). Sitagliptin is used in the treatment of type 2 diabetes mellitus (p. 459.1).

Sitagliptin is given as the phosphate, but doses are in terms of the base; 128.5 mg of sitagliptin phosphate is equivalent to about 100 mg of sitagliptin. The usual oral dose is the equivalent of 100 mg of sitagliptin once daily. When given with metformin, sitagliptin may be given in 2 divided doses. The dose of sulfonylurea or insulin may need to be lowered when used with sitagliptin. Sitagliptin may be taken with or without food. Dosage should be adjusted in patients with renal impairment (see p. 502.1).

References.
1. Lyseng-Williamson KA. Sitagliptin. *Drugs* 2007; 67: 587–97.
2. Florentin M, *et al.* Sitagliptin in clinical practice: a new approach in the treatment of type 2 diabetes. *Expert Opin Pharmacother* 2008; 9: 1705–20.
3. Richter B, *et al.* Dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes mellitus. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 01/07/09).
4. Williams-Herman D, *et al.* Efficacy and safety of initial combination therapy with sitagliptin and metformin in patients with type 2 diabetes: a 54-week study. *Curr Med Res Opin* 2009; 25: 569–83.
5. Dhillon S. Sitagliptin: a review of its use in the management of type 2 diabetes mellitus. *Drugs* 2010; 70: 489–512.
6. Chwieduk CM. Sitagliptin/metformin fixed-dose combination: in patients with type 2 diabetes mellitus. *Drugs* 2011; 71: 349–61.
7. Baetta R, Corsini A. Pharmacology of dipeptidyl peptidase-4 inhibitors: similarities and differences. *Drugs* 2011; 71: 1441–67.

Administration in renal impairment. Sitagliptin has been studied in patients with type 2 diabetes mellitus and renal impairment.[1] Licensed product information suggests the following oral doses of sitagliptin in patients with renal impairment, based on creatinine clearance (CC):

- mild impairment (CC 50 mL/min or more): no adjustment necessary, 100 mg once daily
- moderate impairment (CC 30 to less than 50 mL/min): 50 mg once daily
- severe impairment (CC less than 30 mL/min) or end-stage renal disease requiring haemodialysis or peritoneal dialysis: 25 mg once daily. It may be given without regard to the timing of haemodialysis

1. Chan JC, *et al.* Safety and efficacy of sitagliptin in patients with type 2 diabetes and chronic renal insufficiency. *Diabetes Obes Metab* 2008; 10: 545–55.

Adverse Effects, Treatment, and Precautions

Adverse effects reported with sitagliptin include headache, dizziness, and gastrointestinal disturbances. Peripheral oedema has occurred, particularly in patients also being treated with a thiazolidinedione. Upper respiratory-tract infections and nasopharyngitis have also occurred, but a causal relationship has not been established. Rashes and other hypersensitivity reactions including anaphylaxis, angioedema, urticaria, cutaneous vasculitis, and Stevens-Johnson syndrome have been reported. There have also been isolated cases of elevated liver enzyme values and pancreatitis, including haemorrhagic and necrotising pancreatitis. Impaired renal function, including acute renal failure (sometimes requiring dialysis), has also been reported. Hypoglycaemia is unlikely with sitagliptin given alone, but it may contribute to hypoglycaemia caused by other oral antidiabetics such as sulfonylureas.

Sitagliptin should not be used in type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. The dose of sitagliptin should be reduced in moderate and severe renal impairment. It is recommended that renal function is assessed before starting treatment and periodically thereafter.

Incidence of adverse effects. A pooled analysis included data from 12 studies of sitagliptin given as monotherapy or with other oral antidiabetics, and compared with placebo or other oral antidiabetics, in 6139 patients treated for up to 2 years.[1] Overall, the incidence of adverse experiences did not significantly differ between patients exposed to sitagliptin and those who were not. About 13% of patients given sitagliptin had an adverse experience that was determined to be possibly, probably, or definitely drug-related; 0.2% had a serious adverse experience. As expected, hypoglycaemia occurred more often during co-treatment with a sulfonylurea. For those not given a sulfonylurea the incidence of hypoglycaemia was 2.6% in patients given sitagliptin, which was similar to 2.3% in those not exposed to sitagliptin.

1. Williams-Herman D, *et al.* Safety and tolerability of sitagliptin in patients with type 2 diabetes: a pooled analysis. *BMC Endocr Disord* 2008; 8: 14. Available at: http://www.biomedcentral.com/content/pdf/1472-6823-8-14.pdf (accessed 14/09/09)

Driving. Diabetes mellitus, its complications, and the medications used to treat it, may affect a patient's ability to drive safely—see under Insulin (p. 485.2) for restrictions applied to diabetic patients in the UK.

Effects on the immune system. In addition to regulating glucose homoeostasis, dipeptidyl peptidase-4 (DPP-4) has many diverse functions such as modulating cell growth, differentiation, and transformation, and immune function. Long-term inhibition of this enzyme by drugs, such as sitagliptin, may cause immune suppression and increase the risk of cancer.[1-3] A case-control study has shown an increased incidence of reports of infections, especially upper respiratory-tract infections, in users of DPP-4 inhibitors compared with users of other antidiabetic drugs.[4]

1. Stulc T, Sedo A. Inhibition of multifunctional dipeptidyl peptidase-IV: is there a risk of oncological and immunological adverse effects? *Diabetes Res Clin Pract* 2010; 88: 125–31.
2. Elashoff M, *et al.* Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. *Gastroenterology* 2011; 141: 150–6.
3. Spranger J, *et al.* GLP-1-based therapies: the dilemma of uncertainty. *Gastroenterology* 2011; 141: 20–3.
4. Willemen MJ, *et al.* Use of dipeptidyl peptidase-4 inhibitors and the reporting of infections: a disproportionality analysis in the World Health Organization VigiBase. *Diabetes Care* 2011; 34: 369–74.

Effects on the pancreas. There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal haemorrhagic or necrotising pancreatitis, associated with sitagliptin use;[1,2] licensed product information states that if pancreatitis is suspected, sitagliptin should be stopped at once.

Patients with type 2 diabetes may have a greater incidence of pancreatitis when compared with non-diabetic subjects,[3] and some observational studies have not found a further increase in risk with sitagliptin itself.[3,4] However, a review of the FDA Adverse Event Reporting System (AERS) database from 2004 to 2009 showed that pancreatitis was six times more likely to be reported with sitagliptin (or exenatide) than other therapies in type 2 diabetes.[5]

1. FDA. Information for healthcare professionals: acute pancreatitis and sitagliptin (marketed as Januvia and Janumet) [issued 25th September, 2009]. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm183764.htm (accessed 26/09/11)
2. Anonymous. Sitagliptin: too many cases of pancreatitis. *Prescrire Int* 2010; 19: 75.
3. Garg R, *et al.* Acute pancreatitis in type 2 diabetes treated with exenatide or sitagliptin: a retrospective observational pharmacy claims analysis. *Diabetes Care* 2010; 33: 2349–54.
4. Dore DD, *et al.* Use of a claims-based active drug safety surveillance system to assess the risk of acute pancreatitis with exenatide or sitagliptin compared to metformin or glyburide. *Curr Med Res Opin* 2009; 25: 1019–27.
5. Elashoff M, *et al.* Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. *Gastroenterology* 2011; 141: 150–6.

Overdosage. In the UK, the *National Poisons Information Service* states that oral activated charcoal may be considered in adults and children who have ingested more than 15 mg/kg of sitagliptin and present within 1 hour, provided they are conscious and the airway can be protected. Hypoglycaemia should be treated with urgency; the general management of hypoglycaemia is described under insulin (see p. 484.3).

Interactions

The efficacy of sitagliptin may be affected by other drugs that have an independent effect on blood glucose. For more details and examples of drugs that can increase or decrease blood-glucose concentrations, see Interactions under Sulfonylureas, p. 504.3. For reports of a possible interaction between sitagliptin and statins, see Antidiabetics under Simvastatin, p. 1495.1.

References.
1. Scheen AJ. Dipeptidylpeptidase-4 inhibitors (gliptins): focus on drug-drug interactions. *Clin Pharmacokinet* 2010; 49: 573–88.

Pharmacokinetics

Sitagliptin is absorbed from the gastrointestinal tract, with a peak plasma concentration occurring about 1 to 4 hours after an oral dose, and a bioavailability of about 87%. It undergoes minimal metabolism, mainly by the cytochrome P450 isoenzyme CYP3A4, and to a lesser extent by CYP2C8. About 79% of a dose is excreted unchanged in the urine. Renal excretion of sitagliptin involves active tubular secretion; it is a substrate for organic anion transporter-3 and P-glycoprotein. Its terminal half-life is about 12 hours.

References.
1. Scheen AJ. Pharmacokinetics of dipeptidylpeptidase-4 inhibitors. *Diabetes Obes Metab* 2010; 12: 648–58.
2. Golightly LK, *et al.* Comparative clinical pharmacokinetics of dipeptidyl peptidase-4 inhibitors. *Clin Pharmacokinet* 2012; 51: 501–14. Correction. *ibid.*: 831.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Januvia; *Austral.*: Januvia; *Austria*: Januvia; *Belg.*: Januvia; *Braz.*: Januvia; *Canad.*: Januvia; *Chile*: Januvia; *China*: Januvia (捷诺维); *Cz.*: Januvia; Ristaben; Tesavel; Xelevia: *Denm.*: Januvia; *Fr.*: Januvia; Xelevia; *Ger.*: Januvia; Xelevia; *Gr.*: Januvia; Xelevia: *Hong Kong*: Januvia; *Hung.*: Januvia; Xelevia; *India*: Januvia; *Indon.*: Januvia; *Irl.*: Januvia; Ristaben; Tesavel; Xelevia; *Israel*: Januvia; *Ital.*: Januvia; Tesavel; Xelevia; *Jpn*: Glactiv; Januvia; *Malaysia*: Januvia; *Mex.*: Januvia; *Neth.*: Januvia; Ristaben; Tesavel; Xelevia: *Norw.*: Januvia; *NZ*: Januvia; *Philipp.*: Januvia; *Pol.*: Januvia; Ristaben; Tesavel; Xelevia; *Port.*: Januvia; Ristaben; Tesavel; Xelevia: *Rus.*: Januvia (Янувия); *Singapore*: Januvia; *Spain*: Januvia; Ristaben; Tesavel; Xelevia: *Swed.*: Januvia; *Switz.*: Januvia; Xelevia; *Thai.*: Januvia; *Turk.*: Januvia; *UK*: Januvia; *Ukr.*: Yanuvia (Янувия); *USA*: Januvia.

Multi-ingredient Preparations. *Arg.*: Janumet; *Austral.*: Janumet; *Austria*: Janumet; Velmetia; *Belg.*: Janumet; *Braz.*: Janumet; *Canad.*: Janumet; *Chile*: Janumet; *Cz.*: Efficib; Janumet; Ristfor; Velmetia; *Denm.*: Janumet; *Fr.*: Janumet; Velmetia; *Ger.*: Janumet; Velmetia; *Gr.*: Janumet; *Hong Kong*: Janumet; *Hung.*: Janumet; Velmetia; *India*: Janumet; *Irl.*: Efficib; Janumet; Ristfor; Velmetia; *Israel*: Januet; *Ital.*: Efficib; Janumet; Velmetia; *Malaysia*: Janumet; *Neth.*: Efficib; Janumet; Ristfor; Velmetia; *Norw.*: Janumet; *NZ*: Janumet; *Philipp.*: Janumet; *Pol.*: Efficib; Janumet; Ristfor; Velmetia; *Port.*: Efficib; Janumet; Ristfor; Velmetia; *Singapore*: Janumet; *Spain*: Efficib; Janumet; Ristfor; Velmetia; *Swed.*: Janumet; *Switz.*: Janumet; Velmetia; *Thai.*: Janumet; *UK*: Janumet; *Ukr.*: Janumet (Янумет); *USA*: Janumet; Juvisync.

Sulfonylurea Antidiabetics

Antidiabéticos sulfonilureas; Sulphonylurea Antidiabetics.

Uses and Administration

The sulfonylurea antidiabetics are a class of oral antidiabetic drugs used in the treatment of type 2 diabetes mellitus (p. 459.1). They are given to supplement treatment by diet modification and exercise when these have not proved effective on their own, although the biguanide metformin is preferred in patients who are obese.

Sulfonylureas, often described as insulin secretagogues, appear to have several modes of action, apparently mediated by inhibition of ATP-sensitive potassium channels. Initially, secretion of insulin by functioning islet beta cells is increased. However, insulin secretion subsequently falls again but the hypoglycaemic effect persists and may be due to inhibition of hepatic glucose production and increased sensitivity to any available insulin; this may explain the clinical improvement seen in glycaemic control. The duration of action of sulfonylureas is variable; drugs such as tolbutamide are relatively short-acting (about 6 to 12 hours) while chlorpropamide has a prolonged action (over 24 hours).

Sulfonylurea therapy may be combined with metformin or other oral hypoglycaemics in patients who fail to respond to a single type of drug; such combination therapy is usually tried (in the absence of contra-indications) before considering the addition of, or transfer to, insulin therapy.

Reviews.
1. Rendell M. The role of sulphonylureas in the management of type 2 diabetes mellitus. *Drugs* 2004; 64: 1339–58.
2. Bell DS. Practical considerations and guidelines for dosing sulfonylureas as monotherapy or combination therapy. *Clin Ther* 2004; 26: 1714–27.

Administration in children. Although rare, the incidence of type 2 diabetes mellitus in children and adolescents is increasing, related in part to the increase in obesity occurring particularly in westernised countries. There is limited experience with the use of sulfonylureas in children, and the biguanide metformin is generally preferred. The *BNFC* suggests that oral treatment should only be started under specialist supervision, and that initial doses for adolescents should be given at the lower end of the adult dose range before adjusting according to response. The *BNFC* also sug-

gests that longer-acting sulfonylureas such as chlorpropamide and glibenclamide should generally be avoided because of the risk of hypoglycaemia, and that shorter-acting alternatives such as tolbutamide may be preferred.

For details on the use of sulfonylureas in neonatal diabetes, see p. 503.1.

Diabetes mellitus. *Neonatal diabetes mellitus* (a diagnosis of diabetes within the first 6 months of life) in the absence of pancreatic islet autoantibodies is generally the result of mutation in the genes that regulate beta-cell function. Some forms of neonatal diabetes are transient, but the most common cause of permanent neonatal diabetes is mutation in the KCNJ11 gene, which encodes the Kir6.2 subunit of the beta cell ATP-sensitive potassium channel.[1] Insulin treatment is necessary, but there has been some interest in a possible role for sulfonylureas because of their action at this potassium channel.

The use of sulfonylureas has been described in 49 patients with Kir6.2 mutations ranging in age from 3 months to 36 years old.[2] Most were given glibendamide, but a few were treated with gliclazide, glimepiride, glipizide, or tolbutamide. Patients managed in hospital were started on an oral glibenclamide dose of 100 micrograms/kg twice daily, which was increased daily by 200 micrograms/kg; those managed as outpatients started with 100 micrograms/kg daily and had the dose increased by 100 micrograms/kg once each week. Insulin therapy was gradually withdrawn during this dose escalation period, in which glibenclamide dosage was increased until insulin independence or a dose of at least 800 micrograms/kg daily was reached. Of the 49 patients, 44 were successfully transferred to a sulfonylurea at a median dose equivalent to glibenclamide 450 micrograms/kg daily (range 50 micrograms/kg to 1.5 mg/kg daily), with improved glycated haemoglobin and no change in the frequency of hypoglycaemic episodes. Over time, the dose of sulfonylurea could be reduced. Neurological features including developmental delay and epilepsy were much more prevalent in the patients who could not be transferred to a sulfonylurea. Similar success has also been described in a group of 10 children aged between 6 months and 10 years old, using either glibenclamide or glipizide.[3]

Mutations of the ABCC8 gene, which encodes the sulfonylurea receptor 1 subunit of the beta cell ATP-sensitive potassium channel, can cause transient or permanent neonatal diabetes. Patients with this condition have also been successfully transferred from insulin to sulfonylurea therapy, although the dosage requirement appears to be lower than that for patients with Kir6.2 mutations. In 23 of 27 patients aged from 2 months to 46 years, a median glibenclamide dose of 260 micrograms/kg daily (or the dose equivalent using gliclazide, glipizide, or tolbutamide) was found to be effective.[4]

1. Hattersley A, *et al.* ISPAD Clinical Practice Consensus Guidelines 2009 compendium: the diagnosis and management of monogenic diabetes in children and adolescents. *Pediatr Diabetes* 2009; **10** (suppl 12): 33–42. Also available at: http://www.ispad.org/FileCenter/ISPAD%20Guidelines%202009%20-%20Monogenic%20diabetes.pdf (accessed 09/02/11)
2. Pearson ER, *et al.* Neonatal Diabetes International Collaborative Group. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. *N Engl J Med* 2006; **355**: 467–77.
3. Tonini G, *et al.* Early-Onset Diabetes Study Group of the Italian Society of Paediatric Endocrinology and Diabetology. Sulfonylurea treatment outweighs insulin therapy in short-term metabolic control of patients with permanent neonatal diabetes mellitus due to activating mutations of the KCNJ11 (KIR6.2) gene. *Diabetologia* 2006; **49**: 2210–13.
4. Rafiq M, *et al.* Neonatal Diabetes International Collaborative Group. Effective treatment with oral sulfonylureas in patients with diabetes due to sulfonylurea receptor 1 (SUR1) mutations. *Diabetes Care* 2008; **31**: 204–9.

Adverse Effects

Gastrointestinal disturbances such as nausea, vomiting, heartburn, anorexia, diarrhoea, and a metallic taste may occur with sulfonylureas and are usually mild and dose-dependent; increased appetite and weight gain may occur. Rashes and pruritus may occur and photosensitivity has been reported. Rashes are usually hypersensitivity reactions and may progress to more serious disorders (see below). Facial flushing may develop in patients receiving sulfonylureas, particularly chlorpropamide, when alcohol is consumed (see under Interactions, p. 505.2).

Mild hypoglycaemia may occur; severe hypoglycaemia is usually an indication of overdosage and is relatively uncommon. Hypoglycaemia is more likely with long-acting sulfonylureas such as chlorpropamide and glibenclamide, which have been associated with severe, prolonged, and sometimes fatal hypoglycaemia.

Other severe effects may be manifestations of a hypersensitivity reaction. They include altered liver enzyme values, hepatitis and cholestatic jaundice, leucopenia, thrombocytopenia, aplastic anaemia, agranulocytosis, haemolytic anaemia, erythema multiforme or the Stevens-Johnson syndrome, exfoliative dermatitis, and erythema nodosum.

The sulfonylureas, particularly chlorpropamide, occasionally induce a syndrome of inappropriate secretion of antidiuretic hormone (SIADH) characterised by water retention, hyponatraemia, and CNS effects. However, some sulfonylureas, such as glibenclamide, glipizide, and tolazamide are also stated to have mild diuretic actions.

Work on tolbutamide has suggested that the sulfonylureas might be associated with an increase in cardiovascular mortality; this has been the subject of considerable debate (see Effects on the Cardiovascular System, p. 503.2).

Reviews.
1. Paice BJ, *et al.* Undesired effects of the sulphonylurea drugs. *Adverse Drug React Acute Poisoning Rev* 1985; **4**: 23–36.
2. Harrower ADB. Comparative tolerability of sulphonylureas in diabetes mellitus. *Drug Safety* 2000; **22**: 313–20.
3. Salas M, Caro JJ. Are hypoglycaemia and other adverse effects similar among sulphonylureas? *Adverse Drug React Toxicol Rev* 2002; **21**: 205–17.

Effects on the blood. There have been isolated reports of thrombocytopenia in patients given sulfonylurea antidiabetics.[1,2] Cases of haemolytic anaemia have also been described,[3,4] some in patients found to have G6PD deficiency.[5,6]

1. Israeli A, *et al.* Glibenclamide causing thrombocytopenia and bleeding tendency: case reports and a review of the literature. *Klin Wochenschr* 1988; **66**: 223–4.
2. Cartron G, *et al.* Glimepiride-induced thrombocytopenic purpura. *Ann Pharmacother* 2000; **34**: 120.
3. Nataas OB, Nesthus I. Immune haemolytic anaemia induced by glibenclamide in selective IgA deficiency. *BMJ* 1987; **295**: 366–7.
4. Noto H, *et al.* Glyburide-induced hemolysis in myelodysplastic syndrome. *Diabetes Care* 2000; **23**: 129.
5. Meloni G, Meloni T. Glyburide-induced acute haemolysis in a G6PD-deficient patient with NIDDM. *Br J Haematol* 1996; **92**: 159–60.
6. Vinzio S, *et al.* Glibenclamide-induced acute haemolytic anaemia revealing a G6PD-deficiency. *Diabetes Res Clin Pract* 2004; **64**: 181–3.

Effects on the cardiovascular system. A multicentre study carried out under the University Group Diabetes Program (UGDP) reported an increased incidence in mortality from cardiovascular complications in diabetic patients given tolbutamide as compared with those treated with diet alone or insulin;[1] a similar increase was also noted in patients given phenformin.[2] The reports from the UGDP aroused prolonged controversy, which was not entirely settled by detailed reassessment of relevant studies.[3] Eventually in 1984 the FDA made it a requirement that sulfonylurea oral antidiabetics be labelled with a specific warning about the possibility of increased cardiovascular mortality associated with the use of these drugs.[4] Subsequently the cardiovascular effects of the sulfonylureas were reviewed.[5] It has been hypothesised that the action of the sulfonylureas in preventing the opening of ATP-sensitive potassium channels in the myocardium may abolish adaptive changes (ischaemic preconditioning) that protect the heart against ischaemic insult.[6]

There is still debate about the risk of death and cardiovascular events in patients taking sulfonylureas. The UK Prospective Diabetes Study did not find any adverse cardiovascular effects associated with sulfonylurea therapy.[7] However, other studies have suggested that there are increased risks associated with sulfonylurea use. A retrospective cohort study[8] found that among patients newly treated for type 2 diabetes, sulfonylurea monotherapy was associated with an increased risk of death, which also appeared to be dose related, compared with metformin therapy. Using data from the UK General Practice Research Database, another retrospective cohort study[9] also found an excess risk for all cause mortality associated with sulfonylureas when compared with metformin. An increased risk of myocardial infarction was no longer statistically significant in the fully adjusted model, but newer sulfonylureas were associated with an increased risk of congestive heart failure. The results of a case-control study[10] suggested that the risk of myocardial infarction was higher in users of older sulfonylureas (glibenclamide, glipizide, and tolbutamide) than of newer drugs (gliclazide and glimepiride) or non-sulfonylurea antidiabetics (mainly metformin). The risk was higher again in patients receiving insulin, and worst in those not receiving any drug treatment for their diabetes. A retrospective cohort study[11] also found a trend suggesting that, in terms of mortality risk, glimepiride might be preferred in patients with a history of coronary artery disease.

A few observational studies have looked at in-hospital events in diabetic patients admitted with acute myocardial infarction. One study[12] found that prior use of a sulfonylurea was not associated with an increased risk of death in hospital, and actually suggested that outcome was better in those who had been taking a sulfonylurea compared with those who had not (other treatments were generally metformin or insulin). Another[13] compared different sulfonylureas and found a lower risk of in-hospital arrhythmias, ischaemic complications, or death in patients who had been taking gliclazide or glimepiride before admission, compared with glibenclamide. Relating survival effects to pre-admission therapy, an epidemiological study[14] suggested that use of a sulfonylurea (glibenclamide, glimepiride, or glipizide) before the myocardial infarction did not adversely affect mortality rates up to 1 year later compared with insulin.

The effects of sulfonylureas given after discharge following myocardial infarction have also been studied. Follow-up[15] over about 2 years in patients who had taken part in the DIGAMI 2 study suggested a neutral effect on the risk of non-fatal myocardial infarction and stroke compared with a decreased risk from metformin and an increased risk from insulin. In a cohort study[16] of diabetic patients who were not treated with percutaneous coronary intervention within 48 hours of admission, follow-up for about 2 years found an increased risk of non-fatal myocardial infarction and cardiovascular mortality in patients taking sulfonylureas compared with metformin. Only gliclazide was not associated with an increased risk of cardiovascular events.

1. University Group Diabetes Program. Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes III: clinical implications of UGDP results. *JAMA* 1971; **218**: 1400–10.
2. University Group Diabetes Program. Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes IV: a preliminary report on phenformin results. *JAMA* 1971; **217**: 777–84.
3. Report of the Committee for the Assessment of Biometric Aspects of Controlled Trials of Hypoglycemic Agents. *JAMA* 1975; **231**: 583–600.
4. FDA. Class labeling for oral hypoglycemics. *FDA Drug Bull* 1984; **14**: 16–17.
5. Huupponen R. Adverse cardiovascular effects of sulphonylurea drugs: clinical significance. *Med Toxicol* 1987; **2**: 190–209.
6. Yellon DM, *et al.* Angina reassessed: pain or protector? *Lancet* 1996; **347**: 1159–62.
7. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; **352**: 837–53. Correction. *ibid.* 1999; **354**: 602.
8. Simpson SH, *et al.* Dose-response relation between sulfonylurea drugs and mortality in type 2 diabetes mellitus: a population-based cohort study. *Can Med Assoc J* 2006; **174**: 169–74.
9. Tzoulaki I, *et al.* Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database. *BMJ* 2009; **339**: b4731.
10. Johnsen SP, *et al.* Risk and short-term prognosis of myocardial infarction among users of antidiabetic drugs. *Am J Ther* 2006; **13**: 134–40.
11. Pantalone KM, *et al.* The risk of overall mortality in patients with type 2 diabetes receiving glipizide, glyburide, or glimepiride monotherapy: a retrospective analysis. *Diabetes Care* 2010; **33**: 1224–9.
12. Danchin N, *et al.* Role of previous treatment with sulfonylureas in diabetic patients with acute myocardial infarction: results from a nationwide French registry. *Diabetes Metab Res Rev* 2005; **21**: 143–9.
13. Zeller M, *et al.* Impact of type of preadmission sulfonylureas on mortality and cardiovascular outcomes in diabetic patients with acute myocardial infarction. *J Clin Endocrinol Metab* 2010; **95**: 4993–5002.
14. Arruda-Olson AM, *et al.* Effect of second-generation sulfonylureas on survival in patients with diabetes mellitus after myocardial infarction. *Mayo Clin Proc* 2009; **84**: 28–33.
15. Mellbin LG, *et al.* The impact of glucose lowering treatment on long-term prognosis in patients with type 2 diabetes and myocardial infarction: a report from the DIGAMI 2 trial. *Eur Heart J* 2008; **29**: 166–76.
16. Jørgensen CH, *et al.* Effects of oral glucose-lowering drugs on long term outcomes in patients with diabetes mellitus following myocardial infarction not treated with emergent percutaneous coronary intervention-a retrospective nationwide cohort study. *Cardiovasc Diabetol* 2010; **9**: 54. Available at: http://www.cardiab.com/content/pdf/1475-2840-9-54.pdf (accessed 14/03/11)

Effects on the eyes. When a diabetic patient who had had bilateral visual loss for several months and who had been taking chlorpropamide for a year stopped treatment, visual acuity improved and colour vision rapidly returned.[1] A 5-day challenge with chlorpropamide resulted in a mild decrease in acuity followed by return to baseline values when treatment was again stopped. Drug-induced optic neuropathy was considered to have occurred. There is also a report of a patient with type 2 diabetes mellitus who developed myopia 2 days after starting treatment with glibenclamide 10 mg daily.[2] Visual difficulties resolved a few days after stopping glibenclamide.

1. Wymore J, Carter JE. Chlorpropamide-induced optic neuropathy. *Arch Intern Med* 1982; **142**: 381.
2. Teller J, *et al.* Accommodation insufficiency induced by glybenclamide. *Ann Ophthalmol* 1989; **21**: 275–6.

Effects on the kidneys. The nephrotic syndrome has been reported in a patient treated with chlorpropamide.[1] Serological testing and renal biopsy showed that the glomerular lesions were of an immune-complex nature. Both the nephrotic syndrome and the glomerulonephritis resolved after treatment was stopped. The patient also developed a skin eruption, hepatitis, and eosinophilia.

1. Appel GB, *et al.* Nephrotic syndrome and immune complex glomerulonephritis associated with chlorpropamide therapy. *Am J Med* 1983; **74**: 337–42.

Effects on the liver. Chlorpropamide was implicated[1] in 8 of 53 cases of drug-induced acute liver disease admitted to a hospital in Jamaica over the years 1973 to 1988. Hepatocanalicular cholestasis occurred in 5 cases and diffuse necrosis in 3. One patient with massive hepatic necrosis died. Other hepatic reactions associated with sulfonylurea antidiabetics have included intrahepatic cholestasis with glibenclamide[2-4] and glimepiride,[5,6] and acute hepatitis-like reactions with glibenclamide,[7] glimepiride,[8] and gliclazide.[9,10] A case of mixed liver damage involving necrosis, intrahepatic cholestasis, and hepatitis with gliben-

clamide[11] has been described. Granulomatous hepatitis has also been reported with glibenclamide.[12]

1. Lee MG, *et al.* Drug-induced acute liver disease. *Postgrad Med J* 1989; **65**: 367–70.
2. Wongpaitoon V, *et al.* Intrahepatic cholestasis and cutaneous bullae associated with glibenclamide therapy. *Postgrad Med J* 1981; **57**: 244–6.
3. Krivoy N, *et al.* Fatal toxic intrahepatic cholestasis secondary to glibenclamide. *Diabetes Care* 1996; **19**: 385–6.
4. Tholakanahalli VN, *et al.* Glibenclamide-induced cholestasis. *West J Med* 1998; **168**: 274–7.
5. Sitruk V, *et al.* Hépatite aiguë cholestatique induite par le glimépiride. *Gastroenterol Clin Biol* 2000; **24**: 1233–4.
6. Chounta A, *et al.* Cholestatic liver injury after glimepiride therapy. *J Hepatol* 2005; **42**: 944–6.
7. Goodman RC, *et al.* Glyburide-induced hepatitis. *Ann Intern Med* 1987; **106**: 837–9.
8. Dusoleil A, *et al.* Hépatite aiguë induite par le glimépiride. *Gastroenterol Clin Biol* 1999; **23**: 1096–7.
9. Dourakis SP, *et al.* Gliclazide-induced acute hepatitis. *Eur J Gastroenterol Hepatol* 2000; **12**: 119–21.
10. Chitturi S, *et al.* Gliclazide-induced acute hepatitis with hypersensitivity features. *Dig Dis Sci* 2002; **47**: 1107–10.
11. Petrogiannopoulos C, Zacharof A. Glibenclamide and liver disease. *Diabetes Care* 1997; **20**: 1215.
12. Saw D, *et al.* Granulomatous hepatitis associated with glyburide. *Dig Dis Sci* 1996; **41**: 322–5.

Effects on the thyroid. See under Precautions, p. 504.3.

Hypoglycaemia. All sulfonylurea antidiabetics can cause hypoglycaemia. Those with a prolonged action, such as chlorpropamide and glibenclamide, appear to cause severe hypoglycaemia more often than shorter-acting drugs such as tolbutamide.[1] Newer short-acting sulfonylureas, such as glibornuride, gliclazide, glimepiride, and glipizide, also appear to be less often associated with severe hypoglycaemia.[1-3] The risk of hypoglycaemia in patients receiving sulfonylureas may be increased by missed or irregular meals, older age, hepatic or renal impairment, and drug interactions.[3] A small study[4] has also suggested that the presence of the rare cytochrome P450 isoenzyme genotypes CYP2C9*2/*3 or *3/*3, which are predictive of impaired metabolism of many sulfonylureas, might be considered an additional, but not major, risk factor for severe hypoglycaemia.

See also under Abuse, p. 504.2, and Overdosage, p. 504.1.

1. Shorr RI, *et al.* Individual sulfonylureas and serious hypoglycemia in older people. *J Am Geriatr Soc* 1996; **44**: 751–5.
2. Stahl M, Berger W. Higher incidence of severe hypoglycaemia leading to hospital admission in type 2 diabetic patients treated with long-acting versus short-acting sulphonylureas. *Diabet Med* 1999; **16**: 586–90.
3. Amiel SA, *et al.* Hypoglycaemia in type 2 diabetes. *Diabet Med* 2008; **25**: 245–54.
4. Holstein A, *et al.* Association between CYP2C9 slow metabolizer genotypes and severe hypoglycaemia on medication with sulphonylurea hypoglycaemic agents. *Br J Clin Pharmacol* 2005; **60**: 103–6.

Overdosage. An analysis[1] found that hypoglycaemia developed only in 56 of 185 children reported to 10 regional poison centres in the USA after ingesting sulfonylureas. A lack of hypoglycaemia during the first 8 hours after ingestion was predictive of a benign outcome, and it was recommended that suspected cases be observed for 8 hours with frequent blood glucose monitoring and free access to oral foods. Children who developed signs of hypoglycaemia, or in whom blood glucose fell below 3.3 mmol/litre could be given intravenous glucose if necessary. Others[2] have suggested that because multiple fingerstick blood sampling can be painful and stressful to young children, overnight monitoring for clinical signs of hypoglycaemia may be adequate for asymptomatic toddlers thought to have ingested a sulfonylurea. The use of prophylactic intravenous glucose (before clinical or laboratory evidence of hypoglycaemia) has also been discouraged,[2] because it may delay the onset and detection of hypoglycaemia, and confound the diagnosis of sulfonylurea poisoning.

1. Spiller HA, *et al.* Prospective multicenter study of sulfonylurea ingestion in children. *J Pediatr* 1997; **131**: 141–6.
2. Caiello DP, *et al.* Case files of the Medical Toxicology Fellowship Training Program at the Children's Hospital of Philadelphia: a pediatric exploratory sulfonylurea ingestion. *J Med Toxicol* 2006; **2**: 19–24.

Treatment of Adverse Effects

Oral activated charcoal may be given in acute poisoning with sulfonylureas, if the patient presents within 1 hour of ingestion and is conscious, and the airway can be protected. Gastric lavage might be considered, particularly after a potentially life-threatening overdose, but it is generally of limited benefit and not necessary if activated charcoal can be given promptly. Hypoglycaemia should be treated with urgency; the general management of hypoglycaemia is described under insulin (see p. 484.3). The patient should be observed over several days in case hypoglycaemia recurs. Octreotide has been used in the treatment of severe refractory cases of sulfonylurea-induced hypoglycaemia.

References.

1. Spiller HA. Management of antidiabetic medication in overdose. *Drug Safety* 1998; **19**: 411–24.

Octreotide. Octreotide inhibits the secretion of insulin and has, therefore, been tried in addition to the usual management of sulfonylurea overdosage (above). It has been used to manage prolonged or refractory hypoglycaemia, and to prevent rebound hypoglycaemia, in cases of poisoning and in sulfonylurea-treated patients with renal impairment. A review[1] of reported cases found that octreotide was usually given by subcutaneous injection, in doses ranging from 40 to 100 micrograms; the most commonly used regimen was 50 micrograms given 2 or 3 times daily. There have also been reports of using a continuous intravenous infusion of 1.8 micrograms/kg per hour. In most cases, octreotide treatment was continued for 12 to 72 hours, but it may be needed for several days after long-acting sulfonylureas or modified-release preparations. Patients should be observed for at least 12 to 24 hours after the last dose of octreotide, to monitor for rebound hypoglycaemia.

There have also been a few reports of the use of intravenous octreotide in children.[2,3] In a girl aged 2 years and 9 months, an initial dose of 2 micrograms/kg was followed by an infusion of 2 micrograms/kg per hour.[2] In another case,[2] a 12-month-old boy was given a single dose of 2.5 micrograms/kg. It has also been suggested[1] that a subcutaneous dose of 1 to 1.25 micrograms/kg might be suitable for children.

The use of octreotide has also been studied[4] in patients presenting with hypoglycaemia during sulfonylurea treatment (none were believed to have taken a large amount of drug as a suicide attempt). The small controlled study found that, compared with placebo, there were higher serum-glucose concentrations in the 8 hours after a single dose of subcutaneous octreotide 75 micrograms, and recurrent hypoglycaemic episodes were less frequent.

1. Lheureux PER, *et al.* Bench-to-bedside review: antidotal treatment of sulfonylurea-induced hypoglycaemia with octreotide. *Crit Care* 2005; **9**: 543–9.
2. Rath S, *et al.* Octreotide in children with hypoglycaemia due to sulfonylurea ingestion. *J Paediatr Child Health* 2008; **44**: 383–4.
3. Glatstein M, *et al.* Sulfonylurea intoxication at a tertiary care paediatric hospital. *Can J Clin Pharmacol* 2010; **17**: e51–6. Available at: http://www.cjcp.ca/cjcp_09023_koren3_e51_e56-pdf-r108986 (accessed 22/09/11)
4. Fasano CJ, *et al.* Comparison of octreotide and standard therapy versus standard therapy alone for the treatment of sulfonylurea-induced hypoglycemia. *Ann Emerg Med* 2008; **51**: 400–406.

Precautions

Sulfonylureas should not be used in type 1 diabetes mellitus. Use in type 2 diabetes mellitus is contra-indicated in patients with ketoacidosis and in those with severe infection, trauma, or other severe conditions where the sulfonylurea is unlikely to control the hyperglycaemia; insulin should be used in such situations.

Insulin is also preferred for therapy during pregnancy although there is growing interest in the use of glibenclamide in the management of gestational diabetes (see Pregnancy, p. 504.3).

Sulfonylureas are associated with an increased risk of hypoglycaemia. They should therefore be used with caution or avoided in patients with impaired renal or hepatic function, and a similar precaution would tend to apply in other groups with an increased susceptibility to this effect, such as the elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency. Irregular mealtimes, missed meals, changes in diet, or prolonged exercise may also provoke hypoglycaemia. Sulfonylureas with a long half-life, such as chlorpropamide and glibenclamide, should be avoided in those at risk. Where a sulfonylurea needs to be used in at-risk patients, a short-acting drug such as tolbutamide or gliclazide may be preferred; these 2 sulfonylureas, being mainly inactivated in the liver, are perhaps particularly suitable in renal impairment, although careful monitoring of blood-glucose concentration is essential.

Sulfonylureas should be used with caution in patients with G6PD deficiency, because of a risk of haemolytic anaemia.

Abuse. Severe hypoglycaemia, at first thought to be due to insulinoma but later found to be due to nesidioblastosis [proliferation of the islet cells], was reported in a woman covertly taking chlorpropamide.[1] Other sulfonylureas have been detected in blood samples from patients with unexplained hypoglycaemia; some cases may have been related to factitious drug ingestion.[2,3]

The presence of glibenclamide, in illegal products promoted in Singapore for sexual enhancement, in levels up to 40 times those used in the management of diabetes mellitus had been responsible for cases of severe hypoglycaemia and several deaths.[4] The rationale for including glibenclamide in such products was unknown.

1. Rayman G, *et al.* Hyperinsulinaemic hypoglycaemia due to chlorpropamide-induced nesidioblastosis. *J Clin Pathol* 1984; **37**: 651–4.
2. Kwong PYP, Teale JD. Screening for sulphonylureas in the investigation of hypoglycaemia. *J R Soc Med* 2002; **95**: 381–5.
3. Trenque T, *et al.* Prevalence of factitious hypoglycaemia associated with sulphonylurea drugs in France in the year 2000. *Br J Clin Pharmacol* 2002; **54**: 548.
4. Low M-Y, *et al.* Safety and quality assessment of 175 illegal sexual enhancement products seized in red-light districts in Singapore. *Drug Safety* 2009; **32**: 1141–6.

Administration. It has been suggested that continuously high plasma concentrations of sulfonylureas may lead to the development of tolerance, and that therefore the maximum recommended doses should be reduced.[1] Also, the addition of an insulin sensitiser, to improve glucose transport into the tissues, has been advocated for patients with insulin resistance, instead of increasing the sulfonylurea dose.[2]

1. Melander A, *et al.* Is there a concentration-effect relationship for sulphonylureas? *Clin Pharmacokinet* 1998; **34**: 181–8.
2. Rambiritch V, *et al.* Dose-response relationships of sulfonylureas: will doubling the dose double the response? *South Med J* 2007; **100**: 1132–6.

Breast feeding. The sulfonylureas chlorpropamide (p. 470.2) and tolbutamide (p. 504.3) have been detected in breast milk, and this class of drug is generally avoided during breast feeding because of the risk of hypoglycaemia in the breast-fed infant. However, neither glibenclamide nor glipizide was detected in breast milk in a small study of 5 women with type 2 diabetes, and normal blood-glucose concentrations were found in the 3 infants who were wholly breast fed.

1. Feig DS, *et al.* Transfer of glyburide and glipizide into breast milk. *Diabetes Care* 2005; **28**: 1851–5.

Driving. Diabetes mellitus, its complications, and the medications used to treat it, may affect a patient's ability to drive safely—see under Insulin (p. 485.2) for restrictions applied to diabetic patients in the UK.

Fasting. For the suggestion that sulfonylureas should be used with caution in fasting Muslim patients during Ramadan, and that chlorpropamide is contra-indicated in this group, see under Precautions of Insulin, p. 485.3.

Pregnancy. Insulin is generally preferred for the management of diabetes mellitus during pregnancy, and sulfonylurea antidiabetics are avoided. Chlorpropamide and tolbutamide cross the placenta, and symptomatic hypoglycaemia has been reported in some exposed neonates. Pharmacokinetic data are lacking for other sulfonylureas, but some studies show only poor placental transfer of glibenclamide.[1] There is no strong evidence that sulfonylureas have teratogenic effects during the first trimester, but their safety has not been established.[2]

Sulfonylureas have also generally been avoided in the management of gestational diabetes, but there is increasing interest in their use. Studies have found glibenclamide to be safe and effective, but these have mostly been observational and non-randomised.[3,4] Although some reviewers have cautioned against the use of glibenclamide until further evidence is available,[5] some guidelines now suggest that it may be considered as an adjunct or alternative to insulin in gestational diabetes.[6]

1. Garcia-Bournissen F, *et al.* Maternal-fetal transport of hypoglycaemic drugs. *Clin Pharmacokinet* 2003; **42**: 303–13.
2. Feig DS, *et al.* Oral antidiabetic agents in pregnancy and lactation: a paradigm shift? *Ann Pharmacother* 2007; **41**: 1174–80.
3. Moore TR. Glyburide for the treatment of gestational diabetes: a critical appraisal. *Diabetes Care* 2007; **30** (suppl): S209–S213.
4. Moretti ME, *et al.* Safety of glyburide for gestational diabetes: a meta-analysis of pregnancy outcomes. *Ann Pharmacother* 2008; **42**: 483–90.
5. Kimber-Trojnar Ż., *et al.* Glyburide for the treatment of gestational diabetes mellitus. *Pharmacol Rep* 2008; **60**: 308–18.
6. National Collaborating Centre for Women's and Children's Health / NICE. Diabetes in pregnancy: management of diabetes and its complications from preconception to the postnatal period (issued March 2008, reissued July 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/DiabetesFullGuidelineRevisedJULY2008.pdf (accessed 06/03/09)

Thyroid disorders. There are conflicting reports concerning the effects of sulfonylureas on thyroid function, with some studies suggesting an increased incidence of thyroid dysfunction in patients treated with tolbutamide or chlorpropamide,[1] while other suggest no antithyroid action.[2,3] Some licensed product information consequently recommends that chlorpropamide should be avoided in patients with impaired thyroid function. Changes in thyroid function may conversely affect glycaemic control—for mention of the possible effects of thyroid hormones on antidiabetic drug requirements see under Interactions, p. 504.1.

1. Hunton RB, *et al.* Hypothyroidism in diabetics treated with sulphonylurea. *Lancet* 1965; **ii**: 449–51.
2. Burke G, *et al.* Effect of long-term sulfonylurea therapy on thyroid function in man. *Metabolism* 1967; **16**: 651–7.
3. Feely J, *et al.* Antithyroid effect of chlorpropamide? *Hum Toxicol* 1983; **2**: 149–53.

Interactions

Many interactions have been reported with the sulfonylureas, largely representing either pharmacokinetic interactions (due to the displacement of the antidiabetic from plasma proteins or alteration in its metabolism or excretion) or pharmacological interactions with drugs having an independent effect on blood glucose. In the former class

most reports concern older sulfonylureas such as chlorpropamide and tolbutamide, although the possibility of such reactions with newer drugs should be borne in mind.

- A *reduced* hypoglycaemic effect, possibly requiring an increased dose of sulfonylurea, has been seen or might be expected on theoretical grounds with adrenaline, aminoglutethimide, chlorpromazine, corticosteroids, diazoxide, oral contraceptives, rifamycins, thiazide diuretics, and thyroid hormones.
- An *increased* hypoglycaemic effect has occurred or might be expected with ACE inhibitors, alcohol, allopurinol, some analgesics (notably azapropazone, phenylbutazone, and the salicylates), azole antifungals (fluconazole, ketoconazole, and miconazole), chloramphenicol, cimetidine, clarithromycin, clofibrate and related compounds, coumarin anticoagulants, disopyramide, fluoroquinolones, heparin, MAOIs, ranitidine, SSRIs, sulfinpyrazone, sulfonamides (including co-trimoxazole), tetracyclines, and tricyclic antidepressants.

Beta blockers may reduce the efficacy of sulfonylureas by impairing the release of insulin from the pancreas; cardioselective beta blockers may have less of an effect than non-selective ones. Beta blockers can also inhibit the normal physiological response to hypoglycaemia and mask the typical sympathetic warning signs. There are sporadic and conflicting reports of a possible interaction with calcium-channel blockers, but overall any effect seems to be of little clinical significance. Octreotide can inhibit sulfonylurea-induced release of insulin from the pancreas; this effect has been exploited in the management of sulfonylurea overdose (see under Treatment of Adverse Effects, p. 502.2).

In addition to producing hypoglycaemia alcohol can interact with chlorpropamide to produce an unpleasant flushing reaction. Such an effect is rare with other sulfonylureas and alcohol.

General references.

1. O'Byrne S, Feely J. Effects of drugs on glucose tolerance in non-insulin-dependent diabetics (part I). *Drugs* 1990; 40: 6–18.
2. O'Byrne S, Feely J. Effects of drugs on glucose tolerance in non-insulin-dependent diabetics (part II). *Drugs* 1990; 40: 203–19.
3. Girardin E, *et al.* Hypoglycémies induites par les sulfamides hypoglycémiants. *Ann Med Interne (Paris)* 1992; 143: 11–17.
4. Tirkkonen T, *et al.* Potential CYP2C9-mediated drug-drug interactions in hospitalized type 2 diabetes mellitus patients treated with the sulphonylureas glibenclamide, glimepiride or glipizide. *J Intern Med* 2010; 268: 359–66.

ACE inhibitors. There are sporadic reports of marked hypoglycaemia developing in patients taking a sulfonylurea who are given an ACE inhibitor (mainly *captopril* or *enalapril*),[1-3] and 2 case-control studies have indicated that the combination is associated with an increased risk of developing severe hypoglycaemia.[4,5] However, other studies have failed to find much evidence of a problem.[6-10]

1. McMurray J, Fraser DM. Captopril, enalapril, and blood glucose. *Lancet* 1986; i: 1035.
2. Rett K, *et al.* Hypoglycemia in hypertensive diabetic patients treated with sulfonylureas, biguanides, and captopril. *N Engl J Med* 1988; 319: 1609.
3. Arauz-Pacheco C, *et al.* Hypoglycemia induced by angiotensin-converting enzyme inhibitors in patients with non-insulin-dependent diabetes receiving sulfonylurea therapy. *Am J Med* 1990; 89: 811–13.
4. Herings RMC, *et al.* Hypoglycaemia associated with use of inhibitors of angiotensin converting enzyme. *Lancet* 1995; 345: 1195–8.
5. Morris AD, *et al.* ACE inhibitor use is associated with hospitalization for severe hypoglycemia in patients with diabetes. *Diabetes Care* 1997; 20: 1363–7.
6. Ferriere M, *et al.* Captopril and insulin sensitivity. *Ann Intern Med* 1985; 102: 134–5.
7. Passa P, *et al.* Enalapril, captopril, and blood glucose. *Lancet* 1986; i: 1447.
8. Winocour P, *et al.* Captopril and blood glucose. *Lancet* 1986; ii: 461.
9. Shorr RI, *et al.* Antihypertensives and the risk of serious hypoglycemia in older persons using insulin or sulfonylureas. *JAMA* 1997; 278: 40–3.
10. Moore N, *et al.* Reports of hypoglycaemia associated with the use of ACE inhibitors and other drugs: a case/non-case study in the French pharmacovigilance system database. *Br J Clin Pharmacol* 1997; 44: 513–18.

Alcohol. Sulfonylurea-induced alcohol intolerance is seen mainly but not exclusively with chlorpropamide;[1,2] this is similar to the disulfiram-alcohol interaction, although it is not clear whether the mechanism is the same. The main symptom of the reaction is facial flushing.

Alcohol has been reported both to increase and to decrease the half-life of tolbutamide depending on whether the alcohol administration was acute or chronic.[3] Alcohol may also have a variable effect of its own on blood-glucose concentrations; there is a general tendency to increased hypoglycaemia when alcohol and sulfonylureas are taken concurrently.[2,4]

1. Pui SNT, *et al.* Epidemiological study of prevalence of chlorpropamide alcohol flushing in insulin dependent diabetes, non-insulin dependent diabetics, and non-diabetics. *BMJ* 1983; 287: 1509–12.
2. Lao B, *et al.* Alcohol tolerance in patients with non-insulin-dependent (type 2) diabetes treated with sulphonylurea derivatives. *Arzneimittelforschung* 1994; 44: 727–34.
3. Sellers EM, Holloway MR. Drug kinetics and alcohol ingestion. *Clin Pharmacokinet* 1978; 3: 440–52.
4. Burge MR, *et al.* Low-dose ethanol predisposes elderly fasted patients with type 2 diabetes to sulfonylurea-induced low blood glucose. *Diabetes Care* 1999; 22: 2037–43.

Analgesics. *Phenylbutazone*[1,2] and related drugs such as *azapropazone*[3] have been associated with acute hypoglycaemic episodes when given to patients receiving sulfonylureas (in most reports, tolbutamide). Other analgesics may enhance the hypoglycaemic effect of sulfonylureas, including *indobufen*,[4] *fenclofenac*,[5] and the *salicylates*.[6,7] Although a study in healthy subjects found no interaction,[7] there has been a report of hypoglycaemia with *ibuprofen* in a diabetic patient who had been stabilised on glibenclamide.[8]

1. Tannenbaum H, *et al.* Phenylbutazone-tolbutamide drug interaction. *N Engl J Med* 1974; 290: 344.
2. Dent LA, Jue SG. Tolbutamide-phenylbutazone interaction. *Drug Intell Clin Pharm* 1976; 10: 711.
3. Andreasen PB, *et al.* Hypoglycaemia induced by azapropazone-tolbutamide interaction. *Br J Clin Pharmacol* 1981; 12: 581–3.
4. Elvander-Ståhl E, *et al.* Indobufen interacts with the sulphonylurea, glipizide, but not with the β-adrenergic receptor antagonists, propranolol and atenolol. *Br J Clin Pharmacol* 1984; 18: 773–8.
5. Allen PA, Taylor RT. Fenclofenac and thyroid function tests. *BMJ* 1980; 281: 1642.
6. Richardson T, *et al.* Enhancement by sodium salicylate of the blood glucose lowering effect of chlorpropamide—drug interaction or summation of similar effects? *Br J Clin Pharmacol* 1986; 22: 43–8.
7. Kubacka RT, *et al.* Effects of aspirin and ibuprofen on the pharmacokinetics and pharmacodynamics of glyburide in healthy subjects. *Ann Pharmacother* 1996; 30: 20–6.
8. Sone H, *et al.* Ibuprofen-related hypoglycemia in a patient receiving sulfonylurea. *Ann Intern Med* 2001; 134: 344.

Antibacterials. *Chloramphenicol* markedly inhibits the metabolism of tolbutamide and increases its half-life,[1] which can result in hypoglycaemia. Sulfonamides,[2] including *co-trimoxazole*,[3-5] may also enhance the hypoglycaemic effects of the sulfonylureas. There have been rare reports of elevated glibenclamide concentrations[6] and hypoglycaemia[6,7] when *ciprofloxacin* was given to patients who were on stable glibenclamide therapy. Profound and prolonged hypoglycaemia after an intravenous dose of *levofloxacin* contributed to the death of an elderly patient also taking glibenclamide.[8] For reports of hypoglycaemia when *gatifloxacin* was given to patients already receiving a sulfonylurea (glimepiride in one case, and glibenclamide plus pioglitazone in another), see p. 304.1. *Clarithromycin* may increase the absorption of glibenclamide[9] and tolbutamide.[10] There have also been a few cases of severe hypoglycaemia when clarithromycin was given to patients taking glibenclamide[11,12] or glipizide;[11] renal impairment may have played a role in some of these cases.[11] A case controlled study[13] concluded that the infection itself or its sequelae may increase the risk of severe hypoglycaemia in patients on glipizide or glibenclamide; co-administration of clarithromycin, co-trimoxazole, ciprofloxacin, or levofloxacin appeared to increase the risk of hypoglycaemia even further.

Rifampicin (and probably other rifamycins) can enhance the metabolism and decrease the effect of tolbutamide, chlorpropamide,[14,15] and glibenclamide[16] and dosage of the hypoglycaemic drug may need to be increased. The effects on glipizide[16] and glimepiride[17] appear to be less pronounced, but gliclazide may be more severely affected.[18] In one case report, the established dose of gliclazide had to be eventually doubled in an attempt to maintain glycaemic control in a patient given rifampicin.[19]

1. Christensen LK, Skovsted L. Inhibition of drug metabolism by chloramphenicol. *Lancet* 1969; ii: 1397–9.
2. Soeldner JS, Steinke J. Hypoglycemia in tolbutamide-treated diabetes: report of two cases with measurement of serum insulin. *JAMA* 1965; 193: 148–9.
3. Wing LMH, Miners JO. Cotrimoxazole as an inhibitor of oxidative drug metabolism: effects of trimethoprim and sulphamethoxazole separately and combined on tolbutamide disposition. *Br J Clin Pharmacol* 1985; 20: 482–5.
4. Johnson JF, Dobmeier ME. Symptomatic hypoglycemia secondary to a glipizide-trimethoprim/sulfamethoxazole drug interaction. *DICP Ann Pharmacother* 1990; 24: 250–1.
5. Abad S, *et al.* Possible interaction between gliclazide, fluconazole and sulfamethoxazole resulting in severe hypoglycaemia. *Br J Clin Pharmacol* 2001; 52: 456–7.
6. Roberge RJ, *et al.* Glyburide-ciprofloxacin interaction with resistant hypoglycemia. *Ann Emerg Med* 2000; 36: 160–3.
7. Lin G, *et al.* Refractory hypoglycemia from ciprofloxacin and glyburide interaction. *J Toxicol Clin Toxicol* 2004; 42: 295–7.
8. Friedrich LV, Dougherty R. Fatal hypoglycemia associated with levofloxacin. *Pharmacotherapy* 2004; 24: 1807–12.
9. Lilja JJ, *et al.* Effects of clarithromycin and grapefruit juice on the pharmacokinetics of glibenclamide. *Br J Clin Pharmacol* 2007; 63: 732–40.
10. Jayasagar G, *et al.* Effect of clarithromycin on the pharmacokinetics of tolbutamide. *Drug Metabol Drug Interact* 2000; 16: 207–15.
11. Bussing R, Gende A. Severe hypoglycemia from clarithromycin-sulfonylurea drug interaction. *Diabetes Care* 2002; 25: 1659–61.
12. Leiba A, *et al.* An unusual case of hypoglycemia in a diabetic patient. *Ann Emerg Med* 2004; 44: 427–8.
13. Schelleman H, *et al.* Anti-infectives and the risk of severe hypoglycemia in users of glipizide or glyburide. *Clin Pharmacol Ther* 2010; 88: 214–22.
14. Syvälahti EKG, *et al.* Rifampicin and drug metabolism. *Lancet* 1974; ii: 232–3.
15. Self TH, Morris T. Interaction of rifampin and chlorpropamide. *Chest* 1980; 77: 800–801.
16. Niemi M, *et al.* Effects of rifampin on the pharmacokinetics and pharmacodynamics of glyburide and glipizide. *Clin Pharmacol Ther* 2001; 69: 400–406.
17. Niemi M, *et al.* Effect of rifampicin on the pharmacokinetics and pharmacodynamics of glimepiride. *Br J Clin Pharmacol* 2000; 50: 591–5.
18. Park J-Y, *et al.* Effect of rifampin on the pharmacokinetics and pharmacodynamics of gliclazide. *Clin Pharmacol Ther* 2003; 74: 334–40.
19. Kihara Y, Otsuki M. Interaction of gliclazide and rifampicin. *Diabetes Care* 2000; 23: 1204–5.

Anticoagulants. *Dicoumarol* increases serum concentrations and therefore the hypoglycaemic effects of tolbutamide, and possibly chlorpropamide. In addition, sulfonylureas may affect anticoagulant function (p. 1531.3).

Antiepileptics. For references to *phenytoin* toxicity when tolbutamide or tolazamide was given, see under Phenytoin p. 543.1.

Antifungals. Increased plasma concentrations of tolbutamide have been reported when *fluconazole* was given,[1] but there was no evidence of hypoglycaemia, and no hypoglycaemic symptoms were seen in 29 women receiving gliclazide or glibenclamide who were given fluconazole or *clotrimazole* for vulvovaginitis.[2] A study in healthy subjects found that fluconazole increased plasma concentrations of glimepiride, but again there was no significant effect on glucose concentrations.[3] However, there are reports of hypoglycaemia in a patient who took fluconazole with glipizide,[4] and another who took fluconazole and co-trimoxazole with gliclazide.[5] Additionally in a large study, from the United States, the risk of severe hypoglycaemia was increased when fluconazole was used with either glipizide or glibenclamide.[6] Similar interactions have been reported for *ketoconazole* (with tolbutamide, in healthy subjects),[7] *miconazole* (with tolbutamide, in a diabetic),[8] and *voriconazole* (with glimepiride, in a diabetic),[9] suggesting that such combinations should be regarded with caution.

1. Lazar JD, Wilner DK. Drug interactions with fluconazole. *Rev Infect Dis* 1990; 12 (suppl 3): S327–S333.
2. Rowe BR, *et al.* Safety of fluconazole in women taking oral hypoglycaemic agents. *Lancet* 1992; 339: 255–6.
3. Niemi M, *et al.* Effects of fluconazole and fluvoxamine on the pharmacokinetics and pharmacodynamics of glimepiride. *Clin Pharmacol Ther* 2001; 69: 194–200.
4. Fournier JP, *et al.* Coma hypoglycémique chez une patiente traitée par glipizide et fluconazole: une possible interaction? *Therapie* 1992; 47: 446–7.
5. Abad S, *et al.* Possible interaction between gliclazide, fluconazole and sulfamethoxazole resulting in severe hypoglycaemia. *Br J Clin Pharmacol* 2001; 52: 456–7.
6. Schelleman H, *et al.* Anti-infectives and the risk of severe hypoglycemia in users of glipizide or glyburide. *Clin Pharmacol Ther* 2010; 88: 214–22.
7. Krishnaiah YSR, *et al.* Interaction between tolbutamide and ketoconazole in healthy subjects. *Br J Clin Pharmacol* 1994; 37: 205–7.
8. Meurice JC, *et al.* Interaction miconazole et sulfamides hypoglycémiants. *Presse Med* 1983; 12: 1670.
9. Shobha JC, Muppidi MR. Interaction between voriconazole and glimepiride. *J Postgrad Med* 2010; 56: 44–5.

Ciclosporin. For the effect of glibenclamide on blood concentrations of ciclosporin see Hypoglycaemic Drugs, p. 1956.3.

Colesevelam. A study[1] has shown that co-administration of colesevelam reduced the absorption of glibenclamide. The authors concluded that glibenclamide should be given at least 4 hours before colesevelam to avoid this interaction.

1. Brown KS, *et al.* Effect of the bile acid sequestrant colesevelam on the pharmacokinetics of pioglitazone, repaglinide, estrogen estradiol, norethindrone, levothyroxine, and glyburide. *J Clin Pharmacol* 2010; 50: 554–65.

Endothelin receptor antagonists. The combination of glibenclamide and *bosentan* should be avoided. The plasma concentrations of both drugs may be reduced with concomitant use; however, this does not explain the elevated liver transaminase levels that have been reported when used together.[1]

1. van Giersbergen PLM, *et al.* In vivo and in vitro studies exploring the pharmacokinetic interaction between bosentan, a dual endothelin receptor antagonist, and glyburide. *Clin Pharmacol Ther* 2002; 71: 253–62.

Metformin. Results apparently suggesting increased mortality in patients who received intensive drug therapy with metformin and a sulfonylurea were reported by the UK Prospective Diabetes Study.[1] This was considered to be artefactual, since it was not confirmed by epidemiological analysis, and such combinations are widely used in practice, but some concern remained and further study thought necessary. A meta-analysis[2] of 9 observational studies found that the combination was associated with an increased risk of a composite end-point of fatal or non-fatal cardiovascular events, but in separate analyses of cardiovascular death or all-cause mortality there was no significant effect. The authors hypothesised that an increased risk may be related to the likely use of combination therapy in patients who have a more aggressive form of diabetes and therefore a more rapid deterioration in glycaemic control; also, weight gain induced by sulfonylureas could negate any weight loss or other beneficial effects on cardiovascular risk factors associated with metformin. They also felt that further studies were still needed.

1. UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with

type 2 diabetes (UKPDS 34). *Lancet* 1998; 352: 854–65. Correction. *ibid.*: 1558.
2. Rao AD, *et al.* Is the combination of sulfonylureas and metformin associated with an increased risk of cardiovascular disease or all-cause mortality? A meta-analysis of observational studies. *Diabetes Care* 2008; 31: 1672–8.

Thyroid hormones. It has been suggested that starting thyroid replacement therapy may increase the requirement for insulin or oral antidiabetic drugs in diabetic patients, which would not seem unreasonable given the stimulant effects of thyroid hormones on metabolic function. For a discussion of the mooted effects of sulfonylureas on thyroid function, see under Precautions, p. 502.3.

Pharmacokinetics

Reviews.
1. Marchetti P, Navalesi R. Pharmacokinetic-pharmacodynamic relationships of oral hypoglycaemic agents: an update. *Clin Pharmacokinet* 1989; 16: 100–28.
2. Marchetti P, *et al.* Pharmacokinetic optimisation of oral hypoglycaemic therapy. *Clin Pharmacokinet* 1991; 21: 308–17.
3. Harrower AD. Pharmacokinetics of oral antihyperglycaemic agents in patients with renal insufficiency. *Clin Pharmacokinet* 1996; 31: 111–19.

Metabolism. The cytochrome P450 isoenzyme CYP2C9 is the main enzyme involved in the metabolism of many sulfonylureas, and its activity can be altered by genetic polymorphism. Sulfonylurea clearance has been found to be significantly reduced in healthy subjects with the homozygous CYP2C9*3/*3 genotype, compared with the most extensive metabolism in wild-type *1/*1 carriers; metabolism in homozygous *2/*2 carriers and heterozygous genotypes ranges between these two.[1] It has been suggested that genotyping might be a useful tool for dosage adjustment, to optimise efficacy and reduce adverse effects[1] (see also Hypoglycaemia, p. 502.1). While the relevance of genotype to serum-glucose and insulin levels in diabetic patients treated with sulfonylureas is still unclear,[1,2] a further study of over 1000 patients[3] found that carriers of the *2 or *3 variant were more likely to achieve a treatment target haemoglobin A_{1c} compared with wild-type *1 carriers. Additionally *2 and *3 carriers were less likely to have treatment failure.

1. Kirchheiner J, *et al.* Effect of genetic polymorphisms in cytochrome P450 (CYP) 2C9 and CYP2C8 on the pharmacokinetics of oral antidiabetic drugs: clinical relevance. *Clin Pharmacokinet* 2005; 44: 1209–25.
2. Becker ML, *et al.* Cytochrome P450 2C9 *2 and *3 polymorphisms and the dose and effect of sulfonylurea in type II diabetes mellitus. *Clin Pharmacol Ther* 2008; 83: 288–92.
3. Zhou K, *et al.* Loss-of-function CYP2C9 variants improve therapeutic response to sulfonylureas in type 2 diabetes: a Go-DARTS study. *Clin Pharmacol Ther* 2010; 87: 52–6.

Teneligliptin *(rINN)*

Teneligliptina; Ténégliptine; Teneligliptinum; Тенелиглиптин.

{(2*S*,4*S*)-4-[4-(3-Methyl-1-phenyl-1*H*-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-yl}(1,3-thiazolidin-3-yl)methanone.

$C_{22}H_{30}N_6OS$=426.6

CAS — 760937-92-6.

UNII — 28ZHI4CF9C.

Profile

Like sitagliptin (p. 500.1), teneligliptin is an inhibitor of dipeptidylpeptidase-4. Teneligliptin hydrobromide is used orally in the treatment of type 2 diabetes mellitus.

References.
1. Eto T, *et al.* Effects of once-daily teneligliptin on 24-h blood glucose control and safety in Japanese patients with type 2 diabetes mellitus: a 4-week, randomized, double-blind, placebo-controlled trial. *Diabetes Obes Metab* 2012; 14: 1040–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Tenelia.

Tolazamide *(BAN, USAN, rINN)*

NSC-70762; Tolatsamidi; Tolazamid; Tolazamida; Tolazamidum; U-17835; Толазамид.

1-(Perhydroazepin-1-yl)-3-tosylurea; 1-(Perhydroazepin-1-yl)-3-*p*-tolylsulphonylurea.

$C_{14}H_{21}N_3O_3S$=311.5

CAS — 1156-19-0.

ATC — A10BB05.

ATC Vet — QA10BB05.

UNII — 9LT1BRO48Q.

Pharmacopoeias. In *Br.*, *Jpn*, and *US*.

BP 2014: (Tolazamide). A white or almost white, odourless or almost odourless, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol; soluble in acetone; freely soluble in chloroform.

USP 36: (Tolazamide). A white or off-white crystalline powder, odourless or having a slight odour. Very slightly soluble in water; slightly soluble in alcohol; soluble in acetone; freely soluble in chloroform.

Uses and Administration

Tolazamide is a sulfonylurea antidiabetic (p. 500.3). It is given orally in the treatment of type 2 diabetes mellitus (p. 459.1) and has a duration of action of at least 10 hours and sometimes up to 20 hours. The usual initial dose is 100 to 250 mg daily given as a single dose with breakfast. Dosage may be increased if necessary at weekly intervals by 100 to 250 mg to a usual maintenance dose of 250 to 500 mg daily, or a maximum of 1 g daily; no further benefit is likely to be gained with higher doses. Doses of more than 500 mg daily may be given in divided doses.

Adverse Effects, Treatment, and Precautions

As for sulfonylureas in general, p. 501.1, p. 502.1, and p. 502.2.

Interactions

As for sulfonylureas in general, p. 502.3.

Pharmacokinetics

Tolazamide is slowly absorbed from the gastrointestinal tract, peak plasma concentrations occurring 4 to 8 hours after an oral dose, and is extensively bound to plasma proteins. It has a half-life of about 7 hours. It is metabolised in the liver to metabolites with some hypoglycaemic activity. About 85% of an oral dose is excreted in the urine, chiefly as metabolites.

Preparations

Pharmacopoeial Preparations
BP 2014: Tolazamide Tablets;
USP 36: Tolazamide Tablets.

Tolbutamide *(BAN, rINN)*

Butamidum; Tolbutamid; Tolbutamida; Tolbutamidas; Tolbutamidi; Tolbutamidum; Tolglybutamide; Тольбутамид.

1-Butyl-3-tosylurea; 1-Butyl-3-*p*-tolylsulphonylurea.

$C_{12}H_{18}N_2O_3S$=270.3

CAS — 64-77-7 (tolbutamide); 473-41-6 (tolbutamide sodium).

ATC — A10BB03; V04CA01.

ATC Vet — QA10BB03; QV04CA01.

UNII — 982XCM1FOI.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Tolbutamide). A white or almost white, crystalline powder. Practically insoluble in water; soluble in alcohol and in acetone. It dissolves in dilute solutions of alkali hydroxides. Store in airtight containers.

USP 36: (Tolbutamide). A white or practically white, practically odourless, crystalline powder. Practically insoluble in water; soluble in alcohol and in chloroform.

Uses and Administration

Tolbutamide is a sulfonylurea antidiabetic (p. 500.3). It is given orally in the treatment of type 2 diabetes mellitus (p. 459.1) and has a duration of action of about 10 hours.

The usual initial dose in type 2 diabetes mellitus may range from 1 to 2 g daily, given either as a single dose with breakfast or, more usually, in divided doses. Maintenance doses usually range from 0.25 to 2 g daily. Although it is unlikely that the response will be improved by increasing the dose further, daily doses of 3 g have been given. For doses used in adolescents, see p. 504.2.

Tolbutamide sodium ($C_{12}H_{17}N_2NaO_3S$ = 292.3) has sometimes been used in the diagnosis of insulinoma as well as other pancreatic disorders including diabetes mellitus. The equivalent of 1 g of tolbutamide is given by intravenous injection as a 5% solution usually over 2 to 3 minutes. Tolbutamide sodium 1.08 g is equivalent to about 1 g of tolbutamide.

Administration in children. There is limited experience with the use of sulfonylureas in children with type 2 diabetes mellitus, and the biguanide metformin is generally preferred. The *BNFC* suggests that oral treatment should only be started under specialist supervision and that shorter-acting alternatives such as tolbutamide may be preferred to longer-acting sulfonylureas that have a greater risk of hypoglycaemia. Although not licensed for use in children in the UK, the *BNFC* suggests that tolbutamide may be given to adolescents aged 12 to 18 years in an oral dose of 0.5 to 1.5 g daily, to a maximum of 2 g daily. It may be given in divided doses, with or immediately after meals, or as a single dose at breakfast.

Diagnosis and testing. References.
1. McMahon MM, *et al.* Diagnostic interpretation of the intravenous tolbutamide test for insulinoma. *Mayo Clin Proc* 1989; 64: 1481–8.
2. Marks V. Diagnosis and differential diagnosis of hypoglycemia. *Mayo Clin Proc* 1989; 64: 1558–61.

Adverse Effects, Treatment, and Precautions

As for sulfonylureas in general, p. 501.1, p. 502.1, and p. 502.2. Tolbutamide was implicated in the controversial reports of excess cardiovascular mortality associated with oral hypoglycaemic therapy (see under Sulfonylureas: Effects on the Cardiovascular System, p. 501.2).

Thrombophlebitis with thrombosis has occurred after the intravenous injection of tolbutamide sodium, but this is usually painless and the vein gradually recovers. Rapid injection may cause a transient mild pain or sensation of heat in the vein.

The *BNF* has suggested that tolbutamide may be suitable for use in patients with renal impairment, but that careful monitoring of blood-glucose concentration is essential and that the smallest possible dose for adequate control should be used. UK licensed product information recommends that it should not be used in patients with severe renal impairment.

Breast feeding. Tolbutamide is distributed into breast milk in relatively low quantities.[1] The last available guidance from the American Academy of Pediatrics[2] stated that although usually compatible with breast feeding, use of tolbutamide by breast-feeding mothers may possibly result in jaundice in the infant.

1. Miniel RH, Ryan JR. Tolbutamide urinase in human breast milk. *Clin Pediatr (Phila)* 1967; 6: 480.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/07/04)

Porphyria. UK licensed product information states that tolbutamide is contra-indicated in porphyria.

Interactions

As for sulfonylureas in general, p. 502.3.

Pharmacokinetics

Tolbutamide is readily absorbed from the gastrointestinal tract and is extensively bound to plasma proteins; the half-life is generally within the range of 4 to 7 hours but may be considerably longer. Tolbutamide is metabolised in the liver by hydroxylation mediated by the cytochrome P450 isoenzyme CYP2C9. It is excreted in the urine chiefly as metabolites with little hypoglycaemic activity. Tolbutamide has been detected in breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Rastinon†; *Cz.*: Dirastan†; *Denm.*: Arcosal; *Gr.*: Rastinon; *Hong Kong*: Diatol; *Israel*: Orsinon†; *Mex.*: Artosin; Dabetil; Diatelan; Diaval; Flusan; Rastinon; *NZ*: Diatol†; *Pol.*: Diabetol†; *S.Afr.*: Tydadex†; *Singapore*: Tobumide; Tolmide; *USA*: Orinase Diagnostic†; Orinase†.

Pharmacopoeial Preparations
BP 2014: Tolbutamide Tablets;
USP 36: Tolbutamide for Injection; Tolbutamide Tablets.

Vildagliptin *(BAN, rINN)*

LAF-237; NVP-LAF-237; Vildagliptina; Vildagliptine; Vildagliptinum; Вильдаглиптин.

(2*S*)-{[(3-Hydroxyadamantan-1-yl)amino]acetyl}pyrrolidine-2-carbonitrile.

$C_{17}H_{25}N_3O_2$=303.4

CAS — 274901-16-5.

ATC — A10BH02.

ATC Vet — QA10BH02.

UNII — I6B4B2U96P.

Uses and Administration

Like sitagliptin (p. 500.1), vildagliptin is an inhibitor of dipeptidylpeptidase-4 and is used in the treatment of type 2 diabetes mellitus (p. 459.1). It is given orally in a usual dose of 50 mg twice daily with or without food. A total daily dose of more than 100 mg of vildagliptin is not recommended. When given with metformin and a sulfonylurea, the usual dose of vildagliptin may be used; in dual therapy with a sulfonylurea, a dose of vildagliptin 50 mg once daily in the morning is recommended because higher doses were found to be no more effective. The dose of sulfonylurea may need to be lowered when used with vildagliptin. Dosage may need to be adjusted in patients with renal impairment (see p. 505.1).

References.
1. Pratley RE, *et al.* Management of type 2 diabetes in treatment-naive elderly patients: benefits and risks of vildagliptin monotherapy. *Diabetes Care* 2007; **30**: 3017–22.
2. Scherbaum WA, *et al.* Evidence that vildagliptin attenuates deterioration of glycaemic control during 2-year treatment of patients with type 2 diabetes and mild hyperglycaemia. *Diabetes Obes Metab* 2008; **10**: 1114–24.
3. Croxtall JD, Keam SJ. Vildagliptin: a review of its use in the management of type 2 diabetes mellitus. *Drugs* 2008; **68**: 2387–2409.
4. Banerjee M, *et al.* Vildagliptin in clinical practice: a review of literature. *Expert Opin Pharmacother* 2009; **10**: 2745–57.
5. Matthews DR, *et al.* Vildagliptin add-on to metformin produces similar efficacy and reduced hypoglycaemic risk compared with glimepiride, with no weight gain: results from a 2-year study. *Diabetes Obes Metab* 2010; **12**: 780–9.
6. Keating GM. Vildagliptin: a review of its use in type 2 diabetes mellitus. *Drugs* 2010; **70**: 2089–2112.
7. Schweizer A, *et al.* Clinical experience with vildagliptin in the management of type 2 diabetes in a patient population ≥ 75 years: a pooled analysis from a database of clinical trials. *Diabetes Obes Metab* 2011; **13**: 55–64.
8. Baetta R, Corsini A. Pharmacology of dipeptidyl peptidase-4 inhibitors: similarities and differences. *Drugs* 2011; **71**: 1441–67.

Administration in renal impairment. UK licensed product information says that no dose adjustment is required in patients with mild renal impairment (creatinine clearance 50 mL/min or more). In patients with more severe renal impairment or with end-stage renal disease (ESRD), the recommended oral dose of vildagliptin is 50 mg once daily.

Adverse Effects, Treatment, and Precautions

As for Sitagliptin Phosphate, p. 500.1. Arthralgia has also been reported for vildagliptin. Dosage should be reduced in patients with moderate or severe renal impairment or end-stage renal disease.

Rare cases of hepatic dysfunction, including hepatitis, have been reported. Vildagliptin should not be used in patients with hepatic impairment; liver function should be tested before starting the drug, and monitored during therapy (every 3 months in the first year and periodically thereafter). Vildagliptin should be stopped if there is a persistent increase of 3 or more times the upper limit of normal in alanine aminotransferase (ALT) or aspartate aminotransferase (AST), or if the patient develops jaundice or other signs of liver dysfunction; in such cases, it should not be restarted.

References.
1. Schweizer A, *et al.* Assessing the cardio-cerebrovascular safety of vildagliptin: meta-analysis of adjudicated events from a large phase III type 2 diabetes population. *Diabetes Obes Metab* 2010; **12**: 485–94.
2. Ligueros-Saylan M, *et al.* An assessment of adverse effects of vildagliptin versus comparators on the liver, the pancreas, the immune system, the skin and in patients with impaired renal function from a large pooled database of phase II and III clinical trials. *Diabetes Obes Metab* 2010; **12**: 495–509.
3. Banerji MA, *et al.* Safety and tolerability of vildagliptin vs. thiazolidinedione as add-on to metformin in type 2 diabetic patients with and without mild renal impairment: a retrospective analysis of the GALIANT study. *Diabetes Res Clin Pract* 2010; **90**: 182–90.
4. Schweizer A, *et al.* Assessing the general safety and tolerability of vildagliptin: value of pooled analyses from a large safety database versus evaluation of individual studies. *Vasc Health Risk Manag* 2011; **7**: 49–57.

Overdosage. In the UK, the *National Poisons Information Service* states that oral activated charcoal may be considered in adults and children who have ingested more than 15 mg/kg of vildagliptin and present within 1 hour, provided they are conscious and the airway can be protected. Hypoglycaemia should be treated with urgency; the general management of hypoglycaemia is described under insulin (see p. 484.3).

Interactions

The efficacy of vildagliptin may be affected by other drugs that have an independent effect on blood glucose. For more details and examples of drugs that can increase or decrease blood-glucose concentrations, see Interactions under Sulfonylureas, p. 502.3.

Pharmacokinetics

Vildagliptin is rapidly absorbed from the gastrointestinal tract and peak plasma concentrations occur about 1.7 hours after an oral dose. It has a bioavailability of 85%. About 69% of a dose is metabolised, mainly by hydrolysis in the kidney. About 85% of a dose is excreted in the urine (23% is unchanged drug), and 15% in the faeces. The elimination half-life of vildagliptin is about 2 hours after intravenous injection, and about 3 hours after an oral dose.

References.
1. He Y-L. Clinical pharmacokinetics and pharmacodynamics of vildagliptin. *Clin Pharmacokinet* 2012; **51**: 147–62.

Hepatic impairment. Although much of a dose of vildagliptin is hydrolysed by the kidney, the liver is also an important site for its metabolism. A small pharmacokinetic study[1] found that exposure to vildagliptin was decreased in subjects with mild (Child-Pugh score 5 or 6) or moderate (score 7 to 9) hepatic impairment, and increased in those with severe impairment (score 10 to 12), compared with healthy subjects. However, the differences were less than 30% and not consistent with the severity of hepatic impairment. The authors did not consider the differences to be clinically meaningful and concluded that initial dose adjustment of vildagliptin would not be necessary. Nevertheless, licensed product information cautions against its use in diabetic patients with hepatic impairment (see above).

1. He Y-L, *et al.* The influence of hepatic impairment on the pharmacokinetics of the dipeptidyl peptidase IV (DPP-4) inhibitor vildagliptin. *Eur J Clin Pharmacol* 2007; **63**: 677–86.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Galvus; Zomarist; ***Austral.***: Galvus; ***Austria***: Galvus; ***Belg.***: Galvus; ***Braz.***: Galvus; ***Chile***: Galvus; ***China***: Galvus (佳维乐); ***Cz.***: Galvus; Jalra; Xiliarx; ***Denm.***: Galvus; ***Fr.***: Galvus; ***Ger.***: Galvus; Jalra; ***Gr.***: Galvus; Jalra; Xiliarx; ***Hong Kong***: Galvus; ***Hung.***: Galvus; ***India***: Galvus; ***Indon.***: Galvus; ***Irl.***: Galvus; Jalra; Xiliarx; ***Israel***: Galvus; ***Ital.***: Galvus; ***Malaysia***: Galvus; ***Mex.***: Galvus; ***Neth.***: Galvus; Jalra; Xiliarx; ***Norw.***: Galvus; ***Philipp.***: Galvus; ***Pol.***: Galvus; Jalra; ***Port.***: Galvus; Jalra; Xiliarx; ***Rus.***: Galvus (Галвус); ***Singapore***: Galvus; ***Spain***: Galvus; Jalra; Xiliarx; ***Swed.***: Galvus; ***Switz.***: Galvus; ***Thai.***: Galvus; ***Turk.***: Galvus; ***UK***: Galvus; ***Ukr.***: Galvus (Гальвус).

Multi-ingredient Preparations. *Arg.*: Galvus Met; Zomarist Met; ***Austral.***: Galvumet; ***Austria***: Eucreas; ***Belg.***: Eucreas; ***Braz.***: Galvus Met; ***Chile***: Galvus Met; ***Cz.***: Eucreas; Icandra; Zomarist; ***Denm.***: Eucreas; ***Fr.***: Eucreas; ***Ger.***: Eucreas; Icandra; ***Gr.***: Eucreas; Icandra; Zomarist; ***Hong Kong***: GalvusMet; ***Hung.***: Eucreas; ***India***: Galvusmet; ***Indon.***: Galvusmet; ***Irl.***: Eucreas; Icandra; Zomarist; ***Israel***: Eucreas; ***Ital.***: Eucreas; ***Malaysia***: Galvus Met; ***Mex.***: Galvus Met; ***Neth.***: Eucreas; Icandra; Zomarist; ***Norw.***: Eucreas; ***Philipp.***: Galvusmet; ***Pol.***: Eucreas; Zomarist; ***Port.***: Eucreas; Icandra; Zomarist; ***Rus.***: Galvus Met (Галвус Мет); ***Singapore***: Galvusmet; ***Spain***: Eucreas; Icandra; Zomarist; ***Swed.***: Eucreas; ***Switz.***: Galvumet; ***Thai.***: Galvus Met; ***Turk.***: Galvus Met; ***UK***: Eucreas; ***Ukr.***: Galvusmet (Гальвусмет).

Voglibose *(USAN, rINN)*

A-71100; AO-128; Voglibosa; Voglibosum; Воглиболза.

3,4-Dideoxy-4-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-2-C-(hydroxymethyl)-D-epi-inositol.

$C_{10}H_{21}NO_7$=267.3

CAS — 83480-29-9.

ATC — A10BF03.

ATC Vet — QA10BF03.

UNII — 577P977AG8.

Pharmacopoeias. In *Jpn*.

Profile

Voglibose is an alpha-glucosidase inhibitor with general properties similar to those of acarbose (p. 466.2). It is used in the treatment of diabetes mellitus (p. 459.1) in oral doses of 200 to 300 micrograms three times daily, immediately before meals. Voglibose is also under investigation for the prevention of type 2 diabetes in patients with impaired glucose tolerance.

References.
1. Kawamori R, *et al.* Voglibose Ph-3 Study Group. Voglibose for prevention of type 2 diabetes mellitus: a randomised, double-blind trial in Japanese individuals with impaired glucose tolerance. *Lancet* 2009; **373**: 1607–14.

Hepatic encephalopathy. Voglibose has been investigated[1] in the management of hepatic encephalopathy (p. 1811.2).

1. Uribe M, *et al.* Beneficial effect of carbohydrate maldigestion induced by a disaccharidase inhibitor (AO-128) in the treatment of chronic portal systemic encephalopathy: a double-blind, randomized controlled trial. *Scand J Gastroenterol* 1998; **33**: 1099–1106.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Basen (恬欣); *Jpn*: Basen; ***Philipp.***: Basen; ***Thai.***: Basen.

Multi-ingredient Preparations. *Jpn*: Glubes.

Antiepileptics

Epilepsy, p. 506
Epilepsy and breast feeding, p. 508
Epilepsy, cognition, and mood, p. 508
Epilepsy and driving, p. 509
Epilepsy and pregnancy, p. 509
Status epilepticus, p. 510
Other convulsive disorders, p. 511
Alcohol withdrawal syndrome, p. 511
Eclampsia and pre-eclampsia, p. 511
Febrile convulsions, p. 511
Myoclonus, p. 511
Neonatal seizures, p. 511
Porphyria, p. 512
Reflex anoxic seizures, p. 512

This chapter describes drugs whose main use is in the management of epilepsy, status epilepticus, and other convulsive disorders.

Epilepsy

Epilepsy is a common neurological disorder. An individual's lifetime risk of developing epilepsy is between 3 and 5%; neonates, children, and the elderly are at the highest risk of developing the disorder.

Definitions and classification. An epileptic seizure has been defined as a paroxysmal discharge of cerebral neurones accompanied by clinical phenomena apparent to the patient or to an observer. The phenomena can be motor, sensory, or autonomic and there may also be impairment or complete loss of consciousness. Motor disturbances may include convulsions—which are involuntary, violent, and spasmodic—or prolonged contraction of skeletal muscles. The word 'fit' is often used colloquially to describe an epileptic seizure. Epilepsy is defined as a condition characterised by a recurrence of such seizures. A patient should not be described as having epilepsy until a second non-febrile seizure occurs.

The following is a broad account of the classification of seizures, epilepsies, and epileptic syndromes based on the views of the International League Against Epilepsy (ILAE) in 1981[1] and 1989.[2] A later proposed revision of the classification[3] does not yet seem to have been widely adopted.

- **Partial seizures** or **focal seizures** (localisation-related seizures) are epileptic seizures in which the initial neuronal discharges are localised in one area of the brain. The phenomena associated with such a seizure depend on the site of origin of the discharge. If there is no loss of consciousness, the seizure has been known as a *simple partial seizure* and includes Jacksonian epilepsy, which may be associated with motor or sensory disturbances. If there is impaired consciousness the seizure has been referred to as a *complex partial-seizure*. Partial seizures were formerly referred to as psychomotor epilepsy or temporal lobe epilepsy, but the terms are not synonymous and should be avoided. Partial seizures may become *secondarily generalised seizures* if the neuronal discharge spreads to involve the entire brain
- **Generalised seizures** are characterised by neuronal discharges involving both cerebral hemispheres simultaneously from the outset. Subclassifications are based on the presence or absence of different types of convulsions.
  Absences (petit mal) are generalised seizures, usually occurring in children, characterised by a sudden loss of consciousness lasting for a few seconds. There is usually accompanying motor activity which may vary in degree from eyelid blinking to more extensive clonic body movements. *Atypical absence seizures* are those with a slower onset and longer duration.
  Myoclonic seizures are epileptic seizures in which the motor manifestation is myoclonus (see p. 511.3).
  Clonic seizures are characterised by loss of consciousness, autonomic symptoms, and rhythmic clonic contractions of all muscles.
  Tonic seizures are also associated with loss of consciousness and autonomic symptoms accompanied by tonic contractions of the limbs. *Tonic-clonic seizures* (grand mal) are characterised by disordered contraction of muscles. During the tonic phase, all the muscles go into spasm followed up to a minute later by rhythmic clonic contractions. Finally, the patient enters a deep stupor followed by a period of confusion as consciousness is regained.
  Atonic seizures are characterised by loss of postural tone; the head sags or the patient falls down.

Within the categories of partial and generalised epilepsies, seizures have also been classified as **idiopathic, symptomatic** (in which the seizures are associated with diagnosable underlying disorders), or **cryptogenic** or **probably symptomatic** (in which the epilepsies are known or suspected to be symptomatic but the cause is not clear).

Partial **syndromes** include Rolandic and occipital epilepsies (both idiopathic), while generalised idiopathic syndromes include childhood absence epilepsies, juvenile myoclonic epilepsy, and the cryptogenic or symptomatic generalised syndromes include infantile spasms (as for example in West's syndrome), Lennox-Gastaut syndrome, and epilepsy with myoclonic absences. A third unclassified category covers undetermined epilepsies and epileptic syndromes. **Special syndromes** include conditions such as febrile convulsions (see p. 511.2) in which seizures are related to specific situations.

It has been suggested that classification based on seizure type is the most useful in choice of antiepileptic drug whereas the syndrome classification has more benefits in deciding an overall therapeutic strategy and assessing long-term prognosis.

Status epilepticus has previously been defined as a seizure lasting more than 30 minutes or several distinct episodes without restoration of consciousness in between (but see p. 510.2).

Other convulsive disorders include alcohol withdrawal syndrome p. 1735.1, eclampsia and pre-eclampsia p. 511.1, myoclonus p. 511.3, neonatal seizures p. 511.3, and porphyria p. 512.1.

Starting antiepileptic therapy. A single seizure does not constitute epilepsy and therefore does not necessarily warrant immediate treatment with antiepileptics. The decision to start antiepileptic therapy should be based on whether the risks of further seizures outweigh the risks of treatment.

- Starting antiepileptic therapy *too early* means that the patient may be unnecessarily exposed to the adverse effects of the drugs used, and may have social implications if erroneously diagnosed, such as the loss of a patient's driving licence
- However, the implications of *delaying* treatment must also be considered. Although there has long been concern that seizures may damage the brain and intellectual capabilities, or even cause death, there are insufficient data to support these claims. Status epilepticus, rather than individual or frequent seizures, may be the factor associated with brain injury or death, but the risks of a newly diagnosed epileptic patient developing status epilepticus are unknown. The most compelling reasons for treatment are risk of personal injury or causing injury to others during a seizure, and the psychosocial consequences of untreated epilepsy such as low self-esteem, anxiety, and domestic and employment difficulties

There has been a long-held belief that seizures beget seizures. This is not necessarily borne out by epidemiological studies,[4] and there is evidence in children[5] and adults[6] that the risk of recurrence after a first unprovoked seizure may be 50% or less. Furthermore, a decelerating disease process with successively longer intervals between seizures has been shown[7] in untreated children with newly diagnosed tonic-clonic seizures followed up for 2 years. Results from another study[8] suggested that seizure control or the prospects for and success of eventual withdrawal of therapy is little influenced by the number of pretreatment seizures up to 10 seizures; above this number there was a reduced chance of completely controlling seizures. Similarly, although patients treated immediately after a first seizure have a lower 2-year risk of recurrence than patients whose treatment is deferred, immediate treatment does not affect the probability of achieving longer-term seizure control.[6,9-11]

However, epilepsy is a heterogeneous disorder and there is some experimental evidence[12] that certain seizure types can have a detrimental effect on prognosis. Differences in reported risks in seizure recurrence may be attributable to differences in methodology as well as different important risk factors in the populations studied; also, few studies have followed up patients for more than 2 to 4 years.

Whether antiepileptic therapy should be started early to improve prognosis or delayed or avoided altogether therefore remains contentious.[13-15] Some neurologists do not advise treatment of a first seizure but prefer to wait for evidence of recurrence unless clinical features such as more than one seizure type or a neurological deficit predispose to poor seizure control. However, a first nonconvulsive seizure may go undetected.[15] Furthermore, as single partial seizures appear to occur less frequently than single generalised tonic-clonic seizures, many neurologists assume that the first detected attack of a nonconvulsive seizure is in fact one of multiple seizures and begin treatment. UK guidelines[16,17] suggest that antiepileptic therapy should be offered to patients after a first tonic-clonic seizure if a previous myoclonic, absence, or partial seizure has occurred, if the EEG shows unequivocal epileptic discharges, if congenital neurological deficits are present, or if the risk of recurrence is unacceptable to the patient.

Choice of antiepileptic. Once a decision to treat has been made, the choice of antiepileptic is determined mainly by its efficacy against the type of seizures experienced and its potential adverse effects.[16-30]

In recent years many newer drugs have been licensed and added to the classical treatments for epilepsy, and others continue to be developed.[31,32] The role of these drugs relative to the classical agents is only slowly becoming established, and evidence of relative efficacy on which to base a choice is limited. Many new drugs have been promoted on the basis of superior tolerance and quality of life for epileptic patients, but even this is not always well established, and will, in any case, vary from patient to patient, as individuals will differ in the symptoms they find intolerable. In consequence, guidelines have often reserved their use for situations in which the older drugs are less suitable.

Certain principles of management are, however, well established:

- monotherapy is preferable to a multiple-drug regimen and treatment is therefore begun with a single drug, increasing the dose gradually until seizures are brought under control or adverse effects become unacceptable
- if treatment with the first drug fails, it is preferable to try alternative single first-line antiepileptics before giving combinations of drugs. It has been suggested that for practical purposes a patient should be considered to have refractory epilepsy if seizure control is not obtained with consecutive trials of 2 well tolerated antiepileptics[27]
- the change-over from one antiepileptic to another should be made cautiously, withdrawing the first drug only when the new regimen has been largely established
- if combinations are necessary in intractable cases, regimens should avoid the inclusion, where possible, of sedating drugs such as the barbiturates or benzodiazepines
- drugs with different modes of action should be selected for combined therapy, to reduce the risk that adverse effects will be additive
- many antiepileptics interact with each other through complex mechanisms. Dosage adjustments may be necessary to maintain plasma concentrations within the therapeutic range during combination therapy; plasma monitoring may be advisable. (UK guidelines[17] recommend regular monitoring of antiepileptic drug concentrations only when clinically indicated, e.g. to manage pharmacokinetic interactions, or in cases of suspected toxicity or non-adherence)
- if trials of combination therapy do not produce worthwhile benefits, treatment should revert to the regimen (monotherapy or combination) that has provided the most acceptable balance of seizure control and adverse effects

Around 60% of patients with newly diagnosed epilepsy will respond to monotherapy with the first- or second-choice antiepileptic without developing intolerable adverse effects. The remaining 30 to 40% will have epilepsy that is difficult to control from the start, although some of these patients will respond to combination therapy.[27] Patients who fail to respond to adequate medical treatment may be considered for resective surgery; vagus nerve stimulation by means of an implanted device has also proved effective in those with severe intractable epilepsy who have an aura before the onset of a seizure.[18,19] UK guidelines recommend consideration of the adjunctive use of vagus nerve

stimulation in patients refractory to drug therapy but unsuitable for resective surgery.[16,17]

Partial seizures with or without **secondary generalisation** may be treated with *carbamazepine* or *valproate*, or with the newer drugs *lamotrigine* or *oxcarbazepine*.[16,17,33] *Topiramate* is also used, as monotherapy or as an adjunct to other treatments (in the UK, it is considered a first-line option in some circumstances[17,23]). Other second-line drugs are *phenytoin*, *clobazam*, or the newer antiepileptics *gabapentin*, *levetiracetam*, *pregabalin*, *tiagabine*, or *zonisamide*,[17,24,33] but whether these are recommended for monotherapy or adjunctive treatment may vary from country to country. Other drugs that have been used[17] include *acetazolamide*, *clonazepam*, and the barbiturates *phenobarbital* or *primidone*, although the latter in particular are little used now because of the problems of sedation. *Vigabatrin* is licensed in the UK for adjunctive use in patients in whom all other combinations have failed.

The response rate is somewhat lower for partial seizures than for tonic-clonic seizures associated with primary generalised epilepsy (see below). There is some evidence in favour of carbamazepine rather than valproate in the treatment of partial seizures.[34] More recently, some evidence was found in favour of lamotrigine rather than carbamazepine,[35,36] and of oxcarbazepine rather than phenytoin,[37] in terms of tolerability and time to treatment failure. However, there is no evidence of any significant difference between phenytoin and carbamazepine[38] or valproate[39] in partial seizures.

Calcium-channel blockers such as *flunarizine* have been studied with equivocal results in patients with refractory epilepsy, particularly those with partial seizures.[40]

The drugs used most often to treat **generalised** tonic-clonic seizures are *carbamazepine*, *lamotrigine*, or *valproate*. For tonic-clonic seizures as part of the syndrome of primary generalised epilepsy, valproate is the drug of choice, although systematic reviews were unable to establish evidence for this.[34,39] *Topiramate* is also considered a first choice in patients in whom the other older drugs are unsuitable or ineffective.[17,23] More recently, valproate was found to be better tolerated than topiramate and more effective than lamotrigine in generalised and unclassified epilepsy.[41] Second-line drugs in UK guidelines are *clobazam*, *levetiracetam*, and *oxcarbazepine*, while other drugs that may be considered include *acetazolamide*, *clonazepam*, *phenobarbital*, *phenytoin*, or *primidone*.[17] *Tiagabine* or *vigabatrin* should be avoided as they may worsen the seizures.[17]

The drugs of choice for **absence seizures** are *ethosuximide*, *valproate*, or, where these are unsuitable, *lamotrigine*,[17,24,42] although the evidence base to support this use is weak.[43] Second-choice drugs include *clobazam*, *clonazepam*, and *topiramate*, but *carbamazepine*, *gabapentin*, *oxcarbazepine*, *phenytoin*, *tiagabine*, and *vigabatrin* should be avoided as they may worsen seizures.[17,42] Since absence seizures occur mainly in children the precautions concerning valproate hepatotoxicity apply. However, where absence seizures are associated with tonic-clonic seizures valproate is the drug of choice since it is effective in both conditions; valproate is also preferred for atypical absence seizures. *Levetiracetam* may be used as an alternative for the syndrome of juvenile absence epilepsy.[17]

Valproate is normally the drug of choice for **myoclonic seizures**, including those associated with juvenile myoclonic epilepsy.[44,45] *Lamotrigine* may also be used in juvenile myoclonic epilepsy,[17,45] although some forms of myoclonus may be exacerbated;[17,44] *topiramate* may be considered, particularly for severe myoclonic epilepsy of infancy (in which *stiripentol* may also be effective), and second-line drugs also include *clobazam* and *clonazepam*, and adjunctive *levetiracetam* or *piracetam*.[17] *Zonisamide*[45] has also been used, as has *ethosuximide*.

The classical antiepileptics may not be particularly effective for **atonic** or **tonic seizures**, which are often associated with specific epileptic syndromes or with cerebral damage or mental retardation. UK guidelines suggest *valproate* or *lamotrigine* as first-line drugs; *clobazam*, *clonazepam*, *levetiracetam*, or *topiramate* are possible second-line drugs. Others that have been tried include *acetazolamide* and the barbiturates such as *phenobarbital*, while *phenytoin* may be considered for tonic seizures.[17] The *BNF* suggests *ethosuximide* may occasionally be helpful.

In **catamenial epilepsy** (epilepsy associated with menstruation) seizures can be predicted and intermittent therapy with *clobazam* may be useful. Hormonal manipulation has also been tried using *progestogens*, *gonadorelin analogues*, and *clomifene*.[46]

The **Lennox-Gastaut syndrome** begins in early childhood and is particularly difficult to treat because multiple seizure types co-exist; seizures rarely remit entirely. *Valproate* is most frequently used[47] because of its broad spectrum of activity; UK guidelines consider *lamotrigine* or *topiramate* as alternative first-line drugs if valproate is unsuitable; second-line choices include *clobazam*, *clonazepam*, *ethosuximide*, or *levetiracetam*.[17] *Rufinamide* is licensed in the UK for adjunctive use. *Felbamate* has also been used. The optimum treatment remains uncertain, but monotherapy with any drug has not been shown to be particularly effective.[48]

The classical antiepileptics are often ineffective in **infantile spasms** (as for example in **West's syndrome**).[49] UK guidelines recommend treatment with *corticotropin* or a *corticosteroid*, or else with *vigabatrin*;[17] in the USA, however, the American Academy of Neurology considers that the evidence does not support the use of corticosteroids, although corticotropin or vigabatrin appear to be of benefit.[50] *Vigabatrin* is effective either as adjunctive treatment or monotherapy. Many consider that, despite the risk of visual field defects,[51] it should replace corticotropin or corticosteroids as the treatment of choice,[52-58] although others disagree.[59,60] A systematic review[61] found that treatment with corticotropin or *tetracosactide*, or a corticosteroid such as *prednisone* resolved spasms in more infants than vigabatrin; a high dosage of prednisone or vigabatrin has been recommended but the optimum dose of corticotropin or tetracosactide is unknown. However, vigabatrin may offer the best first option in the treatment of infantile spasms due to tuberous sclerosis.[58,61,62] In some countries, *valproate*, alone or with *clonazepam* and/or *pyridoxine*, has been tried for initial management of infantile spasms.[63] Other second-line drugs include *clobazam* and *topiramate*;[17] *nitrazepam*,[17,57] *felbamate*,[49,64] and *lamotrigine*[49,64] have also been used. It is unclear to what extent treatment improves long-term outcome.[42,50,61]

Choice of antiepileptics in children. The use of antiepileptics in general in children has been reviewed.[42,64-71] Again, appropriate treatment depends on seizure type, but there is a lack of evidence to support many therapeutic choices,[66,71-73] in part because of the difficulties in undertaking studies in this population. In addition, children may be particularly susceptible to some adverse effects, including effects on behaviour, cognition, and development; behavioural problems have been associated particularly with phenobarbital.[71,74] Nonetheless the principles of pharmacological management are similar to those in adults (above) although UK guidelines recommend that treatment should only be begun by a specialist.[17] Dietary modification (the ketogenic diet) may also be tried.[71,75-78]

Withdrawal of antiepileptic therapy. Concern over the potential adverse effects of antiepileptic therapy clearly makes withdrawal attractive in patients who achieve prolonged seizure-free periods; however, the practical and social consequences of seizure recurrence may be considerable (for example, loss of driving licence and restricted employment prospects). The incidence of relapse after withdrawal has been variously estimated to range from 12% to over 60%.[79,80] Many studies have been carried out in children; data in adults is more scanty and given the differences between the populations, extrapolation of results in children to adults may be invalid.[79] A meta-analysis[81] that included 25 studies and 5354 patients (children and adults) found the overall rate of relapse in seizure-free patients after stopping antiepileptic therapy was 25% at 1 year and 29% at 2 years. There was a higher risk for relapse in adolescent- and adult-onset epilepsy compared with childhood-onset epilepsy. A more recent longitudinal population-based study[82] following 148 patients long-term from the onset of epilepsy in childhood found that of 90 patients in whom antiepileptic therapy was stopped, 33 relapsed and although in most cases relapse took place within 3 years, in one case it occurred 28 years after withdrawal.

Although these findings indicate that it is often possible to withdraw therapy successfully, it is more difficult to offer an individual *prognosis*.[11,83] It has been suggested that adult patients whose livelihood or lifestyle depends on being seizure-free would be generally ill advised to contemplate drug withdrawal.[84] Several strategies for predicting the likely outcome after withdrawal of antiepileptic therapy in individuals have been published.[85-87] Recognising that epilepsy is a heterogeneous disorder, scoring systems to allow for various risk factors have been devised.[85,86]

Prognostic risk factors (some of which are likely to be surrogate measures for the underlying condition) may include:

- the *aetiology* of the condition.[79,88] Patients classified as having symptomatic or cryptogenic epilepsy generally fare less well than those with idiopathic epilepsy with regard to seizure control, and withdrawal is less likely to be successful
- the *seizure type* and *syndrome*.[79,80,88] Studies have identified an increased risk of relapse in patients with particular seizure types; in particular, patients with partial, generalised tonic-clonic, and mixed seizure types seem to be at increased risk. However, it has been pointed out that increased risk has been associated with almost all seizure types other than generalised absence seizures, which seem to have a favourable prognosis; the context in which the seizure arises, such as the associated epilepsy syndrome and the aetiology, is more important than the type alone when considering withdrawal.[79] Examples of syndromes associated with a favourable outcome for withdrawal include benign childhood epilepsy with centrotemporal spikes, childhood absence epilepsy, and benign neonatal convulsions. However, withdrawal is inappropriate in juvenile myoclonic epilepsy, despite its good response to treatment, as relapse occurs in over 90% of patients
- the presence of accompanying *neurological* or *mental deficits*.[79] Some studies have suggested that mental retardation or other neurological deficits are associated with a poorer prognosis on withdrawal; these are probably surrogate markers for symptomatic epilepsy. However, mental retardation is not a contra-indication to withdrawal, and these patients may benefit from the elimination of any sedative effects if other risk factors are absent[79]
- the *age at onset*.[79,80,88] Several studies have identified a markedly increased risk of relapse on withdrawal in patients with seizure onset in adolescence or adulthood, whereas those with onset before 10 to 12 years of age have a generally more favourable prognosis. This is probably a surrogate marker for particular epileptic syndromes or aetiologies
- the *duration of remission*.[79,80,88,89] There is evidence in children that waiting for at least 2 seizure-free years before attempting withdrawal is associated with less risk of relapse than doing so earlier. However, the 2-year period was chosen arbitrarily, and the true optimum timing is unknown.[89] There is little evidence to guide the timing of withdrawal in adults.[89] However, in practice most support a requirement of at least 2 years free from seizures before drug withdrawal[79,80,88] and some suggest at least 4 years[83]
- the *response to therapy*.[79] Refractory epilepsy, as indicated by the occurrence of seizures once therapy has been begun, or the need for adjunctive or combination therapy to control seizures, is a poor prognostic sign for withdrawal. Patients with a history of multiple seizures before beginning therapy are also at increased risk on withdrawal

There is less agreement about the prognostic significance of some other factors:

- it is unclear whether the *type of drug* used to control seizures affects the risk of recurrence on withdrawal. It has been suggested that patients taking phenobarbital or benzodiazepines may be at increased risk of relapse, but there is little supportive evidence.[79] A poorer prognosis for patients taking valproate has also been reported;[90] a study in patients given combination therapy noted an increased risk when the carbamazepine component of the regimen was withdrawn.[91] It should be borne in mind that withdrawal of an enzyme-inducing antiepileptic may alter the serum concentrations of other drugs in the regimen[92]
- there is also controversy about the prognostic value of the *EEG* for the success of withdrawal.[79-81,88] Although an abnormal EEG before withdrawal was a negative prognostic factor in many studies, EEG abnormalities are not present in all epileptic patients, and some antiepileptic drugs suppress EEG abnormalities and can lead to false-negative results[79]

When a decision to withdraw is made, it is agreed that the *withdrawal regimen* should be gradual to reduce the risk of provoking withdrawal seizures. Drugs should be withdrawn one at a time but there is no agreement on the order or the optimum rate of withdrawal for individual drugs. It has been suggested that tapering therapy over less than 6 months increases the relapse rate.[79] However, one study in children indicated no significant difference in seizure recurrence rate when various antiepileptics, including barbiturates, were withdrawn over 6 weeks or 9 months.[93] Nonetheless, it has been pointed out that relapses tended to occur earlier in the group tapered more rapidly, and in practice it is rarely necessary to withdraw medication more rapidly than over a 6-month period.[79] It may be possible to withdraw phenytoin or valproate quickly (over a few days in hospital) if necessary.

If seizures recur on withdrawal it is almost always possible to restore good control by *re-instituting therapy*, and morbidity, mortality, and incidence of status epilepticus are reported to be low in the setting of prescribed antiepileptic drug withdrawal.[79] However, in a very small number of patients intractable seizures may develop.[83,94]

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Epilepsy and breast feeding. Antiepileptics are generally distributed into breast milk (although this information is not always known for the newer ones), but for most of the older established drugs, the concentrations are lower than in maternal plasma, and breast feeding is considered to be safe for these antiepileptics when given in usual doses.[1-7] The American Academy of Pediatrics[8] also considers that most of the older antiepileptics, specifically *carbamazepine, ethosuximide, phenytoin,* and *valproate,* are usually compatible with breast feeding; however, they also recommend that *phenobarbital* and *primidone* should be used with caution as significant adverse effects have occurred in nursing infants. Problems of neonatal sedation may occur with the *benzodiazepines* and *barbiturates* (including primidone). Ethosuximide is distributed in significant amounts into breast milk; hyperexcitability and poor suckling have been reported in the infant. There is little data for the new antiepileptics regarding breast feeding (the manufacturers and the UK Drugs in Lactation Advisory Service[9] generally recommend that breast feeding should be avoided). *Lamotrigine* may accumulate in breast-fed infants, as the metabolic pathway for lamotrigine may not be fully developed in newborns;[1,10] the American Academy of Pediatrics[8] considers that the use of lamotrigine during breast feeding may be of concern. *Gabapentin,*[11] *levetiracetam,*[12] and *topiramate*[13] are transferred into breast milk in significant amounts, but serum concentrations in breast-fed infants are very low. The American Academy of Neurology and American Epilepsy Society, while noting[14] that gabapentin, lamotrigine, levetiracetam, and topiramate were transferred into breast milk to a greater extent than carbamazepine, phenobarbital, phenytoin, and valproate (as was primidone), considered that the clinical effects of indirect exposure to antiepileptics via breast milk were not well enough explored.

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Epilepsy, cognition, and mood. Patients with epilepsy are at increased risk of **cognitive** and **behavioural** deficits. These are often multifactorial in origin: the disease itself and its underlying pathology, psychosocial and environmental factors, and the effects of antiepileptic treatment may all play a role.[1-8] Children are particularly vulnerable: recurrent seizures in the immature brain appear to have an adverse effect on the development of brain structure and function;[8] furthermore, behavioural and cognitive deficits may not be detected for a long time, while imposing detrimental effects on development and learning.[4,6] Because of the multifactorial nature of the problem, and the difficulties of assessing often subtle changes in cognition, it has proved difficult to study appropriately, and evidence is often scanty. Many studies have been small, and have had methodological flaws.[4,6] In addition, there is a need for studies in patient populations at greater risk, such as children.[5,6]

There is particular interest in assessing the risks associated with antiepileptic treatment, since it is perhaps the most readily modifiable factor. Strategies such as avoiding unnecessary polytherapy, using the lowest effective dose of an antiepileptic, keeping drug concentrations in therapeutic ranges, and slow titration when doses are increased, have been associated with fewer cognitive adverse effects. However, it should also be borne in mind that appropriate treatment and good seizure control may offset the negative cognitive effects.[4] (There is an interesting suggestion that suppression of interictal discharges in the EEG with lamotrigine may be associated with an improvement in behaviour in children with epilepsy and behavioural problems.[9])

The most common cognitive effects seem to be sedation, somnolence, distractibility, memory impairment, insomnia, and dizziness; adult patients often have depression (see below), whereas in children hyperactivity and aggression may occur.[5] (Aggression has also been reported in adults.[10]) More subtle effects on cognitive function and neuropsychological variables also occur. It has proved difficult, for the reasons mentioned above, to establish the comparative severity of cognitive effects between different antiepileptics. However, it seems to be generally agreed that barbiturate antiepileptics such as *phenobarbital*, and (particularly in the elderly) benzodiazepines such as *clobazam* and *clonazepam*, have the worst profiles, including decreased arousal and deterioration in most areas of cognitive performance;[4] in children, phenobarbital may decrease IQ and impair academic achievement.[2-7] Other standard antiepileptics such as *phenytoin*, *carbamazepine*, and *valproate* seem to have more modest, and broadly comparable, effects.[2,4-6] Most of the newer antiepileptics appear to be better tolerated; however, *topiramate*, and to some extent *zonisamide*, do produce impairment. There is also limited evidence that *gabapentin*, *lamotrigine*, and *vigabatrin* may enhance cognitive function. However, further data are required for the newer antiepileptics before a definitive assessment can be made.[1-7]

In view of the potential effect of antiepileptics on cognition, the recommendations of the Committee on Drugs of the American Academy of Pediatrics[11] include:

- the relative influence of each antiepileptic on cognitive and behavioural function should be considered along with all other potential adverse effects
- the child's behaviour and academic progress should be monitored through routine questioning of parents and teachers as well as by the physician's own observations of cognitive function, mood, and behaviour
- should behavioural or cognitive changes occur in relation to starting antiepileptic therapy, the need for medication and/or possible alteration of medication must be reassessed

For comment on the potential effects of maternal antiepileptic therapy on fetal neurodevelopment, see Epilepsy and Pregnancy, below.

Epilepsy is also associated with a greater prevalence of mood disorders, particularly **depression**, than is seen in the general population.[12-15] There have been concerns that antiepileptic drugs may play a significant role in exacerbating these. A review[16] has suggested that the commoner antiepileptics could be classified by the risk of associated depression as follows:

- highest risk (about 10% of patients):
  - barbiturate antiepileptics such as phenobarbital
  - topiramate
  - vigabatrin
  - zonisamide (associated with mood disorders in about 7% of those taking high doses)
- intermediate risk (4% or less):
  - felbamate
  - levetiracetam
  - tiagabine
- lower risk (less than 1%; some might actually have positive effects on mood):
  - carbamazepine
  - ethosuximide
  - gabapentin
  - lamotrigine
  - oxcarbazepine
  - phenytoin
  - pregabalin
  - valproate

In January 2008, the FDA issued an alert[17] after analysis of 199 placebo-controlled studies of antiepileptic drugs in the management of not only epilepsy but also psychiatric disorders (including bipolar disorder and depression) and other conditions such as migraine and neuropathic pain. This analysis, which involved 27 863 drug-treated patients and 16 029 controls, found that the risk of suicidal ideation or behaviour was about twice as great in the drug treatment groups (0.43%) as in those given placebo (0.22%). The relative risk was greater in patients with epilepsy than in those with other disorders. Drugs implicated by this analysis were carbamazepine, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, valproate, and zonisamide. However, the FDA considered that the increased risk was a class effect that would be shared by *all* antiepileptics except those indicated only for short-term use. It was recommended that prescribers and patients and their families should be aware of the risk, and should be alert for behavioural changes and other warning signs that might signal suicidal ideation. Similar advice has been issued in the EU.[18] The risk factors (particularly antiepileptic drugs) for suicidal ideation in patients with epilepsy have been reviewed.[19]

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Epilepsy and driving. Driving by patients with epilepsy is generally regulated[1,2] and restricted to those whose seizures are adequately controlled. Also, antiepileptic drugs may produce CNS-related adverse effects, including dizziness and drowsiness, that could impair a patient's ability to drive a vehicle or operate machinery, particularly during the initial stages of therapy.

In the UK,[3,4] patients suffering from epilepsy may drive a motor vehicle (but not a heavy goods or public service vehicle) provided that:

- they have had a seizure-free period of 1 year *or*
- if subject to attacks while asleep and awake, have established a 3-year period without an awake attack *or*
- if subject only to attacks while asleep have an established pattern of attack for 1-year

It is recommended that patients should not drive during withdrawal of antiepileptic drugs, or for 6 months afterwards. Drivers of heavy goods and public service vehicles must have been seizure-free for 10 years without antiepileptic treatment.

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Epilepsy and pregnancy. The management of epilepsy during pregnancy may present problems for both the mother and the fetus.[1-10]

The outcome of pregnancy in women with epilepsy is generally recognised to be poorer than that in the general population. Still-births and neonatal loss are increased, and maternal deaths are more common;[3,6] there is also an increased incidence of preterm delivery and low birthweight at term.[4] In addition, there is a clearly increased risk of fetal malformation. The factors responsible for this poorer outcome are complex, and may include the disease itself, seizure frequency during pregnancy, and socio-economic factors, as well as the effects of antiepileptic drugs.[1,3,4,6,11-13]

A single generalised seizure does not usually pose clinical problems for the fetus, but both mother and fetus are at risk of serious trauma from maternal falls, and intra-uterine deaths have been reported. It is widely considered that status epilepticus is associated with significant mortality in mother and fetus.

The frequency of seizures may increase during pregnancy in some women; this might be related to hormonal or other factors such as lack of sleep, but one of the main reasons is likely to be decreased plasma-antiepileptic concentrations due to changes in drug clearance and binding as pregnancy progresses. Therapeutic drug monitoring has been recommended[14,15] in at-risk patients; the American Academy of Neurology and American Epilepsy Society (AAN/AES),[8] have particularly recommended monitoring the serum concentrations of carbamazepine, lamotrigine, and phenytoin, and possibly levetiracetam and oxcarbazepine. However, analysis[16] of 1956 pregnancies of 1882 epileptic women recorded in an international antiepileptic drugs and pregnancy registry (EURAP) found that 58.3% were seizure-free throughout pregnancy. Seizures occurred during delivery in 3.5%, most commonly in those who had seizures earlier during pregnancy, and status epilepticus occurred in 1.8%, with one case of still-birth and none of miscarriage or maternal mortality. The authors noted that publication bias favoured the reporting of adverse outcomes in pregnancy. An evidence-based review[9] suggested that freedom from seizures for at least 9 months before pregnancy is associated with a high likelihood (84 to 92%) of remaining seizure-free during pregnancy.

As with many other aspects of epilepsy, it is difficult to disentangle the potential adverse effects of therapy from those of the disease. However, although the risk of **major malformations** such as congenital heart defects, neural tube defects, urogenital defects, and orofacial clefts is somewhat increased in offspring of all women with epilepsy,[1,6] there is clear evidence that in children of women treated with antiepileptic drugs it is 2 to 3 times that in the general population, and the risk is higher in women taking multiple drugs or in those who take antiepileptics during the first trimester.[6]

Despite this, evidence linking specific drugs with particular patterns of malformation is limited and often unclear. There appears to be strong evidence for a dose-related increased risk of major malformation with *valproate*,[4,10-13,17-21] and increased risk has been reported for *carbamazepine*, *phenobarbital*, and *primidone*.[6,11,12] The rate of major abnormality with *phenytoin* does not seem to be higher than in the general population.[6] However, a well established **fetal antiepileptic syndrome** (FAS) has been reported with phenytoin, as with other antiepileptic drugs,[4] including some older drugs such as *trimethadione*. Although early reports associated syndromes with specific drugs, such as fetal hydantoin syndrome (phenytoin), or fetal valproate syndrome, there is considerable overlap in the reported effects and recent reviews consider these as manifestations of a single condition, FAS.[4,12] The dysmorphic facial changes characteristic of FAS can be quite subtle, and may become less apparent as the child grows.[6]

Evidence for any effect of the newer antiepileptics on the fetus is particularly scanty. It is unclear if *oxcarbazepine* is associated with an increased risk in major malformation,[6] and limited data have not so far suggested a significant increase in risk with *lamotrigine*[12,21,22] and *levetiracetam*.[23] There are reports suggestive of an increased risk with *topiramate*[6] and licensed product information for this drug, and also *pregabalin* and *zonisamide* advises against use in pregnancy on the basis of *animal* studies and lack of human data. Caution is also advised with *tiagabine* and *vigabatrin*. There appears to be little evidence of teratogenic potential for *felbamate* or *gabapentin* in *animal* studies to date, although cases of malformation have been seen in pregnancies exposed to gabapentin.[6]

In a study[20] of the UK Epilepsy and Pregnancy Register that examined the outcome of 3607 pregnancies in mothers with epilepsy, the overall rate of major congenital malformations was 3.5% in those untreated with antiepileptics and 4.2% in those given antiepileptics during pregnancy, with rates of 3.7% and 6.0% in those given monotherapy or polytherapy, respectively. For monotherapy, the malformation rates for individual drugs were topiramate (7.1%), valproate (6.2%), phenytoin (3.7%), gabapentin (3.2%), lamotrigine (3.2%), and carbamazepine (2.2%). For polytherapy, those regimens containing valproate had a significantly higher risk of major congenital malformations than valproate-free combinations. A relationship between malformations and dose was seen for lamotrigine monotherapy and although the trend with valproate dosage did not reach statistical significance, infants exposed to more than 1 g of valproate daily had the highest rate of malformations for any monotherapy. The authors also noted that for lamotrigine the risk with doses more than 200 mg daily was no different to that associated with 1 g or less of valproate daily.

There is evidence that antiepileptic therapy is associated with lower birth-weight at term, presumably due to drug-induced **intra-uterine growth retardation**; the effect may be seen largely in women taking multiple antiepileptic drugs.[6]

Additional problems that may occur in the immediate postpartum period include the potential for neonatal **sedation** and **dependence** with drugs such as phenobarbital or *benzodiazepines*, if given close to term. Evidence of withdrawal symptoms has also been reported in infants exposed to sodium valproate or phenytoin. Some antiepileptics induce hepatic enzymes and may also increase the risk of vitamin K deficiency and **neonatal bleeding**.[4,6]

There is also increasing concern about the possibility of long-term **impairment of neurodevelopment** in children exposed to antiepileptic drugs *in utero*.[3,6,11,12,24,25] A population-based cohort study[26] in young men with epileptic mothers found lower IQ scores and shorter adult heights than in those born to mothers without epilepsy, although information on fetal exposure to individual antiepileptic drugs was unavailable. Again, most evidence implicates valproate;[6,10-12,27,28] some consider that there is also evidence for phenytoin[6,10-12] and carbamazepine,[6,11,12] and perhaps phenobarbital,[10,11] although a systematic review could not find evidence to implicate any individual antiepileptic,[24] and a study involving 182 children exposed to carbamazepine monotherapy could not find evidence of a reduction in verbal and nonverbal IQ scores.[29]

Patients with epilepsy should be offered **pre-conception advice** and treatment should be individualised.[1,2,4,6] Women should be advised to plan their pregnancies, and informed of the potential risks of seizures to mother and baby as well as the risks of antiepileptics;[6] fatalities have been associated with the mother stopping her antiepileptic regimen inappropriately.[3] It should be borne in mind that some antiepileptics may reduce the efficacy of oral contraception and increase the risk of unplanned pregnancy.[4,12] Equally, there is some evidence that a degree of sexual dysfunction and impaired fertility may occur in both women[4,12] and men[30,31] with epilepsy.

In women with epilepsy who intend to become pregnant, certain guidelines and principles are widely followed.

- Withdrawal of antiepileptic therapy may be an option if the patient has been seizure-free for at least 2 years (for further details of drug withdrawal, see p. 506.1); resumption of therapy may be considered after the end of the first trimester.
- If antiepileptics are to be continued throughout pregnancy, monotherapy is preferred using the lowest possible effective dose, although doses may have to be increased in response to changes in drug disposition during pregnancy, with the necessary readjustments being made after delivery.
- High daily doses of valproate (more than 1 g daily) should be avoided if possible, and peak plasma concentrations may be reduced by dividing the daily dose into 3 or 4 parts or by giving a modified-release preparation.
- Since there is a risk of fetal malformations with all the established antiepileptics, and a lack of data for the newer ones, it is generally considered that as long as there is good seizure control there is little to be gained from changing a pregnant patient's antiepileptic.

For those patients who first present when **already pregnant** there is probably little to be gained in altering potentially teratogenic antiepileptics as the time for intervention has almost certainly passed.[1,2,6,10] If a patient becomes pregnant while taking carbamazepine, phenytoin, or valproate she should be counselled regarding the risk of neural tube and other defects and should be offered antenatal screening. Adequate supplementation of folic acid is advised before pregnancy and during the first trimester to counteract the risk of neural tube defects. It has been suggested that women taking antiepileptics should be given folic acid in similar doses to those used in women who have previously given birth to an infant with neural tube defects, i.e. 4 or 5 mg daily (for further details, see Neural Tube Defects under Folic Acid, p. 2064.3). However, the AAN/AES[8] only suggest supplementation with the standard female dose of at least 400 micrograms daily of folic acid, before and during pregnancy, as it is unknown whether higher doses offer greater benefit in these patients. Although folic acid can reduce serum-phenytoin concentrations this does not appear to be a problem in practice (see Vitamins, p. 545.2).

To counteract the risk of neonatal bleeding associated with enzyme-inducing antiepileptics it is particularly important that the neonate be given vitamin K after delivery[4-6] (for further details, see Vitamin K Deficiency Bleeding, p. 2123.2). Some have advocated oral doses for the mother in the last 4 weeks of pregnancy,[4] but the justification for prophylactic maternal dosage is unclear[8,32] given the available evidence.

Patients with epilepsy have also a higher risk of preterm delivery and antenatal corticosteroid therapy may, therefore, be warranted. High doses of corticosteroid may be required in those women receiving enzyme-inducing antiepileptics.[1]

Status epilepticus during pregnancy should be treated in the same way as for the general population (see below). First seizures occurring during the second half of pregnancy may be part of eclampsia (see p. 511.1) and should be differentiated from epilepsy.

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Status epilepticus

Although status epilepticus has been defined as continuous or repeated seizure activity lasting 30 minutes or more without any regaining of normal consciousness, current definitions generally consider it to be any continuous seizure of more than 5 minutes, or 2 or more seizures without regaining normal consciousness.[1-8] Although status may occur with any seizure type, generalised convulsive status is the most common clinical presentation,[4] with an estimated mortality rate of about 20%; it is most frequent in young children and the elderly.[1-3,9] It is a medical emergency, and the longer seizures continue, the more difficult they are to control and the higher the morbidity and mortality; permanent neuronal damage can occur after 30 minutes of seizure activity.[8]

Management of status epilepticus varies slightly between centres and countries, but the general principles seem to be fairly well established.[1-12]

- In **initial management**, it is important to secure the airway and give oxygen as required, assess cardiac and respiratory function, and establish intravenous access. Blood glucose should be assessed and any hypoglycaemia corrected with glucose; intravenous thiamine should be given if there is any suggestion of alcohol abuse or inadequate nutrition.[1,4-7,11]
- Initial antiepileptic treatment is usually with benzodiazepine. Although *diazepam* has been widely used in the past, intravenous *lorazepam* is now preferred for first-line treatment in most protocols,[1-7,9-15] as it appears to be more effective and has a longer duration of antiepileptic action.[6,7,13] *Clonazepam*[16] or diazepam followed immediately by phenytoin or fosphenytoin[1] have been proposed as alternatives where intravenous lorazepam is not available. Rectal diazepam or buccal *midazolam* may be used in the home setting or where intravenous access is not available.[4,5,12,14,17] (Rectal diazepam may also have a role in this setting to treat acute repetitive seizures,[18] which may evolve into status epilepticus.) Both midazolam[19,20] and lorazepam[21] have also been given intranasally.
- For sustained control in patients with established epilepsy their usual antiepileptic regimen may be given orally or by nasogastric tube once immediate control is established, or if necessary, for those drugs with an intravenous formulation, parenterally.[4,5]
- In other patients, or in patients with **established status** not abolished by the benzodiazepine, additional treatment with one of several first-line antiepileptics is normally required. The choice is usually between intravenous *phenytoin*, *fosphenytoin*, or *phenobarbital*,[1,4,5,7,8] all of which are effective. Repeat doses may need to be given. Although there is some evidence that phenobarbital is more effective than phenytoin in abolishing seizures,[22] many favour the use of the barbiturate only in patients who do not respond to phenytoin or fosphenytoin,[1-3,9,10] because of the risk of severe respiratory depression. ECG monitoring is required in patients given intravenous phenytoin or fosphenytoin.[4]
- Other antiepileptics have been used for established status. Some have found intravenous *valproate* to be useful in this situation,[8,23-25] and have incorporated it into local protocols. Other alternatives have included *paraldehyde* rectally or by deep intramuscular injection, and intravenous *clomethiazole edisilate* was formerly available. Rectal paraldehyde has been noted to cause little respiratory depression and may therefore be useful where facilities for resuscitation are poor. Another option is to give *lidocaine* intravenously.[1] *Pyridoxine* may be tried in children under 3 years of age with established convulsive status epilepticus, in case the seizures are pyridoxine dependent or responsive.[2]
- Once seizures have continued for 60 to 90 minutes despite treatment with a benzodiazepine and one of the first-line antiepileptics, the patient is considered to have **refractory status epilepticus**.[1,5,26] At this point general anaesthesia should be instituted. The usual choice is between treatment with *propofol*, *midazolam*, or a short-acting barbiturate anaesthetic such as *pentobarbital* or *thiopental*.[1,4-10,15,26,27] Midazolam may be the preferred alternative in children.[16] The anaesthetic should be continued for 12 to 24 hours after the last clinical or electrographic seizure and the dose then gradually reduced.[3,26] Some consider that all patients unresponsive to first-line therapy with a benzodiazepine should be considered refractory and proceed to treatment with propofol or midazolam.[6]
- Other drugs tried in refractory status include the inhalational anaesthetics *desflurane* and *isoflurane*,[28] *Tiagabine* and *ketamine* have also been suggested,[6] as has *valproate*,[8,27] and there are a few reports of responses to *levetiracetam*[29] and *topiramate*.[30-32]

Evidence to support the management of **nonconvulsive** forms of status epilepticus (NCSE) is scanty. The *BNF* recommends that usual oral antiepileptics should initially be continued or restarted in patients with incomplete loss of awareness. Otherwise, it has been suggested that management should be as for convulsive status,[6] albeit less aggressive,[33] with intravenous benzodiazepines the first choice for initial management.[4-6,11,15,33] Subsequent man-

agement will probably be influenced by the drugs known to be effective in the given seizure type. The prognosis depends on the aetiology and level of consciousness: comatose patients with refractory NCSE have a poorer prognosis and general anaesthesia may be appropriate.[6] Conscious patients generally have a more favourable outcome and termination of status is considered less urgent; general anaesthetics should thus be used more cautiously.[11,33]

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Other convulsive disorders

Disorders that feature convulsions or epileptic seizures but are not considered to be forms of epilepsy are described below.

Alcohol withdrawal syndrome. For a discussion of the management of seizures associated with alcohol withdrawal syndrome, see p. 1735.1.

Eclampsia and pre-eclampsia. Pre-eclampsia is a hypertensive disorder occurring in pregnancy that entails increased blood pressure together with proteinuria, and sometimes abnormal coagulation, liver dysfunction, and oedema; rarely the disorder may progress to eclampsia, which is a convulsive phase. It is difficult to identify those patients who will have eclamptic seizures. The treatment of pre-eclampsia and eclampsia is mainly aimed at reducing hypertension (see Hypertension in Pregnancy, under Hypertension, p. 1251.1) and treating or preventing resultant seizures. However, the treatment of the hypertension alone may not be sufficient to prevent the progression of pre-eclampsia to eclampsia.

Eclampsia in the UK was traditionally treated with *diazepam*, *clomethiazole*, or *phenytoin*. *'Lytic cocktails'* consisting of chlorpromazine, pethidine, and/or promethazine have also been used in some countries in the management of pre-eclampsia and imminent eclampsia but they result in heavy sedation and the use of phenothiazines is generally not recommended late in pregnancy. *Magnesium sulfate* is now the drug of choice for the treatment of eclampsia;[1-3] it has been the preferred treatment of eclampsia in the USA for many years, on the grounds that it is more effective and causes fewer adverse effects than other antiepileptics. A meta-analysis[4] of 9 randomised studies involving 2390 patients with pre-eclampsia and 1743 patients with eclampsia concluded that magnesium sulfate was more effective than phenytoin or no therapy in prevention of seizures in pre-eclamptic patients. In eclamptic patients, magnesium sulfate was superior to phenytoin, diazepam, or a lytic cocktail in terms of seizure recurrence, a result that was confirmed in subsequent systematic reviews.[5-7]

Until recently there has been insufficient evidence to establish the benefits and hazards of antiepileptics in the prevention of eclampsia in pre-eclamptic patients although it was considered that magnesium sulfate was the best choice if an antiepileptic was needed.[8-10] Some commentators suggested,[11] in the light of evidence of possible neonatal toxicity, that magnesium sulfate should be restricted to use in more severe pre-eclampsia or eclampsia. However, the significant benefits of magnesium sulfate in the prevention of eclampsia were confirmed in a large, international study,[12] and follow-up studies found that magnesium sulfate was not associated with an increased risk of death or disability in the children at 18 months[13] and in the mothers at 2 years.[14]

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Febrile convulsions. Febrile convulsions have been defined[1] as epileptic seizures occurring between the ages of 6 months to 5 years and associated with a fever arising from an infectious illness outside the CNS. They usually occur during the rising phase of fever early in the course of the infection and are not considered to be a form of epilepsy.[2,3]

Febrile convulsions are considered to be benign if limited to a single tonic or tonic-clonic seizure lasting less than 15 minutes without any focal characteristics[2] (also known as simple febrile convulsions).[4] About one-third of children who have a benign febrile convulsion will have a recurrence.[1,2,5] Risk factors for recurrence include a young onset age, a history of epilepsy or febrile seizures in a first-degree relative, subsequent episodes of fever, and a first complex febrile seizure.[5] The risk of developing epilepsy is low, but nevertheless it is 2 to 3 times greater than the risk in the population as a whole.[2] Unless they are recurrent, benign febrile convulsions need only simple treatment to lower body temperature[1,2] such as that described under Fever and Hyperthermia, p. 11.3.

Prolonged febrile convulsions lasting longer than 15 minutes and associated with some focal characteristics are not considered to be benign (also known as complex febrile convulsions[4]) and further increase the risk of developing epilepsy.[2,3] When they are prolonged or recurrent they are treated with *diazepam* intravenously, or as a rectal solution, to prevent possible brain damage resulting from continued seizure activity, although any such effect appears to be rare.[6]

The prophylactic use of *antiepileptics* in children thought to be at risk of recurrence of febrile convulsions remains controversial. Many consider that even if recurrences can be prevented there is no evidence that the risk of developing epilepsy is reduced.[1,2,5] A working group of the Royal College of Physicians and the British Paediatric Association considered that pooled analyses of studies of the prophylactic use of *phenobarbital* or *sodium valproate* showed that long-term prophylaxis was rarely indicated.[1] Although some have found that intermittent prophylaxis with phenobarbital or diazepam[7] given at the onset of and during fever could prevent recurrence of febrile convulsions, the working group did not recommend their routine use in this way.[1] Other workers have found that giving paracetamol as an antipyretic and diazepam for intermittent prophylaxis failed to prevent recurrences of febrile convulsions.[8] A later meta-analysis[9] concluded that neither continuous nor intermittent prophylaxis could be recommended as the benefits did not outweigh the potential adverse effects, a view endorsed by the American Academy of Pediatrics.[4]

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9. Rantala H, *et al.* A meta-analytic review of the preventative treatment of recurrences of febrile seizures. *J Pediatr* 1997; 131: 922–5.

Myoclonus. Myoclonus consists of brief, involuntary, jerky movements of sudden onset which may be focal, segmental, or generalised, and are caused by muscular contractions (positive myoclonus) or inhibitions/pauses (negative myoclonus). The term 'myoclonus' is non-specific and classification is important in order to decide on treatment:[1-6]

- physiological (in normal subjects)
- essential (no known cause)
- epileptic (seizures dominate)
- symptomatic (encephalopathy dominates—causes include storage diseases, neurodegenerative syndromes, toxic and drug-induced syndromes, and hypoxia)

In epileptic myoclonus, epileptic seizures (myoclonic seizures in which the motor manifestation is myoclonus) dominate. Their treatment is discussed under Epilepsy, p. 506.1. Essential myoclonus may benefit from *clonazepam*. *Botulinum toxin* has been used successfully for spasmodic movements in some forms of myoclonus.

Myoclonus may also be subdivided into cortical, reticular, or spinal forms. Cortical myoclonus is considered to be a subset of epilepsy and responds best to antiepileptics, usually *valproate* and/or clonazepam; *piracetam* or *levetiracetam* are also used, usually as adjunctive therapy. Reticular myoclonus is usually caused by anoxia or acute encephalopathy and may be treated with clonazepam; *serotonin* or serotonergic agonists have also been tried. Posthypoxic myoclonus occurring after hypoxic coma may respond to *oxitriptan* or serotonin combined with *carbidopa*; antiepileptics may help.

1. Caviness JN. Myoclonus. *Mayo Clin Proc.* 1996; 71: 679–88.
2. Blindauer K. Myoclonus and its disorders. *Neurol Clin North Am* 2001; 19: 723–34.
3. Agarwal P, Frucht SJ. Myoclonus. *Curr Opin Neurol* 2003; 16: 515–21.
4. Caviness JN, Brown P. Myoclonus: current concepts and recent advances. *Lancet Neurol* 2004; 3: 598–607.
5. Andrade DM, *et al.* Treatment options for epileptic myoclonus and epilepsy syndromes associated with myoclonus. *Expert Opin Pharmacother* 2009; 10: 1549–60.
6. Caviness JN. Pathophysiology and treatment of myoclonus. *Neurol Clin* 2009; 27: 757–77.

Neonatal seizures. Neonatal seizures differ from epilepsy, and the definitions in the 1989 international classification of epilepsy and epileptic syndromes (see p. 506.1) may be of little value; (a study[1] has suggested that the proposed 2001 classification may be more helpful). They are frequently subtle and difficult to recognise.[2] Causes include asphyxia, glucose or electrolyte imbalance, infection, CNS or cerebrovascular lesions, inborn errors of metabolism, and drug withdrawal or intoxication.[3-5]

Neonatal seizures represent a neurological emergency in the newborn and rapid diagnosis and treatment is essential.[3-7] Infusion of glucose or electrolytes may be of benefit.[4,5] Current practice involves giving antiepileptic

drugs to control seizures, although there is no consensus on, nor good evidence for, their use.[2,7] ***Phenobarbital*** and ***phenytoin*** are the most widely used.[3-6] Traditionally, phenobarbital has been considered to be the mainstay of treatment for all types of seizures in neonates; however response rates are variable.[6-8] If seizures persist, phenytoin may be added to therapy.[8] Other drugs that have been tried include ***carbamazepine, levetiracetam,[9] benzodiazepines,***[3-5,8,10,11] ***lidocaine,***[3,8,11] and ***primidone.***[4,5] Pyridoxine-dependent seizures can be abolished by regular large doses of the vitamin[4,5] (see p. 2106.2).

1. Mastrangelo M, *et al.* Epileptic seizures, epilepsy and epileptic syndromes in newborns: a nosological approach to 94 new cases by the 2001 proposed diagnostic scheme for people with epileptic seizures and with epilepsy. *Seizure* 2005; **14:** 304–11.
2. Rennie J, Boylan G. Treatment of neonatal seizures. *Arch Dis Child Fetal Neonatal Ed* 2007; **92:** F148–F150.
3. Evans D, Levene M. Neonatal seizures. *Arch Dis Child Fetal Neonatal Ed* 1998; **78:** F70–F75.
4. Hill A. Neonatal seizures. *Pediatr Rev* 2000; **21:** 117–21.
5. Painter MJ, Alvin J. Neonatal seizures. *Curr Treat Options Neurol* 2001; **3:** 237–48.
6. Painter MJ, *et al.* Phenobarbital compared with phenytoin for the treatment of neonatal seizures. *N Engl J Med* 1999; **341:** 485–9.
7. Booth D, Evans DJ. Anticonvulsants for neonates with seizures. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 09/06/08).
8. Boylan GB, *et al.* Second-line anticonvulsant treatment of neonatal seizures: a video-EEG monitoring study. *Neurology* 2004; **62:** 486–8.
9. Shoemaker MT, Rotenberg JS. Levetiracetam for the treatment of neonatal seizures. *J Child Neurol* 2007; **22:** 95–8.
10. Castro Conde JR, *et al.* Midazolam in neonatal seizures with no response to phenobarbital. *Neurology* 2005; **64:** 876–9.
11. Shany E, *et al.* Comparison of continuous drip of midazolam or lidocaine in the treatment of intractable neonatal seizures. *J Child Neurol* 2007; **22:** 255–9.

Porphyria. Convulsions may occur at the peak of an attack of acute porphyria (p. 1556.1) but usually disappear as the attack resolves and therapy should be aimed at the underlying disease. However, some patients continue to have convulsions while in remission and their management poses a major therapeutic problem as all the first-line antiepileptics have been associated with acute attacks.

The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies and gives recommendations for drug use based on the risk of porphyrinogenicity; for details see the individual monographs in this chapter and also clomethiazole (p. 1054.3), diazepam (p. 1067.3), and magnesium sulfate (p. 1791.1).

Reflex anoxic seizures. For a discussion of the management of reflex anoxic seizures, see p. 1311.3.

4-Amino-3-hydroxybutyric Acid

Ácido 4-amino-3-hidroxibutírico; Buxamin; GABOB; Gamma-amino-beta-hydroxybutyric acid; γ-Amino-β-hydroxybutyric acid; 4-Амино-3-оксимасляная Кислота.

$C_4H_9NO_3$=119.1

CAS — 352-21-6.

UNII — 1ZHM019FLD.

Profile

Aminohydroxybutyric acid has been claimed to be of value in a variety of neurological disorders including use as an adjunct in the treatment of epilepsy. It has also been promoted as a dietary supplement for its supposed beneficial effects on the CNS and growth hormone. It should be distinguished from its isomer 3-amino-4-hydroxybutyric acid (GOBAB), which is reported to possess anti-inflammatory and antifungal activity.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Gabimex; *Braz.*: Gamibetal; *Ital.*: Gamibetal; *Mex.*: Gamibetal.

Multi-ingredient Preparations. *Arg.*: Gabimex Plus; *Chile*: Gamalate B6; Gamavit B6; *Ital.*: Gamibetal Complex; Gamibetal Plus; Parvisedil; *Mex.*: Gamibetal Complex†; *Spain*: Dorken†; Gamalate B6; Redutona†; *Ukr.*: Gamalate B6 (Гамалате В6).

Barbexaclone *(rINN)*

Barbeksaklon; Barbexaclona; Barbexaclonum; Барбексаклон.

Compound of (-)-*N*,α-Dimethylcyclohexaneethylamine with 5-ethyl-5-phenylbarbituric acid.

$C_{12}H_{12}N_2O_3.C_{10}H_{21}N$=387.5

CAS — 4388-82-3.

ATC — N03AA04.

ATC Vet — QN03AA04.

UNII — 291GX1YB65.

Profile

Barbexaclone is a compound of levopropylhexedrine (see under Propylhexedrine, p. 2330.1) with phenobarbital (p. 535.2). It is used in the treatment of various types of epilepsy (p. 506.1). Usual adult doses are 200 to 400 mg daily given orally in divided doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Maliasin; *Braz.*: Maliasin†; *Gr.*: Maliasin; *Ital.*: Maliasin; *Switz.*: Maliasin†; *Turk.*: Maliasin.

Benzobarbital *(rINN)*

Benzobarbitalum; Benzobarbitone; Benzonal; Benzonalum; Бензобарбитал.

1-Benzoyl-5-ethyl-5-phenylbarbituric acid.

$C_{19}H_{16}N_2O_4$=336.3

CAS — 744-80-9.

UNII — YNJ788D0AH.

NOTE. The name benzonal has also been used as a proprietary name for benzonatate (p. 1656.2).

Pharmacopoeias. In *Int.*

Profile

Benzobarbital is a barbiturate that has been used in the treatment of epilepsy.

Brivaracetam *(USAN, rINN)*

Brivaracétam; Brivaracetamum; UCB-34714; Бривацетам.

(2*S*)-2-[(4*R*)-2-Oxo-4-propylpyrrolidin-1-yl]butanamide.

$C_{11}H_{20}N_2O_2$=212.3

CAS — 357336-20-0.

UNII — U863JGG2IA.

Profile

Brivaracetam is under investigation for the treatment of various types of epilepsy including progressive myoclonic epilepsy and refractory partial seizures.

References.
1. Sargentini-Maier ML, *et al.* The pharmacokinetics, CNS pharmacodynamics and adverse event profile of brivaracetam after single increasing oral doses in healthy males. *Br J Clin Pharmacol* 2007; **63:** 680–8.
2. Rolan P, *et al.* The pharmacokinetics, CNS pharmacodynamics and adverse event profile of brivaracetam after multiple increasing oral doses in healthy men. *Br J Clin Pharmacol* 2008; **66:** 71–5.
3. Malawska B, Kulig K. Brivaracetam: a new drug in development for epilepsy and neuropathic pain. *Expert Opin Invest Drugs* 2008; **17:** 361–9.

Carbamazepine *(BAN, USAN, rINN)*

Carbamazepin; Carbamazepina; Carbamazépine; Carbamazepinum; G-32883; Karbamatsepiini; Karbamazepin; Karbamazepinas; Karbamazepinum; Карбамазепин.

5*H*-Dibenz[*b*,*f*]azepine-5-carboxamide.

$C_{15}H_{12}N_2O$=236.3

CAS — 298-46-4.

ATC — N03AF01.

ATC Vet — QN03AF01.

UNII — 33CM23913M.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Carbamazepine). A white or almost white crystalline powder. It exhibits polymorphism. Very slightly soluble in water; sparingly soluble in alcohol and in acetone; freely soluble in dichloromethane. Store in airtight containers.

USP 36: (Carbamazepine). A white or off-white powder. Practically insoluble in water; soluble in alcohol and in acetone. Store in airtight containers.

Incompatibility. Carbamazepine suspension should be mixed with an equal volume of diluent before nasogastric use as undiluted suspension is adsorbed onto PVC nasogastric tubes.[1]

The FDA has received a report of a patient who passed an orange rubbery mass in his faeces the day after taking a carbamazepine suspension (*Tegretol: Novartis, USA*) followed immediately by chlorpromazine solution (*Thorazine; GSK, USA*). Subsequent testing showed that mixing the same carbamazepine suspension with a thioridazine hydrochloride solution (*Mellaril; Novartis, USA*) also resulted in the precipitation of a rubbery orange mass.

1. Clark-Schmidt AL, *et al.* Loss of carbamazepine suspension through nasogastric feeding tubes. *Am J Hosp Pharm* 1990; **47:** 2034–7.

Stability. FDA studies indicate that carbamazepine tablets could lose up to one-third of their efficacy if stored in humid conditions.[1] This appears to be due to formation of a dihydrate form which leads to hardening of the tablet and poor dissolution and absorption.[2,3] As the dihydrate has also been detected after storage under ambient conditions some suggest that storage with silica gel sachets may be necessary to avoid physical deterioration of carbamazepine tablets.[2]

1. Anonymous. Moisture hardens carbamazepine tablets, FDA finds. *Am J Hosp Pharm* 1990; **47:** 958.
2. Lowes MMJ. More information on hardening of carbamazepine tablets. *Am J Hosp Pharm* 1991; **48:** 2130–1.
3. Wang JT, *et al.* Effects of humidity and temperature on in vitro dissolution of carbamazepine tablets. *J Pharm Sci* 1993; **82:** 1002–5.

Uses and Administration

Carbamazepine is a dibenzazepine derivative with antiepileptic and psychotropic properties. It is used to control secondarily generalised tonic-clonic seizures and partial seizures, and in some primary generalised seizures. Carbamazepine is also used in the treatment of trigeminal neuralgia and has been tried with variable success in glossopharyngeal neuralgia and other severe pain syndromes associated with neurological disorders such as tabes dorsalis and multiple sclerosis. Another use of carbamazepine is in the management of bipolar disorder unresponsive to lithium.

In the treatment of **epilepsy** (p. 513.2), the dose of carbamazepine should be adjusted to the needs of the individual patient to achieve adequate control of seizures; this usually requires total plasma-carbamazepine concentrations of about 4 to 12 micrograms/mL (17 to 50 micromoles/litre). A low initial dose of carbamazepine is recommended to minimise adverse effects. The suggested initial oral dose is 100 to 200 mg once or twice daily gradually increased by increments of up to 200 mg daily every week to a usual maintenance dose of 0.8 to 1.2 g daily in divided doses; up to 2 g daily may occasionally be necessary.

For details of doses in children, see p. 513.1.

Oral carbamazepine is usually given in divided doses 2 to 4 times daily. A twice-daily regimen may sometimes be suitable for monotherapy, and be associated with improved compliance but can produce widely fluctuating plasma-carbamazepine concentrations that lead to intermittent adverse effects. Modified-release formulations can minimise fluctuations in plasma concentration and may also allow effective twice-daily use. The time and manner of taking carbamazepine should be standardised for the patient since variations might affect absorption with consequent fluctuations in the plasma concentrations. Different preparations vary in bioavailability and it may be prudent to avoid changing the formulation.

Carbamazepine may be given by the rectal route in doses up to a maximum of 250 mg every 6 hours to patients for whom oral treatment is temporarily not possible. The dosage should be increased by about 25% when changing from an oral formulation to suppositories, and it is recommended that the rectal route should not be used for longer than 7 days.

As with other antiepileptics, withdrawal of carbamazepine therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1.

The treatment of **trigeminal neuralgia** (p. 513.3) is typically begun with low oral doses, such as 100 mg of carbamazepine twice daily (although up to 200 mg twice daily has been suggested in the UK), and increased gradually as needed to maintain freedom from pain. This is usually at maintenance doses of 400 to 800 mg in divided doses; up to 1.2 g is the maximum daily dose recommended in the USA, while UK licensed product information considers that up to 1.6 g daily may be needed in some patients. When pain relief has been obtained attempts should be made to reduce, and if possible stop, therapy, until another attack occurs.

For the management of **bipolar disorder** (p. 513.1), carbamazepine is given in an initial oral dose of 400 mg daily in divided doses, increased gradually as necessary up to a maximum of 1.6 g daily; the usual maintenance dose range is 400 to 600 mg daily.

Administration. A modified-release formulation of carbamazepine can reduce fluctuations in carbamazepine concentrations,[1] and tolerability and seizure control in patients with epilepsy may be improved.[2,3] Such formulations should be considered in patients receiving high doses who suffer intermittent adverse effects, and might also permit a reduction to twice- or even, in some patients, once-daily dosage.[2,4] However, bioavailability appears to be slightly less than conventional preparations and dosage

adjustments may be required when changing between formulations.[1]

1. McKee PJW, *et al.* Monotherapy with conventional and controlled-release carbamazepine: a double-blind, double-dummy comparison in epileptic patients. *Br J Clin Pharmacol* 1991; 32: 99–104.
2. Anonymous. Carbamazepine update. *Lancet* 1989; ii: 595–7.
3. Ryan SW, *et al.* Slow release carbamazepine in treatment of poorly controlled seizures. *Arch Dis Child* 1990; 65: 930–5.
4. McKee PJW, *et al.* Double dummy comparison between once and twice daily dosing with modified-release carbamazepine in epileptic patients. *Br J Clin Pharmacol* 1993; 36: 257–61.

Administration in children. In the UK, the usual recommended oral dose of carbamazepine for generalised tonic-clonic and partial seizures in children is 10 to 20 mg/kg daily in divided doses. Alternatively the daily dose may be given according to age as follows:

- up to 1 year: 100 to 200 mg
- 1 to 5 years: 200 to 400 mg
- 5 to 10 years: 400 to 600 mg
- 10 to 15 years: 0.6 to 1 g

As with adults, children should be started on a low initial dose of carbamazepine to minimise adverse effects; the *BNFC* suggests that those aged 1 month to 12 years may initially be given 5 mg/kg at night or 2.5 mg/kg twice daily, increasing by 2.5 to 5 mg/kg every 3 to 7 days as necessary to a usual maintenance dose of 5 mg/kg 2 or 3 times daily. Older children may be given the usual adult dose (see p. 512.3) although a maximum of 1.8 g daily has been suggested.

The *BNFC* also states that these doses may be used for the treatment of trigeminal neuralgia and prophylaxis of bipolar disorder.

Carbamazepine may be given rectally to children in whom oral treatment is temporarily not possible; the *BNFC* suggests this route may be used from 1 month of age. Doses should be about 25% greater than the corresponding oral dose, to a maximum of 250 mg, and given up to 4 times daily.

Bipolar disorder. Carbamazepine may be given as an alternative to lithium or valproate in patients with bipolar disorder (p. 397.2). Studies of its efficacy have been conflicting; although clearly effective in some patients, at least one early study suggested that short-term benefit was not sustained in the longer term.[1] More recent results[2,3] have suggested that lithium or valproate are generally more effective, but that carbamazepine may conceivably have a role in patients with nonclassical features. Carbamazepine has also been used with lithium, particularly in patients unresponsive to either drug alone; although there are suggestions that the combination may be more effective than monotherapy, particularly in patients with a history of rapid cycling,[4] it is associated with a potential risk of serious neurotoxicity—see Antidepressants, under Interactions, p. 516.2. While some commentators have suggested that carbamazepine is falling out of favour with specialists prescribing for bipolar disorder,[5] more recent reviews[6,7] have concluded that it may still be a feasible treatment option.

1. Frankenburg FR, *et al.* Long-term response to carbamazepine: a retrospective study. *J Clin Psychopharmacol* 1988; 8: 130–2.
2. Kleindienst N, Greil W. Differential efficacy of lithium and carbamazepine in the prophylaxis of bipolar disorder: results of the MAP study. *Neuropsychobiology* 2000; 42 (suppl 1): 2–10.
3. Vasudev K, *et al.* Carbamazepine and valproate monotherapy: feasibility, relative safety and efficacy, and therapeutic drug monitoring in manic disorder. *Psychopharmacology (Berl)* 2000; 150: 15–23.
4. Denicoff KD, *et al.* Comparative prophylactic efficacy of lithium, carbamazepine, and the combination in bipolar disorder. *J Clin Psychiatry* 1997; 58: 470–8.
5. Ferrier IN. Developments in mood stabilisers. *Br Med Bull* 2001; 57: 179–92.
6. Stoner SC, *et al.* Historical review of carbamazepine for the treatment of bipolar disorder. *Pharmacotherapy* 2007; 27: 68–88.
7. Ceron-Litvoc D, *et al.* Comparison of carbamazepine and lithium in treatment of bipolar disorder: a systematic review of randomized controlled trials. *Hum Psychopharmacol* 2009; 24: 19–28.

Depression. Carbamazepine has been tried[1-4] for the augmentation of antidepressant therapy in the treatment of resistant depression (p. 398.1). However, such combined therapy may lead to interactions—see also Antidepressants, under Interactions, p. 516.2.

1. De la Fuente JM, Mendlewicz J. Carbamazepine addition in tricyclic antidepressant-resistant unipolar depression. *Biol Psychiatry* 1992; 32: 369–74.
2. Otani K, *et al.* Carbamazepine augmentation therapy in three patients with trazodone-resistant depression. *Int Clin Psychopharmacol* 1996; 11: 55–7.
3. Ciusani E, *et al.* Combination therapy with venlafaxine and carbamazepine in depressive patients not responding to venlafaxine: pharmacokinetic and clinical aspects. *J Psychopharmacol* 2004; 18: 559–66.
4. Zhang Z-J, *et al.* The effectiveness of carbamazepine in unipolar depression: a double-blind, randomized, placebo-controlled study. *J Affect Disord* 2008; 109: 91–7.

Diabetes insipidus. Cranial diabetes insipidus (p. 2348.2) is usually treated by replacement therapy with antidiuretic hormone (ADH) in the form of desmopressin. Carbamazepine is one of a variety of other drugs that have been tried to promote ADH secretion, although some consider that it is usually ineffective and has unwanted effects.[1,2] Oral doses of 200 to 600 mg daily have been given. See also Effects on Electrolytes, under Adverse Effects, p. 514.2.

1. Seckl J, Dunger D. Postoperative diabetes insipidus. *BMJ* 1989; 298: 2–3.
2. Singer I, *et al.* The management of diabetes insipidus in adults. *Arch Intern Med* 1997; 157: 1293–1301.

Epilepsy. Carbamazepine is one of the drugs of choice for partial seizures with or without secondary generalisation (p. 506.1). It has been used for generalised tonic-clonic seizures (although valproate is the drug of choice where these occur in primary generalised epilepsy), but it may exacerbate absence and myoclonic seizures.

Hemifacial spasm. Carbamazepine has been reported to have been of help in the treatment of hemifacial spasm (p. 2018.3).

Hiccup. For the management of intractable hiccups see under Chlorpromazine, p. 1046.3. Carbamazepine may be of value for the treatment of neurogenic hiccups such as those that occur in multiple sclerosis.[1] Carbamazepine has also been reported to have been of benefit in 3 patients with diaphragmatic flutter,[2] a rare disorder associated with involuntary contractions of the diaphragm.

1. McFarling DA, Susac JO. Hoquet diabolique: intractable hiccups as a manifestation of multiple sclerosis. *Neurology* 1979; 29: 797–801.
2. Vantrappen G, *et al.* High-frequency diaphragmatic flutter: symptoms and treatment by carbamazepine. *Lancet* 1992; 339: 265–7.

Hyperactivity. When drugs are indicated for attention deficit hyperactivity disorder (p. 2314.1) initial treatment is usually with a central stimulant but meta-analysis of a small number of studies has provided evidence that carbamazepine may be effective.[1]

1. Silva RR, *et al.* Carbamazepine use in children and adolescents with features of attention-deficit hyperactivity disorder: a meta-analysis. *J Am Acad Child Adolesc Psychiatry* 1996; 35: 352–8.

Lesch-Nyhan syndrome. The severe self-mutilation that occurs in patients with Lesch-Nyhan syndrome (p. 1047.1) has been reported to improve in those given antiepileptics such as carbamazepine.[1]

1. Roach ES, *et al.* Carbamazepine trial for Lesch-Nyhan self-mutilation. *J Child Neurol* 1996; 11: 476–8.

Movement disorders. Carbamazepine is one of many drugs that have been tried in the symptomatic treatment of *chorea* (p. 1029.3); there have been anecdotal reports of benefit in both non-hereditary[1,2] and hereditary choreas.[3] Carbamazepine is also among the drugs that have been tried in the treatment of *dystonias* (p. 903.3) that have not responded to levodopa or antimuscarinics. Although some patients may benefit from carbamazepine, it is not generally recommended because of a relatively low success rate and the possibility of adverse effects.[4] Carbamazepine therapy has also been associated with movement disorders—see Effects on the Nervous System: Extrapyramidal Effects, under Adverse Effects, p. 515.1.

Carbamazepine has also been used in resistant cases of *tardive dyskinesia* (see under Extrapyramidal Disorders, p. 1049.2).

1. Roig M, *et al.* Carbamazepine: an alternative drug for the treatment of nonhereditary chorea. *Pediatrics* 1988; 82: 492–5.
2. García González MM, *et al.* Corea de Sydenham: presentación de un caso tratado con carbamazepina con excelente respuesta clínica. *An Pediatr (Barc)* 2007; 66: 80–3.
3. Roulet E, Deonna T. Successful treatment of hereditary dominant chorea with carbamazepine. *Pediatrics* 1989; 83: 1077.
4. Anonymous. Dystonia: underdiagnosed and undertreated? *Drug Ther Bull* 1988; 26: 33–6.

Neonatal seizures. Carbamazepine has been tried in the management of neonatal seizures (p. 511.3).

Neuropathic pain. As well as being used to ease the pain of trigeminal neuralgia (see below) carbamazepine may be of use in other neuropathic pain including that associated with diabetic neuropathy (p. 8.2). A systematic review[1] concluded that about two-fifths of patients who take carbamazepine for neuropathic pain will achieve moderate pain relief, but this was based on small studies. The authors found no evidence that carbamazepine was effective for acute pain.

Carbamazepine has also been tried in an attempt to prevent the painful sensory neuropathy associated with oxaliplatin treatment (see Effects on the Nervous System, p. 838.3); results of small studies have been conflicting.[2-4]

1. Wiffen PJ, *et al.* Carbamazepine for acute and chronic pain in adults. Available in the Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 09/06/08).
2. Eckel F, *et al.* Prophylaxe der Oxaliplatin-induzierten Neuropathie mit Carbamazepin: eine Pilotstudie. *Dtsch Med Wochenschr* 2002; 127: 78–82.
3. Wilson RH, *et al.* Acute oxaliplatin-induced peripheral nerve hyperexcitability. *J Clin Oncol* 2002; 20: 1767–74.
4. von Delius S, *et al.* Carbamazepine for prevention of oxaliplatin-related neurotoxicity in patients with advanced colorectal cancer: final results of a randomised, controlled, multicenter phase II study. *Invest New Drugs* 2007; 25: 173–80.

Nocturnal enuresis. Carbamazepine has been reported to be of benefit in the treatment of primary nocturnal enuresis; a dose of 200 mg at night for 15 nights markedly decreased the frequency of bed-wetting episodes in 8 children.[1]

For the conventional management of nocturnal enuresis see p. 2349.1.

1. Al-Waili NS, *et al.* Effect of carbamazepine on urinary volume and osmolality, water clearance, and serum osmolality in patients with primary enuresis. *Eur Urol* 2006; 50: 844–9.

Psychiatric disorders. Carbamazepine has psychotropic properties and has been tried in the management of several psychiatric disorders, particularly in patients with *bipolar disorder* (see above). Carbamazepine has also been used with mixed results in various disorders for the control of symptoms such as agitation, aggression, and rage[1-4] (see Disturbed Behaviour, p. 1030.2). It may produce modest benefit when used as an adjunct to antipsychotics in the *management of refractory schizophrenia* (p. 1031.3) but any improvement appears to be related to its mood stabilising effect.[5] However, a more recent systematic review,[6] albeit based on small studies, found carbamazepine to have no significant benefit either as monotherapy or as an adjunct to antipsychotics; the authors considered that further randomised studies may be warranted. Carbamazepine also has the potential to reduce serum concentrations of antipsychotics, resulting in clinical deterioration (see under Interactions of Chlorpromazine, p. 1052.2). Carbamazepine has also been tried[7] in *post-traumatic stress disorder* (p. 1029.2).

1. Mattes JA. Comparative effectiveness of carbamazepine and propranolol for rage outbursts. *J Neuropsychiatr Clin Neurosci* 1990; 2: 159–64.
2. Gleason RP, Schneider LS. Carbamazepine treatment of agitation in Alzheimer's outpatients refractory to neuroleptics. *J Clin Psychiatry* 1990; 51: 115–18.
3. Tariot PN, *et al.* Efficacy and tolerability of carbamazepine for agitation and aggression in dementia. *Am J Psychiatry* 1998; 155: 54–61.
4. Cueva JE, *et al.* Carbamazepine in aggressive children with conduct disorder: a double-blind and placebo-controlled study. *J Am Acad Child Adolesc Psychiatry* 1996; 35: 480–90.
5. Okuma T. Use of antiepileptic drugs in schizophrenia: a review of efficacy and tolerability. *CNS Drugs* 1994; 1: 269–84.
6. Leucht S, *et al.* Carbamazepine for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 09/06/08).
7. Wolf ME, *et al.* Posttraumatic stress disorder in Vietnam veterans: clinical and EEG findings: possible therapeutic effects of carbamazepine. *Biol Psychiatry* 1988; 23: 642–4.

Restless legs syndrome. The aetiology of restless legs syndrome (see Sleep-associated Movement Disorders, p. 1034.2) is obscure and treatment has been largely empirical. In a double-blind study involving 174 patients carbamazepine appeared to be more effective than placebo.[1] Oxcarbazepine has been reported[2] to be of benefit in restless legs syndrome induced by paroxetine.

1. Telstad W, *et al.* Treatment of the restless legs syndrome with carbamazepine: a double blind study. *BMJ* 1984; 288: 444–6.
2. Öztürk Ö, *et al.* Oxcarbazepine treatment for paroxetine-induced restless leg syndrome. *Gen Hosp Psychiatry* 2006; 28: 264–5.

Tinnitus. Treatment of tinnitus (p. 1994.1) is difficult, and many drugs have been tried. Although carbamazepine has been reported to be effective in some patients, it is rarely used because of its adverse effects.

Trigeminal neuralgia. Carbamazepine is the drug of choice in the treatment of the acute stages of trigeminal neuralgia (p. 11.2). Satisfactory pain relief may be achieved in 70% or more of patients, although increasingly larger doses may be required and adverse effects can be troublesome.

Although not licensed in the UK for trigeminal neuralgia in children, the *BNFC* suggests that carbamazepine may be tried in doses similar to those used for the treatment of epilepsy (see Administration in Children, above).

Withdrawal syndromes. Carbamazepine has been tried in the prophylaxis and treatment of various withdrawal syndromes. Reduction in *cocaine use* associated with carbamazepine treatment was found in one short-term controlled study,[1] although a systematic review[2] of data from later studies concluded that there was no evidence to support the use of antiepileptics, including carbamazepine, in the treatment of cocaine dependence (p. 1990.1). It has been reported[3,4] to be of benefit in some patients during *benzodiazepine withdrawal* but such adjunct therapy is not usually indicated (see p. 1065.1). Carbamazepine has been shown[5,6] to be effective in the treatment of symptoms of the *alcohol withdrawal syndrome* (p. 1735.1) but as there are limited data on its efficacy in preventing associated delirium tremens and seizures it is usually recommended that it should only be used as an adjunct to benzodiazepine therapy. Carbamazepine has also been studied[7] as an aid in the treatment of alcohol dependence.

1. Halikas JA, *et al.* Cocaine reduction in unmotivated crack users using carbamazepine versus placebo in a short-term, double-blind crossover design. *Clin Pharmacol Ther* 1991; 50: 81–95.

2. Minozzi S, *et al.* Anticonvulsants for cocaine dependence. Available in The Cochrane Database of Systematic Reviews: Issue 2. Chichester: John Wiley; 2008 (accessed 24/07/09).
3. Schweizer E, *et al.* Carbamazepine treatment in patients discontinuing long-term benzodiazepine therapy: effects on withdrawal severity and outcome. *Arch Gen Psychiatry* 1991; **48:** 448–52.
4. Klein E, *et al.* Alprazolam withdrawal in patients with panic disorder and generalized anxiety disorder: vulnerability and effect of carbamazepine. *Am J Psychiatry* 1994; **151:** 1760–6.
5. Malcolm R, *et al.* Double-blind controlled trial comparing carbamazepine to oxazepam treatment of alcohol withdrawal. *Am J Psychiatry* 1989; **146:** 617–21.
6. Stuppaeck CH, *et al.* Carbamazepine versus oxazepam in the treatment of alcohol withdrawal: a double-blind study. *Alcohol Alcohol* 1992; **27:** 153–8.
7. Mueller TI, *et al.* A double-blind, placebo-controlled pilot study of carbamazepine for the treatment of alcohol dependence. *Alcohol Clin Exp Res* 1997; **21:** 86–92.

Adverse Effects

Fairly common adverse effects of carbamazepine, particularly in the initial stages of therapy, include dizziness, drowsiness, and ataxia. Gastrointestinal disturbances, such as nausea and vomiting, and mild skin reactions are also common. These effects may be minimised by starting therapy with a low dose. Drowsiness and disturbances of cerebellar and oculo-motor function (with ataxia, nystagmus, and diplopia) are also symptoms of excessive plasma concentrations of carbamazepine, and may disappear spontaneously with continued treatment or at reduced or divided dosage.

Although rare, generalised erythematous rashes can be severe and treatment may have to be withdrawn. Photosensitivity reactions, urticaria, alopecia, exfoliative dermatitis, toxic epidermal necrolysis, erythema multiforme and Stevens-Johnson syndrome, and SLE (but see p. 515.2) have also been reported.

Transient leucopenia is common and usually resolves with continued therapy; however, rarer blood disorders reported include agranulocytosis, aplastic anaemia, eosinophilia, persistent leucopenia, leucocytosis, thrombocytopenia, and purpura. Lymphadenopathy, splenomegaly, pneumonitis, abnormalities of liver and kidney function, hepatitis, and cholestatic jaundice have occurred. Some or all of these symptoms as well as fever and rashes may represent a generalised hypersensitivity reaction to carbamazepine.

Gastrointestinal symptoms reported to be less common include dry mouth, abdominal pain, anorexia, and diarrhoea or constipation. Hyponatraemia, and sometimes oedema, have occurred. Other adverse effects reported include paraesthesia, headache, arrhythmias and heart block, heart failure, impotence, male infertility, gynaecomastia, galactorrhoea, and dystonias and dyskinesias with asterixis. Rectal use has resulted in local irritation.

Overdosage may be manifested by many of the adverse effects listed above, especially those on the CNS, and may result in stupor, coma, convulsions, respiratory depression, and death.

In rare cases, carbamazepine has been reported to exacerbate seizures in patients suffering from mixed-type epilepsy—see Precautions, p. 515.3.

Congenital malformations have been reported in infants born to women given carbamazepine during pregnancy.

Effects on the blood. Occasional reports of fatal haematological reactions associated with carbamazepine led the manufacturers to recommend extensive blood monitoring during therapy. However, because of the rarity of such reactions these recommendations were questioned and the manufacturers subsequently modified their guidelines (see Precautions, p. 515.3).

Case reports and studies of carbamazepine's haematological effects have been reviewed.[1] The incidence of haematological reactions to carbamazepine has been estimated to range between 1:10 800 and 1:38 000 per year while one group reported the rate of bone marrow suppression to be between 1:10 000 and 1:50 000 cases. The incidence of aplastic anaemia has been calculated to be 1:200 000 per year. Another investigator indicated that 2.2 deaths per million exposures were associated with aplastic anaemia and agranulocytosis. However, of 27 reports of aplastic anaemia (16 fatal) associated with carbamazepine many were found to have had co-incidental disease or were receiving multiple-drug therapy. Benign or clinically insignificant leucopenia has occurred, usually during the first 3 months of treatment, in about 12% of children and 7% of adults but in most patients this resolved despite continuation of therapy. Mild transient thrombocytopenia has occurred in about 2% of patients; transient eosinophilia has also occurred.

The reviewers[1] suggested that all patients should have blood and platelet counts before treatment. Patients with low white cell and neutrophil counts were at risk of developing leucopenia and should be monitored every 2 weeks for the first 1 to 3 months. If counts fell further the dose should be reduced or treatment stopped. It should be noted that the *BNF* doubts the practical value of routine monitoring: in particular, aplastic anaemia, agranulocytosis, and thrombocytopenia have a rapid onset and are best monitored by instructing the patient to report warning symptoms (see Precautions, p. 515.3).

For a discussion of the effects of antiepileptics, including carbamazepine, on serum folate, see Folic Acid Deficiency, under Phenytoin, p. 540.2.

1. Sobotka JL, *et al.* A review of carbamazepine's hematologic reactions and monitoring recommendations. *DICP Ann Pharmacother* 1990; **24:** 1214–19.

Effects on bone. For the effects of antiepileptics including carbamazepine on bone and on calcium and vitamin D metabolism, see under Phenytoin, p. 540.2.

Effects on electrolytes. There have been reports of *hyponatraemia* or *water intoxication* in patients receiving carbamazepine.[1-7] One review[8] states that although hyponatraemia occurs in 10 to 15% of patients taking carbamazepine, it is seldom symptomatic or severe enough to cause fluid retention. However, care should be taken to distinguish the confusion, dizziness, nausea and headache of water intoxication from the central and gastrointestinal effects of the drug.[2] The mechanism is uncertain; although some studies suggest an increase in secretion of antidiuretic hormone in subjects given carbamazepine,[3,4,6] others indicate the reverse,[5,9] and the fact that the hyponatraemic effects of carbamazepine can be partly reversed by demeclocycline[5] is cited as evidence for an effect on the kidney, either directly upon the distal tubule or by increasing sensitivity to the effects of antidiuretic hormone. Risk factors for developing carbamazepine-induced hyponatraemia include age of over 40 years, use of sodium-depleting drugs, and low pre-treatment plasma-sodium concentrations; it is unclear whether this adverse effect is dose-related.[7]

1. Henry DA, *et al.* Hyponatraemia during carbamazepine treatment. *BMJ* 1977; **1:** 83–4.
2. Stephens WP, *et al.* Water intoxication due to carbamazepine. *BMJ* 1977; **1:** 754–5.
3. Ashton MG, *et al.* Water intoxication associated with carbamazepine treatment. *BMJ* 1977; **1:** 1134–5.
4. Smith NJ, *et al.* Raised plasma arginine vasopressin concentration in carbamazepine-induced water intoxication. *BMJ* 1977; **2:** 804.
5. Ballardie FW, Mucklow JC. Partial reversal of carbamazepine-induced water intolerance by demeclocycline. *Br J Clin Pharmacol* 1984; **17:** 763–5.
6. Sørensen PS, Hammer M. Effects of long-term carbamazepine treatment on water metabolism and plasma vasopressin concentration. *Eur J Clin Pharmacol* 1984; **26:** 719–22.
7. Kuz GM, Manssourian A. Carbamazepine-induced hyponatremia: assessment of risk factors. *Ann Pharmacother* 2005; **39:** 1943–6.
8. Mucklow J. Selected side-effects 2: carbamazepine and hyponatraemia. *Prescribers' J* 1991; **31:** 61–4.
9. Stephens WP, *et al.* Plasma arginine vasopressin concentrations and antidiuretic action of carbamazepine. *BMJ* 1978; **1:** 1445–7.

Effects on the endocrine system. Carbamazepine may reduce serum concentrations of *thyroid* hormones through enzyme induction—see under Interactions of Levothyroxine, p. 2341.3.

For mention of the effects of antiepileptics on *sexual function* in male epileptic patients, see under Phenytoin, p. 540.3.

Effects on the eyes. On rare occasions lenticular opacities have been associated with carbamazepine.[1] Retinotoxicity associated with long-term carbamazepine use has been reported[2] in 2 patients. After stopping the drug visual function and retinal morphological changes improved. A review[3] of the effect of antiepileptics on the eyes noted that despite reports of colour vision disturbances and impaired contrast sensitivity associated with carbamazepine therapy, studies in healthy subjects had shown conflicting results.

1. Anonymous. Adverse ocular effects of systemic drugs. *Med Lett Drugs Ther* 1976; **18:** 63–4.
2. Nielsen NV, Syvertsen K. Possible retinotoxic effect of carbamazepine. *Acta Ophthalmol (Copenh)* 1986; **64:** 287–90.
3. Hilton EJR, *et al.* The effect of antiepileptic drugs on visual performance. *Seizure* 2004; **13:** 113–28.

Effects on the heart. A review[1] of reports of cardiac effects associated with carbamazepine revealed that patients could be divided into 2 distinct groups based on their symptoms. One group consisted mainly of young patients with non life-threatening sinus tachycardia after carbamazepine overdosage while the other group was composed of older female patients with potentially life-threatening bradycardia or AV block associated with therapeutic or modestly raised blood concentrations of carbamazepine. However, there has been a report of fatal syncope, probably due to ventricular asystole, in a 20-year-old patient.[2] Carbamazepine should be avoided in patients who develop conduction abnormalities, or who have conditions such as myotonic dystrophy in which conduction abnormalities are likely.[1]

Elevation of ventricular and atrial stimulation thresholds was reported in a 59-year-old man with a permanent dual-chamber pacemaker, 5 days after starting carbamazepine for mania.[3]

For a report of carbamazepine producing fatal eosinophilic myocarditis, see under Hypersensitivity, p. 515.1.

1. Kasarkis EJ, *et al.* Carbamazepine-induced cardiac dysfunction: characterization of two distinct clinical syndromes. *Arch Intern Med* 1992; **152:** 186–91.
2. Stone S, Lange LS. Syncope and sudden unexpected death attributed to carbamazepine in a 20-year-old epileptic. *J Neurol Neurosurg Psychiatry* 1986; **49:** 1460–1.
3. Ambrosi P, *et al.* Carbamazepine and pacing threshold. *Lancet* 1993; **342:** 365.

Effects on the immune system. There have been reports of hypogammaglobulinaemia associated with carbamazepine.[1-4] The authors of one report[2] stated that this was a recognised but rare adverse effect of carbamazepine and noted that the UK CSM had 9 reports on file of hypogammaglobulinaemia or gammaglobulin abnormalities related to the use of carbamazepine.

1. Moschione Castro APB, *et al.* Secondary hypogammaglobulinemia after use of carbamazepine: case report and review. *Rev Hosp Clin Fac Med Sao Paulo* 2001; **56:** 189–92.
2. Hayman G, Bansal A. Antibody deficiency associated with carbamazepine. *BMJ* 2002; **325:** 1213.
3. Rice CM, *et al.* Recurrent herpes simplex virus encephalitis secondary to carbamazepine induced hypogammaglobulinaemia. *J Neurol Neurosurg Psychiatry* 2007; **78:** 1011–12.
4. Tamada T, *et al.* Secondary bronchiolitis obliterans organising pneumonia in a patient with carbamazepine-induced hypogammaglobulinemia. *Thorax* 2007; **62:** 100.

Effects on the liver. A report in 1990 commented that of 499 reports of unwanted effects of carbamazepine on the liver about half comprised only abnormal results from liver function tests;[1] however, deaths have occurred from liver failure[1,2] or hepatic necrosis.[3] Reversible vanishing bile duct syndrome has been associated with long-term use of carbamazepine.[4]

Hepatotoxicity may form part of the antiepileptic hypersensitivity syndrome reported with carbamazepine (see p. 515.1).

1. Hadžić N, *et al.* Acute liver failure induced by carbamazepine. *Arch Dis Child* 1990; **65:** 315–17.
2. Zucker P, *et al.* Fatal carbamazepine hepatitis. *J Pediatr* 1977; **91:** 667–8.
3. Smith DW, *et al.* Fatal hepatic necrosis associated with multiple anticonvulsant therapy. *Aust N Z J Med* 1988; **18:** 575–81.
4. Ramos AMO, *et al.* Reversible vanishing bile duct syndrome induced by carbamazepine. *Eur J Gastroenterol Hepatol* 2002; **14:** 1019–22.

Effects on mental function. Carbamazepine therapy has been associated in a few patients with the development of acute psychotic and paranoid symptoms[1-3] and with phobias[2] and mood disturbances, including mania[4] and melancholia.[5] One case of acute paranoid psychosis was associated with the addition of carbamazepine to long-term sodium valproate therapy in a patient subsequently diagnosed as having a schizotypal personality.[3] For nonconvulsive status epilepticus associated with carbamazepine presenting as psychiatric disorders, see under Effects on the Nervous System, p. 515.1. The problems of antiepileptic therapy adversely affecting cognition and the risk of mood disorders, including suicidal ideation, are discussed on p. 508.3.

1. Berger H. An unusual manifestation of Tegretol(carbamazepine) toxicity. *Ann Intern Med* 1971; **74:** 449–50.
2. Mathew G. Psychiatric symptoms associated with carbamazepine. *BMJ* 1988; **296:** 1071.
3. McKee RJW, *et al.* Acute psychosis with carbamazepine and sodium valproate. *Lancet* 1989; **i:** 167.
4. Reiss AL, O'Donnell DJ. Carbamazepine-induced mania in two children: case report. *J Clin Psychiatry* 1984; **45:** 272–4.
5. Gardner DL, Cowdry RW. Development of melancholia during carbamazepine treatment in borderline personality disorder. *J Clin Psychopharmacol* 1986; **6:** 236–9.

Effects on the nervous system. *ASEPTIC MENINGITIS.* Aseptic meningitis has developed in a patient with Sjögren's syndrome given carbamazepine. It abated when the drug was withdrawn and symptoms recurred on rechallenge. Aseptic meningitis has also been associated with carbamazepine in patients without Sjögren's syndrome.[2-4]

1. Hilton E, Stroh EM. Aseptic meningitis associated with administration of carbamazepine. *J Infect Dis* 1989; **159:** 363–4.
2. Simon LT, *et al.* Carbamazepine-induced aseptic meningitis. *Ann Intern Med* 1990; **112:** 627–8.
3. Hemet C, *et al.* Aseptic meningitis secondary to carbamazepine treatment of manic-depressive illness. *Am J Psychiatry* 1994; **151:** 1393.
4. Dang CT, Riley DK. Aseptic meningitis secondary to carbamazepine therapy. *Clin Infect Dis* 1996; **22:** 729–30.

ENCEPHALOPATHY. Carbamazepine-induced encephalopathy with symptoms resembling Creutzfeldt-Jakob disease was reported in a 71-year-old man; the cognitive decline, bradykinesia, tremor, and abnormal EEG improved on stopping carbamazepine.[1] In another report,[2] carbamazepine use was associated with the development of hyperammonaemia and associated behavioural changes on 2 occasions.

1. Horvath J, *et al.* Carbamazepine encephalopathy masquerading as Creutzfeldt-Jakob disease. *Neurology* 2005; **65:** 650–1.
2. Adams EN, *et al.* Carbamazepine-induced hyperammonemia. *Am J Health-Syst Pharm* 2009; **66:** 1468–70.

EXTRAPYRAMIDAL EFFECTS. Although carbamazepine has been associated with extrapyramidal adverse effects,[1-4] it has also been tried in the treatment of movement disorders—see under Uses and Administration, p. 513.2.

1. Schwartzman MJ, Leppik IE. Carbamazepine-induced dyskinesia and ophthalmoplegia. *Cleve Clin J Med* 1990; 57: 367–72.
2. Soman P, *et al.* Dystonia—a rare manifestation of carbamazepine toxicity. *Postgrad Med J* 1994; 70: 54–5.
3. Lee JW. Persistent dystonia associated with carbamazepine therapy: a case report. *N Z Med J* 1994; 107: 360–1.
4. Stryjer R, *et al.* Segmental dystonia as the sole manifestation of carbamazepine toxicity. *Gen Hosp Psychiatry* 2002; 24: 114–15.

STATUS EPILEPTICUS. Nonconvulsive status epilepticus, misdiagnosed as behavioural and psychiatric disorders, was reported[1] to have been precipitated by carbamazepine in 2 patients; seizure control and behaviour improved when carbamazepine was stopped and replaced with valproate.

1. Marini C, *et al.* Nonconvulsive status epilepticus precipitated by carbamazepine presenting as dissociative and affective disorders in adolescents. *J Child Neurol* 2005; 20: 693–6.

Effects on the skin. Rashes occurring with carbamazepine may form part of an antiepileptic hypersensitivity syndrome (see below). In a report,[1] erythema multiforme occurred when a generic formulation was given instead of a proprietary brand of carbamazepine. Skin lesions resolved when the patient stopped taking the generic formulation and did not recur when the proprietary brand was restarted. In another report, a 6-year-old boy developed Stevens-Johnson syndrome 5 weeks after carbamazepine was added to valproic acid, which he had been taking as sole antiepileptic therapy for several weeks.[2] Carbamazepine was stopped and the patient eventually made a full recovery; valproic acid was continued because it was not thought to be the causative agent (but see under Valproate, p. 556.1). Fatal toxic epidermal necrolysis has been seen when carbamazepine was given to a patient who had previously had Stevens-Johnson syndrome during carbamazepine treatment.[3] Pseudo mycosis fungoides with lymphoid cell infiltration of the dermis and raised liver enzymes has been reported[4] in a 54-year-old man who was taking carbamazepine for seizures; symptoms resolved within about 2 weeks of stopping therapy.

For a warning that severe skin reactions may be more likely in patients of certain genotypes, see Skin Reactions, under Precautions, p. 516.1. For the relative incidence of skin reactions to different antiepileptics, see under Phenytoin, p. 541.1.

1. Busch RL. Generic carbamazepine and erythema multiforme: generic-drug nonequivalency. *N Engl J Med* 1989; 321: 692–3.
2. Keating A, Blahunka P. Carbamazepine-induced Stevens-Johnson syndrome in a child. *Ann Pharmacother* 1995; 29: 538–9.
3. Huang L-Y, *et al.* Fatal toxic epidermal necrolysis induced by carbamazepine treatment in a patient who previously had carbamazepine-induced Stevens-Johnson syndrome. *J Formos Med Assoc* 2007; 106: 1032–7.
4. Gül Ü, *et al.* Carbamazepine-induced pseudo mycosis fungoides. *Ann Pharmacother* 2003; 37: 1441–3.

Hypersensitivity. An antiepileptic hypersensitivity syndrome, comprising fever, rash, and lymphadenopathy and less commonly hepatosplenomegaly and eosinophilia, has been associated with some antiepileptic drugs including carbamazepine.[1-3] Although a literature search[1] was only able to find 20 published cases to 1986, 22 cases had been reported to the Australian Adverse Drug Reactions Advisory Committee between 1975 and 1990. Some have estimated the incidence at 1 in 1000 to 1 in 10 000 new exposures to aromatic anticonvulsants,[2,3] but the true incidence is uncertain due to variations in presentation and reporting. Most reactions occurred within 30 days of the start of carbamazepine treatment,[1] although symptoms may occur anywhere between 1 and 8 weeks after exposure.[2] In previously sensitised individuals the reactions may occur within 1 day of rechallenge. The potential for cross-reactivity between carbamazepine, phenobarbital, and phenytoin is about 75%, and patients who develop the syndrome, and their close relatives, should be warned of the risk associated with use of these antiepileptics.[2] Suspected cross-sensitivity between carbamazepine and lamotrigine has also been reported in a patient.[4]

Carbamazepine antibodies were detected in an 8-year-old child who developed symptoms of serum sickness including fever, skin rash, oedema, and lymphadenopathy during treatment with carbamazepine.[5] Hypersensitivity to carbamazepine with multisystem effects clinically resembling a mononucleosis syndrome was reported in a 15-year-old boy 2 weeks after starting monotherapy with carbamazepine;[6] all symptoms resolved on stopping carbamazepine and giving prednisone. There have been other cases[7-9] of an infectious mononucleosis syndrome associated with hypersensitivity to carbamazepine, leading the authors to suggest that reactivation of human herpesvirus 6 or 7 infection is a cofactor and an early manifestation of carbamazepine hypersensitivity syndrome; however, further studies are warranted.

A hypersensitivity reaction producing fatal eosinophilic myocarditis has been reported in a 13-year-old patient; initial symptoms mimicked scarlet fever.[10] A 21-year-old woman developed fatal fulminant hepatic failure after taking carbamazepine for about 2 months; she had presented with initial symptoms of fever, breathlessness, bloody diarrhoea, and a spreading rash.[11]

Generalised erythroderma with renal, hepatic, and bone-marrow failure (characterised by hypercellularity and dyserythropoiesis) has been reported[12] in an 81-year-old man 50 days after starting carbamazepine therapy. Symptoms recurred following an inadvertent rechallenge. The presence of underlying lymphoproliferative disease may have potentiated the severe drug-induced reaction.

If the antiepileptic hypersensitivity syndrome develops, immediate withdrawal of carbamazepine is recommended. In most cases this is all that is required and does not seem to predipitate an increase in seizures, compared with gradual withdrawal.[13]

Successful desensitisation to carbamazepine was reported[14] in a 12-year-old boy who was sensitive to carbamazepine, sodium valproate, and phenytoin. Starting with a low dose of carbamazepine 100 micrograms daily the dose was doubled, generally every 2 days, up to 100 mg daily. The dose was then gradually increased over 4 weeks to a maintenance dose of 200 mg twice daily. The same technique was used to desensitise 7 patients, all of whom developed dramatic skin rashes when first exposed to carbamazepine.[15] Carbamazepine therapy in full doses was achieved without problem in about 6 weeks. Some[2] consider that desensitisation is not to be recommended in patients with full-blown antiepileptic hypersensitivity syndrome.

1. Anonymous. Anticonvulsants and lymphadenopathy. *WHO Drug Inf* 1991; 5: 11.
2. Knowles SR, *et al.* Anticonvulsant hypersensitivity syndrome: incidence, prevention and management. *Drug Safety* 1999; 21: 489–501.
3. Bessmertny O, *et al.* Antiepileptic hypersensitivity syndrome in children. *Ann Pharmacother* 2001; 35: 533–8.
4. Aouam K, *et al.* Hypersensitivity syndrome induced by anticonvulsants: possible cross-reactivity between carbamazepine and lamotrigine. *J Clin Pharmacol* 2009; 49: 1488–91.
5. Hosoda N, *et al.* Anticarbamazepine antibody induced by carbamazepine in a patient with severe serum sickness. *Arch Dis Child* 1991; 66: 722–3.
6. Merino N, *et al.* Multisystem hypersensitivity reaction to carbamazepine. *Ann Pharmacother* 1994; 28: 402–3.
7. Zeller A, *et al.* Drug hypersensitivity syndrome to carbamazepine and human herpes virus 6 infection: case report and literature review. *Infection* 2003; 31: 254–6.
8. Alhara Y, *et al.* Carbamazepine-induced hypersensitivity syndrome associated with transient hypogammaglobulinaemia and reactivation of human herpesvirus 6 infection demonstrated by real-time quantitative polymerase chain reaction. *Br J Dermatol* 2003; 149: 165–9.
9. Oskay T, *et al.* Association of anticonvulsant hypersensitivity syndrome with Herpesvirus 6, 7. *Epilepsy Res* 2006; 70: 27–40.
10. Salzman MB, *et al.* Carbamazepine and fatal eosinophilic myocarditis. *N Engl J Med* 1997; 336: 878–9.
11. Syu W-K, *et al.* Carbamazepine-induced acute liver failure as part of the DRESS syndrome. *Int J Clin Pract* 2005; 59: 988–91. Correction. *ibid.*; 1371.
12. Lombardi SM, *et al.* Severe multisystemic hypersensitivity reaction to carbamazepine including dyserythropoietic anemia. *Ann Pharmacother* 1999; 33: 571–5.
13. Pirmohamed M, *et al.* Hypersensitivity to carbamazepine and lamotrigine: clinical considerations. *Br J Clin Pharmacol* 2000; 49: 519P–520P.
14. Smith H, Newton R. Adverse reactions to carbamazepine managed by desensitisation. *Lancet* 1985; i: 753.
15. Eames P. Adverse reactions to carbamazepine managed by desensitisation. *Lancet* 1989; i: 509–10.

Sudden unexplained death in epilepsy. Sudden unexplained death in epilepsy (SUDEP), a common cause of seizure-related mortality in patients with chronic epilepsy, has been reviewed.[1,2] Risk factors may include early onset of epilepsy, frequent generalised tonic-clonic seizures, intractability, frequent medication changes, and polytherapy. *Carbamazepine* use has also been implicated but the evidence was considered to be tenuous although frequent dose change resulting in plasma-carbamazepine levels outside the therapeutic range was found to be an independent risk factor. Although the FDA in the USA had required data about the specific risk of SUDEP to be included in the prescribing information for the newer antiepileptic drugs *gabapentin, lamotrigine, tiagabine, topiramate,* and *zonisamide,* some commentators[3] consider that none of these antiepileptics have shown an associated change in the risk of SUDEP. It has been suggested[2,3] that the incidence of SUDEP is related to the disease rather than a specific drug effect.

1. Walczak T. Do antiepileptic drugs play a role in sudden unexpected death in epilepsy? *Drug Safety* 2003; 26: 673–83.
2. Nashef L, *et al.* Risk factors in sudden death in epilepsy (SUDEP): the quest for mechanisms. *Epilepsia* 2007; 48: 859–71.
3. Lathers CM, Schraeder PL. Clinical pharmacology: drugs as a benefit and/or risk in sudden unexpected death in epilepsy? *J Clin Pharmacol* 2002; 42: 123–36.

Systemic lupus erythematosus. A review[1] of 80 cases of SLE-like syndromes associated with carbamazepine that had been reported to the manufacturer suggested that the frequency of reports (less than 0.001%) was below that for idiopathic lupus. There have been subsequent reports[2-4] of late-onset SLE occurring after up to 8 years of carbamazepine therapy without previous adverse effects. The symptoms due to carbamazepine usually resolved on stopping treatment.

1. Jain KK. Systemic lupus erythematosus (SLE)-like syndromes associated with carbamazepine therapy. *Drug Safety* 1991; 6: 350–60.
2. Toepfer M, *et al.* Drug-induced systemic lupus erythematosus after 8 years of treatment with carbamazepine. *Eur J Clin Pharmacol* 1998; 54: 193–4.
3. Pelizza L, *et al.* Drug-induced systemic lupus erythematosus after 7 years of treatment with carbamazepine. *Acta Biomed* 2006; 77: 17–19.
4. Amerio P, *et al.* Drug-induced cutaneous lupus erythematosus after 5 years of treatment with carbamazepine. *Eur J Dermatol* 2006; 16: 281–3.

Treatment of Adverse Effects

In the treatment of carbamazepine overdosage repeated doses of activated charcoal may be given orally to adults and children who have ingested more than 20 mg/kg; the aim is not only to prevent absorption but also to aid elimination. Gastric lavage may be considered if undertaken within 1 hour of ingestion. Supportive and symptomatic therapy alone may then suffice, with particular attention to correcting hypoxia and hypotension; haemoperfusion has been suggested for severe poisoning. If there is doubt about the diagnosis, or if multiple-dose oral activated charcoal is being considered, then monitoring plasma-carbamazepine concentration can be useful; it may also help determine when carbamazepine therapy should be restarted. See also Overdosage, below.

Hypersensitivity reactions. For reference to successful desensitisation in patients sensitive to carbamazepine, see Hypersensitivity under Adverse Effects, above.

Overdosage. Carbamazepine poisoning and its management has been reviewed.[1] Management is mainly supportive, with prompt attention to airway management and seizure control. Activated charcoal should be given; although multiple-dose activated charcoal has been recommended for carbamazepine overdosage, care must be taken to protect the airway since carbamazepine inhibits intestinal motility and there is a significant risk of aspiration. In patients with seizures unresponsive to benzodiazepines phenobarbital should be used; phenytoin is not a drug of choice in this situation. Hypotension is rare, and should be managed with fluid and vasopressor support; hypotension with refractory seizures should be treated aggressively as it has led to permanent neurological disability and death.

Haemodialysis or haemoperfusion may be warranted in patients with unstable cardiac status or status epilepticus complicated by bowel hypomotility and unresponsive to more conventional therapy. However, a report[2] of the use of plasmapheresis in the treatment of an acute overdose of carbamazepine concluded that plasmapheresis removed a very small percentage of the total body load of carbamazepine and could not be recommended. As carbamazepine is highly protein-bound, albumin-enhanced continuous venovenous haemodialysis was tried and found to be effective in the treatment of a 10-year-old child after ingestion of 1.4 g of carbamazepine.[3]

1. Spiller HA. Management of carbamazepine overdose. *Pediatr Emerg Care* 2001; 17: 452–6.
2. Kale PB, *et al.* Evaluation of plasmapheresis in the treatment of an acute overdose of carbamazepine. *Ann Pharmacother* 1993; 27: 866–70.
3. Askenazi DJ, *et al.* Management of a severe carbamazepine overdose using albumin-enhanced continuous venovenous hemodialysis. *Pediatrics* 2004; 113: 406–9.

Precautions

Carbamazepine should be avoided in patients with AV conduction abnormalities. It should not be given to patients with a history of bone marrow depression. Carbamazepine should be given with caution to patients with a history of blood disorders or haematological reactions to other drugs, or of cardiac, hepatic, or renal disease. Patients or their carers should be told how to recognise signs of blood, liver, and skin toxicity and they should be advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, bruising, or bleeding develop. Carbamazepine should be withdrawn, if necessary under cover of a suitable alternative antiepileptic, if severe, progressive, or symptomatic leucopenia develops, or if symptoms suggestive of Stevens-Johnson syndrome or toxic epidermal necrolysis occur. Licensed product information recommends blood counts and hepatic and renal-function tests before starting carbamazepine therapy and periodically during treatment, but the *BNF* considers the evidence of practical value unsatisfactory. Clinical monitoring is of primary importance throughout treatment. Some patients of Asian ancestry may be at increased risk of severe skin reactions; for recommendations that such patients' genotype should be tested before beginning carbamazepine, see Skin Reactions, p. 516.1.

Care is required in identifying patients with mixed seizure disorders that include generalised absence or atypical absence seizures, who may be at risk of an increase

in generalised seizures if given carbamazepine. Carbamazepine may also exacerbate absence and myoclonic seizures.

Care is required when withdrawing carbamazepine therapy—see also Uses and Administration, p. 512.3.

Since carbamazepine has mild antimuscarinic properties caution should be observed in patients with glaucoma or raised intra-ocular pressure; scattered punctate lens opacities occur rarely with carbamazepine and it has been suggested that patients should be examined periodically for eye changes.

Abuse. Overdosage requiring hospital admission has been reported after abuse of carbamazepine.[1]

1. Crawford PJ, Fisher BM. Recreational overdosage of carbamazepine in Paisley drug abusers. *Scott Med J* 1997; **42**: 44–5.

Breast feeding. The American Academy of Pediatrics considers[1] that carbamazepine is usually compatible with breast feeding, although there have been reports[2] of transient cholestatic hepatitis in breast-fed infants.

For further comment on antiepileptic therapy and breast feeding, see p. 508.3.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 09/06/08)
2. Frey B, *et al.* Neonatal cholestatic hepatitis from carbamazepine exposure during pregnancy and breast feeding. *Ann Pharmacother* 2002; **36**: 644–7.

Driving. For comment on antiepileptic drugs and driving, see p. 509.2.

Multiple sclerosis. Exacerbation of symptoms of multiple sclerosis has been reported[1] in 5 patients on starting carbamazepine therapy for paroxysmal neurological symptoms and pain. There was a close temporal association between starting carbamazepine and worsening of symptoms, followed by resolution when it was stopped. A 3-year follow-up observational study[2] found that out of 36 multiple sclerosis patients who received carbamazepine therapy, 12 developed neurological adverse effects that mimicked a relapse. The authors concluded that carbamazepine was associated with higher rates of adverse effects and stopping therapy than gabapentin or lamotrigine.

1. Ramsaransing G, *et al.* Worsening of symptoms of multiple sclerosis associated with carbamazepine. *BMJ* 2000; **320**: 1113.
2. Solaro C, *et al.* Antiepileptic medications in multiple sclerosis: adverse effects in a three-year follow-up study. *Neurol Sci* 2005; **25**: 307–10.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies carbamazepine as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pregnancy. For comments on the management of epilepsy during pregnancy, see p. 509.2.

There is an increased risk of neural tube defects in infants exposed *in utero* to antiepileptics including carbamazepine; syndromes such as craniofacial and digital abnormalities and, less commonly, cleft lip and palate have also been described. Exposure to carbamazepine has been calculated to carry a 1% risk of spina bifida.[1] A 'carbamazepine syndrome' characterised by facial dysmorphic features and mild mental retardation has been described;[2] such syndromes are now often seen as aspects of a single 'fetal antiepileptic syndrome'. There is also a risk of neonatal bleeding.

1. Rosa FW. Spina bifida in infants of women treated with carbamazepine during pregnancy. *N Engl J Med* 1991; **324**: 674–7.
2. Ornoy A, Cohen E. Outcome of children born to epileptic mothers treated with carbamazepine during pregnancy. *Arch Dis Child* 1996; **75**: 517–20.

Skin reactions. The FDA has issued a warning[1] that severe and potentially fatal skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis are significantly more common in patients with the HLA allele HLA-B*1502, which occurs almost exclusively in persons of Asian ancestry. They recommend that patients with such ancestry should be screened for the presence of this allele before beginning therapy with carbamazepine, and if present the risks and benefits of therapy should be considered with particular care; those who have already taken carbamazepine for more than a few months without developing skin reactions are, however, at low risk of them ever developing, regardless of genotype. Similar recommendations have since been issued in the UK by the MHRA.[2] See also under Phenytoin, p. 542.1.

1. FDA. Information for healthcare professionals: dangerous or even fatal skin reactions–carbamazepine (marketed as Carbatrol, Equetro, Tegretol, and generics) (issued 12th December, 2007). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124718.htm (accessed 25/08/10)
2. MHRA/CHM. Carbamazepine: genetic testing recommended in some Asian populations. *Drug Safety Update* 2008:1 (9): 5. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON014506&RevisionSelectionMethod=Latest (accessed 09/06/08)

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy.

The metabolism of carbamazepine is reported to be less susceptible to inhibition by other drugs than that of phenytoin but a few drugs are reported to inhibit its metabolism by the cytochrome P450 isoenzyme CYP3A4, resulting in raised plasma concentrations and associated toxicity. Conversely, drugs that induce CYP3A4 may increase the metabolism of carbamazepine, leading to reduced plasma concentrations and potentially a decrease in therapeutic effect. Licensed product information advises that, in such situations, the dose of carbamazepine should be adjusted accordingly and/or the plasma concentrations monitored.

Carbamazepine is itself a hepatic enzyme inducer, and induces its own metabolism as well as that of several other drugs including some antibacterials (notably, doxycycline), anticoagulants, and sex hormones (notably oral contraceptives). Carbamazepine and phenytoin may mutually enhance one another's metabolism. The metabolism of carbamazepine is similarly enhanced by enzyme inducers such as phenobarbital.

General references.

1. Spina E, *et al.* Clinically significant pharmacokinetic drug interactions with carbamazepine: an update. *Clin Pharmacokinet* 1996; **31**: 198–214.

Alcohol. Alcohol may exacerbate the CNS adverse effects of carbamazepine and vice versa.

Analgesics. *Dextropropoxyphene* has been reported to cause substantial elevation of serum-carbamazepine concentrations[1] and carbamazepine toxicity,[1,2] probably due to inhibition of carbamazepine metabolism.[1]

Use of enzyme-inducing antiepileptics such as carbamazepine affects the threshold for use of antidote in the treatment of *paracetamol* poisoning, see p. 118.3.

For the effect of carbamazepine on *methadone*, see p. 90.3, and on *tramadol*, see p. 140.3.

1. Dam M, Christiansen J. Interaction of propoxyphene with carbamazepine. *Lancet* 1977; **ii**: 509.
2. Yu YL, *et al.* Interaction between carbamazepine and dextropropoxyphene. *Postgrad Med J* 1986; **62**: 231–3.

Anthelmintics. For the effect of carbamazepine on *mebendazole* and *praziquantel*, see p. 160.1 and p. 165.2, respectively.

Antibacterials. The antimycobacterial *isoniazid*[1,2] and macrolides[3] such as *clarithromycin, erythromycin,* and *troleandomycin* have been reported to cause substantial elevations of serum concentrations of carbamazepine and symptoms of carbamazepine toxicity. Clarithromycin has also been reported to have caused hyponatraemia when added to carbamazepine therapy in a 30-year-old epileptic woman.[4] *Rifampicin* and isoniazid decreased the serum concentrations of carbamazepine in a 44-year-old woman being treated for bipolar disorder and suspected tuberculosis, resulting in hypomania.[5]

Use of carbamazepine with isoniazid may increase the risk of isoniazid-induced hepatotoxicity.

1. Valsalan VC, Cooper GL. Carbamazepine intoxication caused by interaction with isoniazid. *BMJ* 1982; **285**: 261–2.
2. Wright JM, *et al.* Isoniazid-induced carbamazepine toxicity and vice versa. *N Engl J Med* 1982; **307**: 1325–7.
3. Pauwels O. Factors contributing to carbamazepine-macrolide interactions. *Pharmacol Res* 2002; **45**: 291–8.
4. Kanbay M, *et al.* Hyponatremia due to an additive effect of carbamazepine and clarithromycin. *South Med J* 2007; **100**: 222.
5. Zolezzi M. Antituberculosis agents and carbamazepine. *Am J Psychiatry* 2002; **159**: 874.

Anticoagulants. For the effect of carbamazepine on *warfarin*, see p. 1532.1.

Antidepressants. As with all antiepileptics, antidepressants may antagonise the antiepileptic activity of carbamazepine by lowering the convulsive threshold.

Antidepressants such as *desipramine,*[1] *fluoxetine,*[2] *fluvoxamine,*[3] *nefazodone*[4] (and perhaps *trazodone*[5]), and *viloxazine*[6] increase plasma concentrations of carbamazepine and may induce carbamazepine toxicity. A toxic serotonin syndrome (see p. 443.2) has been reported in a patient who received fluoxetine with carbamazepine.[7] Severe neurotoxicity reported during therapy with *lithium* and carbamazepine[8,9] may be due to a synergistic effect as reports indicate that either drug was tolerated when not given with the other and measured plasma concentrations did not indicate overdosage.[9] However, toxic serum concentrations of lithium have also been reported, due to carbamazepine-induced acute renal failure (see p. 431.3).

Because of the structural similarity to tricyclic antidepressants licensed product information suggests that carbamazepine should not be given to patients taking an *MAOI* or within 14 days of stopping such treatment.

St John's wort has been shown to induce several drug metabolising enzymes (see p. 449.3) and consequently it has been suggested that it might reduce the blood concentrations of carbamazepine leading to an increased risk of seizure.[10] However, a multiple-dose study[11] in healthy subjects reported that St John's wort had no significant effect on the pharmacokinetics of carbamazepine or its active epoxide metabolite.

For the effect of carbamazepine on antidepressants, see Bupropion (p. 410.2), Fluoxetine (p. 424.2), Mianserin (p. 435.2), Nefazodone (p. 439.2), and Amitriptyline (p. 406.2).

1. Lesser I. Carbamazepine and desipramine: a toxic reaction. *J Clin Psychiatry* 1984; **45**: 360.
2. Pearson HJ. Interaction of fluoxetine with carbamazepine. *J Clin Psychiatry* 1990; **51**: 126.
3. Fritze J, *et al.* Interaction between carbamazepine and fluvoxamine. *Acta Psychiatr Scand* 1991; **84**: 583–4.
4. Ashton AK, Wolin RE. Nefazodone-induced carbamazepine toxicity. *Am J Psychiatry* 1996; **153**: 733.
5. Sánchez Romero A, *et al.* Interaction between trazodone and carbamazepine. *Ann Pharmacother* 1999; **33**: 1370.
6. Scarpello JHB, Cottrell N. Overuse of monitoring of blood concentrations of antiepileptic drugs. *BMJ* 1987; **294**: 1355.
7. Dursun SM, *et al.* Toxic serotonin syndrome after fluoxetine plus carbamazepine. *Lancet* 1993; **342**: 442–3.
8. Andrus PF. Lithium and carbamazepine. *J Clin Psychiatry* 1984; **45**: 125.
9. Chaudhry RP, Waters BGH. Lithium and carbamazepine interaction: possible neurotoxicity. *J Clin Psychiatry* 1983; **44**: 30–1.
10. CSM/MCA. Reminder: St John's wort (Hypericum perforatum) interactions. *Current Problems* 2000; **26**: 6–7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)
11. Burstein AH, *et al.* Lack of effect of St John's Wort on carbamazepine pharmacokinetics in healthy volunteers. *Clin Pharmacol Ther* 2000; **68**: 605–12.

Antiepileptics. Interactions of varying degrees of clinical significance have been reported between carbamazepine and other antiepileptics.

Serum concentrations of carbamazepine are reported to be reduced by *phenobarbital,* but without loss of seizure control;[1,2] this reduction is probably due to induction of carbamazepine metabolism.

The interaction with *phenytoin* is somewhat more complex and the consequences vary. There is evidence of a lowering of serum-carbamazepine concentrations, presumably due to induction of metabolism by phenytoin;[1-3] in return carbamazepine has been reported both to lower and increase serum phenytoin—see p. 543.2. Again, these reports do not indicate a loss of seizure control or toxicity resulting from the interaction, although the possibility presumably exists. Gradually withdrawing phenytoin from 2 patients who had been receiving carbamazepine and phenytoin resulted in a dramatic increase in plasma-carbamazepine concentrations;[4] one patient exhibited neurotoxic symptoms. The authors recommended that plasma-carbamazepine monitoring should be carried out whenever phenytoin is withdrawn in patients taking these two drugs together.

Valproic acid produces an increase in serum concentrations of the active epoxide metabolite of carbamazepine. This is usually attributed to inhibition of its hydrolysis by epoxide hydrolase, although an additional proposed mechanism[5] is inhibition of the glucuronidation of carbamazepine-10,11-trans-diol, the compound to which the epoxide is converted under normal circumstances. Adverse effects may be a problem if unusually high epoxide concentrations arise but, in general, this interaction is of limited clinical significance. However, *valpromide,* the amide derivative, is a much more powerful inhibitor of epoxide hydrolase than valproic acid,[6-8] and therefore produces greater increases in epoxide plasma concentrations with clinical signs of toxicity.[7] Switching from sodium valproate to valpromide has resulted in toxicity in patients also receiving carbamazepine.[7] Neither valproic acid nor valpromide have any significant effect on plasma concentrations of the parent drug, carbamazepine. *Valnoctamide,* an isomer of valpromide, appears to be at least as potent as valpromide in inhibiting the elimination of the epoxide metabolite of carbamazepine.[9] Valnoctamide has been used as an anxiolytic, although it does appear to possess some antiepileptic activity. For a report of acute psychosis associated with the combination of carbamazepine and sodium valproate, see Effects on Mental Function under Adverse Effects, p. 514.3. For the effects of carbamazepine on valproate, see p. 557.3.

Of the other antiepileptics *stiripentol*[10,11] has been reported to inhibit carbamazepine metabolism, while *felbamate* causes a significant fall in plasma-carbamazepine concentrations which may require an increase in the dose of carbamazepine.[12] However, another study[13] has shown a

significant increase in plasma-concentrations of the active epoxide metabolite, which may counteract the effect of the decrease in plasma concentrations of the parent compound. Neurotoxicity has been seen after use of carbamazepine with *lamotrigine*.[14] The suggestion that this was due to raised concentrations of carbamazepine epoxide was not confirmed in a controlled study in which the 2 drugs were used together safely and effectively.[15] Toxic epidermal necrolysis occurred[16] when lamotrigine was added to carbamazepine therapy in a patient who had been taking carbamazepine for 3 years; symptoms resolved progressively when both drugs were stopped. Symptoms of carbamazepine toxicity have been reported[17] when *levetiracetam* was added to carbamazepine therapy; this interaction appeared to be due to a pharmacodynamic mechanism as blood levels of carbamazepine and its epoxide metabolite were not altered. There have also been reports[18] of carbamazepine toxicity when *topiramate* was added to carbamazepine therapy; symptoms resolved when the dose of carbamazepine was reduced. Fulminant liver failure has been reported[19] after an increase in adjunctive topiramate dose in a patient maintained on carbamazepine for 2 years without any signs of hepatotoxicity. The GABA agonist *progabide* has increased plasma concentrations of the epoxide metabolite, probably due to inhibition of microsomal epoxide hydrolase.[20] *Vigabatrin* is reported[21] to increase the clearance of carbamazepine by about 35%.

For the effects of carbamazepine on *ethosuximide*, see p. 521.3, on *lamotrigine*, see p. 530.1, on *oxcarbazepine*, see p. 534.2, on *primidone*, see p. 547.3, on *tiagabine*, see p. 550.3, and on *topiramate*, see p. 552.3. For interactions with benzodiazepines, see below.

1. Cereghino JJ, *et al.* The efficacy of carbamazepine combinations in epilepsy. *Clin Pharmacol Ther* 1975; **18:** 733–41.
2. Rane A, *et al.* Kinetics of carbamazepine and its 10,11-epoxide metabolite in children. *Clin Pharmacol Ther* 1976; **19:** 276–83.
3. Christiansen J, Dam M. Influence of phenobarbital and diphenylhydantoin on plasma carbamazepine levels in patients with epilepsy. *Acta Neurol Scand* 1973; **49:** 543–6.
4. Chapron DJ, *et al.* Unmasking the significant enzyme-inducing effects of phenytoin on serum carbamazepine concentrations during phenytoin withdrawal. *Ann Pharmacother* 1993; **27:** 708–11.
5. Bernus I, *et al.* The mechanism of the carbamazepine-valproate interaction in humans. *Br J Clin Pharmacol* 1997; **44:** 21–7.
6. Levy RH, *et al.* Inhibition of carbamazepine epoxide elimination by valpromide and valproic acid. *Epilepsia* 1986; **27:** 592.
7. Meijer JWA, *et al.* Possible hazard of valpromide-carbamazepine combination therapy in epilepsy. *Lancet* 1984; **i:** 802.
8. Pisani F, *et al.* Effect of valpromide on the pharmacokinetics of carbamazepine-10,11-epoxide. *Br J Clin Pharmacol* 1988; **25:** 611–13.
9. Pisani F, *et al.* Impairment of carbamazepine-10,11-epoxide elimination by valnoctamide, a valpromide isomer, in healthy subjects. *Br J Clin Pharmacol* 1992; **34:** 85–7.
10. Levy RH, *et al.* Stiripentol level-dose relationship and interaction with carbamazepine in epileptic patients. *Epilepsia* 1985; **26:** 544–5.
11. Cazali N, *et al.* Inhibitory effect of stiripentol on carbamazepine and saquinavir metabolism in human. *Br J Clin Pharmacol* 2003; **56:** 526–36.
12. Albani F, *et al.* Effect of felbamate on plasma levels of carbamazepine and its metabolites. *Epilepsia* 1991; **32:** 130–2.
13. Wagner ML, *et al.* Effect of felbamate on carbamazepine and its major metabolites. *Clin Pharmacol Ther* 1993; **53:** 536–43.
14. Warner T, *et al.* Lamotrigine-induced carbamazepine toxicity: an interaction with carbamazepine-10,11-epoxide. *Epilepsy Res* 1992; **11:** 147–50.
15. Stolarek I, *et al.* Vigabatrin and lamotrigine in refractory epilepsy. *J Neurol Neurosurg Psychiatry* 1994; **57:** 921–4.
16. Mansouri F, *et al.* Toxic epidermal necrolysis associated with concomitant use of lamotrigine and carbamazepine: a case report. *Arch Dermatol* 2005; **141:** 788–9.
17. Sisodiya SM, *et al.* Carbamazepine toxicity during combination therapy with levetiracetam: a pharmacodynamic interaction. *Epilepsy Res* 2002; **48:** 217–19.
18. Mack CJ, *et al.* Interaction of topiramate with carbamazepine: two case reports and a review of clinical experience. *Seizure* 2002; **11:** 464–7.
19. Bjøro K, *et al.* Topiramate and fulminant liver failure. *Lancet* 1998; **352:** 1119.
20. Kroetz DL, *et al.* In vivo and in vitro correlation of microsomal epoxide hydrolase inhibition by progabide. *Clin Pharmacol Ther* 1993; **54:** 485–97.
21. Sánchez-Alcaraz A, *et al.* Effect of vigabatrin on the pharmacokinetics of carbamazepine. *J Clin Pharm Ther* 2002; **27:** 427–30.

Antifungals. Malaise, myoclonus, and trembling were reported[1] to have developed in a patient receiving carbamazepine after the addition of *miconazole* to therapy. *Ketoconazole* was associated with a significant increase in plasma-carbamazepine concentrations in 8 epileptic patients stabilised on carbamazepine;[2] plasma concentrations of the epoxide metabolite were unchanged. A threefold increase in serum-carbamazepine concentrations, reported[3] in a patient after addition of *fluconazole* to carbamazepine therapy, did not result in toxicity; however, the latter has been reported[4,5] in 2 patients stabilised on carbamazepine who were given fluconazole. *Terbinafine* has also been reported[6] to cause possible carbamazepine toxicity.

For the effect of carbamazepine on *itraconazole*, see p. 585.1.

1. Loupi E, *et al.* Interactions médicamenteuses et miconazole. *Therapie* 1982; **37:** 437–41.
2. Spina E, *et al.* Elevation of plasma carbamazepine concentrations by ketoconazole in patients with epilepsy. *Ther Drug Monit* 1997; **19:** 535–8.
3. Finch CK, *et al.* Fluconazole-carbamazepine interaction. *South Med J* 2002; **95:** 1099–1100.
4. Nair DR, Morris HH. Potential fluconazole-induced carbamazepine toxicity. *Ann Pharmacother* 1999; **33:** 790–2.
5. Ulivelli M, *et al.* Clinical evidence of fluconazole-induced carbamazepine toxicity. *J Neurol* 2004; **251:** 622–3.
6. Baath NS, *et al.* Possible carbamazepine toxicity with terbinafine. *Can J Clin Pharmacol* 2006; **13:** e228–e231.

Antihistamines. *Terfenadine* and carbamazepine are both highly protein bound and therefore may compete for protein binding sites. An 18-year-old woman receiving carbamazepine as an antiepileptic had symptoms of neurotoxicity shortly after starting treatment with terfenadine for rhinitis.[1] The concentration of free carbamazepine in the plasma was higher than normal and returned to normal on stopping terfenadine.

1. Hirschfeld S, Jarosinski P. Drug interaction of terfenadine and carbamazepine. *Ann Intern Med* 1993; **118:** 907–8.

Antimalarials. *Chloroquine* and *mefloquine* may antagonise the antiepileptic activity of carbamazepine by lowering the convulsive threshold.

Antiprotozoals. A patient receiving carbamazepine for bipolar disorder developed dizziness, diplopia, and nausea 4 days after the addition of *metronidazole* for diverticulitis.[1]

1. Patterson BD. Possible interaction between metronidazole and carbamazepine. *Ann Pharmacother* 1994; **28:** 1303–4.

Antipsychotics. As with all antiepileptics, antipsychotics may antagonise the antiepileptic activity of carbamazepine by lowering the convulsive threshold.

Increased plasma concentrations of carbamazepine epoxide have been reported to occur during therapy with carbamazepine and *loxapine*[1] or *quetiapine*,[2] possibly due to induction of carbamazepine metabolism or inhibition of metabolism of the epoxide. Raised serum concentrations of carbamazepine have also been reported in patients receiving *haloperidol*.[3]

For the effect of carbamazepine on antipsychotics, see under Chlorpromazine, p. 1052.2.

1. Collins DM, *et al.* Potential interaction between carbamazepine and loxapine: case report and retrospective review. *Ann Pharmacother* 1993; **27:** 1180–3.
2. Fitzgerald BJ, Okos AJ. Elevation of carbamazepine-10,11-epoxide by quetiapine. *Pharmacotherapy* 2002; **22:** 1500–3.
3. Iwahashi K, *et al.* The drug-drug interaction effects of haloperidol on plasma carbamazepine levels. *Clin Neuropharmacol* 1995; **18:** 233–6.

Antivirals. The HIV-protease inhibitor *ritonavir* inhibits several microsomal liver enzymes and therefore may potentially increase plasma concentrations of carbamazepine. Licensed product information for ritonavir advises that such combinations may require monitoring. Carbamazepine toxicity has been reported[1,2] after interaction with ritonavir. In one report,[2] the patient was also taking *nelfinavir* and *lopinavir*, both of which are substrates and inhibitors of cytochrome P450 isoenzymes.

For the effect of carbamazepine on HIV-protease inhibitors, see p. 987.3.

Concurrent use of carbamazepine and the NNRTI *efavirenz* reduces the levels of both drugs; for further information see under Efavirenz, p. 976.1.

1. Mateu-de Antonio J, Grau S. Ritonavir-induced carbamazepine toxicity. *Ann Pharmacother* 2001; **35:** 125–6.
2. Bates DE, Herman RJ. Carbamazepine toxicity induced by lopinavir/ritonavir and nelfinavir. *Ann Pharmacother* 2006; **40:** 1190–5.

Anxiolytics. For a discussion of the potential interaction between carbamazepine and the anxiolytic *valnoctamide*, an isomer of the antiepileptic valpromide, see Antiepileptics, p. 516.3.

See also Benzodiazepines, below.

Benzodiazepines. The metabolism of benzodiazepines may be enhanced by induction of hepatic drug-metabolising enzymes in patients who have received long-term therapy with carbamazepine; benzodiazepine plasma concentrations are reduced, half-life is shorter, and clearance is increased[1,2] (see also Antiepileptics, under Interactions of Diazepam, p. 1069.1).

Some benzodiazepines may also affect carbamazepine. One group of workers reported that after addition of *clobazam* to carbamazepine therapy a dose reduction for the latter was required due to increased blood concentrations.[3] In a later study[4] it appeared that clobazam could produce a moderate increase in the metabolism of carbamazepine. The plasma ratio of metabolites of carbamazepine, including carbamazepine-10,11-epoxide, to parent compound was increased in patients taking clobazam and carbamazepine.

1. Dhillon S, Richens A. Pharmacokinetics of diazepam in epileptic patients and normal volunteers following intravenous administration. *Br J Clin Pharmacol* 1981; **12:** 841–4.
2. Lai AA, *et al.* Time-course of interaction between carbamazepine and clonazepam in normal man. *Clin Pharmacol Ther* 1978; **24:** 316–23.
3. Franceschi M, *et al.* Clobazam in drug-resistant and alcoholic withdrawal seizures. *Clin Trials J* 1983; **20:** 119–25.
4. Muñoz JJ, *et al.* The effect of clobazam on steady state plasma concentrations of carbamazepine and its metabolites. *Br J Clin Pharmacol* 1990; **29:** 763–5.

Calcium-channel blockers. Six patients with steady-state carbamazepine concentrations had symptoms of neurotoxicity consistent with carbamazepine intoxication within 36 to 96 hours of the first dose of *verapamil*.[1] In 5 patients, in whom plasma concentrations were measured, there was a mean increase of 46% in total carbamazepine and 33% in free carbamazepine; no effect on the plasma protein binding of carbamazepine was seen. The results suggested that verapamil inhibits the metabolism of carbamazepine to an extent likely to have important clinical repercussions. There has also been a report[2] of a patient in whom *diltiazem*, but not *nifedipine*, precipitated carbamazepine neurotoxicity.

For the effect of carbamazepine on dihydropyridine calcium-channel blockers, see under Nifedipine, p. 1453.3.

1. Macphee GJA, *et al.* Verapamil potentiates carbamazepine neurotoxicity: a clinically important inhibitory interaction. *Lancet* 1986; **i:** 700–703.
2. Brodie MJ, Macphee GJA. Carbamazepine neurotoxicity precipitated by diltiazem. *BMJ* 1986; **292:** 1170–1.

Ciclosporin. For the effect of carbamazepine on ciclosporin, see p. 1956.3.

Corticosteroids. For the effect of carbamazepine on corticosteroids, see p. 1619.3.

Danazol. Use of danazol with carbamazepine has been reported to increase the half-life and decrease clearance of carbamazepine,[1] resulting in increases in plasma-carbamazepine concentrations of up to 100%[1,2] and resultant toxicity in several patients.[2]

1. Krämer G, *et al.* Carbamazepine-danazol drug interaction: its mechanism examined by a stable isotope technique. *Ther Drug Monit* 1986; **8:** 387–92.
2. Zielinski JJ, *et al.* Clinically significant danazol-carbamazepine interaction. *Ther Drug Monit* 1987; **9:** 24–7.

Dermatological drugs. Addition of *isotretinoin* to regular carbamazepine therapy appeared to reduce plasma concentrations of the latter and its active epoxide metabolite.[1] However, no adverse events were noted during a 6-week period of treatment with isotretinoin. Nonetheless, licensed product information for carbamazepine recommends that the levels of carbamazepine are monitored if both are used together.

1. Marsden JR. Effect of isotretinoin on carbamazepine pharmacokinetics. *Br J Dermatol* 1988; **119:** 403–4.

Diuretics. There has been a report of symptomatic hyponatraemia associated with use of carbamazepine and a diuretic (*hydrochlorothiazide* or *furosemide*—see under Interactions of Furosemide, p. 1390.1). Carbamazepine serum concentrations are increased by *acetazolamide*.[1]

1. McBride MC. Serum carbamazepine levels are increased by acetazolamide. *Ann Neurol* 1984; **16:** 393.

Gastrointestinal drugs. *Cimetidine* is reported to produce a transient increase in plasma-carbamazepine concentrations, with a return to pre-cimetidine values within about a week;[1] some increase in adverse effects was seen. *Ranitidine* does not appear to affect plasma-carbamazepine concentrations.[2] Neurotoxicity has been seen in a patient receiving carbamazepine and *metoclopramide*.[3]

1. Dalton MJ, *et al.* Cimetidine and carbamazepine: a complex drug interaction. *Epilepsia* 1986; **27:** 553–8.
2. Dalton MJ, *et al.* Ranitidine does not alter single-dose carbamazepine pharmacokinetics in healthy adults. *Drug Intell Clin Pharm* 1985; **19:** 941–4.
3. Sandyk R. Carbamazepine and metoclopramide interaction: possible neurotoxicity. *BMJ* 1984; **288:** 830.

Grapefruit juice. The bioavailability and plasma concentrations of carbamazepine have been reported[1] to be increased by grapefruit juice.

1. Garg SK, *et al.* Effect of grapefruit juice on carbamazepine bioavailability in patients with epilepsy. *Clin Pharmacol Ther* 1998; **64:** 286–8.

Levothyroxine. For the effect of carbamazepine on levothyroxine, see p. 2341.3.

Neuromuscular blockers. For the effect of carbamazepine on *suxamethonium*, see p. 2039.3 and on *competitive neuromuscular blockers*, see under Atracurium, p. 2032.1.

Sex hormones. For the effect of carbamazepine on *oral contraceptives*, see p. 2243.2 and for the possible effect on *tibolone*, see p. 2310.2.

See also Danazol, above

Theophylline. A decrease in serum-carbamazepine concentrations of about 50% was reported[1] in an epileptic patient given theophylline. The patient had seizures and the proposed mechanism was that theophylline had increased the metabolism of carbamazepine.

For the effect of carbamazepine on theophylline, see p. 1235.1.

1. Mitchell EA, *et al.* Interaction between carbamazepine and theophylline. *N Z Med J* 1986; **99:** 69–70.

Vitamins. The plasma concentration of carbamazepine was increased in 2 patients given *nicotinamide*.[1]

For the effect of antiepileptics, including carbamazepine, on *vitamin D* concentrations, see Effects on Bone under the Adverse Effects of Phenytoin, p. 540.2.

1. Bourgeois BFD, *et al.* Interactions between primidone, carbamazepine, and nicotinamide. *Neurology* 1982; 32: 1122–6.

Pharmacokinetics

Carbamazepine is slowly and irregularly absorbed from the gastrointestinal tract and has a bioavailability of 85 to 100%. It is extensively metabolised in the liver, notably by the cytochrome P450 isoenzymes CYP3A4 and CYP2C8. One of its primary metabolites, carbamazepine-10,11-epoxide, is also active. Carbamazepine is excreted in the urine almost entirely in the form of its metabolites; some are also excreted in faeces. Elimination of carbamazepine is reported to be more rapid in children and accumulation of the active metabolite may often be higher than in adults.

Carbamazepine is widely distributed throughout the body and is about 70 to 80% bound to plasma proteins. It induces its own metabolism so that the plasma half-life may be considerably reduced after repeated dosage. The mean plasma half-life of carbamazepine on repeated dosage is about 12 to 24 hours; it appears to be considerably shorter in children than in adults. Moreover, the metabolism of carbamazepine is readily induced by drugs that induce hepatic microsomal enzymes (see Interactions, p. 516.2).

Monitoring of plasma concentrations may be performed when clinically indicated and the therapeutic range of total plasma-carbamazepine is usually quoted as being about 4 to 12 micrograms/mL (17 to 50 micromoles/litre), although this is subject to considerable variation. It has been suggested by some, but not all investigators, that measurement of free carbamazepine concentrations in plasma may prove more reliable, and concentrations in saliva or tears, which contain only free carbamazepine, have also been measured.

Carbamazepine crosses the placental barrier and is distributed into breast milk.

The pharmacokinetics of carbamazepine are affected by use with other antiepileptics (see under Interactions, p. 516.3).

References.

1. Schmidt D, Haenel F. Therapeutic plasma levels of phenytoin, phenobarbital, and carbamazepine: individual variation in relation to seizure frequency and type. *Neurology* 1984; 34: 1252–5.
2. Bertilsson L, Tomson T. Clinical pharmacokinetics and pharmacological effects of carbamazepine and carbamazepine-10,11-epoxide: an update. *Clin Pharmacokinet* 1986; 11: 177–98.
3. Gilman JT. Carbamazepine dosing for pediatric seizure disorders: the highs and lows. *DICP Ann Pharmacother* 1991; 25: 1109–12.
4. Kodama Y, *et al.* In vivo binding characteristics of carbamazepine and carbamazepine-10,11-epoxide to serum proteins in paediatric patients with epilepsy. *Eur J Clin Pharmacol* 1993; 44: 291–3.
5. Bernus I, *et al.* Early stage autoinduction of carbamazepine metabolism in humans. *Eur J Clin Pharmacol* 1994; 47: 355–60.
6. Caraco Y, *et al.* Carbamazepine pharmacokinetics in obese and lean subjects. *Ann Pharmacother* 1995; 29: 843–7.
7. Mahmood I, Chamberlin N. A limited sampling method for the estimation of AUC and C_{max} of carbamazepine and carbamazepine epoxide following a single and multiple dose of a sustained-release product. *Br J Clin Pharmacol* 1998; 45: 241–6.
8. Cohen H, *et al.* Feasibility and pharmacokinetics of carbamazepine oral loading doses. *Am J Health-Syst Pharm* 1998; 55: 1134–40.
9. Bondareva IB, *et al.* Population pharmacokinetic modelling of carbamazepine in epileptic elderly patients: implications for dosage. *J Clin Pharm Ther* 2006; 31: 211–21.
10. Vucićević K, *et al.* Population pharmacokinetic model of carbamazepine derived from routine therapeutic drug monitoring data. *Ther Drug Monit* 2007; 29: 781–8.
11. Tothfalusi L, *et al.* Exposure-response analysis reveals that clinically important toxicity difference can exist between bioequivalent carbamazepine tablets. *Br J Clin Pharmacol* 2008; 65: 110–22.
12. Makmor-Bakry M, *et al.* Genetic variants in microsomal epoxide hydrolase influence carbamazepine dosing. *Clin Neuropharmacol* 2009; 32: 205–12.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Actinerval; Carbagramon; Carbamat; Conformal; Elebe; Tegretol; *Austral.*: Tegretol; Teril; *Austria*: Deleptin; Neurotop; Tegretol; *Belg.*: Tegretol; *Braz.*: Carmazin; Convulsan; Tegretard; Tegretol; Tegrex; Tegrezin; Uni Carbamaz; *Canad.*: Mazepine; Novo-Carbamaz†; Tegretol; *Chile*: Eposal; Tegretal; *China*: Li Zhen (粒珍); Tegretol (得理多); *Cz.*: Biston; Neurotop; Tegretol; Timonil; *Denm.*: Tegretol; Timonil; Trimonil; *Fin.*: Neurotol; Tegretol; *Fr.*: Tegretol; *Ger.*: Carba†; Carbabeta; Carbaflux; Carbagamma†; Finlepsin; Tegretal; Timonil; *Gr.*: Tegretol; *Hong Kong*: Convulzine†; CP-Carba; Tegretol; Teril; *Hung.*: Neurotop; Stazepine; Tegretol; Timonil; *India*: Acetol; Antilep; Carbacontin†; Carbadac; Carbasure; Carbatol; Cariv; Carizine; Carmaz; Carmeg; Carzep; Carzine; Cincar; Cizetol; Corgone; Epinil; Epix; Maze; Mazetol; Mezapin; Mezaril; Tegrital; *Indon.*: Bamgetol; Lepsitol; Tegretol; Teril†; *Irl.*: Gericarb; Tegretol; *Israel*: Tegretol; Teril; Timonil; *Ital.*: Tegretol; *Malaysia*: Taver; Tegretol; *Mex.*: Bioneuril; Carbalan; Carbasal; Carbaval†; Carbazep; Carbazina; Carpin; Cinazel; Clostedal; Dateril†; Neugeron; Neurolep; Sepibest; Tegretol; Trendr; Trepina†; Ultrepyl; Volutol; Zepiken; *Neth.*: Tegretol; *Norw.*: Tegretol; Trimonil; *NZ*: Tegretol; Teril†; *Philipp.*: Carbapsy; Carbilepp†; Epazin; Epikor; Lestremor; Tegrepin; Tegretol; *Pol.*: Amizepin; Finlepsin; Neurotop; Tegretol; Timonil; *Port.*: Tegretol; *Rus.*: Carbalepsin (Карбалепсин); Carbapin (Карбапин)†; Finlepsin (Финлепсин); Mazepine (Мазепин); Tegretol (Тегретол); Zeptol (Зептол); *S.Afr.*: Degranol; Tegretol; *Singapore*: Carbatol; Carzepin; Mazetol; Neurotop; Storilat; Tegretol; *Spain*: Tegretol; *Swed.*: Hermolepsin; Tegretol; Trimonil; *Switz.*: Carsol; Neurotop†; Tegretol; Timonil; *Thai.*: Antafit; Carbazene; Carmapine; Carpine; Carzepine; Mapezine; Panitol†; Pantol; Taver†; Tegretol; Zeptol; *Turk.*: Karazepin; Karbalex; Karbasif; Karberol; Kazepin; Tegretol; Teril; *UAE*: Fitzecalm; *UK*: Arbil; Carbagen; Epimaz; Tegretol; *Ukr.*: Carbapin (Карбапин); Finlepsin (Финлепсин); Tegretol (Тегретол); *USA*: Carbatrol; Epitol; Equetro; Tegretol; Teril; *Venez.*: Convulex; Tanfedin; Tegretol.

Pharmacopoeial Preparations

BP 2014: Carbamazepine Tablets;

USP 36: Carbamazepine Extended-Release Tablets; Carbamazepine Oral Suspension; Carbamazepine Tablets.

Carisbamate *(USAN, rINN)*

Carisbamato; Carisbamatum; JNJ-10234094; RWJ-333369; YKP-509; Карисбамат.

(+)-(2*S*)-2-(2-Chlorophenyl)-2-hydroxyethyl carbamate.

$C_9H_{10}ClNO_3$=215.6

CAS — 194085-75-1.

ATC — N03AX19.

ATC Vet — QN03AX19.

UNII — P772S19V3Z.

Profile

Carisbamate is under investigation for the management of infantile spasms. It has also been investigated for adjunctive treatment of partial-onset seizures in adults.

References.

1. Novak GP, *et al.* Carisbamate (RWJ-333369). *Neurotherapeutics* 2007; 4: 106–9.
2. Sperling MR, *et al.* Carisbamate as adjunctive treatment of partial onset seizures in adults in two randomized, placebo-controlled trials. *Epilepsia* 2010; 51: 333–43.
3. Moore K, *et al.* Effect of mild and moderate hepatic impairment on the pharmacokinetics and safety of carisbamate. *J Clin Pharmacol* 2012; 52: 738–46.

Clobazam *(BAN, USAN, rINN)*

Clobazamum; H-4723; HR-376; Klobatsaami; Klobazam; Klobazamas; LM-2717; Клобазам.

7-Chloro-1,5-dihydro-1-methyl-5-phenyl-1,5-benzodiazepine-2,4(3*H*)-dione.

$C_{16}H_{13}ClN_2O_2$=300.7

CAS — 22316-47-8.

ATC — N05BA09.

ATC Vet — QN05BA09.

UNII — 2MRO291B4U.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Clobazam). A white or almost white crystalline powder. Slightly soluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane.

Uses and Administration

Clobazam is a long-acting 1,5-benzodiazepine with uses similar to those of diazepam (a 1,4-benzodiazepine; see p. 1063.3). It may be used as an adjunct with other antiepileptics in the treatment of epilepsy including seizures associated with the Lennox-Gastaut syndrome, although its use may be limited by the development of tolerance or sedation (but see below). It is also used in the short-term treatment of acute anxiety (p. 1028.1).

As an adjunct in **epilepsy** usual oral doses are 20 to 30 mg daily, increased if necessary to a maximum of 60 mg daily.

For doses in children, see below.

As with other antiepileptics, withdrawal of clobazam therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1 and under Clonazepam, p. 520.1.

For the short-term management of acute **anxiety** usual oral doses of 10 to 30 mg daily may be taken in divided doses or as a single dose at night; up to 80 mg daily has been used in hospitalised patients with severe anxiety states. Low initial doses and cautious increments to a usual daily dose of 10 to 20 mg are recommended in elderly or debilitated patients.

Administration in children. In the UK, clobazam is licensed for use as an adjunct in epilepsy in children over 6 years of age; the recommended usual initial oral dose is 5 mg daily with a maintenance dose range of 0.3 to 1 mg/kg daily (up to a maximum of 60 mg daily). Doses of up to 30 mg daily may be given as a single dose at bedtime; higher doses should be divided. For younger children, the *BNFC* suggests the following oral doses according to age:

- 1 month to 6 years: initially 125 micrograms/kg twice daily, increased every 5 days to a usual maintenance dose of 250 micrograms/kg twice daily. The maximum dose is 500 micrograms/kg twice daily and should not exceed 15 mg twice daily

The *BNFC* also suggests that clobazam may be given for cluster seizures and as monotherapy under specialist supervision for catamenial seizures (usually for 7 to 10 days each month just before and during menstruation).

In the USA, clobazam is licensed specifically for the adjunctive treatment of seizures associated with the Lennox-Gastaut syndrome in patients aged 2 years or older. Doses are calculated according to body-weight:

- 30 kg or less, the initial oral dose is 5 mg daily, increased to 10 mg daily on day 7 then to 20 mg daily on day 14, according to response
- more than 30 kg, the initial dose is 10 mg daily, increased to 20 mg daily on day 7 then to 40 mg daily on day 14, according to response

Doses greater than 5 mg daily should be given in 2 divided doses.

Epilepsy. Benzodiazepines are sometimes used in the management of epilepsy (p. 506.1), but their long-term use is limited by problems of sedation, dependence, and tolerance to the antiepileptic effects.

Clobazam, a 1,5-benzodiazepine, is considered to be somewhat better tolerated than conventional benzodiazepines, and has been widely used for adjunctive oral therapy in patients with epilepsy.[1,2] Clobazam is active against partial and generalised seizures in epilepsy of widely differing aetiology in patients of all ages and has also been used for short-term cover in patients with intermittent seizures, including in women with catamenial epilepsy (seizures associated with menstruation) or patients whose epileptic attacks occur in clusters. Clobazam has also been tried with some success in children, including those with refractory epilepsy,[3-5] epileptic encephalopathy,[6] and Lennox-Gastaut syndrome.[7-9] However, a systematic review[10] concluded that although clobazam may reduce seizure frequency and may be most effective in partial onset seizures, it was not clear who would best benefit from its use and over what time-frame.

1. Trimble MR. On the use of tranquillisers in epilepsy. *Epilepsia* 2002; 43 (suppl 2): 25–7.
2. Ng Y-T, Collins SD. Clobazam. *Neurotherapeutics* 2007; 4: 138–44.
3. Munn R, Farrell K. Open study of clobazam in refractory epilepsy. *Pediatr Neurol* 1993; 9: 465–9.
4. Sheth RD, *et al.* Clobazam for intractable pediatric epilepsy. *J Child Neurol* 1995; 10: 205–8.
5. Canadian Study Group for Childhood Epilepsy. Clobazam has equivalent efficacy to carbamazepine and phenytoin as monotherapy for childhood epilepsy. *Epilepsia* 1998; 39: 952–9.
6. Silva RC, *et al.* Clobazam as add-on therapy in children with epileptic encephalopathy. *Can J Neurol Sci* 2006; 33: 209–13.
7. Conry JA, *et al.* Clobazam in the treatment of Lennox-Gastaut syndrome. *Epilepsia* 2009; 50: 1158–66.
8. Ng YT, *et al.* OV-1012 Study Investigators. Randomized, phase III study results of clobazam in Lennox-Gastaut syndrome. *Neurology* 2011; 77: 1473–81.
9. Leahy JT, *et al.* Clobazam as an adjunctive therapy in treating seizures associated with Lennox-Gastaut syndrome. *Neuropsychiatr Dis Treat* 2011; 7: 673–81.
10. Michael B, Marson AG. Clobazam as an add-on in the management of refractory epilepsy. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 16/06/08).

Neuropathic pain. There has been a mention[1] of the complete relief of *phantom limb pain* (p. 10.3) refractory to other therapy in an elderly patient given clobazam 10 mg three times daily.

1. Rice-Oxley CP. The limited list: clobazam for phantom limb pain. *BMJ* 1986; 293: 1309.

Dependence and Withdrawal

As for Diazepam, p. 1065.1.

For the purpose of withdrawal regimens, 10 mg of clobazam may be considered equivalent to about 5 mg of diazepam.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p. 1065.3.

Breast feeding. Benzodiazepines, such as clobazam, given to the mother may cause neonatal sedation and breast feeding should be avoided. For comments on antiepileptic therapy and breast feeding, see p. 508.3.

Driving. For a comment on antiepileptic drugs and driving, see p. 509.2.

Effects on menstruation. Occasionally the use of clobazam before menstruation for catamenial epilepsy appeared to delay the period.[1]

1. Feely M. Prescribing anticonvulsant drugs 3: clonazepam and clobazam. *Prescribers' J* 1989; 29: 111–15.

Effects on mental function. For a review of the effects of antiepileptic therapy, including clobazam, on *cognition* and *mood*, including risk of suicidal ideation, see p. 508.3.

Effects on the skin. Report[1] of toxic epidermal necrolysis that developed in light-exposed areas in a patient being treated with clobazam.

1. Redondo P, *et al.* Photo-induced toxic epidermal necrolysis caused by clobazam. *Br J Dermatol* 1996; 135: 999–1002.

Pregnancy. For comments on the management of epilepsy during pregnancy, see p. 509.2.

Interactions

As for Diazepam, p. 1068.1.

Antiepileptics. For reference to the interactions of clobazam with *felbamate* and *stiripentol*, see under Diazepam, p. 1069.1.

Pharmacokinetics

Clobazam is well absorbed from the gastrointestinal tract and peak plasma concentrations occur 1 to 4 hours after oral doses. It is about 85% bound to plasma proteins. Clobazam is highly lipophilic and rapidly crosses the blood-brain barrier. It is metabolised in the liver by demethylation and hydroxylation; the cytochrome P450 isoenzyme CYP2C19 plays a role in its metabolism. Unlike the 1,4-benzodiazepines such as diazepam, clobazam, a 1,5-benzodiazepine, is hydroxylated at the 4-position rather than the 3-position (see also Metabolism, under Diazepam, p. 1071.1). Clobazam is excreted unchanged and as metabolites mainly in the urine. Mean half-lives of 18 hours and 42 hours have been reported for clobazam and its main active metabolite *N*-desmethylclobazam, respectively.

References.

1. Greenblatt DJ, *et al.* Clinical pharmacokinetics of the newer benzodiazepines. *Clin Pharmacokinet* 1983; 8: 233–52.
2. Ochs HR, *et al.* Single and multiple dose kinetics of clobazam, and clinical effects during multiple dosage. *Eur J Clin Pharmacol* 1984; 26: 499–503.
3. Kinoshita M, *et al.* Efficacy of low-dose, add-on therapy of clobazam (CLB) is produced by its major metabolite, N-desmethyl-CLB. *J Neurol Sci* 2007; 263: 44–8.
4. Seo T, *et al.* Impact of CYP2C19 polymorphisms on the efficacy of clobazam therapy. *Pharmacogenomics* 2008; 9: 527–37.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Clozam; Karidium; *Austral.*: Frisium; *Austria*: Frisium; *Belg.*: Frisium; *Braz.*: Frisium; Urbanil; *Canad.*: Frisium; *Chile*: Grifoclobam; *Cz.*: Frisium; *Denm.*: Frisium; *Fin.*: Frisium; *Fr.*: Urbanyl; *Ger.*: Frisium†; *Gr.*: Etaco; Frisium; *Hong Kong*: Frisium; *Hung.*: Frisium; *India*: Aedon; Bazzy; Cloba; Clobastar; Clobator; Clodus; Clozam; Czam; Frisium; Lobazam; *Indon.*: Anxibloc; Asabium; Clobium; Clofritis; Frisium; Proclozam; *Irl.*: Frisium; *Israel*: Frisium; *Ital.*: Frisium; *Malaysia*: Frisium; *Mex.*: Frisium; *Neth.*: Frisium; *NZ*: Frisium; *Pol.*: Frisium; *Port.*: Castilium; *S.Afr.*: Urbanol; *Singapore*: Frisium; *Spain*: Noiafren; *Switz.*: Urbanyl; *Thai.*: Frisium; *UK*: Frisium; Tapclob; *USA*: Onfi; *Venez.*: Frisium.

Pharmacopoeial Preparations

BP 2014: Clobazam Oral Suspension; Clobazam Tablets.

Clonazepam *(BAN, USAN, rINN)*

Clonazépam; Clonazepamum; Klonatsepaami; Klonazepam; Klonazepám; Klonazepamas; Ro-5-4023; Клоназепам.

5-(2-Chlorophenyl)-1,3-dihydro-7-nitro-1,4-benzodiazepin-2-one.

$C_{15}H_{10}ClN_3O_3$=315.7

CAS — 1622-61-3.

ATC — N03AE01.

ATC Vet — QN03AE01.

UNII — 5PE9FDE8G8.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of clonazepam:

K-Pins; Klondike Bars; Klonnies; Klons; La Roche; Pin; Pins; R2; R-2; Roaches; Roachies; Roche.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Clonazepam). A slightly yellowish, crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in methyl alcohol. Protect from light.

USP 36: (Clonazepam). A light yellow powder having a faint odour. Insoluble in water; slightly soluble in alcohol and in ether; sparingly soluble in acetone and in chloroform. Store in airtight containers. Protect from light.

Sorption. Significant loss of clonazepam (up to 50% over 24 hours) has been reported[1] from solutions infused through PVC tubing; the effect was concentration dependent. The authors recommended that non-PVC tubing should always be used.

1. Schneider JJ, *et al.* Effect of tubing on loss of clonazepam administered by continuous subcutaneous infusion. *J Pain Symptom Manage* 2006; 31: 563–7.

Uses and Administration

Clonazepam is a benzodiazepine derivative similar to diazepam (p. 1063.3), with marked antiepileptic properties.

It may be used in the treatment of all types of epilepsy and seizures (p. 506.1), including status epilepticus (p. 510.2), but its usefulness in chronic treatment is sometimes limited by the development of tolerance and by sedation, and other antiepileptics are often preferred. It may also be used in myoclonus (p. 511.3) and associated abnormal movements, and for the treatment of panic disorder (see Psychiatric Disorders, below).

For **epilepsy** and **myoclonus**, treatment is started with small doses that are progressively increased to an optimum dose according to response. Total daily doses may initially be taken in 3 or 4 divided doses; however, once the maintenance dose has been reached, the daily amount may be given as a single dose at night. In the UK the initial oral dose is 1 mg (500 micrograms in the elderly) at night for 4 nights gradually increased over 2 to 4 weeks to a usual maintenance dose of 4 to 8 mg daily; it is recommended that the total dose should not exceed 20 mg daily. Dosage recommendations in the USA are generally similar although initial doses of up to 1.5 mg daily are permitted and dosage increments of 0.5 to 1 mg every 3 days are recommended. There is little value in routinely monitoring plasma-clonazepam concentrations.

Clonazepam may be an alternative to other benzodiazepines in the emergency management of **status epilepticus**. The usual dose is 1 mg given by slow intravenous injection over at least 2 minutes or by intravenous infusion, repeated if necessary to a maximum total dose of 20 mg.

For doses in children, see below.

As with other antiepileptics, withdrawal of clonazepam therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1 and p. 520.1.

In the treatment of **panic disorder**, clonazepam is given in an initial oral dose of 250 micrograms twice daily. This may be increased after 3 days to a total of 1 mg daily; a few patients may benefit from further increases, up to a maximum of 4 mg daily. In order to minimise drowsiness, clonazepam may be taken as a single dose at bedtime. Withdrawal should again be gradual.

Administration. Serum concentrations of clonazepam after buccal, intranasal, or intravenous dosage were measured in a crossover study[1] in 7 healthy males. The results showed that intranasal clonazepam may offer an alternative to buccal use in patients with serial seizures but the initial concentrations were too low to recommend its use as an alternative to intravenous clonazepam in the management of status epilepticus. The nasal formulation used in this study contained dimethyl-β-cyclodextrin as a solubiliser and absorption enhancer.

1. Scholz-Hendriks MWG, *et al.* Absorption of clonazepam after intranasal and buccal administration. *Br J Clin Pharmacol* 1995; 39: 449–51.

Administration in children. For **epilepsy** and **myoclonus** treatment with clonazepam is started with small doses that are progressively increased to an optimum dose according to response. Total daily doses are taken in 3 divided doses; however, once the maintenance dose has been reached, the daily amount may be given as a single dose at night. Alternatively, the *BNFC* suggests giving the initial dose at night for 4 nights and gradually increasing it over 2 to 4 weeks. In the UK, the recommended initial oral daily dose is up to 250 micrograms for infants and children aged up to 5 years, or up to 500 micrograms for older children. The following usual maintenance doses are given according to age:

- neonate to 1 year (although the *BNFC* recommends a minimum age of 1 month): 0.5 to 1 mg daily
- 1 to 5 years: 1 to 3 mg daily
- 5 to 12 years: 3 to 6 mg daily

Older children may be given the usual adult dose (see above).

If control of childhood epilepsy ceases to be adequate with clonazepam, the dose may be increased, or treatment interrupted for 2 or 3 weeks. The *BNFC* states that the UK injection formulation (*Rivotril; Roche, UK*) can be given orally if necessary; this may not apply to other injection formulations available elsewhere.

In the USA, doses may be given according to bodyweight. Infants and children aged up to 10 years or weighing up to 30 kg may be given an initial daily dose of 10 to 30 micrograms/kg (maximum 50 micrograms/kg) in 2 or 3 divided doses. This may be increased by a total of 250 to 500 micrograms every 3 days to a maintenance dose of 100 to 200 micrograms/kg daily given in 3 divided doses.

In the emergency management of **status epilepticus**, clonazepam is used as an alternative to other benzodiazepines. The usual dose in children is 500 micrograms given by slow intravenous injection or by intravenous infusion. Alternatively, the *BNFC* suggests giving the following doses by slow intravenous injection over at least 2 minutes according to age:

- neonates: 100 micrograms/kg, repeated if necessary after 24 hours
- 1 month to 12 years: 50 micrograms/kg (maximum 1 mg), repeated if necessary

Older children may be given the usual adult dose (see Uses and Administration, above).

In children aged over 1 month, these doses by injection may be followed by an intravenous infusion of 10 micrograms/kg per hour, adjusted according to response to a maximum of 60 micrograms/kg per hour.

Extrapyramidal disorders. Clonazepam may be of benefit in some extrapyramidal disorders. It has been tried in the management of patients with *tic disorders* such as *Tourette's syndrome* (p. 1030.1) but evidence of efficacy from controlled studies is limited.[1] Some use clonazepam in preference to haloperidol[2] since it does not carry the risk of tardive dyskinesia associated with such antipsychotics and a case report[3] described the successful use of clonazepam for haloperidol-induced tardive Tourette's syndrome in an adult patient. There is also limited evidence of benefit with clonazepam in antipsychotic-induced *akathisia*[4,5] and *tardive dyskinesia*[6,7] (see under Extrapyramidal Disorders, p. 1049.2), and of improvement in *dysarthria* in a study in patients with parkinsonism.[8]

1. Goetz CG. Clonidine and clonazepam in Tourette syndrome. *Adv Neurol* 1992; 58: 245–51.
2. Truong DD, *et al.* Clonazepam, haloperidol, and clonidine in tic disorders. *South Med J* 1988; 81: 1103–5.
3. Reid SD. Neuroleptic-induced tardive Tourette treated with clonazepam: a case report and literature review. *Clin Neuropharmacol* 2004; 27: 101–4.
4. Kutcher S, *et al.* Successful clonazepam treatment of neuroleptic-induced akathisia in older adolescents and young adults: a double-blind, placebo-controlled study. *J Clin Psychopharmacol* 1989; 9: 403–6.
5. Pujalte D, *et al.* A double-blind comparison of clonazepam and placebo in the treatment of neuroleptic-induced akathisia. *Clin Neuropharmacol* 1994; 17: 236–42.
6. Thaker GK, *et al.* Clonazepam treatment of tardive dyskinesia: a practical GABAmimetic strategy. *Am J Psychiatry* 1990;147: 445–51.
7. Shapleske J, *et al.* Successful treatment of tardive dystonia with clozapine and clonazepam. *Br J Psychiatry* 1996; 168: 516–18.
8. Biary N, *et al.* A double-blind trial of clonazepam in the treatment of parkinsonian dysarthria. *Neurology* 1988; 38: 255–8.

Hiccup. For the management of intractable hiccups see under Chlorpromazine, p. 1046.3. Clonazepam may also be of value, especially in neurogenic hiccups.

Neuropathic pain. The management of *phantom limb pain* (p. 10.3) can be difficult, and tricyclic antidepressants and antiepileptics are used for the neuropathic components of the pain. Rapid and marked pain relief was achieved in 2 patients with lancinating phantom limb pain after treatment with clonazepam with or without amitriptyline.[1]

Although carbamazepine is the drug of choice in the treatment of *trigeminal neuralgia* (p. 11.2), clonazepam may be used in carbamazepine-intolerant patients.

1. Bartusch SL, *et al.* Clonazepam for the treatment of lancinating phantom limb pain. *Clin J Pain* 1996; 12: 59–62.

Psychiatric disorders. Although the risk of dependence with benzodiazepines may outweigh their benefits in panic disorder (p. 1029.1), clonazepam has been used for the treatment of panic disorder with or without agoraphobia, and reported benefit in such patients[1] suggests a similar action to alprazolam. A literature review[2] evaluated the use of clonazepam in a range of psychiatric disorders and found that it may also be effective in the treatment of social anxiety disorder (see Phobic Disorders, p. 1029.1) although further studies are warranted. There was evidence to suggest that clonazepam may be useful in acute mania (see Bipolar Disorder, p. 397.2) and for the augmentation of antidepressant therapy with SSRIs in depression (p. 398.1). A study[3] found that augmentation was significantly more effective with a daily dose of 3 mg of clonazepam than with lower doses; a later review[4] suggested that doses of between 2 and 6 mg daily were recommended, and that clonazepam should be withdrawn if no response was seen in 2 to 4 weeks.

1. Davidson JRT, Moroz G. Pivotal studies of clonazepam in panic disorder. *Psychopharmacol Bull* 1998; 34: 169–74.
2. Nardi AE, Perna G. Clonazepam in the treatment of psychiatric disorders: an update. *Int Clin Psychopharmacol* 2006; 21: 131–42.
3. Morishita S, Aoki S. Clonazepam in the treatment of prolonged depression. *J Affect Disord* 1999; 53: 275–8.
4. Morishita S. Clonazepam as a therapeutic adjunct to improve the management of depression: a brief review. *Hum Psychopharmacol* 2009; 24: 191–8.

Sleep-associated movement disorders. Treatment of sleep-associated movement disorders (p. 1034.2) including

sleep behaviour disorder, restless legs syndrome, and periodic limb movements in sleep is largely empirical, but benzodiazepines such as clonazepam are often used.[1] Small studies have provided some evidence of benefit with clonazepam therapy in these disorders,[2-4] including bruxism.[5]

1. Schenck CH, Mahowald MW. Long-term, nightly benzodiazepine treatment of injurious parasomnias and other disorders of disrupted nocturnal sleep in 170 adults. *Am J Med* 1996; **100:** 333–7.
2. Montagna P, *et al.* Clonazepam and vibration in restless legs syndrome. *Acta Neurol Scand* 1984; **69:** 428–30.
3. Peled R, Lavie P. Double-blind evaluation of clonazepam on periodic leg movements in sleep. *J Neurol Neurosurg Psychiatry* 1987; **50:** 1679–81.
4. Saletu M, *et al.* Restless legs syndrome (RLS) and periodic limb movement disorder (PLMD): acute placebo-controlled sleep laboratory studies with clonazepam. *Eur Neuropsychopharmacol* 2001; **11:** 153–61.
5. Saletu A, *et al.* On the pharmacotherapy of sleep bruxism: placebo-controlled polysomnographic and psychometric studies with clonazepam. *Neuropsychobiology* 2005; **51:** 214–25.

Stiff-man syndrome. Clonazepam has been used as an alternative to diazepam in the management of stiff-man syndrome (see under Muscle Spasm, p. 1064.3) and is reported[1] to be effective for familial startle disease, a rare congenital form of stiff-man syndrome.

1. Ryan SG, *et al.* Startle disease, or hyperekplexia: response to clonazepam and assignment of the gene (STHE) to chromosome 5q by linkage analysis. *Ann Neurol* 1992; **31:** 663–8.

Tinnitus. Clonazepam is one of many drugs that have been tried in tinnitus (p. 1994.1), but although it has been reported to be effective in some patients it is rarely used because of problems with adverse effects.

References.

1. Ganança MM, *et al.* Clonazepam in the pharmacological treatment of vertigo and tinnitus. *Int Tinnitus J* 2002; **8:** 50–3.
2. Albertino S, *et al.* Pulsatile tinnitus: treatment with clonazepam and propranolol. *Rev Bras Otorrinolaringol (Engl Ed)* 2005; **71:** 111–13.

Dependence and Withdrawal

As for Diazepam, p. 1065.1.

For the purpose of withdrawal regimens, 250 micrograms of clonazepam may be considered equivalent to about 5 mg of diazepam.

Abuse. The liability of clonazepam for abuse has been evaluated[1] from analysis of a drug prescription database.

1. Prauger E, *et al.* Estimation of clonazepam abuse liability: a new method using a reimbursed drug database. *Int Clin Psychopharmacol* 2009; **24:** 318–24.

Withdrawal. A study[1] of the withdrawal of clonazepam therapy in 40 epileptic children found that 19 had withdrawal symptoms of increased seizure frequency, either alone or with other symptoms, but that this effect was transient. Withdrawal seizures and status might become an obstacle to the removal of useless or even deleterious therapy with clonazepam because the transient nature of these effects was not always recognised. Clonazepam should not be used for more than 3 to 6 months and should be stopped if clear and lasting therapeutic benefit could not be shown.

See also Uses and Administration, p. 519.2.

1. Specht U, *et al.* Discontinuation of clonazepam after long-term treatment. *Epilepsia* 1989; **30:** 458–63.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p. 1065.3.

The principal adverse effect of clonazepam is drowsiness, which occurs in about 50% of all patients when starting therapy. Salivary or bronchial hypersecretion may cause respiratory problems in children. Thrombophlebitis has been associated with intravenous use and may be avoided by injection into a large vein at a rate not exceeding 500 micrograms/minute. Respiration and blood pressure should also be monitored.

Care is required when withdrawing clonazepam therapy—see above.

Breast feeding. Benzodiazepines, such as clonazepam, given to the mother may cause neonatal sedation and breast feeding should be avoided. For comments on antiepileptic therapy and breast feeding, see p. 508.3.

Driving. For a comment on antiepileptic drugs and driving, see p. 509.2.

Effects on the endocrine system. Precocious development of secondary sexual characteristics occurred in a 15-month-old girl 2 months after starting treatment with clonazepam 500 micrograms twice daily for convulsions.[1] Symptoms regressed upon withdrawal of clonazepam.

1. Choonara IA, *et al.* Clonazepam and sexual precocity. *N Engl J Med* 1985; **312:** 185.

Effects on mental function. For a review of the effects of antiepileptic therapy, including clonazepam, on *cognition* and *mood*, including the risk of suicidal ideation, see p. 508.3.

Effects on the mouth. A 52-year-old woman developed burning mouth syndrome after starting clonazepam;[1] some improvement was noted when the dose was reduced but symptoms were still intolerable and clonazepam was withdrawn. Subsequently, symptoms resolved within 3 weeks.

1. Culhane NS, Hodle AD. Burning mouth syndrome after taking clonazepam. *Ann Pharmacother* 2001; **35:** 874–6.

Effects on sexual function. Sexual dysfunction was reported[1] in 18 of 42 male patients receiving clonazepam for the treatment of post-traumatic stress disorder; symptoms resolved when therapy was changed to diazepam in 17 patients and lorazepam in the remaining patient.

1. Fossey MD, Hamner MB. Clonazepam-related sexual dysfunction in male veterans with PTSD. *Anxiety* 1994-95; **1:** 233–6.

Extrapyramidal disorders. For reference to extrapyramidal disorders associated with the use of benzodiazepines including clonazepam, see Effects on the Nervous System, under Diazepam, p. 1066.1. However, clonazepam is also used in the treatment of some extrapyramidal disorders as discussed under Uses and Administration, p. 519.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies clonazepam as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pregnancy. For comments on the management of epilepsy during pregnancy, see p. 509.2.

Interactions

As for Diazepam, p. 1068.1.

Antiepileptics. For reference to possible interactions between clonazepam and other antiepileptics, see under Diazepam, p. 1069.1 and Benzodiazepines, under Interactions of Phenytoin, p. 544.2.

Pharmacokinetics

Clonazepam is quickly absorbed after oral doses with a bioavailability of about 90%; peak plasma concentrations occur between 1 and 4 hours after ingestion. It is extensively metabolised in the liver, its principal metabolite being 7-aminoclonazepam, which has no antiepileptic activity; minor metabolites are the 7-acetamido- and 3-hydroxy-derivatives. It is excreted mainly in the urine almost entirely as its metabolites in free or conjugated form. It is about 85% bound to plasma proteins and estimations of its elimination half-life range from about 20 to 40 hours, and occasionally more.

A therapeutic range of plasma concentrations has not been established.

Clonazepam crosses the placental barrier and is distributed into breast milk.

The pharmacokinetics of clonazepam may be affected by use with other antiepileptics (see under Interactions, above).

A single-dose pharmacokinetic study[1] in healthy subjects found that absorption of clonazepam was slower and intersubject variability was greater after intramuscular injection than after an oral dose. The pharmacokinetics of a modified-release subcutaneous injection have also been studied in healthy subjects;[2] plasma-clonazepam concentrations were sustained and elimination occurred slowly over 13 days.

1. Crevoisier C, *et al.* Comparative single-dose pharmacokinetics of clonazepam following intravenous, intramuscular and oral administration to healthy volunteers. *Eur Neurol* 2003; **49:** 173–7.
2. Greenblatt DJ, *et al.* Clonazepam pharmacokinetics: comparison of subcutaneous microsphere injection with multiple-dose oral administration. *J Clin Pharmacol* 2005; **45:** 1288–93.

Bioavailability. It has been suggested, on the basis of anecdotal evidence,[1] that there may be differences in bioavailability, and hence in clinical effect, between formulations of clonazepam tablets.

1. Rapaport MH. Clinical differences between the generic and nongeneric forms of clonazepam. *J Clin Psychopharmacol* 1997; **17:** 424.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Alerion†; Ciclox; Clonabay; Clonagin; Clonasedan; Clonax; Clonazen 2; Cloner; Diocam; Edictum; Felanor†; Flozepan; Induzepam; Leptic; Miozepam†; Neuryl; Olimer†; Paditex; Placidiax†; Ribocler; Riuclonaz; Rivocler; Rivotril; Sedovanon; Sensaton; Sollidin; Tecepin; ***Austral.***: Paxam; Rivotril; ***Austria***: Rivotril; ***Belg.***: Rivotril; ***Braz.***: Clonotril; Clopan†; Epileptil; Navotrax; Rivotril; Uni Clonazepax; ***Canad.***: Clonapam; Rivotril; ***Chile***: Acepran; Celaxin; Clonapam; Clonex; Clozanil; Crismol; Neuryl; Ravotril; Ropsil; Valpax; ***China***: Jing Kang (静康); ***Cz.***: Rivotril; ***Denm.***: Rivotril; ***Fin.***: Rivatril; ***Fr.***: Rivotril; ***Ger.***: Rivotril; ***Gr.***: Rivotril; ***Hong Kong***: Rivotril; ***Hung.***: Clonapam†; Rivotril; ***India***: Alkona; Anxrea; Clon; Clonafit; Clonapax; Clonapik; Clonatrac; Clonopam; Clonotril; Clopam; Closed; Clozep; Convadon; Copam; Czap; Epcon; Epitril; Epizam; Incloz; Logen-MD; Lonazep; Lonin; Lonna; Lozep; Melzap; Norep; Onz; Ozepam; Pinlik; ***Indon.***: Riklona; Rivotril; ***Irl.***: Rivotril; ***Israel***: Clonex; Rivotril; ***Ital.***: Rivotril; ***Malaysia***: Rivopam; Rivotril; ***Mex.***: Clozer; Kenoket; Kriadex; Panazeclox; Rivotril; Zymanta; ***Neth.***: Rivotril; ***Norw.***: Rivotril; ***NZ***: Paxam; Rivotril; ***Philipp.***: Clonotril; Rivotril; ***Pol.***: Rivotril†; ***Port.***: Rivotril; ***Rus.***: Rivotril (Ривотрил); ***S.Afr.***: Rivotril; ***Singapore***: Clonotril; Rivotril; ***Spain***: Rivotril; ***Swed.***: Iktorivil; ***Switz.***: Rivotril; ***Thai.***: Clonaril; Convulsil; Povanil; Prenarpil; Rivotril; ***Turk.***: Rivotril; ***UK***: Rivotril; ***USA***: Klonopin; ***Venez.***: Rivotril.

Multi-ingredient Preparations. *India*: C-Pram-S Plus; Cita-S Forte; Cita-S Plus; Ecitalop-C; Escin Plus; Escita Plus; Escicrac-CZ; Esfany-CZ; Esitor Forte; Esjoy Plus; Espar-CL; Estorline Zee; Estomine-SF; Feliz-S Plus; Nexito Forte; Nexito-Plus.

Pharmacopoeial Preparations

BP 2014: Clonazepam Injection; Clonazepam Oral Suspension; Clonazepam Tablets;

USP 36: Clonazepam Oral Suspension; Clonazepam Orally Disintegrating Tablets; Clonazepam Tablets.

Eslicarbazepine *(BAN, USAN, rINN)*

BIA-2-194; Eslicarbazepina; Eslicarbazépine; Eslicarbazepinum; Эсликарбазепин.

(10*S*)-10-Hydroxy-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide.

$C_{15}H_{14}N_2O_2$=254.3

CAS — 104746-04-5.

ATC — N03AF04.

ATC Vet — QN03AF04.

UNII — SSVXA428R4.

Eslicarbazepine Acetate *(BANM, USAN, rINNM)*

Acetato de eslicarbazepina; BIA-2-093; Eslicarbazépine, Acétate d'; Eslicarbazepini Acetas; SEP-0002093; Эсликарбазепин Ацетат.

$C_{17}H_{16}N_2O_3$=296.3

CAS — 236395-14-5.

ATC — N03AF04.

ATC Vet — QN03AF04.

UNII — BEA68ZVB2K.

NOTE. The name Stedesa has been used as a trade mark for eslicarbazepine acetate.

Profile

Eslicarbazepine is the *S*-enantiomer of licarbazepine, the active monohydroxy metabolite of oxcarbazepine (p. 533.2). It is used as adjunctive therapy in partial seizures with or without secondary generalisation (p. 506.1) in patients aged 18 years and older. Eslicarbazepine is given orally as the acetate and doses are expressed in terms of this salt.

The initial dose is 400 mg once daily, increased to 800 mg daily after 1 or 2 weeks. This dose may be further increased to 1.2 g daily according to response.

Reduced doses are recommended in patients with renal impairment (see below).

References.

1. Almeida L, *et al.* Single-dose and steady-state pharmacokinetics of eslicarbazepine acetate (BIA 2-093) in healthy elderly and young subjects. *J Clin Pharmacol* 2005; **45:** 1062–6.
2. McCormack PL, Robinson DM. Eslicarbazepine acetate. *CNS Drugs* 2009; **23:** 71–9.
3. Elger C, *et al.* Efficacy and safety of eslicarbazepine acetate as adjunctive treatment in adults with refractory partial-onset seizures: a randomized, double-blind, placebo-controlled, parallel-group phase III study. *Epilepsia* 2009; **50:** 454–63.
4. Rauchenzauner M, Luef G. Update on treatment of partial onset epilepsy: role of eslicarbazepine. *Neuropsychiatr Dis Treat* 2010; **6:** 723–30.
5. Chang XC, *et al.* Eslicarbazepine acetate add-on for drug-resistant partial epilepsy. Available in The Cochrane Database of Systematic Reviews; Issue 12. Chichester: John Wiley; 2011 (accessed 16/11/12).
6. Bialer M, Soares-da-Silva P. Pharmacokinetics and drug interactions of eslicarbazepine acetate. *Epilepsia* 2012; **53:** 935–46.

Administration in renal impairment. The initial oral dose of eslicarbazepine acetate for patients with a creatinine clearance (CC) of 30 to 60 mL/min is 400 mg every other day for 2 weeks followed by a once-daily dose of 400 mg; this dose may be further increased according to response. Use in severe impairment (CC less than 30 mL/min) is not recommended due to a lack of data.

Reference to the effect of renal impairment on the pharmacokinetics of eslicarbazepine acetate.[1]

1. Maia J, *et al.* Effect of renal impairment on the pharmacokinetics of eslicarbazepine acetate. *Int J Clin Pharmacol Ther* 2008; **46:** 119–30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Zebinix; *Cz.*: Exalief†; Zebinix; *Denm.*: Zebinix; *Fr.*: Zebinix; *Ger.*: Zebinix; *Gr.*: Zebinix; *Irl.*: Exalief†; Zebinix; *Neth.*: Exalief†; Zebinix; *Norw.*: Zebinix; *Pol.*: Exalief†; Zebinix; *Port.*: Exalief†; Zebinix; *Spain*: Zebinix; *Swed.*: Zebinix; *UK*: Zebinix; *USA*: Aptiom.

Ethosuximide *(BAN, USAN, rINN)*

CI-366; CN-10395; Ethosuximid; Éthosuximide; Ethosuximidum; Etosüksimid; Etosuksimidas; Etosuksimidi; Etosuksymid; Etosuximid; Etosuximida; Etoszuximid; NSC-64013; PM-671; Этосуксимид.

2-Ethyl-2-methylsuccinimide.

$C_7H_{11}NO_2$=141.2

CAS — 77-67-8.

ATC — N03AD01.

ATC Vet — QN03AD01.

UNII — 5SEH9X1D1D.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Ethosuximide). A white or almost white powder or waxy solid. It exhibits polymorphism. Freely soluble in water; very soluble in alcohol and in dichloromethane. Protect from light.

USP 36: (Ethosuximide). A white to off-white crystalline powder or waxy solid, having a characteristic odour. Freely soluble in water and in chloroform; very soluble in alcohol and in ether; very slightly soluble in petroleum spirit. Store in airtight containers.

Uses and Administration

Ethosuximide is a succinimide antiepileptic used in the treatment of absence seizures (below). It may also be used for myoclonic seizures. Ethosuximide is ineffective against tonic-clonic seizures and may unmask them if given alone in mixed seizure types. However, it is occasionally helpful for atonic and tonic seizures.

A plasma-ethosuximide concentration of 40 to 100 micrograms/mL (about 300 to 700 micromoles/litre) appears to be generally necessary. The initial oral dose is 500 mg daily. The dosage is then adjusted in steps of 250 mg every 4 to 7 days, according to response. Control of seizures is usually produced with a daily dose of 1 to 1.5 g, although some patients may require doses of up to 2 g; strict supervision is necessary when the dose exceeds 1.5 g. Daily doses at the higher end of the range should be given in 2 divided doses.

For doses in children, see below.

As with other antiepileptics, withdrawal of ethosuximide therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1.

Administration in children. Ethosuximide may be used in the treatment of absence (petit mal) seizures and for myoclonic seizures in infants and children. In the UK, the following recommended oral doses are given according to age:

- up to 6 years of age: an initial dose of 250 mg daily, increased gradually in small steps every few days to a usual dose of 20 mg/kg daily; licensed information for one product (*Emeside; Chemidex, UK*) recommends that the dose should not exceed 1 g. (Similar dosages are recommended in the USA for children aged between 3 to 6 years). The *BNFC* suggests giving the daily dose as 2, or if necessary 3, divided doses
- aged 6 years and above: usual adult doses (see above)

Epilepsy. Ethosuximide is a drug of choice in the treatment of absence seizures; it may also be used for myoclonic, atonic, and tonic seizures but is ineffective in other forms of epilepsy (p. 506.1). Ethosuximide may be given with other antiepileptics in the treatment of mixed-seizure syndromes that include absences. It has been suggested that ethosuximide may provoke tonic-clonic seizures, but there is not a great deal of evidence for this. One early report indicated that 22 of 85 patients receiving a regimen of ethosuximide, mesuximide, and trimethadione for absence seizures developed tonic-clonic seizures[1] and another of similar vintage reported exacerbation of mixed-seizure types in 7 patients receiving ethosuximide.[2] However, it is recognised that patients with absence seizures have a high incidence of generalised tonic-clonic seizures[3] and it would presumably be difficult to distinguish such attacks from any putative effect of ethosuximide. Furthermore, ethosuximide is not effective against tonic-clonic seizures, and in patients with mixed-seizure types it might be expected to unmask the non-absence components of the disease. A retrospective comparison[4] in patients with absence seizures found no evidence that ethosuximide was associated with a greater risk of generalised tonic-clonic seizures than valproate.

Ethosuximide has also been tried in the management of absence status epilepticus (p. 510.2).

1. Friedel B, Lempp R. Grand-mal-Provokation bei der Behandlung kindlicher petit-mal mit Oxazolidinen oder Succinimiden und ihre therapeutischen Konsequenzen. *Z Kinderheilk* 1962; **87**: 42–51.
2. de Haas AML, Kuilman M. Ethosuximide (α -ethyl- α -methylsuccinimide) and grand mal. *Epilepsia* 1964; **5**: 90–6.
3. Glauser TA. Succinimides: Adverse Effects. In: Levy RG, *et al.*, eds. *Antiepileptic drugs* 5th ed. Philadelphia: Lippincott Williams & Wilkins, 2002: 658–64.
4. Schmitt B, *et al.* Is ethosuximide a risk factor for generalised tonic-clonic seizures in absence epilepsy? *Neuropediatrics* 2007; **38**: 83–7.

Adverse Effects and Treatment

Gastrointestinal adverse effects including nausea, vomiting, diarrhoea, anorexia, gastric upset, and abdominal pain occur quite often with ethosuximide. Other effects that may occur include headache, fatigue, lethargy, drowsiness, dizziness, ataxia, hiccup, and mild euphoria.

More rarely dyskinesias, personality changes, depression, psychosis, sleep disturbances including night terrors, skin rashes, erythema multiforme or Stevens-Johnson syndrome, SLE, photophobia, gum hypertrophy, tongue swelling, myopia, increased libido, and vaginal bleeding have been reported. There are a few reports of blood disorders including eosinophilia, leucopenia, agranulocytosis, thrombocytopenia, pancytopenia, and aplastic anaemia; fatalities have occurred.

Abnormal renal and liver function values have been recorded.

Effects on mental function. For the effects of antiepileptic therapy on *cognition* and *mood*, including the risk of suicidal ideation, see p. 508.3.

Precautions

Ethosuximide should be used with caution in patients with impaired hepatic or renal function. Licensed product information recommends regular hepatic and renal-function tests (and some suggest blood counts) during treatment with ethosuximide, although the practical value of such monitoring has been questioned. Patients or their carers should be told how to recognise signs of blood toxicity and they should be advised to seek immediate medical attention if symptoms such as fever, sore throat, mouth ulcers, bruising, or bleeding develop.

Care is required when withdrawing ethosuximide therapy—see also Uses and Administration, above.

Breast feeding. Ethosuximide is distributed in significant amounts into breast milk; hyperexcitability and poor suckling have been reported in the infant. Although licensed product information recommends that breast feeding should be avoided, the American Academy of Pediatrics[1] considers that ethosuximide is usually compatible with breast feeding.

For further comment on antiepileptic therapy and breast feeding, see p. 508.3.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 09/06/08)

Driving. For a comment on antiepileptic drugs and driving, see p. 509.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ethosuximide as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pregnancy. For comments on the management of epilepsy during pregnancy, see p. 509.2.

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy.

Antibacterials. *Isoniazid* raises the plasma concentration of ethosuximide and increases the risk of toxicity. Psychotic behaviour has been reported[1] in a patient stabilised on ethosuximide and sodium valproate, after the introduction of isoniazid. Serum-ethosuximide concentrations rose substantially until both ethosuximide and isoniazid were stopped.

1. van Wieringen A, Vrijlandt CM. Ethosuximide intoxication caused by interaction with isoniazid. *Neurology* 1983; **33**: 1227–8.

Antidepressants. As with all antiepileptics, antidepressants may antagonise the antiepileptic activity of ethosuximide by lowering the convulsive threshold.

Antiepileptics. Since ethosuximide has a limited spectrum of antiepileptic action, patients with mixed seizure syndromes may require addition of other antiepileptics. *Carbamazepine, phenobarbital,* and *phenytoin* have all been shown[1] to increase the clearance of ethosuximide and thus reduce plasma concentrations. This interaction is likely to be clinically relevant and higher ethosuximide dosages may be necessary to achieve therapeutic drug levels. The effect of *valproic acid* on ethosuximide concentrations is unclear. One study[2] showed a marked increase in serum ethosuximide concentrations once valproate was added to combination therapies; increases in ethosuximide concentrations have also been noted in healthy subjects when taken with valproic acid.[3] Conversely, other studies have reported reductions[4] or no significant changes in serum ethosuximide concentrations[5,6] with valproic acid. For the effect of ethosuximide on valproic acid, see p. 557.3.

1. Giaccone M, *et al.* Effect of enzyme inducing anticonvulsants on ethosuximide pharmacokinetics in epileptic patients. *Br J Clin Pharmacol* 1996; **41**: 575–9.
2. Mattson RH, Cramer JA. Valproic acid and ethosuximide interaction. *Ann Neurol* 1980; **7**: 583–4.
3. Pisani F, *et al.* Valproic acid-ethosuximide interaction: a pharmacokinetic study. *Epilepsia* 1984; **25**: 229–33.
4. Battino D, *et al.* Ethosuximide plasma concentrations: influence of age and associated concomitant therapy. *Clin Pharmacokinet* 1982; **7**: 176–80.
5. Fowler GW. Effect of dipropylacetate on serum levels of anticonvulsants in children. *Proc West Pharmacol Soc* 1978; **21**: 37–40.
6. Bauer LA, *et al.* Ethosuximide kinetics: possible interaction with valproic acid. *Clin Pharmacol Ther* 1982; **31**: 741–5.

Antipsychotics. As with all antiepileptics, antipsychotics may antagonise the antiepileptic activity of ethosuximide by lowering the convulsive threshold.

Pharmacokinetics

Ethosuximide is readily absorbed from the gastrointestinal tract and extensively hydroxylated in the liver to its principal metabolite which is reported to be inactive. Ethosuximide is excreted in the urine mainly in the form of its metabolites, either free or conjugated, but about 12 to 20% is also excreted unchanged.

Ethosuximide is widely distributed throughout the body, but is not significantly bound to plasma proteins. A half-life of about 40 to 60 hours has been reported for adults with a shorter half-life of about 30 hours in children.

Monitoring of plasma concentrations has been suggested as an aid in assessing control and the therapeutic range of ethosuximide is usually quoted as being 40 to 100 micrograms/mL (about 300 to 700 micromoles/litre); concentrations in saliva and tears have also been measured.

Ethosuximide crosses the placental barrier, and is distributed into breast milk.

The pharmacokinetics of ethosuximide are affected by use with other antiepileptics (see under Interactions, above).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Zarontin; *Austral.*: Zarontin; *Austria*: Petinimid; Suxinutin†; *Belg.*: Zarontin; *Braz.*: Etoxin; *Canad.*: Zarontin; *Chile*: Suxinutin†; *Cz.*: Petinimid; *Denm.*: Zarondan; *Fr.*: Zarontin; *Ger.*: Petnidan; Suxilep; *Gr.*: Petinimid; Zarontin; *Hung.*: Petnidan; *Irl.*: Zarontin; *Ital.*: Zarontin; *Mex.*: Fluozoid; *Neth.*: Ethymal; *NZ*: Zarontin; *Pol.*: Petinimid; *Rus.*: Suxilep (Сукилеп); *S.Afr.*: Zarontin; *Swed.*: Suxinutin; *Switz.*: Petinimid; *Turk.*: Petimid; *UK*: Emeside; Zarontin; *USA*: Zarontin.

Pharmacopoeial Preparations

BP 2014: Ethosuximide Capsules; Ethosuximide Oral Solution;
USP 36: Ethosuximide Capsules; Ethosuximide Oral Solution.

Ethotoin *(BAN, rINN)*

Ethotoïne; Ethotoinum; Etotoiini; Etotoin; Etotoína; Этотоин.

3-Ethyl-5-phenylhydantoin.

$C_{11}H_{12}N_2O_2$=204.2

CAS — 86-35-1.

ATC — N03AB01.

ATC Vet — QN03AB01.

UNII — 46QG38NC4U.

Pharmacopoeias. In *US*.

USP 36: (Ethotoin). A white crystalline powder. Insoluble in water; freely soluble in dehydrated alcohol and in chloroform; soluble in ether. Store in airtight containers.

Profile

Ethotoin is a hydantoin antiepileptic with actions similar to those of phenytoin (p. 538.2), but it is reported to be both less toxic and less effective and is not commonly used in epilepsy (p. 506.1).

Ethotoin is given orally for tonic-clonic and complex partial seizures in initial doses of up to 1 g daily, increased gradually at intervals of several days to 2 to 3 g daily, given in 4 to 6 divided doses after meals.

Administration. A study[1] of the pharmacokinetics of ethotoin given at more convenient intervals of every 8 hours.

1. Browne TR, Szabo GK. A pharmacokinetic rationale for three times daily administration of ethotoin (Peganone). *J Clin Pharmacol* 1989; 29: 270–1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Peganone.

Pharmacopoeial Preparations
USP 36: Ethotoin Tablets.

Felbamate *(USAN, rINN)*

AD-03055; Felbamato; Felbamatum; W-554; Фелбамат.
2-Phenyl-1,3-propanediol dicarbamate.
$C_{11}H_{14}N_2O_4$=238.2
CAS — 25451-15-4.
ATC — N03AX10.
ATC Vet — QN03AX10.
UNII — X72RBB02N8.

Pharmacopoeias. In *US*.

USP 36: (Felbamate). A white to off-white powder. Very slightly soluble in water; sparingly soluble in methyl alcohol; freely soluble in dimethyl sulfoxide; slightly soluble in acetonitrile.

Uses and Administration

Felbamate is a carbamate structurally related to meprobamate (p. 1083.3). It is used in the treatment of epilepsy (below); however, because of its toxicity, it should only be used in severe cases unresponsive to other drugs.

Felbamate is given orally as monotherapy or adjunctive therapy for refractory partial seizures with or without secondary generalisation. It is used in children as adjunctive therapy in controlling the seizures associated with the Lennox-Gastaut syndrome (see below).

The initial dose of felbamate when given as *monotherapy* is 1.2 g daily in 3 or 4 divided doses. The daily dose should be increased gradually under close supervision; increments of 600 mg every 2 weeks are given according to response, up to 2.4 g daily. Thereafter doses may be further increased to a maximum of 3.6 g daily if necessary.

Similar initial doses are given as *adjunctive* therapy, but the doses of the other antiepileptics should be decreased as necessary. This adjunctive dose may be increased by 1.2 g at weekly intervals, up to a maximum of 3.6 g daily.

As with other antiepileptics, withdrawal of felbamate therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1.

References.
1. Pellock JM, *et al.* Felbamate: consensus of current clinical experience. *Epilepsy Res* 2006; 71: 89–101.

Administration in children. As an adjunct in Lennox-Gastaut syndrome, the initial oral dose of felbamate in children aged 2 to 14 years is 15 mg/kg daily in 3 or 4 divided doses. This may be increased gradually in increments of 15 mg/kg at weekly intervals to a maximum of 45 mg/kg daily; the doses of other antiepileptics should be decreased as necessary. The efficacy and tolerability of felbamate in children under 4 years of age have been discussed.[1]

Those aged 14 years and over may be given the usual adult dose (see above) as monotherapy or adjunctive therapy for refractory partial seizures with or without secondary generalisation.

1. Grosso S, *et al.* Efficacy and safety of felbamate in children under 4 years of age: a retrospective chart review. *Eur J Neurol* 2008; 15: 940–6.

Administration in the elderly. The elderly may require lower initial doses of felbamate and slower dose titration. After single doses of felbamate, plasma concentrations and half-lives were greater and mean clearance lower in elderly than in young subjects, whereas pharmacokinetic parameters after multiple dosing schedules were similar.[1]

1. Richens A, *et al.* Single and multiple dose pharmacokinetics of felbamate in the elderly. *Br J Clin Pharmacol* 1997; 44: 129–34.

Administration in renal impairment. A single-dose pharmacokinetic study[1] indicated that in patients with renal impairment the initial dose of felbamate may need to be lower and increases made more cautiously than in patients with normal renal function (licensed product information suggests halving initial and maintenance doses).

1. Glue P, *et al.* Single-dose pharmacokinetics of felbamate in patients with renal dysfunction. *Br J Clin Pharmacol* 1997; 44: 91–3.

Epilepsy. Although felbamate was well tolerated in clinical studies, rare but serious adverse effects were noted during early postmarketing use.[1,2] Aplastic anaemia and serious hepatotoxic reactions, sometimes with fatal outcomes, developed in some patients. Patients taking felbamate should have frequent blood counts and monitoring of liver enzymes. However there is no evidence that such monitoring will prevent adverse outcomes; in addition, the risk of aplastic anaemia is thought to decrease after the first year of therapy, and the need for ongoing blood counts is still less clear.[3] Successful long-term use has been described.[4] Even if detected early, aplastic anaemia and hepatic impairment may not be reversible.[1] Usage in the USA is restricted to patients with refractory partial seizures with or without secondary generalisation or for adjunctive therapy for children with Lennox-Gastaut syndrome. Guidelines on appropriate use have been issued.[3]

The overall management of epilepsy is discussed on p. 506.1.

1. Dichter MA, Brodie MJ. New antiepileptic drugs. *N Engl J Med* 1996; 334: 1583–90.
2. Appleton RE. The new antiepileptic drugs. *Arch Dis Child* 1996; 75: 256–62.
3. French J, *et al.* The use of felbamate in the treatment of patients with intractable epilepsy. Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia* 1999; 40: 803–8. Also available at: http://www3.interscience.wiley.com/cgi-bin/fulltext/119061174/PDFSTART (accessed 01/09/08)
4. White JR, *et al.* Long-term use of felbamate: clinical outcomes and effect of age and concomitant antiepileptic drug use on its clearance. *Epilepsia* 2009; 50: 2390–6.

Adverse Effects

The most frequently reported adverse effects with felbamate are anorexia, weight loss, nausea and vomiting, rash, insomnia, headache, dizziness, somnolence, and diplopia. Aplastic anaemia or acute liver failure, sometimes fatal, have occurred rarely, and there have been reports of Stevens-Johnson syndrome.

Effects on the kidneys. A 15-year-old boy given up to 3 g of felbamate daily developed urethral obstruction due to formation of urethral stones composed of felbamate.[1] Records revealed that 2 years earlier unidentified urinary crystals had been found in the patient's urine.

For reports of crystalluria associated with felbamate overdosage, see below.

1. Sparagana SP, *et al.* Felbamate urolithiasis. *Epilepsia* 2001; 42: 682–5.

Effects on mental function. For the effects of antiepileptic therapy on *cognition* and *mood*, including the risk of suicidal ideation, see p. 508.3

Effects on the skin. Toxic epidermal necrolysis has been reported[1] in a patient 16 days after she started monotherapy with felbamate for partial complex seizures.

1. Travaglini MT, *et al.* Toxic epidermal necrolysis after initiation of felbamate therapy. *Pharmacotherapy* 1995; 15: 260–4.

Overdosage. A 20-year-old woman presented with slurred speech and nausea 4 hours after ingesting 18 g of felbamate and 12 to 25 g of sodium valproate.[1] Over the next 4 to 5 hours she became combative, uncooperative, and progressively obtunded and eventually required endotracheal intubation and assisted ventilation. Peak plasma concentrations of 200 micrograms/mL for felbamate and 470 micrograms/mL for sodium valproate occurred 12 and 14 hours, respectively, after ingestion. Large quantities of macroscopic crystals, identified as containing felbamate, were noted in the urine 18 hours after ingestion and the patient developed renal failure. The crystalluria and renal failure responded to parenteral hydration. In another case report,[2] a 3-year-old child ingested 232 mg/kg of felbamate resulting in ataxia, vomiting, crystalluria, haematuria, and mild tachycardia. The plasma concentration of felbamate 15 hours after ingestion was 138 micrograms/mL. She was successfully treated with an infusion of sodium chloride 0.9% and intravenous metoclopramide; no renal impairment was seen.

1. Rengstorff DS, *et al.* Felbamate overdose complicated by massive crystalluria and acute renal failure. *J Toxicol Clin Toxicol* 2000; 38: 667–9.
2. Meier KH, *et al.* Acute felbamate overdose with crystalluria. *Clin Toxicol* 2005; 43: 189–92.

Precautions

Felbamate is contra-indicated in patients with a history of blood disorders or hepatic impairment. It should be used only in the treatment of severe epilepsy refractory to other antiepileptics because of the risk of fatal aplastic anaemia or acute liver failure. Patients or their carers should be advised of the symptoms of aplastic anaemia and be told to report immediately should any such symptoms develop. Complete blood counts should be carried out before the patient starts treatment and regularly during treatment (but see Epilepsy, under Uses and Administration, above). Aplastic anaemia may occur after felbamate has been stopped so patients should continue to be monitored for some time. Liver function tests are also recommended before starting and regularly (at 1- to 2-week intervals) during treatment. Felbamate should be stopped if there is any evidence of bone marrow depression or liver abnormalities.

Felbamate should be used with caution in patients with renal impairment. Felbamate may cause photosensitivity reactions and patients should be advised to take protective measures against exposure to UV radiation.

Care is required when withdrawing felbamate therapy — see also Uses and Administration, above.

Breast feeding. For comment on antiepileptic therapy and breast feeding, see p. 508.3.

Driving. For a comment on antiepileptic drugs and driving, see p. 509.2.

The elderly. Felbamate may need to be given with care in elderly patients (see Administration in the Elderly, above).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies felbamate as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pregnancy. For comments on the management of epilepsy during pregnancy, see p. 509.2.

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy. The metabolism of felbamate is enhanced by enzyme inducers such as phenytoin, phenobarbital, or carbamazepine. In contrast, the half-life of felbamate may be prolonged by gabapentin. Felbamate inhibits or enhances the metabolism of several other antiepileptics and care is required when it is added to therapy.

Anticoagulants. For the effect of felbamate on *warfarin*, see p. 1532.1.

Antiepileptics. For some references to the effect of felbamate on other antiepileptics, see under *Carbamazepine*, p. 516.3, *Phenobarbital*, p. 537.2, *Phenytoin*, p. 543.2, and *Valproate* p. 557.3.

Sex hormones. For the effect of felbamate on *oral contraceptives*, see p. 2243.2 and also under Gestodene, p. 2279.3.

Pharmacokinetics

Felbamate is well absorbed from the gastrointestinal tract and peak plasma concentrations have occurred 1 to 6 hours after oral doses. Protein binding is reported to be about 22 to 25%. It is partly metabolised in the liver by hydroxylation and conjugation to inactive metabolites. Felbamate is excreted mainly in the urine as metabolites and unchanged drug (40 to 50%); less than 5% appears in the faeces. The terminal half-life is reported to be between 16 and 23 hours. Felbamate is distributed into breast milk.

The pharmacokinetics of felbamate are reported to be linear at clinical doses. Therapeutic plasma concentrations have been reported to be between 30 and 80 micrograms/mL.

The pharmacokinetics of felbamate are affected by use with other antiepileptics (see Interactions, above).

See under Uses and Administration (above) for mention of pharmacokinetic studies of felbamate in the elderly and in patients with renal impairment.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Felbamyl; *Austria*: Taloxa; *Belg.*: Taloxa; *Fr.*: Taloxa; *Ger.*: Taloxa; *Gr.*: Taloxa; *Hung.*: Taloxa; *Ital.*: Taloxa; *Neth.*: Taloxa; *Norw.*: Taloxa; *Port.*: Taloxa; *Swed.*: Taloxa; *Switz.*: Taloxa; *USA*: Felbatol.

Pharmacopoeial Preparations
USP 36: Felbamate Oral Suspension; Felbamate Tablets.

Fosphenytoin Sodium

(BANM, USAN, rINNM)

ACC-9653-010; ACC-9653; CI-982 (fosphenytoin or fosphenytoin sodium); Fosfenitoin Sodyum; Fosfenitoína sódica; Fosphénytoïne Sodique; Natrii Fosphenytoinum; PD-135711-158; Натрий Фосфенитоин.

5,5-Diphenyl-3-[(phosphonooxy)methyl]-2,4-imidazolidinedione disodium; 3-(Hydroxymethyl)-5,5-diphenylhydantoin disodium phosphate; 2,5-Dioxo-4,4-diphenylimidazolidin-1-ylmethyl phosphate disodium.

$C_{16}H_{13}N_2Na_2O_6P$=406.2

CAS — 93390-81-9 (fosphenytoin); 92134-98-0 (fosphenytoin sodium).

ATC — N03AB05.

ATC Vet — QN03AB05.

UNII — 7VLR55452Z.

Pharmacopoeias. In *US*.

USP 36: (Fosphenytoin Sodium). A white to pale yellow solid. Freely soluble in water. pH of a 7.5% solution in water is between 8.5 and 9.5. Store in airtight containers.

Stability. References.
1. Fischer JH, *et al.* Stability of fosphenytoin sodium with intravenous solutions in glass bottles, polyvinyl chloride bags, and polypropylene syringes. *Am Pharmacother* 1997; 31: 553–9.

Uses and Administration

Fosphenytoin is a prodrug of phenytoin (p. 538.2) used similarly as part of the emergency treatment of status epilepticus (p. 510.2). It is also used for the prevention and treatment of post-traumatic seizures (p. 539.3) associated with neurosurgery or head trauma and as a short-term parenteral substitute for oral phenytoin in the management of epilepsy (p. 506.1).

Fosphenytoin is given as the sodium salt and doses of fosphenytoin sodium are expressed as phenytoin sodium equivalents (PSE); therefore no adjustment in dosage is necessary when substituting fosphenytoin for phenytoin or vice versa. Fosphenytoin may be given by intramuscular injection or intravenous infusion; only the intravenous route is recommended in children.

The maximum rate of intravenous infusion in PSE is 150 mg/minute and should not be exceeded. Continuous monitoring of ECG, blood pressure, and respiratory function is recommended during intravenous infusion. Patients should also be observed for at least 30 minutes after the end of infusion.

In the treatment of tonic-clonic status epilepticus a benzodiazepine such as diazepam or lorazepam is usually given initially intravenously or rectally followed by fosphenytoin. In the UK, the loading dose in PSE is 15 mg/kg given as a single dose by intravenous infusion at a rate of 100 to 150 mg/minute. The intramuscular route is not appropriate for the management of status epilepticus because peak phenytoin concentrations will not be reached quickly enough. The loading dose for seizures other than in status epilepticus is 10 to 15 mg/kg given as a single dose by intramuscular injection or by intravenous infusion at a rate of 50 to 100 mg/minute. Initial maintenance doses for status epilepticus and other seizures are 4 to 5 mg/kg daily given in 1 or 2 divided doses by intramuscular injection or by intravenous infusion at a rate of 50 to 100 mg/minute. Subsequent doses are dependent on patient response and trough plasma-phenytoin concentrations.

Fosphenytoin given intramuscularly or by intravenous infusion at a rate of 50 to 100 mg/minute may be substituted for oral phenytoin at the same equivalent total daily dose for up to 5 days.

In the USA, loading doses in PSE of up to 20 mg/kg are permitted, and initial maintenance doses are 4 to 6 mg/kg daily.

For doses in children, see below.

A lower loading dose and/or infusion rate, and lower or less frequent maintenance dosing may be necessary for elderly patients; UK licensed product information suggests a reduction in dose or rate of 10 to 25%. Similar reductions are suggested for patients with renal or hepatic impairment (see also below) or in those with hypoalbuminaemia, except in the treatment of status epilepticus.

References.
1. Wilder BJ, *et al.* Safety and tolerance of multiple doses of intramuscular fosphenytoin substituted for oral phenytoin in epilepsy or neurosurgery. *Arch Neurol* 1996; 53: 764–8.
2. Meek PD, *et al.* Guidelines for nonemergency use of parenteral phenytoin products: proceedings of an expert panel consensus process. *Arch Intern Med* 1999; 159: 2639–44.
3. Heafield MTE. Managing status epilepticus: new drug offers real advantages. *BMJ* 2000; 320: 953–4.
4. DeToledo JC, Ramsay RE. Fosphenytoin and phenytoin in patients with status epilepticus: improved tolerability versus increased costs. *Drug Safety* 2000; 22: 459–66.
5. McCleane GJ. Intravenous infusion of fosphenytoin produces prolonged pain relief: a case report. *J Pain* 2002; 3: 156–8.
6. Fischer JH, *et al.* Fosphenytoin: clinical pharmacokinetics and comparative advantages in the acute treatment of seizures. *Clin Pharmacokinet* 2003; 42: 33–58.
7. Rudis MI, *et al.* Cost-effectiveness of oral phenytoin, intravenous phenytoin, and intravenous fosphenytoin in the emergency department. *Ann Emerg Med* 2004; 43: 386–97.
8. Eriksson K, *et al.* Fosphenytoin. *Expert Opin Drug Metab Toxicol* 2009; 5: 695–701.

Administration in children. In the UK, fosphenytoin sodium may be given to children over 5 years of age for the emergency treatment of status epilepticus, the prevention and treatment of post-traumatic seizures associated with neurosurgery or head trauma, and as a short-term parenteral substitute for oral phenytoin in the management of epilepsy. It is given by intravenous infusion and doses are expressed as phenytoin sodium equivalents (PSE).

In the treatment of tonic-clonic status epilepticus, the loading dose in PSE is 15 mg/kg given as a single dose at a rate of 2 to 3 mg/kg per minute; however, the *BNFC* allows 20 mg/kg. In the treatment or prophylaxis of seizures other than in status epilepticus, the loading dose in PSE is 10 to 15 mg/kg given as a single dose at a rate of 1 to 2 mg/kg per minute. The maximum rate of infusion of loading doses is 3 mg/kg per minute or 150 mg/minute and should not be exceeded. Initial maintenance doses in PSE for status epilepticus and other seizures are 4 to 5 mg/kg daily given in 1 to 4 divided doses at a rate of 1 to 2 mg/kg per minute, not exceeding 100 mg/minute. Subsequent doses are dependent on patient response and trough plasma-phenytoin concentrations.

Fosphenytoin given at a rate of 1 to 2 mg/kg per minute, not exceeding 50 to 100 mg/minute, may be substituted for oral phenytoin at equivalent total daily doses for up to 5 days.

Similar precautions to those in adults apply to the monitoring of clinical parameters and plasma-phenytoin concentrations in children (see above).

Administration in hepatic or renal impairment. The rate and extent of conversion of fosphenytoin to phenytoin in patients with hepatic cirrhosis or renal impairment requiring dialysis was not found to be significantly different from those for healthy controls.[1] However, there was a trend towards an increase in fosphenytoin clearance and a decrease in the time to peak phenytoin concentrations in those with hepatic or renal impairment. Consequently, the authors recommended that fosphenytoin may need to be given at lower doses or infused more slowly (see above for the licensed product recommendations).

1. Aweeka FT, *et al.* Pharmacokinetics of fosphenytoin in patients with hepatic or renal disease. *Epilepsia* 1999; 40: 777–82.

Adverse Effects and Precautions

As for Phenytoin, p. 540.1.

Severe cardiovascular reactions, sometimes fatal, have been reported after intravenous doses of fosphenytoin. Therefore, continuous monitoring of ECG, blood pressure, and respiratory function is recommended during the infusion, and the patient should be kept under observation for at least 30 minutes after the end of the infusion. Hypotension may occur with recommended doses and rates of infusion; a reduction in the infusion rate or stopping therapy may be necessary. Fosphenytoin is contra-indicated in patients with sinus bradycardia, sino-atrial block, second- or third-degree AV block, or Stokes-Adams syndrome.

Burning, itching, and paraesthesia, particularly in the groin area, have also been reported after intravenous fosphenytoin; reducing the rate of, or temporarily stopping, the infusion may relieve the discomfort.

Caution should be exercised when giving fosphenytoin to patients in whom phosphate restriction is necessary. The rate of metabolism of fosphenytoin to phenytoin may be increased in patients with hepatic or renal disease, or in those with hypoalbuminaemia, and consequently there is an increased risk of adverse effects in such patients.

Effects on the cardiovascular system. The UK CSM[1] stated in May 2000 that worldwide there had been reports of 21 cases of asystole, ventricular fibrillation, or cardiac arrest associated with intravenous use of fosphenytoin. Of these, 5 cases had received doses or infusion rates greater than recommended. There had also been 34 reports of hypotension, 15 of bradycardia, and 10 of varying degrees of heart block. Most reactions had occurred within 30 minutes of the infusion. A review[2] of adverse events associated with fosphenytoin infusion received by the FDA Adverse Event Reporting System between 1997 and 2002 identified 29 of adverse cardiac events, including 10 fatalities. Of these reports, 5 were of sinus arrest, 4 of AV block, and 8 of asystole. The authors acknowledged that the majority of patients had serious confounders including renal failure, stroke, acute cardiac ischaemia or failure, overdose, or infection.

ECG changes consistent with hypocalcaemia have occurred in a patient who received 1500 mg-equivalents of phenytoin over 85 minutes as an intravenous infusion of fosphenytoin.[3] The patient had initially been normocalcaemic and it was suggested that the effect may have been due to acute inorganic phosphate toxicity.

1. CSM/MCA. Fosphenytoin sodium (Pro-Epanutin): serious arrhythmias and hypotension. *Current Problems* 2000; 26: 1. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)
2. Adams BD, *et al.* Fosphenytoin may cause hemodynamically unstable bradydysrhythmias. *J Emerg Med* 2006; 30: 75–9.
3. Keegan MT, *et al.* Hypocalcemia-like electrocardiographic changes after administration of intravenous fosphenytoin. *Mayo Clin Proc* 2002; 77: 584–6.

Effects on the skin. For a possibly increased risk of severe skin reactions to fosphenytoin in patients with the HLA allele HLA-B*1502, see Skin Reactions, under Precautions of Phenytoin, p. 542.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fosphenytoin as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

As for Phenytoin, p. 542.1.

Pharmacokinetics

Plasma concentrations of fosphenytoin are maximal at the end of intravenous infusion and about 30 minutes after intramuscular injection. Protein binding of fosphenytoin is high (95 to 99%), mainly to albumin, and is saturable. Fosphenytoin displaces phenytoin from protein binding sites which increases the fraction of unbound phenytoin to up to 30% for about half to one hour post-infusion. Fosphenytoin is rapidly and completely hydrolysed to phenytoin with a conversion half-life of about 15 minutes; 1 mmol of fosphenytoin yields 1 mmol of phenytoin, and the same of phosphate and formate. Metabolites of phenytoin are excreted in the urine. For the pharmacokinetics of phenytoin, see p. 545.2.

References.
1. Fischer JH, *et al.* Fosphenytoin: clinical pharmacokinetics and comparative advantages in the acute treatment of seizures. *Clin Pharmacokinet* 2003; 42: 33–58.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Cerebyx; *Denm.*: Pro-Epanutin; *Fin.*: Pro-Epanutin; *Fr.*: Prodilantin; *Gr.*: Pro-Epanutin; *India*: Fosolin; Fosphen; *Irl.*: Pro-Epanutin; *Jpn*: Fostoin; *Norw.*: Pro-Epanutin; *Swed.*: Pro-Epanutin; *Thai.*: Cereneu; *UK*: Pro-Epanutin; *USA*: Cerebyx.

Pharmacopoeial Preparations
USP 36: Fosphenytoin Sodium Injection.

Gabapentin *(BAN, USAN, rINN)*

CI-945; Gabapentiini; Gabapentina; Gabapentine; Gabapentinum; GOE-3450; Габапентин.

1-(Aminomethyl)cyclohexaneacetic acid.

$C_9H_{17}NO_2$=171.2

CAS — 60142-96-3.

ATC — N03AX12.

ATC Vet — QN03AX12.

UNII — 6CW7F3G59X.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Gabapentin). A white or almost white crystalline powder. It shows polymorphism. Sparingly soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane. It dissolves in dilute acids and dilute solutions of alkali hydroxides.

USP 36: (Gabapentin). A white to off-white, crystalline solid. Freely soluble in water and in alkaline and acidic solutions. A 2% solution in water has a pH of 6.5 to 8.0.

Gabapentin Enacarbil (USAN, rINN)

ASP-8825; Gabapentina Enacarbilo; Gabapentine Énacarbil; Gabapentinum Enacarbilum; GSK-1838262; XP-13512; Габапентин Энакарбил.

(1-{[((1*RS*)-1-{(2-Methylpropanoyl)oxy}ethoxy)carbonyl]amino}methyl)cyclohexyl)acetic acid.

$C_{16}H_{27}NO_6$=329.4

CAS — 478296-72-9.

UNII — 75OCL1SP8Q.

Uses and Administration

Gabapentin is an antiepileptic used as monotherapy or adjunctive therapy in the treatment of partial seizures with or without secondary generalisation. It is not generally considered effective for absence seizures. Although gabapentin is an analogue of gamma-aminobutyric acid (GABA), it is neither a GABA agonist nor antagonist and its mechanism of action is unknown. Gabapentin is also used in the treatment of neuropathic pain and restless legs syndrome.

In the UK, the initial oral dose of *gabapentin* for the treatment of **epilepsy** (below) is 300 mg on the first day of treatment, 300 mg twice daily on the second day, and 300 mg three times daily on the third day; alternatively, gabapentin may be given as 300 mg three times daily on the first day of treatment. Thereafter the dose may be increased in increments of 300 mg every 2 to 3 days until effective antiepileptic control is achieved, which is usually within the range of 0.9 to 3.6 g daily. Higher doses up to a maximum of 4.8 g daily have been reported to be well tolerated. Similar doses are used in the USA. The total daily dose should be taken in three equally divided doses and the maximum dosage interval should not exceed 12 hours.

For details of doses in children, see below.

In the treatment of **neuropathic pain** (p. 525.1) in adults, doses of gabapentin should be titrated to a usual maximum of 1.8 g daily in three divided doses, in a similar manner to that recommended above for the treatment of epilepsy. Higher doses have sometimes been given. In some countries, a modified-release preparation of gabapentin is also available for once-daily dosing.

A prodrug of gabapentin, *gabapentin enacarbil*, is available as an oral modified-release preparation for use in adults. In the treatment of moderate to severe **restless legs syndrome**, 600 mg is given once daily with food at about 5 p.m. For the treatment of **postherpetic neuralgia**, an initial dose of 600 mg is given in the morning for 3 days, then increased to 600 mg twice daily. Gabapentin enacarbil is also being investigated for the treatment of painful diabetic neuropathy and for migraine prophylaxis.

As with other antiepileptics, withdrawal of gabapentin therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. Licensed product information for gabapentin recommends reducing the dose gradually over at least 7 days regardless of indication; licensed information for gabapentin enacarbil states that doses over 600 mg daily should be tapered to 600 mg once daily before stopping. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1.

Dosage of gabapentin and gabapentin enacarbil should be reduced in patients with renal impairment (see below).

Administration in children. In the UK, for the treatment of partial seizures with or without secondary generalisation, gabapentin is licensed for use as adjunctive therapy in children aged 6 years and over and as monotherapy in those aged 12 years and over. As *adjunctive therapy*, gabapentin may be given in an initial oral dose of 10 to 15 mg/kg daily, titrated over a period of about 3 days until effective antiepileptic control is achieved, which is usually within the range of 25 to 35 mg/kg daily given in 3 divided doses. Higher doses up to a maximum of 50 mg/kg daily have been reported to be well tolerated. Although not licensed for use in younger children, the *BNFC* suggests similar titration from an initial daily dose of 10 mg/kg in those aged 2 years and over, up to a usual maintenance dose of 30 to 70 mg/kg daily given in 3 divided doses; a maximum dose of 70 mg/kg daily has also been suggested in children aged 6 to 12 years. Older children may be given the usual adult dosage regimen (see above) titrated to a maximum of 3.6 g daily. When used as *monotherapy*, the usual adult dosage regimen is given.

In the USA, gabapentin is licensed for *adjunctive* use in children aged 3 years and over. Initial doses are as for the UK; the maintenance dose for children aged 3 to 4 years is 40 mg/kg daily, and for those aged 5 years and over is 25 to 35 mg/kg daily. Children aged 12 years and over may be given the usual adult dosage regimen (see above).

The total daily dose should be taken in 3 equally divided doses and the maximum dosage interval should not exceed 12 hours.

For a pharmacokinetic study suggesting that initial doses in younger children should be proportionately higher than in older ones, see Children, under Pharmacokinetics p. 526.2.

Administration in renal impairment. Reduced doses of *gabapentin* are recommended for patients with renal impairment or those undergoing haemodialysis. Licensed UK product information recommends the following maintenance doses based on creatinine clearance (CC) and given as 3 divided doses:

- CC 50 to 79 mL/minute: 600 to 1800 mg daily
- CC 30 to 49 mL/minute: 300 to 900 mg daily
- CC 15 to 29 mL/minute: 300 mg on alternate days to 600 mg daily
- CC less than 15 mL/minute: 300 mg on alternate days to 300 mg daily

For those undergoing haemodialysis who have never received gabapentin, the recommended loading dose is 300 to 400 mg followed by 200 to 300 mg after each 4 hours of haemodialysis. On dialysis-free days no doses of gabapentin should be given (see also Overdosage, p. 525.3).

Reduced doses are also recommended for the modified-release preparation *gabapentin enacarbil* based on indication and CC, as follows:

- **restless legs syndrome**
  - CC 30 to 59 mL/minute: 300 mg daily initially, increased to 600 mg daily, if necessary
  - CC 15 to 29 mL/minute: 300 mg daily
  - CC less than 15 mL/minute: 300 mg on alternate days
  - haemodialysis: not recommended
- **postherpetic neuralgia**
  - CC 30 to 59 mL/minute: 300 mg in the morning for the first 3 days followed by 300 mg twice daily; a further increase to 600 mg twice daily may be made
  - CC 15 to 29 mL/minute: 300 mg in the morning on days 1 and 3 followed by 300 mg daily in the morning; a further increase to 300 mg twice daily may be made
  - CC less than 15 mL/minute: 300 mg in the morning on alternate days; a further increase to 300 mg daily in the morning may be made
  - haemodialysis: 300 mg after each dialysis session, increased to 600 mg, if necessary

Ciguatera poisoning. Gabapentin has relieved some of the neurological symptoms associated with ciguatera poisoning (p. 1428.2).

Epilepsy. Gabapentin is used in epilepsy (p. 506.1) as adjunctive therapy for partial seizures with or without secondary generalisation in patients refractory to standard antiepileptics. In double-blind placebo-controlled studies[1-4] in such patients seizure frequency was reduced when gabapentin was added to treatment. Long-term efficacy has been encouraging,[5-7] and its lack of potential for interactions with other antiepileptics is considered to make it particularly suitable for adjunctive treatment. Dosage is adjusted against clinical response rather than by monitoring blood concentrations. Gabapentin is also used as monotherapy in partial epilepsy;[8-10] its efficacy as adjunctive treatment in generalised seizures remains to be determined.

Gabapentin has been found to be effective as adjunctive therapy in children with refractory partial seizures.[11]

1. UK Gabapentin Study Group. Gabapentin in partial epilepsy. *Lancet* 1990; 335: 1114–17.
2. Sivenius J, *et al.* Double-blind study of gabapentin in the treatment of partial seizures. *Epilepsia* 1991; 32: 539–42.
3. US Gabapentin Study Group. Gabapentin as add-on therapy in refractory partial epilepsy: a double-blind, placebo-controlled, parallel-group study. *Neurology* 1993; 43: 2292–8.
4. Anhut H, *et al.* International Gabapentin Study Group. Gabapentin (Neurontin) as add-on therapy in patients with partial seizures: a double-blind, placebo-controlled study. *Epilepsia* 1994; 35: 795–801.
5. US Gabapentin Study Group. The long-term safety and efficacy of gabapentin (Neurontin) as add-on therapy in drug-resistant partial epilepsy. *Epilepsy Res* 1994; 18: 67–73.
6. Sivenius J, *et al.* Long-term study with gabapentin in patients with drug-resistant epileptic seizures. *Arch Neurol* 1994; 51: 1047–50.
7. Anhut H, *et al.* Long-term safety and efficacy of gabapentin (Neurontin) as add-on therapy in patients with refractory partial seizures. *J Epilepsy* 1995; 8: 44–50.
8. Ojemann LM, *et al.* Long-term treatment with gabapentin for partial epilepsy. *Epilepsy Res* 1992; 13: 159–65.
9. Beydoun A, *et al.* Gabapentin monotherapy II: a 26-week, double-blind, dose-controlled multicenter study of conversion from polytherapy in outpatients with refractory complex partial or secondarily generalized seizures. *Neurology* 1997; 49: 746–52.
10. Chadwick DW, *et al.* A double-blind trial of gabapentin monotherapy for newly diagnosed partial seizures. *Neurology* 1998; 51: 1282–8.
11. Appleton R, *et al.* Gabapentin as add-on therapy in children with refractory partial seizures: a 12-week, multicentre, double-blind, placebo-controlled study. *Epilepsia* 1999; 40: 1147–54.

Headache. Benefit has been reported[1] from the use of gabapentin in the prophylaxis of *migraine* (p. 670.3). Gabapentin may also be effective[2,3] in the management of *cluster headache* (p. 670.1), and has been tried[4] in the prophylaxis of *chronic daily headache* and headache associated with *high-altitude disorders* (p. 1276.2).[5]

A prodrug of gabapentin, gabapentin enacarbil, is under investigation for migraine prophylaxis.

1. Mathew NT, *et al.* Efficacy of gabapentin in migraine prophylaxis. *Headache* 2001; 41: 119–128.
2. Leandri M, *et al.* Drug-resistant cluster headache responding to gabapentin: a pilot study. *Cephalalgia* 2001; 21: 744–6.
3. Schuh-Hofer S, *et al.* The use of gabapentin in chronic cluster headache patients refractory to first-line therapy. *Eur J Neurol* 2007; 14: 694–7.
4. Spira PJ, Beran RG. Australian Gabapentin Chronic Daily Headache Group. Gabapentin in the prophylaxis of chronic daily headache: a randomized, placebo-controlled study. *Neurology* 2003; 61: 1753–9.
5. Jafarian S, *et al.* Gabapentin for prevention of hypobaric hypoxia-induced headache: randomized double-blind clinical trial. *J Ner vol Neurosurg Psychiatry* 2008; 79: 321–3.

Hiccup. Gabapentin has been tried[1,2] in the treatment of hiccups. For the management of intractable hiccups see under Chlorpromazine, p. 1046.3.

1. Hernández JL, *et al.* Gabapentin for intractable hiccup. *Am J Med* 2004; 117: 279–81.
2. Alonso-Navarro H, *et al.* Refractory hiccup: successful treatment with gabapentin. *Clin Neuropharmacol* 2007; 30: 186–7.

Hot flushes. Gabapentin appears to be of benefit in the management of hot flushes associated with treatment of breast cancer; a study involving 420 women with breast cancer experiencing hot flushes (excluding women on active chemotherapy, but most of whom were receiving adjuvant endocrine therapy), found that an oral dose of 900 mg daily in three divided doses for 8 weeks was effective, although a dose of 300 mg daily was not.[1]

There is also evidence of benefit[2,3] from gabapentin in the same dose (900 mg daily) in women who have hot flushes as a symptom of the menopause (p. 2245.1). Another randomised placebo-controlled study[4] found gabapentin 2.4 g daily to be as effective as conjugated oestrogens 625 micrograms daily in the treatment of hot flushes in postmenopausal women. A meta-analysis[5] concluded that gabapentin resulted in a 20 to 30% reduction in the frequency and severity of hot flushes in women with natural or chemotherapy-induced menopause, although this was at the price of adverse effects such as dizziness and somnolence which resulted in many women withdrawing from treatment. A later literature review[6] of randomised controlled studies found gabapentin to be safe and effective for short-term (12 weeks or less) therapy of menopausal hot flushes; an initial dose of 300 to 400 mg at night, increased as required every 3 to 7 days to a usual dose of 0.6 to 2.1 g daily in 2 or 3 divided doses was suggested for women with natural menopause who are having moderate to severe hot flushes.

1. Pandya KJ, *et al.* Gabapentin for hot flashes in 420 women with breast cancer: a randomised double-blind placebo-controlled trial. *Lancet* 2005; 366: 818–24.
2. Guttuso T, *et al.* Gabapentin's effects on hot flashes in postmenopausal women: a randomized controlled trial. *Obstet Gynecol* 2003; 101: 337–45.
3. Loprinzi CL, *et al.* Phase III trial of gabapentin alone or in conjunction with an antidepressant in the management of hot flashes in women who have inadequate control with an antidepressant alone: NCCTG N03C. *J Clin Oncol* 2007; 25: 308–12.
4. Reddy SY, *et al.* Gabapentin, estrogen, and placebo for treating hot flushes: a randomized controlled trial. *Obstet Gynecol* 2006; 108: 41–8.
5. Toulis KA, *et al.* Gabapentin for the treatment of hot flashes in women with natural or tamoxifen-induced menopause: a systematic review and meta-analysis. *Clin Ther* 2009; 31: 221–35.
6. Hayes LP, *et al.* Use of gabapentin for the management of natural or surgical menopausal hot flashes. *Ann Pharmacother* 2011; 45: 388–95.

Lesch-Nyhan syndrome. The severe self-mutilation that occurs in patients with Lesch-Nyhan syndrome (p. 1047.1) has been reported to improve in those given antiepileptics such as gabapentin.[1]

1. McManaman J, Tam DA. Gabapentin for self-injurious behavior in Lesch-Nyhan syndrome. *Pediatr Neurol* 1999; 20: 381–2.

Motor neurone disease. Interest has been shown in gabapentin as a potential therapy for amyotrophic lateral sclerosis (see Motor Neurone Disease, p. 2605.2) because it may inhibit glutamate formation. Results from an early study[1] showed a trend towards a beneficial effect; however, a randomised study[2] failed to confirm any benefit from gabapentin on disease progression or symptoms.

1. Miller RG, *et al.* Placebo-controlled trial of gabapentin in patients with amyotrophic lateral sclerosis. *Neurology* 1996; 47: 1383–8.
2. Miller RG, *et al.* Phase III randomized trial of gabapentin in patients with amyotrophic lateral sclerosis. *Neurology* 2001; 56: 843–8.

Multiple sclerosis. Gabapentin has been found to control pain, spasm, and spasticity in patients with multiple sclerosis (p. 996.3).[1-6] It may also be of benefit in acquired nystagmus secondary to multiple sclerosis.[7]

1. Mueller ME, *et al.* Gabapentin for relief of upper motor neuron symptoms in multiple sclerosis. *Arch Phys Med Rehabil* 1997; 78: 521–4.
2. Samkoff LM, *et al.* Amelioration of refractory dysesthetic limb pain in multiple sclerosis by gabapentin. *Neurology* 1997; 49: 304–5.
3. Solaro C, *et al.* An open-label trial of gabapentin treatment of paroxysmal symptoms in multiple sclerosis patients. *Neurology* 1998; 51: 609–11.
4. Dunevsky A, Perel AB. Gabapentin for relief of spasticity associated with multiple sclerosis. *Am J Phys Med Rehabil* 1998; 77: 451–4.

5. Cutter NC, *et al.* Gabapentin effect on spasticity in multiple sclerosis: a placebo-controlled, randomized trial. *Arch Phys Med Rehabil* 2000; 81: 164–9.
6. Solaro C, *et al.* Gabapentin is effective in treating nocturnal painful spasms in multiple sclerosis. *Multiple Sclerosis* 2000; 6: 192–3.
7. Shery T, *et al.* The effects of gabapentin and memantine in acquired and congenital nystagmus: a retrospective study. *Br J Ophthalmol* 2006; 90: 839–43.

Neuropathic pain. Antiepileptics are among the drugs used to manage neuropathic pain, which is often insensitive to opioid analgesics (see Choice of Analgesic, p. 4.2). Gabapentin is used in the treatment of neuropathic pain,[1-5] including central pain[6] (p. 7.3), complex regional pain syndrome (p. 8.1), postherpetic neuralgia[7-9] (p. 10.3), trigeminal neuralgia (p. 11.2), and painful diabetic neuropathy[10,11] (p. 8.2). There is also interest in its use for postoperative pain (see below).

In a small study of patients with diabetic polyneuropathy or postherpetic neuralgia, gabapentin given with nortriptyline was more effective than use of either alone for control of neuropathic pain.[12]

A prodrug of gabapentin, gabapentin enacarbil, is used in the treatment of postherpetic neuralgia[13] and is under investigation for the treatment of painful diabetic neuropathy.

1. Rose MA, Kam PC. Gabapentin: pharmacology and its use in pain management. *Anaesthesia* 2002; 57: 451–62.
2. Backonja M, Glanzman RL. Gabapentin dosing for neuropathic pain: evidence from randomized, placebo-controlled clinical trials. *Clin Ther* 2003; 25: 81–104.
3. Gilron I. Gabapentin and pregabalin for chronic neuropathic and early postsurgical pain: current evidence and future directions. *Curr Opin Anaesthesiol* 2007; 20: 456–72.
4. Tzellos TG, *et al.* Efficacy of pregabalin and gabapentin for neuropathic pain in spinal-cord injury: an evidence-based evaluation of the literature. *Eur J Clin Pharmacol* 2008; 64: 851–8.
5. Moore RA, *et al.* Gabapentin for chronic neuropathic pain and fibromyalgia in adults. Available in The Cochrane Database of Systematic Reviews, Issue 3. Chichester: John Wiley; 2011 (accessed 11/07/12).
6. Schachter SC, Sauter MK. Treatment of central pain with gabapentin: case reports. *J Epilepsy* 1996; 9: 223–5.
7. Rowbotham M, *et al.* Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. *JAMA* 1998; 280: 1837–42.
8. Rice ASC, Maton S. Gabapentin in postherpetic neuralgia: a randomised, double blind, placebo controlled study. *Pain* 2001; 94: 215–24.
9. Singh D, Kennedy DH. The use of gabapentin for the treatment of postherpetic neuralgia. *Clin Ther* 2003; 25: 852–89.
10. Backonja M, *et al.* Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. *JAMA* 1998; 280: 1831–6.
11. Morello CM, *et al.* Randomized double-blind study comparing the efficacy of gabapentin with amitriptyline on diabetic peripheral neuropathy pain. *Arch Intern Med* 1999; 159: 1931–7.
12. Gilron I, *et al.* Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind, randomised controlled crossover trial. *Lancet* 2009; 374: 1252–61.
13. Backonja MM, *et al.* Efficacy of gabapentin enacarbil vs placebo in patients with postherpetic neuralgia and a pharmacokinetic comparison with oral gabapentin. *Pain Med* 2011; 12: 1098–1108.

Parkinsonism. While some overall ratings of Parkinson's disease (p. 889.1) appeared to be improved by gabapentin in a double-blind study involving 19 patients with advanced parkinsonism, improvements in individual signs and symptoms were not significant.[1] It was also reported that 5 of 6 other patients with progressive supranuclear palsy had experienced worsening of their disease when given gabapentin. Another study[2] in 15 patients with motor complications failed to find any clinically significant benefit from gabapentin therapy.

1. Olson WL, *et al.* Gabapentin for parkinsonism: a double-blind, placebo-controlled, crossover trial. *Am J Med* 1997; 102: 60–6.
2. Van Blercom N, *et al.* Effects of gabapentin on the motor response to levodopa: a double-blind, placebo-controlled, crossover study in patients with complicated Parkinson disease. *Clin Neuropharmacol* 2004; 27: 124–8.

Postoperative pain. There is growing interest in the use of analgesic adjuvants including antiepileptics such as gabapentin to modulate opioid dosage and efficacy for postoperative pain (p. 6.1).[1,2] A systematic review of 4 unpublished studies found a single oral dose of gabapentin 250 mg to be statistically superior to placebo in the treatment of acute postoperative pain; however, it was considered to be of limited clinical value and inferior to other commonly used analgesics.[3] Nevertheless, another systematic review found that perioperative use of gabapentin effectively reduced opioid consumption and postoperative pain; further studies were considered warranted.[4] It has been suggested that perioperative use of gabapentin may have other benefits, including pre-operative anxiolysis, attenuation of the haemodynamic response to intubation, and reduction in postoperative nausea and vomiting.[5]

1. Dahl JB, *et al.* Protective premedication': an option with gabapentin and related drugs? A review of gabapentin and pregabalin in the treatment of post-operative pain. *Acta Anaesthesiol Scand* 2004; 48: 1130–6.
2. Dauri M, *et al.* Gabapentin and pregabalin for the acute post-operative pain management: a systematic-narrative review of the recent clinical evidences. *Curr Drug Targets* 2009; 10: 716–33.
3. Straube S, *et al.* Single dose oral gabapentin for established acute postoperative pain in adults. Available in The Cochrane Database of Systematic Reviews; Issue 5. Chichester: John Wiley; 2010 (accessed 12/07/12).
4. Tiippana EM, *et al.* Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. *Anesth Analg* 2007; 104: 1545–56.
5. Kong VKF, Irwin MG. Gabapentin: a multimodal perioperative drug? *Br J Anaesth* 2007; 99: 775–86.

Psychiatric disorders. Gabapentin has psychotropic properties and has been tried in the management of several psychiatric disorders, including as an adjunct in the treatment of resistant *depression*[1] (p. 398.1) and in the treatment of *post-traumatic stress disorder*[2] (p. 1029.2). Although early open studies[3] found that gabapentin may be of benefit in patients with *bipolar disorder* (p. 397.2) randomised controlled studies have so far failed to confirm this effect.[4-6] Gabapentin is under investigation for the treatment of *social anxiety disorder* (see Phobic Disorders, p. 1029.1).

1. Yasmin S, *et al.* Adjunctive gabapentin in treatment-resistant depression: a retrospective chart review. *J Affect Disord* 2001; 63: 243–7.
2. Malek-Ahmadi P. Gabapentin and posttraumatic stress disorder. *Ann Pharmacother* 2003; 37: 664–6.
3. Maldment ID. Gabapentin treatment for bipolar disorders. *Ann Pharmacother* 2001; 35: 1264–9.
4. Pande AC, *et al.* Gabapentin in bipolar disorder: a placebo-controlled trial of adjunctive therapy. *Bipolar Disord* 2000; 2: 249–55.
5. Frye MA, *et al.* A placebo-controlled study of lamotrigine and gabapentin monotherapy in refractory mood disorders. *J Clin Psychopharmacol* 2000; 20: 607–14.
6. Vieta E, *et al.* A double-blind, randomized, placebo-controlled, prophylaxis study of adjunctive gabapentin for bipolar disorder. *J Clin Psychiatry* 2006; 67: 473–7.

Restless legs syndrome. The aetiology of restless legs syndrome (see Sleep-associated Movement Disorders, p. 1034.2) is obscure and treatment has been largely empirical. Two small randomised double-blind crossover studies[1,2] found 6 weeks of treatment with gabapentin to produce improvement in symptoms; in patients undergoing haemodialysis the effects were seen with a dose of 300 mg after each of the 3 dialysis sessions per week,[1] although in patients with idiopathic disease the mean effective dose was 1.855 g daily.[2]

A prodrug of gabapentin, gabapentin enacarbil, is licensed for the treatment of restless legs syndrome in adults.[3]

1. Thorp ML, *et al.* A crossover study of gabapentin in treatment of restless legs syndrome among hemodialysis patients. *Am J Kidney Dis* 2001; 38: 104–8.
2. Garcia-Borreguero D, *et al.* Treatment of restless legs syndrome with gabapentin: a double-blind, cross-over study. *Neurology* 2002; 59: 1573–9.
3. Hayes WJ, *et al.* Gabapentin enacarbil for treatment of restless legs syndrome in adults. *Ann Pharmacother* 2012; 46: 229–39.

Soft-tissue rheumatism. Gabapentin may be of benefit in some patients with fibromyalgia (p. 14.2). In a randomised controlled study treatment with oral gabapentin 1.2 to 2.4 g daily in 75 patients produced a greater improvement in mean pain score over 12 weeks than placebo in 75 controls.[1] Sleep problems were also improved, but there was no difference between the groups in a depression rating scale. The drug was generally well tolerated. A meta-analysis[2] of this and 4 further studies confirmed the apparent benefits of gabapentin in reducing pain and improving sleep, but again showed no effect on depression, or anxiety or fatigue.

1. Arnold LM, *et al.* Gabapentin in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled, multicenter trial. *Arthritis Rheum* 2007; 56: 1336–44.
2. Häuser W, *et al.* Treatment of fibromyalgia syndrome with gabapentin and pregabalin—a meta-analysis of randomized controlled trials. *Pain* 2009; 145: 69–81.

Stiff-man syndrome. Gabapentin may improve the symptoms of stiff-man syndrome (see under Muscle Spasm, p. 1064.3) in patients unable to tolerate benzodiazepine therapy.

Tremor. A beta blocker is often the first drug used in patients with essential tremor who require regular treatment (p. 1318.3); however, gabapentin has also been tried with some success.[1-3]

1. Gironell A, *et al.* A randomized placebo-controlled comparative trial of gabapentin and propranolol in essential tremor. *Arch Neurol* 1999; 56: 475–80.
2. Ondo W, *et al.* Gabapentin for essential tremor: a multiple-dose, double-blind, placebo-controlled trial. *Mov Disord* 2000; 15: 678–82.
3. Faulkner MA, *et al.* Gabapentin for the treatment of tremor. *Ann Pharmacother* 2003; 37: 282–6.

Adverse Effects and Precautions

The most commonly reported adverse effects associated with gabapentin are somnolence, dizziness, ataxia, and fatigue. Nystagmus, tremor, diplopia, amblyopia, pharyngitis, rhinitis, dysarthria, nausea and vomiting, weight gain, oedema, dyspepsia, amnesia, weakness, paraesthesia, arthralgia, myalgia, headache, purpura, leucopenia, anxiety, and urinary-tract infection may occur less frequently. Rarely, pancreatitis, altered liver function tests, erythema multiforme, Stevens-Johnson syndrome, and blood glucose fluctuations in diabetics have been reported. Common psychiatric effects include confusion, depression, and nervousness, and, more rarely, hallucinations and psychoses. Other adverse effects include acute renal failure, allergic reactions, alopecia, angioedema, chest pain, hepatitis, jaundice, movement disorders such as choreoathetosis, dyskinesia and dystonia, palpitations, thrombocytopenia, and tinnitus.

An antiepileptic hypersensitivity syndrome, comprising fever, rash, eosinophilia, and lymphadenopathy, along with other organ involvement such as hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis, has been associated with some antiepileptic drugs including gabapentin. Early manifestations, such as fever and/or lymphadenopathy, may be present without evident rash; patients with such signs or symptoms should be evaluated immediately and therapy stopped in the absence of a clear aetiology.

Overdosage of gabapentin, particularly in combination with other CNS depressants, may result in coma (see also below).

Gabapentin should be used with caution in patients with renal impairment and in those undergoing haemodialysis. False positive readings have been reported with some urinary protein tests in patients taking gabapentin.

Care is required when withdrawing gabapentin therapy—see also Uses and Administration, p. 524.1.

Incidence of adverse effects. A postmarketing surveillance study[1] of 3100 patients taking gabapentin identified drowsiness or sedation as the most frequent adverse effect, occurring in about 6.7%. The incidences of other adverse effects were: headache, 3.6%; fatigue, 3.5%; nausea and vomiting, 2.6%; and dizziness, 2.4%. Less common adverse events included rash, visual defect, and ataxia. Overall, adverse effects were reported as the reason for stopping treatment in about 10% of patients. In the 136 children aged under 12 years whose data were included in the study, the most frequently reported treatment-related adverse events were eczema, rash, and vomiting. In this study, none of the 11 infants born to mothers taking gabapentin throughout pregnancy had congenital abnormalities.

1. Wilton LV, Shakir S. A postmarketing surveillance study of gabapentin as add-on therapy for 3,100 patients in England. *Epilepsia* 2002; 43: 983–92.

Breast feeding. For mention of the pharmacokinetics of gabapentin during pregnancy and breast feeding, see under Pharmacokinetics, p. 526.2.

For comment on antiepileptic therapy and breast feeding, see p. 508.3.

Carcinogenicity. It had been reported[1] that studies on gabapentin had been temporarily stopped in 1990 when pancreatic tumours were seen in *rodent* studies. However, the tumours were benign, occurred only with large doses, and were not thought to relate to humans.

1. Ramsay RE. Clinical efficacy and safety of gabapentin. *Neurology* 1994; 44 (suppl 5): S23–S30.

Driving. For a comment on antiepileptic drugs and driving, see p. 509.2.

Effects on bone. For the effects of antiepileptics, including gabapentin, on bone and on calcium and vitamin D metabolism, see under Phenytoin, p. 540.2.

Effects on the liver. A report[1] of a patient who developed cholestatic jaundice 2 weeks after starting therapy with gabapentin 300 mg three times daily for diabetic neuropathy. Clinical symptoms and liver function tests improved on withdrawal of gabapentin.

1. Richardson CE, *et al.* Gabapentin induced cholestasis. *BMJ* 2002; 325: 635.

Effects on mental function. For a review of the effects of antiepileptic therapy including gabapentin on *cognition*, and on *mood* (including the risk of suicidal ideation), see p. 508.3.

Effects on skeletal muscle. A report[1] of rhabdomyolysis with myoglobinuria and acute renal impairment associated with gabapentin use in a diabetic patient. Resolution gradually occurred on stopping the drug.

1. Bilgir O, *et al.* Gabapentin-induced rhabdomyolysis in a patient with diabetic neuropathy. *Intern Med* 2009; 48: 1085–7.

Effects on the skin. For a suggestion that skin reactions are less common with gabapentin than with some other antiepileptics, see under Phenytoin, p. 541.1.

Overdosage. A 16-year-old girl complained of dizziness 6 hours after ingesting 48.9 g of gabapentin and was lethargic but arousable 2 hours later.[1] Her gabapentin plasma concentration was 62 micrograms/mL 8.5 hours after ingestion. By 18 hours she was alert and had no further complaints of lethargy or dizziness. In another report[2] a patient with renal failure inadvertently received inappro-

priately high doses of gabapentin for 3 weeks and had a serum gabapentin concentration of 85 micrograms/mL without serious adverse effects. However, a patient with end-stage renal disease who twice took extra doses of gabapentin between haemodialysis sessions developed marked somnolence and hypoxia severe enough to require intubation on both occasions; haemodialysis produced rapid improvement.[3] A prospective observational study[4] of gabapentin exposures reported to 3 poison centers has described a case series of 20 patients who took from 50 mg to 35 g of gabapentin alone. Of these, 12 had clinical symptoms including drowsiness, dizziness, gastrointestinal disturbance, hypotension, and mild tachycardia. These effects developed in under 5 hours and lasted for less than 24 hours; toxicity was generally mild and there were no fatalities.

1. Fischer JH, *et al.* Lack of serious toxicity following gabapentin overdose. *Neurology* 1994; **44:** 982–3.
2. Verma A, *et al.* A case of sustained massive gabapentin overdose without serious side effects. *Ther Drug Monit* 1999; **21:** 615–17.
3. Jones H, *et al.* Gabapentin toxicity requiring intubation in a patient receiving long-term hemodialysis. *Ann Intern Med* 2002; **137:** 74.
4. Klein-Schwartz W, *et al.* Characterization of gabapentin overdose using a poison center case series. *J Toxicol Clin Toxicol* 2003; **41:** 11–15.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies gabapentin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pregnancy. For mention of the pharmacokinetics of gabapentin during pregnancy and breast feeding, see under Pharmacokinetics, below.

For comments on the management of epilepsy during pregnancy, see p. 509.2.

Withdrawal. Withdrawal symptoms, including akathisia, anxiety, confusion, diaphoresis, headache, and palpitations, have been reported[1-3] after abrupt withdrawal of gabapentin. A withdrawal syndrome with flu-like symptoms has also been reported[4] after gradual withdrawal over 1 week. A literature search[3] found 10 case reports with symptoms that occurred from 12 hours to 3 days after stopping gabapentin and generally resolved on restarting; patients had been taking doses that ranged from 0.4 to 8 g daily for durations of 3 weeks to 5 years.

1. Hellwig TR, *et al.* Withdrawal symptoms after gabapentin discontinuation. *Am J Health-Syst Pharm* 2010; **67:** 910–12.
2. Finch CK, *et al.* Gabapentin withdrawal syndrome in a post-liver transplant patient. *J Pain Palliat Care Pharmacother* 2010; **24:** 236–8.
3. See S, *et al.* Akathisia induced by gabapentin withdrawal. *Ann Pharmacother* 2011; **45:** e31.
4. Tran KT, *et al.* Gabapentin withdrawal syndrome in the presence of a taper. *Bipolar Disord* 2005; **7:** 302–4.

Interactions

The absorption of gabapentin from the gastrointestinal tract is reduced by antacids containing aluminium with magnesium; it is recommended that gabapentin is taken at least 2 hours after any such antacid. Morphine has been reported to reduce the clearance of gabapentin; patients receiving both drugs should be monitored for signs of CNS depression and doses should be reduced accordingly. Cimetidine has also been reported to reduce the renal clearance of gabapentin but licensed product information does not consider this to be of clinical importance. For references to possible interactions with other antiepileptics, see under Phenytoin, p. 543.2 and under Felbamate, p. 522.3.

Pharmacokinetics

Gabapentin is absorbed from the gastrointestinal tract by means of a saturable mechanism. After multiple dosing peak plasma concentrations usually occur within 2 to 3 hours of a dose and a steady state within 1 to 2 days. When given as its prodrug, gabapentin enacarbil, peak plasma concentrations are reached in 5 hours in fasted subjects and 7.3 hours in fed subjects; the bioavailability of gabapentin from its prodrug is increased when given with food, particularly meals high in fat.

Gabapentin enacarbil undergoes extensive first-pass metabolism, mainly in enterocytes and to a lesser extent in the liver, to form gabapentin, carbon dioxide, acetaldehyde, and isobutyric acid; blood levels of the enacarbil are low and transient. Gabapentin itself is not appreciably metabolised and most of a dose is excreted unchanged in the urine with the remainder appearing in the faeces. Gabapentin is widely distributed throughout the body but binding to plasma proteins is minimal. The elimination half-life has been reported to be about 5 to 7 hours. Gabapentin is distributed into breast milk.

References.

1. Blum RA, *et al.* Pharmacokinetics of gabapentin in subjects with various degrees of renal function. *Clin Pharmacol Ther* 1994; **56:** 154–9.
2. Elwes RDC, Binnie CD. Clinical pharmacokinetics of newer antiepileptic drugs: lamotrigine, vigabatrin, gabapentin and oxcarbazepine. *Clin Pharmacokinet* 1996; **30:** 403–15.
3. Berry DJ, *et al.* The absorption of gabapentin following high dose escalation. *Seizure* 2003; **12:** 28–36.
4. Cundy KC, *et al.* Clinical pharmacokinetics of XP13512, a novel transported prodrug of gabapentin. *J Clin Pharmacol* 2008; **48:** 1378–88.
5. Chen C, *et al.* Pharmacokinetics of gabapentin in a novel gastric-retentive extended-release formulation: comparison with an immediate-release formulation and effect of dose escalation and food. *J Clin Pharmacol* 2011; **51:** 346–58.
6. Lal R, *et al.* Clinical pharmacokinetics of gabapentin after administration of gabapentin enacarbil extended-release tablets in patients with varying degrees of renal function using data from an open-label, single-dose pharmacokinetic study. *Clin Ther* 2012; **34:** 201–13.

Children. A study[1] of the pharmacokinetics of single doses of gabapentin in healthy children aged 1 month to 12 years found that peak plasma concentrations occurred 2 to 3 hours after the dose in all age groups but that the mean value was higher in those older than 5 years than in younger children, and the exposure was calculated to be about 30% less in the younger age group. As a result it was suggested that the initial dose of gabapentin in studies of safety and efficacy should be 40 mg/kg daily in children aged from 1 month up to 5 years, and 30 mg/kg daily in children aged 5 to 12 years. (For licensed doses, see Administration in Children, p. 524.1.) A pharmacokinetics study[2] in children with uncontrolled seizures (aged from 3 to about 15 years) also found a markedly higher mean oral clearance of gabapentin when compared with adults.

1. Haig GM, *et al.* Single-dose gabapentin pharmacokinetics and safety in healthy infants and children. *J Clin Pharmacol* 2001; **41:** 507–14.
2. Tallian KB, *et al.* Pharmacokinetics of gabapentin in paediatric patients with uncontrolled seizures. *J Clin Pharm Ther* 2004; **29:** 511–15.

Pregnancy and breast feeding. The pharmacokinetics of gabapentin were studied[1] in 6 women, and in their offspring, during pregnancy, delivery, and breast feeding. Findings suggested that gabapentin is actively transported across the placenta and accumulates in the fetus although its effect was unclear. All the deliveries, including one preterm, were uneventful and all of the infants were healthy, apart from one who became cyanosed and mildly hypotonic 8 hours after birth.

The distribution of gabapentin into breast milk was extensive and neonates were found to have a lower capacity to eliminate gabapentin than adults, with an elimination half-life of about 14 hours. However, the plasma concentrations in the breast-fed infants appeared to be low and the relative infant dose was estimated to be 1.3 to 3.8% of the mothers' weight-adjusted dose at 0.2 to 1.3 mg/kg daily. No adverse effects were reported in the infants, and the authors considered that gabapentin was generally safe during breast feeding.

1. Öhman I, *et al.* Pharmacokinetics of gabapentin during delivery, in the neonatal period, and lactation: does a fetal accumulation occur during pregnancy? *Epilepsia* 2005; **46:** 1621–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Abaglin; Alidial; Elifer; Logistic; Neurontin; Ultraneural; ***Austral.***: Gabahexal†; Gabaran; Gabatine; Gantin; Neurontin; Nupentin; Pendine†; ***Austria***: Gabatal; Neurontin; ***Belg.***: Neurontin; ***Braz.***: Gabaneurin; Neurontin; Progresse; ***Canad.***: Neurontin; ***Chile***: Dineurin; Gabacross; Gabex; Gabictal; Neugabin†; Normatol; Ritmenal; ***China***: Die Li (迭力); Neurontin (纽诺汀); Pai Ting (派汀); Wei Nuo Ding (维诺定); *Cz.*: Apo-Gab; Gabagamma; Gabalept†; Gabanox; Gabatem; Gabator; Gabenta†; Gordius; Grimodin; Neurontin; Nurabax†; ***Denm.***: Gabadoz; Gabalept; Gabalix; Gabamed; Gabanicht; Gabaratio; Gabatifin; Neuril; Neurontin; Pentagab; ***Fin.***: Gabrion; Neurontin; ***Fr.***: Neurontin; ***Ger.***: Gabagamma; GabaLich; Gabax; Neurontin; ***Gr.***: Belgabin; Brilian; Gabantin; Gabapen; Gabaront; Gabental; Gabiton; Gapenten; Medivapom; Neurontin; Neuros; Pentin; Peronten; Seni-Ven; ***Hong Kong***: Gabenil; Neurontin; ***Hung.***: Gabagamma; Gordius; Grimodin; Neuroba; Neurontin; ***India***: Encentin; Gaba; Gabacap; Gabacent; Gabalept; Gabantin; Gabapin; Gabata; Gabatin; Gabator; Gaby; Gentin; Goben; Mygaba; Neogaba; Neupent AF; Neurontin; ***Indon.***: Alpentin; Epiven; Gabexal; Galepsi; Ganin; Nepatic; Neurontin; Repligen; Sipentin; Tineuron; ***Irl.***: Gabin; Gabture; Neurontin; Neurostil; Rangabax; ***Israel***: Neurontin; ***Ital.***: Apentin; Gabexine; Neurontin; Semerial†; Yalipent†; ***Jpn***: Gabapen; Regnite; ***Malaysia***: Neurontin; ***Mex.***: Aconeuba; Bapex; Blugat; Clozepaxel; Compulxine†; Gabantin; Gapridol; Microlepitin; Neurontin; Nopatic; Nyepzyl; Wermy; ***Neth.***: Neurontin; ***Norw.***: Neurontin; ***NZ***: Neurontin; Nupentin; ***Philipp.***: Calmpent; Gabalept; Gabatin; Gabatrex; Gabix; Gonnaz; Neurontin; Reinin; ***Pol.***: Gabagamma; Gabatem; Gabax†; Neuran; Neurontin; Symleptic; ***Port.***: Anabix†; Aneptir; Gabacalma; Gabamox; Mengaptrix†; Molnarux; Neurontin; ***Rus.***: Convalis (Конвалис); Gabagamma (Габагамма); Gapentek (Гапентек); Katena (Катэна); Lepsitin (Лепситин); Neurontin (Нейронтин); Tebantin (Тебантин); ***S.Afr.***: Epleptin; Neurexal; Neurontin; ***Singapore***: Neurontin; Nupentin; ***Spain***: Equipax†; Gabamerck†; Gabatur; Gabmylan†; Neurontin; ***Swed.***: Neurontin; ***Switz.***: Gabantine; Neurontin; ***Thai.***: Gabantin; Gabutin; Neurontin; Neverpentin; Rontin; Vultin; ***Turk.***: Gabaset; Gabateva; Gabtin; Nepitin; Neruda; Neurontin; ***UK***: Neurontin; ***Ukr.***: Gabagamma (Габагамма); Gabalept (Габалепт); Gabantin (Габантин); Gatonin (Гатонин)†; Meditan (Медитан); Tebantin (Тебантин); ***USA*** Gabarone; Gralise; Horizant; Neurontin; ***Venez.***: Neurontin.

Multi-ingredient Preparations. *India*: Alcobal; Alnacob-G; Arme G; Bigvin Forte; Capin-G; Chiny-GP; Cobalvit-GT; Cobanerve G; Cobaver-M; Cobsa-G; Doloneuron; Electa-GP; Encentir Plus; Encentin-AM; Encentin-M; G-Care; G-Neuro; Gaba-MC Gabafact; Gabaneuron; Gabanez-M; Gabapentin Forte; Gabasta M; Gabator M; Gabaz; Gabil; Gabin-M; Gabion-M; Gabsoft-M Game; Gamet; GBN-M; Gelina-M; Gentin-MC; Gibi Forte; Gic M; Hyteron-M; Indcobal; Magic-M; Malzix-GB; Marinol-GB Me-Gab; Mecobal-GB; Mecoday-G; Mecoriv-G; Melife-G; Meri cobal-G; Methipas-GP; Mewin-GB; Miko G; Mokia-G; Motri GB; Mycovit-GB; Nervic-G; Nervicin-G; Nervimax-G; Nervon GM; Nervoptin; Nervuptin; Nervz-G; Nerwin-GT; Neuro-GM Neuroage GF; Neurocap-G; Neurogab; Neuromas-G; Neu romed-GF; Neuropill; Neurotop-G; Nexcob-G; Novomine-GB NTOmec-G; Nuroclad-GB; Nurokind-G; Nuthyl-GB; Orogab-M *Mex.*: Gavindo; Tremecox; Tremepen.

Pharmacopoeial Preparations

USP 36: Gabapentin Capsules; Gabapentin Tablets.

Lacosamide *(BAN, USAN, rINN)*

ADD-234037; Erlosamida; Erlosamide; Erlosamidum; Harkoseride; Lacosamida; Lacosamidum; SPM-927; Эрльозамид.

(2*R*)-2-(Acetylamino)-*N*-benzyl-3-methoxypropanamide.

$C_{13}H_{18}N_2O_3$=250.3

CAS — 175481-36-4.

ATC — N03AX18.

ATC Vet — QN03AX18.

UNII — 563KS2PQY5.

Uses and Administration

Lacosamide is an antiepileptic used as adjunctive therapy in partial seizures with or without secondary generalisation (below) in patients aged 16 years and older.

The initial oral dose of lacosamide is 100 mg daily, increased to 200 mg daily after 1 week. Further weekly increments of 100 mg may be given, according to response and tolerability, to a maximum daily dose of 400 mg. The total daily dose of lacosamide should be given in 2 equally divided doses.

When oral use is not feasible, lacosamide may be given by intravenous infusion over 15 to 60 minutes in the same doses as those used orally. Licensed product information states that there is experience with the use of intravenous lacosamide for up to 5 days.

Reduced doses are recommended by some authorities in patients with hepatic and severe renal impairment (see below).

As with other antiepileptics, withdrawal of lacosamide therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. Licensed product information recommends reducing the dose of lacosamide by 200 mg each week. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1.

Lacosamide is also being studied for use in fibromyalgia, osteoarthritis, and migraine prophylaxis.

Administration in hepatic impairment. Although UK licensed product information states that no dosage adjustment of lacosamide is needed for patients with mild to moderate hepatic impairment, US licensed information suggests a maximum dose of 300 mg daily orally or by intravenous infusion; use in severe impairment is not recommended due to lack of data.

Administration in renal impairment. In patients with severe renal impairment (creatinine clearance of 30 mL/min or less) and in those with end-stage renal disease, UK licensed product information recommends a maximum daily dose of lacosamide 250 mg orally or by intravenous infusion whereas US licensed information recommends a maximum dose of 300 mg daily.

In patients undergoing haemodialysis a supplemental dose of up to 50% of the morning dose should be given at the end of the procedure.

Epilepsy. Lacosamide is used in the treatment of epilepsy (p. 506.1) as adjunctive therapy for partial seizures with or without secondary generalisation. It has also been investigated as a second-line drug in status epilepticus.

References.

1. Doty P, *et al.* Lacosamide. *Neurotherapeutics* 2007; **4:** 145–8.
2. Ben-Menachem E, *et al.* Efficacy and safety of oral lacosamide as adjunctive therapy in adults with partial-onset seizures. *Epilepsia* 2007; **48:** 1308–17.
3. Biton V, *et al.* Intravenous lacosamide as replacement for oral lacosamide in patients with partial-onset seizures. *Epilepsia* 2008; **49:** 418–24.
4. Cross SA, Curran MP. Lacosamide: in partial-onset seizures. *Drugs* 2009; **69:** 449–59.

5. Wehner T, *et al.* Six months of postmarketing experience with adjunctive lacosamide in patients with pharmacoresistant focal epilepsy at a tertiary epilepsy center in Germany. *Epilepsy Behav* 2009; 16: 423–5.
6. Kellinghaus C. Lacosamide as treatment for partial epilepsy: mechanisms of action, pharmacology, effects, and safety. *Ther Clin Risk Manag* 2009; 5: 757–66.
7. Kellinghaus C, *et al.* Intravenous lacosamide as successful treatment for nonconvulsive status epilepticus after failure of first-line therapy. *Epilepsy Behav* 2009; 14: 429–31.

Neuropathic pain. Lacosamide is being studied in the management of neuropathic pain[1-3] but its role, if any, remains to be established.[4]

1. Wymer JP, *et al.* Efficacy and safety of lacosamide in diabetic neuropathic pain: an 18-week double-blind placebo-controlled trial of fixed-dose regimens. *Clin J Pain* 2009; 25: 376–85.
2. Shaibani A, *et al.* Lacosamide in painful diabetic neuropathy: an 18-week double-blind placebo-controlled trial. *J Pain* 2009; 10: 818–28.
3. Ziegler D, *et al.* Efficacy and safety of lacosamide in painful diabetic neuropathy. *Diabetes Care* 2010; 33: 839–41.
4. McCleane G. Lacosamide for pain. *Expert Opin Invest Drugs* 2010; 19: 1129–34.

Adverse Effects and Precautions

The most frequently reported adverse effects with lacosamide are usually mild to moderate in severity, and include dizziness, headache, nausea, and diplopia. Other commonly reported adverse effects include depression, CNS disorders such as abnormal coordination, memory impairment, somnolence, tremor, and nystagmus, blurred vision, vertigo, gastrointestinal disorders such as vomiting, constipation, and flatulence, pruritus, gait disturbance, asthenia, and fatigue. The incidence and severity of CNS and gastrointestinal disorders usually decrease over time.

Lacosamide has been associated with a dose-related increase in the PR interval, and should be used with caution in patients with cardiac conduction disorders or severe cardiac disease such as a history of myocardial infarction or heart failure. It is contra-indicated in those with second- or third-degree AV block.

Doses of lacosamide should be titrated cautiously in patients with renal impairment.

Care is required when withdrawing lacosamide therapy—see also Uses and Administration, p. 526.3.

Breast feeding. For comment on antiepileptic therapy and breast feeding, see p. 508.3.

Driving. For a comment on antiepileptic drugs and driving, see p. 509.2.

Effects on mental function. For the effects of antiepileptic therapy on *cognition* and *mood*, including the risk of suicidal ideation, see p. 508.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lacosamide as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pregnancy. For comments on the management of epilepsy during pregnancy, see p. 509.2.

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy. Lacosamide plasma concentrations may be reduced by carbamazepine, phenytoin, and phenobarbital.

Systemic exposure to lacosamide may be reduced by strong inducers of cytochrome P450 isoenzymes such as rifampicin or St John's wort. Lacosamide should be used with caution in patients also receiving other drugs that prolong the PR interval, and with class I antiarrhythmics.

Pharmacokinetics

Lacosamide is quickly and completely absorbed after oral doses. The oral bioavailability is about 100% and peak plasma concentrations occur within 4 hours. Steady state is achieved after 3 days. About 95% of a dose is excreted in the urine, about 40% as unchanged drug and less than 30% as the inactive *O*-desmethyl metabolite. Less than 0.5% of a dose is excreted in the faeces. The elimination half-life of lacosamide is about 13 hours. Lacosamide is removed by haemodialysis.

The pharmacokinetics of lacosamide are affected by use with other antiepileptics (see Interactions, above).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Vimpat; *Austral.*: Vimpat; *Austria*: Vimpat; *Belg.*: Vimpat; *Canad.*: Vimpat; *Cz.*: Vimpat; *Denm.*: Vimpat; *Fr.*: Vimpat; *Ger.*: Vimpat; *Gr.*: Vimpat; *Irl.*: Vimpat; *Israel*: Vimpat; *Neth.*: Vimpat; *Norw.*: Vimpat; *NZ*: Vimpat; *Pol.*: Vimpat; *Port.*: Vimpat; *Rus.*: Vimpat (Вимпат); *Spain*: Vimpat; *Swed.*: Vimpat; *Switz.*: Vimpat; *UK*: Vimpat; *Ukr.*: Vimpat (Вимпат); *USA*: Vimpat.

Lamotrigine *(BAN, USAN, rINN)*

BW-430C; Lamotrigilni; Lamotrigin; Lamotrigina; Lamotrigi-num; Lamotrijin; Ламотриги́н.

6-(2,3-Dichlorophenyl)-1,2,4-triazine-3,5-diyldiamine.

$C_9H_7Cl_2N_5$=256.1

CAS — 84057-84-1.

ATC — N03AX09.

ATC Vet — QN03AX09.

UNII — U3H27498KS.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Lamotrigine). A white or almost white powder. Very slightly soluble in water; slightly soluble in dehydrated alcohol.

USP 36: (Lamotrigine). A white to pale cream-coloured powder. Slightly soluble in water, in methyl alcohol, in 0.1N hydrochloric acid, and in acetone. Store in airtight containers.

Uses and Administration

Lamotrigine, a phenyltriazine compound, is an antiepileptic used mainly for monotherapy or adjunctive treatment of partial seizures and primary and secondarily generalised tonic-clonic seizures. It may be used for seizures associated with the Lennox-Gastaut syndrome and for the maintenance treatment of bipolar disorder.

The doses given below for the use of lamotrigine in **epilepsy** (p. 528.1) are those licensed in the UK; similar doses are given in the USA although the use of lamotrigine is more limited than in the UK.

- The initial oral dose for use as *monotherapy* is 25 mg once daily for 2 weeks followed by 50 mg once daily for 2 weeks; thereafter the dose is increased by a maximum of 50 to 100 mg every 1 to 2 weeks to usual maintenance doses of 100 to 200 mg daily, given as a single dose or in 2 divided doses. Some patients have required up to 500 mg daily.
- In those taking lamotrigine as an *adjunct* to therapy but *not taking valproate or enzyme-inducing or -inhibiting antiepileptics* the dosage regimen is as for monotherapy.
- The initial oral dose of lamotrigine for use as an adjunct to therapy *with enzyme-inducing antiepileptics* (but *not with valproate*) is 50 mg once daily for 2 weeks followed by 50 mg twice daily for 2 weeks; thereafter the dose is increased by a maximum of 100 mg every 1 to 2 weeks to usual maintenance doses of 200 to 400 mg daily given in 2 divided doses. Some patients have required up to 700 mg daily.
- In those *taking valproate* (and regardless of any other concomitant drugs) the initial oral dose of lamotrigine is 25 mg every other day for 2 weeks followed by 25 mg once daily for 2 weeks; thereafter the dose is increased by a maximum of 25 to 50 mg every 1 to 2 weeks to usual maintenance doses of 100 to 200 mg daily given as a single dose or in 2 divided doses.

If the potential for interaction with adjunctive antiepileptics is unknown, treatment with lamotrigine should be started with lower doses such as those used with valproate. For comment on the need to modify maintenance doses when starting or stopping oral contraceptives, see Sex Hormones, under Interactions, p. 530.2.

For doses in children, see below.

In the management of **bipolar disorder** (below), the target dose of lamotrigine is 200 mg daily as *monotherapy*; for patients *taking valproate* the target dose is 100 mg daily and in those taking enzyme-inducing drugs (but *not with valproate*) the target dose is 400 mg daily. Lamotrigine should be started at a reduced dose and increased gradually to the target dose in a regimen similar to that used in the treatment of epilepsy (see above).

Doses should be reduced in patients with hepatic impairment regardless of indication (see below).

As with other antiepileptics, withdrawal of lamotrigine therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1. In patients with epilepsy the withdrawal of lamotrigine should be tapered over at least 2 weeks. A step-wise reduction is also suggested when lamotrigine is stopped in patients with bipolar disorder although a more abrupt withdrawal may be considered if there are safety concerns.

Administration in children. Lamotrigine is used as an adjunct in the treatment of partial seizures and primary and secondarily generalised tonic-clonic seizures in children aged 2 to 12 years; it is also used as monotherapy for typical absence seizures in children aged 2 to 12 years. Lamotrigine may also be used for seizures associated with the Lennox-Gastaut syndrome.

The doses given below are those licensed in the UK; similar doses are given in the USA although the use of lamotrigine is more limited than in the UK.

- The initial oral dose of lamotrigine for use as *monotherapy* in typical absence seizures, given as a single dose or in 2 divided doses, is 300 micrograms/kg daily for 2 weeks, followed by 600 micrograms/kg daily for 2 weeks; thereafter the dose is increased by a maximum of 600 micrograms/kg every 1 to 2 weeks to usual maintenance doses of 1 to 10 mg/kg daily. Some patients have required up to 15 mg/kg daily.
- In those taking lamotrigine as an *adjunct* to therapy but *not taking valproate or enzyme-inducing or -inhibiting antiepileptics* the initial oral dose of lamotrigine, given as a single dose or in 2 divided doses, is 300 micrograms/kg daily for 2 weeks, followed by 600 micrograms/kg daily for 2 weeks; thereafter the dose is increased by a maximum of 600 micrograms/kg every 1 to 2 weeks to usual maintenance doses of 1 to 10 mg/kg daily. The maximum dose is 200 mg daily.
- In those *taking enzyme-inducing antiepileptics* (but *not with valproate*) the initial oral dose of lamotrigine is 600 micrograms/kg daily in 2 divided doses for 2 weeks followed by 1.2 mg/kg daily for 2 weeks; thereafter the dose is increased by a maximum of 1.2 mg/kg every 1 to 2 weeks to usual maintenance doses of 5 to 15 mg/kg daily, given as a single dose or in 2 divided doses. The maximum dose is 400 mg daily.
- In those *taking valproate* the initial oral dose of lamotrigine is 150 micrograms/kg once daily for 2 weeks followed by 300 micrograms/kg once daily for 2 weeks; thereafter the dose is increased by a maximum of 300 micrograms/kg every 1 to 2 weeks to usual maintenance doses of 1 to 5 mg/kg daily, given as a single dose or in 2 divided doses. The maximum dose is 200 mg daily.
- In those taking lamotrigine as adjunctive therapy with drugs where it is not known if an interaction may occur, the doses as recommended for lamotrigine with concurrent valproate should be used.

If the calculated daily dose of lamotrigine lies between 1 and 2 mg, then 2 mg may be given on alternate days for the first 2 weeks of therapy. Lamotrigine should not be given if the calculated daily dose is less than 1 mg.

The use and doses of lamotrigine in children over 12 years of age is as for adults (see above).

Administration in hepatic impairment. UK licensed product information for lamotrigine recommends that doses should be reduced by about 50% in patients with moderate hepatic impairment (Child-Pugh category B), and by about 75% in severe impairment (Child-Pugh category C). US licensed product information recommends that doses should be reduced by about 25% in patients with moderate to severe hepatic impairment without ascites, and by about 50% in those with severe hepatic impairment with ascites.

Anxiety disorders. Small studies have suggested that lamotrigine may relieve some of the symptoms of post-traumatic stress disorder (p. 1029.2).

References.
1. Hertzberg MA, *et al.* A preliminary study of lamotrigine for the treatment of posttraumatic stress disorder. *Biol Psychiatry* 1999; 45: 1226–9.
2. Hageman I, *et al.* Post-traumatic stress disorder: a review of psychobiology and pharmacotherapy. *Acta Psychiatr Scand* 2001; 104: 411–22.

Bipolar disorder. In a multicentre placebo-controlled study involving 195 patients, oral lamotrigine 50 or 200 mg daily produced dose-related improvement in patients with bipolar disorder (p. 397.2) experiencing a major depressive episode.[1] Further data from randomised controlled studies[2-8] and meta-analysis[9] have confirmed benefit for depressive symptoms (although not for mania), and reviews[10-14] have generally favoured its use, although some have queried the strength of the evidence.[15] Guidelines for the treatment of bipolar disorder now recommend lamotrigine as a first-line option for bipolar depression, and it is licensed for such use in some countries (see also Uses and Administration, above).

1. Calabrese JR, *et al.* A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. *J Clin Psychiatry* 1999; 60: 79–88.
2. Bowden CL, *et al.* Lamotrigine in the treatment of bipolar depression. *Eur Neuropsychopharmacol* 1999; 9 (suppl 4): S113–S117.

3. Calabrese JR, *et al.* A double-blind, placebo-controlled, prophylaxis study of lamotrigine in rapid-cycling bipolar disorder. *J Clin Psychiatry* 2000; 61: 841–50.
4. Ichim L, *et al.* Lamotrigine compared with lithium in mania: a double-blind randomized controlled trial. *Ann Clin Psychiatry* 2000; 12: 5–10.
5. Obrocea GV, *et al.* Clinical predictors of response to lamotrigine and gabapentin monotherapy in refractory affective disorders. *Biol Psychiatry* 2002; 51: 253–60.
6. Bowden CL, *et al.* A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. *Arch Gen Psychiatry* 2003; 60: 392–400. Correction. *ibid.* 2004; 61: 680.
7. Calabrese JR, *et al.* A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. *J Clin Psychiatry* 2003; 64: 1013–24.
8. Nierenberg AA, *et al.* Treatment-resistant bipolar depression: a STEP-BD equipoise randomized effectiveness trial of antidepressant augmentation with lamotrigine, inositol, or risperidone. *Am J Psychiatry* 2006; 163: 210–16.
9. Geddes JR, *et al.* Lamotrigine for treatment of bipolar depression: independent meta-analysis and meta-regression of individual patient data from five randomised trials. *Br J Psychiatry* 2009; 194: 4–9.
10. Engle PM, Heck AM. Lamotrigine for the treatment of bipolar disorder. *Ann Pharmacother* 2000; 34: 258–62.
11. Hurley SC. Lamotrigine update and its use in mood disorders. *Ann Pharmacother* 2002; 36: 860–73.
12. Goldsmith DR, *et al.* Lamotrigine: a review of its use in bipolar disorder. *Drugs* 2003; 63: 2029–50.
13. Muzina DJ, *et al.* Lamotrigine and antiepileptic drugs as mood stabilizers in bipolar disorder. *Acta Psychiatr Scand Suppl* 2005; 21–8.
14. Smith LA, *et al.* Effectiveness of mood stabilizers and antipsychotics in the maintenance phase of bipolar disorder: a systematic review of randomized controlled trials. *Bipolar Disord* 2007; 9: 394–412.
15. van der Loos MLM, *et al.* Lamotrigine bij de behandeling van bipolaire stoornissen: een overzicht. *Tijdschr Psychiatr* 2007; 49: 95–103.

Epilepsy. Lamotrigine is used in the treatment of epilepsy (p. 506.1). It is used in partial seizures with or without secondary generalisation, and in generalised tonic-clonic seizures, although valproate is the drug of choice in the latter where these are associated with the syndrome of primary generalised epilepsy. It is also recommended in absence seizures, although the evidence base is not particularly strong, and may be used in juvenile myoclonic epilepsy and tried in tonic or atonic seizures.

As monotherapy for partial seizures with or without secondary generalisation, lamotrigine was found to be better than carbamazepine (the established first-line drug) in terms of time to treatment failure and tolerability.[1] In patients with newly-diagnosed partial seizures with or without secondary generalisation, lamotrigine had a similar efficacy to carbamazepine, but again was better tolerated.[2] A systematic review[3] of randomised, placebo-controlled studies concluded that lamotrigine is also effective in reducing the seizure frequency when added to current antiepileptic regimens in patients with refractory partial seizures.

As monotherapy for primary generalised and unclassifiable seizures lamotrigine was found[4] to be significantly inferior to valproate (the established first-line drug) in terms of seizure control, with almost twice the failure rate; valproate was also significantly more effective for achieving 12-month remission and prolonging the time to first seizure. Benefit was seen with adjunctive lamotrigine when compared with placebo in children[5] and adults[6] for treatment-resistant primary generalised seizures; it was also suggested[6] that lamotrigine therapy may be appropriate when determination of the type of epilepsy in these patients is not possible.

Lamotrigine appears to be an effective adjunctive treatment in children with the Lennox-Gastaut syndrome.[7,8]

It has also been found to be effective and well tolerated as adjunctive therapy in paediatric patients with refractory epilepsy including those with developmental impairment;[9] it was particularly effective in absence and atypical seizures in this open-label study. (Evidence for the use of lamotrigine to treat absence seizures, as for the other common alternatives ethosuximide and valproate, is, however, generally poor.[10])

1. Marson AG, *et al.* SANAD Study Group. The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblinded randomised controlled trial. *Lancet* 2007; 369: 1000–15.
2. Brodie MJ, *et al.* UK Lamotrigine/Carbamazepine Monotherapy Trial Group. Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. *Lancet* 1995; 345: 476–9.
3. Ramaratnam S, *et al.* Lamotrigine add-on for drug-resistant partial epilepsy. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2001 (accessed 09/06/08).
4. Marson AG, *et al.* SANAD Study Group. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. *Lancet* 2007; 369: 1016–26.
5. Trevathan E, *et al.* Lamotrigine adjunctive therapy among children and adolescents with primary generalized tonic-clonic seizures. Abstract: *Pediatrics* 2006; 118: 777–8. Full version: http://www.pediatrics.org/cgi/content/full/118/2/e371 (accessed 09/06/08)
6. Biton V, *et al.* Double-blind, placebo-controlled study of lamotrigine in primary generalized tonic-clonic seizures. *Neurology* 2005; 65: 1737–43.
7. Donaldson JA, *et al.* Lamotrigine adjunctive therapy in childhood epileptic encephalopathy (the Lennox Gastaut Syndrome). *Epilepsia* 1997; 38: 68–73.
8. Motte J, *et al.* Lamotrigine for generalized seizures associated with the Lennox-Gastaut syndrome. *N Engl J Med* 1997; 337: 1807–12. Correction. *ibid.* 1998; 339: 851–2.
9. Besag FMC, *et al.* Lamotrigine for the treatment of epilepsy in childhood. *J Pediatr* 1995; 127: 991–7.
10. Posner EB, *et al.* Ethosuximide, sodium valproate or lamotrigine for absence seizures in children and adolescents. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 09/06/08).

Migraine. Case reports[1] and open studies[2,3] have suggested that lamotrigine may be of benefit in the prophylaxis of migraine aura.

1. d'Onofrio F, *et al.* Basilar-type migraine responsive to lamotrigine: three case reports. *Neurol Sci* 2007; 28: S239–S241.
2. Pascual J, *et al.* Preventing disturbing migraine aura with lamotrigine: an open study. *Headache* 2004; 44: 1024–8.
3. Lampl C, *et al.* Lamotrigine reduces migraine aura and migraine attacks in patients with migraine with aura. *J Neurol Neurosurg Psychiatry* 2005; 76: 1730–2.

Motor neurone disease. Lamotrigine has been tried as a potential therapy for amyotrophic lateral sclerosis (see Motor Neurone Disease, p. 2605.2) but with disappointing results.[1]

1. Ryberg H, *et al.* A double-blind randomized clinical trial in amyotrophic lateral sclerosis using lamotrigine: effects on CSF glutamate, aspartate, branched-chain amino acid levels and clinical parameters. *Acta Neurol Scand* 2003; 108: 1–8.

Movement disorders. Symptomatic improvement and a trend towards decreased chorea was reported[1] with lamotrigine in a double-blind, placebo-controlled study of 64 patients with Huntington's chorea (p. 1029.3) with motor signs of less than 5 years' duration. There was, however, no clear evidence that lamotrigine retarded the progression of early Huntington disease over a period of 30 months.

1. Kremer B, *et al.* Influence of lamotrigine on progress of early Huntington disease: a randomized clinical trial. *Neurology* 1999; 53: 1000–11.

Neuropathic pain. There is growing evidence that lamotrigine is of use in the management of neuropathic pain.[1] It was effective when used with carbamazepine or phenytoin in the treatment of refractory *trigeminal neuralgia*[2] (p. 11.2), and has also shown promise in the treatment of pain associated with *HIV-related distal sensory neuropathy*[3] (p. 958.3). Some benefit has been found[4] in the treatment of *diabetic neuropathy* (see p. 8.2). Case reports[5] and a placebo-controlled study[6] have also indicated that lamotrigine may be effective in *central post-stroke pain* (p. 7.3). More recently, the use of lamotrigine in neuropathic pain has been reviewed.[7,8] Based on the same studies, one review[7] concluded that lamotrigine is an effective treatment for various types of neuropathic pain and that further studies are warranted while another[8] concluded that it is unlikely to be of benefit and that further studies are probably not justified.

1. McCleane GJ. Lamotrigine in the management of neuropathic pain: a review of the literature. *Clin J Pain* 2000; 16: 321–6.
2. Zakrewska JM, *et al.* Lamotrigine (Lamictal) in refractory trigeminal neuralgia: results from a double-blind placebo controlled crossover study. *Pain* 1997; 73: 223–30.
3. Simpson DM, *et al.* Lamotrigine for HIV-associated painful sensory neuropathies: a placebo-controlled trial. *Neurology* 2003; 60: 1508–14.
4. Eisenberg E, *et al.* Lamotrigine reduces painful diabetic neuropathy: a randomized, controlled study. *Neurology* 2001; 57: 505–9.
5. Canavero S, Bonicalzi V. Lamotrigine control of central pain. *Pain* 1996; 68: 179–81.
6. Vestergaard K, *et al.* Lamotrigine for central post-stroke pain: a randomized controlled trial. *Neurology* 2001; 56: 184–90.
7. Eisenberg E, *et al.* Lamotrigine for neuropathic pain. *Expert Rev Neurother* 2005; 5: 729–35.
8. Wiffen PJ, Rees J. Lamotrigine for acute and chronic pain. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 09/06/08).

Schizophrenia. Lamotrigine has been tried[1] as adjunctive therapy in treatment-resistant schizophrenia (p. 1031.3) and a benefit has been reported in few studies,[2-4] although patient numbers have been small. A systematic review[5] of the use of lamotrigine in schizophrenia concluded that the evidence for its use was poor, although it was suggestive of a positive effect on symptoms. However, a later meta-analysis[6] concluded that severely ill patients with treatment-refractory schizophrenia might get significant clinical benefit from augmentation with lamotrigine.

1. Large CH, *et al.* The potential role of lamotrigine in schizophrenia. *Psychopharmacology (Berl)* 2005; 181: 415–36.
2. Tiihonen J, *et al.* Lamotrigine in treatment-resistant schizophrenia: a randomized placebo-controlled crossover trial. *Biol Psychiatry* 2003; 54: 1241–8.
3. Kremer I, *et al.* Placebo-controlled trial of lamotrigine added to conventional and atypical antipsychotics in schizophrenia. *Biol Psychiatry* 2004; 56: 441–6.
4. Zoccali R, *et al.* The effect of lamotrigine augmentation of clozapine in a sample of treatment-resistant schizophrenic patients: a double-blind, placebo-controlled study. *Schizophr Res* 2007; 93: 109–16.
5. Premkumar TS, Pick J. Lamotrigine for schizophrenia. Available in the Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 09/06/08).
6. Tiihonen J, *et al.* The efficacy of lamotrigine in clozapine-resistant schizophrenia: a systematic review and meta-analysis. *Schizophr Res* 2009; 109: 10–14.

Adverse Effects and Treatment

Skin rashes may occur during therapy with lamotrigine; severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported, especially in children, and usually occur within 8 weeks of starting lamotrigine (see Effects on the Skin, p. 529.1). Symptoms such as fever, malaise, flu-like symptoms, drowsiness, lymphadenopathy, facial oedema and, rarely, hepatic dysfunction have been reported. Blood dyscrasias such as leucopenia, neutropenia, and thrombocytopenia have also been reported, sometimes with rashes as part of a hypersensitivity syndrome.

Movement disorders such as tics, ataxia, nystagmus, and tremor have occurred; lamotrigine may worsen symptoms in patients with pre-existing Parkinson's disease. Other adverse effects include angioedema, photosensitivity, diplopia, blurred vision, conjunctivitis, dizziness, drowsiness, insomnia, headache, tiredness, nausea and vomiting, irritability and aggression, hallucinations, agitation, and confusion. Very rarely, lupus-like reactions and increases in seizure frequency have been reported.

Licensed product information states that there have been rare instances of death after a rapidly progressive illness involving status epilepticus, multi-organ dysfunction, and disseminated intravascular coagulation in patients taking multiple antiepileptics including lamotrigine, although the role of lamotrigine remains to be established. It has been suggested[1] that multi-organ failure and disseminated intravascular coagulation, with associated rhabdomyolysis, are complications of severe convulsive seizures rather than of lamotrigine therapy. However, there has been a report[2] of a patient with no history of generalised seizures who developed a syndrome of disseminated intravascular coagulation, rhabdomyolysis, renal failure, maculopapular rash, and ataxia 14 days after lamotrigine was added to her antiepileptic regimen. Two cases of disseminated intravascular coagulation were found in a cohort of 11 316 patients involved in prescription-event monitoring of lamotrigine therapy in general practice.[3]

1. Yuen AWC, Bihari DJ. Multiorgan failure and disseminated intravascular coagulation in severe convulsive seizures. *Lancet* 1992; 340: 618.
2. Schaub JEM, *et al.* Multisystem adverse reaction to lamotrigine. *Lancet* 1994; 344: 481.
3. Mackay FJ, *et al.* Safety of long-term lamotrigine in epilepsy. *Epilepsia* 1997; 38: 881–6.

Effects on the blood. Septic shock secondary to leucopenia occurred in a patient when lamotrigine was added to therapy with sodium valproate.[1] There has also been a report of agranulocytosis in a child started on high-dose lamotrigine monotherapy.[2] The fall in the blood count was noted several days after lamotrigine had been stopped due to skin rash. The UK CSM subsequently reported[3] that 7 cases of aplastic anaemia, 12 of bone-marrow depression, and 20 of pancytopenia associated with lamotrigine had been received worldwide. Given the extensive usage of lamotrigine the CSM considered the risk of aplastic anaemia to be small and routine blood monitoring was not recommended. However, prescribers were warned to be alert for symptoms and signs suggestive of bone-marrow depression.

1. Nicholson RJ, *et al.* Leucopenia associated with lamotrigine. *BMJ* 1995; 310: 504.
2. de Camargo OAK, Bode H. Agranulocytosis associated with lamotrigine. *BMJ* 1999; 318: 1179.
3. CSM/MCA. Lamotrigine (Lamictal): rare blood dyscrasias. *Current Problems* 2000; 26: 4. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)

Effects on bone. For the effects of antiepileptics including lamotrigine on bone and on calcium and vitamin D metabolism, see under Phenytoin, p. 540.2.

Effects on the liver. Fatal fulminant hepatic failure has been reported[1] in a patient after addition of lamotrigine to antiepileptic therapy with sodium valproate and carbamazepine. Another fatal case was reported[2] in a patient who was given lamotrigine for bipolar disorder; she was also taking other drugs for pain and insomnia. Reversible eosinophilic hepatitis occurred[3] as part of a hypersensitivity syndrome in a patient given lamotrigine for seizures. Others[4] have also suggested that fulminant hepatitis is a manifestation of an antiepileptic hypersensitivity syndrome.

1. Makin AJ, *et al.* Fulminant hepatic failure induced by lamotrigine. *BMJ* 1995; 311: 292.
2. Overstreet K, *et al.* Fatal progressive hepatic necrosis associated with lamotrigine treatment: a case report and literature review. *Dig Dis Sci* 2002; 47: 1921–5.
3. Fix OK, *et al.* Eosinophilic hepatitis caused by lamotrigine. *Clin Gastroenterol Hepatol* 2006; 4: xxvi.
4. Ouellet G, *et al.* Fulminant hepatitis induced by lamotrigine. *South Med J* 2009; 102: 82–4.

Effects on the lungs. Interstitial pneumonitis with pulmonary infiltrates occurred when lamotrigine was added to

antiepileptic therapy in a 57-year-old woman; the condition resolved when lamotrigine was stopped.[1]

1. Saravanan N, *et al.* Interstitial pneumonitis during lamotrigine therapy. *Br J Clin Pharmacol* 2005; 60: 666–7.

Effects on mental function. Acute *psychosis* was reported[1] in 6 out of about 1400 patients when lamotrigine was added to antiepileptic therapy and/or when the dose of lamotrigine was increased. Symptoms resolved when lamotrigine was stopped, and recurred in 1 case of rechallenge. Psychiatric symptoms associated with lamotrigine use have been reviewed.[2]

For a review of the effects of antiepileptic therapy including lamotrigine on *cognition*, and on *mood* (including the risk of suicidal ideation), see p. 508.3.

1. Brandt C, *et al.* Development of psychosis in patients with epilepsy treated with lamotrigine: report of six cases and review of the literature. *Epilepsy Behav* 2007; 11: 133–9.
2. Villari V, *et al.* Psychiatric symptoms related to the use of lamotrigine: a review of the literature. *Funct Neurol* 2008; 23: 133–6.

Effects on the nervous system. Of 93 patients with idiopathic generalised epilepsy who were treated with lamotrigine, 5 adults had *de novo* or exacerbated myoclonic jerks.[1] In each case, symptoms resolved when the dose of lamotrigine was reduced by 25 to 50% or stopped altogether. In another report, a 17-year-old girl with idiopathic Rolandic epilepsy had a sudden increase in seizure frequency when lamotrigine was added to therapy with sodium valproate; other adverse effects included emotional lability, headaches, and drowsiness.[2] Again symptoms resolved when lamotrigine was stopped.[2]

Overdose of lamotrigine has been known to cause seizures (see below).

Aseptic meningitis has been associated with lamotrigine use.[3] A total of 40 cases have been submitted to the FDA between December 1994 and November 2009; symptoms reported included headache, fever, nausea, vomiting, nuchal rigidity, photophobia, and myalgias and occurred within a mean of 16 days of starting therapy. Most patients recovered when lamotrigine was stopped although 15 patients reported a rapid return of symptoms when rechallenged.

1. Crespel A, *et al.* Lamotrigine associated with exacerbation or de novo myoclonus in idiopathic generalized epilepsies. *Neurology* 2005; 65: 762–4.
2. Cerminara C, *et al.* Lamotrigine-induced seizure aggravation and negative myoclonus in idiopathic rolandic epilepsy. *Neurology* 2004; 63: 373–5.
3. FDA. News release: aseptic meningitis risk with use of seizure drug Lamictal (issued 12th August, 2010). http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm222212.htm (accessed 24/08/10)

Effects on the skin. Rashes account for withdrawal from therapy in about 2% of those given lamotrigine,[1,2] and serious skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis occur in about 1 in 1000 adult patients.[3,4] The majority of rashes resolve once lamotrigine has been stopped; however, some patients have developed permanent scarring and there have been rare reports of fatalities. The main risk factors appear to be use with valproate, exceeding the recommended initial dose of lamotrigine or the recommended rate of dose escalation, and a history of antiepileptic-induced rash. The risk appears to be greater in children[1,4–6] and has been estimated to be between 1 in 300 and 1 in 50. These skin reactions usually occur within 8 weeks of starting therapy with lamotrigine, but onset as early as the first day and as late as 2 years has been noted.[7] After continuing reports of serious skin reactions in children, UK recommended dosage regimens for children have been revised to further reduce the risk of such reactions.[8] For the relative incidence of rash with different antiepileptics see under Phenytoin, p. 541.1.

1. Mackay FJ, *et al.* Safety of long-term lamotrigine in epilepsy. *Epilepsia* 1997; 38: 881–6.
2. Messenheimer J, *et al.* Safety review of adult clinical trial experience with lamotrigine. *Drug Safety* 1998; 18: 281–96.
3. CSM/MCA. Lamotrigine (Lamictal) and serious skin reactions. *Current Problems* 1996; 22: 12. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON20156226RevisionSelectionMethod=LatestReleased (accessed 09/06/08)
4. CSM/MCA. Lamotrigine (Lamictal): increased risk of serious skin reactions in children. *Current Problems* 1997; 23: 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON20232305RevisionSelectionMethod=LatestReleased (accessed 09/06/08)
5. Mitchell P. Paediatric lamotrigine use hit by rash reports. *Lancet* 1997; 349: 1080.
6. Hirsch LJ, *et al.* Predictors of lamotrigine-associated rash. *Epilepsia* 2006; 47: 318–22.
7. Adverse Drug Reactions Advisory Committee (ADRAC). Lamotrigine and severe skin reactions. *Aust Adverse Drug React Bull* 1997; 16: 3. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr9702.htm (accessed 09/06/08)
8. CSM/MCA. Lamotrigine (Lamictal): revised doses for children. *Current Problems* 2000; 26: 3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON0074626RevistonSelectionMethod=LatestReleased (accessed 09/06/08)

Hypersensitivity. For reference to a case of suspected cross-sensitivity between carbamazepine and lamotrigine, see p. 515.1.

Overdosage. An evaluation[1] of 493 cases of lamotrigine-only overdoses reported to the American Association of Poison Control Centers over a 2-year period found that 52.1% of patients had no toxic effects. The most commonly reported adverse effects were drowsiness, nausea, vomiting, and ataxia. Serious effects such as seizures, coma, and respiratory depression were reported in 0.6 to 1.2% of cases; no deaths were reported.

No serious toxicity was seen in a patient who deliberately took an overdose of 1.35 g of lamotrigine and was subsequently treated with gastric lavage and activated charcoal.[2] Symptoms at presentation one hour after ingestion had included nystagmus and muscle hypertonicity. ECG monitoring had revealed widening of the QRS interval. Low-grade fever, erythema, and periorbital oedema suggestive of a hypersensitivity syndrome developed in another patient who inadvertently received lamotrigine 2.7 g daily for 4 days.[3] The patient recovered after corticosteroid treatment and stopping lamotrigine. Generalised tonic-clonic seizures, tremor, muscle weakness, ataxia, and hypertonia were reported[4] in a 2-year-old child after ingestion of 800 mg of lamotrigine. Symptoms resolved within 24 hours after treatment with gastric lavage and activated charcoal, midazolam, and fluids. Plasma-lamotrigine concentrations were in the high adult therapeutic range (3.8 micrograms/mL) with a slow elimination rate. Generalised seizures also occurred[5] after an unknown quantity of lamotrigine was ingested by a 19-month-old child who had no history of seizures; other presenting symptoms included tachycardia and vomiting. The serum-lamotrigine concentration measured 1 hour post ingestion was 20.3 mg/L. Symptoms resolved within 24 hours after treatment with trimethobenzamide and activated charcoal.

1. Lofton AL, Klein-Schwartz W. Evaluation of lamotrigine toxicity reported to poison centers. *Ann Pharmacother* 2004; 38: 1811–15.
2. Buckley NA, *et al.* Self-poisoning with lamotrigine. *Lancet* 1993; 342: 1552–3.
3. Mylonakis E, *et al.* Lamotrigine overdose presenting as anticonvulsant hypersensitivity syndrome. *Ann Pharmacother* 1999; 33: 557–9.
4. Briassoulis G, *et al.* Lamotrigine childhood overdose. *Pediatr Neurol* 1998; 19: 239–42.
5. Thundiyil JG, *et al.* Lamotrigine-induced seizures in a child: case report and literature review. *Clin Toxicol* 2007; 45: 169–72.

Precautions

Lamotrigine should be given with caution to patients with hepatic or renal impairment. All patients should be warned to see their doctor immediately if rashes or symptoms associated with hypersensitivity develop. To minimise the risk of developing serious skin reactions, dosage recommendations should not be exceeded. Particular care is needed in patients also receiving valproate—see under Interactions, p. 530.1.

Withdrawal of lamotrigine should be considered if rash, fever, flu-like symptoms, drowsiness, or worsening of seizure control occurs. Care is required when withdrawing lamotrigine therapy—see also Uses and Administration, p. 527.2. Abrupt withdrawal should be avoided unless serious skin reactions have occurred. Lamotrigine should not be restarted in patients with previous hypersensitivity.

Breast feeding. The American Academy of Pediatrics[1] considers that the use of lamotrigine by mothers during breast feeding may be of concern, since there is the potential for therapeutic serum concentrations to occur in the infant. A report in 4 breast-fed infants whose mothers were taking lamotrigine found that although serum concentrations of the drug 10 days after birth were about 30% of maternal concentrations in 3 infants, no short-term adverse effects were seen; the drug was undetectable in the fourth.[2] A study[3] in 6 mothers taking lamotrigine found that the relative dose in their breast-fed infants was 7.6% (mean absolute dose: 450 micrograms/kg daily) and infant plasma concentrations were 18% of maternal concentrations; no adverse effects were reported. The authors also noted that no adverse effects were reported in 12 previous cases. However, there has been a report[4] of severe apnoea in a neonate exposed to lamotrigine via breast milk; drug concentrations in the infant were 4.87 micrograms/mL at admission, which was towards the upper end of the therapeutic range, and his calculated intake in breast milk was at least 1.15 mg/kg daily.

For further comment on antiepileptic therapy and breast feeding, see p. 508.3.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *Ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 09/06/08)
2. Liporace J, *et al.* Concerns regarding lamotrigine and breast-feeding. *Epilepsy Behav* 2004; 5: 102–5.
3. Page-Sharp M, *et al.* Transfer of lamotrigine into breast milk. *Ann Pharmacother* 2006; 40: 1470–1.
4. Nordmo E, *et al.* Severe apnea in an infant exposed to lamotrigine in breast milk. *Ann Pharmacother* 2009; 43: 1893–7.

Driving. For a comment on antiepileptic drugs and driving, see p. 509.2.

Hepatic impairment. The pharmacokinetics of lamotrigine were not significantly altered in patients with moderate cirrhosis;[1] however, those with severe cirrhosis showed significantly lower oral clearance and longer elimination half-lives than those in healthy subjects.

The recommended licensed doses in patients with hepatic impairment are given under Uses and Administration, p. 527.3.

1. Marcellin P, *et al.* Influence of cirrhosis on lamotrigine pharmacokinetics. *Br J Clin Pharmacol* 2001; 51: 410–14.

Intellectual impairment. Aggressive behaviour has been reported in intellectually impaired patients given lamotrigine.[1] Of 19 such patients given lamotrigine, aggressive behaviour developed in 9; the drug was stopped in 5, and stopped but reintroduced in a further 2, together with psychiatric management. One patient responded to a reduction in lamotrigine dosage.

1. Beran RG, Gibson RJ. Aggressive behaviour in intellectually challenged patients with epilepsy treated with lamotrigine. *Epilepsia* 1998; 39: 280–2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lamotrigine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pregnancy. For comments on the management of epilepsy during pregnancy, see p. 509.2. For reference to alteration of lamotrigine pharmacokinetics in pregnancy, see under Pharmacokinetics, p. 530.3.

There is a theoretical risk of teratogenicity with lamotrigine because, like valproate, it is a folate antagonist. In 2002 the manufacturer of lamotrigine, *GlaxoSmithKline*, reported[1] that it had follow-up information on 395 outcomes of pregnancies exposed to lamotrigine between September 1992 and September 2001 from the International Lamotrigine Pregnancy Registry. Major birth defects were found in 13 infants but no distinctive pattern of abnormalities suggestive of a common cause could be identified. Of the 168 who had been exposed to lamotrigine monotherapy during the first trimester, birth defects were reported in 3 (1.8%). The frequency of major birth defects in pregnancies exposed to polytherapy containing lamotrigine with valproate was 10% compared with 4.3% in lamotrigine polytherapy without valproate. Although it was considered that the sample sizes were too small to rule out a small increase in the frequency of major birth defects, it was noted that the frequency of malformations after lamotrigine monotherapy did not differ from that reported in the literature for women with epilepsy receiving antiepileptic monotherapy. Updated results from 785 pregnancies up to March 2004 included 414 first-trimester exposures to lamotrigine monotherapy, of which 12 were associated with a major abnormality.[2] As of March 2006, the registry had recorded 802 first-trimester exposures to lamotrigine monotherapy with major abnormalities occurring in 22; there was no evidence to suggest a dose-response relationship with daily doses of up to 400 mg.[3]

In August 2006, the manufacturer[4] reported that data from the North American Antiepileptic Drug Pregnancy Registry suggested an association between lamotrigine and an increased risk of oral clefts. Of 564 first-trimester exposures to lamotrigine monotherapy, 5 cases of oral clefts were reported giving an incidence rate of 8.9 per 1000 compared with 0.37 per 1000 in the reference population. Again, however, no increase in the overall risk of major malformations was found. Analysis of data from other pregnancy registries found 4 additional cases of oral clefts in about 2200 first-trimester exposures to lamotrigine monotherapy.

1. Tennis P, Eldridge RR. International Lamotrigine Pregnancy Registry Scientific Advisory Committee. Preliminary results on pregnancy outcomes in women using lamotrigine. *Epilepsia* 2002; 43: 1161–7.
2. Cunnington M, Tennis P. International Lamotrigine Pregnancy Registry Scientific Advisory Committee. Lamotrigine and the risk of malformations in pregnancy. *Neurology* 2005; 64: 955–60.
3. Cunnington M, *et al.* International Lamotrigine Pregnancy Registry Scientific Advisory Committee. Effect of dose on the frequency of major birth defects following fetal exposure to lamotrigine monotherapy in an international observational study. *Epilepsia* 2007; 48: 1207–10.
4. GlaxoSmithKline, Canada. Association of Lamictal (lamotrigine) with an increased risk of non-syndromic oral clefts (issued 1st August, 2006). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/lamictal_2_hpc-cps-eng.pdf (accessed 01/09/08)

Renal impairment. Results from a pharmacokinetic study[1] indicated that impaired renal function was likely to have little effect on plasma concentrations of lamotrigine. The drug is mainly cleared by metabolism and although the

glucuronide metabolite accumulates it is inactive. Nevertheless, there is limited clinical experience with lamotrigine in such patients and caution was recommended.

1. Wootton R, *et al.* Comparison of the pharmacokinetics of lamotrigine in patients with chronic renal failure and healthy volunteers. *Br J Clin Pharmacol* 1997; 43: 23–7.

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy. The metabolism of lamotrigine is enhanced by the enzyme inducers carbamazepine, phenytoin, phenobarbital, and primidone, and inhibited by valproate (see below).

Analgesics. *Paracetamol* affects the metabolic disposition of lamotrigine but the clinical significance of this interaction remains to be determined.[1] Paracetamol reduced the area under the plasma concentration-time curve for lamotrigine, reduced lamotrigine's half-life, and increased the percentage of lamotrigine recovered in the urine.

1. Depot M, *et al.* Kinetic effects of multiple oral doses of acetaminophen on a single oral dose of lamotrigine. *Clin Pharmacol Ther* 1990; 48: 346–55.

Antibacterials. Use with *rifampicin* significantly increased the clearance of lamotrigine.[1] The total urinary excretion of lamotrigine and the amount excreted as glucuronide were significantly higher compared with placebo.

1. Ebert U, *et al.* Effects of rifampicin and cimetidine on pharmacokinetics and pharmacodynamics of lamotrigine in healthy subjects. *Eur J Clin Pharmacol* 2000; 56: 299–304.

Antidepressants. An epileptic patient maintained on lamotrigine 200 mg daily complained[1] of increasing confusion and cognitive impairment after starting *sertraline* 25 mg daily for post-traumatic disorder; after 6 weeks her lamotrigine blood concentrations had risen from 2.5 to 5.1 micrograms/mL during this period. The adverse effects cleared and blood concentrations of lamotrigine fell to 3.1 micrograms/mL within 3 weeks of changing the daily dosage to lamotrigine 100 mg and sertraline 50 mg. A patient, with poorly controlled epilepsy, who initially had been taking lamotrigine 450 mg and sertraline 75 mg together daily for 6 weeks without adverse effects had marked sedation, fatigue, and decreased cognition 6 weeks after the daily dosage of lamotrigine was increased to 600 mg. Her lamotrigine blood concentration was 19.3 micrograms/mL. The patient was subsequently stabilised on lamotrigine 800 mg and sertraline 50 mg daily and had less sedation and fatigue and clearer cognition; blood concentrations of lamotrigine fell to 9.8 micrograms/mL.

1. Kaufman KR, Gerner R. Lamotrigine toxicity secondary to sertraline. *Seizure* 1998; 7: 163–5.

Antiepileptics. *Valproate* can inhibit the metabolism of lamotrigine resulting in increased concentrations of lamotrigine. This effect can be beneficial in the control of certain seizures, although careful monitoring is required as toxicity may occur. Disabling tremor that occurred in 3 patients taking such a combination resolved when the dose of lamotrigine or valproate was reduced.[1] Other reports of toxicity, resolving on reduction of the lamotrigine dose, were marked by sedation, ataxia, and fatigue,[2] or delirium.[3] Symptoms of neurotoxicity were reported in 3 patients on lamotrigine therapy who were given valproate, intravenously then orally, for absence status epilepticus. Serum concentrations of lamotrigine in these patients were raised about three- to sevenfold.[4] Reversible encephalopathy has been reported[5] when sodium valproate was substituted for phenytoin in a patient also taking lamotrigine, although her clinical condition had been satisfactory on this new regimen for several months. Symptoms improved when the doses of both valproate and lamotrigine were reduced. Pharmacokinetic studies[6,7] in healthy adults have attempted to elucidate the mechanism of the interaction between lamotrigine and valproate. The clearance of lamotrigine was found to be reduced, and exposure and elimination half-life increased when valproate was also given. Renal elimination was not affected and the investigators[6] suggested that there was hepatic competition for glucuronidation between valproate and lamotrigine. However, there was no substantial alteration in the linear kinetics of lamotrigine in the presence of therapeutic plasma concentrations of valproate.[7] Similar observations were made when lamotrigine was added to existing antiepileptic regimens in children,[8] although the clinical relevance of the influence of age on the pharmacokinetics remains to be determined. Both young age and use with valproate are risk factors for lamotrigine-induced dermatological toxicity—see Effects on the Skin, p. 529.1.

For details of dosage reductions required for lamotrigine used with valproate, see Uses and Administration, p. 527.2.

Other antiepileptics also affect plasma concentrations of lamotrigine. In contrast to valproate, *carbamazepine, phenytoin,* or *phenobarbital* all markedly induced the elimination of lamotrigine.[9] Others have confirmed a reduction in plasma-lamotrigine concentrations when given with phenytoin and other enzyme-inducing antiepileptics,[10] but analysis of results from another study[11] suggested that the increase in lamotrigine clearance by phenytoin and carbamazepine was of minimal clinical significance. For reports of an interaction between lamotrigine and carbamazepine, see p. 516.3. *Oxcarbazepine* has also been reported[12] to decrease serum-lamotrigine concentrations (although to a lesser extent than carbamazepine). However, a study[13] in healthy subjects found that oxcarbazepine did not affect the pharmacokinetics of lamotrigine, although adverse effects occurred more frequently when they were used together (for a report of severe toxicity associated with such use see p. 534.2). *Mesuximide* was found[12,14] to have a marked inducing effect on the metabolism of lamotrigine. In one study,[14] plasma-lamotrigine concentrations were significantly reduced when given together.

For the effect of lamotrigine on *clonazepam* concentrations, see p. 1069.1.

1. Reutens DC, *et al.* Disabling tremor after lamotrigine with sodium valproate. *Lancet* 1993; 342: 185–6.
2. Pisani F, *et al.* Interaction of lamotrigine with sodium valproate. *Lancet* 1993; 341: 1224.
3. Mueller TH, Beeber AR. Delirium from valproic acid with lamotrigine. *Am J Psychiatry* 2004; 161: 1128–9.
4. Burneo JG, *et al.* Neurotoxicity following addition of intravenous valproate to lamotrigine therapy. *Neurology* 2003; 60: 1991–2.
5. Hennessy MJ, Wiles CM. Lamotrigine encephalopathy. *Lancet* 1996; 347: 974–5.
6. Yuen AWC, *et al.* Sodium valproate acutely inhibits lamotrigine metabolism. *Br J Clin Pharmacol* 1992; 33: 511–13.
7. Anderson GD, *et al.* Bidirectional interaction of valproate and lamotrigine in healthy subjects. *Clin Pharmacol Ther* 1996; 60: 145–56.
8. Vauzelle-Kervroëdan F, *et al.* Influence of concurrent antiepileptic medication on the pharmacokinetics of lamotrigine as add-on therapy in epileptic children. *Br J Clin Pharmacol* 1996; 41: 325–30.
9. May TW, *et al.* Serum concentrations of lamotrigine in epileptic patients: the influence of dose and comedication. *Ther Drug Monit* 1996; 18: 523–31.
10. Battino D, *et al.* Lamotrigine plasma concentrations in children and adults: influence of age and associated therapy. *Ther Drug Monit* 1997; 19: 620–7.
11. Grasela TH, *et al.* Population pharmacokinetics of lamotrigine adjunctive therapy in adults with epilepsy. *J Clin Pharmacol* 1999; 39: 373–84.
12. May TW, *et al.* Influence of oxcarbazepine and methsuximide on lamotrigine concentrations in epileptic patients with and without valproic acid comedication: results of a retrospective study. *Ther Drug Monit* 1999; 21: 175–81.
13. Theis JGW, *et al.* Lack of pharmacokinetic interaction between oxcarbazepine and lamotrigine. *Neuropsychopharmacology* 2005; 30: 2269–74.
14. Besag FM, *et al.* Methsuximide lowers lamotrigine blood levels: a pharmacokinetic antiepileptic drug interaction. *Epilepsia* 2000; 41: 624–7.

Antipsychotics. An apparent interaction between lamotrigine and *aripiprazole,* resulting in Stevens-Johnson syndrome, has been reported[1] in 2 patients with schizophrenia after the introduction of lamotrigine; both patients recovered with supportive treatment.

1. Shen Y-C, *et al.* Concomitant use of lamotrigine and aripiprazole increases risk of Stevens-Johnson syndrome? *Int Clin Psychopharmacol* 2007; 22: 247–8.

Antivirals. A study[1] in healthy subjects found that *ritonavir-boosted lopinavir* decreased the steady-state minimum plasma concentration of lamotrigine by about 55%; doubling the dose of lamotrigine achieved concentrations similar to those with lamotrigine alone.

1. van der Lee MJ, *et al.* Lopinavir/ritonavir reduces lamotrigine plasma concentrations in healthy subjects. *Clin Pharmacol Ther* 2006; 80: 159–68.

Sex hormones. Studies in patients taking lamotrigine have indicated that *combined oral contraceptives*[1,2] may halve plasma concentrations of the antiepileptic. Other studies[3,4] have also found a significant increase in lamotrigine-plasma concentrations within one week of stopping contraceptive therapy; however, wide interpatient variability was noted in one study.[3] Significant adjustments in maintenance doses of lamotrigine may be needed if combined contraceptives are started or stopped (see below), and patients should be warned not to make changes in their contraceptive therapy without consulting their physician.[5] However, in a study,[6] progestogen-only contraceptives did not appear to affect lamotrigine concentrations. Licensed product information recommends that, when starting treatment with combined oral contraceptives, the dose of lamotrigine may need to be increased by as much as twofold in those women not taking drugs known to induce cytochrome P450-mediated metabolism of lamotrigine; conversely, the dose of lamotrigine may need to be halved when stopping contraceptive therapy in women not taking enzyme inducers. Dosage adjustment may not be necessary when starting or stopping combined oral contraceptive therapy in women taking lamotrigine with known enzyme inducers.

Adjustments may also be needed if other hormonal preparations are taken with lamotrigine.

Some reduction in plasma concentrations of levonorgestrel, and to a lesser extent ethinylestradiol, may also occur with lamotrigine, and there have been reports of breakthrough bleeding and unexpected pregnancies.[5]

1. Sabers A, *et al.* Oral contraceptives reduce lamotrigine plasma levels. *Neurology* 2003; 61: 570–1.
2. Sidhu J, *et al.* The pharmacokinetic and pharmacodynamic consequences of the co-administration of lamotrigine and a combined oral contraceptive in healthy female subjects. *Br J Clin Pharmacol* 2006; 61: 191–9.
3. Contin M, *et al.* Variation in lamotrigine plasma concentrations with hormonal contraceptive monthly cycles in patients with epilepsy. *Epilepsia* 2006; 47: 1573–5.
4. Christensen J, *et al.* Oral contraceptives induce lamotrigine metabolism: evidence from a double-blind, placebo-controlled trial. *Epilepsia* 2007; 48: 484–9.
5. GlaxoSmithKline, Canada. Important new safety information concerning the antiepileptic, Lamictal (lamotrigine) (issued September 2004). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/lamictal_hpc-cps-eng.pdf (accessed 01/09/08)
6. Reimers A, *et al.* Ethinyl estradiol, not progestogens, reduces lamotrigine serum concentrations. *Epilepsia* 2005; 46: 1414–17.

Pharmacokinetics

Lamotrigine is rapidly absorbed from the gastrointestinal tract with an absolute bioavailability of 98%. Peak plasma concentrations occur about 2.5 hours after oral doses. It is widely distributed in the body and is reported to be about 55% bound to plasma proteins. It is extensively metabolised in the liver and excreted almost entirely in urine, principally as an inactive glucuronide conjugate. It slightly induces its own metabolism and the mean elimination half-life is reported to be 24 to 35 hours. Clearance is reported to be higher in children aged up to 12 years than in adults, with the highest values occurring in those under 5 years of age. Lamotrigine is distributed into breast milk.

The pharmacokinetics of lamotrigine are affected by other antiepileptics (see Interactions, above).

General references.

1. Rambeck B, Wolf P. Lamotrigine clinical pharmacokinetics. *Clin Pharmacokinet* 1993; 25: 433–43.
2. Elwes RDC, Binnie CD. Clinical pharmacokinetics of newer antiepileptic drugs: lamotrigine, vigabatrin, gabapentin and oxcarbazepine. *Clin Pharmacokinet* 1996; 30: 403–15.
3. Reimers A, *et al.* Lamotrigine in children and adolescents: the impact of age on its serum concentrations and on the extent of drug interactions. *Eur J Clin Pharmacol* 2007; 63: 687–92.
4. Punyawudho B, *et al.* Population pharmacokinetics of lamotrigine in elderly patients. *J Clin Pharmacol* 2008; 48: 455–63.

Hepatic impairment. See under Precautions, p. 529.3.

Pregnancy. Decreased plasma-lamotrigine concentrations have occurred during pregnancy, with deterioration of seizure control and a need for dosage adjustment in some patients.

References

1. Pennell PB, *et al.* The impact of pregnancy and childbirth on the metabolism of lamotrigine. *Neurology* 2004; 62: 292–5.
2. de Haan G-J, *et al.* Gestation-induced changes in lamotrigine pharmacokinetics: a monotherapy study. *Neurology* 2004; 63: 571–3.
3. Petrenaite V, *et al.* Individual changes in lamotrigine plasma concentrations during pregnancy. *Epilepsy Res* 2005; 65: 185–8.
4. Pennell PB, *et al.* Lamotrigine in pregnancy: clearance, therapeutic drug monitoring, and seizure frequency. *Neurology* 2008; 70: 2130–6.

Renal impairment. See under Precautions, p. 529.3.

Therapeutic drug monitoring. A literature review[1] concluded that a clear relationship between lamotrigine concentrations and toxicity or antiepileptic efficacy has not been shown. Routine therapeutic drug monitoring was therefore not recommended and clinical end-points rather than plasma concentrations remained the best guide for dosage adjustment of lamotrigine.

1. Chong E, Dupuis LL. Therapeutic drug monitoring of lamotrigine. *Ann Pharmacother* 2002; 36: 917–20.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dafex; Epilepax; Lagotran; Lamictal; Lamirax; Lamocas; Lamotril†; Latrigin; ***Austral.***: Elmendos†; Lamictal; Lamidus; Lamitrin†; Lamogine; Seaze; ***Austria***: Gerolamic; Lamictal; ***Belg.***: Doclamotri†; Lambipol; Lamictal; ***Braz.***: Lamictal; Lamitor; Lamoctril; Lamotrix; Neural; Neurium; Nortrigin; ***Canad.***: Lamictal; ***Chile***: Daksol; Flamus; Lafigin; Lamictal; Lomarin; Meganox; Tradox; Trigilab; Trizol; ***China***: An Xian (安闲); Lamictal (利必通); ***Cz.***: Danoptin†; Epimil; Epiral†; Lameton†; Lamictal; Lamiger†; Lamogine†; Lamolep†; Lamotax; Lamotri†; Lamotrix; Latrigil†; Plexxo; Rubimar; Triginet†; ***Denm.***: Delitrig†; Ginalam†; Lamictal; Raklam†; ***Fin.***: Lamictal; ***Fr.***: Lamictsart†; Lamictal; ***Ger.***: Elmendos†; Lamictal; Lamo-Q†; Lamo†; Lamotrig†; ***Gr.***: Dezepil; Lamictal; Lamot; Lamotrix; ***Hong Kong***: Lamictal; Lamotrin; ***Hung.***: Epitrigine; Gerolamic; Lamictal; Lamitrin; Lamolep; Plexxo†; ***India***: Epitic; Favlam; Lamepil; Lamepril; Lametec; Lamidus; Lamitor; Lamogin; Lamorig; Lamosyn; Lemogen; ***Indon.***: Lamictal; ***Irl.***: Bymot†; Lameutral; Lamictal; Lamoro; Larig; ***Israel***: Lamictal; Lamodex; Lamogine; ***Ital.***: Lamictal; ***Jpn***: Lamictal; ***Malaysia***:

Lamictal; Lamotrix; *Mex.*: Fenebra; Lamdra; Lamictal; Latrigin; Limatic; Motricord; Prilkenzide; Protalgine; Ramitrine; Trimolep; *Neth.*: Lambipol; Lamictal; Lamopan†; Lamotrigal; Symla†; *Norw.*: Lamictal; *NZ*: Lamictal; Logem; Mogine; *Philipp.*: Lamictal; Lamitor; *Pol.*: Danoptin†; Epilactal†; Epitrigine; Lameptil; Lamexim; Lamia†; Lamilept; Lamitrin; LamoMerck; Lamotrihexal†; Lamotrix; Lamox†; Lamozor; Plexxo; Symla; Triginet†; Trogine; *Port.*: Lamictal; Lamix; Motrigi; *Rus.*: Convulsan (Конвульсан); Lameptil (Ламептил); Lamictal (Ламиктал); Lamitor (Ламитор); Lamolep (Ламолеп); Sazar (Сейзар); Triginet (Тригинет); *S.Afr.*: Epitec; Lamictin; Lamidus; Lamitor; *Singapore*: Lamictal; Lanotrix; *Spain*: Crisomet; Labileno; Lamictal; Lamomylan; Lavinol†; Silam†; *Swed.*: Lamictal; *Switz.*: Lamictal; Lamotrine; *Thai.*: Lamictal; *Turk.*: Lamictal; Pinral; *UK*: Lamictal; *Ukr.*: Epileptal (Эпилептал); Epimil (Эпимил); Lameton (Ламетон)†; Lamictal (Ламиктал); Lamidum (Ламидум)†; Lamotrin (Ламотрин); Latrigil (Латригил); Latrigin (Латриджин); *USA*: Epitrogine; Lamictal; *Venez.*: Lamictal.

Pharmacopoeial Preparations
BP 2014: Dispersible Lamotrigine Tablets; Lamotrigine Tablets; USP 36: Lamotrigine Tablets for Oral Suspension; Lamotrigine Tablets.

Levetiracetam *(BAN, USAN, rINN)*

S-Etiracetam; Lévétiracétam; Levetiracetamum; Levetiracetam; SIB-S1; UCB-22059; UCB-L059; Леветирацетам.
(*S*)-2-(2-Oxopyrrolidin-1-yl)butanamide.
$C_8H_{14}N_2O_2$=170.2
CAS — 102767-28-2.
ATC — N03AX14.
ATC Vet — QN03AX14.
UNII — 44YRR34555.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Levetiracetam). A white or almost white powder. Very soluble in water; soluble in acetonitrile; practically insoluble in hexane.

USP 36: (Levetiracetam). A white to almost white powder. Very soluble in water; soluble in acetonitrile; practically insoluble in hexane.

Uses and Administration

Levetiracetam is an analogue of piracetam (p. 393.3) used in the treatment of epilepsy (below). Details of licensed indications, ages at which levetiracetam may be used, and the route employed, vary from country to country. The following indications and age limits apply to oral use. It is used as an adjunct in the treatment of partial seizures with or without secondary generalisations in adults and children from 1 month of age. In the UK, adults and adolescents aged 16 years and over may also be given levetiracetam as monotherapy in the treatment of partial seizures with or without secondary generalisation. In addition, levetiracetam is licensed in both the UK and the USA for adjunctive use in the treatment of myoclonic seizures in adults and children aged 12 years and over with juvenile myoclonic epilepsy. It is also licensed for use as an adjunct in the treatment of primary generalised tonic-clonic seizures in adults and children with idiopathic generalised epilepsy; for this indication, in the UK, licensed use is restricted to children aged 12 years and over, whereas in the USA, it is licensed from 6 years of age.

The daily oral dose of levetiracetam is given in two divided doses.

- The initial adult dose when used *as an adjunct* is 1 g on the first day of treatment; thereafter, the daily dose may be increased in steps of 1 g every 2 to 4 weeks until effective antiepileptic control is achieved, up to a maximum dose of 3 g daily.
  The initial dose in children aged from 1 month to less than 6 months is 14 mg/kg daily which may be increased in steps of 14 mg/kg every 2 weeks to a maximum of 42 mg/kg daily.
  The initial dose in children aged from 6 months and weighing less than 50 kg is 20 mg/kg daily which may be increased in steps of 20 mg/kg every 2 weeks to a maximum of 60 mg/kg daily.
  Children and adolescents weighing 50 kg or more should be given the usual adult dose (see above).
- When used as *monotherapy*, the initial dose of levetiracetam is 500 mg daily, increased after 2 weeks to 1 g daily. Further increases may be made in steps of 500 mg every 2 weeks up to a maximum of 3 g daily.

A modified-release preparation is available for once-daily dosing *as an adjunct* in the treatment of partial seizures in patients aged 16 years and over.

When oral use is not feasible, levetiracetam may be given by intravenous infusion over 15 minutes in doses similar to those used orally. As with the oral formulation, details of licensed uses and ages may vary from country to country; in the UK, it is licensed in adults and children from 4 years of age, whereas in the USA, use is restricted to those aged 16 years and over. UK licensed product information states that there has been no experience with the use of intravenous levetiracetam for more than 4 days.

Reduced doses are recommended in renal and severe hepatic impairment (see below).

As with other antiepileptics, withdrawal of levetiracetam therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. UK licensed product information recommends reducing the daily dose in patients weighing more than 50 kg by 1 g every 2 to 4 weeks, and in those weighing less than 50 kg, the dose reduction should not exceed 20 mg/kg every 2 weeks. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1).

References.

1. De Smedt T, *et al.* Levetiracetam: the profile of a novel anticonvulsant drug—part I: preclinical data. *CNS Drug Rev* 2007; 13: 43–56.
2. De Smedt T, *et al.* Levetiracetam: part II, the clinical profile of a novel anticonvulsant drug. *CNS Drug Rev* 2007; 13: 57–78.
3. Crepeau AZ, Treiman DM. Levetiracetam: a comprehensive review. *Expert Rev Neurother* 2010; 10: 159–71.

Administration in children. Licensed indications and doses of levetiracetam in children vary from country to country, see Uses and Administration, above, and Administration in Renal Impairment, below.

Levetiracetam is mainly used for partial and myoclonic seizures, and in idiopathic generalised epilepsy, often as an adjunct. It has also been tried in children with status epilepticus (p. 532.1). A retrospective review[1] of 122 children aged from 1 month to 2 years given levetiracetam either as monotherapy (48 patients) or adjunctive therapy (74 patients) found that 70 achieved seizure remission. Of these, a longer duration of remission was seen in those receiving less than 30 mg/kg daily of levetiracetam. A case series[2] of 3 infants aged from 2 days to 3 months reported that levetiracetam 30 mg/kg daily was effective in the treatment of refractory neonatal seizures. A randomised multicentre study[3] of 116 children aged from 1 month to under 4 years with refractory partial seizures found that adjunctive levetiracetam significantly reduced the frequency of seizures and was generally well tolerated.

1. Perry MS, Benatar M. Efficacy and tolerability of levetiracetam in children younger than 4 years: a retrospective review. *Epilepsia* 2007; 48: 1123–7.
2. Shoemaker MT, Rotenberg JS. Levetiracetam for the treatment of neonatal seizures. *J Child Neurol* 2007; 22: 95–8.
3. Piña-Garza JE, *et al.* Levetiracetam N01009 Study Group. Adjunctive levetiracetam in infants and young children with refractory partial-onset seizures. *Epilepsia* 2009; 50: 1141–9.

Administration in hepatic impairment. No dose adjustment of levetiracetam is needed in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, creatinine clearance (CC) may underestimate concomitant renal impairment, and UK licensed product information recommends that the usual adult maintenance dose (see above) should be reduced by 50% in those with a CC of less than 60 mL/minute per 1.73 m^2.

Administration in renal impairment. Reduced doses of levetiracetam are recommended for patients with renal impairment. Suitable daily doses for adults and adolescents weighing more than 50 kg according to UK and US licensed product information and based on creatinine clearance (CC) per 1.73 m^2, are:

- CC 50 to 79 mL/minute: 1 to 2 g
- CC 30 to 49 mL/minute: 0.5 to 1.5 g
- CC less than 30 mL/minute: 0.5 to 1 g
- Patients receiving dialysis may be given a loading dose of 750 mg when starting levetiracetam followed by doses of 0.5 to 1 g once daily; a supplemental dose of 250 to 500 mg is recommended after dialysis

UK licensed product information also gives suitable daily doses for children weighing less than 50 kg with renal impairment:

In children aged from 6 months:

- CC 50 to 79 mL/minute: 20 to 40 mg/kg
- CC 30 to 49 mL/minute: 10 to 30 mg/kg
- CC less than 30 mL/minute: 10 to 20 mg/kg
- Those receiving dialysis may be given a loading dose of 15 mg/kg when starting levetiracetam followed by doses of 10 to 20 mg/kg once daily; a supplemental dose of 5 to 10 mg/kg is recommended after dialysis

In children aged 1 month to less than 6 months:

- CC 50 to 79 mL/minute: 14 to 28 mg/kg
- CC 30 to 49 mL/minute: 7 to 21 mg/kg
- CC less than 30 mL/minute: 7 to 14 mg/kg
- Those receiving dialysis may be given a loading dose of 10.5 mg/kg when starting levetiracetam followed by doses of 7 to 14 mg/kg once daily; a supplemental dose of 3.5 to 7 mg/kg is recommended after dialysis

Doses may be given orally or intravenously, as necessary, in 2 divided doses.

See also above for dosage recommendations in those patients with severe hepatic impairment and concomitant renal impairment.

Epilepsy. Levetiracetam is used in epilepsy (p. 506.1) as an adjunct or monotherapy in the management of partial seizures with or without secondary generalisation.[1] It is also used as an adjunct in myoclonic seizures and for generalised tonic-clonic seizures,[1] although valproate is the drug of choice in the latter where these are associated with the syndrome of primary generalised epilepsy. Levetiracetam may be considered as second-line drug for atonic or tonic seizures, and has been tried in Lennox-Gastaut syndrome and in juvenile absence epilepsy.[2] In children, levetiracetam has also been tried as adjunctive therapy for nonconvulsive status epilepticus,[3] in infantile spasms,[4] and in severe myoclonic epilepsy of infancy,[5] and as monotherapy in partial and generalised epilepsy.[6]

1. Lyseng-Williamson KA. Levetiracetam: a review of its use in epilepsy. *Drugs* 2011; 71: 489–514.
2. NICE. The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care (issued October 2004). Available at: http://www.nice.org.uk/nicemedia/pdf/CG020fullguideline.pdf (accessed 09/06/08)
3. Trabacca A, *et al.* Levetiracetam in nonconvulsive status epilepticus in childhood: a case report. *J Child Neurol* 2007; 22: 639–41.
4. Mikati MA, *et al.* Response of infantile spasms to levetiracetam. *Neurology* 2008; 70: 574–5.
5. Striano P, *et al.* An open-label trial of levetiracetam in severe myoclonic epilepsy of infancy. *Neurology* 2007; 69: 250–4.
6. Khurana DS, *et al.* Levetiracetam monotherapy in children with epilepsy. *Pediatr Neurol* 2007; 36: 227–30.

Movement disorders. Levetiracetam may be of benefit in some movement disorders. It has been tried in antipsychotic-induced *tardive dyskinesia*[1-3] and with equivocal benefit in levodopa-induced tardive dyskinesia[4,5] (see under Extrapyramidal Disorders on p. 1049.2). There is also limited evidence of benefit with levetiracetam for the treatment of *chorea* (p. 1029.3) in Huntington's disease[6,7] and in *paroxysmal kinesigenic choreoathetosis*.[8]

1. Konitsiotis S, *et al.* Levetiracetam in tardive dyskinesia: an open label study. *Mov Disord* 2006; 21: 1219–21.
2. Meco G, *et al.* Levetiracetam in tardive dyskinesia. *Clin Neuropharmacol* 2006; 29: 265–8.
3. Woods SW, *et al.* Effects of levetiracetam on tardive dyskinesia: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 2008; 69: 546–54.
4. Zesiewicz TA, *et al.* Open-label pilot study of levetiracetam (Keppra) for the treatment of levodopa-induced dyskinesias in Parkinson's disease. *Mov Disord* 2005; 20: 1205–9.
5. Lyons KE, Pahwa R. Efficacy and tolerability of levetiracetam in Parkinson disease patients with levodopa-induced dyskinesia. *Clin Neuropharmacol* 2006; 29: 148–53.
6. Zesiewicz TA, *et al.* Open-label pilot study of levetiracetam (Keppra) for the treatment of chorea in Huntington's disease. *Mov Disord* 2006; 21: 1998–2001.
7. de Tommaso M, *et al.* Efficacy of levetiracetam in Huntington disease. *Clin Neuropharmacol* 2005; 28: 280–4.
8. Chatterjee A, *et al.* Levetiracetam in the treatment of paroxysmal kinesiogenic choreoathetosis. *Mov Disord* 2002; 17: 614–15.

Muscle spasm. Levetiracetam has been tried with some success in *Meige's syndrome*,[1] and *hemifacial spasm*.[2] For use in *stiff-man syndrome* see p. 532.1.

1. Yardimci N, *et al.* Levetiracetam in Meige's syndrome. *Acta Neurol Scand* 2006; 114: 63–6.
2. Deleu D. Levetiracetam in the treatment of idiopathic hemifacial spasm. *Neurology* 2004; 62: 2134–5.

Psychiatric disorders. Levetiracetam has psychotropic properties and has been tried in the management of *anxiety disorders*[1,2] (p. 1028.1) including *social anxiety disorder*[2-4] (see Phobic Disorders, p. 1029.1), *post-traumatic stress disorder*[2,5] (p. 1029.2), and *panic disorder*[2,6] (p. 1029.1). There is also limited evidence[7] from case reports and small open-label studies that levetiracetam may be of benefit in the treatment of *bipolar disorder* (p. 397.2); however, a later randomised placebo-controlled study[8] found that adjunctive levetiracetam was not superior to placebo in the short-term treatment of depression in these patients.

1. Kinrys G, *et al.* Levetiracetam as adjunctive therapy for refractory anxiety disorders. *J Clin Psychiatry* 2007; 68: 1010–13.
2. Farooq MU, *et al.* Levetiracetam for managing neurologic and psychiatric disorders. *Am J Health-Syst Pharm* 2009; 66: 541–61.
3. Simon NM, *et al.* An open-label study of levetiracetam for the treatment of social anxiety disorder. *J Clin Psychiatry* 2004; 65: 1219–22.
4. Stein MB, *et al.* Levetiracetam in generalized social anxiety disorder: a double-blind, randomized controlled trial. *J Clin Psychiatry* 2010; 71: 627–31.
5. Kinrys G, *et al.* Levetiracetam for treatment-refractory posttraumatic stress disorder. *J Clin Psychiatry* 2006; 67: 211–14.
6. Papp LA. Safety and efficacy of levetiracetam for patients with panic disorder: results of an open-label, fixed-flexible dose study. *J Clin Psychiatry* 2006; 67: 1573–6.
7. Muralidharan A, Bhagwagar Z. Potential of levetiracetam in mood disorders: a preliminary review. *CNS Drugs* 2006; 20: 969–79.
8. Saricicek A, *et al.* Levetiracetam in the management of bipolar depression: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 2011; 72: 744–50.

Restless legs syndrome. Levetiracetam has been reported to be of benefit in the treatment of refractory restless legs syndrome (see Sleep-associated Movement Disorders, p. 1034.2).[1]

1. Della Marca G, *et al.* Levetiracetam can be effective in the treatment of restless legs syndrome with periodic limb movements in sleep: report of two cases. *J Neurol Neurosurg Psychiatry* 2006; 77: 566–7.

Status epilepticus. Levetiracetam has been tried, with some success, in the management of nonconvulsive status epilepticus[1] and refractory status epilepticus,[2-7] including in children.[5-7] For the conventional management of status epilepticus see p. 510.2.

1. Rupprecht S, *et al.* Levetiracetam as a treatment option in non-convulsive status epilepticus. *Epilepsy Res* 2007; 73: 238–44.
2. Patel NC, *et al.* The use of levetiracetam in refractory status epilepticus. *Seizure* 2006; 15: 137–41.
3. Eue S, *et al.* Two years of experience in the treatment of status epilepticus with intravenous levetiracetam. *Epilepsy Behav* 2009; 15: 467–9.
4. Möddel G, *et al.* Intravenous levetiracetam: a new treatment alternative for refractory status epilepticus. *J Neurol Neurosurg Psychiatry* 2009; 80: 689–92.
5. Kirmani BF, *et al.* Role of intravenous levetiracetam in acute seizure management of children. *Pediatr Neurol* 2009; 41: 37–9.
6. Abend NS, *et al.* Intravenous levetiracetam in critically ill children with status epilepticus or acute repetitive seizures. *Pediatr Crit Care Med* 2009; 10: 505–10.
7. Gallentine WB, *et al.* Levetiracetam in children with refractory status epilepticus. *Epilepsy Behav* 2009; 14: 215–8.

Stiff-man syndrome. In a report[1] of a patient with stiff-man syndrome (see under Muscle Spasm, p. 1064.3), substitution of levetiracetam for previous valproate therapy (because of suspected valproate-induced parkinsonism) resulted in complete suppression of paroxysmal spasms; benefit was sustained with continued therapy over 2 years of follow-up.

1. Rüegg SJ, *et al.* Levetiracetam improves paroxysmal symptoms in a patient with stiff-person syndrome. *Neurology* 2004; 62: 338.

Tremor. A beta blocker is often the first drug used in patients with essential tremor (p. 1318.3) who require regular treatment. Levetiracetam has also been tried with some success;[1] however, an evidence-based guideline[2] found no benefit and recommended against such use. An open-label study reported[3] benefit with levetiracetam in the treatment of tremor secondary to multiple sclerosis but, again, a later randomised placebo-controlled study found[4] that it did not affect the severity of tremor or functionality in this patient group.

1. Bushara KO, *et al.* The effect of levetiracetam on essential tremor. *Neurology* 2005; 64: 1078–80.
2. Zesiewicz TA, *et al.* Evidence-based guideline update: treatment of essential tremor: report of the Quality Standards subcommittee of the American Academy of Neurology. *Neurology* 2011; 77: 1752–5. Also available at: http://www.neurology.org/content/77/19/1752.full.pdf+html (accessed 01/05/12)
3. Striano P, *et al.* Levetiracetam for cerebellar tremor in multiple sclerosis: an open-label pilot tolerability and efficacy study. *J Neurol* 2006; 253: 762–6.
4. Peys P, *et al.* The effect of levetiracetam on tremor severity and functionality in patients with multiple sclerosis. *Multiple Sclerosis* 2009; 15: 371–8.

Adverse Effects and Precautions

The most commonly reported adverse effects associated with levetiracetam are somnolence, weakness, and dizziness. Anorexia, diarrhoea, dyspepsia, nausea, weight gain or loss, myalgia, ataxia, headache, amnesia, depression, emotional lability, insomnia, nervousness, tremor, vertigo, diplopia, and rash (see below) may occur less frequently. Other adverse effects include paraesthesia, pancreatitis, hepatic failure, and hepatitis. A raised incidence of mild infections, such as the common cold and upper respiratory-tract infections, has been reported. Alopecia may also develop; in some cases, stopping levetiracetam has resulted in regrowth of hair.

Other adverse effects reported include abnormal behaviour, aggression, anger, anxiety, confusion, hallucinations, irritability, and psychotic disorders; these adverse effects may be more common in children than in adults. Blood dyscrasias such as neutropenia, pancytopenia, and thrombocytopenia may develop. Severe skin reactions including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have occurred rarely.

Levetiracetam should be used with caution in patients with renal impairment, and/or severe hepatic impairment.

Care is required when withdrawing levetiracetam therapy—see also Uses and Administration, p. 531.1.

Breast feeding. For comment on antiepileptic therapy and breast feeding, see p. 508.3.

Driving. For a comment on antiepileptic drugs and driving, see p. 509.2.

Effects on the endocrine system. Hyponatraemia developed[1] in a patient given levetiracetam in whom carbamazepine had previously caused the syndrome of inappropriate antidiuretic hormone secretion; symptoms resolved on stopping levetiracetam and recurred on rechallenge.

For mention of the effects of antiepileptics on *sexual function*, including a lack of effect of levetiracetam, see under Phenytoin, p. 540.3.

1. Nasrallah K, Silver B. Hyponatremia associated with repeated use of levetiracetam. *Epilepsia* 2005; 46: 972–3.

Effects on the liver. Fulminant hepatic failure requiring transplantation has been reported[1] in a patient 1 month after switching from oxcarbazepine to levetiracetam to improve seizure control. Levetiracetam was restarted after transplantation, resulting in rapid deterioration of liver function tests which subsequently normalised 4 weeks after the drug was stopped. In another case,[2] severe acute hepatitis occurred 3 weeks after levetiracetam was added to antiepileptic therapy with valproate; symptoms (such as fever, rash, eosinophilia, and interstitial pulmonary infiltrates) suggestive of an antiepileptic hypersensitivity syndrome were also reported. The patient made a full recovery after levetiracetam was stopped.

1. Tan TCH, *et al.* Levetiracetam as a possible cause of fulminant liver failure. *Neurology* 2008; 71: 685–6.
2. Lens S, *et al.* Severe acute hepatitis in the dress [sic] syndrome: report of two cases. *Ann Hepatol* 2010; 9: 198–201.

Effects on the lungs. Diffuse interstitial lung disease developed[1] after a dose increase of levetiracetam in a 9-year-old girl who had been taking the drug for 2 years. The condition resolved when levetiracetam was stopped and treatment with corticosteroids was given.

1. Newsome SD, *et al.* Levetiracetam-induced diffuse interstitial lung disease. *J Child Neurol* 2007; 22: 628–30.

Effects on mental function. For a review of the effects of antiepileptic therapy on *cognition*, and the effects of levetiracetam on *mood* (including the risk of suicidal ideation), see p. 508.3.

Effects on the skin. For a suggestion that skin reactions are less common with levetiracetam than with some other antiepileptics, see under Phenytoin, p. 541.1.

Hypersensitivity. For mention of antiepileptic hypersensitivity syndrome possibly associated with levetiracetam, see Effects on the Liver, above.

Movement disorders. Levetiracetam has been associated with symptoms of parkinsonism including resting tremor, bradykinesia, and rigidity when used to treat Huntington's chorea in a 58-year-old man;[1] symptoms resolved within 7 days of stopping levetiracetam. The patient was also taking other drugs at the time and the authors suggested that these symptoms might have been caused by a drug interaction. However, levetiracetam has been tried in the treatment of some movement disorders as discussed under Uses and Administration, p. 531.3.

1. Zesiewicz TA, *et al.* Levetiracetam-induced parkinsonism in a Huntington disease patient. *Clin Neuropharmacol* 2005; 28: 188–90.

Overdosage. A 38-year-old woman who ingested 30 g of levetiracetam vomited 4 hours later and presented with hypoxia, hypotension, and respiratory depression 6 hours after ingestion; peak plasma-levetiracetam concentration was 400 micrograms/mL.[1] The patient recovered without sequelae over 48 hours with symptomatic treatment.

1. Barrueto F, *et al.* A case of levetiracetam (Keppra) poisoning with clinical and toxicokinetic data. *J Toxicol Clin Toxicol* 2002; 40: 881–4.

Porphyria. Levetiracetam has been successfully used in a few patients with porphyria[1,2] and the Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies levetiracetam as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[3]

1. Paul F, Meencke HJ. Levetiracetam in focal epilepsy and hepatic porphyria: a case report. *Epilepsia* 2004; 45: 559–60.
2. Bilo L, *et al.* Levetiracetam in idiopathic generalised epilepsy and porphyria cutanea tarda. *Clin Drug Investig* 2006; 26: 357–9.
3. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pregnancy. For comments on the management of epilepsy during pregnancy, see p. 509.2.

The UK Epilepsy and Pregnancy Register[1] provided data as of July 2005 from 117 first-trimester exposures to levetiracetam with 39 to monotherapy and 78 to adjunctive therapy. In the former group, 4 infants had a low birthweight and 4 were born at 37 weeks of gestation or less. In the latter, 10 had a low birth-weight, 18 were born at 37 weeks of gestation or less, and 3 had major congenital malformations. A subsequent review[2] commented that the risk of malformation with levetiracetam appeared low. Clearance of levetiracetam is increased during pregnancy, and monitoring of serum concentrations may be desirable, especially in the third trimester.

1. Hunt S, *et al.* Levetiracetam in pregnancy: preliminary experience from the UK Epilepsy and Pregnancy Register. *Neurology* 2006; 67: 1876–9.
2. Longo B, *et al.* Levetiracetam use in pregnancy. *Ann Pharmacother* 2009; 43: 1692–5.

Interactions

Evidence of significant interactions between levetiracetam and other antiepileptics is mostly lacking. However, for the effects of levetiracetam on carbamazepine, see p. 516.3.

Pharmacokinetics

Levetiracetam is readily absorbed from the gastrointestinal tract with a bioavailability of almost 100%; peak plasma concentrations usually occur within 1.3 hours of oral doses and steady state after 2 days. Plasma protein binding is minimal at less than 10%. Levetiracetam is not extensively metabolised; about 25% of a dose is metabolised by hydroxylation to inactive metabolites. Around 95% of a dose is excreted as unchanged drug and metabolites in the urine. The plasma elimination half-life has been reported to be about 7 hours in adults and children aged 12 years and over; the half-life may be shorter in younger children. Levetiracetam is distributed into breast milk.

References.

1. Radtke RA. Pharmacokinetics of levetiracetam. *Epilepsia* 2001; 42 (suppl 4): 24–7.
2. Pellock JM, *et al.* Pharmacokinetic study of levetiracetam in children. *Epilepsia* 2001; 42: 1574–9.
3. Coupez R, *et al.* Levetiracetam: relative bioavailability and bioequivalence of a 10% oral solution (750 mg) and 750-mg tablets. *J Clin Pharmacol* 2003; 43: 1370–6.
4. Patsalos PN. Clinical pharmacokinetics of levetiracetam. *Clin Pharmacokinet* 2004; 43: 707 24.
5. Brockmöller J, *et al.* Pharmacokinetics of levetiracetam in patients with moderate to severe liver cirrhosis (Child-Pugh classes A, B, and C): characterization by dynamic liver function tests. *Clin Pharmacol Ther* 2005; 77: 529–41.
6. Glauser TA, *et al.* Pharmacokinetics of levetiracetam in infants and young children with epilepsy. *Epilepsia* 2007; 48: 1117–22.
7. Tomson T, *et al.* Pharmacokinetics of levetiracetam during pregnancy, delivery, in the neonatal period, and lactation. *Epilepsia* 2007; 48: 1111–16.
8. Hirsch LJ, *et al.* Effect of age and comedication on levetiracetam pharmacokinetics and tolerability. *Epilepsia* 2007; 48: 1351–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Callexe; Keppra; Levron; Molival; Vecetam; *Austral.*: Kepcet; Keppra; Kevtam; Levitam; *Austria*: Keppra; *Belg.*: Keppra; *Canad.*: Keppra; *Chile*: Ceumid; Keppra; Kopodex; Kredit; *China*: Keppra (开浦兰); *Cz.*: Keppra; *Denm.*: Keppra; *Fin.*: Keppra; *Fr.*: Keppra; *Ger.*: Keppra; *Gr.*: Keppra; *Hong Kong*: Keppra; *Hung.*: Keppra; *India*: Epictal; Keppra; Lenerve; Levecetam; Levera; Levesam; Levexx; Levipil; Levroxa; Levtam; *Indon.*: Keppra; *Irl.*: Keppra; Matever; *Israel*: Keppra; Levetrim; *Ital.*: Keppra; *Jpn*: E Keppra; *Malaysia*: Keppra; *Mex.*: Keppra; *Neth.*: Cezarius; Dretacen; Eliptus; Keppra; Latrea; Matever; Trund; Vetira; *Norw.*: Keppra; *NZ*: Keppra; *Philipp.*: Ivetra; Keppra; *Pol.*: Keppra; *Port.*: Keppra; *Rus.*: Keppra (Кеппра); *S.Afr.*: Keppra; Redilev; *Singapore*: Keppra; *Spain*: Keppra; Laurak; Tirbas; *Swed.*: Keppra; *Switz.*: Keppra; Rivoleve; *Thai.*: Keppra; *Turk.*: Epileptal; Epitam; Epixx: Keppra; Lev-End; Netrolex; Vetria; *UK*: Desitrend; Keppra; *Ukr.*: Keppra (Кеппра); Levicitam (Левицитам); *USA*: Keppra.

Pharmacopoeial Preparations

USP 36: Levetiracetam Extended-Release Tablets; Levetiracetam Oral Solution; Levetiracetam Tablets.

Mephenytoin *(BAN, USAN, rINN)*

Mefenitoína; Mefenytoiini; Mefenytoin; Mephenetoin; Méphénytoïne; Mephenytoinum; Methantoin; Methoin; NSC-34652; Phenantoin; Мефенитоин.

5-Ethyl-3-methyl-5-phenylhydantoin.

$C_{12}H_{14}N_2O_2$=218.3

CAS — 50-12-4.

ATC — N03AB04.

ATC Vet — QN03AB04.

UNII — R420KW629U.

Pharmacopoeias. In *US.*

USP 36: (Mephenytoin). Store in airtight containers.

Profile

Mephenytoin is a hydantoin antiepileptic with actions similar to those of phenytoin (p. 538.2), but it is more toxic. Because of its potential toxicity it is not one of the main drugs used in the treatment of epilepsy (p. 506.1) and has been given orally only to patients unresponsive to other treatment. Some of the adverse effects of mephenytoin may be due to the metabolite, 5-ethyl-5-phenylhydantoin (also termed nirvanol). Like phenytoin the rate of metabolism of mephenytoin is subject to genetic polymorphism.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Epilan†.

Pharmacopoeial Preparations
USP 36: Mephenytoin Tablets.

Mesuximide *(BAN, rINN)*

Mesuksimidi; Mesuximid; Mesuximida; Mésuximide; Mesuximidum; Methsuximide; PM-396; Мезуксимид.

N,2-Dimethyl-2-phenylsuccinimide.

$C_{12}H_{13}NO_2$=203.2

CAS — 77-41-8.

ATC — N03AD03.

ATC Vet — QN03AD03.

UNII — 0G76K8X6C0.

Pharmacopoeias. In *US*.

USP 36: (Methsuximide). A white to greyish-white crystalline powder. Is odourless or has a slight odour. Soluble 1 in 350 of water, 1 in 3 of alcohol, 1 in less than 1 of chloroform, and 1 in 2 of ether. Store in airtight containers.

Profile

Mesuximide is a succinimide antiepileptic with actions similar to those of ethosuximide (p. 521.1) that is used in the treatment of absence seizures; although it also has some activity in complex partial seizures it is reported to be less well tolerated than ethosuximide, and is usually only given to patients unresponsive to other antiepileptic treatment (below). It is thought to owe its activity to its major metabolite *N*-desmethylmesuximide.

The usual initial oral dosage is a single dose of 300 mg daily for the first week, and this is increased by 300 mg at weekly intervals to an optimum dosage, according to response. The suggested maximum daily dose is 1.2 g in divided doses.

Epilepsy. Mesuximide is used for absence seizures that are refractory to less toxic antiepileptics such as ethosuximide or valproate, which are the usual first-line drugs (see p. 506.1). Mesuximide has also been tried in complex partial seizures and myoclonic seizures.

References.
1. Tennison MB, *et al.* Methsuximide for intractable childhood seizures. *Pediatrics* 1991; 87: 186–9.
2. Sigler M, *et al.* Effective and safe but forgotten: methsuximide in intractable epilepsies in childhood. *Seizure* 2001; 10: 120–4.

Interactions. For the effect of mesuximide on lamotrigine and valproate, see p. 530.1 and p. 557.3, respectively.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Celontin; *Ger.*: Petinutin; *Switz.*: Petinutin; *USA*: Celontin.

Pharmacopoeial Preparations
USP 36: Methsuximide Capsules.

Methylphenobarbital *(BAN, rINN)*

Enphenemalum; Mephobarbital; Methylfenobarbital; Méthylphénobarbital; Methylphenobarbitalum; Methylphenobarbitone; Metilfenobarbital; Metilfenobarbitál; Metilfenobarbitalis; Metylfenobarbital; Metyylifenobarbitaali; Phemitone; Метилфенобарбитал.

5-Ethyl-1-methyl-5-phenylbarbituric acid.

$C_{13}H_{14}N_2O_3$=246.3

CAS — 115-38-8.

ATC — N03AA01.

ATC Vet — QN03AA01.

UNII — 5NC67NU76B.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Methylphenobarbital). A white or almost white, crystalline powder or colourless crystals. Practically insoluble in water; very slightly soluble in dehydrated alcohol. It forms water-soluble compounds with alkali hydroxides and carbonates, and with ammonia.

USP 36: (Mephobarbital). A white, odourless, crystalline powder. Slightly soluble in water, in alcohol, and in ether; soluble in chloroform and in solutions of fixed alkali hydroxides and carbonates. Its saturated solution in water is acid to litmus.

Profile

Methylphenobarbital is demethylated to phenobarbital (p. 535.2) and has been used similarly in the treatment of epilepsy; it has also been used as a sedative.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Mebaral†.

Multi-ingredient Preparations. *Arg.*: Cumatil-L†; *Ital.*: Dintoinale; Metinal-Idantoina L; Metinal-Idantoina.

Pharmacopoeial Preparations
BP 2014: Methylphenobarbital Tablets;
USP 36: Mephobarbital Tablets.

Oxcarbazepine *(BAN, USAN, rINN)*

GP-47680; KIN-493; Okskarbatsepiini; Okskarbazepin; Oxcarbazepin; Oxcarbazepina; Oxcarbazépine; Oxcarbazepinum; Окскарбазепин.

10,11-Dihydro-10-oxo-5*H*-dibenz[*b*,*f*]azepine-5-carboxamide.

$C_{15}H_{12}N_2O_2$=252.3

CAS — 28721-07-5.

ATC — N03AF02.

ATC Vet — QN03AF02.

UNII — VZI5B1W380.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Oxcarbazepine). A white or faintly orange, crystalline powder. Practically insoluble in water and in alcohol; slightly soluble in dichloromethane.

USP 36: (Oxcarbazepine). Light orange to creamish white or off-white powder. Practically insoluble in water, sparingly soluble in chloroform; soluble in acetic acid. Store at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Oxcarbazepine is a derivative of carbamazepine (p. 512.3) with similar actions. It is used as monotherapy or adjunctive therapy in the treatment of partial seizures with or without secondary generalisation (below). The initial oral dose for monotherapy and adjunctive therapy is 600 mg daily, given in 2 divided doses. The daily dose may be increased thereafter, if necessary, in maximum increments of 600 mg at about weekly intervals until the desired clinical response has been achieved. Maintenance doses are usually in the range of 600 mg to 1.2 g daily or up to 2.4 g daily if given as adjunctive therapy or in refractory patients switched from other antiepileptics.

For doses in children, see below.

Reduced initial doses are recommended in patients with renal impairment (see below).

As with other antiepileptics, withdrawal of oxcarbazepine therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1.

Administration in children. Oxcarbazepine is used in children as monotherapy or adjunctive therapy in the treatment of partial seizures with or without secondary generalisation. In the UK, the recommended initial oral dose for monotherapy and adjunctive therapy in those aged 6 years and over is 8 to 10 mg/kg daily, given in 2 divided doses. The daily dose may be increased thereafter, if necessary, in maximum increments of 10 mg/kg at about weekly intervals to a maximum dose of 46 mg/kg daily; usual maintenance doses in adjunctive therapy are around 30 mg/kg daily. In the USA, similar doses are recommended for adjunctive therapy in children aged 2 years and over (the initial dose may be doubled in those weighing under 20 kg), and for monotherapy in those aged 4 years and over; a maximum daily dose of 60 mg/kg is permitted for adjunctive therapy.

Administration in renal impairment. Initial doses of oxcarbazepine for adult patients with a creatinine clearance of less than 30 mL/minute should be 300 mg daily (half the usual starting dose, above), increased at weekly intervals or longer.

Bipolar disorder. Like the related drug carbamazepine (p. 513.1), oxcarbazepine has antimanic properties and has been tried in the management of patients with bipolar disorder (p. 397.2). Reviews[1,2] have suggested that it may be useful in treating acute mania and in patients with refractory disease; however, the evidence base is weak[3] and further studies are needed.

1. Pratoomsri W, *et al.* Oxcarbazepine in the treatment of bipolar disorder: a review. *Can J Psychiatry* 2006; 51: 540–5.
2. Popova E, *et al.* Oxcarbazepine in the treatment of bipolar and schizoaffective disorders. *Expert Rev Neurother* 2007; 7: 617–26.
3. Vasudev A, *et al.* Oxcarbazepine in the maintenance treatment of bipolar disorder. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 09/06/08).

Epilepsy. Oxcarbazepine is used in the treatment of epilepsy (p. 506.1) and may be a useful alternative in patients unable to tolerate carbamazepine. A systematic review[1] found them to be of similar efficacy in partial seizures.

In a double-blind study[2] involving newly diagnosed adult patients, oxcarbazepine was of similar efficacy and tolerability to valproate for partial or generalised tonic-clonic seizures. Oxcarbazepine was of similar efficacy to phenytoin, but was better tolerated in adults and children with newly diagnosed partial or generalised tonic-clonic seizures.[3,4] Further randomised controlled studies and 2 small systematic reviews[5,6] have also confirmed the efficacy and tolerability of oxcarbazepine as adjunctive therapy[3,7] or monotherapy[6,8–10] in refractory partial seizures in children and adults.

1. Koch MW, Polman SKL. Oxcarbazepine versus carbamazepine monotherapy for partial onset seizures. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 24/11/09).
2. Christe W, *et al.* A double-blind controlled clinical trial: oxcarbazepine versus sodium valproate in adults with newly diagnosed epilepsy. *Epilepsy Res* 1997; 26: 451–60.
3. Bill PA, *et al.* A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in adults with previously untreated epilepsy. *Epilepsy Res* 1997; 27: 195–204.
4. Guerreiro MM, *et al.* A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in children and adolescents with epilepsy. *Epilepsy Res* 1997; 27: 205–13.
5. Castillo SM, *et al.* Oxcarbazepine add-on for drug-resistant partial epilepsy. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2000 (accessed 09/06/08).
6. Muller M, *et al.* Oxcarbazepine versus phenytoin monotherapy for epilepsy. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 09/06/08).
7. Glauser TA, *et al.* Adjunctive therapy with oxcarbazepine in children with partial seizures. *Neurology* 2000; 54: 2237–44.
8. Beydoun A, *et al.* Oxcarbazepine monotherapy for partial-onset seizures: a multicenter, double-blind, clinical trial. *Neurology* 2000; 54: 2245–51.
9. Sachdeo R, *et al.* Oxcarbazepine (Trileptal) as monotherapy in patients with partial seizures. *Neurology* 2001; 57: 864–71.
10. Herranz Fernández JL, *et al.* Oxcarbacepina en monoterapia en 324 pacientes con crisis parciales (estudio TRINOVA). *Rev Neurol* 2004; 39: 601–6.

Neuropathic pain. Antiepileptics are among the drugs used to manage neuropathic pain, which is often insensitive to opioid analgesics (see Choice of Analgesic, p. 4.2). Oxcarbazepine has been tried in various neuropathic pain syndromes[1] including painful diabetic neuropathy[2–4] (see p. 8.2), postherpetic neuralgia[5,6] (p. 10.3), complex regional pain syndrome[7] (p. 8.1), glossopharyngeal neuralgia,[8] oxaliplatin-induced neuropathy[9] (see Effects on the Nervous System, p. 838.3), and trigeminal neuralgia (p. 11.2).

1. Magenta P, *et al.* Oxcarbazepine is effective and safe in the treatment of neuropathic pain: pooled analysis of seven clinical studies. *Neurol Sci* 2005; 26: 218–26.
2. Dogra S, *et al.* Oxcarbazepine in painful diabetic neuropathy: a randomized, placebo-controlled study. *Eur J Pain* 2005; 9: 543–54.
3. Grosskopf J, *et al.* A randomized, placebo-controlled study of oxcarbazepine in painful diabetic neuropathy. *Acta Neurol Scand* 2006; 114: 177–80.
4. Beydoun S, *et al.* Long-term safety and tolerability of oxcarbazepine in painful diabetic neuropathy. *Acta Neurol Scand* 2007; 115: 284–8.
5. Criscuolo S, *et al.* Oxcarbazepine (Trileptal) monotherapy dramatically improves quality of life in two patients with postherpetic neuralgia refractory to carbamazepine and gabapentin. *J Pain Symptom Manage* 2004; 28: 535–6.
6. Criscuolo S, *et al.* Oxcarbazepine monotherapy in postherpetic neuralgia unresponsive to carbamazepine and gabapentin. *Acta Neurol Scand* 2005; 111: 229–32.
7. Lalwani K, *et al.* Use of oxcarbazepine to treat a pediatric patient with resistant complex regional pain syndrome. *J Pain* 2005; 6: 704–6.
8. Luef G, Poewe W. Oxcarbazepine in glossopharyngeal neuralgia: clinical response and effect on serum lipids. *Neurology* 2004; 63: 2447–8.
9. Argyriou AA, *et al.* Efficacy of oxcarbazepine for prophylaxis against cumulative oxaliplatin-induced neuropathy. *Neurology* 2006; 67: 2253–5.

Psychiatric disorders. Case reports[1,2] in children and adolescents and a randomised, placebo-controlled study[3] in adults have indicated some benefit from oxcarbazepine in the treatment of *aggression* and *disturbed behaviour* (p. 1030.2). A retrospective review[4] of 14 children and adolescents with various psychiatric and behavioural disorders found moderate symptomatic improvement in 50% after the addition of oxcarbazepine. Oxcarbazepine has also been tried in the treatment of *schizophrenia*[5] (p. 1031.3) and *post-traumatic stress disorder*[6] (p. 1029.2). For use in *bipolar disorder* see above.

1. Kapetanovic S. Oxcarbazepine in youths with autistic disorder and significant disruptive behaviors. *Am J Psychiatry* 2007; 164: 832–3.
2. Gaudino MP, *et al.* Use of oxcarbazepine for treatment-resistant aggression. *Psychiatr Serv* 2003; 54: 1166–7.
3. Mattes JA. Oxcarbazepine in patients with impulsive aggression: a double-blind, placebo-controlled trial. *J Clin Psychopharmacol* 2005; 25: 575–9.
4. Stafler JA, *et al.* Oxcarbazepine in the treatment of child psychiatric disorders: a retrospective chart review. *J Child Adolesc Psychopharmacol* 2005; 15: 964–9.
5. Leweke FM, *et al.* Oxcarbazepine as an adjunct for schizophrenia. *Am J Psychiatry* 2004; 161: 1130–1.
6. Malek-Ahmadi P, Hanretta AT. Possible reduction in posttraumatic stress disorder symptoms with oxcarbazepine in a patient with bipolar disorder. *Ann Pharmacother* 2004; 38: 1852–4.

Withdrawal syndromes and abstinence. Oxcarbazepine has been tried in the prophylaxis and treatment of various withdrawal syndromes. Although it was not found[1] to be superior to placebo in the treatment of symptoms of the *alcohol withdrawal syndrome* (p. 1735.1), oxcarbazepine has been reported[2–4] to be of benefit in relapse prevention; further studies are considered warranted. It has been

given with tiapride.[5] It has also been tried[6,7] during *benzodiazepine withdrawal* but such adjunct therapy is not usually indicated (see p. 1065.1).

1. Koethe D, *et al.* Oxcarbazepine—efficacy and tolerability during treatment of alcohol withdrawal: a double-blind, randomized, placebo-controlled multicenter pilot study. *Alcohol Clin Exp Res* 2007; 31: 1188–94.
2. Croissant B, *et al.* Oxcarbazepine in alcohol relapse prevention: a case series. *Pharmacopsychiatry* 2004; 37: 306–7.
3. Croissant B, *et al.* A pilot study of oxcarbazepine versus acamprosate in alcohol-dependent patients. *Alcohol Clin Exp Res* 2006; 30: 630–5.
4. Martinotti G, *et al.* High and low dosage oxcarbazepine versus naltrexone for the prevention of relapse in alcohol-dependent patients. *Hum Psychopharmacol* 2007; 22: 149–56.
5. Croissant B, *et al.* Oxcarbazepine in combination with Tiaprid in inpatient alcohol-withdrawal—a RCT. *Pharmacopsychiatry* 2009; 42: 175–81.
6. Croissant B, *et al.* Scheme-based benzodiazepine detoxification with oxcarbazepine: a case report. *Pharmacopsychiatry* 2005; 38: 222–3.
7. Croissant B, *et al.* Oxcarbazepine in rapid benzodiazepine detoxification. *Am J Drug Alcohol Abuse* 2008; 34: 534–40.

Adverse Effects, Treatment, and Precautions

As for Carbamazepine, p. 514.1.

Hypersensitivity reactions occur less frequently with oxcarbazepine than with carbamazepine (see also under Carbamazepine, p. 515.1). However, cross-sensitivity does occur and about 25 to 30% of patients hypersensitive to carbamazepine may have such reactions with oxcarbazepine. Immediate (type I) hypersensitivity reactions including rash, pruritus, urticaria, angioedema, and anaphylaxis have occurred with oxcarbazepine therapy. Angioedema and anaphylaxis involving the larynx, glottis, lips, and eyelids have been reported in patients after the first or subsequent doses. Treatment should be stopped in those who develop hypersensitivity reactions to oxcarbazepine.

Reductions in plasma-sodium levels have also been seen with oxcarbazepine (see Hyponatraemia, below). Patients with cardiac insufficiency and secondary heart failure should be weighed regularly to detect fluid retention. Oxcarbazepine may, very rarely, impair cardiac conduction and patients with pre-existing conduction disorders should be carefully monitored. Very rarely, oxcarbazepine treatment has been associated with pancreatitis.

Dosage reductions are recommended in renal impairment.

Breast feeding. For comment on antiepileptic therapy and breast feeding, see p. 508.3.

Driving. For a comment on antiepileptic drugs and driving, see p. 509.2.

Effects on the blood. Although it would appear that oxcarbazepine is less likely than carbamazepine to cause blood dyscrasias such as leucopenia, individual cases have been reported. In one such case leucopenia and hyponatraemia developed in a 57-year-old woman while taking oxcarbazepine;[1] she recovered after treatment with filgrastim. It was noted that the patient had had a similar reaction when taking carbamazepine. Oxcarbazepine has also been associated with reversible pancytopenia[2] in a 40-year-old woman, and reversible thrombocytopenia[3] in a 63-year-old woman.

1. Ryan M, *et al.* Hyponatremia and leukopenia associated with oxcarbazepine following carbamazepine therapy. *Am J Health-Syst Pharm* 2001; 58: 1637–9.
2. Calamaras MR, *et al.* Pancytopenia associated with the introduction of oxcarbazepine. *J Clin Psychopharmacol* 2007; 27: 217–18.
3. Mahmud J, *et al.* Oxcarbazepine-induced thrombocytopenia. *Psychosomatics* 2006; 47: 73–4.

Effects on mental function. For a review of the effects of antiepileptic therapy on *cognition*, and the effects of oxcarbazepine on *mood* (including the risk of suicidal ideation), see p. 508.3.

Effects on sexual function. For mention of the effects of antiepileptics including oxcarbazepine on sexual function in male epileptic patients, see Effects on the Endocrine System, under Phenytoin, p. 540.3.

Hyponatraemia. Hyponatraemia appears to be more pronounced at clinical doses of oxcarbazepine than with carbamazepine. Hyponatraemia was reported[1] in 12 of 15 patients in whom oxcarbazepine was substituted for carbamazepine therapy. The fall in plasma-sodium concentrations appeared to be related to the dose of oxcarbazepine. In another report[2] hyponatraemia occurred in 23% of 350 patients whose serum-sodium concentrations were monitored. The manufacturers state that in 14 controlled studies sodium levels of less than 125 mmol/litre occurred in 2.5% of 1524 patients treated with oxcarbazepine compared with no such patients in the control groups. Most patients remain asymptomatic but some may experience drowsiness, increase in seizure frequency, and impaired consciousness.[3] In a later study[4] in 97 patients taking oxcarbazepine and 451 taking carbamazepine, hyponatraemia occurred in 29 (12 severe) of the former and in 61 (13 severe) of the latter. The authors failed to find a correlation between high doses of oxcarbazepine and the occurrence of hyponatraemia.

It has been suggested that serum-sodium concentrations should be measured before the start of therapy but routine monitoring, may be indicated only in elderly patients or if a high dosage is used.[5] Licensed product information recommends that monitoring be considered in those with pre-existing conditions associated with low sodium levels and in those taking other medications known to interfere with sodium levels, for example NSAIDs and diuretics.

Severe hyponatraemia has been reported[6] in a 12-year-old child during treatment with oxcarbazepine. A review of 48 other children who had received oxcarbazepine in the same centre, found that 9 had hyponatraemia, and the authors suggested that sodium levels should be monitored in paediatric patients. In another case,[7] a 7-year old boy developed a reversible coma caused by oxcarbazepine-induced hyponatraemia.

1. Pendlebury SC, *et al.* Hyponatraemia during oxcarbazepine therapy. *Hum Toxicol* 1989; 8: 337–44.
2. Priis ML, *et al.* Therapeutic experiences with 947 epileptic out-patients in oxcarbazepine treatment. *Acta Neurol Scand* 1993; 87: 224–7.
3. Steinhoff BJ, *et al.* Hyponatraemic coma under oxcarbazepine therapy. *Epilepsy Res* 1992; 11: 67–70.
4. Dong X, *et al.* Hyponatremia from oxcarbazepine and carbamazepine. *Neurology* 2005; 65: 1976–8.
5. Kälviäinen R, *et al.* Place of newer antiepileptic drugs in the treatment of epilepsy. *Drugs* 1993; 46: 1009–24.
6. Borusiak P, *et al.* Hyponatremia induced by oxcarbazepine in children. *Epilepsy Res* 1998; 30: 241–6.
7. Paliwal V, *et al.* Oxcarbazepine induced hyponatremic coma. *Neurol India* 2006; 54: 214–15.

Overdosage. A 36-year-old man[1] who ingested 30.6 g of oxcarbazepine showed no serious signs of toxicity. Serum concentrations of oxcarbazepine were 31.6 mg/litre 2 hours after ingestion; corresponding serum concentrations of the active monohydroxy metabolite were 37.2 mg/litre, which later peaked at 59.0 mg/litre 7 hours after ingestion. The patient remained conscious, though somnolent, and had fully recovered within 2 days.

1. van Opstal JM, *et al.* Severe overdosage with the antiepileptic drug oxcarbazepine. *Br J Clin Pharmacol* 2004; 58: 329–31.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies oxcarbazepine as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pregnancy. For comments on the management of epilepsy during pregnancy, see p. 509.2.

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy. Plasma concentrations of the active monohydroxy metabolite of oxcarbazepine may be reduced by strong inducers of cytochrome P450 isoenzymes, such as carbamazepine, phenytoin, or phenobarbital. Oxcarbazepine appears to induce hepatic enzymes to a lesser extent than carbamazepine. However, oxcarbazepine and its active metabolite do inhibit the cytochrome P450 isoenzyme CYP2C19, and in high doses may raise plasma concentrations of phenobarbital or phenytoin. Oxcarbazepine and its metabolite also have the capacity to induce CYP3A4 and CYP3A5 with the possibility of reducing plasma concentrations of drugs such as carbamazepine (but see below), dihydropyridine calcium-channel blockers, and oral contraceptives.

References.

1. Sallas WM, *et al.* Pharmacokinetic drug interactions in children taking oxcarbazepine. *Clin Pharmacol Ther* 2003; 74: 138–49.

Antiepileptics. In a study[1] of epileptic patients the area under the concentration-time curve (AUC) seen with monotherapy of *carbamazepine*, *phenytoin*, or *valproate* was unchanged when oxcarbazepine was added to treatment; only carbamazepine affected the pharmacokinetics of oxcarbazepine, producing a reduction in the AUC for the active metabolite hydroxycarbazepine. It was considered that there was unlikely to be any clinically relevant pharmacokinetic interaction if oxcarbazepine was used with any of these antiepileptics, including carbamazepine. However, increases in plasma-phenytoin concentration have been reported after use with oxcarbazepine (see p. 543.2).

There is a report of severe toxicity occurring when oxcarbazepine was used with *lamotrigine*.[2] For the effect of oxcarbazepine on lamotrigine concentrations, see p. 530.1.

1. McKee PJW, *et al.* A double-blind, placebo-controlled interaction study between oxcarbazepine and carbamazepine, sodium valproate and phenytoin in epileptic patients. *Br J Clin Pharmacol* 1994; 37: 27–32.
2. Alving J. Case of severe acute intoxication with oxcarbazepine combined with lamotrigine. *Epilepsia* 1994; 35 (suppl 7): 72.

Pharmacokinetics

Oxcarbazepine is completely absorbed from the gastrointestinal tract. It is rapidly and extensively metabolised in the liver to the principal metabolite 10,11-dihydro-10-hydroxy-carbamazepine (licarbazepine, often referred to as MHD), which also possesses antiepileptic activity. The monohydroxy metabolite is widely distributed in the body and is about 40% bound to plasma proteins, mainly albumin. The plasma half-life has been reported to be about 2 hours for oxcarbazepine, and about 9 hours for the monohydroxy metabolite; consequently the latter provides most of the antiepileptic activity. Clearance of the monohydroxy metabolite is reported to be about 40% higher in children aged 4 to 12 years, and about 80% higher in those aged 2 to 4 years, than in adults. Oxcarbazepine is excreted in the urine mainly as metabolites; less than 1% is excreted as unchanged drug.

Oxcarbazepine and its monohydroxy metabolite cross the placental barrier and are distributed into breast milk.

The pharmacokinetics of oxcarbazepine and its monohydroxy metabolite are affected by use with other antiepileptics (see Interactions, above).

References.

1. Dickinson RG, *et al.* First dose and steady-state pharmacokinetics of oxcarbazepine and its 10-hydroxy metabolite. *Eur J Clin Pharmacol* 1989; 37: 69–74.
2. Patsalos PN, *et al.* Protein binding of oxcarbazepine and its primary active metabolite, 10-hydroxycarbazepine, in patients with trigeminal neuralgia. *Eur J Clin Pharmacol* 1990; 39: 413–15.
3. Kumps A, Wurth C. Oxcarbazepine disposition: preliminary observations in patients. *Biopharm Drug Dispos* 1990; 11: 365–70.
4. van Heiningen PNM, *et al.* The influence of age on the pharmacokinetics of the antiepileptic agent oxcarbazepine. *Clin Pharmacol Ther* 1991; 50: 410–19.
5. Elwes RDC, Binnie CD. Clinical pharmacokinetics of newer antiepileptic drugs: lamotrigine, vigabatrin, gabapentin and oxcarbazepine. *Clin Pharmacokinet* 1996; 30: 403–15.
6. May TW, *et al.* Clinical pharmacokinetics of oxcarbazepine. *Clin Pharmacokinet* 2003; 42: 1023–42.
7. Rey E, *et al.* Oxcarbazepine pharmacokinetics and tolerability in children with inadequately controlled epilepsy. *J Clin Pharmacol* 2004; 44: 1290–1300.
8. Flesch G. Overview of the clinical pharmacokinetics of oxcarbazepine. *Clin Drug Investig* 2004; 24: 185–203.
9. Bring P, Ensom MH. Does oxcarbazepine warrant therapeutic drug monitoring? A critical review. *Clin Pharmacokinet* 2008; 47: 767–78.

Pregnancy. Clearance of the active monohydroxy metabolite of oxcarbazepine was reported to increase[1,2] during pregnancy and to decrease[2] after delivery; one study[1] reported a reduction in plasma concentrations of about 36% during the third trimester. However, sample sizes in both studies were small.

1. Christensen J, *et al.* Oxcarbazepine concentrations during pregnancy: a retrospective study in patients with epilepsy. *Neurology* 2006; 67: 1497–9.
2. Mazzucchelli I, *et al.* Changes in the disposition of oxcarbazepine and its metabolites during pregnancy and the puerperium. *Epilepsia* 2006; 47: 504–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Aurene; Oxca†; Rupox; Trileptal; *Austral.*: Trileptal; *Austria*: Trileptal; *Belg.*: Trileptal; *Braz.*: Alzepinol; Auram; Leptard; Oleptal; Oxcarb; Trileptal; Zyoxipina; *Canad.*: Trileptal; *Chile*: Oxicodal; Trileptal; Tussdra; *China*: Ren Ao (仁奥); Trileptal (曲美); Wan Yi (万仪); *Cz.*: Trileptal†; *Denm.*: Apydan; Trileptal; *Fin.*: Apydan; Trileptal; *Fr.*: Trileptal; *Ger.*: Apydan; Timox; Trileptal; *Gr.*: Trileptal; *Hong Kong*: Trileptal; *Hung.*: Apydan†; Trileptal; *India*: Carbox; Mezalog; Oleptal; Oxana; Oxcarb; Oxcazo; Oxep; Oxeptal; Oxetol; Oxine; Oxmazetol; Oxrate; Oxzey; *Indon.*: Barzepin; Prolepsi; Trileptal; *Irl.*: Trileptal; *Israel*: Trexapin; Trileptin; *Ital.*: Tolep; *Malaysia*: Trileptal; *Mex.*: Actinium; Deprectal; Oxetol; Trileptal; *Neth.*: Trileptal; *Norw.*: Trileptal; *NZ*: Trileptal; *Philipp.*: Trileptal; *Pol.*: Apydan†; Karbagen; Trileptal; *Port.*: Epilfarmo; Proaxen; Trileptal; Zigabal; *Rus.*: Trileptal (Трилептал); *S.Afr.*: Trileptal; *Spain*: Epilexter†; Oxcarmylan†; Trileptal; *Swed.*: Trileptal; *Switz.*: Apydan; Trileptal; *Thai.*: Trileptal; *Turk.*: Apilep; Epsile; Oxilepsi; Trileptal; *UK*: Trileptal; *USA*: Oxtellar; Trileptal; *Venez.*: Trileptal.

Pharmacopoeial Preparations

USP 36: Oxcarbazepine Oral Suspension; Oxcarbazepine Tablets.

Perampanel *(USAN, rINN)*

E-2007; ER-155055-90; Pérampanel; Perampanelum; Перампанел.

5′-(2-Cyanophenyl)-1′-phenyl-2,3′-bipyridinyl-6′(1′*H*)-one.

$C_{23}H_{15}N_3O$=349.4

CAS — 380917-97-5.

ATC — N03AX22.

ATC Vet — QN03AX22.

UNII — H821664NPK.

Uses and Administration

Perampanel, an α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor antagonist, is an antiepileptic used as adjunctive therapy in partial seizures with or without secondary generalisation (below) in patients aged 12 years and older. It is given orally as a single dose before bedtime. The initial dose is 2 mg daily, increased, according to response in steps of 2 mg at intervals of not less than 2 weeks, to a maximum of 12 mg daily. Maintenance doses are usually in the range of 4 to 8 mg daily. Patients who are also taking drugs that shorten the half-life of perampanel should be titrated at intervals of not less than 1 week (see also Interactions, below).

Reduced doses are recommended in patients with hepatic impairment (see below).

As with other antiepileptics, withdrawal of perampanel therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. However, due to its long half-life and slow decline in plasma concentrations, it can be stopped abruptly if absolutely necessary. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1.

Administration in hepatic impairment. Patients with mild or moderate hepatic impairment may be given the usual initial oral dose of perampanel (see Uses and Administration, above), increased according to response and tolerability to a maximum of 8 mg daily. Use in severe impairment is not recommended.

Epilepsy. Perampanel is one of the newer drugs used as adjunctive therapy in patients with partial seizures with or without secondary generalisation (p. 506.1). It appears to be reasonably well tolerated. Perampanel has also been investigated for the treatment of generalised epilepsy and epileptic syndromes such as Lennox-Gastaut syndrome.

References.
1. Krauss GL, *et al.* Randomized phase III study 306: adjunctive perampanel for refractory partial-onset seizures. *Neurology* 2012; 78: 1408–15.
2. French JA, *et al.* Adjunctive perampanel for refractory partial-onset seizures: randomized phase III study 304. *Neurology* 2012; 79: 589–96.
3. French JA, *et al.* Evaluation of adjunctive perampanel in patients with refractory partial-onset seizures: results of randomized global phase III study 305. *Epilepsia* 2012. Available at: doi:10.1111/j.1528-1167.2012.03638.x
4. Krauss GL, *et al.* Perampanel, a selective, noncompetitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist, as adjunctive therapy for refractory partial-onset seizures: interim results from phase III, extension study 307. *Epilepsia* 2012. Available at: doi:10.1111/j.1528-1167.2012.03648.x
5. Rektor I, *et al.* Perampanel Study 207: long-term open-label evaluation in patients with epilepsy. *Acta Neurol Scand* 2012; 126: 263–9.

Adverse Effects and Precautions

The most frequently reported adverse effects with perampanel are dizziness and somnolence. Other commonly reported adverse effects include ataxia, dysarthria, gait disturbance, balance disorders, vertigo, irritability, aggression, anger, anxiety, confusion, increased or decreased appetite, nausea, fatigue, back pain, diplopia, and blurred vision. An increased risk of falls has also been reported, particularly in the elderly.

Aggression appears to be dose-related; most cases were reported to be mild or moderate with recovery occurring spontaneously or after dosage adjustment, however, therapy had to be stopped in severe cases. Dosage reduction should be considered in patients who develop persistent symptoms of aggression.

Perampanel should be used with caution in those with a history of substance abuse.

Due to a lack of data, perampanel is not recommended in patients with severe hepatic impairment, or moderate or severe renal impairment, and in those undergoing haemodialysis. It should be used with caution in patients with mild or moderate hepatic impairment.

Care is required when withdrawing perampanel therapy—see also Uses and Administration, above.

Breast feeding. For comment on antiepileptic therapy and breast feeding, see p. 508.3.

Driving. For a comment on antiepileptic drugs and driving, see p. 509.2.

Effects on mental function. For the effects of antiepileptic therapy on *cognition* and *mood*, including the risk of suicidal ideation, see p. 508.3.

Pregnancy. For comments on the management of epilepsy during pregnancy, see p. 509.2.

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy. The hepatic metabolism of perampanel is increased by antiepileptics that induce the cytochrome P450 isoenzyme CYP3A subfamily such as carbamazepine, oxcarbazepine, or phenytoin. Plasma concentrations of perampanel may be reduced up to threefold by use with these drugs and dosage adjustments may be necessary. Use with other drugs that induce or inhibit enzymes of the cytochrome P450 system may also alter plasma concentrations of perampanel and adjustments to the dosage of perampanel may be required. (For details, see Uses and Administration, above.)

Sex hormones. An oral dose of perampanel 12 mg daily for 21 days in healthy women also taking a combined *oral contraceptive* was found to decrease both the AUC and peak concentration of levonorgestrel by 40%; peak concentrations of ethinylestradiol were also reduced by 18%. No effects were noted in women receiving lower doses of perampanel.

A possible decrease in the efficacy of oral contraceptives, and a need for additional non-hormonal contraceptives, should be considered in women taking perampanel 12 mg daily.

Pharmacokinetics

Perampanel is readily absorbed after oral doses; food may delay absorption but does not affect the extent of absorption. It is about 95% bound to plasma proteins. Perampanel is extensively metabolised by oxidation, via the cytochrome P450 isoenzyme CYP3A subfamily, and glucuronidation. It is excreted in the urine and faeces mainly as oxidative and conjugated metabolites. The average half-life is about 105 hours, although this may be reduced to 25 hours by carbamazepine, a potent liver-enzyme inducer (see also Interactions, above).

Distribution into milk has been found in studies in *rats*.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Denm.*: Fycompa; *Norw.*: Fycompa; *Switz.*: Fycompa; *UK*: Fycompa; *USA*: Fycompa.

Pheneturide *(BAN, rINN)*

Ethylphenacemide; Feneturida; Phénéturide; Pheneturidum; S-46; Фенетурид.

(2-Phenylbutyryl)urea.

$C_{11}H_{14}N_2O_2$=206.2

CAS — 90-49-3.

ATC — N03AX13.

ATC Vet — QN03AX13.

UNII — 878CEJ4HGX.

Profile

Pheneturide is an acetylurea antiepileptic that has been used orally in the treatment of complex partial seizures with or without secondary generalisation (p. 506.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Laburide.

Phenobarbital *(BAN, rINN)*

Ácido feniletilbarbitúrico; Fenobarbitaali; Fenobarbital; Fenobarbitál; Fenobarbitalis; Fenobarbitona; Phenemalum; Phénobarbital; Phenobarbitalum; Phenobarbitone; Phenylethylbarbituric Acid; Phenylethylmalonylurea; Фенобарбитан.

5-Ethyl-5-phenylbarbituric acid.

$C_{12}H_{12}N_2O_3$=232.2

CAS — 50-06-6.

ATC — N03AA02.

ATC Vet — QN03AA02.

UNII — YQE403BP4D.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of phenobarbital:

Feenies; Phennies; Phenos.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Phenobarbital). A white or almost white, crystalline powder or colourless crystals. Very slightly soluble in water; freely soluble in alcohol. It forms water-soluble compounds with alkali hydroxides and carbonates, and with ammonia.

USP 36: (Phenobarbital). White, odourless, glistening, small crystals or a white crystalline powder. It may exhibit polymorphism. Soluble 1 in 1000 of water and 1 in 10 of alcohol; sparingly soluble in chloroform; soluble in ether and in solutions of fixed alkali hydroxides and carbonates. A saturated solution in water has a pH of about 5.

Phenobarbital Sodium *(BANM, rINN)*

Fenobarbitaalinatrium; Fenobarbital sódico; Fenobarbital sodná sůl; Fenobarbital sodowy; Fenobarbitalio natrio druska; Fenobarbitalnatrium; Fenobarbital-natrium; Natrii Phenobarbitalum; Phenemalnatrium; Phenobarbital-Natrium; Phénobarbital Sodique; Phenobarbitalum natricum; Phenobarbitone Sodium; Sodium Phenylethylbarbiturate; Soluble Phenobarbitone; Натрий Фенобарбитал.

Sodium 5-ethyl-5-phenylbarbiturate.

$C_{12}H_{11}N_2NaO_3$=254.2

CAS — 57-30-7.

ATC — N03AA02.

ATC Vet — QN03AA02.

UNII — SW9M9BB5K3.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Phenobarbital Sodium). A white or almost white, hygroscopic, crystalline powder. Freely soluble in carbon dioxide-free water (a small amount may be insoluble); soluble in alcohol; practically insoluble in dichloromethane. A 10% solution in water has a pH not greater than 10.2. Store in airtight containers.

USP 36: (Phenobarbital Sodium). Flaky crystals, or white crystalline granules, or a white powder. It is odourless and hygroscopic. Very soluble in water; soluble in alcohol; practically insoluble in chloroform and in ether. pH of a 10% solution in water is between 9.2 and 10.2. Solutions decompose on standing. Store in airtight containers.

Incompatibility. Phenobarbital sodium is incompatible with many other drugs and phenobarbital may be precipitated from mixtures containing phenobarbital sodium. This precipitation is dependent upon the concentration and the pH, and also on the presence of other solvents.

Stability. Extemporaneous oral preparations of phenobarbital 10 mg/mL in a 1:1 mixture of *Ora-Plus* and either *Ora-Sweet* or *Ora-Sweet SF* (*Paddock, USA*) were found[1] to be stable for at least 115 days in amber plastic bottles stored at room temperature.

1. Cober MP, Johnson CE. Stability of an extemporaneously prepared alcohol-free phenobarbital suspension. *Am J Health-Syst Pharm* 2007; 64: 644–6.

Uses and Administration

Phenobarbital is a barbiturate that may be used as an antiepileptic to control partial and generalised tonic-clonic seizures (p. 536.1). It is also used as part of the emergency management of acute seizures including status epilepticus (p. 536.2).

The dose should be adjusted to the needs of the individual patient to achieve adequate control of seizures; this usually requires plasma concentrations of 15 to 40 micrograms/mL or around 60 to 180 micromoles/litre. However, plasma-drug concentration monitoring is less useful than with other drugs because tolerance occurs. In the UK, the usual oral dose is 60 to 180 mg daily, taken at night. In the USA, total daily doses of up to 300 mg have been given.

Phenobarbital sodium may be given parenterally as part of the emergency management of acute seizures including status epilepticus. In the UK, for the control of status epilepticus, doses of 10 mg/kg to a maximum of 1 g may be given intravenously. The *BNF* recommends that intravenous injection solutions should be diluted 1 in 10 and given at a rate not exceeding 100 mg/minute. In some countries intramuscular doses of up to 320 mg have been used, repeated after 6 hours if necessary. However, doubts have been expressed about the efficacy of the intramuscular route owing to the delay in achieving adequate blood concentrations, and the subcutaneous route may cause tissue necrosis.

For doses in children, see p. 536.1.

As with other antiepileptics, withdrawal of phenobarbital therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1.

Phenobarbital has also been used as a hypnotic and sedative but drugs such as the benzodiazepines are preferred.

Phenobarbital stimulates the enzymes in hepatic microsomes responsible for the metabolism of some drugs and normal body constituents including bilirubin, and for

this reason it has been used to reduce hyperbilirubinaemia in neonatal jaundice.

Phenobarbital magnesium and phenobarbital diethylamine have also been used.

Tetrabamate is a complex of phenobarbital, difebarbamate, and febarbamate but its use has been associated with the development of hepatitis.

Administration in children. Phenobarbital may be used in children as an antiepileptic to control all forms of epilepsy except absence seizures. It is also used as part of the emergency management of status epilepticus. The doses given below for all indications are those recommended by the *BNFC* in the UK.

For treatment of epilepsy, the following doses are given orally, unless stated otherwise, according to age:

- neonates: an initial dose of 20 mg/kg by slow intravenous injection, then 2.5 to 5 mg/kg once daily by slow intravenous injection or orally, adjusted according to response
- 1 month to 12 years: an initial dose of 1 to 1.5 mg/kg twice daily, increased by 2 mg/kg daily if necessary to a usual maintenance dose of 2.5 to 4 mg/kg once or twice daily
- 12 to 18 years: 60 to 180 mg once daily

For status epilepticus, the following doses are given intravenously, according to age:

- neonate to 12 years: an initial dose of 20 mg/kg, followed by 2.5 to 5 mg/kg once or twice daily
- 12 to 18 years: an initial dose of 20 mg/kg (to a maximum of 1 g), followed by 300 mg twice daily

Intravenous injection solutions should be diluted 1 in 10 and given at a rate not exceeding 1 mg/kg per minute.

Cerebral malaria. Various studies have investigated whether antiepileptics are beneficial in preventing seizures or long-term neurological disability that may be associated with cerebral malaria (p. 644.1). Single intramuscular doses of phenobarbital ranging from 3.5 mg/kg to 20 mg/kg have been reported to be effective anticonvulsants[1,2] but it was also found that the higher dose was associated with a doubling of mortality.[2] A systematic review,[3] that included these two studies as well as other data, concluded that phenobarbital should not be given routinely to patients with cerebral malaria as it might increase mortality. WHO[4] has also expressed the opinion that prophylactic anticonvulsants cannot be recommended.

If convulsions do occur, WHO[4] has noted that treatment should be similar to that for repeated seizures from any cause.

1. White NJ, *et al.* Single dose phenobarbitone prevents convulsions in cerebral malaria. *Lancet* 1988; ii: 64–6.
2. Crawley J, *et al.* Effect of phenobarbitone on seizure frequency and mortality in childhood cerebral malaria: a randomized, controlled intervention study. *Lancet* 2000; 355: 701–6.
3. Meremikwu MM, Marson AG. Routine anticonvulsants for treating cerebral malaria. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2002 (accessed 09/06/08).
4. WHO. *Guidelines for the treatment of malaria.* 2nd ed. Geneva: 2010. Also available at: http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf (accessed 08/06/10) Update (issued April 2011), available at: http://www.who.int/malaria/publications/atoz/mal_treatchild_revised.pdf (accessed 20/05/11)

Epilepsy. Phenobarbital is used in the treatment of epilepsy (p. 506.1) for partial seizures with or without secondary generalisation and for primary generalised tonic-clonic seizures. It may also be tried for atypical absence, atonic, and tonic seizures but is not effective in absence seizures. However, the usefulness of phenobarbital is limited by problems of sedation in adults and paradoxical excitement in children. There is also concern about its effects on behaviour and cognition in children. Phenobarbital is therefore usually reserved for use in cases unresponsive to other antiepileptics, although some have suggested that its low cost and broad efficacy make it a suitable first-line drug in developing countries.

References.

1. Pal DK, *et al.* Randomised controlled trial to assess acceptability of phenobarbital for childhood epilepsy in rural India. *Lancet* 1998; 351: 19–23.
2. Kwan P, Brodie MJ. Phenobarbital for the treatment of epilepsy in the 21st century: a critical review. *Epilepsia* 2004; 45: 1141–9.
3. Wilmshurst JM, van Toorn R. Use of phenobarbitone for treating childhood epilepsy in resource-poor countries. *S Afr Med J* 2005; 95: 392, 394, 396.
4. Wang WZ, *et al.* Efficacy assessment of phenobarbital in epilepsy: a large community-based intervention trial in rural China. *Lancet Neurol* 2006; 5: 46–52.

Febrile convulsions. Phenobarbital has been used prophylactically in children thought to be at risk of recurrence of febrile convulsions (p. 511.2), but routine use of antiepileptics is no longer recommended.

References.

1. Newton RW. Randomised controlled trials of phenobarbitone and valproate in febrile convulsions. *Arch Dis Child* 1988; 63: 1189–91.
2. Farwell JR, *et al.* Phenobarbital for febrile seizures: effects on intelligence and on seizure recurrence. *N Engl J Med* 1990; 322: 364–9. Correction. *ibid.* 1992; 326: 144.

Neonatal abstinence syndrome. For reference to the use of phenobarbital for the treatment of neonates with opioid abstinence syndrome, see p. 110.1.

Neonatal intraventricular haemorrhage. Phenobarbital is one of several drugs that has been tried to prevent the development of neonatal intraventricular haemorrhage (p. 1128.3). Initial studies[1-3] of antenatal use in the mother were promising, but a larger randomised study[4] in 610 women failed to show any effect of antenatal phenobarbital on incidence or severity of intraventricular haemorrhage. An assessment of surviving infants that could be traced at about 20 months of age also found that antenatal phenobarbital had no apparent effect on neurodevelopmental outcome.[5] A systematic review[6] of these and other studies concluded that giving phenobarbital before preterm birth cannot be recommended for routine clinical practice; strategies for future studies were suggested to improve methodology. Studies of use in neonates have also shown inconsistent results. A systematic review[7] of studies of phenobarbital for prophylaxis of intraventricular haemorrhage in preterm neonates concluded that postnatal use cannot be recommended either, and is associated with an increased need for mechanical ventilation.

1. Kaempf JW, *et al.* Antenatal phenobarbital for the prevention of periventricular and intraventricular hemorrhage: a double-blind, randomized, placebo-controlled, multihospital trial. *J Pediatr* 1990; 117: 933–8.
2. Barnes ER, Thompson DF. Antenatal phenobarbital to prevent or minimize intraventricular hemorrhage in the low-birthweight neonate. *Ann Pharmacother* 1993; 27: 49–52.
3. Thorp JA, *et al.* Antepartum vitamin K and phenobarbital for preventing intraventricular hemorrhage in the premature newborn: a randomized, double-blind, placebo-controlled trial. *Obstet Gynecol* 1994; 83: 70–6.
4. Shankaran S, *et al.* The effect of antenatal phenobarbital therapy on neonatal intracranial hemorrhage in preterm infants. *N Engl J Med* 1997; 337: 466–71.
5. Shankaran S, *et al.* Neurodevelopmental outcome of premature infants after antenatal phenobarbital exposure. *Am J Obstet Gynecol* 2002; 187: 171–7.
6. Crowther CA, *et al.* Phenobarbital prior to preterm birth for preventing neonatal periventricular haemorrhage. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 25/08/10).
7. Whitelaw A, Odd D. Postnatal phenobarbital for the prevention of intraventricular hemorrhage in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 09/06/08).

Neonatal seizures. Some consider phenobarbital to be the mainstay of treatment for all types of neonatal seizures (p. 511.3). In a study[1] in 120 neonates with clinical seizure activity of varying aetiology, 48 were controlled by an initial intravenous loading dose of phenobarbital 15 to 20 mg/kg over 10 to 15 minutes, and a further 37 were controlled by sequential bolus doses of phenobarbital 5 to 10 mg/kg every 20 to 30 minutes up to a serum concentration of 40 micrograms/mL. Of the remaining 35 neonates only 7 responded when the serum-phenobarbital concentration was increased to 100 micrograms/mL, 13 required addition of a second antiepileptic (phenytoin or lorazepam) and 4 were controlled by addition of a third drug. Phenobarbital alone can effectively control seizures in the majority of neonates with recurrent seizure activity.

Phenobarbital given prophylactically as a single dose of about 40 mg/kg intravenously over one hour has also been shown to be effective in reducing the incidence of seizures in 15 infants with severe perinatal asphyxia compared with a control group who only received phenobarbital if there was clinical evidence of seizures.[2] Subsequent follow-up over 3 years suggested that prophylactic phenobarbital might also improve later neurological outcome.[2] However, a later retrospective cohort study[3] found no significant difference in the rate of seizure recurrence and developmental outcome between infants who were discharged with prophylactic phenobarbital (33 patients) and those who were discharged without any antiepileptics (99).

1. Gilman JT, *et al.* Rapid sequential phenobarbital treatment of neonatal seizures. *Pediatrics* 1989; 83: 674–8.
2. Hall RT, *et al.* High-dose phenobarbital therapy in term newborn infants with severe perinatal asphyxia: a randomized, prospective study with three-year follow-up. *J Pediatr* 1998; 132: 345–8.
3. Guillet R, Kwon J. Seizure recurrence and developmental disabilities after neonatal seizures: outcomes are unrelated to use of phenobarbital prophylaxis. *J Child Neurol* 2007; 22: 389–95.

Status epilepticus. Phenobarbital given intravenously is an alternative to intravenous phenytoin in the management of status epilepticus (p. 510.2). It should not be used in patients who have recently received oral phenobarbital or primidone.

Although one study[1] suggested that phenobarbital might be at least as effective, safe, and practical as diazepam with phenytoin for the initial treatment of convulsive status epilepticus, it tends to be reserved for patients who do not respond to benzodiazepines or phenytoin.

1. Shaner DM, *et al.* Treatment of status epilepticus: a prospective comparison of diazepam and phenytoin versus phenobarbital and optional phenytoin. *Neurology* 1988; 38: 202–7.

Withdrawal syndromes. Phenobarbital is used in some centres for the management of alcohol withdrawal syndrome (p. 1735.1), but has a lower safety profile than benzodiazepines (the treatment of choice) and creates the potential for multiple drug interactions. Additionally, a lack of well-defined studies make its role difficult to assess.[1] However, it has been reported of use in resistant cases.[2]

1. Rodgers JE, Crouch MA. Phenobarbital for alcohol withdrawal syndrome. *Am J Health-Syst Pharm* 1999; 56: 175–8.
2. Hayner CE, *et al.* Phenobarbital treatment in a patient with resistant alcohol withdrawal syndrome. *Pharmacotherapy* 2009; 29: 875–8.

Dependence and Withdrawal

As for the barbiturates (see Amobarbital, p. 1038.1).

Adverse Effects

The most frequent adverse effect associated with phenobarbital is sedation, but this often becomes less marked with continued use. Like some of the other antiepileptics, phenobarbital may produce subtle mood changes and impairment of cognition and memory that may not be apparent without testing. Depression may occur.

Prolonged use can occasionally result in folate deficiency; rarely, megaloblastic anaemia has been reported. There is some evidence that phenobarbital interferes with vitamin D metabolism.

At high doses nystagmus and ataxia may occur and the typical barbiturate-induced respiratory depression may become severe. Overdosage can prove fatal; toxic effects include coma, severe respiratory and cardiovascular depression, with hypotension and shock leading to renal failure. Hypothermia may occur, with associated pyrexia during recovery. Skin blisters (bullae) reportedly occur in about 6% of patients with barbiturate overdose.

Sodium salts of barbiturates have a very high pH in solution, and necrosis has followed subcutaneous injection or extravasation. Intravenous injections can be hazardous and cause hypotension, shock, laryngospasm, and apnoea, especially if given too rapidly.

Hypersensitivity reactions occur in a small proportion of patients; skin reactions are reported in 1 to 3% of patients taking phenobarbital, and are most commonly maculopapular, morbilliform, or scarlatiniform rashes. More severe reactions such as exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis are extremely rare. Hepatitis and disturbances of liver function have been reported.

Paradoxical excitement, restlessness, and confusion may sometimes occur in the elderly, and irritability and hyperactivity may occur in children.

Neonatal drug dependence and symptoms resembling vitamin K deficiency have been reported in infants born to mothers who received phenobarbital during pregnancy. Congenital malformations have been reported in children of women who received phenobarbital during pregnancy but the causal role of the drug is a matter of some debate.

Effects on the blood. For the effects of antiepileptics including phenobarbital on serum folate, see under Phenytoin, p. 540.2.

Effects on bone. For the effects of antiepileptics including phenobarbital on bone and on calcium and vitamin D metabolism, see under Phenytoin, p. 540.2.

Effects on connective tissue. The use of phenobarbital and primidone has been associated with the development of Dupuytren's contracture, frozen shoulder, Ledderhose's syndrome, Peyronie's disease, fibromas, and general joint pain.[1]

1. Marson RH, *et al.* Barbiturate-related connective tissue disorders. *Arch Intern Med* 1989; 149: 911–14.

Effects on the endocrine system. For mention of the effects of antiepileptics on *sexual function* in male epileptic patients, see under Phenytoin, p. 540.3.

Barbiturates may reduce serum concentrations of *thyroid* hormones through enzyme induction—see under Interactions of Levothyroxine, p. 2341.3.

Effects on the liver. For mention of the effects of phenobarbital on the liver, see under Phenytoin, p. 541.1.

Effects on mental function. For a review of the effects of antiepileptics, including phenobarbital, on *cognition* and *mood* (including the risk of suicidal ideation), see p. 508.3.

DEPRESSION. Follow-up of 28 patients aged 6 to 16 who had received phenobarbital or carbamazepine for epilepsy indi-

cated that the rate of major depression was significantly higher in those receiving phenobarbital.[1] It was recommended that treatment with phenobarbital should be avoided particularly in patients with a personal or family history of an affective disorder; patients who do receive it should be monitored for symptoms of depression.

1. Brent DA, *et al.* Phenobarbital treatment and major depressive disorder in children with epilepsy: a naturalistic follow-up. *Pediatrics* 1990; **85**: 1086–91.

DISTURBED BEHAVIOUR. Disturbed behaviour is a recognised adverse effect of phenobarbital, especially in children and the elderly; however, no excess in behavioural adverse effects was seen[1] on follow-up for up to 12 months in 40 children who took phenobarbital when compared with 45 who took carbamazepine.

1. Banu SH, *et al.* Side effects of phenobarbital and carbamazepine in childhood epilepsy: randomised controlled trial. Abridged version: *BMJ* 2007; **334**: 1207–10. Full version: http://www.bmj.com/cgi/reprint/334/7605/1207 (accessed 09/06/08)

Hypersensitivity. An antiepileptic hypersensitivity syndrome, comprising fever, rash, and lymphadenopathy and less commonly lymphocytosis, and liver and other organ involvement, has been associated with some antiepileptics including phenobarbital.[1,2] Some have estimated the incidence at 1 in 1000 to 1 in 10 000 new exposures to aromatic anticonvulsants,[1,2] but the true incidence is unknown due to variations in presentation and reporting. The syndrome occurs most frequently on first exposure to the drug, with initial symptoms starting anywhere between 1 and 8 weeks after exposure. In previously sensitised individuals the reaction may occur within 1 day of rechallenge. The potential for cross-reactivity between carbamazepine, phenobarbital, and phenytoin is about 75%, and patients who develop the syndrome, and their close relatives, should be warned of the risk associated with use of these antiepileptics.[1]

1. Knowles SR, *et al.* Anticonvulsant hypersensitivity syndrome: incidence, prevention and management. *Drug Safety* 1999; **21**: 489–501.
2. Bessmertny O, *et al.* Antiepileptic hypersensitivity syndrome in children. *Ann Pharmacother* 2001; **35**: 533–8.

Treatment of Adverse Effects

As for the barbiturates (see Amobarbital, p. 1038.1).

Precautions

Phenobarbital and other barbiturates should be used with care in children and in elderly or debilitated patients, in those in acute pain, and in those with depressive disorders. Phenobarbital should be used with caution in patients with impaired hepatic, renal, or respiratory function; its use is contra-indicated in those with severe respiratory depression.

Breast feeding. The American Academy of Pediatrics[1] considers that phenobarbital should be given with caution to breast-feeding mothers, since there have been significant adverse effects including sedation and methaemoglobinaemia in nursing infants. The *BNF* also advises caution during breast feeding. Both authorities make similar recommendations for primidone.

For further comment on antiepileptic therapy and breast feeding, see p. 508.3.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 09/06/08)

Driving. For a comment on antiepileptic drugs and driving, see p. 509.2.

Neonates. Care should be taken when giving phenobarbital orally as the elixir to neonates because regular dosing could result in alcohol toxicity [the BP 2014 formulation contains 38% v/v alcohol].[1] Aqueous preparations are more readily made using the sodium salt than the acid.[2]

1. Colquhoun-Flannery W, Wheeler R. Treating neonatal jaundice with phenobarbitone: the inadvertent administration of significant doses of ethyl alcohol. *Arch Dis Child* 1992; **67**: 152.
2. Leach F. Treating neonatal jaundice with phenobarbitone: the inadvertent administration of significant doses of ethyl alcohol. *Arch Dis Child* 1992; **67**: 152.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies phenobarbital as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pregnancy. For comments on the management of epilepsy during pregnancy, see p. 509.2.

Congenital craniofacial and digital abnormalities and, less commonly, cleft lip and palate have been described with antiepileptics including phenobarbital. *In utero* exposure to phenobarbital might result in neonatal sedation and drug dependence and also in neonatal bleeding due to vitamin K deficiency.

Interactions

There are complex interactions between antiepileptics, and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy. Valproate and phenytoin have been reported to cause rises in phenobarbital (and primidone) concentrations in plasma.

The effects of phenobarbital and other barbiturates are enhanced by other CNS depressants including alcohol.

Phenobarbital and other barbiturates may reduce the activity of many drugs by increasing the rate of metabolism through induction of drug-metabolising enzymes in liver microsomes.

Analgesics. *Dextropropoxyphene* 65 mg given three times daily to 4 epileptic patients stabilised on phenobarbital therapy increased serum-phenobarbital concentration by 8 to 29% but this was not considered of major importance in light of the normally accepted therapeutic range for phenobarbital.[1]

For the effect of phenobarbital on *fenoprofen, methadone,* and *pethidine,* see p. 59.3, p. 90.3, and p. 123.2, respectively. Enzyme-inducing antiepileptics such as phenobarbital also affect the threshold for the use of antidote in the treatment of *paracetamol* poisoning, see p. 118.3.

1. Hansen BS, *et al.* Influence of dextropropoxyphene on steady state serum levels and protein binding of three anti-epileptic drugs in man. *Acta Neurol Scand* 1980; **61**: 357–67.

Antiarrhythmics. For the effect of barbiturates such as phenobarbital on *disopyramide, lidocaine,* and *quinidine,* see p. 1365.2, p. 1995.1, and p. 1483.1, respectively.

Antibacterials. Serum concentrations of phenytoin and phenobarbital in a previously stabilised patient were increased when he took *chloramphenicol.*[1] Subsequent monitoring revealed a similar effect when chloramphenicol was taken with phenobarbital alone. In turn, phenobarbital may affect serum concentrations of chloramphenicol (see p. 259.1).

Barbiturates such as phenobarbital and primidone may enhance the metabolism of *doxycycline.*[2]

1. Koup JR, *et al.* Interaction of chloramphenicol with phenytoin and phenobarbital. *Clin Pharmacol Ther* 1978; **24**: 571–5.
2. Neuvonen PJ, *et al.* Effect of antiepileptic drugs on the elimination of various tetracycline derivatives. *Eur J Clin Pharmacol* 1975; **9**: 147–54.

Anticoagulants. For the effect of barbiturates such as phenobarbital and primidone on *warfarin* and other coumarins, see p. 1532.1.

Antidepressants. As with all antiepileptics, antidepressants may antagonise the antiepileptic activity of phenobarbital by lowering the convulsive threshold.

St John's wort has been shown to induce several drug metabolising enzymes (see p. 449.3) and so might reduce the blood concentrations of phenobarbital, and increase the seizure risk.[1]

For the effect of phenobarbital on antidepressants, see under the monographs for *amitriptyline* (under Barbiturates, p. 406.3), *bupropion* (p. 410.2), *fluoxetine* (p. 424.2), *lithium* (p. 431.3), and *mianserin* (p. 435.2).

Inhibition of drug-metabolising enzymes by *MAOIs* may enhance the effects of barbiturates.

1. CSM/MCA. Reminder: St John's wort (Hypericum perforatum) interactions. *Current Problems* 2000; **26**: 6–7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)

Antiepileptics. Interactions may occur if phenobarbital is given with other antiepileptics, of which probably the most significant is the interaction with *valproate.* Valproate increases plasma-phenobarbital concentration by a reported 17 to 48%,[1] and it may be necessary to reduce the dose of phenobarbital in some patients.[1,2] The mechanism for the increase appears to be inhibition of the metabolism of phenobarbital, resulting in reduced clearance;[2,3] valproate appears to inhibit both the direct *N*-glucosidation of phenobarbital and the *O*-glucuronidation of *p*-hydroxyphenobarbital.[4] However, phenobarbital reciprocally increases the clearance of valproate, and the valproate dose may also need to be adjusted.[5]

A similarly complex interaction exists between phenobarbital and *phenytoin.* Phenytoin can increase plasma concentrations of phenobarbital in some patients[6] since the two drugs compete for metabolism by the same enzyme system, but other evidence suggests that where this occurs it is rarely of significant magnitude.[7] Similarly, although phenobarbital induces the metabolism of phenytoin it is also, as stated, a competitive inhibitor and in practice the two effects appear to balance out, with rarely any need for dose adjustment.[7-9] However, dosage adjustment of phenobarbital may be crucial for some patients.[10] Measurement of serum concentrations of phenytoin and phenobarbital in one patient[10] showed that, in her case, large increases in serum-phenobarbital concentrations resulted from use with phenytoin; the increases were concentration-dependent.

The GABA-agonist, *progabide* has also been reported to cause a significant increase in phenobarbital concentrations when the two were given together to healthy subjects.[11]

Neurotoxicity, attributed to an increase in plasma concentrations of phenobarbital, has been seen[12] in one patient taking phenobarbital and sodium valproate when *felbamate* was added to treatment. The dosage of phenobarbital had already been reduced before treatment with felbamate was started. Data from a pharmacokinetic study[13] indicated that the interaction may result from the inhibition of phenobarbital hydroxylation by felbamate.

Vigabatrin has been reported to lower plasma concentrations of phenobarbital in some patients,[14] although dosage changes were not necessary in these patients.

High dose of *oxcarbazepine* may increase the plasma concentrations of phenobarbital but this was thought unlikely to be clinically significant;[15] conversely phenobarbital may reduce the plasma concentrations of the active metabolite of oxcarbazepine (p. 534.2).

For the effect of phenobarbital on the metabolism of other antiepileptics, see under *Carbamazepine,* p. 516.3, *Diazepam,* p. 1069.1, *Ethosuximide,* p. 521.3, *Lamotrigine,* p. 530.1, *Tiagabine,* p. 550.3, and *Zonisamide,* p. 561.3.

1. Richens A, Ahmad S. Controlled trial of sodium valproate in severe epilepsy. *BMJ* 1975; **4**: 255–6.
2. Patel IH, *et al.* Phenobarbital-valproic acid interaction. *Clin Pharmacol Ther* 1980; **27**: 515–21.
3. Kapetanović IM, *et al.* Mechanism of valproate-phenobarbital interaction in epileptic patients. *Clin Pharmacol Ther* 1981; **29**: 480–6.
4. Bernus I, *et al.* Inhibition of phenobarbitone N-glucosidation by valproate. *Br J Clin Pharmacol* 1994; **38**: 411–16.
5. Perucca E, *et al.* Disposition of sodium valproate in epileptic patients. *Br J Clin Pharmacol* 1978; **5**: 495–9.
6. Morselli PL, *et al.* Interaction between phenobarbital and diphenylhydantoin in animals and in epileptic patients. *Ann N Y Acad Sci* 1971; **179**: 88–107.
7. Eadie MJ, *et al.* Factors influencing plasma phenobarbitone levels in epileptic patients. *Br J Clin Pharmacol* 1977; **4**: 541–7.
8. Cucinell SA, *et al.* Drug interactions in man: lowering effect of phenobarbital on plasma levels of bishydroxycoumarin (Dicumarol) and diphenylhydantoin (Dilantin). *Clin Pharmacol Ther* 1965; **6**: 420–9.
9. Booker HE, *et al.* Concurrent administration of phenobarbital and diphenylhydantoin: lack of an interference effect. *Neurology* 1971; **21**: 383–5.
10. Kuranari M, *et al.* Effect of phenytoin on phenobarbital pharmacokinetics in a patient with epilepsy. *Ann Pharmacother* 1995; **29**: 83–4.
11. Bianchetti G, *et al.* Pharmacokinetic interactions of progabide with other antiepileptic drugs. *Epilepsia* 1987; **28**: 68–73.
12. Gidal BE, Zupanc ML. Potential pharmacokinetic interaction between felbamate and phenobarbital. *Ann Pharmacother* 1994; **28**: 455–8.
13. Reidenberg P, *et al.* Effects of felbamate on the pharmacokinetics of phenobarbital. *Clin Pharmacol Ther* 1995; **58**: 279–87.
14. Browne TR, *et al.* A multicentre study of vigabatrin for drug-resistant epilepsy. *Br J Clin Pharmacol* 1989; **27** (suppl): 95S–100S.
15. Hossain M, *et al.* Drug-drug interaction profile of oxcarbazepine in children and adults. *Neurology* 1999; **52** (suppl 2): A525.

Antifungals. For the effect of phenobarbital on *griseofulvin,* see p. 583.1, and on *itraconazole,* see p. 585.1.

Antineoplastics. For the effect of phenobarbital on *teniposide,* see p. 867.2.

Antiprotozoals. For the effect of phenobarbital on *metronidazole,* see p. 939.2.

Antipsychotics. As with all antiepileptics, antipsychotics may antagonise the antiepileptic activity of phenobarbital by lowering the convulsive threshold.

For the effect of phenobarbital on antipsychotics, see under Chlorpromazine, p. 1052.2.

Antivirals. A patient stabilised on phenobarbital 100 mg daily had an episode of seizures 4 weeks after starting *HAART* therapy with abacavir, didanosine, ritonavir-boosted tipranavir, and enfuvirtide.[1] The patient's phenobarbital plasma concentrations had fallen from 16 to 8 micrograms/mL and an increase in the phenobarbital dosage to 150 mg daily was required to restore concentrations. The tipranavir/ritonavir component of HAART therapy was considered to be responsible.

For the possible effect of phenobarbital on *HIV-protease inhibitors,* see p. 987.3.

1. Bonora S, *et al.* Clinically significant drug interaction between tipranavir-ritonavir and phenobarbital in an HIV-infected subject. *Clin Infect Dis* 2007; **45**: 1654–5.

Beta blockers. For the effect of barbiturates on beta blockers, see Anxiolytics and Antipsychotics, under Interactions of Beta Blockers, p. 1322.1.

Calcium-channel blockers. For the effect of phenobarbital on *dihydropyridine calcium-channel blockers*, see under Nifedipine, p. 1453.3, and on *verapamil*, see p. 1525.2.

Cardiac glycosides. Phenobarbital may greatly accelerate the metabolism of *digitoxin* (p. 1353.2).

Ciclosporin. For the effect of phenobarbital on ciclosporin, see p. 1956.3.

Corticosteroids. For the effect of phenobarbital on corticosteroids, see p. 1619.3.

Diuretics. Serum-phenobarbital concentrations were raised in 8 of 10 epileptic patients taking phenobarbital and additional antiepileptics when given *furosemide* 40 mg three times daily for 4 weeks.[1] This might have been the cause of drowsiness in 5 of 14 patients, 3 of whom had to stop furosemide.

1. Ahmad S, *et al.* Controlled trial of frusemide as an antiepileptic drug in focal epilepsy. *Br J Clin Pharmacol* 1976; 3: 621–5.

Levothyroxine. For the effects of barbiturates on levothyroxine, see p. 2341.3.

Montelukast. For the effect of phenobarbital on montelukast, see p. 1216.1.

Sex hormones. For the effect of phenobarbital on sex hormones in *oral contraceptives*, see p. 2243.2.

Theophylline. For the effect of phenobarbital on theophylline, see p. 1235.1.

Vaccines. *Influenza vaccination* can cause prolonged rises in serum-phenobarbital concentrations in some patients.[1]

1. Jann MW, Fidone GS. Effect of influenza vaccine on serum anticonvulsant concentrations. *Clin Pharm* 1986; 5: 817–20.

Vitamins. *Pyridoxine* reduced serum-phenobarbital concentrations in 5 patients.[1] Plasma concentrations of phenobarbital and primidone are possibly reduced by *folic acid* and *folinic acid*. For the effect of antiepileptics, including phenobarbital, on *vitamin D* concentrations, see Effects on Bone, under Adverse Effects of Phenytoin, p. 540.2.

1. Hansson O, Sillanpaa M. Pyridoxine and serum concentration of phenytoin and phenobarbitone. *Lancet* 1976; i: 256.

Pharmacokinetics

Like other barbiturates phenobarbital is readily absorbed from the gastrointestinal tract, although it is relatively lipid-insoluble; peak concentrations occur about 2 hours after oral doses and within 4 hours of intramuscular doses.

Phenobarbital is about 45 to 60% bound to plasma proteins and is only partly metabolised in the liver. About 25% of a dose is excreted in the urine unchanged at normal urinary pH. The plasma half-life is about 75 to 120 hours in adults but is greatly prolonged in neonates, and shorter (about 21 to 75 hours) in children. Phenobarbital kinetics show considerable interindividual variation.

Monitoring of plasma concentrations has been performed as an aid in assessing control and the therapeutic range of plasma-phenobarbital has been quoted as 15 to 40 micrograms/mL or around 60 to 180 micromoles/litre.

Phenobarbital crosses the placental barrier and is distributed into breast milk.

The pharmacokinetics of phenobarbital are affected if given with other antiepileptics (see under Interactions, p. 537.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Alepsal; Gardenal; Luminal; Luminaletas; Neurogabaf†; *Belg.*: Gardenal; *Braz.*: Barbitron; Carbital; Edhanol; Fenocris; Garbital; Gardenal; Unifenobarb; *Cz.*: Luminal; Phenaemal; Phenaemaletten; *Denm.*: Fenemal; *Fr.*: Aparoxal; Gardenal; Kaneuron; *Ger.*: Luminal; Luminaletten; *Gr.*: Gardenal; Kaneuron; Lumidrops; *Hong Kong*: Uni-Feno†; *Hung.*: Sevenal; Sevenaletta; *India*: Barbee; Emgard; Epitan; Fenobarb; Gardenal; Luminal; Phenetone; *Indon.*: Sibital; *Ital.*: Gardenale; Luminale; *Mex.*: Alepsal; Fenabbott†; *Norw.*: Fenemal; *Philipp.*: Luminal; *Pol.*: Luminalum; *Port.*: Bialminal; Luminal; Luminaletas; *Rus.*: Valocordin (Валокордин); *S.Afr.*: Lethyl; Sedabarb; *Spain*: Gardenal; Luminal; Luminaletas; *Swed.*: Fenemal; *Switz.*: Aphenylbarbit; Luminal†; *Thal.*: Elixir Phenobarb; Gardenal; Menobarb†; Phenobarb; Phenoco†; Phenotal; *Turk.*: Luminal; Luminaletten; *USA*: Luminal; *Venez.*: Gardenal.

Multi-ingredient Preparations. *Arg.*: Cumatil-L†; Lotoquis; *Belg.*: Vethoine; *Braz.*: Vagostesyl; *Canad.*: Bellergal; Diclophen†; *Chile*: Abalgin; Baldmin; Bufacyl; Ergobelan; Sinpasmon; Valpin; *China*: Xi Li Shu (希力舒); *Cz.*: Alnagon†; Sanepil†; *Fr.*: Alepsal; *Gr.*: Diphenal; *Hong Kong*: Sedral†; Uni-Theodal†; *Hung.*: Germicid-C; Meristin; Radipon†; Troparinum; *India*: Alergin; Asmapax; Barbitoin; Beetal; Cadiphylate; Cortasthma; Dilantin with Phenobarbital†; Epilan C; Epiphen; Episol Plus; Ergophen; Garoin; *Indon.*: Bellapheen; Ditalin; Piptal; *Israel*: Philinal†; Phillinet†; *Ital.*: Gamibetal Complex; Metinal-Idantoina L; *Jpn*: Trancolon P; *Mex.*: Alepsal Compuesto; Gamibetal Complex†; Paliatil; *Pol.*: Bellergot; Milocardin; *Port.*: Anti-Asmatico†; *Rus.*: Andipal (Андипал); Barboval (Барбовал); Bellataminal (Беллятаминал); Pagluferal (Пагмоферал); Pentabufen (Пентабуфен); Pentalgin Plus (Пенталгин Плюс); Pentalgin-N (Пенталгин-Н); Pyralgin (Пиралгин); Quintalgine (Квинталгин); Santoperalgin (Сантопералгин); Santotitralgin (Сантотитралгин); Sedal-M (Седал-М); Sedalgin-Neo (Седальгин-Нео); Tetralgin (Тетралгин); Theophedrinum-N (Теофедрин-Н); Valoserdin (Валосердин); *S.Afr.*: Adco-Phenobarbitone Vitalet; Donnatal†; Millerspas†; Natrophylline Compound†; Propain Forte; *Spain*: Redutona†; *Thal.*: Benera†; Neuramizone; *Turk.*: Bellergal; Para-Nox; Pedimat; *Ukr.*: Barboval (Барбовал); Corvaldinum (Корвалдин); Corvaltab (Корвалтаб); Pentased (Пентасед); Sedal-M (Седал-М); Tetralgin (Тетралгин); *USA*: Alkabel; Antispasmodic Elixir; Bel-Phen-Ergot S†; Bellacane; Bellamine†; Bellatal; Bellergal-S; Donnatal; Folergot-DF; Hyosophen; PB-Hyos; Phenerbel-S; Quadrapax; Quadrinal; Se-Donna PB HYOS; Servira; Susano; Tedrigen; Theodrine; *Venez.*: Ervostal; Traveget.

Pharmacopoeial Preparations

BP 2014: Paediatric Phenobarbital Oral Solution; Phenobarbital Elixir; Phenobarbital Injection; Phenobarbital Sodium Tablets; Phenobarbital Tablets;

USP 36: Phenobarbital Elixir; Phenobarbital Oral Suspension; Phenobarbital Sodium for Injection; Phenobarbital Sodium Injection; Phenobarbital Tablets; Theophylline, Ephedrine Hydrochloride, and Phenobarbital Tablets.

Phensuximide *(BAN, rINN)*

Fensuksimidi; Fensuximid; Fensuximida; Phensuximidum; Фенсуксимид.

N-Methyl-2-phenylsuccinimide.

$C_{11}H_{11}NO_2$=189.2

CAS — 86-34-0.

ATC — N03AD02.

ATC Vet — QN03AD02.

UNII — 6WVL9C355G.

Pharmacopoeias. In *US*.

USP 36: (Phensuximide). A white to off-white crystalline powder. Is odourless or has not more than a slight odour. Slightly soluble in water; soluble in alcohol; very soluble in chloroform. Store in airtight containers.

Profile

Phensuximide is a succinimide antiepileptic with actions similar to those of ethosuximide (p. 521.1), but it is reported to be less effective.

Preparations

Pharmacopoeial Preparations

USP 36: Phensuximide Capsules.

Phenytoin *(BAN, USAN, rINN)*

Difenilhidantoína; Diphenylhydantoin; Fanantina; Fenantoína; Fenitoin; Fenitoína; Fenitoinas; Fenytoiini; Fenytoin; Fenytoina; Phenantoinum; Phénytoïne; Phenytoinum; Фенитоин.

5,5-Diphenylhydantoin; 5,5-Diphenylimidazolidine-2,4-dione.

$C_{15}H_{12}N_2O_2$=252.3

CAS — 57-41-0.

ATC — N03AB02.

ATC Vet — QN03AB02.

UNII — 6158TKW0C5.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Phenytoin). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; very slightly soluble in dichloromethane. It dissolves in dilute solutions of alkali hydroxides.

USP 36: (Phenytoin). A white, odourless powder. Practically insoluble in water; soluble in hot alcohol; slightly soluble in cold alcohol, in chloroform, and in ether. Store in airtight containers.

Phenytoin Sodium *(BANM, rINNM)*

Diphenin; Fenitoin Sodyum; Fenitoína sódica; Fenitoinnátrium; Fenitoino natrio druska; Fenytoilninatrium; Fenytoin sodná sůl; Fenytoina sodowa; Fenytoinnatrium; Natrii Phenytoinum; Phenytoin-Natrium; Phénytoïne sodique; Phenytoinum natricum; Soluble Phenytoin; Натрий Фенитоин.

$C_{15}H_{11}N_2NaO_2$=274.3

CAS — 630-93-3.

ATC — N03AB02.

ATC Vet — QN03AB02.

UNII — 4182431BJH.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *U.S.*

Ph. Eur. 8: (Phenytoin Sodium). A white or almost white, slightly hygroscopic, crystalline powder. Soluble in water and in alcohol; practically insoluble in dichloromethane. Store in airtight containers.

USP 36: (Phenytoin Sodium). A white, odourless powder. Is somewhat hygroscopic and on exposure to air gradually absorbs carbon dioxide. Freely soluble in water, the solution usually being somewhat turbid due to partial hydrolysis and absorption of carbon dioxide; soluble in alcohol; practically insoluble in chloroform and in ether. Store in airtight containers.

Incompatibility. Phenytoin sodium only remains in solution when the pH is considerably alkaline (about 10 to 12) and there have been reports of loss of clarity or precipitation of phenytoin crystals when solutions of phenytoin sodium for injection have been mixed with other drugs[1] or added to intravenous infusion fluids,[7-10] while binding has been reported after addition to enteral nutrition solutions.[11] A phenytoin precipitate has blocked implanted central venous access devices after the inadvertent admixture of phenytoin sodium with glucose 5% or glucose in sodium chloride (pH 4);[12,13] the blockage can be successfully cleared by the local instillation of sodium bicarbonate 8.4% to increase the pH of the medium.

1. Misgen R. Compatibilities and incompatibilities of some intravenous solution admixtures. *Am J Hosp Pharm* 1965; 22: 92–4.
2. Patel JA, Phillips GL. A guide to physical compatibility of intravenous drug admixtures. *Am J Hosp Pharm* 1966; 23: 409–11.
3. Klamerus KJ, *et al.* Stability of nitroglycerin in intravenous admixtures *Am J Hosp Pharm* 1984; 41: 303–5.
4. Hasegawa GR, Eder JF. Visual compatibility of dobutamine hydrochloride with other injectable drugs. *Am J Hosp Pharm* 1984; 41: 949–51.
5. Gayed AA, *et al.* Visual compatibility of diltiazem injection with various diluents and medications during simulated Y-site injection. *Am J Health Syst Pharm* 1995; 52: 516–20.
6. Trissel LA, *et al.* Compatibility of propofol injectable emulsion with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; 54: 1287–92.
7. Bauman JL, *et al.* Phenytoin crystallization in intravenous fluids. *Drug Intell Clin Pharm* 1977; 11: 646–9.
8. Bauman JL, Siepler JK. Intravenous phenytoin (concluded). *N Engl J Med* 1977; 296: 111.
9. Cloyd JC, *et al.* Concentration-time profile of phenytoin after admixture with small volumes of intravenous fluids. *Am J Hosp Pharm* 1978; 35: 45–8.
10. Giacona N, *et al.* Crystallization of three phenytoin preparations in intravenous solutions. *Am J Hosp Pharm* 1982; 39: 630–4.
11. Miller SW, Strom JG. Stability of phenytoin in three enteral nutrient formulas. *Am J Hosp Pharm* 1988; 45: 2529–32.
12. Akinwande KI, Keehn DM. Dissolution of phenytoin precipitate with sodium bicarbonate in an occluded central various access device. *Ann Pharmacother* 1995; 29: 707–9.
13. Tse CST, Abdullah R. Dissolving phenytoin precipitate in central venous access device. *Ann Intern Med* 1998; 128: 1049.

Uses and Administration

Phenytoin is a hydantoin antiepileptic used to control partial and generalised tonic-clonic seizures (see Epilepsy, p. 539.2). It is also used as part of the emergency treatment of status epilepticus (p. 539.3) and has been used for the prevention and treatment of seizures associated with neurosurgery or severe traumatic injury to the head (see Post-traumatic Seizures, p. 539.3). Phenytoin has also been used in the treatment of trigeminal neuralgia. It is a class Ib antiarrhythmic and has been used to treat cardiac arrhythmias.

Doses may be expressed in terms of phenytoin or phenytoin sodium; although phenytoin 92 mg is equivalent to about 100 mg of phenytoin sodium these molecular equivalents are not necessarily biologically equivalent. In the UK an oral suspension of phenytoin 90 mg in 15 mL may be considered about equivalent in therapeutic effect to capsules or tablets containing phenytoin sodium 100 mg. In the USA a suspension containing phenytoin 125 mg in 5 mL is available.

For **epilepsy** the dose of phenytoin should be adjusted to the needs of the individual patient to achieve adequate control of seizures, preferably with monitoring of plasma concentrations; in many patients control requires total plasma-phenytoin concentrations of 10 to 20 micrograms/mL (40 to 80 micromoles/litre), but some have control at concentrations outside this range. A suggested initial oral dose of phenytoin or phenytoin sodium given as a single dose or in divided doses is 3 to 4 mg/kg daily or 150 to 300 mg daily progressively increased with care to 600 mg daily if necessary; the suggested minimum interval between increments has ranged from about 7 to 10 days. Particular care is needed at higher doses, where saturation of metabolism may mean that a small increment produces a large rise in plasma concentrations. A usual maintenance dose is 200 to 500 mg daily.

The practice of starting phenytoin therapy with initial small doses means that more than a week may be required before therapeutic plasma concentrations are attained; it has been reported that it may even be several weeks before a steady-state concentration is established. An initial loading

dose may therefore be given, with the usual maintenance dosage being instituted 24 hours after the loading dose. Once the patient is stabilised the long half-life of phenytoin may permit the total daily dose to be given in two daily divisions or as a single dose, usually at night.

Although clinical evidence is lacking, different brands of phenytoin, as well as different formulations from the same manufacturer, may vary in their bioavailability and patients may need to be restabilised in the event of a change.

In order to lessen gastric irritation, phenytoin should be taken with or after food. The time and manner of taking phenytoin should be standardised for the patient since variations might affect absorption with consequent fluctuations in the plasma concentrations.

As with other antiepileptics, withdrawal of phenytoin therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1.

Treatment of tonic-clonic **status epilepticus** is usually begun with a benzodiazepine such as diazepam or lorazepam given intravenously or rectally, and followed by phenytoin sodium intravenously. A suggested dose of phenytoin sodium is 10 to 15 mg/kg given by slow intravenous injection or by intermittent infusion at a uniform rate of not more than 50 mg/minute. Thereafter maintenance doses of 100 mg orally or intravenously are given every 6 to 8 hours; the rate and dose should be reduced according to body-weight.

For doses in children, see below.

Deaths have been caused by the over-rapid intravenous injection of phenytoin sodium and continuous monitoring of the ECG and blood pressure is recommended whenever phenytoin sodium is given intravenously.

Phenytoin sodium is absorbed slowly and erratically from the intramuscular site and therefore intramuscular injections are not appropriate for the emergency arrest of status epilepticus. They may, however, be used in certain situations to maintain or establish therapeutic plasma concentrations of phenytoin in patients who are unconscious or otherwise unable to take phenytoin orally. Owing to the slower absorption of phenytoin from intramuscular sites, patients stabilised on the oral route require an increase in the intramuscular dose of about 50%; it is recommended that, if possible, intramuscular injections of phenytoin sodium should not be continued for longer than one week. On transfer back to the oral route the patient should receive 50% of the original oral dose for the same period of time as intramuscular injections were given, to allow for continued absorption of the residual phenytoin in the intramuscular sites. For the **prevention and treatment of seizures associated with neurosurgery** in patients who have not previously taken phenytoin sodium, a suggested intramuscular dose is 100 to 200 mg given at 4-hourly intervals during surgery and continued post-operatively for 48 to 72 hours. Thereafter, the dose should be reduced to a maintenance dose of 300 mg daily and adjusted according to plasma-phenytoin concentrations. If more than one week of intramuscular therapy is required, an alternative route such as gastric intubation should be used.

Administration in children. Phenytoin may be given to children for the control of all forms of epilepsy except absence seizures. It is also used as part of the emergency treatment of status epilepticus and has been used for the prevention and treatment of seizures associated with neurosurgery or severe traumatic injury to the head.

For **epilepsy** the dose of phenytoin should be adjusted to the needs of the individual patient to achieve adequate control of seizures, preferably with monitoring of plasma concentrations; young children may require a higher dose per kg body-weight than adults due to more rapid metabolism. In many patients control requires total plasma-phenytoin concentrations of 10 to 20 micrograms/mL (40 to 80 micromoles/litre), but some are controlled at concentrations outside this range; the *BNFC* suggests concentrations of 6 to 15 micrograms/mL (25 to 60 micromoles/litre) in neonates and those aged up to 3 months. The recommended initial oral dose of phenytoin or phenytoin sodium for children is 5 mg/kg daily in 2 or 3 divided doses up to a maximum of 300 mg daily; the usual maintenance dose is 4 to 8 mg/kg daily in divided doses. Alternatively, the *BNFC* suggests the following doses given according to age:

- neonates: an initial loading dose of 18 mg/kg by slow intravenous injection, over 20 to 30 minutes, followed by oral doses of 2.5 to 5 mg/kg twice daily adjusted as necessary to a usual maximum of 7.5 mg/kg twice daily
- 1 month to 12 years: an initial oral dose of 1.5 to 2.5 mg/kg twice daily followed by 2.5 to 5 mg/kg twice daily adjusted as necessary to a usual maximum of 7.5 mg/kg twice daily or 300 mg daily
- 12 years and older: usual adult doses (see p. 538.3)

For **status epilepticus** and for the **prevention and treatment of seizures associated with neurosurgery or trauma** the *BNFC* suggests the following doses of phenytoin sodium given by slow intravenous injection or infusion according to age:

- neonates and children up to 12 years: a loading dose of 20 mg/kg followed by 2.5 to 5 mg/kg twice daily
- 12 to 18 years: a loading dose of 20 mg/kg followed by up to 100 mg 3 or 4 times daily

Intravenous injections and infusions of phenytoin sodium should be given at a rate not exceeding 1 mg/kg per minute (a maximum of 50 mg per minute).

A comparison of methods[1] for the prediction of required phenytoin dosage in paediatric patients indicated that all methods produced a sizeable number of predictions with an error of more than 10% and that close monitoring of serum concentrations and clinical status was recommended regardless of the method chosen to adjust dosage. Similar conclusions have been made regarding the need to monitor plasma concentrations of phenytoin in the newborn and young infants.[2]

1. Yuen GJ, *et al.* Phenytoin dosage predictions in paediatric patients. *Clin Pharmacokinet* 1989; 16: 254–60.
2. Loughnan PM, *et al.* Pharmacokinetic observations of phenytoin disposition in the newborn and young infant. *Arch Dis Child* 1977; 52: 302–9.

Administration in the elderly. Pharmacokinetic studies in elderly patients have shown reduced binding to plasma proteins which was not itself an indication for dosage change,[1] but a study showing a decreased metabolism[2] did indicate that elderly patients may need lower doses of phenytoin than younger adults to maintain similar serum concentrations.

1. Patterson M, *et al.* Plasma protein binding of phenytoin in the aged: in vivo studies. *Br J Clin Pharmacol* 1982; 13: 423–5.
2. Bauer LA, Blouin RA. Age and phenytoin kinetics in adult epileptics. *Clin Pharmacol Ther* 1982; 31: 301–4.

Cardiac arrhythmias. Phenytoin has been given intravenously in the treatment of ventricular arrhythmias (p. 1266.1), especially those caused by overdosage with cardiac glycosides. Although this use now appears to be obsolete, in the UK the licensed dose of phenytoin sodium is 3.5 to 5 mg/kg given by slow intravenous injection at a uniform rate of not more than 50 mg/minute, repeated once if necessary.

Eclampsia and pre-eclampsia. Phenytoin has been used for eclampsia but now treatment with magnesium sulfate is preferred, see p. 511.1.

Epidermolysis bullosa. There have been reports[1-3] of a favourable but variable clinical response to phenytoin in patients with some variants of epidermolysis bullosa (p. 1684.3), a condition for the severe forms of which there is no truly effective treatment. However, a double-blind placebo-controlled study[4] concluded that phenytoin was not an effective treatment for the recessive dystrophic variant, and offered no overall benefit when compared with placebo.

1. Bauer EA, *et al.* Phenytoin therapy of recessive dystrophic epidermolysis bullosa. *N Engl J Med* 1980; 303: 776–81.
2. Cooper TW, Bauer EA. Therapeutic efficacy of phenytoin in recessive dystrophic epidermolysis. *Arch Dermatol* 1984; 120: 490–5.
3. Scheinfeld N. Phenytoin in cutaneous medicine: its uses, mechanisms and side effects. *Dermatol Online J* 2003; 9: 6.
4. Caldwell-Brown D, *et al.* Lack of efficacy of phenytoin in recessive dystrophic epidermolysis bullosa. *N Engl J Med* 1992; 327: 163–7.

Epilepsy. Phenytoin has long been used in the treatment of partial seizures with or without secondary generalisation and in primarily generalised tonic-clonic seizures, although other drugs may be better tolerated and easier to use (see p. 506.1). It is also effective in other forms of epilepsy with the exception of absence and myoclonic seizures.

Hiccup. Phenytoin may be of value for the treatment of intractable hiccups,[1] especially those of neurogenic origin. For the management of intractable hiccups, see under Chlorpromazine, p. 1046.3.

1. Petroski D, Patel AN. Diphenylhydantoin for intractable hiccups. *Lancet* 1974; i: 739.

Myotonia. A review[1] of myotonia congenita, a hereditary muscular disorder characterised by symptoms of muscle stiffness especially after rest and on starting to move. Where treatment is necessary it is usually with phenytoin or procainamide, the former being preferred as being better tolerated.

1. Gutmann L, *et al.* Myotonia congenita. *Semin Neurol* 1991; 11: 244–8.

Neonatal seizures. Phenytoin is one of the antiepileptics that may be used in the management of neonatal seizures (p. 511.3).

Neuropathic pain. Phenytoin is used alone or added to treatment in trigeminal neuralgia (p. 11.2) in patients unresponsive to or intolerant of carbamazepine. It has also been used in the treatment of painful diabetic neuropathy (p. 8.2).

Post-traumatic seizures. About 12% of patients with severe traumatic brain injury develop seizures and the rate may be more than 50% for those with penetrating missile injuries.[1] The use of antiepileptics to treat such seizures is standard but there has been some debate about prophylactic use. Evidence suggests that prophylaxis with phenytoin (and perhaps carbamazepine or levetiracetam) is effective in preventing early seizures (arbitrarily defined as those occurring up to 7 days after trauma), but prophylaxis with these or other antiepileptics such as phenobarbital valproate, has not been shown to be effective for preventing late seizures, disability, or death.[1-7] Guidelines and recommendations for such use have been issued.[1,8,9] Children with severe, acute neurotrauma were found to have markedly altered protein binding and phenytoin metabolism, and therefore may require increased doses.[10]

1. Chang BS, Lowenstein DH. Practice parameter: antiepileptic drug prophylaxis in severe traumatic brain injury. Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2003; 60: 10–16. Also available at: http://www.neurology.org/cgi/reprint/60/1/10.pdf (accessed 09/06/08)
2. Schierhout G, Roberts I. Anti-epileptic drugs for preventing seizures following acute traumatic brain injury. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 09/06/08).
3. Chadwick D. Seizures and epilepsy after traumatic brain injury. *Lancet* 2000; 355: 334–5.
4. Temkin NR. Antiepileptogenesis and seizure prevention trials with antiepileptic drugs: meta-analysis of controlled trials. *Epilepsia* 2001; 42: 515–24.
5. Agrawal A, *et al.* Post-traumatic epilepsy: an overview. *Clin Neurol Neurosurg* 2006; 108: 433–9.
6. Beghi E. Overview of studies to prevent posttraumatic epilepsy. *Epilepsia* 2003; 44 (suppl 10): 21–6.
7. Jones KE, *et al.* Levetiracetam versus phenytoin for seizure prophylaxis in severe traumatic brain injury. *Neurosurg Focus* 2008; 25: E3. Also available at: http://thejns.org/doi/pdf/10.3171/FOC.2008.25.10.E3 (accessed 25/11/09)
8. Meek PD, *et al.* Guidelines for nonemergency use of parenteral phenytoin products. *Arch Intern Med* 1999; 159: 2639–44.
9. Bratton SL, *et al.* Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons, and Joint Section on Neurotrauma and Critical Care, AANS/CNS. Guidelines for the management of severe traumatic brain injury—XIII: antiseizure prophylaxis. *J Neurotrauma* 2007; 24 (suppl 1): S-83–S-86. Also available at: https://www.braintrauma.org/pdf/protected/Guidelines_Management_2007w_bookmarks.pdf (accessed 25/08/10)
10. Stowe CD, *et al.* Altered phenytoin pharmacokinetics in children with severe, acute traumatic brain injury. *J Clin Pharmacol* 2000; 40: 1452–61.

Status epilepticus. A benzodiazepine is the usual choice to abort an attack of status epilepticus (p. 510.2). If this fails to control the seizures or the seizures recur, then intravenous phenytoin may be given.

Once seizures have been brought under control, maintenance antiepileptic therapy may be started.

Syndrome of inappropriate ADH secretion. Phenytoin has been used occasionally to inhibit pituitary antidiuretic hormone (ADH) secretion in patients with the syndrome of inappropriate ADH secretion (SIADH), the management of which is discussed on p. 2351.2.

Tinnitus. Phenytoin is one of many drugs that have been tried in tinnitus (p. 1994.1), but although it has been reported to be effective in some patients it is rarely used because of problems with adverse effects.

Withdrawal syndromes. Phenytoin has little place in the management of seizures associated with the *alcohol withdrawal syndrome* (p. 1735.1). Prophylaxis with phenytoin has been shown[1,2] to be ineffective for prevention of recurrent alcohol-related seizures and therefore drugs such as the benzodiazepines or clomethiazole, which are effective both for the treatment and prophylaxis of such seizures, are preferred.

Results from a double-blind study[3] indicated that phenytoin was associated with a reduction in *cocaine abuse* compared with placebo. A later review,[4] which included this study, found insufficient evidence to support the use of antiepileptics (carbamazepine, gabapentin, lamotrigine, phenytoin, tiagabine, topiramate, and valproate) for the treatment of cocaine dependence. The authors noted that although the methodological quality of the included studies was high, the sample sizes were small. The abuse of cocaine is discussed on p. 1988.3 and treatment of cocaine withdrawal on p. 1990.1.

1. Chance JF. Emergency department treatment of alcohol withdrawal seizures with phenytoin. *Ann Emerg Med* 1991; 20: 520–2.
2. Rathlev NK, *et al.* The lack of efficacy of phenytoin in the prevention of recurrent alcohol-related seizures. *Ann Emerg Med* 1994; 23: 513–8.
3. Crosby RD, *et al.* Phenytoin in the treatment of cocaine abuse: a double-blind study. *Clin Pharmacol Ther* 1996; 59: 458–68.
4. Minozzi S, *et al.* Anticonvulsants for cocaine dependence. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 31/07/09).

Wounds and ulcers. Phenytoin has been used to promote wound healing (p. 1690.1). Topical application of phenytoin has produced encouraging results in the healing of various types of ulcers[1-7] and large abscess cavities.[8] It has been suggested that phenytoin may reduce bacterial colonisation by changing the pH or by a direct antibacterial effect.[2] The enhanced wound healing may also be due to increased fibroblast proliferation and increased collagen content.[2] Limited absorption from the wound site may occur[9,10] and patients may need to be monitored for signs of toxicity. A systematic review,[11] which included some of these studies, found evidence to support the use of phenytoin in the treatment of leg ulcers, leprosy wounds, chronic wounds, and diabetic foot ulcers despite the poor methodological quality in the majority of studies.

1. Muthukumarasamy MG, *et al.* Topical phenytoin in diabetic foot ulcers. *Diabetes Care* 1991; **14**: 909–11.
2. Pendse AK, *et al.* Topical phenytoin in wound healing. *Int J Dermatol* 1993; **32**: 214–17.
3. Anstead GM, *et al.* Phenytoin in wound healing. *Ann Pharmacother* 1996; **30**: 768–75.
4. Adjei O, *et al.* Phenytoin in the treatment of Buruli ulcer. *Trans R Soc Trop Med Hyg* 1998; **92**: 108–9.
5. Rhodes RS, *et al.* Topical phenytoin treatment of stage II decubitus ulcers in the elderly. *Ann Pharmacother* 2001; **35**: 675–81.
6. Bhatia A, *et al.* Topical phenytoin suspension and normal saline in the treatment of leprosy trophic ulcers: a randomized, double-blind, comparative study. *J Dermatolog Treat* 2004; **15**: 321–7.
7. Younes N, *et al.* Wound bed preparation with 10 percent phenytoin ointment increases the take of split-thickness skin graft in large diabetic ulcers. *Dermatol Online J* 2006; **12**: 5. Available at: http://dermatology.cdlib.org/126/pearls/phenytoin/younes.html (accessed 09/06/08)
8. Lodha SC, *et al.* Role of phenytoin in healing of large abscess cavities. *Br J Surg* 1991; **78**: 105–8.
9. Gore R, *et al.* Topical phenytoin. *Pharm J* 1991; **247**: 620.
10. Lewis WG, Rhodes RS. Systemic absorption of topical phenytoin sodium. *Ann Pharmacother* 1994; **28**: 961.
11. Shaw J, *et al.* The clinical effect of topical phenytoin on wound healing: a systematic review. *Br J Dermatol* 2007; **157**: 997–1004.

Adverse Effects

Adverse effects are fairly frequent in patients receiving phenytoin, but some remit with dose reduction or continued use. Often reported are CNS-related effects (such as headache, dizziness, tremor, transient nervousness, and insomnia), and gastrointestinal disturbances including nausea, vomiting, and constipation. Tenderness and hyperplasia of the gums often occur, particularly in younger patients. Acne, hirsutism, and coarsening of the facial features may be associated with phenytoin therapy, and may be particularly undesirable in adolescents and women.

Phenytoin toxicity may be manifested as a syndrome of cerebellar, vestibular, and ocular effects, notably nystagmus, diplopia, slurred speech, and ataxia. Mental confusion, sometimes severe, may occur, and dyskinesias and exacerbations of seizure frequency have been noted. Hyperglycaemia has been associated with toxic concentrations.

Overdosage may result in hypotension, coma, and respiratory depression. Hypotension and CNS depression may also follow intravenous dosage, if too rapid, as may cardiac arrhythmias and impaired cardiac conduction. Solutions for injection are very alkaline and may result in irritation at the injection site or phlebitis. A syndrome of distal limb oedema, discoloration, and pain ('purple glove syndrome') has been reported occasionally.

Prolonged therapy may produce subtle effects on mental function and cognition, especially in children. In addition there is some evidence that phenytoin interferes with vitamin D and folate metabolism. Rickets and osteomalacia have occurred in a few patients not exposed to adequate sunlight. A proportion of patients develop peripheral neuropathies, usually mild, and occasional cases of megaloblastic anaemia have been seen.

Mild hypersensitivity reactions are common, with skin rashes, often morbilliform, sometimes accompanied by fever. Bullous, exfoliative, or purpuric rashes may be symptoms of rare but severe reactions such as lupus erythematosus, erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis. Eosinophilia, lymphadenopathy, hepatitis, polyarteritis nodosa, and blood disorders such as aplastic anaemia, leucopenia, thrombocytopenia, and agranulocytosis, have occurred rarely; some of these conditions may also represent hypersensitivity reactions.

Hypoprothrombinaemia of the newborn after use of phenytoin during pregnancy has been reported. Congenital malformations have been seen in the offspring of mothers receiving phenytoin during pregnancy (see under Precautions, p. 542.1).

Effects on the blood. *AGRANULOCYTOSIS.* Fatal agranulocytosis has been reported[1] in a patient 17 years after starting therapy with phenytoin and primidone. Between 1963 and 1994 the UK CSM had received reports of 3 previous cases of fatal agranulocytosis associated with phenytoin and none associated with primidone. The most likely cause was considered to be a direct toxic effect of phenytoin although other possible mechanisms included the ability of both drugs to produce folate deficiency. For a discussion of the effect of antiepileptics on serum folate, see below.

1. Laurenson IF, *et al.* Delayed fatal agranulocytosis in an epileptic taking primidone and phenytoin. *Lancet* 1994; **344**: 332–3.

FOLIC ACID DEFICIENCY. Antiepileptic therapy has long been associated with folate deficiency: early studies suggested that more than half of all patients on long-term therapy with drugs such as phenytoin, phenobarbital, and primidone had subnormal serum-folate concentrations.[1,2] Megaloblastic haematopoiesis is often present,[3] but clinical megaloblastic anaemia appears to be rare.

The relative importance of individual antiepileptics in causing folate deficiency and macrocytosis has been difficult to establish, because of the tendency to use combination regimens; with greater emphasis on single drug therapy there is evidence that monotherapy may produce less significant changes.[4,5] Despite suggestions that carbamazepine has relatively little effect on folic acid concentrations, its effects have been found to be comparable with those of phenytoin;[5] however, valproate had little or no effect on red cell folate concentrations.

The mechanism by which phenytoin and similar antiepileptics reduce serum folate is uncertain; there is good evidence for a reduction in absorption of glutamate both *in vitro*[6] and *in vivo*,[7] but the drugs associated with subnormal serum folate are all enzyme inducers and it has been suggested that enzyme induction and enhanced folate metabolism may also play a role.[2,5,8] Adverse blood changes also result from hypersensitivity (see p. 541.2).

1. Horwitz SJ, *et al.* Relation of abnormal folate metabolism to neuropathy developing during anticonvulsant drug therapy. *Lancet* 1968; **i**: 563–5.
2. Maxwell JD, *et al.* Folate deficiency after anticonvulsant drugs: an effect of hepatic enzyme induction? *BMJ* 1972; **1**: 297–9.
3. Wickramasinghe SN, *et al.* Megaloblastic erythropoiesis and macrocytosis in patients on anticonvulsants. *BMJ* 1975; **4**: 136–7.
4. Dellaportas DL *et al.* Chronic toxicity in epileptic patients receiving single-drug treatment. *BMJ* 1982; **285**: 409–10.
5. Goggin T, *et al.* A comparative study of the relative effects of anticonvulsant drugs and dietary folate on the red cell folate status of patients with epilepsy. *Q J Med* 1987; **NS65** (247): 911–9.
6. Hoffbrand AV, Necheles TF. Mechanism of folate deficiency in patients receiving phenytoin. *Lancet* 1968; **ii**: 528–30.
7. Rosenberg IH, *et al.* Impairment of intestinal deconjugation of dietary folate. *Lancet* 1968; **ii**: 530–2.
8. Kishi T, *et al.* Mechanism for reduction of serum folate by antiepileptic drugs during prolonged therapy. *J Neurol Sci* 1997; **145**: 109–12.

Effects on bone. There are many reports indicating effects of antiepileptics on bone and on calcium and vitamin D metabolism. Therapy with *carbamazepine, phenobarbital,* or *phenytoin* has been associated with reduction in serum-calcium concentration to hypocalcaemic values, significant reduction in 25-hydroxycholecalciferol concentrations, and elevated alkaline phosphatase.[1] In this study, involving 226 outpatients with epilepsy, the association was not seen with *valproate*. The effects were significantly greater in the group of patients receiving polytherapy, and there was limited evidence that these biochemical changes were exacerbated by reduced exposure to sunlight.

Measurements of bone mineral density (BMD) found that children treated for epilepsy have reduced BMD during the first 1 to 5 years of therapy and that this progressively deteriorates thereafter.[2] Studies[3-5] of children receiving antiepileptic monotherapy revealed a reduction in density in those taking *valproate*; no reduction was found with *carbamazepine*.[3,4] The authors of one study[5] concluded that longer duration of therapy and higher doses resulted in lower BMD, and that this effect appeared to be more prominent in children under 5 years of age. A study[6] in 54 male patients followed for 12 to 29 months revealed that treatment with antiepileptics was associated with bone loss at the hip in the absence of vitamin D deficiency. There was no evidence that any particular drug produced more bone loss than another. Risk factors appear to include treatment duration of more than 2 years, age of over 40 years, and use of enzyme-inducing antiepileptics; the greatest rate of bone loss occurred in those with a combination of risk factors.[7] In a large cohort study[8] of women aged 65 years and older, continuous use of antiepileptics, particularly *phenytoin*, almost doubled the rate of bone loss.

A review[9] stated that there have been no significant reports of altered bone metabolism associated with the newer antiepileptics (*gabapentin, lamotrigine, topiramate,* and *vigabatrin*). However, short stature, low BMD, and reduced bone formation have been reported with long-term *lamotrigine* treatment, particularly when used with *valproate*;[10] further study is needed. *Oxcarbazepine* was found to have[11] similar effects on bone and vitamin D metabolism to *carbamazepine*; both drugs were associated with a reduction in 25-hydroxycholecalciferol serum concentrations and an increased bone turnover.

A more recent literature review[12] considered that most studies to date have been limited by factors such as small sample size, possible selection bias, lack of appropriate controls, and not adjusting for potential confounders. Nevertheless, long-term antiepileptic therapy was found to have an adverse effect on BMD and to increase fracture risk in some patients; there was little information regarding the relative risk with different types of antiepileptics. The authors suggested monitoring indices of bone health, optimising lifestyle factors, maintaining vitamin D and calcium status, and preventing falls in patients on long-term therapy.

Despite these alterations in bone metabolism reports of clinical osteomalacia associated with antiepileptics are rare.[13] A study in 20 epileptic outpatients who had received antiepileptic therapy for a mean of 14½ years failed to show any clinical evidence of osteomalacia although there was some evidence of altered calcium metabolism.[14] Similarly osteomalacia was seen in only 1 of 19 elderly inpatients in another study,[15] a rate similar to that previously seen in elderly patients with acute illness not receiving antiepileptic therapy. There was evidence of femoral osteopenia in over half of a group of 30 patients on long-term phenytoin therapy,[16] which was higher than that in the general population, and one male patient had clinical osteoporosis.

After review of data from studies[7,17,18] and data submitted to its Yellow Card scheme, the UK MHRA[19] considered that long-term treatment with *carbamazepine, phenytoin, primidone,* and *valproate* is associated with decreased BMD resulting in an increased risk of osteopenia, osteoporosis, and fractures in patients who are immobilised for long periods, or have inadequate sun exposure, or inadequate dietary calcium intake. In addition, *carbamazepine, phenytoin,* and *primidone* therapy were found to be associated with an increased risk of osteomalacia. The MHRA advises that vitamin D supplementation should be considered in at-risk patients on long-term therapy with these antiepileptics.

1. Gough H, *et al.* A comparative study of the relative influence of different anticonvulsant drugs, UV exposure and diet on vitamin D and calcium metabolism in out-patients with epilepsy. *Q J Med* 1986; **NS59** (230): 569–77.
2. Sheth RD, *et al.* Progressive bone deficit in epilepsy. *Neurology* 2008; **70**: 170–6.
3. Sheth RD, *et al.* Effect of carbamazepine and valproate on bone mineral density. *J Pediatr* 1995; **127**: 256–62.
4. Kafali G, *et al.* Effect of antiepileptic drugs on bone mineral density in children between ages 6 and 12 years. *Clin Pediatr (Phila)* 1999; **38**: 93–8
5. Öner N, *et al.* Bone mineral metabolism changes in epileptic children receiving valproic acid. *J Paediatr Child Health* 2004; **40**: 470–3.
6. Andress DL, *et al.* Antiepileptic drug-induced bone loss in young male patients who have seizures. *Arch Neurol* 2002; **59**: 781–6.
7. Petty SJ, *et al.* Effect of antiepileptic medication on bone mineral measures. *Neurology* 2005; **65**: 1358–63.
8. Ensrud KE, *et al.* Antiepileptic drug use increases rates of bone loss in older women: a prospective study. *Neurology* 2004; **62**: 2051–7.
9. Pack AM, Morrell MJ. Adverse effects of antiepileptic drugs on bone structure: epidemiology, mechanisms and therapeutic indications. *CNS Drugs* 2001; **15**: 633–42.
10. Guo C-Y, *et al.* Long-term valproate and lamotrigine treatment may be a marker for reduced growth and bone mass in children with epilepsy *Epilepsia* 2001; **42**: 1141–7.
11. Mintzer S, *et al.* Vitamin D levels and bone turnover in epilepsy patients taking carbamazepine or oxcarbazepine. *Epilepsia* 2006; **47**: 510–15.
12. Petty SJ, *et al.* Anti-epileptic medication and bone health. *Osteoporos Int* 2007; **18**: 129–42.
13. Beghi E, *et al.* Adverse effects of anticonvulsant drugs: a critical review. *Adverse Drug React Acute Poisoning Rev* 1986; **2**: 63–86.
14. Fogelman I, *et al.* Do anticonvulsant drugs commonly induce osteomalacia? *Scott Med J* 1982; **27**: 136–42.
15. Harrington MG, Rodkinson HM. Anticonvulsant drugs and bone disease in the elderly. *J R Soc Med* 1987; **80**: 425–7.
16. Moro-Alvarez MJ, *et al.* Bone disease induced by phenytoin therapy: clinical and experimental study. *Eur Neurol* 2009; **62**: 219–30.
17. Pack AM, *et al.* Bone disease associated with antiepileptic drugs. *Cleve Clin J Med* 2004; **71** (suppl 2): S42–S48.
18. Vestergaard P. Epilepsy, osteoporosis and fracture risk: a meta-analysis. *Acta Neurol Scand* 2005; **112**: 277–86.
19. MHRA/CHM. Antiepileptics: adverse effects on bone. *Drug Safety Update* 2009; **2** (9): 2. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON043810&RevisionSelectionMethod=LatestReleased (accessed 25/08/10)

Effects on the endocrine system and metabolism. Although it may be difficult to separate from the effects of the disease itself, there is some evidence that antiepileptics can diminish *sexual potency* and *fertility* in male epileptics. Phenytoin is excreted in human semen in small quantities and might affect sperm morphology and motility. Reduced plasma concentrations of free testosterone have been detected in male epileptic patients receiving one or more of the following: carbamazepine, phenytoin, primidone, and sodium valproate.[1] There is, however, some evidence[2] that some of the changes in sex hormone concentrations induced by antiepileptics in men and women are reversible. A higher frequency of sperm abnormalities has been found[3] in men given carbamazepine, oxcarbazepine, or valproate monotherapy when compared with healthy controls; those on valproate also had reduced testicular volume. Women may also have altered reproductive function and impaired fertility associated with antiepileptic therapy, particularly with the enzyme-inducing antiepileptics and valproate.[4] There is less information about the newer antiepileptic drugs. However, a comparison[5] in men and women taking carbamazepine, lamotrigine, or levetiracetam found that lamotrigine and levetiracetam did not seem to affect sexual function in men, and improved it in women. There was some evidence of decreased androstenedione concentrations in both sexes with lamotrigine,

and in women prasterone (dehydroepiandrosterone) concentrations were increased by the drug. Levetiracetam had no significant hormonal effects in women but again was associated with decreased androstenedione in men (it was considered possible that this was an effect of the disease rather than the drugs).

Gynaecomastia has been reported[6] in 5 men receiving long-term antiepileptic treatment; one also complained of impotence but libido was stated to be normal in all 5. Phenytoin was a component of therapy in all patients and was the sole drug used in one.

Phenytoin may cause reversible *hyperglycaemia* at toxic doses but it does not appear to produce long-term effects on glucose tolerance when used in therapeutic doses.[7] Paradoxically, phenytoin has also been reported to improve insulin resistance in some patients. There has been a case report[8] of severe *hypoglycaemia* in a patient who was given intravenous phenytoin for the treatment of status epilepticus; symptoms resolved when glucose 5% was infused and no further episodes of hypoglycaemia occurred after phenytoin infusion was stopped.

Phenytoin may reduce serum concentrations of *thyroid* hormones through enzyme induction—see under Interactions of Levothyroxine, p. 2341.3.

1. Dana-Haeri J, *et al.* Reduction of free testosterone by antiepileptic drugs. *BMJ* 1982; **284**: 85–6.
2. Lossius MI, *et al.* Reversible effects of antiepileptic drugs on reproductive endocrine function in men and women with epilepsy—a prospective randomized double-blind withdrawal study. *Epilepsia* 2007; **48**: 1875–82.
3. Isojärvi JI, *et al.* Effect of epilepsy and antiepileptic drugs on male reproductive health. *Neurology* 2004; **62**: 247–53.
4. Isojärvi J. Disorders of reproduction in patients with epilepsy: antiepileptic drug related mechanisms. *Seizure* 2008; **17**: 111–19.
5. Svalheim S, *et al.* Differential effects of levetiracetam, carbamazepine, and lamotrigine on reproductive endocrine function in adults. *Epilepsy Behav* 2009; **16**: 281–7.
6. Monson JP, Scott DF. Gynaecomastia induced by phenytoin in men with epilepsy. *BMJ* 1987; **294**: 612.
7. Hurel SJ, Taylor R. Drugs and glucose tolerance. *Adverse Drug React Bull* 1995; **174**: 659–62.
8. Di Gennaro G, *et al.* Hypoglycaemia induced by phenytoin treatment for partial status epilepticus. *J Neurol Neurosurg Psychiatry* 2002; **73**: 349–50.

Effects on the liver. There have been occasional reports of liver damage, probably due to hypersensitivity, associated with phenobarbital and phenytoin; the authors of an early study suggested that such drugs need not be withdrawn if there were merely transient elevations in transaminase values,[1] but care is needed to distinguish such effects from the early symptoms of the antiepileptic hypersensitivity syndrome (see below).

1. Aiges HW, *et al.* The effects of phenobarbital and diphenylhydantoin on liver function and morphology. *J Pediatr* 1980; **97**: 22–6.

Effects on the lungs. Pulmonary eosinophilia and acute respiratory failure requiring mechanical ventilation have been reported[1] in a patient receiving phenytoin; other pulmonary symptoms associated with phenytoin were reviewed.

1. Mahatma M, *et al.* Phenytoin-induced acute respiratory failure with pulmonary eosinophilia. *Am J Med* 1989; **87**: 93–4.

Effects on mental function. For a review of the effects of antiepileptic therapy including phenytoin on *cognition* and *mood* (including the risk of suicidal ideation), see p. 508.3.

Effects on the skin. A retrospective analysis involving 1890 outpatients taking antiepileptics found that rates of skin reactions associated with treatment varied with different drugs, the risk being greatest with carbamazepine, lamotrigine, and phenytoin, and lowest with gabapentin, levetiracetam, and valproate.[1] Overall, the rate of skin reactions in this study was 2.8%, but as also mentioned in Hypersensitivity, below (where more details on phenytoin-associated skin reactions are given), there appeared to be cross-sensitivity; risk in this study was increased to 8.8% in those who had previously had a rash with another antiepileptic drug.

Rare, but severe reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have also occurred. For a warning that severe skin reactions may be more likely in patients of certain genotypes, see Skin Reactions, under Precautions, p. 542.1.

For reference to cutaneous manifestations of zinc deficiency, possibly due to chelation with phenytoin, see under Valproate, p. 556.1.

1. Arif H, *et al.* Comparison and predictors of rash associated with 15 antiepileptic drugs. *Neurology* 2007; **68**: 1701–9.

Gingival hyperplasia. Gingival hyperplasia, characterised by inflammation and a marked fibrotic response, may affect up to 50% of patients receiving phenytoin. It usually becomes apparent within the first few months of therapy and occurs more frequently in children; there is no increase in alveolar bone loss. The mechanism underlying its development is unknown, although the main metabolite of phenytoin, 5-(4-hydroxyphenyl)-5-phenylhydantoin, has been implicated.[1-3]

1. Ball DE, *et al.* Plasma and saliva concentrations of phenytoin and 5-(4-hydroxyphenyl)-5-phenylhydantoin (HPPH) in relation to gingival overgrowth in epileptic patients. *Br J Clin Pharmacol* 1995; **39**: 539P–588P.
2. Ieiri I, *et al.* Effect of 5-(p-hydroxyphenyl)-5-phenylhydantoin (p-HPPH) enantiomers, major metabolites of phenytoin, on the occurrence of chronic-gingival hyperplasia: in vivo and in vitro study. *Eur J Clin Pharmacol* 1995; **49**: 51–6.
3. Zhou LX, *et al.* Metabolism of phenytoin by the gingiva of normal humans: the possible role of reactive metabolites of phenytoin in the initiation of gingival hyperplasia. *Clin Pharmacol Ther* 1996; **60**: 191–8.

Hypersensitivity. An antiepileptic hypersensitivity syndrome, comprising fever, rash, and lymphadenopathy and less commonly lymphocytosis, and liver and other organ involvement, has been associated with some antiepileptic drugs including phenytoin.[1-3] Clinical manifestations may include interstitial nephritis, anaemia, interstitial pulmonary infiltrates, thrombocytopenia, eosinophilia, myopathy, and diffuse intravascular coagulation.[1,2] Some have estimated the incidence at 1 in 1000 to 1 in 10 000 new exposures to aromatic antiepileptics,[2,3] but the true incidence is unknown due to variations in presentation and reporting. The syndrome occurs most frequently on first exposure to the drug, with initial symptoms starting anywhere between 1 and 8 weeks after exposure. The mean interval to onset is 17 to 21 days with phenytoin. In previously sensitised individuals the reaction may occur within 1 day of rechallenge. The potential for cross-reactivity between carbamazepine, phenobarbital, and phenytoin is about 75%, and patients who develop the syndrome, and their close relatives, should be warned of the risk associated with use of these antiepileptics.[2] An early review[1] of the syndrome in patients taking phenytoin commented that it occurred mainly in black male patients and should not be confused with more common mild general hypersensitivity reactions. More recent evidence does not suggest that ethnic origin predicts differences in risk.[2]

Most cases resolve spontaneously on withdrawal of the drug and symptomatic management. The use of corticosteroids in the management of severe cases remains controversial in the absence of controlled studies of their efficacy.[1,2]

Phenytoin-induced pseudolymphoma mimicking cutaneous T-cell lymphoma has also been reported.[2,4] In most cases, symptoms resolve within 7 to 14 days of stopping the drug, and the condition is not considered premalignant.[2] However, in one report[4] the cutaneous eruption and lymphadenopathy persisted after withdrawal of phenytoin for one year when the patient eventually became asymptomatic.

In a prospective study[5] of 306 patients given phenytoin there was an overall incidence of 8.5% of morbilliform rash, but there was a marked seasonal incidence with most reactions occurring during the summer months. The results did not appear to be due to photosensitivity and might represent seasonal alterations in the immune system.

1. Flowers FP, *et al.* Phenytoin hypersensitivity syndrome. *J Emerg Med* 1987; **5**: 103–8.
2. Knowles SR, *et al.* Anticonvulsant hypersensitivity syndrome: incidence, prevention and management. *Drug Safety* 1999; **21**: 489–501.
3. Bessmertny O, *et al.* Antiepileptic hypersensitivity syndrome in children. *Ann Pharmacother* 2001; **35**: 533–8.
4. Harris DWS, *et al.* Phenytoin-induced pseudolymphoma: a report of a case and review of the literature. *Br J Dermatol* 1992; **127**: 403–6.
5. Leppik IE, *et al.* Seasonal incidence of phenytoin allergy unrelated to plasma levels. *Arch Neurol* 1985; **42**: 120–2.

Peripheral neuropathies. Electrophysiological abnormalities after prolonged phenytoin treatment are common, but clinically significant peripheral neuropathy is rare.[1] The neuropathy usually involves sensory nerves and lesions are generally mild and asymptomatic.[2] Much of the reported clinical neuropathy has been associated with multiple drug therapy of epilepsy and with exposure to toxic concentrations of phenytoin.[1,3] Although an association with folate deficiency has been suggested, a study in 52 patients on long-term antiepileptic therapy failed to find any convincing evidence of a relationship between serum-folate concentration and peripheral neuropathy.[4]

1. Bruni J. Phenytoin and other hydantoins: adverse effects. In: Levy RH, *et al.*, eds. *Antiepileptic drugs*. 5th ed. Philadelphia: Lippincott Williams & Wilkins, 2002: 605–10.
2. Argov Z, Mastaglia FL. Drug-induced peripheral neuropathies. *BMJ* 1979; **1**: 663–6.
3. Toth C, Kotecha SA. Prolonged and excessive phenytoin therapy leading to a severe and partially reversible polyneuropathy. *J Peripher Nerv Syst* 2004; **9**: 198–9.
4. Horwitz SJ, *et al.* Relation of abnormal folate metabolism to neuropathy developing during anticonvulsant drug therapy. *Lancet* 1968; **i**: 563–5.

Treatment of Adverse Effects

Treatment of poisoning with phenytoin tends to be supportive. Repeated doses of activated charcoal may be given orally to adults and children who present within 1 hour of ingesting more than 20 mg/kg; the aim is not only to prevent absorption but also to aid elimination. Gastric lavage may be considered if a very large amount has been taken within 1 hour.

Multiple oral doses of activated charcoal may reduce the absorption of phenytoin[1,2] but the degree of clinical benefit is unclear.[3] The value of charcoal haemoperfusion in the management of phenytoin overdosage is debatable. A review of haemoperfusion included data from 2 patients who ingested phenytoin[4] but, although it was suggested that haemoperfusion should contribute significantly to drug removal, results are difficult to evaluate in these patients who had also ingested phenobarbital. An evaluation in a patient who had also taken primidone[5] suggested that, although initial clearance of phenytoin was promising, the system rapidly became saturated and there was little overall benefit. A review[3] of the features and management of phenytoin poisoning concluded that supportive care is the mainstay of treatment. Gastric lavage and multiple-dose activated charcoal should not be used routinely, although they might be considered for life-threatening ingestion. They were most effective when used within 1 hour of ingestion; the airway should be secured first. Extracorporeal methods of elimination (e.g. haemodialysis, haemoperfusion, peritoneal dialysis, or plasmapheresis) had not been shown to be of benefit;[3] however, some such procedures may be beneficial in patients with renal failure[3] or hypoalbuminaemia[6] in whom free phenytoin concentrations are raised.

1. Weidle PJ, *et al.* Multiple-dose activated charcoal as adjunct therapy after chronic phenytoin intoxication. *Clin Pharm* 1991; **10**: 711–14.
2. Dolgin JG, *et al.* Pharmacokinetic simulation of the effect of multiple-dose activated charcoal in phenytoin poisoning—report of two pediatric cases. *DICP Ann Pharmacother* 1991; **25**: 646–9.
3. Craig S. Phenytoin poisoning. *Neurocrit Care* 2005; **3**: 161–70.
4. Pond S, *et al.* Pharmacokinetics of haemoperfusion for drug overdose. *Clin Pharmacokinet* 1979; **4**: 329–54.
5. Baehler RW, *et al.* Charcoal hemoperfusion in the therapy for methsuximide and phenytoin overdose. *Arch Intern Med* 1980; **140**: 1466–8.
6. De Schoenmakere G, *et al.* Phenytoin intoxication in critically ill patients. *Am J Kidney Dis* 2005; **45**: 189–92.

Precautions

Phenytoin is metabolised in the liver and should be given with care to patients with impaired liver function. Caution is also advocated in diabetic patients because of the potential effects of phenytoin on blood sugar.

Protein binding may be reduced in certain disease states such as uraemia, and in certain patient populations such as neonates, pregnant women, and the elderly. Although phenytoin is extensively protein bound this may be of little clinical significance in itself, provided that hepatic function is not impaired, because the concentration of free (pharmacologically active) drug in the plasma often remains more or less unchanged, due to distribution, metabolism, and excretion. Thus, an alteration in protein binding would not necessarily require a change in dosage of phenytoin to be made although, when plasma concentrations are being monitored, relatively lower total plasma-phenytoin concentrations will be found to be effective since there is less bound (pharmacologically inactive) phenytoin available for measurement.

Intravenous phenytoin must be given slowly and extravasation and intra-arterial injection must be avoided. Phenytoin should not be given intravenously to patients with sinus bradycardia, heart block, or Stokes-Adams syndrome, and should be used with caution in patients with hypotension, heart failure, or myocardial infarction; monitoring of blood pressure and the ECG is recommended during intravenous use.

Patients or their carers should be told how to recognise signs of blood or skin toxicity and they should be advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, bruising, or bleeding develop. Phenytoin should be stopped, if necessary under cover of a suitable alternative antiepileptic, if leucopenia which is severe, progressive, or associated with clinical symptoms develops. It should also be stopped if a skin rash develops; in the case of mild rashes phenytoin may be reintroduced cautiously, but should be stopped immediately and permanently if the rash recurs.

Care is required when withdrawing phenytoin therapy—see also Uses and Administration, p. 538.3.

Phenytoin may interfere with some tests of thyroid function as it can reduce free and circulating concentrations of levothyroxine, mainly by enhanced conversion to triiodothyronine, and it may also produce lower than normal values for dexamethasone and metyrapone suppression tests.

Breast feeding. The American Academy of Pediatrics[1] considers that phenytoin is usually compatible with breast feeding, although there had been an early case report of methaemoglobinaemia in a breast-fed infant.

For further comment on antiepileptic therapy and breast feeding, see p. 508.3.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. [Retired May

2010] Correction. *Ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 09/06/08)

Driving. For comment on antiepileptic drugs and driving, see p. 509.2.

Infections. A 52-year-old woman previously well-controlled on phenytoin 400 mg daily suffered phenytoin toxicity after a viral infection;[1] her plasma-phenytoin concentration had increased from 16 to 51 micrograms/mL. Six weeks later she had recovered and was re-stabilised on phenytoin 400 mg daily.

1. Levine M, Jones MW. Toxic reaction to phenytoin following a viral infection. *Can Med Assoc J* 1983; 128: 1270–1.

AIDS. Renal abnormalities or hypoalbuminaemia associated with AIDS may increase the risk of elevated free phenytoin concentrations and subsequent toxicity. Altered protein binding resulted in marked phenytoin toxicity, with lethargy and seizure-like activity, in an HIV-positive patient with profound hypoalbuminaemia and moderate renal insufficiency.[1] Therapeutic drug monitoring in 21 patients with AIDS indicated that although total serum concentrations of phenytoin were lower than in a reference population, the fraction of unbound drug was higher.[2] These changes might be attributed to hypoalbuminaemia and it was suggested that free rather than total phenytoin concentrations should be measured in HIV-infected patients with hypoalbuminaemia.

Phenytoin itself was associated with reversible hypogammaglobulinaemia in an HIV-positive patient who previously had borderline hypergammaglobulinaemia.[3]

1. Toler SM, *et al.* Severe phenytoin intoxication as a result of altered protein binding in AIDS. *DICP Ann Pharmacother* 1990; 24: 698–700.
2. Burger DM, *et al.* Therapeutic drug monitoring of phenytoin in patients with the acquired immunodeficiency syndrome. *Ther Drug Monit* 1994; 16: 616–20.
3. Britigan BE. Diphenylhydantoin-induced hypogammaglobulinemia in a patient infected with human immunodeficiency virus. *Am J Med* 1991; 90: 524–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies phenytoin as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pregnancy. For comments on the management of epilepsy during pregnancy, see p. 509.2.

There is an increased risk of neural tube defects in infants exposed *in utero* to antiepileptics including phenytoin; syndromes such as craniofacial and digital abnormalities and, less commonly, cleft lip and palate have been described. Specific syndromes such as the 'fetal hydantoin syndrome' with phenytoin have been linked to individual antiepileptics. However, there is overlap between the effects seen with different antiepileptics and these are now often seen as aspects of a single 'fetal antiepileptic syndrome'. There is also a risk of neonatal bleeding with phenytoin.

Skin reactions. In November 2008, the FDA[1] reported that it was analysing preliminary data[2,3] which suggested that patients of Asian ancestry with the HLA allele HLA-B*1502 may be at increased risk of severe skin reactions with phenytoin therapy; this increased risk also applies to fosphenytoin, a prodrug of phenytoin. There is currently insufficient evidence to recommend routine screening for the presence of HLA-B*1502 in this patient group before starting therapy with these 2 antiepileptics. However, phenytoin and fosphenytoin should be avoided in patients with such ancestry who are known to be positive for this allele. Similar recommendations have since been issued in the UK by the MHRA.[4] See also under Carbamazepine, p. 516.1.

1. FDA. Phenytoin (marketed as Dilantin, Phenytek and generics) and fosphenytoin sodium (marketed as Cerebyx and generics)—healthcare professional sheet text version (issued 24th November, 2008). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124788.htm (accessed 30/07/09)
2. Man CBL, *et al.* Association between HLA-B*1502 allele and antiepileptic drug-induced cutaneous reactions in Han Chinese. *Epilepsia* 2007; 48: 1015–18. Correction. *ibid.* 2008; 49: 941.
3. Locharernkul C, *et al.* Carbamazepine and phenytoin induced Stevens-Johnson syndrome is associated with HLA-B*1502 allele in Thai population. *Epilepsia* 2008; 49: 2087–91. Correction. *ibid.* 2009; 50: 971.
4. MHRA/CHM. Phenytoin: risk of Stevens-Johnson syndrome associated with HLA-B*1502 allele in patients of Thai or Han Chinese ethnic origin. *Drug Safety Update* 2010; 3(6): 2–3. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON068298&RevisionSelectionMethod=LatestReleased (accessed 13/01/10)

Interactions

There are complex interactions between antiepileptics, and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy.

Since phenytoin is extensively bound to plasma proteins it can be displaced by drugs competing for protein-binding sites, thus liberating more free (pharmacologically active) phenytoin into the plasma. However, elevation of free phenytoin is reported to be of little clinical significance provided hepatic function is not impaired (see Precautions, p. 541.3). A potentially more serious type of interaction may occur because phenytoin metabolism is saturable: toxic concentrations of phenytoin can develop in patients given drugs that inhibit phenytoin metabolism even to quite a minor degree. Phenytoin itself is also a potent enzyme inducer, and induces the metabolism of many drugs, including some antibacterials, anticoagulants, corticosteroids, quinidine, and sex hormones (notably, oral contraceptives).

The hypotensive properties of dopamine and the cardiac depressant properties of drugs such as lidocaine may be dangerously enhanced by intravenous phenytoin.

General references.

1. Nation RL, *et al.* Pharmacokinetic drug interactions with phenytoin (part I). *Clin Pharmacokinet* 1990; 18: 37–60.
2. Nation RL, *et al.* Pharmacokinetic drug interactions with phenytoin (part II). *Clin Pharmacokinet* 1990; 18: 131–50.

Anaesthetics. A 10-year-old girl with epilepsy who had been treated with phenytoin 100 mg three times daily for 5 years and who had lateral nystagmus developed symptoms of phenytoin intoxication after anaesthesia with *halothane*.[1] The plasma concentration of phenytoin 72 hours after anaesthesia was 41 microgram/mL. It was suggested that temporary liver dysfunction was responsible for impaired metabolism of phenytoin.

1. Karlin JM, Kutt H. Acute diphenylhydantoin intoxication following halothane anesthesia. *J Pediatr* 1970; 76: 941–4.

Analgesics. *Aspirin* is reported to displace phenytoin from plasma binding[1,2] but there is no evidence of any effect on metabolism and effects are unlikely to be clinically significant.[3,4] *Paracetamol* is reported to have no significant effect on serum-phenytoin concentrations.[4] (However, enzyme-inducing antiepileptics such as phenytoin affect the threshold for use of antidote in the treatment of paracetamol poisoning, see p. 118.3.) Alterations of the pharmacokinetics of phenytoin have been reported with *bromfenac*, but it was thought unlikely that a change in phenytoin dose would be necessary.[5]

Other analgesic and anti-inflammatory drugs may have clinically significant effects. *Phenylbutazone* has been reported to cause an initial decrease in serum phenytoin, followed by an increase;[6] in addition to effects on protein binding it inhibits phenytoin metabolism[6] and severe phenytoin toxicity may result.[7] *Azapropazone* appears to be a competitive inhibitor of phenytoin metabolism and has also been implicated in interactions resulting in toxicity.[8,9] Substantial increases in serum phenytoin have been found in healthy subjects given the analgesic and muscle relaxant *fenyramidol*,[10] indicating a potential for toxicity. There is a single report of toxicity in a patient receiving *ibuprofen* with phenytoin[11] but in a study in 9 healthy subjects, ibuprofen had no effect on the pharmacokinetics of phenytoin.[12] In another report, phenytoin toxicity developed[13] in a patient who was also taking *celecoxib*.

The opioid analgesic *dextropropoxyphene* has also been reported to affect phenytoin metabolism, with the resultant development of toxic blood-phenytoin concentrations;[14] however, the patient in this case was taking relatively high doses of dextropropoxyphene (650 mg daily). For the effect of phenytoin on *methadone* and *pethidine*, see p. 90.3 and p. 123.2, respectively.

1. Fraser DG, *et al.* Displacement of phenytoin from plasma binding sites by salicylate. *Clin Pharmacol Ther* 1980; 27: 165–9.
2. Paxton JW. Effects of aspirin on salivary and serum phenytoin kinetics in healthy subjects. *Clin Pharmacol Ther* 1980; 27: 170–8.
3. Leonard RF, *et al.* Phenytoin-salicylate interaction. *Clin Pharmacol Ther* 1981; 29: 56–60.
4. Neuvonen PJ, *et al.* Antipyretic analgesics in patients on antiepileptic drug therapy. *Eur J Clin Pharmacol* 1979; 15: 263–8.
5. Gumbhir-Shah K, *et al.* Evaluation of pharmacokinetic interaction between bromfenac and phenytoin in healthy males. *J Clin Pharmacol* 1997; 37: 160–8.
6. Andreasen PB, *et al.* Diphenylhydantoin half-life in man and its inhibition by phenylbutazone: the role of genetic factors. *Acta Med Scand* 1973; 193: 561–4.
7. Kristensen MB. Drug interactions and clinical pharmacokinetics. *Clin Pharmacokinet* 1976; 1: 351–72.
8. Roberts CJC, *et al.* Anticonvulsant intoxication precipitated by azapropazone. *Postgrad Med J* 1981; 57: 191–2.
9. Geaney DP, *et al.* Interaction of azapropazone with phenytoin. *BMJ* 1982; 284: 1373.
10. Solomon HM, Schrogie JJ. The effect of phenyramidol on the metabolism of diphenylhydantoin. *Clin Pharmacol Ther* 1967; 8: 554–6.
11. Sandyk R. Phenytoin toxicity induced by interaction with Ibuprofen. *S Afr Med J* 1982; 62: 592.
12. Townsend RJ, *et al.* The effects of ibuprofen on phenytoin pharmacokinetics. *Drug Intell Clin Pharm* 1985; 19: 447–8.
13. Keeling KL, *et al.* Prolonged elimination half-life of phenytoin in an elderly patient also on celecoxib. *Clin Chem* 2002; 48 (suppl): A52–A53.
14. Kutt H. Interactions between anticonvulsants and other commonly prescribed drugs. *Epilepsia* 1984; 25 (suppl 2): S118–S131.

Anthelmintics. For report of an interaction between phenytoin and *levamisole* with fluorouracil, see Antineoplastics, p. 544.1. For the effect of phenytoin on *mebendazole* and *praziquantel*, see p. 160.1 and p. 165.2, respectively.

Antiarrhythmics. There have been reports of phenytoin toxicity associated with substantial rises in serum-phenytoin concentrations after addition of *amiodarone* to the therapeutic regimen.[1,2] For the effect of phenytoin on amiodarone, see p. 1303.2.

For the effect of phenytoin on other antiarrhythmics, see p. 1365.2 (*disopyramide*), p. 1437.2 (*mexiletine*), p. 1483.1 (*quinidine*), and p. 1995.1 (*lidocaine*).

1. Gore JM, *et al.* Interaction of amiodarone and diphenylhydantoin. *Am J Cardiol* 1984; 54: 1145.
2. McGovern B, *et al.* Possible interaction between amiodarone and phenytoin. *Ann Intern Med* 1984; 101: 650.

Antibacterials. Interactions, some clinically significant, may occur between phenytoin and various antibacterials. Giving *chloramphenicol* with phenytoin has resulted in moderate[1] to marked[2] elevation of serum-phenytoin concentrations due to inhibition of phenytoin metabolism;[2] toxicity has resulted.[3,4] In turn, phenytoin may affect serum concentrations of chloramphenicol (see p. 259.1).

Phenytoin may enhance the metabolism of *doxycycline*.

There is limited evidence that *erythromycin* decreases phenytoin clearance[6] but this was subject to considerable interindividual variation and is of unknown clinical significance. Results from another study[7] suggested that *clarithromycin* might also raise phenytoin levels.

The interaction with *isoniazid* is well documented and potentially significant in slow acetylators of isoniazid who may develop raised phenytoin concentrations and signs of toxicity;[8,9] in at least one case, death has resulted.[10] Plasma isoniazid concentrations may become sufficiently raised in slow acetylators of isoniazid to produce marked inhibition of the hepatic microsomal enzymes responsible for the metabolism of phenytoin.

There have been conflicting reports of the effect of *ciprofloxacin* on serum concentrations of phenytoin. While some report no effect[11] others have reported reduced[12–16] or increased[17,18] concentrations of phenytoin in patients given ciprofloxacin. A fall in serum-phenytoin concentrations and resultant loss of seizure control has been reported in a patient in whom *nitrofurantoin* was added to therapy.[19] The mechanism of this interaction is unknown although a combination of impaired absorption and increased metabolism of the phenytoin was suggested. Something similar was reported in a patient given *oxacillin* in whom plasma phenytoin concentrations dropped markedly and status epilepticus developed.[20] This effect was thought to be due to impaired phenytoin absorption.

Rifampicin can also reduce plasma-phenytoin concentrations and markedly increase its clearance;[21,22] this is in marked contrast to the effects of isoniazid, and when given together it overrides the effects of isoniazid on phenytoin even in slow acetylators.[22]

Various sulfonamides are reported to interact with phenytoin, reducing clearance and prolonging half-life. *Sulfaphenazole* is reportedly the strongest inhibitor of phenytoin metabolism but *sulfamethizole* also inhibits phenytoin metabolism and the latter has been implicated in producing phenytoin toxicity.[23] *Co-trimoxazole* reportedly inhibits phenytoin metabolism to a modest degree; a case of phenytoin toxicity in a child given co-trimoxazole has been reported[24] but the role of the co-trimoxazole is uncertain since the patient was also receiving sultiame. Fatal acute fulminant hepatic failure in a 60-year-old patient was suggested[25] to be due to phenytoin-induced hepatitis exacerbated by addition of co-trimoxazole to her drug regimen.

See also Antiprotozoals, p. 544.1.

1. Koup JR, *et al.* Interaction of chloramphenicol with phenytoin and phenobarbital. *Clin Pharmacol Ther* 1978; 24: 571–5.
2. Christensen LK, Skovsted L. Inhibition of drug metabolism by chloramphenicol. *Lancet* 1969; ii: 1397–9.
3. Ballek RE, *et al.* Inhibition of diphenylhydantoin metabolism by chloramphenicol. *Lancet* 1973; i: 150.
4. Rose JQ, *et al.* Intoxication caused by interaction of chloramphenicol and phenytoin. *JAMA* 1977; 237: 2630–1.
5. Neuvonen PJ, *et al.* Effect of antiepileptic drugs on the elimination of various tetracycline derivatives. *Eur J Clin Pharmacol* 1975; 9: 147–54.
6. Bachmann K, *et al.* Single dose phenytoin clearance during erythromycin treatment. *Res Commun Chem Pathol Pharmacol* 1984; 46: 207–17.
7. Burger DM, *et al.* Therapeutic drug monitoring of phenytoin in patients with the acquired immunodeficiency syndrome. *Ther Drug Monit* 1994; 16: 616–20.
8. Brennan RW, *et al.* Diphenylhydantoin intoxication attendant to slow inactivation of isoniazid. *Neurology* 1970; 20: 687–93.
9. Kutt H, *et al.* Diphenylhydantoin intoxication: a complication of isoniazid therapy. *Am Rev Respir Dis* 1970; 101: 377–84.
10. Johnson J, Freeman RL. Death due to isoniazid (INH) and phenytoin. *Br J Psychiatry* 1976; 129: 511.
11. Slavich IL, *et al.* Grand mal epileptic seizures during ciprofloxacin therapy. *JAMA* 1989; 261: 538–9.
12. Dillard ML, *et al.* Ciprofloxacin-phenytoin interaction. *Ann Pharmacother* 1992; 26: 263.

13. Pollak PT, Slayter KL. Hazards of doubling phenytoin dose in the face of an unrecognized interaction with ciprofloxacin. *Ann Pharmacother* 1997; 31: 61–4.
14. Brouwers PJ, *et al.* Ciprofloxacin-phenytoin interaction. *Ann Pharmacother* 1997; 31: 498.
15. McLeod R, Trinkle R. Unexpectedly low phenytoin concentration in a patient receiving ciprofloxacin. *Ann Pharmacother* 1998; 32: 1110–11.
16. Otero M-J, *et al.* Interaction between phenytoin and ciprofloxacin. *Ann Pharmacother* 1999; 33: 251–2.
17. Schroeder D, *et al.* Effect of ciprofloxacin on serum phenytoin concentrations in epileptic patients. *Pharmacotherapy* 1991; 11: 276.
18. Hull RL. Possible phenytoin-ciprofloxacin interaction. *Ann Pharmacother* 1993; 27: 1283.
19. Heipertz R, Pilz H. Interaction of nitrofurantoin with diphenylhydantoin. *J Neurol* 1978; 218: 297–301.
20. Fincham RW, *et al.* Use of phenytoin serum levels in a case of status epilepticus. *Neurology* 1976; 26: 879–81.
21. Wagner JC, Slama TG. Rifampin-phenytoin drug interaction. *Drug Intell Clin Pharm* 1984; 18: 497.
22. Kay L, *et al.* Influence of rifampicin and isoniazid on the kinetics of phenytoin. *Br J Clin Pharmacol* 1985; 20: 323–6.
23. Siersbaek-Nielsen K, *et al.* Sulfamethizole-induced inhibition of diphenylhydantoin and tolbutamide metabolism in man. *Clin Pharmacol Ther* 1973; 14: 148.
24. Gillman MA, Sandyk R. Phenytoin toxicity and co-trimoxazole. *Ann Intern Med* 1985; 102: 559.
25. Ilario MJ-M, *et al.* Acute fulminant hepatic failure in a woman treated with phenytoin and trimethoprim-sulfamethoxazole. *Arch Pathol Lab Med* 2000; 124: 1800–3.

Anticoagulants. Serum-phenytoin concentrations have been reported to be markedly elevated by *dicoumarol*[1,2] and elevated to a lesser extent by *phenprocoumon*.[2] *Acenocoumarol* and *warfarin* have also been implicated in phenytoin toxicity,[3,4] although other evidence suggests that warfarin has no effect on serum-phenytoin concentrations in most patients.[2]

For the effect of phenytoin on anticoagulants such as dicoumarol and warfarin, see p. 1532.1.

1. Hansen JM, *et al.* Dicoumarol-induced diphenylhydantoin intoxication. *Lancet* 1966; ii: 265–6.
2. Skovsted L, *et al.* The effect of different oral anticoagulants on diphenylhydantoin and tolbutamide metabolism. *Acta Med Scand* 1976; 199: 513–5.
3. Rothermich NO. Diphenylhydantoin intoxication. *Lancet* 1966; ii: 640.
4. Jose L, *et al.* Acenocoumarol and phenytoin toxicity in the presence of CYP2C9 mutation. *J Assoc Physicians India* 2008; 56: 250–2.

Antidepressants. As with all antiepileptics, antidepressants may antagonise the antiepileptic activity of phenytoin by lowering the convulsive threshold.

Plasma-phenytoin concentrations rose in 2 epileptic patients also receiving *imipramine* 75 mg daily for about 3 months for depression.[1] In one patient the concentration gradually increased over several weeks to more than twice the pretreatment figure and he showed mild signs of phenytoin intoxication, which remitted after imipramine was stopped. Increased serum-phenytoin concentration and phenytoin toxicity possibly precipitated by addition of *trazodone* has been described;[2] licensed product information for trazodone recommends monitoring serum-phenytoin concentrations in patients receiving these two drugs. Elevated plasma-phenytoin concentrations, in some cases accompanied by signs and symptoms of phenytoin toxicity, have also been reported with *fluoxetine*,[3] *fluvoxamine*,[4,5] *sertraline*,[6] and *viloxazine*.[7] Product information for *mianserin* also recommends that plasma concentrations of phenytoin should be monitored carefully when both are given.

St John's wort has been shown to induce several drug metabolising enzymes (see p. 449.3) and consequently it might reduce the blood concentrations of phenytoin leading to an increased risk of seizure.[8] Some licensed product information for phenytoin in the UK therefore recommends that phenytoin should not be used with St John's wort and warns that the effects of St John's wort may persist for at least 2 weeks after it was last used.

For the effects of phenytoin on antidepressants, see under Amitriptyline (p. 406.2), Fluoxetine (p. 424.2), and Lithium (p. 431.3).

1. Perucca E, Richens A. Interaction between phenytoin and imipramine. *Br J Clin Pharmacol* 1977; 4: 485–6.
2. Dorn JM. A case of phenytoin toxicity possibly precipitated by trazodone. *J Clin Psychiatry* 1986; 47: 89–90.
3. Nightingale SL. Fluoxetine labeling revised to identify phenytoin interaction and to recommend against use in nursing mothers. *JAMA* 1994; 271: 1067.
4. Feldman D, *et al.* Cas clinique d'interaction médicamenteuse entre phénytoïne et fluvoxamine. *J Pharm Clin* 1995; 14: 296–7.
5. Mamiya K, *et al.* Phenytoin intoxication induced by fluvoxamine. *Ther Drug Monit* 2001; 23: 75–7.
6. Haselberger MB, *et al.* Elevated serum phenytoin concentrations associated with coadministration of sertraline. *J Clin Psychopharmacol* 1997; 17: 107–9.
7. Pisani F, *et al.* Elevation of plasma phenytoin by viloxazine in epileptic patients: a clinically significant interaction. *J Neurol Neurosurg Psychiatry* 1992; 55: 126–7.
8. CSM/MCA. Reminder: St John's wort (Hypericum perforatum) interactions. *Current Problems* 2000; 26: 6–7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)

Antidiabetics. Transient rises in the amount of non-protein-bound phenytoin occurred in 17 patients when *tolbutamide* was given in addition to phenytoin, but none developed signs of intoxication.[1] Toxic symptoms were reported in another patient given phenytoin with tolbutamide, although she had tolerated this combination on a previous occasion.[2]

Symptoms of phenytoin toxicity are known to have occurred[1] in one patient receiving *tolazamide* and phenytoin.

1. Wesseling H, Mols-Thürkow I. Interaction of diphenylhydantoin (DPH) and tolbutamide in man. *Eur J Clin Pharmacol* 1975; 8: 75–8.
2. Beech E, *et al.* Phenytoin toxicity produced by tolbutamide. *BMJ* 1988; 297: 1613–14.

Antiepileptics. Interactions may occur when phenytoin is used with other antiepileptics, but these are often variable in their effect and difficult to predict.

For a discussion of the effect of *benzodiazepines* on plasma concentrations of phenytoin, see Benzodiazepines, p. 544.2.

Carbamazepine has been generally reported to lower serum-phenytoin concentrations,[1,2] although reports exist of elevated serum-phenytoin concentrations when the two were given concurrently.[3] It should be noted that phenytoin also reduces serum-carbamazepine values—see p. 516.3. These studies have not indicated any loss of seizure control due to this interaction.

For the effects of phenytoin on *ethosuximide*, see p. 521.3.

Felbamate has caused increases in serum-phenytoin concentrations, and in some cases toxicity requiring a reduction in phenytoin dose.[4,5]

Increased plasma concentrations of phenytoin with symptoms of toxicity have been reported in a patient receiving phenytoin, carbamazepine, and clobazam after *gabapentin* was added to treatment.[6]

Phenytoin reduces plasma concentrations of *lamotrigine* as described on p. 530.1.

Phenytoin plasma concentrations may be increased by high doses of *oxcarbazepine*;[7] licensed product information for oxcarbazepine suggests that doses of phenytoin may need to be reduced when high doses of oxcarbazepine are given.

Phenobarbital both induces the metabolism of phenytoin and competes with it for metabolism by the same enzyme system; in practice there is rarely sufficient alteration for a change in phenytoin dosage to be necessary.[8-10] For the effect of phenytoin on phenobarbital, see p. 537.2. Phenytoin has also been reported to enhance the metabolism of *primidone* to phenobarbital, see p. 547.3.

The GABA agonist *progabide* increased blood-phenytoin concentrations[11] and *stiripentol* appears to produce a dose-dependent reduction in phenytoin clearance.[12]

Sultiame causes substantial increases in plasma-phenytoin concentrations, in some cases resulting in phenytoin toxicity;[13] the dose of phenytoin may therefore require adjustment if these drugs are given together.

Modest increases in plasma-phenytoin concentrations have occurred in some patients when *topiramate* was added to therapy, but it was considered that dosage adjustments were unlikely to be necessary.[14] For the effect of phenytoin on topiramate, see p. 552.3.

The interaction between phenytoin and *valproate* is complex. Valproate displaces phenytoin from serum binding sites and may inhibit its metabolism;[15] the former effect increases the concentration of free drug but reduces total serum phenytoin.[16,17] Most studies seem to suggest that the dose of phenytoin need only rarely be adjusted, but the possibility of loss of seizure control, or phenytoin toxicity, does exist.[15] Interestingly there is some evidence that the interactions may be affected by circadian variations in valproate concentrations.[18] Total plasma-phenytoin concentrations rose significantly in 9 of 11 patients, 2 of whom developed toxic symptoms, when the formulation of sodium valproate that they were taking with phenytoin was changed from a standard tablet to a slow-release form.[19] The authors hypothesised that reduced diurnal fluctuations in plasma-valproate concentrations due to the use of slow-release tablets reduced the displacement interaction between phenytoin and valproate, thereby increasing total plasma-phenytoin concentrations. Phenytoin may also cause a fall in serum concentrations of valproate—see p. 557.3.

Gradual or delayed reductions in plasma-phenytoin concentrations have been seen in several studies in patients given *vigabatrin*;[20] a review[20] states that concentrations have been reduced by 20 to 30%. The manufacturer of vigabatrin considers that this is unlikely to be of clinical significance although in a study the reduction was considered to compromise seizure control.[21]

1. Hansen JM, *et al.* Carbamazepine-induced acceleration of diphenylhydantoin and warfarin metabolism in man. *Clin Pharmacol Ther* 1971; 12: 539–43.
2. Windorfer A, Sauer W. Drug interactions during anticonvulsant therapy in childhood: diphenylhydantoin, primidone, phenobarbitone, clonazepam, nitrazepam, carbamazepin, and dipropylacetate. *Neuropaediatrie* 1977; 8: 29–41.
3. Zielinski JJ, *et al.* Carbamazepine-phenytoin interaction: elevation of plasma phenytoin concentrations due to carbamazepine comedication. *Ther Drug Monit* 1985; 7: 51–3.
4. Sheridan PH, *et al.* Open pilot study of felbamate (ADD03055) in partial seizures. *Epilepsia* 1986; 27: 649.
5. Wilensky AJ, *et al.* Pharmacokinetics of W-554 (ADD 03055) in epileptic patients. *Epilepsia* 1985; 26: 602–6.
6. Tyndel F. Interaction of gabapentin with other antiepileptics. *Lancet* 1994; 343: 1363–4.
7. Hossain M, *et al.* Drug-drug interaction profile of oxcarbazepine in children and adults. *Neurology* 1999; 52 (suppl 2): A525.
8. Morselli PL, *et al.* Interaction between phenobarbital and diphenylhydantoin in animals and in epileptic patients. *Ann N Y Acad Sci* 1971; 179: 88–107.
9. Cucinell SA, *et al.* Drug interactions in man: I. lowering effect of phenobarbital on plasma levels of bishydroxycoumarin (Dicumarol) and diphenylhydantoin (Dilantin). *Clin Pharmacol Ther* 1965; 6: 420–9.
10. Booker HE, *et al.* Concurrent administration of phenobarbital and diphenylhydantoin: lack of an interference effect. *Neurology* 1971; 21: 383–5.
11. Bianchetti G, *et al.* Pharmacokinetic interactions of progabide with other antiepileptic drugs. *Epilepsia* 1987; 28: 68–73.
12. Levy RH, *et al.* Stiripentol kinetics in epileptic patients: nonlinearity and interactions. *Epilepsia* 1984; 25: 657.
13. Hansen JM, *et al.* Sulthiame (Ospolot) as inhibitor of diphenylhydantoin metabolism. *Epilepsia* 1968; 9: 17–22.
14. Bourgeois BFD. Drug interaction profile of topiramate. *Epilepsia* 1996; 37 (suppl 2): S14–S17.
15. Levy RH, Koch KM. Drug interactions with valproic acid. *Drugs* 1982; 24: 543–56.
16. Monks A, Richens A. Effect of single doses of sodium valproate on serum phenytoin levels and protein binding in epileptic patients. *Clin Pharmacol Ther* 1980; 27: 89–95.
17. Perucca E, *et al.* Interaction between phenytoin and valproic acid: plasma protein binding and metabolic effects. *Clin Pharmacol Ther* 1980; 28: 779–89.
18. Riva R, *et al.* Time-dependent interaction between phenytoin and valproic acid. *Neurology* 1985; 35: 510–15.
19. Suzuki Y, *et al.* Interaction between valproate formulation and phenytoin concentrations. *Eur J Clin Pharmacol* 1995; 48: 61–3.
20. Grant SM, Heel RC. Vigabatrin: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in epilepsy and disorders of motor control. *Drugs* 1991; 41: 889–926.
21. Browne TR, *et al.* Vigabatrin for refractory complex partial seizures: multicenter single-blind study with long-term follow-up. *Neurology* 1987; 37: 184–9.

Antifungals. There have been several reports of interactions, sometimes resulting in phenytoin toxicity, between imidazole antifungals and phenytoin. The drug most frequently implicated is *miconazole*.[1-3] The related triazole antifungals *fluconazole*[4-6] and *voriconazole*[7] are also reported to interact with phenytoin,[4-6] possibly due to dose-related inhibition of cytochrome P450 isoenzymes by these antifungals.[4,7]

Phenytoin can decrease plasma concentrations of azole antifungals such as *ketoconazole*, voriconazole, and *itraconazole*.

1. Bourgoin B, *et al.* Interaction pharmacocinétique possible phénytoïne-miconazole. *Therapie* 1981; 36: 347–9.
2. Loupi E, *et al.* Interactions médicamenteuses et miconazole. *Therapie* 1982; 37: 437–41.
3. Rolan PE, *et al.* Phenytoin intoxication during treatment with parenteral miconazole. *BMJ* 1983; 287: 1760.
4. Mitchell AS, Holland JT. Fluconazole and phenytoin: a predictable interaction. *BMJ* 1989; 298: 1315.
5. Howitt KM, Oziemski MA. Phenytoin toxicity induced by fluconazole. *Med J Aust* 1989; 151: 603–4.
6. Cadle RM, *et al.* Fluconazole-induced symptomatic phenytoin toxicity. *Ann Pharmacother* 1994; 28: 191–3.
7. Purkins L, *et al.* Coadministration of voriconazole and phenytoin: pharmacokinetic interaction, safety, and toleration. *Br J Clin Pharmacol* 2003; 56 (suppl 1): 37–44.

Antigout drugs. Licensed product information for *sulfinpyrazone* states that it displaces phenytoin from its protein-binding sites, and also inhibits microsomal liver enzymes. The net result is an increase in plasma-phenytoin concentrations and a prolonged half-life, which is potentially hazardous.

Reduced doses of phenytoin were necessary to avoid toxicity when *allopurinol* was added to the therapy of a child with the Lesch-Nyhan syndrome.[1] Although the authors thought caution was advisable in using these two drugs together, they did emphasise that overgeneralisation may be dangerous since the child also received other antiepileptics and the role his disease may have played was unknown.

1. Yokochi K, *et al.* Phenytoin-allopurinol interaction: Michaelis-Menten kinetic parameters of phenytoin with and without allopurinol in a child with Lesch-Nyhan syndrome. *Ther Drug Monit* 1982; 4: 353–7.

Antihistamines. A young woman developed drowsiness, ataxia, diplopia, tinnitus, and episodes of occipital headaches associated with vomiting after taking phenytoin sodium and *chlorphenamine*.[1] Chlorphenamine might have delayed the hepatic metabolism of phenytoin thereby increasing the plasma concentrations.

1. Pugh RNH, *et al.* Interaction of phenytoin with chlorpheniramine. *Br J Clin Pharmacol* 1975; 2: 173–5.

Antihypertensives. In 2 patients with hypoglycaemia associated with hyperinsulinism, therapeutic serum-phenytoin concentrations could not be achieved while they were also receiving *diazoxide*.[1] It was suggested that an increased rate of metabolism, and possibly a decreased binding, of phenytoin induced by diazoxide might have been responsible.

1. Roe TF, *et al.* Drug interaction: diazoxide and diphenylhydantoin. *J Pediatr* 1975; 87: 480–4.

Antimalarials. Antimalarials may antagonise the antiepileptic activity of phenytoin by lowering the convulsive threshold.

Antineoplastics. There have been reports of decreased plasma-phenytoin concentrations associated with cancer chemotherapy,[1-4] resulting in some cases in loss of seizure control.[2-4] The effect appears to be due to impaired absorption of phenytoin arising from antineoplastic damage to the gastrointestinal mucosa. In a patient a mean of 32% of an oral dose of phenytoin was absorbed after therapy with *cisplatin, vinblastine,* and *bleomycin*; this compared with a reported oral bioavailability of 80% or more.[3] *Trabectedin* may also reduce phenytoin absorption leading to an exacerbation of seizures.

Some licensed product information for *levamisole* reports that increased plasma-phenytoin concentrations have been seen in patients taking phenytoin with levamisole given as an adjuvant to *fluorouracil* therapy. Treatment with fluorouracil (alone or with folinic acid) has also led to phenytoin toxicity in patients on long-term antiepileptic therapy.[5-7] Similar interactions have occurred with *doxifluridine*[8] and *capecitabine*[7] (both prodrugs of fluorouracil), and a combination preparation containing *tegafur* (a prodrug of fluorouracil) with *uracil*. However, a decrease in phenytoin serum concentrations has been seen when such a preparation was given with folinic acid to a patient receiving the antiepileptic.[9] For the potential effect of phenytoin on *busulfan*, see Effects on the Nervous System, under Adverse Effects of Busulfan, p. 755.3. For the effect of phenytoin on the use of *streptozocin* and on *teniposide*, see p. 859.1 and p. 867.2, respectively.

1. Pincham RW, Schottelius DD. Decreased phenytoin levels in antineoplastic therapy. *Ther Drug Monit* 1979; 1: 277–83.
2. Bollini P, *et al.* Decreased phenytoin level during antineoplastic therapy: a case report. *Epilepsia* 1983; 24: 75–8.
3. Sylvester RK, *et al.* Impaired phenytoin bioavailability secondary to cisplatinum, vinblastine, and bleomycin. *Ther Drug Monit* 1984; 6: 302–5.
4. Grossman SA, *et al.* Decreased phenytoin levels in patients receiving chemotherapy. *Am J Med* 1989; 87: 505–10.
5. Gilbar PJ, Brodribb TR. Phenytoin and fluorouracil interaction. *Ann Pharmacother* 2001; 35: 1367–70.
6. Rosemergy I, Findlay M. Phenytoin toxicity as a result of 5-fluorouracil administration. *N Z Med J* 2002; 115: U124.
7. Brickell K, *et al.* Phenytoin toxicity due to fluoropyrimidines (5FU/capecitabine): three case reports. *Br J Cancer* 2003; 89: 615–16.
8. Konishi H, *et al.* Probable metabolic interaction of doxifluridine with phenytoin. *Ann Pharmacother* 2002; 36: 831–4.
9. Veldhorst-Janssen NML, *et al.* Oral tegafur/folinic acid chemotherapy decreases phenytoin efficacy. *Br J Cancer* 2004; 90: 745.

Antiprotozoals. Conflicting results have been reported with *metronidazole*: while one study has suggested only minimal effects on phenytoin concentrations and metabolism,[1] another has indicated inhibition of the metabolism of phenytoin.[2] For the effect of phenytoin on metronidazole, see p. 939.2.

1. Jensen JC, Gugler R. Interaction between metronidazole and drugs eliminated by oxidative metabolism. *Clin Pharmacol Ther* 1985; 37: 407–10.
2. Blyden GT, *et al.* Metronidazole impairs clearance of phenytoin but not of alprazolam or lorazepam. *Clin Pharmacol Ther* 1986; 39: 181.

Antipsychotics. As with all antiepileptics, antipsychotics may antagonise the antiepileptic activity of phenytoin by lowering the convulsive threshold. Two cases of phenytoin toxicity and elevated plasma-phenytoin concentrations associated with the phenothiazine *thioridazine* have been reported;[1] but another study indicated that *thioridazine, chlorpromazine,* or *mesoridazine* reduced serum-phenytoin concentrations.[2]

The non-phenothiazine antipsychotic *loxapine* has also been implicated as producing a fall in serum-phenytoin concentration.[3]

For the effect of phenytoin on antipsychotics in general, see under Chlorpromazine, p. 1052.2. For the effect of phenytoin on *clozapine*, see p. 1061.3.

1. Vincent FM. Phenothiazine-induced phenytoin intoxication. *Ann Intern Med* 1980; 93: 56–7.
2. Haidukewych D, Rodin EA. Effect of phenothiazines on serum antiepileptic drug concentrations in psychiatric patients with seizure disorder. *Ther Drug Monit* 1985; 7: 401–4.
3. Ryan GM, Matthews PA. Phenytoin metabolism stimulated by loxapine. *Drug Intell Clin Pharm* 1977; 11: 428–9.

Antivirals. *Zidovudine* may possibly reduce or increase plasma concentrations of phenytoin. There has been a report[1] of markedly decreased serum-phenytoin concentrations resulting in a recurrence of seizure activity in an epileptic patient after starting *nelfinavir* as part of antiretroviral therapy. Serum concentrations of phenytoin and valproate decreased[2,3] in 2 reports in children after the addition of *aciclovir*. *Ritonavir-boosted lopinavir* was reported[4] to increase the clearance of phenytoin in healthy subjects, probably due to hepatic enzyme induction; phenytoin similarly increased the clearance of the HIV-protease inhibitor. A case report[5] described the inhibition of phenytoin clearance by *efavirenz* resulting in elevated phenytoin plasma concentrations, and subtherapeutic levels of efavirenz resulting from hepatic enzyme induction by phenytoin.

For the possible effect of phenytoin on HIV-protease inhibitors, see p. 987.3.

1. Honda M, *et al.* A generalized seizure following initiation of nelfinavir in a patient with human immunodeficiency virus type 1 infection, suspected due to interaction between nelfinavir and phenytoin. *Intern Med* 1999; 38: 302–3.
2. Parmeggiani A, *et al.* Possible interaction between acyclovir and antiepileptic treatment. *Ther Drug Monit* 1995; 17: 312–15.
3. Iglesias Iglesias A-A, *et al.* Disminución de la concentración sérica de antiepilépticos durante el tratamiento con aciclovir. *Med Clin (Barc)* 2005; 124: 355–6.
4. Lim ML, *et al.* Coadministration of lopinavir/ritonavir and phenytoin results in two-way drug interaction through cytochrome P-450 induction. *J Acquir Immune Defic Syndr* 2004; 36: 1034–40.
5. Robertson SM, *et al.* A potentially significant interaction between efavirenz and phenytoin: a case report and review of the literature. *Clin Infect Dis* 2005; 41: e15–e18.

Anxiolytics. See Benzodiazepines, below.

Benzodiazepines. The metabolism of benzodiazepines may be enhanced as a result of induction of hepatic drug-metabolising enzymes after long-term use of phenytoin. In comparison with healthy subjects, half-lives have been shorter and clearance increased.[1,2]

There are sporadic reports of interactions between phenytoin and benzodiazepines, but the evidence is conflicting. Elevated plasma concentrations of phenytoin have been reported in patients given *diazepam*[3,4] or *chlordiazepoxide*[3] but, in contrast, another study suggested that these drugs produced a significant fall in serum-phenytoin concentrations.[5] It has been suggested that phenytoin intoxication could result from the impaired metabolism associated with the combination[3,4,6] but in practice this seems to be uncommon. There are similar conflicting reports for *clonazepam*.[7-9]

1. Dhillon S, Richens A. Pharmacokinetics of diazepam in epileptic patients and normal volunteers following intravenous administration. *Br J Clin Pharmacol* 1981; 12: 841–4.
2. Scott AK, *et al.* Oxazepam pharmacokinetics in patients with epilepsy treated long-term with phenytoin alone or in combination with phenobarbitone. *Br J Clin Pharmacol* 1983; 16: 441–4.
3. Vajda FJE, *et al.* Interaction between phenytoin and the benzodiazepines. *BMJ* 1971; 1: 346.
4. Murphy A, Wilbur K. Phenytoin-diazepam interaction. *Ann Pharmacother* 2003; 37: 659–63.
5. Houghton GW, Richens A. The effect of benzodiazepines and phenetoin on phenytoin metabolism in man. *Br J Clin Pharmacol* 1974; 1: 344P–345P.
6. Kutt H, McDowell F. Management of epilepsy with diphenylhydantoin sodium: dosage regulation for problem patients. *JAMA* 1968; 203: 969–72.
7. Eeg-Olofsson O. Experiences with Rivotril in treatment of epilepsy—particularly minor motor epilepsy—in mentally retarded children. *Acta Neurol Scand* 1973; 49 (suppl 53): 29–31.
8. Johannessen SI, *et al.* Lack of effect of clonazepam on serum levels of diphenylhydantoin, phenobarbital and carbamazepine. *Acta Neurol Scand* 1977; 55: 506–12.
9. Saavedra IN, *et al.* Phenytoin/clonazepam interaction. *Ther Drug Monit* 1985; 7: 481–4.

Calcium-channel blockers. Raised serum-phenytoin concentration with phenytoin toxicity developed in a patient who had been taking *nifedipine* in addition to phenytoin for 3 weeks;[1] symptoms resolved completely after nifedipine withdrawal. The mechanism of interaction appeared to be complex. Similar effects have been reported with *diltiazem*[2] and *isradipine*.[3]

For the effect of phenytoin on dihydropyridine calcium-channel blockers, see under Nifedipine, p. 1453.3, and on verapamil, see p. 1525.2.

1. Ahmad S. Nifedipine-phenytoin interaction. *J Am Coll Cardiol* 1984; 3: 1582.
2. Bahls FH, *et al.* Interactions between calcium channel blockers and the anticonvulsants carbamazepine and phenytoin. *Neurology* 1991; 41: 740–2.
3. Cachat F, Tufro A. Phenytoin/isradipine interaction causing severe neurologic toxicity. *Ann Pharmacother* 2002; 36: 1399–1402.

Cardiac glycosides. For the effect of phenytoin on cardiac glycosides, see under Digoxin, p. 1357.1.

Corticosteroids. Serum concentrations of phenytoin have been elevated[1] or reduced[2-4] by *dexamethasone* and adjustment of phenytoin dosage may be required.[2-4] For the effect of phenytoin on corticosteroids, see p. 1619.3.

1. Lawson LA, *et al.* Phenytoin-dexamethasone interaction: a previously unreported observation. *Surg Neurol* 1981; 16: 23–4.
2. Wong DD, *et al.* Phenytoin-dexamethasone: a possible drug-drug interaction. *JAMA* 1985; 254: 2062–3.
3. Recuenco L, *et al.* Effect of dexamethasone on the decrease of serum phenytoin concentrations. *Ann Pharmacother* 1995; 29: 935.
4. Lackner TE. Interaction of dexamethasone with phenytoin. *Pharmacotherapy* 1991; 11: 344–7.

Dermatological drugs. For the effect of phenytoin on *methoxsalen*, see p. 1713.3.

Disulfiram. A well-documented interaction exists between phenytoin and disulfiram, which may result in clinical phenytoin toxicity.[1,2] The effect appears to be due to non-competitive inhibition of the metabolism of phenytoin by disulfiram,[2] which results in a substantial increase in phenytoin half-life and a decrease in its clearance.[3]

1. Dry J, Pradalier A. Intoxication par la phénytoïne au cours d'une association thérapeutique avec le disulfirame. *Therapie* 1973; 28: 795–802.
2. Taylor JW, *et al.* Mathematical analysis of a phenytoin-disulfiram interaction. *Am J Hosp Pharm* 1981; 38: 93–5.
3. Svendsen TL, *et al.* The influence of disulfiram on the half-life and metabolic clearance rate of diphenylhydantoin and tolbutamide in man. *Eur J Clin Pharmacol* 1976; 9: 439–41.

Diuretics. Severe osteomalacia in 2 previously active young women taking *acetazolamide* with phenytoin or primidone and phenobarbital has been reported.[1]

For the effect of antiepileptics such as phenytoin on *furosemide*, see p. 1390.1.

1. Mallette LE. Anticonvulsants, acetazolamide and osteomalacia. *N Engl J Med* 1975; 293: 668.

Dopaminergics. For the effect of phenytoin on *levodopa*, see p. 907.2.

Enteral and parenteral nutrition. Therapeutic plasma concentrations of phenytoin may be difficult to achieve in patients receiving enteral or total parenteral nutrition.[1,2] Incompatibility studies indicate that phenytoin probably binds to components of the feed (see Incompatibilities, p. 538.3), which might explain this interaction when both are given together nasogastrically, but the same effect has also been reported when they were given separately by the intravenous route.[2] A review[3] of case reports and studies concluded that the exact role of enteral feeding in this interaction still remained unclear because of a lack of prospective, randomised, controlled studies performed in patients, rather than in healthy subjects. However, because of the amount of literature describing such a phenomenon, it was considered unlikely to occur just by chance. Monitoring of serum-phenytoin concentrations to guide therapy was recommended, and measures such as staggering phenytoin and enteral feeding might be considered to minimise the occurrence of this reaction.

1. Summers VM, Grant R. Nasogastric feeding and phenytoin interaction. *Pharm J* 1989; 243: 181.
2. Messahel FM, *et al.* Does total parenteral nutrition lower serum phenytoin levels? *Curr Ther Res* 1990; 47: 1017–20.
3. Au Yeung SC, Ensom MH. Phenytoin and enteral feedings: does evidence support an interaction? *Ann Pharmacother* 2000 34: 896–905

Gastrointestinal drugs. Evidence for an interaction between phenytoin and *antacids* is conflicting. Some studies have shown a decrease in the bioavailability of phenytoin given with various antacid mixtures[1,2] but others have failed to find any evidence of reduced absorption.[3] Furthermore even those studies that recorded decreased absorption varied in their results with regard to particular drugs, suggesting for example that calcium carbonate both does[1] and does not[2] reduce phenytoin bioavailability. The clinical significance of these data is uncertain but it has been suggested that if antacids and phenytoin are both needed, doses should be spaced several hours apart.[4,5] *Sucralfate* is also reported to reduce phenytoin absorption.[6]

A well documented interaction exists between phenytoin and *cimetidine*, which produces a dose-dependent reduction in phenytoin clearance[7] and a significant elevation of serum-phenytoin concentration.[8] There are reports of phenytoin toxicity when cimetidine was given to epileptic patients[9,10] including a report of severe granulocytopenia.[11] Although some studies have found that neither *ranitidine*[12] nor *famotidine*[13] appear to affect the pharmacokinetics of phenytoin significantly, there have been isolated reports of raised plasma concentrations of phenytoin associated with use of ranitidine[14-16] or famotidine.[17]

Omeprazole 40 mg daily can decrease the plasma clearance of phenytoin[18] and increase the area under the serum-phenytoin concentration-time curve,[19] but one study[20] suggests that the dosage of 20 mg daily usually used for peptic ulcer disease is unlikely to produce a clinically significant effect on the steady-state plasma concentrations of phenytoin in patients with epilepsy.

1. Garnett WR, *et al.* Bioavailability of phenytoin administered with antacids. *Ther Drug Monit* 1979; 1: 435–6.
2. Kulshrestha VK, *et al.* Interaction between phenytoin and antacids. *Br J Clin Pharmacol* 1978; 6: 177–9.
3. O'Brien LS, *et al.* Failure of antacids to alter the pharmacokinetics of phenytoin. *Br J Clin Pharmacol* 1978; 6: 176–7.
4. Cacek AT. Review of alterations in oral phenytoin bioavailability associated with formulation, antacids, and food. *Ther Drug Monit* 1986; 8: 166–71.
5. D'Arcy PF, McElnay JC. Drug-antacid interactions: assessment of clinical importance. *Drug Intell Clin Pharm* 1987; 21: 607–17.
6. Smart HL, *et al.* The effects of sucralfate upon phenytoin absorption in man. *Br J Clin Pharmacol* 1985; 20: 238–40.
7. Bartle WR, *et al.* Dose-dependent effect of cimetidine on phenytoin kinetics. *Clin Pharmacol Ther* 1983; 33: 649–55.
8. Iteogu MO, *et al.* Effect of cimetidine on single-dose phenytoin kinetics. *Clin Pharm* 1983; 2: 302–4.
9. Phillips P, Hansky J. Phenytoin toxicity secondary to cimetidine administration. *Med J Aust* 1984; 141: 602.
10. Hetzel DJ, *et al.* Cimetidine interaction with phenytoin. *BMJ* 1981; 282: 1512.

11. Sazie E, Jaffe JP. Severe granulocytopenia with cimetidine and phenytoin. *Ann Intern Med* 1980; 93: 151–2.
12. Watts RW, *et al.* Lack of interaction between ranitidine and phenytoin. *Br J Clin Pharmacol* 1983; 15: 499–500.
13. Sambol NC, *et al.* A comparison of the influence of famotidine and cimetidine on phenytoin elimination and hepatic blood flow. *Br J Clin Pharmacol* 1989; 27: 83–7.
14. Bramhall D, Levine M. Possible interaction of ranitidine with phenytoin. *Drug Intell Clin Pharm* 1988; 22: 979–80.
15. Tse CST, *et al.* Phenytoin concentration elevation subsequent to ranitidine administration. *Ann Pharmacother* 1993; 27: 1448–51.
16. Tse CST, Lagmin P. Phenytoin and ranitidine interaction. *Ann Intern Med* 1994; 120: 892–3.
17. Shinn AF. Unrecognized drug interactions with famotidine and nizatidine. *Arch Intern Med* 1991; 151: 814.
18. Gugler R, Jensen JC. Omeprazole inhibits oxidative drug metabolism: studies with diazepam and phenytoin in vivo and 7-ethoxycoumarin in vitro. *Gastroenterology* 1985; 89: 1235–41.
19. Prichard PJ, *et al.* Oral phenytoin pharmacokinetics during omeprazole therapy. *Br J Clin Pharmacol* 1987; 24: 543–5.
20. Andersson T, *et al.* A study of the interaction between omeprazole and phenytoin in epileptic patients. *Ther Drug Monit* 1990; 12: 329–33.

Ginkgo biloba. A fatal breakthrough seizure occurred[1] in a 55-year-old man who was taking phenytoin and valproate semisodium for a seizure disorder; he was also taking non-prescription supplements, such as vitamin preparations and herbal medicines including ginkgo biloba extract, without the knowledge of his physician. Autopsy revealed subtherapeutic plasma concentrations of both antiepileptics. Although the exact cause was unclear, the authors postulated that hepatic enzyme induction by ginkgo biloba might have increased the clearance of phenytoin and valproate semisodium.

1. Kupiec T, Raj V. Fatal seizures due to potential herb-drug interactions with ginkgo biloba. *J Anal Toxicol* 2005; 29: 755–8.

Immunosuppressants. Increased plasma-phenytoin concentrations were reported[1] in one patient when *tacrolimus* was added to existing therapy. Phenytoin was stopped until values were within the therapeutic range and then restarted at a lower dose, tacrolimus therapy continuing throughout; phenytoin levels remained stable thereafter.

For the effect of phenytoin on *ciclosporin*, see p. 1956.3.

1. Thompson PA, Mosley CA. Tacrolimus-phenytoin interaction. *Ann Pharmacother* 1996; 30: 544.

Levothyroxine. For the effects of phenytoin on levothyroxine, see p. 2341.3.

Muscle relaxants. An increase in serum concentrations of phenytoin has been reported[1] in a patient when *tizanidine* was added to therapy.

1. Ueno K, *et al.* Phenytoin-tizanidine interaction. *DICP Ann Pharmacother* 1991; 25: 1273.

Neuromuscular blockers. For the effect of phenytoin on *suxamethonium*, see p. 2039.3 and on *competitive neuromuscular blockers*, see under Atracurium, p. 2032.1.

Sex hormones. For the effect of phenytoin on *oral contraceptives*, see p. 2243.2. Similar effects may also be noted in patients receiving *HRT*, see p. 2251.1.

Stimulants and anorectics. Although there has been a report of elevated phenytoin and primidone serum concentrations in a 5-year-old after addition of *methylphenidate* to therapy[1] there was no similar elevation in 2 other children receiving phenobarbital and phenytoin in the same report, nor in 11 patients of varying ages given methylphenidate with antiepileptic therapy as part of a controlled study.[2] The likelihood of an interaction seems small in the majority of patients.

1. Garrettson LK, *et al.* Methylphenidate interaction with both anticonvulsants and ethyl biscoumacetate. *JAMA* 1969; 207: 2053–6.
2. Kupferberg HJ, *et al.* Effect of methylphenidate on plasma anticonvulsant levels. *Clin Pharmacol Ther* 1972; 13: 201–4.

Theophylline. Although most reports of an interaction between phenytoin and theophylline concern effects on theophylline concentrations, one study in 14 healthy subjects suggested that treatment with both could lower serum-phenytoin concentrations, with a subsequent rise in concentration on stopping theophylline.[1] The mechanism was suggested to be enzyme induction by the xanthine resulting in increased phenytoin metabolism.

For the effect of phenytoin on theophylline, see p. 1235.1.

1. Taylor JW, *et al.* The interaction of phenytoin and theophylline. *Drug Intell Clin Pharm* 1980; 14: 638.

Ticlopidine. Acute phenytoin toxicity has been reported in a well-stabilised 44-year-old patient on introduction of ticlopidine to prevent restenosis after placement of a coronary stent.[1] The patient also took metoprolol, aspirin, and for a short period lovastatin, but inhibition of the cytochrome P450 isoenzyme CYP2C19 by ticlopidine was considered the most likely cause of the patient's elevated serum phenytoin. A later report[2] by the same authors found that ticlopidine inhibited the clearance of phenytoin in 6 patients on phenytoin monotherapy; the involvement of CYP2C19 was also supported. The authors recommended that dosage adjustment of phenytoin should be considered if ticlopidine is also given.

A similar interaction occurred in a 72-year-old patient,[3] and the authors postulated that, since steady-state plasma concentrations of ticlopidine are almost twofold higher in elderly patients than those in younger patients, the higher ticlopidine concentrations may have played a role in this drug interaction.

1. Donahue SR, *et al.* Ticlopidine inhibition of phenytoin metabolism mediated by potent inhibition of CYP2C19. *Clin Pharmacol Ther* 1997; 62: 572–7.
2. Donahue S, *et al.* Ticlopidine inhibits phenytoin clearance. *Clin Pharmacol Ther* 1999; 66: 563–8.
3. Klaassen SL. Ticlopidine-induced phenytoin toxicity. *Ann Pharmacother* 1998; 32: 1295–8.

Vaccines. Contradictory results have been reported for the effects of *influenza vaccine* on serum-phenytoin concentrations. A significant elevation in total phenytoin concentration has been reported[1] after vaccination, and was suggested to be due to interferon induction and inhibition of the cytochrome P450 enzyme system. In contrast, other reports have suggested that any increase in serum-phenytoin concentration was temporary and not significant overall[2] or even that there was a slight fall in serum-phenytoin concentration.[3] One study reported a significant increase in total phenytoin concentration two days after vaccination, followed by a return to previous values but this was accompanied by evidence of a gradual and prolonged fall in free phenytoin concentrations.[4] The possibility of either phenytoin toxicity or loss of seizure control may exist in some epileptic patients given influenza vaccine during phenytoin therapy.[5]

1. Jann MW, Fidone GS. Effect of influenza vaccine on serum anticonvulsant concentrations. *Clin Pharm* 1986; 5: 817–20.
2. Levine M, *et al.* Increased serum phenytoin concentration following influenza vaccination. *Clin Pharm* 1984; 3: 505–9.
3. Sawchuk RJ, *et al.* Effect of influenza vaccination on plasma phenytoin concentrations. *Ther Drug Monit* 1979; 1: 285–8.
4. Smith CD, *et al.* Effect of influenza vaccine on serum concentrations of total and free phenytoin. *Clin Pharm* 1988; 7: 828–32.
5. Grabenstein JD. Drug interactions involving immunologic agents, part 1: vaccine-vaccine, vaccine-immunoglobulin, and vaccine-drug interactions. *DICP Ann Pharmacother* 1990; 24: 67–81.

Vitamins. *Pyridoxine* given in large doses produced a reduction in serum-phenytoin concentrations in 7 patients,[1] perhaps reflecting increased activity by pyridoxal phosphate-dependent enzymes involved in phenytoin metabolism.

Correction of antiepileptic-associated folate deficiency with *folic acid* has been reported to result in a decrease in serum-phenytoin concentrations and an increase in seizure frequency.[2-4] The effect has been reported to be most marked in subjects with high initial serum-phenytoin concentrations[5] and is associated with an increased phenytoin metabolism.[4,6] However, in the majority of patients the effect is unlikely to assume clinical significance,[2,5] and there is some evidence that very low doses of folic acid may be used to maintain normal serum-folate values without an increase in seizure frequency.[3] Information regarding the dual and interdependent interaction between phenytoin and folic acid has been reviewed.[7] Although limited numbers of patients and healthy subjects were involved, evaluation of the data suggested that starting phenytoin and folic acid at the same time prevents decreased folate levels and steady-state concentrations of phenytoin are reached sooner. Plasma concentrations of phenytoin are also possibly reduced by *folinic acid* (see also Antineoplastics, p. 544.1).

For the effect of antiepileptics, including phenytoin, on *vitamin D* concentrations, see Effects on Bone, under Adverse Effects, p. 540.2.

1. Hansson O, Sillanpaa M. Pyridoxine and serum concentration of phenytoin and phenobarbitone. *Lancet* 1976; i: 256.
2. Baylis EM, *et al.* Influence of folic acid on blood-phenytoin levels. *Lancet* 1971; i: 62–4.
3. Inoue F. Clinical implications of anticonvulsant-induced folate deficiency. *Clin Pharm* 1982; 1: 372–3.
4. Steinweg DL, Bentley ML. Seizures following reduction in phenytoin level after orally administered folic acid. *Neurology* 2005; 64: 1982.
5. Furlanut M, *et al.* Effects of folic acid on phenytoin kinetics in healthy subjects. *Clin Pharmacol Ther* 1978; 24: 294–7.
6. Berg MJ, *et al.* Phenytoin and folic acid interaction: a preliminary report. *Ther Drug Monit* 1983; 5: 389–94.
7. Lewis DP, *et al.* Phenytoin-folic acid interaction. *Ann Pharmacother* 1995; 29: 726–35.

Pharmacokinetics

Phenytoin is slowly but almost completely absorbed from the gastrointestinal tract. It is largely insoluble at the acid pH of the stomach, most being absorbed from the upper intestine; the rate of absorption is variable and is reported to be affected by the presence of food. Absorption after intramuscular injection is slower than that from the gastrointestinal tract.

Phenytoin is extensively metabolised in the liver to inactive metabolites, chiefly 5-(4-hydroxyphenyl)-5-phenylhydantoin. The rate of metabolism appears to be subject to genetic polymorphism and may also be influenced by racial characteristics; it is reported to be increased during pregnancy and menstruation and to decrease with age. Phenytoin hydroxylation is saturable and is therefore readily inhibited by drugs that compete for its metabolic pathways; this is also the reason why small increments in dose may produce large rises in plasma concentration. Phenytoin undergoes enterohepatic recycling and is excreted in the urine, mainly as its hydroxylated metabolite, in either free or conjugated form.

Phenytoin is widely distributed throughout the body. It is about 90% bound to plasma proteins, although this may be reduced in certain disease states and in certain patient populations (see Precautions, p. 541.3). It has a very variable, dose-dependent half-life, but the mean plasma half-life appears to be about 22 hours at steady state; because phenytoin inhibits its own metabolism it may sometimes be several weeks before a steady-state plasma-phenytoin concentration is attained.

Monitoring of plasma concentrations may be performed as an aid in assessing control, and the therapeutic range of total plasma-phenytoin concentrations is usually quoted as 10 to 20 micrograms/mL (40 to 80 micromoles/litre); some patients, however, achieve control at concentrations outside this range. It has been suggested that, because of differences in protein binding, measurement of free phenytoin concentrations in plasma may prove more reliable; measurement of concentrations in saliva, which contains only free phenytoin, has also been performed.

Phenytoin crosses the placental barrier and small amounts are distributed into breast milk.

The pharmacokinetics of phenytoin are affected by other antiepileptics (see Interactions, p. 542.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Epamin; Etoina; Fenigramon; Fenitenk; Lotoquis Simple; Opliphon; *Austral.*: Dilantin; *Austria*: Epanutin; Epilan-D; *Belg.*: Diphantoine; Epanutin; *Braz.*: Dantalin; Epelin; Fenital; Peniton; Hidantal; Unifenitoin; *Canad.*: Dilantin; Tremytoine; *Chile*: Epamin; *Cz.*: Epanutin; Epilan D; *Fin.*: Hydantin; *Fr.*: Di-Hydan; Dilantin; *Ger.*: Phenhydan; Zentropil†; *Gr.*: Epanutin; *Hong Kong*: Dilantin; Ditoin; *Hung.*: Diphedan; Epanutin; *India*: Dilantin; Epicent; Epileptin; Episol; Epitab; Epsolin; Eptoin; Fentoin; Gentoin; M-Toin; Neptoin; Nutoin; *Indon.*: Dilantin; Ikaphen; Kutoin; Movileps; Phenilep†; *Irl.*: Epanutin; *Israel*: Dilantin; Epanutin; *Ital.*: Aurantin; Dintoina; *Jpn*: Aleviatin; *Malaysia*: Dilantin; Ditoin; *Mex.*: Biodan; Comvufen; Epamin; Fenidantoin S; Feniffler; Fenitron; Hidantoina; *Neth.*: Diphantoine; Epanutin; *Norw.*: Epinat; *NZ*: Dilantin; *Philipp.*: Dilantin; Epilantin†; Fenitin; Lantidin; *Pol.*: Epanutin; *Port.*: Fenitan; Hidantina; *S.Afr.*: Epanutin; *Singapore*: Dilantin; *Spain*: Epanutin; Sinergina; *Swed.*: Epanutin; Fenantoin; Lehydan; *Switz.*: Phenhydan; *Thai.*: Dantoin; Dilantin; Ditoin; Ditomed†; Pepsytoin; Utoin; *Turk.*: Epanutin; Epdantoin; Hidantin; Phenhydan; *UK*: Epanutin; *USA*: Dilantin; Phenytek; *Venez.*: Dantoinal; Dilantin; Epamin; Fentoinal.

Multi-ingredient Preparations. *Arg.*: Cumatil-L†; Lotoquis; *Belg.*: Vethoine; *Braz.*: Dialudon; *China*: Di Er Kang Xin (迪尔康欣); *Cz.*: Sanepil†; *Gr.*: Diphenal; *India*: Barbitoin; Dilantin with Phenobarbital†; Epilan C; Epiphen; Episol Plus; Garoin; *Indon.*: Ditalin; *Ital.*: Dintoinale; Gamibetal Complex; Metinal-Idantoina L; Metinal-Idantoina; *Mex.*: Alepsal Compuesto; Gamibetal Complex†; *Spain*: Redutona†.

Pharmacopoeial Preparations

BP 2014: Phenytoin Capsules; Phenytoin Injection; Phenytoin Oral Suspension; Phenytoin Tablets;

USP 36: Extended Phenytoin Sodium Capsules; Phenytoin Oral Suspension; Phenytoin Sodium Injection; Phenytoin Tablets; Prompt Phenytoin Sodium Capsules.

Pregabalin *(BAN, USAN, rINN)*

CI-1008; PD-144723; Pregabalina; Prégabaline; Pregabalinum; Прегабалин.

(*S*)-3-(Aminomethyl)-5-methylhexanoic acid.

$C_8H_{17}NO_2$=159.2

CAS — 148553-50-8.

ATC — N03AX16.

ATC Vet — QN03AX16.

UNII — 55JG375S6M.

Uses and Administration

Pregabalin is an antiepileptic used as an adjunct in the treatment of partial seizures with or without secondary generalisation (p. 546.1). It is also used in the treatment of generalised anxiety disorder (p. 546.1), neuropathic pain (p. 546.1), and fibromyalgia (see Soft-tissue Rheumatism, p. 546.2).

Pregabalin is given orally in 2 or 3 divided doses daily.

The initial dose in the treatment of **epilepsy** is 150 mg daily increased after 1 week according to response to 300 mg daily and then to 600 mg daily after another week.

In the treatment of **generalised anxiety disorder**, the initial dose is 150 mg daily; this may be increased at weekly intervals in steps of 150 mg, to a maximum of 600 mg daily.

For **neuropathic pain** the initial dose in the UK is 150 mg daily increased after 3 to 7 days according to response to 300 mg daily and then to 600 mg daily after another 7 days. Similar doses are licensed in the USA for the treatment of neuropathic pain in diabetic neuropathy, postherpetic neuralgia, and spinal cord injury, although a maximum daily dose of 300 mg is recommended in diabetic neuropathy.

For **fibromyalgia** the initial dose is 150 mg daily increased after 1 week according to response to 300 mg daily and then to 450 mg daily if necessary.

Dosage of pregabalin should be reduced in patients with renal impairment (see below).

As with other antiepileptics, withdrawal of pregabalin therapy in epilepsy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1. Licensed product information states that if pregabalin therapy has to be stopped, this should be done gradually over a minimum of 1 week, regardless of indication.

References.

1. Shneker BF, McAuley JW. Pregabalin: a new neuromodulator with broad therapeutic indications. *Ann Pharmacother* 2005; 39: 2029–37.
2. Tassone DM, *et al.* Pregabalin: a novel gamma-aminobutyric acid analogue in the treatment of neuropathic pain, partial-onset seizures, and anxiety disorders. *Clin Ther* 2007; 29: 26–48.

Administration in renal impairment. The dose of pregabalin for patients with renal impairment should be reduced according to creatinine clearance (CC):

- CC 30 to less than 60 mL/minute: starting daily dose: 75 mg; maximum daily dose: 300 mg; daily dose given in 2 or 3 divided doses
- CC 15 to less than 30 mL/minute: starting daily dose: 25 to 50 mg; maximum daily dose: 150 mg; daily dose given in 2 divided doses or once daily
- CC less than 15 mL/minute: starting daily dose: 25 mg; maximum daily dose: 75 mg; daily dose given as one dose
- haemodialysis patients should receive in addition to the daily dose a supplementary dose of 25 to 100 mg immediately after each 4-hour haemodialysis session

Anxiety disorders. Pregabalin is used for the treatment of generalised anxiety disorder[1-3] (p. 1028.1); it has also been tried in social anxiety disorder[4-8] (see Phobic Disorders, p. 1029.1).

1. Owen RT. Pregabalin: its efficacy, safety and tolerability profile in generalized anxiety. *Drugs Today* 2007; 43: 601–10.
2. Montgomery S, *et al.* Efficacy and safety of pregabalin in elderly people with generalised anxiety disorder. *Br J Psychiatry* 2008; 193: 389–94.
3. Anonymous. Pregabalin for generalised anxiety disorder. *Drug Ther Bull* 2010; 48: 19–22.
4. Boschen MJ. A meta-analysis of the efficacy of pregabalin in the treatment of generalized anxiety disorder. *Can J Psychiatry* 2011; 56: 558–66.
5. Wensel TM, *et al.* Pregabalin for the treatment of generalized anxiety disorder. *Ann Pharmacother* 2012; 46: 424–9.
6. Pande AC, *et al.* Efficacy of the novel anxiolytic pregabalin in social anxiety disorder: a placebo-controlled, multicenter study. *J Clin Psychopharmacol* 2004; 24: 141–9.
7. Feltner DE, *et al.* Efficacy of pregabalin in generalized social anxiety disorder: results of a double-blind, placebo-controlled, fixed-dose study. *Int Clin Psychopharmacol* 2011; 26: 213–20.
8. Greist JH, *et al.* Efficacy of pregabalin in preventing relapse in patients with generalized social anxiety disorder: results of a double-blind, placebo-controlled 26-week study. *Int Clin Psychopharmacol* 2011; 26: 243–51.

Epilepsy. Pregabalin is one of the newer drugs used as adjunctive therapy in patients with partial seizures with or without secondary generalisation (p. 506.1). It appears to be reasonably well tolerated.

References.

1. Hamandi K, Sander JW. Pregabalin: a new antiepileptic drug for refractory epilepsy. *Seizure* 2006; 15: 73–8.
2. Lozsadi D, *et al.* Pregabalin add-on for drug-resistant partial epilepsy. Available in The Cochrane Database of Systematic Reviews: Issue 1. Chichester: John Wiley; 2008 (accessed 09/06/08).
3. Beydoun A, *et al.* Efficacy and tolerability of pregabalin in partial epilepsy. *Expert Rev Neurother* 2008; 8: 1013–24.
4. Arain AM. Pregabalin in the management of partial epilepsy. *Neuropsychiatr Dis Treat* 2009; 5: 407–13.
5. Gil-Nagel A, *et al.* Add-on treatment with pregabalin for partial seizures with or without generalisation: pooled data analysis of four randomised placebo-controlled trials. *Seizure* 2009; 18: 184–92.
6. Lee BI, *et al.* Pregabalin add-on therapy using a flexible, optimized dose schedule in refractory partial epilepsies: a double-blind, randomized, placebo-controlled, multicenter trial. *Epilepsia* 2009; 50: 464–74.

Neuropathic pain. Antiepileptics are among the drugs used to manage neuropathic pain, which is often insensitive to opioid analgesics (see Choice of Analgesic, p. 4.2). Pregabalin is used in the treatment of peripheral neuropathic pain[1] including postherpetic neuralgia[2-4] (p. 10.3) and painful diabetic neuropathy[5-7] (p. 8.2). It has been studied in the treatment of trigeminal neuralgia[8] (p. 11.2) and post-traumatic peripheral neuropathic pain.[9] Pregabalin may also be used in central neuropathic pain associated with spinal cord injury.[10,11] It has also been tried with some success in the management of central post-stroke pain[12] (p. 7.3). In the UK, NICE recommends pregabalin as first-line and second-line treatment for neuropathic pain in non-specialist settings.[13]

A systematic review[14] of the use of pregabalin in acute and chronic pain found that pregabalin in doses of 300 to 600 mg daily produced clear benefit in chronic neuropathic pain (painful diabetic neuropathy, postherpetic neuralgia, and to a lesser extent central neuropathic pain), and in fibromyalgia (see Soft-tissue Rheumatism, below), but the benefit was high only in a minority of patients, and effective doses were also associated with increased frequency of adverse effects such as dizziness and somnolence. There was no clear evidence of any benefit in acute postoperative pain (see also below).

1. Blommel ML, Blommel AL. Pregabalin: an antiepileptic agent useful for neuropathic pain. *Am J Health-Syst Pharm* 2007; 64: 1475–82.
2. Sabatowski R, *et al.* Pregabalin reduces pain and improves sleep and mood disturbances in patients with post-herpetic neuralgia: results of a randomised, placebo-controlled clinical trial. *Pain* 2004; 109: 26–35.
3. Frampton JE, Foster RH. Pregabalin: in the treatment of postherpetic neuralgia. *Drugs* 2005; 65: 111–18.
4. McKeage K, Keam SJ. Pregabalin: in the treatment of postherpetic neuralgia. *Drugs Aging* 2009; 26: 883–92.
5. Frampton JE, Scott LJ. Pregabalin: in the treatment of painful diabetic peripheral neuropathy. *Drugs* 2004; 64: 2813–20.
6. Freeman R, *et al.* Efficacy, safety, and tolerability of pregabalin treatment for painful diabetic peripheral neuropathy: findings from seven randomized, controlled trials across a range of doses. *Diabetes Care* 2008; 31: 1448–54.
7. Satoh J, *et al.* Efficacy and safety of pregabalin for treating neuropathic pain associated with diabetic peripheral neuropathy: a 14 week, randomized, double-blind, placebo-controlled trial. *Diabet Med* 2011; 28: 109–16.
8. Obermann M, *et al.* Efficacy of pregabalin in the treatment of trigeminal neuralgia. *Cephalalgia* 2008; 28: 174–81.
9. van Seventer R, *et al.* Pregabalin in the treatment of post-traumatic peripheral neuropathic pain: a randomized double-blind trial. *Eur J Neurol* 2010; 17: 1082–9.
10. Siddall PJ, *et al.* Pregabalin in central neuropathic pain associated with spinal cord injury: a placebo-controlled trial. *Neurology* 2006; 67: 1792–800.
11. Vranken JH, *et al.* Pregabalin in patients with central neuropathic pain: a randomized, double-blind, placebo-controlled trial of a flexible-dose regimen. *Pain* 2008; 136: 150–7.
12. Kim JS, *et al.* Safety and efficacy of pregabalin in patients with central post-stroke pain. *Pain* 2011; 152: 1018–23.
13. NICE. Neuropathic pain: the pharmacological management of neuropathic pain in adults in non-specialist settings (issued March 2010). Available at: http://www.nice.org.uk/nicemedia/live/12948/47949/47949.pdf (accessed 07/06/10)
14. Moore RA, *et al.* Pregabalin for acute and chronic pain in adults. Available in The Cochrane Database of Systematic Reviews: Issue 3. Chichester: John Wiley; 2009 (accessed 25/11/09).

Postoperative pain. There is growing interest in the use of analgesic adjuvants including antiepileptics such as pregabalin to modulate opioid dosage and efficacy for postoperative pain (p. 6.1). However, although pregabalin has been investigated for this purpose[1-3] a systematic review found no evidence to support such use (see Neuropathic Pain, above).

1. Dahl JB, *et al.* Protective premedication': an option with gabapentin and related drugs? A review of gabapentin and pregabalin in the treatment of post-operative pain. *Acta Anaesthesiol Scand* 2004; 48: 1130–6.
2. Tiippana EM, *et al.* Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. *Anesth Analg* 2007; 104: 1545–56.
3. Dauri M, *et al.* Gabapentin and pregabalin for the acute post-operative pain management: a systematic-narrative review of the recent clinical evidences. *Curr Drug Targets* 2009; 10: 716–33.

Restless legs syndrome. Pregabalin has been reported[1,2] to be of benefit in the treatment of restless legs syndrome (see Sleep-associated Movement Disorders, p. 1034.2).

1. Garcia-Borreguero D, *et al.* Treatment of restless legs syndrome with pregabalin: a double-blind, placebo-controlled study. *Neurology* 2010; 74: 1897–1904.
2. Allen R, *et al.* A randomized, double-blind, 6-week, dose-ranging study of pregabalin in patients with restless legs syndrome. *Sleep Med* 2010; 11: 512–19.

Soft-tissue rheumatism. Three large, multicentre controlled studies[1-3] have shown that pregabalin in oral doses of between 300 and 600 mg daily is effective in reducing pain and other core symptoms of fibromyalgia (p. 14.2) such as sleep disturbance and fatigue. A small study[4] suggested that it may also be of benefit in refractory disease. The drug was reported to be generally well tolerated, dizziness and somnolence being the most common adverse effects. Pain relief appears to be largely independent of reduction in anxiety or depression scores.[5,6] The use of pregabalin in fibromyalgia has been reviewed.[7,8] For a systematic review that also found some degree of benefit from the use of pregabalin in fibromyalgia see Neuropathic Pain, above.

Although pregabalin is licensed in some countries including the USA for the treatment of fibromyalgia, the EMEA did not authorise such use in the EU; after having reviewed the submitted studies (some of which are cited above), it considered that there were no consistent or relevant reductions in pain in short-term studies, and that maintenance of pregabalin's effect was not shown in a longer study.

1. Crofford LJ, *et al.* Pregabalin 1008-105 Study Group. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2005; 52: 1264–73.
2. Mease PJ, *et al.* A randomized, double-blind, placebo-controlled, phase III trial of pregabalin in the treatment of patients with fibromyalgia. *J Rheumatol* 2008; 35: 502–14.
3. Crofford LJ, *et al.* Fibromyalgia relapse evaluation and efficacy for durability of meaningful relief (FREEDOM): a 6-month, double-blind, placebo-controlled trial with pregabalin. *Pain* 2008; 136: 419–31.
4. Stacey BR, *et al.* Pregabalin in treatment-refractory fibromyalgia. *Open Rheumatol J* 2010; 4: 35–8.
5. Arnold LM, *et al.* The effect of anxiety and depression on improvement in pain in a randomized, controlled trial of pregabalin for treatment of fibromyalgia. *Pain Med* 2007; 8: 633–8.
6. Häuser W, *et al.* Treatment of fibromyalgia syndrome with gabapentin and pregabalin—a meta-analysis of randomized controlled trials. *Pain* 2009; 145: 69–81.
7. Lyseng-Williamson KA, Siddiqui MAA. Pregabalin: a review of its use in fibromyalgia. *Drugs* 2008; 68: 2205–23.
8. Boomershine CS. Pregabalin for the management of fibromyalgia syndrome. *J Pain Res* 2010; 3: 81–8.

Adverse Effects and Precautions

The most common adverse effects reported during therapy with pregabalin are dizziness and somnolence. Other common adverse effects include blurred vision, diplopia, increased appetite and weight gain, dry mouth, constipation (occasionally severe), vomiting, flatulence, euphoria, confusion, reduced libido, erectile dysfunction, irritability, vertigo, ataxia, tremor, dysarthria, paraesthesia, fatigue, and oedema. Disturbances of attention, memory, coordination, and gait also occur frequently. Syncope and congestive heart failure have been reported less frequently. Reversible renal failure, raised liver enzymes, elevation of creatine kinase concentration, and rhabdomyolysis have been reported rarely. Breast enlargement and gynaecomastia have also been reported. Hypersensitivity reactions have occurred shortly after starting pregabalin therapy; symptoms include rash, blisters, urticaria, dyspnoea, and wheezing. Stevens-Johnson syndrome has also been reported. An increased incidence of haemangiosarcoma occurred in *mice* that had been given high doses of pregabalin.

Licensed product information states that care is required when withdrawing pregabalin therapy, regardless of the indication—see also Uses and Administration, p. 545.3.

References.

1. Zaccara G, *et al.* The adverse event profile of pregabalin: a systematic review and meta-analysis of randomized controlled trials. *Epilepsia* 2011; 52: 826–36.

Breast feeding. For comment on antiepileptic therapy and breast feeding, see p. 508.3.

Driving. For a comment on antiepileptic drugs and driving, see p. 509.2.

Effects on mental function. For a review of the effects of antiepileptic therapy on *cognition*, and the effects of pregabalin on *mood* (including the risk of suicidal ideation), see p. 508.3.

Hypersensitivity reactions. The Australian Adverse Drug Reactions Advisory Committee[1] stated in December 2007 that 13% of all pregabalin adverse reaction reports in its database were hypersensitivity reactions. Presenting symptoms included anaphylaxis, skin rash, and angioedema. Of the 22 reports received, 6 women developed symptoms within hours of their first dose and pregabalin was the sole suspected drug in 14.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Reports of hypersensitivity reactions to pregabalin. *Aust Adverse Drug React Bull* 2007; 26: 23. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0712.pdf (accessed 09/06/08)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pregabalin as probably not porphyrinogenic: it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pregnancy. For comments on the management of epilepsy during pregnancy, see p. 509.2.

Pharmacokinetics

Pregabalin is rapidly absorbed after oral doses and peak plasma concentrations occur within 1.5 hours. Oral bioavailability is about 90%. The rate but not the extent of absorption is reduced if given with food but this is not clinically significant. Steady state is achieved after 1 to 2 days. Pregabalin is not bound to plasma proteins and undergoes negligible metabolism. About 98% of a dose is excreted in the urine as unchanged drug. The mean elimination half-life is 6.3 hours. Pregabalin is removed by haemodialysis.

Distribution into milk has been found in studies in *rats*.

References.
1. Randinitis EJ, *et al.* Pharmacokinetics of pregabalin in subjects with various degrees of renal function. *J Clin Pharmacol* 2003; **43**: 277–83.
2. Bockbrader HN, *et al.* A comparison of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin. *Clin Pharmacokinet* 2010; **49**: 661–9.
3. Bockbrader HN, *et al.* Population pharmacokinetics of pregabalin in healthy subjects and patients with chronic pain or partial seizures. *Epilepsia* 2011; **52**: 248–57.
4. Shoji S, *et al.* Population pharmacokinetics of pregabalin in healthy subjects and patients with post-herpetic neuralgia or diabetic peripheral neuropathy. *Br J Clin Pharmacol* 2011; **72**: 63–76.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Axual; Balfibro; Clasica; Gavin; Kablan; Linprel; Lyrica; Mystika; Neuristan; Plenica; Prebanal; *Austral.*: Lyrica; *Austria*: Lyrica; *Belg.*: Lyrica; *Braz.*: Lyrica; *Canad.*: Lyrica; *Chile*: Lyrica; Neurum; Prebictal; Prefaxil; Pregalex; Pregobin; *China*: Lyrica (乐瑞卡); *Cz.*: Lyrica; *Denm.*: Lyrica; *Fin.*: Lyrica; *Fr.*: Lyrica; *Ger.*: Lyrica; *Gr.*: Lyrica; *Hong Kong*: Lyrica; *Hung.*: Lyrica; *India*: Gabafit; Gabanext; Galinerve; Lyrica; Maxgalin; Mygalin; Neugaba; Neupreg; Nuramed; Pregab; *Indon.*: Lyrica; *Irl.*: Lyrica; *Israel*: Lyrica; *Ital.*: Lyrica; *Jpn*: Lyrica; *Malaysia*: Lyrica; *Mex.*: Lyrica; *Neth.*: Lyrica; *Norw.*: Lyrica; *NZ*: Lyrica; *Philipp.*: Lyrica; *Pol.*: Lyrica; *Port.*: Lyrica; *Rus.*: Lyrica (Лирика); *S.Afr.*: Lyrica; *Singapore*: Lyrica; *Spain*: Lyrica; *Swed.*: Lyrica; *Switz.*: Lyrica; *Thai.*: Lyrica; *Turk.*: Lyrica; *UK*: Lyrica; *Ukr.*: Lyrica (Лирика); Pregamed (Преламед); *USA*: Lyrica; *Venez.*: Lyrica.

Multi-ingredient Preparations. *India*: Alnacob-P; Capin Plus; Cobal-PG; Doloneuron-PG; Ecogab; Gaba-PM; Gabafix M; Gabatop; Galinerve M; GB-29; Leogab-M; Macraberin-P; Mahagaba-M; Maxgalin-M; Mecap-P; Mecobil-P; Mecobion-P; Mecoday-PG; Mepik; MGTec-P; Miol-P; Nerjuwin-P; Nervelin-M; Nervijen-P; Nervim-P; Nervon-PM; Nervonic-P; Nervup-PG; Neupreg Forte; Neurica-M; Neutron-OD; Nurocare-PG; Nuromas-PG; Nuromax-PG; Nurovole-PG.

Primidone *(BAN, rINN)*

Desoxifenobarbitona; Hexamidinum; Primaclona; Primaclone; Primidon; Primidona; Primidonas; Primidoni; Primidonum; Prymidon; Примидон.

5-Ethyl-5-phenylperhydropyrimidine-4,6-dione.

$C_{12}H_{14}N_2O_2$=218.3

CAS — 125-33-7.

ATC — N03AA03.

ATC Vet — QN03AA03.

UNII — 13AFD7670Q.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Primidone). A white or almost white, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol. It dissolves in alkaline solutions.

USP 36: (Primidone). A white, odourless, crystalline powder. Soluble 1 in 2000 of water and 1 in 200 of alcohol; very slightly soluble in most organic solvents.

Uses and Administration

Primidone is an antiepileptic that is partially metabolised to phenobarbital (p. 535.3), but is also considered to have some antiepileptic activity in its own right. It may be given to control partial and generalised tonic-clonic seizures (below). Primidone is also used in the management of essential tremor (below).

In the treatment of **epilepsy** the dose of primidone should be adjusted according to response; a limited correlation with plasma concentrations has suggested that concentrations of 5 to 12 micrograms/mL (23 to 55 micromoles/litre) are usually necessary, but the *BNF* recommends monitoring of phenobarbital concentrations instead.

Recommended initial oral doses in the UK are 125 mg at bedtime increased, if necessary, by 125 mg every 3 days to a total of 500 mg daily given in 2 divided doses. If necessary, the daily dose may be increased further every 3 days by 250 mg up to a maximum of 1.5 g daily given in divided doses. Usual maintenance doses are 0.75 to 1.5 g daily; maintenance doses are usually given as 2 divided doses. Dosage recommendations in the USA are generally similar although a maximum daily dose of 2 g is permitted.

For doses in children, see below.

As with other antiepileptics, withdrawal of primidone or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1.

For **essential tremor** primidone is usually started at daily oral doses of 50 mg, increased gradually over 2 to 3 weeks if necessary, to a maximum of 750 mg daily.

Administration in children. Children may be given primidone to control partial and generalised tonic-clonic seizures. Recommended initial oral doses in the UK are 125 mg at bedtime, increased if necessary, by 125 mg every 3 days to the following usual maintenance daily doses (given in 2 divided doses) according to age:

- up to 2 years: 250 to 500 mg
- 2 to 5 years: 500 to 750 mg
- 6 to 9 years: 750 to 1000 mg

Older children may be given the usual adult dose (see above).

In the USA, a lower initial oral dose of 50 mg daily is recommended. This is doubled every 3 days, to reach a usual maintenance dose of 125 to 250 mg 3 times daily (10 to 25 mg/kg daily in divided doses) after 10 or more days. Children over 8 years of age may be given the usual adult dose (see above).

Epilepsy. Primidone, like its metabolite phenobarbital, is used in the treatment of epilepsy (p. 506.1) for partial seizures with or without secondary generalisation and for primary generalised tonic-clonic seizures. However, because of problems of sedation, it is usually reserved for use in cases unresponsive to other antiepileptics. It has been suggested that it may be suitable for use in patients with QT-interval prolongation.[1]

1. Christidis D, *et al.* Is primidone the drug of choice for epileptic patients with QT-prolongation? A comprehensive analysis of literature. *Seizure* 2006; **15**: 64–6.

Neonatal apnoea. Results from a preliminary study suggested that adjunctive treatment with primidone[1] might be of value in neonatal apnoea resistant to first-line therapy with xanthines alone, but subsequent confirmatory studies seem to be lacking.

1. Miller CA, *et al.* The use of primidone in neonates with theophylline-resistant apnea. *Am J Dis Child* 1993; **147**: 183–6.

Neonatal seizures. Primidone has been tried in the management of neonatal seizures (p. 511.3).

Tremor. A beta blocker is often the first drug used in patients with essential tremor who require regular treatment (p. 1318.3) but primidone[1] may also be tried. A high incidence of acute adverse reactions has been reported after initial doses (see Tremor, under Precautions, below). There has been concern that long-term use may produce tolerance to primidone's effects, although a small study has found a reduced response in only a few patients.[2] A later study[3] found a dose of 250 mg daily to be as or more effective than 750 mg daily without there being evidence of loss of efficacy during a 12-month follow-up.

1. Koller WC, Royse VL. Efficacy of primidone in essential tremor. *Neurology* 1986; **36**: 121–4.
2. Sasso E, *et al.* Primidone in the long-term treatment of essential tremor: a prospective study with computerized quantitative analysis. *Clin Neuropharmacol* 1990; **13**: 67–76.
3. Serrano-Dueñas M. Use of primidone in low doses (250 mg/day) versus high doses (750 mg/day) in the management of essential tremor: double-blind comparative study with one-year follow-up. *Parkinsonism Relat Disord* 2003; **10**: 29–33.

Adverse Effects, Treatment, and Precautions

As for Phenobarbital, p. 536.3.

Adverse effects may be more frequent than with phenobarbital. Most patients rapidly develop tolerance to the adverse effects of primidone, including ataxia, dizziness, drowsiness, headache, nausea and vomiting, nystagmus, skin rashes, and visual disturbances.

Care is required when withdrawing primidone therapy—see also Uses and Administration, above.

Effects on the blood. For a report of delayed agranulocytosis in a patient treated with phenytoin and primidone, see p. 540.1.

Effects on the endocrine system. For mention of the effects of antiepileptics on *sexual function* in male epileptic patients, see under Phenytoin, p. 540.3.

Overdosage. Crystalluria has been reported[1] after acute overdosage of primidone and 7 other reported cases were also reviewed. Based on these few reports, crystalluria appears to be associated with serum-primidone concentrations in excess of 80 micrograms/mL. There is evidence from 2 reports of renal damage associated with crystal formation *in vivo*. Vigorous hydration is recommended in patients at risk, in order to lessen the potential for renal toxicity and improve elimination.

1. Lehmann DF. Primidone crystalluria following overdose: a report of a case and an analysis of the literature. *Med Toxicol* 1987; **2**: 383–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies primidone as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Tremor. It was noted that patients receiving primidone for essential tremor have a high incidence of acute adverse reactions after small initial doses.[1] This could be due to the absence of induced hepatic enzymes in these patients previously not exposed to antiepileptics.

1. Findley LJ, *et al.* Primidone in essential tremor of the hands and head: a double blind controlled clinical study. *J Neurol Neurosurg Psychiatry* 1985; **48**: 911–15.

Interactions

Primidone is metabolised in the body in part to phenobarbital, and interactions recorded for phenobarbital (p. 537.2) might potentially occur in patients receiving primidone. In addition, enzyme-inducing drugs enhance this metabolism and have the potential to produce elevated phenobarbital concentrations.

Antiepileptics. Both *phenytoin*[1] and *carbamazepine*[2] have been reported to enhance the metabolism of primidone to phenobarbital and when primidone was combined with phenytoin there have been instances of phenobarbital toxicity.[3] *Vigabatrin* has been reported[4] to lower plasma concentrations of primidone in some patients, although it is unlikely that dosage changes would be necessary. *Valproate* may increase plasma concentrations of primidone and phenobarbital, but patient response seems to be inconsistent.[5-7]

1. Reynolds EH, *et al.* Interaction of phenytoin and primidone. *BMJ* 1975; **2**: 594–5.
2. Baciewicz AM. Carbamazepine drug interactions. *Ther Drug Monit* 1986; **8**: 305–17.
3. Galdames D, *et al.* Interacción fenitoína-primidona: intoxicación por fenobarbital, en un adulto tratado con ambas drogas. *Rev Med Chil* 1980; **108**: 716–20.
4. Browne TR, *et al.* A multicentre study of vigabatrin for drug-resistant epilepsy. *Br J Clin Pharmacol* 1989; **27** (suppl 1): 95S–100S.
5. Windorfer A, *et al.* Elevation of diphenylhydantoin and primidone serum concentration by addition of dipropylacetate, a new anticonvulsant drug. *Acta Paediatr Scand* 1975; **64**: 771–2.
6. Bruni J. Valproic acid and plasma levels of primidone and derived phenobarbital. *Can J Neurol Sci* 1981; **8**: 91–2.
7. Yukawa E, *et al.* The effect of concurrent administration of sodium valproate on serum levels of primidone and its metabolite phenobarbital. *J Clin Pharm Ther* 1989; **14**: 387–92.

Pharmacokinetics

Primidone is readily absorbed from the gastrointestinal tract and is reported to have a plasma half-life ranging from 10 to 15 hours, which is shorter than those of its principal metabolites phenylethylmalonamide and phenobarbital, both of which are active. Therapeutic plasma concentrations of primidone have been suggested to be between 5 and 12 micrograms/mL. It is excreted in urine as unchanged drug (40%) and metabolites.

Primidone is widely distributed but is only partially bound to plasma proteins; it has been suggested that it exhibits variable binding of up to about 20%. It crosses the placenta and is distributed into breast milk.

The pharmacokinetics of primidone may be affected by use with other antiepileptics (see under Interactions, above).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Mysoline; *Austral.*: Mysoline; *Austria*: Mysoline; *Belg.*: Mysoline; *Braz.*: Mysoline; Primid; *Cz.*: Liskantin; *Fr.*: Mysoline; *Ger.*: Mylepsinum; Resimatil†; *Gr.*: Mysoline; *Hung.*: Sertan; *India*: Mysoline; *Irl.*: Mysoline; *Israel*: Prysoline; *Ital.*: Mysoline; *Mex.*: Mysoline; *Neth.*: Mysoline; *Pol.*: Mizodin; *Port.*: Mysoline; *Rus.*: Hexamidin (Гексамидин); *S.Afr.*: Mysoline; *Singapore*: Mysoline; *Spain*: Mysoline; *Switz.*: Mysoline; *Turk.*: Mysoline; *UK*: Mysoline†; *USA*: Mysoline.

Pharmacopoeial Preparations
BP 2014: Primidone Oral Suspension; Primidone Tablets;
USP 36: Primidone Oral Suspension; Primidone Tablets.

Retigabine *(rINN)*

AWD21-360; D-23129; Ezogabine (USAN); GKE-841; GW-582892X; Retigabina; Rétigabine; Retigabinum; WAY-143841; Ретигабин.

Ethyl 2-amino-4-[(*p*-fluorobenzyl)amino]carbanilate.

$C_{16}H_{18}FN_3O_2$=303.3

CAS — 150812-12-7.

ATC — N03AX21.

ATC Vet — QN03AX21.

UNII — 12G0I6B8U.

Uses and Administration

Retigabine is a neuronal potassium channel opener that is used for the adjunctive treatment of partial-onset seizures with or without secondary generalisation (see Epilepsy, p. 506.1) in patients aged 18 years and older. In the EU, its

use is restricted to those who have had an inadequate response to, or are intolerant of, other antiepileptics (for details, see Abnormal Coloration, under Adverse Effects and Precautions, below).

The maximum initial oral dose is 300 mg daily for 1 week; thereafter, the total daily dose may be increased by a maximum of 150 mg weekly, according to response and tolerability, to a usual maintenance dose of between 600 mg to 1.2 g daily. Retigabine should be taken in 3 divided doses daily.

Reduced initial and maintenance doses are recommended in patients aged 65 years and older: 150 mg daily should be taken initially, followed by maximum weekly increments of 150 mg to a maximum maintenance dose of 900 mg daily.

Reduced doses are also recommended in patients with hepatic or renal impairment (see below).

As with other antiepileptics, withdrawal of retigabine therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. Licensed product information recommends reducing the dose over a period of 3 weeks. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1.

References.

1. Blackburn-Munro G, *et al.* Retigabine: chemical synthesis to clinical application. *CNS Drug Rev* 2005; 11: 1–20.
2. Porter RJ, *et al.* Retigabine. *Neurotherapeutics* 2007; 4: 149–54.
3. Brodie MJ, *et al.* RESTORE 2 Study Group. Efficacy and safety of adjunctive ezogabine (retigabine) in refractory partial epilepsy. *Neurology* 2010; 75: 1817–24.
4. Owen RT. Ezogabine: a novel antiepileptic as adjunctive therapy for partial onset seizures. *Drugs Today* 2010; 46: 815–22.
5. French JA, *et al.* RESTORE 1/Study 301 Investigators. Randomized, double-blind, placebo-controlled trial of ezogabine (retigabine) in partial epilepsy. *Neurology* 2011; 76: 1555–63.
6. Deeks ED. Retigabine (ezogabine): in partial-onset seizures in adults with epilepsy. *CNS Drugs* 2011; 25: 887–900.
7. Gunthorpe MJ, *et al.* The mechanism of action of retigabine (ezogabine), a first-in-class K+ channel opener for the treatment of epilepsy. *Epilepsia* 2012; 53: 412–24.
8. Martyn-St James M, *et al.* The efficacy and safety of retigabine and other adjunctive treatments for refractory partial epilepsy: a systematic review and indirect comparison. *Seizure* 2012; 21: 665–78.
9. Yamada M, Welty TE. Ezogabine: an evaluation of its efficacy and safety as adjunctive therapy for partial-onset seizures in adults. *Ann Pharmacother* 2012; 46: 1358–67.
10. Craig D, *et al.* Retigabine for the adjunctive treatment of adults with partial-onset seizures in epilepsy with and without secondary generalization: a NICE single technology appraisal. *Pharmacoeconomics* 2013; 31: 101–10.
11. Amabile CM, Vasudevan A. Ezogabine: a novel antiepileptic for adjunctive treatment of partial-onset seizures. *Pharmacotherapy* 2013; 33: 187–94.

Administration in hepatic or renal impairment. The usual initial dose of retigabine (see p. 547.3) should be reduced by 50% to 150 mg daily in patients with moderate or severe hepatic (Child-Pugh score 7 and over) or renal (creatinine clearance below 50 mL/min) impairment. Thereafter, UK licensed product information recommends weekly increments of 50 mg to a maximum of 600 mg daily; however, US product information permits the usual weekly increments of 150 mg in these patients, and recommends a higher maintenance dose of 750 mg daily in those with moderate hepatic impairment (Child-Pugh score of 7 to 9). No dose adjustment is necessary in mild impairment.

Adverse Effects and Precautions

The most commonly reported adverse effects with retigabine are usually mild to moderate in intensity, occur within the first 8 weeks of therapy, and show a dose-effect relationship; these include dizziness, somnolence, fatigue, confusional state, aphasia, abnormal coordination, tremor, balance disorder, memory impairment, gait disturbance, blurred vision, and constipation. Other commonly reported effects include anxiety, psychotic disorders, paraesthesia, weight increase, nausea, and dyspepsia. Urinary retention and hesitation, and dysuria have also been reported usually within the first 8 weeks to 6 months of therapy; retigabine should be used with caution in patients at risk of urinary retention.

Pigment changes of ocular tissues (including the retina), skin, lips, and nails have been commonly reported after long-term use; retigabine therapy should only be continued in affected patients after careful assessment of the balance of risks and benefits. As some reports of ocular discoloration have been associated with visual impairment, an ophthalmological examination should be performed in all patients at baseline and at least every 6 months thereafter.

Retigabine, at a dose of 1.2 g daily, has been associated with prolongation of the QT interval in healthy subjects; consequently, retigabine should be used with caution in patients with known prolonged QT interval, congestive heart failure, ventricular hypertrophy, hypokalaemia, or hypomagnesaemia, in those who are taking drugs known to prolong the QT interval, and in elderly patients. Such patients should have an ECG before starting therapy; those with a corrected QT of > 440 milliseconds at baseline should also have an ECG on reaching the maintenance dose.

Patients aged 65 years and older may be at increased risk of developing CNS effects, urinary retention, and atrial fibrillation; retigabine must be used with caution and reduced doses are recommended. Lower doses of retigabine are also recommended in patients with moderate to severe hepatic or renal impairment.

Care is required when withdrawing retigabine therapy—see also Uses and Administration, p. 547.3.

Abnormal coloration. Pigment changes or discoloration of ocular tissues, skin, lips, and nails have been reported in long-term studies of retigabine.[1-3] Up to May 2013, 55 patients have been examined and 21 were found to have pigment changes in ocular tissues; of these, 15 had retinal pigmentation (5 of whom also had impaired vision).[3] Almost all cases of retinal pigmentation occurred after at least 3 years of treatment and some have occurred in the absence of skin discoloration.[1] In addition, 51 cases of blue-grey pigmentation of the skin, lips, and nails have been reported;[3] the median time to onset was 4.4 years (range: 4 months to 6.7 years) and symptoms tended to occur at high doses (usually 900 mg or more daily) although they have also been reported with lower doses. The cause and long-term prognosis of pigmentation changes associated with retigabine therapy are unknown. Consequently, both the European Medicines Agency (EMEA)[2] and the FDA[1] have recommended that baseline and periodic ophthalmological examination should be performed in all patients; furthermore, the EMEA[2] has also restricted the use of retigabine to patients who have had an inadequate response to, or are intolerant of, other antiepileptics.

1. FDA. FDA drug safety communication: anti-seizure drug Potiga (ezogabine) linked to retinal abnormalities and blue skin discoloration (issued 26th April, 2013). Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/UCM349554.pdf (accessed 12/09/13)
2. EMEA. European Medicines Agency recommends restricting Trobalt to last-line therapy in partial epilepsy (issued 30th May, 2013). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/human/001245/WC500143799.pdf (accessed 12/09/13)
3. MHRA/CHM. Retigabine (Trobalt): indication restricted to last-line use, and new monitoring requirements after reports of pigment changes in ocular tissue, skin, lips, or nails. *Drug Safety Update* 2013; 6 (12): A2. Available at: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON296401 (accessed 12/09/13)

Breast feeding. For comment on antiepileptic therapy and breast feeding, see p. 508.3.

Driving. For a comment on antiepileptic drugs and driving, see p. 509.2.

Effects on mental function. For the effects of antiepileptic therapy on *cognition* and *mood*, including the risk of suicidal ideation, see p. 508.3.

Pregnancy. For comments on the management of epilepsy during pregnancy, see p. 509.2.

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy. *In-vitro* data indicated a low potential for interaction with other antiepileptics; however, *in-vivo* studies found that carbamazepine and phenytoin reduced the systemic exposure to retigabine by about 33% and 35%, respectively, and an increase in the dosage of retigabine should be considered when adding these drugs.

Alcohol can increase the systemic exposure to retigabine and potentially increase the incidence of adverse effects; such use has resulted in an increase in visual blurring in healthy subjects. Retigabine has been shown to interfere with serum and urine bilirubin assays, resulting in falsely elevated readings.

Pharmacokinetics

Retigabine is readily absorbed after oral doses; peak concentrations occur about half an hour to 2 hours later. The pharmacokinetics of retigabine are reported to be linear at clinical doses. It is well distributed in the body and about 80% bound to plasma proteins. Retigabine is extensively metabolised, mainly undergoing glucuronidation by the uridine diphosphate glucuronosyltransferase 1A4 (UGT1A4) to form inactive *N*-glucuronides, the major metabolites. Retigabine also undergoes acetylation by *N*-acetyltransferase 2 (NAT2) to form an active, but less potent, *N*-acetyl metabolite (NAMR) that is subsequently glucuronidated. About 85% of a dose is excreted in the urine: 36% as unchanged retigabine, 18% as NAMR, and 24% as *N*-glucuronides of retigabine and NAMR. About 14% of a dose is excreted in the faeces, with 3% as unchanged drug. Retigabine and NAMR have similar elimination half-lives of about 6 to 11 hours.

References.

1. Hermann R, *et al.* Effects of age and sex on the disposition of retigabine. *Clin Pharmacol Ther* 2003; 73: 61–70.
2. Tompson DJ, Crean CS. Clinical pharmacokinetics of retigabine/ezogabine. *Curr Clin Pharmacol* 2013; 8: 319–31.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Trobalt; *Cz.*: Trobal; *Denm.*: Trobalt; *Fr.*: Trobalt; *Irl.*: Trobalt; *Israel*: Trobalt; *Neth*: Trobalt; *Norw.*: Trobalt; *Spain*: Trobalt; *Swed.*: Trobalt; *Switz*: Trobalt; *UK*: Trobalt; *USA*: Potiga.

Rufinamide *(BAN, USAN, rINN)*

60231/4; CGP-33101; E-2080; RUF-331; Rufinamida; Rufinamidum; Руфинамид.

1-(2,6-Difluorobenzyl)-1*H*-1,2,3-triazole-4-carboxamide.

$C_{10}H_8F_2N_4O$=238.2

CAS — 106308-44-5.

ATC — N03AF03.

ATC Vet — QN03AF03.

UNII — WFW942PR79.

Pharmacopoeias. In *US.*

USP 36: (Rufinamide). A white, crystalline neutral powder Practically insoluble in water; very slightly soluble in alcohol and in acetonitrile; slightly soluble in methyl alcohol and in tetrahydrofuran. Store in airtight containers at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Rufinamide is an antiepileptic used as an adjunct in the treatment of seizures associated with the Lennox-Gastaut syndrome (see Epilepsy, p. 506.1) in patients aged 4 years and over. Rufinamide is given orally in 2 divided doses daily with food.

In the UK, the recommended initial daily dose in patients weighing less than 30 kg is 200 mg, increased according to response in increments of 200 mg every 2 days to a usual maximum of 1 g daily; the recommended maximum dose in those taking *valproate* is 600 mg daily. In patients weighing more than 30 kg, the initial daily dose is 400 mg, increased according to response in increments of 400 mg every 2 days to a maximum daily dose of 1.8 g in those weighing up to 50 kg, 2.4 g in those weighing up to 70 kg, and 3.2 g in those over 70 kg.

In the USA, the initial daily dose is 400 to 800 mg, increased according to response in increments of 400 to 800 mg every 2 days to a maximum daily dose of 3.2 g. The recommended initial daily dose in children aged 4 years and over is about 10 mg/kg, increased according to response in increments of about 10 mg/kg every other day to a target dose of 45 mg/kg daily or 3.2 g daily, whichever is less.

As with other antiepileptics, withdrawal of rufinamide therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. Licensed product information recommends reducing the daily dose by about 25% every 2 days. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1.

Rufinamide has also been investigated as adjunctive therapy in the treatment of partial and primary generalised tonic-clonic seizures.

References.

1. Deeks ED, *et al.* Rufinamide. *CNS Drugs* 2006; 20: 751–60.
2. Cheng-Hakimian A, *et al.* Rufinamide: pharmacology, clinical trials, and role in clinical practice. *Int J Clin Pract* 2006; 60: 1497–501.
3. Glauser T, *et al.* Rufinamide for generalized seizures associated with Lennox-Gastaut syndrome. *Neurology* 2008; 70: 1950–8.
4. Kluger G, *et al.* Effectiveness and tolerability of rufinamide in children and adults with refractory epilepsy: first European experience. *Epilepsy Behav* 2009; 14: 491–5.
5. Brodie MJ, *et al.* Rufinamide for the adjunctive treatment of partial seizures in adults and adolescents: a randomized placebo-controlled trial. *Epilepsia* 2009; 50: 1899–909.
6. Stafstrom CE. Update on the management of Lennox-Gastaut syndrome with a focus on rufinamide. *Neuropsychiatr Dis Treat* 2009; 5: 547–51.
7. Verrotti A, *et al.* Efficacy of rufinamide in drug-resistant epilepsy: a meta-analysis. *Pediatr Neurol* 2011; 44: 347–9.
8. Coppola G. Update on rufinamide in childhood epilepsy. *Neuropsychiatr Dis Treat* 2011; 7: 399–407.

Administration in children. For doses of rufinamide in children, see above.

Adverse Effects and Precautions

The most common adverse effects with rufinamide include headache, dizziness, fatigue, somnolence, nausea, and vomiting. Other reported adverse effects include anorexia, weight loss, anxiety, insomnia, vertigo, nystagmus, tremor,

dyspepsia, constipation, and diarrhoea. Convulsions, including status epilepticus, have occurred. Lymphadenopathy, abnormal liver function tests, and haematuria, as well as fever and rash, have been reported as part of a hypersensitivity syndrome.

Rufinamide can reduce the QT interval and should be used with caution in those with a shortening of their QT interval or with a family history of congenital short QT syndrome.

Care is required when withdrawing rufinamide therapy—see Uses and Administration, p. 548.3.

Breast feeding. For comment on antiepileptic therapy and breast feeding, see p. 508.3.

Driving. For a comment on antiepileptic drugs and driving, see p. 509.2.

Effects on mental function. For the effects of antiepileptic therapy on *cognition* and *mood*, including the risk of suicidal ideation, see p. 508.3.

Pregnancy. For comments on the management of epilepsy during pregnancy, see p. 509.2.

Interactions

There are complex interactions between antiepileptics, and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy. Rufinamide plasma concentrations are reportedly decreased by carbamazepine, phenobarbital, phenytoin, vigabatrin, or primidone; however, these interactions are not considered to be clinically relevant. In contrast, significant increases in rufinamide plasma concentrations can occur with valproate and dosage adjustments may be necessary (see Uses and Administration, p. 548.3).

Rufinamide induces the cytochrome P450 isoenzyme CYP3A4 and may be expected to decrease plasma concentrations of drugs metabolised by this route, such as oral contraceptives. Rufinamide reportedly increases steady-state plasma concentrations of phenytoin.

Pharmacokinetics

Rufinamide is well absorbed after oral doses; peak plasma concentrations occur after about 6 hours. Food increases the bioavailability of rufinamide by about 34 to 40%. It is 34% bound to serum proteins, mainly to albumin.

Rufinamide is hydrolysed to an inactive metabolite and has a plasma elimination half-life of about 6 to 10 hours, although clearance in children is reported to be slower. It is mainly excreted in urine as the inactive metabolite.

References

1. Cardot JM, *et al.* The influence of food on the disposition of the antiepileptic rufinamide in healthy volunteers. *Biopharm Drug Dispos* 1998; 19: 259–62.
2. Perucca E, *et al.* Rufinamide: clinical pharmacokinetics and concentration-response relationships in patients with epilepsy. *Epilepsia* 2008; 49: 1123–41.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Inovelon; ***Belg.***: Inovelon; ***Canad.***: Banzel; ***Cz.***: Inovelon; ***Denm.***: Inovelon; ***Fr.***: Inovelon; ***Ger.***: Inovelon; ***Gr.***: Inovelon; ***Hung.***: Inovelon; ***Irl.***: Inovelon; ***Israel***: Inovelon; ***Ital.***: Inovelon; ***Jpn***: Inovelon; ***Neth.***: Inovelon; ***Norw.***: Inovelon; ***Pol.***: Inovelon; ***Port.***: Inovelon; ***Spain***: Inovelon; ***Swed.***: Inovelon; ***Switz.***: Inovelon; ***UK***: Inovelon; ***USA***: Banzel.

Pharmacopoeial Preparations
USP 36: Rufinamide Tablets.

Stiripentol *(USAN, rINN)*

BCX-2600; Estiripentol; Stiripentolum; Стирипентол.
4,4-Dimethyl-1-[(3,4-methylenedioxy)phenyl]-1-penten-3-ol.
$C_{14}H_{18}O_3$=234.3
CAS — 49763-96-4.
ATC — N03AX17.
ATC Vet — QN03AX17.
UNII — R02XOT8V8I.

Uses and Administration

Stiripentol is used with clobazam and valproate as adjunctive therapy in the treatment of refractory generalised tonic-clonic seizures in severe myoclonic epilepsy in infancy (below). It is thought to be less potent than some conventional antiepileptics, but may reduce their adverse effects when used adjunctively.

Stiripentol is given orally and should be started at a low dose, gradually increased over 3 days, to the recommended dose of 50 mg/kg daily given in 2 or 3 divided doses with food (but not with dairy products, carbonated drinks, fruit juice, or food and drinks that contain caffeine or theophylline). After starting adjunctive stiripentol therapy, the daily dose of clobazam may be reduced by 25% every week if there are signs of adverse effects or overdosage with clobazam. The daily dose of valproate is not usually adjusted, however, it may be reduced by 30% every week if there are signs of gastrointestinal adverse effects.

Epilepsy. A 24-week study[1] in 10 children found that stiripentol might be effective as adjunctive therapy for the treatment of atypical absence seizures (p. 506.1). Further studies suggested benefit from adjunctive use in children with partial epilepsy[2] and severe myoclonic epilepsy.[2-4]

1. Farwell JR, *et al.* Stiripentol in atypical absence seizures in children: an open trial. *Epilepsia* 1993; 34: 305–11.
2. Perez J, *et al.* Stiripentol: efficacy and tolerability in children with epilepsy. *Epilepsia* 1999; 40: 1618–26.
3. Chiron C, *et al.* Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. *Lancet* 2000; 356: 1638–42.
4. Chiron C. Stiripentol. *Expert Opin Invest Drugs* 2005; 14: 905–11.

Adverse Effects and Precautions

The most common adverse effects of stiripentol include anorexia, weight loss, insomnia, drowsiness, ataxia, hypotonia, and dystonia. Other common adverse effects include nausea, vomiting, and aggressiveness, and other mood or behavioural disorders. Neutropenia is also reported to be common; persistent severe neutropenia usually resolves spontaneously when stiripentol is stopped. Photosensitivity, rash, and urticaria have occurred. Patients may exhibit altered liver enzyme values.

Growth rates, blood counts, and hepatic function should be monitored periodically in patients given stiripentol.

Interactions

Stiripentol is a potent inhibitor of several cytochrome P450 isoenzymes, including CYP1A2, CYP2C19, and CYP3A4, and may markedly reduce clearance of drugs metabolised by these enzymes. The possibility of an effect on stiripentol metabolism by other inhibitors or inducers of these enzymes should also be borne in mind.

For interactions of stiripentol with other antiepileptics, see under Carbamazepine, p. 516.3, Diazepam, p. 1069.1, and Phenytoin, p. 543.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Diacomit; ***Cz.***: Diacomit; ***Denm.***: Diacomit; ***Fr.***: Diacomit; ***Irl.***: Diacomit; ***Jpn***: Diacomit; ***Neth.***: Diacomit; ***Norw.***: Diacomit; ***Pol.***: Diacomit; ***Port.***: Diacomit; ***Swed.***: Diacomit; ***UK***: Diacomit.

Sultiame *(BAN, rINN)*

Riker-594; Sulthiame (USAN); Sulthiamé; Sultiaami; Sultiam; Sultiamo; Sultiamum; Сультиам.
4-(Tetrahydro-2*H*-1,2-thiazin-2-yl)benzenesulphonamide *S,S*-dioxide.
$C_{10}H_{14}N_2O_4S_2$=290.4
CAS — 61-56-3.
ATC — N03AX03.
ATC Vet — QN03AX03.
UNII — I00Q766CZ2.

Pharmacopoeias. In *Jpn*.

Profile

Sultiame is a carbonic anhydrase inhibitor that has been used as an antiepileptic in most forms of epilepsy (p. 506.1) except absence seizures. It has usually been given with other antiepileptics and it is believed that much of its activity is due to the inhibition of metabolism of the other drugs.

Sultiame has been given orally in initial doses of 100 mg twice daily or 50 mg three times daily gradually increased according to response to 200 mg three times daily. A dose of 5 to 10 mg/kg daily, adjusted according to response, has been recommended in Rolandic epilepsy.

Interactions. For the effect of sultiame on *phenytoin*, see p. 543.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ospolot; ***Austral.***: Ospolot; ***Austria***: Ospolot; ***Cz.***: Ospolot; ***Ger.***: Ospolot; ***Gr.***: Ospolot; ***Hung.***: Ospolot; ***Israel***: Ospolot; ***Switz.***: Ospolot.

Tiagabine Hydrochloride

(BANM, USAN, rINNM)

Abbott-70569.1; ABT-569; Hidrocloruro de tiagabina; NNC-05-0328; NO-05-0328; NO-328; Tiagabina, hidrocloruro de; Tiagabine, Chlorhydrate de; Tiagabini Hydrochloridum; Тиагабина Гидрохлорид.
(-)-(*R*)-1-[4,4-Bis(3-methyl-2-thienyl)-3-butenyl]nipecotic acid hydrochloride.
$C_{20}H_{25}NO_2S_2$,HCl=412.0
CAS — 115103-54-3 (tiagabine); 145821-59-6 (tiagabine hydrochloride).
ATC — N03AG06.
ATC Vet — QN03AG06.
UNII — DQH6T6D8OY.

Pharmacopoeias. In *US*.

USP 36: (Tiagabine Hydrochloride). A white to off-white powder. Sparingly soluble in water; freely soluble in alcohol and methyl alcohol; soluble in isopropyl alcohol; very slightly soluble in chloroform; practically insoluble in *n*-heptane. Store in airtight containers at a temperature not exceeding 30 degrees. Protect from light.

Stability. An extemporaneously prepared suspension containing tiagabine hydrochloride 1 mg/mL in a mixture of simple syrup and 1% methylcellulose was found,[1] when stored in plastic amber bottles, to be stable for 6 weeks at 25 degrees or 13 weeks at 4 degrees. When prepared in a 1:1 mixture of *Ora-Plus* and *Ora-Sweet* (*Paddock, USA*), the suspension was stable for 10 weeks at 25 degrees or 13 weeks at 4 degrees.

1. Nahata MC, Morosco RS. Stability of tiagabine in two oral liquid vehicles. *Am J Health-Syst Pharm* 2003; 60: 75–7.

Uses and Administration

Tiagabine is a nipecotic acid derivative used in the treatment of epilepsy (below) as adjunctive therapy for refractory partial seizures with or without secondary generalisation. It inhibits the uptake of GABA into neuronal and glial cells, and therefore increases the availability of GABA at receptor sites.

UK licensing information states that tiagabine hydrochloride is given as the monohydrate, but doses are described in terms of tiagabine; dose forms providing the equivalent of 5, 10, and 15 mg of tiagabine are available. In the USA, however, the licensed product is stated to contain anhydrous tiagabine hydrochloride, and doses are described in terms of this substance; dose forms providing 2, 4, 12, and 16 mg are available. As a result, the doses in the UK and US literature may not be directly comparable.

In the UK, the initial oral daily dose as adjunctive therapy is the equivalent of tiagabine 5 to 10 mg as a single dose or in 2 divided doses, increased weekly as necessary by increments of 5 to 10 mg. The usual maintenance dose is 30 to 45 mg daily, in 2 or 3 divided doses, in patients receiving enzyme-inducing antiepileptics; in patients *not* taking enzyme-inducing drugs an initial maintenance dosage of 15 to 30 mg daily is suggested. Lower initial doses of the hydrochloride are recommended in the USA. Doses should be taken with food to avoid rapid rises in plasma concentrations, thereby reducing the incidence of adverse effects. Reduced doses should be given in hepatic impairment—see below.

As with other antiepileptics, withdrawal of tiagabine therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. UK licensed product information recommends gradual withdrawal over a period of 2 to 3 weeks. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1.

Administration in hepatic impairment. The dose of tiagabine should be reduced, or the dosage interval prolonged, in patients with mild to moderate hepatic impairment. Tiagabine should not be given to patients with severe impairment.

Bipolar disorder. Two systematic reviews[1,2] of the use of tiagabine to treat bipolar disorder (p. 397.2) found that the evidence was anecdotal and insufficiently rigorous to support such use.

1. Vasudev A, *et al.* Tiagabine in the treatment of acute affective episodes in bipolar disorder. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 26/11/09).
2. Vasudev A, *et al.* Tiagabine in the maintenance treatment of bipolar disorders. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 26/11/09).

Epilepsy. Tiagabine is one of several drugs that may be used as adjunctive therapy in patients with partial seizures (with or without secondary generalisation) refractory to standard treatment (p. 506.1). It appears to be reasonably

well tolerated. For the suggestion that it might be tried in refractory status epilepticus, see p. 510.2.

References.
1. Leach JP, Brodie MJ. Tiagabine. *Lancet* 1998; 351: 203–7.
2. Adkins JC, Noble S. Tiagabine: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in the management of epilepsy. *Drugs* 1998; 55: 437–60.
3. Luer MS, Rhoney DH. Tiagabine: a novel antiepileptic drug. *Ann Pharmacother* 1998; 32: 1173–80.
4. Loisean P. Review of controlled trials of gabitril (tiagabine): a clinician's viewpoint. *Epilepsia* 1999; 40 (suppl 9): S14–S19.
5. Anonymous. Tiagabine: add-on treatment for partial seizures. *Drug Ther Bull* 2000; 38: 47–8.
6. Dodrill CB, *et al.* Tiagabine versus phenytoin and carbamazepine as add-on therapies: effects on abilities, adjustment, and mood. *Epilepsy Res* 2000; 42: 123–32.
7. Crawford P, *et al.* Tiagabine: efficacy and safety in adjunctive treatment of partial seizures. *Epilepsia* 2001; 42: 531–8.
8. Biraben A, *et al.* Comparison of twice- and three times daily tiagabine for the adjunctive treatment of partial seizures in refractory patients with epilepsy: an open label, randomised, parallel-group study. *Epileptic Disord* 2001; 3: 91–100.
9. Pereira J, *et al.* Tiagabine add-on for drug-resistant partial epilepsy. Available in the Cochrane Database of Systematic Reviews: Issue 3. Chichester: John Wiley; 2002 (accessed 09/06/08).
10. Arroyo S, *et al.* A randomised open-label study of tiagabine given two or three times daily in refractory epilepsy. *Seizure* 2005; 14: 81–4.

Pain. Antiepileptics are among the drugs used to manage pain (see Choice of Analgesic, p. 4.2); tiagabine has been tried in chronic pain[1] and was found to be effective.

1. Todorov AA, *et al.* Tiagabine and gabapentin for the management of chronic pain. *Clin J Pain* 2005; 21: 358–61.

Psychiatric disorders. Tiagabine has been tried for the treatment of *generalised anxiety disorder*[1-3] (p. 1028.1) and *major depressive disorder* with anxiety[4] (p. 398.1), with variable results. It has also been tried in *post-traumatic stress disorder* (p. 1029.2) with some success in a case series[5] and a small open-label study[6] although a later multicentre placebo-controlled study[7] found no significant difference between tiagabine and placebo; further studies are considered warranted. A preliminary study[8] suggested that tiagabine may be effective and generally well tolerated as augmentation therapy in patients with anxiety disorders.

1. Rosenthal M. Tiagabine for the treatment of generalized anxiety disorder: a randomized, open-label, clinical trial with paroxetine as a positive control. *J Clin Psychiatry* 2003; 64: 1245–9.
2. Pollack MH, *et al.* The selective GABA reuptake inhibitor tiagabine for the treatment of generalized anxiety disorder: results of a placebo-controlled study. *J Clin Psychiatry* 2005; 66: 1401–8.
3. Pollack MH, *et al.* Tiagabine in adult patients with generalized anxiety disorder: results from 3 randomized, double-blind, placebo-controlled, parallel-group studies. *J Clin Psychopharmacol* 2008; 28: 308–16.
4. Carpenter LL, *et al.* Open-label tiagabine monotherapy for major depressive disorder with anxiety. *J Clin Psychiatry* 2006; 67: 66–71.
5. Taylor FB. Tiagabine for posttraumatic stress disorder: a case series of 7 women. *J Clin Psychiatry* 2003; 64: 1421–5.
6. Connor KM, *et al.* Tiagabine for posttraumatic stress disorder: effects of open-label and double-blind discontinuation treatment. *Psychopharmacology (Berl)* 2006; 184: 21–5.
7. Davidson JRT, *et al.* The efficacy and tolerability of tiagabine in adult patients with post-traumatic stress disorder. *J Clin Psychopharmacol* 2007; 27: 85–8.
8. Schwartz TL, *et al.* An open-label study of tiagabine as augmentation therapy for anxiety. *Ann Clin Psychiatry* 2005; 17: 167–72.

Stiff-man syndrome. There have been anecdotal reports[1] of improvement of stiff-man syndrome (see under Muscle Spasm, p. 1064.3) with tiagabine in patients unable to tolerate benzodiazepine therapy.

1. Murinson BB, Rizzo M. Improvement of stiff-person syndrome with tiagabine. *Neurology* 2001; 57: 366.

Adverse Effects

The most common adverse effects include dizziness, nervousness, tiredness, somnolence, and tremor. Other reported adverse effects include irritability, confusion, depression, psychosis, difficulties in concentration, diarrhoea, abdominal pain, nausea, ataxia, emotional lability, and nystagmus. Bruising, rashes, speech difficulties, and a flu-like syndrome of chills, fever, myalgia, and headache have also been reported. Visual field defects have been reported rarely and decreased white blood cell counts have been noted at routine screenings.

Incidence of adverse effects. A systematic review[1] considered 5 double-blind studies involving about 1000 patients of whom 675 were receiving tiagabine as adjunctive therapy for refractory partial seizures. Withdrawal due to adverse effects was infrequent and occurred in 15% of patients receiving tiagabine compared with 5% receiving placebo. Adverse effects were usually associated with dose titration, and were generally mild to moderate in severity, and transient. Another review[2] by the same author on data from all clinical studies (52 studies involving nearly 3100 patients) reported that in 21% of patients receiving tiagabine had the drug stopped for adverse effects, mostly during the first 6 months of therapy. Sub-analysis showed that figures for placebo-controlled, adjunctive studies were similar to those of the earlier review.

1. Leppik IE. Tiagabine: the safety landscape. *Epilepsia* 1995; 36 (suppl 6): S10–S13.
2. Leppik IE, *et al.* Safety of tiagabine: summary of 53 trials. *Epilepsy Res* 1999; 33: 235–46.

Effects on the eyes. Unlike vigabatrin, which is associated with visual field defects (see p. 559.2), studies of visual function in patients taking tiagabine, another GABAergic antiepileptic, have been generally reassuring. However, in a case report[1] a 39-year-old patient was noted to have visual field defects while receiving long-term tiagabine therapy for bipolar disorder. The defects reversed after tiagabine was withdrawn.

1. Kaufman KR, *et al.* Visual fields and tiagabine: a quandary. *Seizure* 2001; 10: 525–9.

Effects on mental function. For a review of the effects of antiepileptic therapy on *cognition*, and the effects of tiagabine on *mood* (including the risk of suicidal ideation), see p. 508.3.

Effects on the nervous system. Acute dystonic reactions occurred in 3 patients when tiagabine was added to their existing carbamazepine treatment;[1] the reactions were associated with an increase in the dose of tiagabine to 20 mg daily or more. In all cases the dystonias disappeared despite continuing tiagabine therapy at the same dose, although in one patient carbamazepine was withdrawn.

There have been case reports of nonconvulsive status epilepticus,[2-4] associated with tiagabine. The authors of one such report[2] noted that, in placebo-controlled studies, the incidence of such an event was no higher in the tiagabine group than in the placebo group. However, a retrospective analysis[5] of inpatients with refractory localised epilepsy found that nonconvulsive status epilepticus occurred more frequently in patients treated with tiagabine (6.7%) than in those who were not (1.1%).

The FDA has warned of the risk of seizures with tiagabine when used in *non-epileptic patients* for unlicensed indications;[6] it had received over 30 reports of new-onset seizures or status epilepticus in such patients. Predisposing factors may include the use of other drugs known to lower the seizure threshold, and probably the dose. Although some cases were noted after doses as low as 4 mg daily, licensed doses in patients with epilepsy take into account the customary use of other enzyme-inducing antiepileptics which can roughly halve the plasma levels of tiagabine by inducing its metabolism. For reports of status epilepticus occurring in non-epileptic patients after tiagabine overdosage, see below.

1. Wolańczyk T, Grabowska-Grzyb A. Transient dystonias in three patients treated with tiagabine. *Epilepsia* 2001; 42: 944–6.
2. Fitzek S, *et al.* Drug-induced nonconvulsive status epilepticus with low dose of tiagabine. *Epileptic Disord* 2001; 3: 147–50.
3. Skardoutsou A, *et al.* Non-convulsive status epilepticus associated with tiagabine therapy in children. *Seizure* 2003; 12: 599–601.
4. Vinton A, *et al.* Tiagabine-induced generalised non convulsive status epilepticus in patients with lesional focal epilepsy. *J Clin Neurosci* 2005; 12: 128–33.
5. Koepp MJ, *et al.* Status epilepticus and tiagabine therapy revisited. *Epilepsia* 2005; 46: 1625–32.
6. FDA. Tiagabine hydrochloride (marketed as Gabitril): seizures in patients without epilepsy (issued 18 February, 2005). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm107285.htm (accessed 25/08/10)

Overdosage. A 30-year-old man who took 320 mg of tiagabine in overdose with 400 mg of phenytoin showed no serious signs of toxicity other than significantly depressed levels of consciousness from which he quickly recovered.[1] Plasma concentrations of tiagabine measured 4 hours after ingestion were 30 times higher than those seen with therapeutic doses; phenytoin concentrations just exceeded the therapeutic range. A 46-year-old woman[2] who ingested about 72 mg of tiagabine exhibited facial grimacing, rigid flexure posturing of the upper extremities, and dilated pupils. She was uncommunicative and unresponsive to commands. Treatment with benzodiazepines was given, and symptoms resolved within 12 hours of admission.

Seizures, including status epilepticus, are a recognised adverse effect of tiagabine (see above); there have been reports of status epilepticus occurring in non-epileptic patients after overdosage, including nonconvulsive status epilepticus[3] in a 14-year-old girl who took about 180 mg of tiagabine, and myoclonic status epilepticus[4] in an 18-year-old man who took 120 mg of tiagabine with 400 mg of lamotrigine. Generalised tonic-clonic seizures were reported[5] in a 2-year-old child who had taken 90 mg of tiagabine.

A retrospective review[6] of 57 overdoses with tiagabine reported to several poison centres in the USA found that the most common adverse effects were lethargy (in 56%), seizures (37%, including status epilepticus in 5%), agitation (32%), confusion (30%), and coma (28%). Other adverse effects included tachycardia, respiratory depression, tremor, and hallucinations; no deaths were reported. The mean onset and duration of symptoms were 1.3 and 9.1 hours, respectively. The lowest dose associated with seizures was 96 mg.

1. Leach JP, *et al.* Deliberate overdose with the novel anticonvulsant tiagabine. *Seizure* 1995; 4: 155–7.
2. Cantrell FL, *et al.* Intentional overdose with tiagabine: an unusual clinical presentation. *J Emerg Med* 2004; 27: 271–2.
3. Jette N, *et al.* Tiagabine-induced nonconvulsive status epilepticus in an adolescent without epilepsy. *Neurology* 2006; 67: 1514–15.
4. Vollmar C, Noachtar S. Tiagabine-induced myoclonic status epilepticus in a nonepileptic patient. *Neurology* 2007; 68: 310.
5. Kazzi ZN, *et al.* Seizures in a pediatric patient with a tiagabine overdose. *J Med Toxicol* 2006; 2: 160–2.
6. Spiller HA, *et al.* Retrospective evaluation of tiagabine overdose. *Clin Toxicol* 2005; 43: 855–9.

Precautions

Hepatic metabolism of tiagabine is reduced in patients with hepatic impairment, and dosage should therefore be reduced and/or the intervals between doses increased. It should not be used in patients with severely impaired hepatic function.

Use of tiagabine in non-epileptic patients may be associated with an increased risk of seizures— see Effects on the Nervous System, above.

Care is required when withdrawing tiagabine therapy— see Uses and Administration, p. 549.3.

Breast feeding. For comment on antiepileptic therapy and breast feeding, see p. 508.3.

Driving. For comment on antiepileptic drugs and driving, see p. 509.2.

Porphyria. Tiagabine has been found to increase hepatic and urinary porphobilinogen concentrations.[1]

1. Solinas C, Vajda FJ. Epilepsy and porphyria: new perspectives. *J Clin Neurosci* 2004; 11: 356–61.

Pregnancy. For comments on the management of epilepsy during pregnancy, see p. 509.2.

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy. The hepatic metabolism of tiagabine is accelerated by antiepileptics that induce enzymes of the cytochrome P450 system such as carbamazepine, phenobarbital, phenytoin, or primidone. Plasma concentrations of tiagabine may be reduced up to threefold by use with these drugs.

Pharmacokinetics

Tiagabine is readily absorbed after oral doses, with a bioavailability of 89%. Food reduces the rate but not the extent of absorption. The absorption and elimination pharmacokinetics of tiagabine are linear within the therapeutic dosage range.

Tiagabine is widely distributed throughout the body and plasma protein binding is 96%.

Tiagabine is extensively metabolised in the liver and excreted as metabolites in the faeces or, to a lesser extent in the urine; less than 2% of a dose is eliminated as unchanged drug. The plasma-elimination half-life is 7 to 9 hours, although this may be reduced to 2 to 3 hours by liver enzyme-inducing drugs (see also Interactions, above).

References.
1. Gustavson LE, Mengel HB. Pharmacokinetics of tiagabine, a γ-aminobutyric acid-uptake inhibitor, in healthy subjects after single and multiples doses. *Epilepsia* 1995; 36: 605–11.
2. So EL, *et al.* Pharmacokinetics of tiagabine as add-on therapy in patients taking enzyme-inducing antiepilepsy drugs. *Epilepsy Res* 1995; 22: 21–6.
3. Snel S, *et al.* The pharmacokinetics of tiagabine in healthy elderly volunteers and elderly patients with epilepsy. *J Clin Pharmacol* 1997; 37: 1015–20.
4. Cato A, *et al.* Effect of renal impairment on the pharmacokinetics and tolerability of tiagabine. *Epilepsia* 1998; 39: 43–7.
5. Samara EE, *et al.* Population analysis of the pharmacokinetics of tiagabine in patients with epilepsy. *Epilepsia* 1998; 39: 868–73.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Gabitril; ***Austria:*** Gabitril; ***Belg.***: Gabitril; Cz.: Gabitril; ***Denm.***: Gabitril†; ***Fin.***: Gabitril†; ***Fr.***: Gabitril; ***Ger.***: Gabitril; ***Gr.***: Gabitril; ***Hung.***: Gabitril †; ***Irl.***: Gabitril; ***Ital.***: Gabitril; ***Pol.***: Gabitril; ***Port.***: Gabitril; ***Spain:*** Gabitril; ***Switz.***: Gabitril; ***UK:*** Gabitril; ***USA:*** Gabitril.

Pharmacopoeial Preparations
USP 36: Tiagabine Hydrochloride Oral Suspension.

Topiramate *(BAN, USAN, rINN)*

KW-6485; McN-4853; RWJ-17021; Topiramaatti; Topiramat; Topiramato; Topiramatum; Топирамат.

2,3:4,5-Di-O-isopropylidene-β-D-fructopyranose sulphamate.

$C_{12}H_{21}NO_8S$=339.4

CAS — 97240-79-4.

ATC — N03AX11.
ATC Vet — QN03AX11.
UNII — 0H73WJJ391.

Pharmacopoeias. In *US.*

USP 36: (Topiramate). A white to off-white powder. Freely soluble in dichloromethane. Store in airtight containers at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Topiramate, a sulfamate-substituted monosaccharide, is an antiepileptic used as adjunctive therapy in refractory partial seizures with or without secondary generalisation, seizures associated with the Lennox-Gastaut syndrome, and primary generalised tonic-clonic seizures (below). It may also be used as monotherapy in patients who have generalised tonic-clonic seizures or partial seizures. Topiramate is also used for the prophylaxis of migraine (see Headache, below) and, as a modified-release combination preparation with phentermine hydrochloride, in the management of obesity (below; see under Phentermine, p. 2329.2, for details of doses).

For both adjunctive and monotherapy of **epilepsy**, the initial oral dose of topiramate is 25 to 50 mg at night for 1 week increased thereafter by increments of 25 or 50 mg at intervals of 1 to 2 weeks until the effective dose is reached. Daily doses of more than 25 mg should be taken in 2 divided doses. The usual daily dose for *adjunctive therapy* is 200 to 400 mg. When used as *monotherapy*, usual doses range from 100 mg daily to a maximum of 500 mg daily.

For doses in children, see below.

As with other antiepileptics, withdrawal of topiramate therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. The daily dose should generally be decreased by 50 to 100 mg at weekly intervals. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1.

In the prophylaxis of **migraine**, topiramate is given orally in initial doses of 25 mg at night for 1 week, increased by 25-mg increments every week, to a usual dose of 50 mg twice daily. If topiramate therapy is to be stopped the daily dose should usually be decreased by 25 to 50 mg at weekly intervals.

Smaller increments or longer intervals between increments may be necessary if patients cannot tolerate the above regimens; doses should be halved in patients with moderate to severe renal impairment regardless of indication (see also below).

Administration in children. Topiramate is used as adjunctive therapy in children for refractory partial seizures with or without secondary generalisation, seizures associated with the Lennox-Gastaut syndrome, and primary generalised tonic-clonic seizures. It may also be used as monotherapy in those with newly diagnosed **epilepsy** who have generalised tonic-clonic seizures or partial seizures.

In the UK, the initial oral dose for *adjunctive* therapy in children from 2 years of age is 25 mg. This is given as a single dose at night for 1 week, then increased by 1 to 3 mg/kg every 1 or 2 weeks until the effective dose is reached; these higher daily doses are divided and given twice daily. About 5 to 9 mg/kg daily is usually required, although up to 30 mg/kg daily has been given.

For *monotherapy*, in children from 6 years of age, the initial daily oral dose is 0.5 to 1 mg/kg at night for the first week, increased thereafter by 0.5 to 1 mg/kg every 1 or 2 weeks, to an initial target dose of 100 mg (about 2 mg/kg) daily in 2 divided doses.

The adult dose (above) is recommended in those over 18 years of age.

In the USA, licensed doses are similar to those in the UK; however, monotherapy is licensed for children as young as 2 years old.

Although unlicensed for the prophylaxis of **migraine** in children, the *BNFC* suggests that the usual adult dose (see above) for this indication may be given to those aged 16 years and older.

Administration in renal impairment. Patients with moderate to severe renal impairment take longer to reach steady-state plasma concentrations of topiramate than patients with normal renal function (see Pharmacokinetics, p. 552.3) and the dosage regimen may need adjusting; the usual adult doses (see above) should be halved in such patients.

In patients undergoing haemodialysis a supplemental dose equal to about one-half of the daily dose should be given in divided doses (at the start and finish of the procedure).

Alcohol withdrawal and abstinence. Topiramate may be of use as an adjunct in achieving and maintaining abstinence in patients with alcohol dependence[1-5] (p. 1735.1).

1. Johnson BA, *et al.* Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. *Lancet* 2003; 361: 1677–85.
2. Johnson BA, *et al.* Topiramate for treating alcohol dependence: a randomized controlled trial. *JAMA* 2007; 298: 1641–51.
3. Johnson BA, *et al.* Improvement of physical health and quality of life of alcohol-dependent individuals with topiramate treatment: US multisite randomized controlled trial. *Arch Intern Med* 2008; 168: 1188–99.
4. Olmsted CL, Kockler DR. Topiramate for alcohol dependence. *Ann Pharmacother* 2008; 42: 1475–80.
5. Kenna GA, *et al.* Review of topiramate: an antiepileptic for the treatment of alcohol dependence. *Curr Drug Abuse Rev* 2009; 2: 135–42.

Bipolar disorder. Mood-stabilising antiepileptics such as carbamazepine and valproate are alternatives to lithium in the management of bipolar disorder (p. 397.2). Topiramate has also been investigated after favourable case reports,[1,2] but randomised controlled studies[3,4] have produced disappointing results and a systematic review[5] found insufficient evidence for its use as monotherapy or adjunctive therapy.

1. Tetter CJ, *et al.* Treatment of affective disorder and obesity with topiramate. *Ann Pharmacother* 2000; 34: 1262–5.
2. Erfurth A, Kuhn G. Topiramate monotherapy in the maintenance treatment of bipolar I disorder: effects on mood, weight and serum lipids. *Neuropsychobiology* 2000; 42 (suppl 1): 50–1.
3. Kushner SF, *et al.* Topiramate monotherapy in the management of acute mania: results of four double-blind placebo-controlled trials. *Bipolar Disord* 2006; 8: 15–27.
4. Chengappa KNR, *et al.* Adjunctive topiramate therapy in patients receiving a mood stabilizer for bipolar I disorder: a randomized, placebo-controlled trial. *J Clin Psychiatry* 2006; 67: 1698–1706.
5. Vasudev K, *et al.* Topiramate for acute affective episodes in bipolar disorder. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 09/06/08).

Epilepsy. Topiramate is used[1-6] in epilepsy (p. 506.1) for refractory partial seizures, for primary generalised tonic-clonic seizures,[7] and in patients with the Lennox-Gastaut syndrome;[8] in the UK, it may be a first-line option in some circumstances. Starting topiramate therapy gradually improves tolerability without delaying therapeutic response.[9]

Topiramate has also been investigated in children with infantile spasms (as for example in West's syndrome),[10] severe myoclonic epilepsy,[11] and juvenile myoclonic epilepsy;[12] it has been tried as a second-line drug in absence seizures and for tonic or atonic seizures. A retrospective review[13] and later studies[14,15] of the use of topiramate in such drug-resistant childhood epilepsies have concluded that it is efficacious and well tolerated.

Topiramate has also been investigated as an alternative antiepileptic in the management of refractory status epilepticus (p. 510.2).[16,17]

1. Sachdeo RC, *et al.* Topiramate: clinical profile in epilepsy. *Clin Pharmacokinet* 1998; 34: 335–46.
2. Garnett WR. Clinical pharmacology of topiramate: a review. *Epilepsia* 2000; 41 (suppl 1): S61–S65.
3. Glauser TA, *et al.* Topiramate monotherapy in newly diagnosed epilepsy in children and adolescents. *J Child Neurol* 2007; 22: 693–9.
4. Lyseng-Williamson KA, Yang LPH. Topiramate: a review of its use in the treatment of epilepsy. *Drugs* 2007; 67: 2231–56.
5. Jette N, *et al.* Topiramate add-on for drug-resistant partial epilepsy. Available in The Cochrane Database of Systematic Reviews: Issue 3. Chichester: John Wiley; 2008 (accessed 27/08/08).
6. *Novotny E, et al.* Randomized trial of adjunctive topiramate therapy in infants with refractory partial seizures. *Neurology* 2010; 74: 714–20.
7. Biton V. A randomized, placebo-controlled study of topiramate in primary generalized tonic-clonic seizures. *Neurology* 1999; 52: 1330–7.
8. Sachdeo RC, *et al.* A double-blind, randomized trial of topiramate in Lennox-Gastaut syndrome. *Neurology* 1999; 52: 1882–7.
9. Biton V, *et al.* Topiramate titration and tolerability. *Ann Pharmacother* 2001; 35: 173–9.
10. Glauser TA, *et al.* Long-term response to topiramate in patients with West syndrome. *Epilepsia* 2000; 41 (suppl 1): S91–S94.
11. Nieto-Barrera M, *et al.* Topiramate in the treatment of severe myoclonic epilepsy in infancy. *Seizure* 2000; 9: 590–4.
12. Biton V, Bourgeois BFD. Topiramate in patients with juvenile myoclonic epilepsy. *Arch Neurol* 2005; 62: 1705–8.
13. Yeung S, *et al.* Topiramate for drug-resistant epilepsies. *Eur J Paediatr Neurol* 2000; 4: 31–3.
14. Al Ajlouni S, *et al.* The efficacy and side effects of topiramate on refractory epilepsy in infants and young children: a multi-center clinical trial. *Seizure* 2005; 14: 459–63.
15. Grosso S, *et al.* Efficacy and safety of topiramate in refractory epilepsy of childhood: long-term follow-up study. *J Child Neurol* 2005; 20: 893–7.
16. Towne AR, *et al.* The use of topiramate in refractory status epilepticus. *Neurology* 2003; 60: 332–4.
17. Bensalem MK, Fakhoury TA. Topiramate and status epilepticus: report of three cases. *Epilepsy Behav* 2003; 4: 757–60.

Headache. Topiramate is used for the prophylaxis of *migraine* (p. 670.3). Results from placebo-controlled studies[1-5] have shown a significant reduction in frequency of migraines in those patients receiving prophylactic topiramate.

Topiramate has been tried for prophylaxis of *cluster headache* attacks[6] (p. 670.1) and chronic *tension-type headache*[7] (p. 671.3). It has also been used to control headache due to *raised intracranial pressure* (see p. 1271.3).

1. Storey JR, *et al.* Topiramate in migraine prevention: a double-blind, placebo-controlled study. *Headache* 2001; 41: 968–75.
2. Brandes JL, *et al.* Topiramate for migraine prevention: a randomized controlled trial. *JAMA* 2004; 291: 965–73.
3. Silberstein SD, *et al.* Topiramate in migraine prevention: results of a large controlled trial. *Arch Neurol* 2004; 61: 490–5.
4. Silberstein SD, *et al.* Efficacy and safety of topiramate for the treatment of chronic migraine: a randomized, double-blind, placebo-controlled trial. *Headache* 2007; 47: 170–80.
5. Diener H-C, *et al.* Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study. *Cephalalgia* 2007; 27: 814–23.
6. Láinez MJA, *et al.* Topiramate in the prophylactic treatment of cluster headache. *Headache* 2003; 43: 784–9.
7. Lampl C, *et al.* A prospective, open-label, long-term study of the efficacy and tolerability of topiramate in the prophylaxis of chronic tension-type headache. *Cephalalgia* 2006; 26: 1203–8.

Hyperhidrosis. Reduced sweating has been associated with topiramate therapy (see Effects on the Nervous System, under Adverse Effects, p. 552.2). There have been 2 case reports[1,2] of the use of topiramate in the treatment of hyperhidrosis.

1. Owen DB, Meffert JJ. The suppression of primary palmar-plantar hyperhidrosis by topiramate. *Br J Dermatol* 2003; 148: 826–7.
2. Hoehn-Saric R. Facial hyperhidrosis-induced social fear alleviated with topiramate. *J Clin Psychiatry* 2006; 67: 1157.

Motor neurone disease. Topiramate has been tried as a potential therapy for amyotrophic lateral sclerosis (see Motor Neurone Disease, p. 2605.2) but with disappointing results.[1]

1. Cudkowicz ME, *et al.* A randomized, placebo-controlled trial of topiramate in amyotrophic lateral sclerosis. *Neurology* 2003; 61: 456–64.

Neuropathic pain. Although carbamazepine is the drug of choice in the treatment of *trigeminal neuralgia* (p. 11.2), topiramate has also been tried successfully.[1] It has also been tried in the treatment of *diabetic neuropathy*[2,3] (p. 8.2), *postherpetic neuralgia*[4] (p. 10.3), and of *phantom limb pain*[5] (p. 10.3). Some benefit in poorly-controlled neuropathic *pain in cancer patients* (p. 7.1) has also been reported.[6]

1. Zvartau-Hind M, *et al.* Topiramate relieves refractory trigeminal neuralgia in MS patients. *Neurology* 2000; 55: 1587–8.
2. Raskin P, *et al.* Topiramate vs placebo in painful diabetic neuropathy: analgesic and metabolic effects. *Neurology* 2004; 63: 865–73.
3. Donofrio PD, *et al.* Safety and effectiveness of topiramate for the management of painful diabetic peripheral neuropathy in an open-label extension study. *Clin Ther* 2005; 27: 1420–31.
4. Fowler JA, *et al.* Successful use of topiramate in a patient with severe postherpetic neuralgia. *Ann Pharmacother* 2009; 43: 139–42.
5. Harden RN, *et al.* Topiramate for phantom limb pain: a time-series analysis. *Pain Med* 2005; 6: 375–8.
6. Bendaly EA, *et al.* Topiramate in the treatment of neuropathic pain in patients with cancer. *Support Cancer Ther* 2007; 4: 241–6.

Obesity. Weight loss has been associated with topiramate therapy (see Adverse Effects, p. 552.1) and it has been tried as an adjunct in the treatment of overweight or obese patients (p. 2315.1); topiramate appears to be reasonably well tolerated and is available in some countries as a combination preparation with phentermine hydrochloride for the management of obesity. Topiramate has also been tried in binge eating (see below).

References.

1. Astrup A, Toubro S. Topiramate: a new potential pharmacological treatment for obesity. *Obes Res* 2004; 12 (suppl): 167S–173S.
2. Kirov G, Tredget J. Add-on topiramate reduces weight in overweight patients with affective disorders: a clinical case series. *BMC Psychiatry* 2005; 5: 19. Available at: http://www.biomedcentral.com/content/pdf/1471-244X-5-19.pdf (accessed 09/06/08)
3. Khazaal Y, *et al.* Long-term topiramate treatment of psychotropic drug-induced weight gain: a retrospective chart review. *Gen Hosp Psychiatry* 2007; 29: 446–9.
4. Eliasson B, *et al.* Weight loss and metabolic effects of topiramate in overweight and obese type 2 diabetic patients: randomized double-blind placebo-controlled trial. *Int J Obes* 2007; 31: 1140–7.
5. Rosenstock J, *et al.* A randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of topiramate controlled release in the treatment of obese type 2 diabetic patients. *Diabetes Care* 2007; 30: 1480–6.
6. Cates ME, *et al.* Efficacy of add-on topiramate therapy in psychiatric patients with weight gain. *Ann Pharmacother* 2008; 42: 505–10.
7. Kramer CK, *et al.* Efficacy and safety of topiramate on weight loss: a meta-analysis of randomized controlled trials. *Obes Rev* 2011; 12: e338–e347.
8. Cameron F, *et al.* Phentermine and topiramate extended release (Qsymia®): first global approval. *Drugs* 2012; 72: 2033–42.
9. Smith SM, *et al.* Phentermine/topiramate for the treatment of obesity. *Ann Pharmacother* 2013; 47: 340–9.
10. Cosentino G, *et al.* Phentermine and topiramate for the management of obesity: a review. *Drug Des Devel Ther* 2013; 7: 267–78.
11. Shin JH, Gadde KM. Clinical utility of phentermine/topiramate (Qsymia®) combination for the treatment of obesity. *Diabetes Metab Syndr Obes* 2013; 6: 131–9.

Psychiatric disorders. Topiramate has been tried in several psychiatric disorders, including *schizophrenia*[1] (p. 1031.3), *disturbed behaviour*[2] (p. 1030.2), *post-traumatic stress disorder*[3,4] (p. 1029.2), and *social anxiety disorder*[5] (see Phobic Disorders, p. 1029.1). It has also been tried in *binge eating*.[6-9] For its use in *bipolar disorder* see above.

1. Tiihonen J, *et al.* Topiramate add-on in treatment-resistant schizophrenia: a randomized, double-blind, placebo-controlled, crossover trial. *J Clin Psychiatry* 2005; 66: 1012–15.
2. Nickel MK, *et al.* Topiramate treatment of aggression in female borderline personality disorder patients: a double-blind, placebo-controlled study. *J Clin Psychiatry* 2004; 65: 1515–19.
3. Berlant JL. Prospective open-label study of add-on and monotherapy topiramate in civilians with chronic nonhallucinatory posttraumatic stress disorder. *BMC Psychiatry* 2004; 4: 24. Available at: http://www.

biomedcentral.com/content/pdf/1471-244X-4-24.pdf (accessed 09/06/08)
4. Alderman CP, *et al.* Topiramate in combat-related posttraumatic stress disorder. *Ann Pharmacother* 2009; **43**: 635–41.
5. Van Ameringen M, *et al.* An open trial of topiramate in the treatment of generalized social phobia. *J Clin Psychiatry* 2004; **65**: 1674–8.
6. Nickel C, *et al.* Topiramate treatment in bulimia nervosa patients: a randomized, double-blind, placebo-controlled trial. *Int J Eat Disord* 2005; **38**: 295–300.
7. Tata AL, Kockler DR. Topiramate for binge-eating disorder associated with obesity. *Ann Pharmacother* 2006; **40**: 1993–7.
8. Claudino AM, *et al.* Double-blind, randomized, placebo-controlled trial of topiramate plus cognitive-behavior therapy in binge-eating disorder. *J Clin Psychiatry* 2007; **68**: 1324–32.
9. Leombruni P, *et al.* Treatment of obese patients with binge eating disorder using topiramate: a review. *Neuropsychiatr Dis Treat* 2009; **5**: 385–92.

Tremor. A beta blocker is often the first drug used in patients with essential tremor who require regular treatment (p. 1318.3); however, topiramate[1,2] has also been tried.

1. Galvez-Jimenez N, Hargreave M. Topiramate and essential tremor. *Ann Neurol* 2000; **47**: 837–8.
2. Ondo WG, *et al.* Topiramate in essential tremor: a double-blind, placebo-controlled trial. *Neurology* 2006; **66**: 672–7.

Adverse Effects

Adverse effects associated with topiramate therapy include ataxia, impaired concentration, confusion, dizziness, fatigue, paraesthesia or hypoaesthesia, drowsiness, and difficulties with memory or cognition. Agitation, anxiety, nervousness, emotional lability, and mood disorders may also occur. Other reported adverse effects include abdominal pain, anorexia, asthenia, diplopia, leucopenia, nausea, nystagmus, insomnia, psychomotor retardation, impaired speech, altered taste, visual disturbances, and weight loss. The risk of developing renal calculi is increased, especially in predisposed patients. Reduced sweating with hyperthermia has occurred particularly in children. Rare cases of acute myopia with secondary angle-closure glaucoma have been reported.

Effects on bone. For the effects of antiepileptics, including topiramate, on bone and on calcium and vitamin D metabolism, see under Phenytoin, p. 540.2.

Effects on electrolytes. Metabolic acidosis has been associated with topiramate treatment. Data from clinical studies estimate that the incidence of persistently decreased serum bicarbonate concentrations ranges from 23 to 67% with topiramate compared with 1 to 10% with placebo;[1] children, in particular, may be at a greater risk than adults.[1,2] A retrospective cohort study also found that 48% of adult patients developed decreased serum bicarbonate concentrations while receiving topiramate.[3] Generally, the decreases in serum bicarbonate are mild to moderate and occur soon after starting topiramate. Clinical signs such as hyperventilation may develop. The mechanism involves inhibition of carbonic anhydrase, which results in impaired reabsorption of bicarbonate ions by the proximal renal tubule and reduced excretion of H^+ by the distal tubule (mixed renal tubular acidosis).[4] As well as the risk of acute symptoms, chronic acidosis may contribute to effects on bone and the development of renal calculi.

Some sources such as the US licensed product information recommend that baseline and periodic serum bicarbonate levels should be monitored during topiramate treatment. If metabolic acidosis develops or persists, it may be necessary to reduce the dose or stop topiramate although, in some cases, correcting the acidosis with alkali therapy may be more appropriate.

1. Janssen-Ortho Inc. Health Canada. Important drug safety information: Topamax (topiramate) use is associated with metabolic acidosis (issued 12 January, 2004). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/topamax_3_hpc-cps-eng.pdf (accessed 01/09/08)
2. Philippi H, *et al.* Topiramate and metabolic acidosis in infants and toddlers. *Epilepsia* 2002; **43**: 744–7.
3. Garris SS, Oles KS. Impact of topiramate on serum bicarbonate concentrations in adults. *Ann Pharmacother* 2005; **39**: 424–6.
4. Mirza N, *et al.* Effect of topiramate on acid-base balance: extent, mechanism and effects. *Br J Clin Pharmacol* 2009; **68**: 655–61.

Effects on the eyes. There have been rare reports of acute myopia with or without secondary angle-closure glaucoma in adults and children receiving topiramate:[1-3] as of April 2002 the UK CSM was aware of 23 cases worldwide occurring with secondary angle-closure glaucoma.[4] Symptoms include decreased visual acuity and ocular pain which generally appear within one month of starting treatment; hyperaemia and raised intra-ocular pressure may be present with or without mydriasis. Choroidal effusions resulting in anterior displacement of lens and iris have been reported. Appropriate measures to reduce intra-ocular pressure should be taken, and topiramate stopped as rapidly as is clinically feasible.[4] A later review[5] of 115 reports of ocular adverse effects associated with topiramate described 83 cases of bilateral and 3 cases of unilateral acute angle-closure glaucoma; of these, 7 sustained permanent loss of vision. Onset of glaucoma was between 1 and 49 days after starting topiramate therapy, with 85% of cases occurring within the first 2 weeks. Also reported were cases of acute bilateral myopia (17 patients), suprachoroidal effusions (9), scleritis (4), blepharospasm (2), oculogyric crisis (2), and myokymia (1). Diplopia and nystagmus were reported with daily doses of at least 200 to 400 mg topiramate.

1. Gubbay SS. The occurrence of drug-induced myopia as a transient side effect of topiramate. *Epilepsia* 1998; **39**: 451.
2. Sen HA, *et al.* Topiramate-induced acute myopia and retinal striae. *Arch Ophthalmol* 2001; **119**: 775–7.
3. Rhee DJ, *et al.* Bilateral angle-closure glaucoma and ciliary body swelling from topiramate. *Arch Ophthalmol* 2001; **119**: 1721–3.
4. CSM/MCA. Topiramate (Topamax): acute myopia and raised intraocular pressure. *Current Problems* 2002; **28**: 4. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON0074546-RevisionSelectionMethod=LatestReleased (accessed 09/06/08)
5. Fraunfelder FW, *et al.* Topiramate-associated acute, bilateral, secondary angle-closure glaucoma. *Ophthalmology* 2004; **111**: 109–11.

Effects on the liver. For reports of hepatotoxicity associated with the addition of topiramate to antiepileptic therapy with carbamazepine or valproate see Antiepileptics, under Interactions, on p. 516.3 and p. 557.3 respectively.

Effects on mental function. For a review of the effects of antiepileptic therapy including topiramate on *cognition* and *mood* (including the risk of suicidal ideation), see p. 508.3.

Effects on the nervous system. Hyperthermia was reported in 10.5% of patients taking topiramate compared with 0.15% of patients taking other antiepileptic drugs in one centre.[1] Children under the age of 6 years, patients on daily doses of 6 mg/kg or more, and those exposed to high ambient temperatures were most at risk. Licensed product information recommends that children should be monitored closely for decreased sweating and hyperthermia, especially during warm or hot weather. Caution is also advised when giving topiramate with other drugs known to cause similar effects, for example, carbonic anhydrase inhibitors and antimuscarinics.

Hemiparesis that resolved on withdrawal of topiramate has been reported[2] in 2 patients, although both already had compromised neurological function.

1. Ziad EK, *et al.* Age, dose, and environmental temperature are risk factors for topiramate-related hyperthermia. *Neurology* 2005; **65**: 1139–40.
2. Stephen LJ, *et al.* Transient hemiparesis with topiramate. *BMJ* 1999; **318**: 845.

Effects on sexual function. Topiramate has been associated with sexual dysfunction[1-3] in male and female patients; in all cases symptoms resolved with dosage reduction or withdrawal of the drug.

1. Holtkamp M, *et al.* Erectile dysfunction with topiramate. *Epilepsia* 2005; **46**: 166–7.
2. Sun C, *et al.* Reversible anorgasmia with topiramate therapy for headache: a report of 7 patients. *Headache* 2006; **46**: 1450–3.
3. Calabrò RS, *et al.* Topiramate-induced erectile dysfunction. *Epilepsy Behav* 2009; **14**: 560–1.

Precautions

Topiramate should be used with caution in patients with renal or hepatic impairment. Adequate hydration is recommended to reduce the risk of developing renal calculi, especially in predisposed patients.

Care is required when withdrawing topiramate therapy—see also Uses and Administration, p. 551.1.

Breast feeding. For comment on antiepileptic therapy and breast feeding, see p. 508.3.

Driving. For a comment on antiepileptic drugs and driving, see p. 509.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies topiramate as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pregnancy. For comments on the management of epilepsy during pregnancy, see p. 509.2.

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy.

References.

1. Bialer M, *et al.* Pharmacokinetic interactions of topiramate. *Clin Pharmacokinet* 2004; **43**: 763–80.

Antiepileptics. In pharmacokinetic studies hepatic enzyme inducers such as *carbamazepine*,[1-3] *phenobarbital*,[2] and *phenytoin*[1,2] were reported to decrease the plasma concentration of topiramate.

For the effect of topiramate on phenytoin and carbamazepine, see p. 543.2 and p. 516.3, respectively. For reports of an increased risk of hepatic impairment in patients taking topiramate with valproate, see p. 557.3.

1. Bourgeois BFD. Drug interaction profile of topiramate. *Epilepsia* 1996; **37**: (suppl 2): S14–S17.
2. Contin M, *et al.* Topiramate therapeutic monitoring in patients with epilepsy: effect of concomitant antiepileptic drugs. *Ther Drug Monit* 2002; **24**: 332–7.
3. Mimrod D, *et al.* A comparative study of the effect of carbamazepine and valproic acid on the pharmacokinetics and metabolic profile of topiramate at steady state in patients with epilepsy. *Epilepsia* 2005; **46**: 1046–54.

Cardiac glycosides. For the effect of topiramate on *digoxin*, see p. 1357.1.

Corticosteroids. For the effect of topiramate on corticosteroids, see p. 1619.3.

Sex hormones. For the effects of antiepileptics including topiramate on *oral contraceptives*, see p. 2243.2.

Pharmacokinetics

Topiramate is readily absorbed after oral doses, with peak plasma concentrations occurring after about 2 hours. Bioavailability is not affected by the presence of food. Protein binding is about 9 to 17%. The volume of distribution in women is about half that in men. Topiramate crosses the placental barrier and is distributed into breast milk.

In healthy subjects topiramate is not extensively metabolised; however, up to 50% of a dose may undergo metabolism in the liver in patients also receiving enzyme inducing drugs. It is eliminated chiefly in urine, as unchanged drug and metabolites; mean plasma elimination half-life is about 21 hours. Steady-state concentrations occur after about 4 to 8 days in patients with normal renal function. Clearance is decreased in patients with impaired renal or hepatic function, and steady-state plasma concentrations may not occur for 10 to 15 days in the former. Children exhibit a higher clearance and shorter elimination half-life than adults.

The pharmacokinetics of topiramate may be affected by use with other antiepileptics (see under Interactions above).

References.

1. Perucca E, Bialer M. The clinical pharmacokinetics of the newer antiepileptic drugs: focus on topiramate, zonisamide, and tiagabine. *Clin Pharmacokinet* 1996; **31**: 29–46.
2. Glauser TA, *et al.* Topiramate pharmacokinetics in infants. *Epilepsia* 1999; **40**: 788–91.
3. Öhman I, *et al.* Topiramate kinetics during delivery, lactation, and in the neonate: preliminary observations. *Epilepsia* 2002; **43**: 1157–60.
4. Perrari AR, *et al.* Influence of dosage, age, and co-medication on plasma topiramate concentrations in children and adults with severe epilepsy and preliminary observations on correlations with clinical response. *Ther Drug Monit* 2003; **25**: 700–8.
5. Battino D, *et al.* Topiramate pharmacokinetics in children and adults with epilepsy: a case-matched comparison based on therapeutic drug monitoring data. *Clin Pharmacokinet* 2005; **44**: 407–16.
6. Britzl M, *et al.* Pharmacokinetic and metabolic investigation of topiramate disposition in healthy subjects in the absence and in the presence of enzyme induction by carbamazepine. *Epilepsia* 2005; **46**: 378–84.
7. Zanotta N, *et al.* Clinical experience with topiramate dosing and serum levels in patients with epilepsy. *Seizure* 2006; **15**: 86–92.
8. Öhman I, *et al.* Pharmacokinetics of topiramate during pregnancy. *Epilepsy Res* 2009; **87**: 124–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Neutop; Topamac; Topictal; Topirex†; Zinalow; ***Austral.***: Epiramax; Epiramax; Tamate; Topamax; ***Austria***: Topamax; Topilex; ***Belg.***: Topamax; ***Braz.***: Amato; Sigmax; Topamax; Toptil; ***Canad.***: Topamax; ***Chile***: Piracross; Topamax; Topictal; Toprel; ***China***: Topamax (妥泰); ***Cz.***: Epimaxan; Erravia; Topafis; Topamax; Topilept; Topilex; Topimark; Topiragist†; Zidoxer; ***Denm.***: Epitomax†; Maritop; Monotop; Topaben; Topamax†; Topimatil†; Topimax; Topiratore; ***Fin.***: Topimax; ***Fr.***: Epitomax; ***Ger.***: Topamax; Topiragamma†; Topiramed†; ***Gr.***: Jadix; Letop; Pirantal; Topamac; Topepil; Topiref; Toramat; ***Hong Kong***: Topamax; ***Hung.***: Epilania; Etopro; Talopam; Topamax; Topepsil; Topilex; ***India***: Epimate; Epitome; Epitop; Nextop; Topamac; Topamate; ***Indon.***: Topamax; ***Irl.***: Topamax; Topirama; Topit; ***Israel***: Topamax; Topitrim; ***Ital.***: Topamax; ***Jpn***: Topina; ***Malaysia***: Topamax; ***Mex.***: Nabian-K†; Topamax; ***Neth.***: Epitomax†; Erudan†; Symtopiram†; Topamax; Topepsil; Topilept; Topitex†; ***Norw.***: Topimax; ***NZ***: Topamax; ***Philipp.***: Epimate; Epitop; Topamax; ***Pol.***: Epimaxan; Epiramat; Epitoram; Erudan; Etopro; Monotop; Symtopiram; Topamax; Topiegis; Topifar; Topigen; TopiLek; Topimatil; Topimerck; Topistad; Toramat; Zidoxer; ***Port.***: Amlix†; Arrosertra; Bluantina†; Olandic; Pirepil; Tomix; Topamax; Toptrix†; Vermedis; ***Rus.***: Maxitopir (Макситопир); Topalepsin (Топалепсин); Topamax (Топамакс); Topiromax (Топиромакс); Topsaver (Топсавер); Toreal (Тореал); ***S.Afr.***: Epitoz; Piramax;

Topalex; Topamax; Toplep; ***Singapore***: Topamax; ***Spain***: Acomicil; Bipomax†; Epilmax; Fagodol; Topamax; Topibrain; Topimylan†; ***Swed.***: Topimax; ***Switz.***: Topamax; ***Thai.***: Topamax; ***Turk.***: Letop; Noromat; Topamax; ***UK***: Topamax; ***Ukr.***: Epiramat (Эпирамат); Rantopir (Рантопир)†; Topilepsin (Топилепсин); Topiromax (Топиромакс); ***USA***: Topamax; Topiragen; Trokendi; ***Venez.***: Topamax.

Multi-ingredient Preparations. ***USA***: Qsymia.

Pharmacopoeial Preparations
USP 36: Topiramate Tablets.

Trimethadione *(BAN, rINN)*

Trimetadion; Trimetadiona; Trimetadionas; Trimetadioni; Trimethadion; Triméthadione; Trimethadionum; Trimethinum; Troxidone; Триметадион.
3,5,5-Trimethyl-1,3-oxazolidine-2,4-dione.
$C_6H_9NO_3$=143.1
CAS — 127-48-0.
ATC — N03AC02.
ATC Vet — QN03AC02.
UNII — R7GV3H6FQ4.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *Jpn.*

Ph. Eur. 8: (Trimethadione). Colourless or almost colourless crystals. Soluble in water; very soluble in alcohol. Protect from light.

Profile

Trimethadione is an oxazolidinedione antiepileptic that has been given in the treatment of absence seizures refractory to other antiepileptics. However, because of its potential toxicity, other antiepileptics are preferred (see Epilepsy, p. 506.1).

Pregnancy. Characteristic congenital malformations, termed the fetal trimethadione syndrome, have been associated with the use of trimethadione in pregnancy.

For comments on the management of epilepsy during pregnancy, see p. 509.2.

Valproate

Valproato; Вальпроат.

NOTE. Valproate is a generic term applied to valproic acid and its salts and esters.

Valproic Acid *(BAN, USAN, rINN)*

Abbott-44089; Acide valproïque; Ácido dipropilacético; Ácido valproico; Acidum Valproicum; Kyselina valproová; Valproico, ácido; Valproiinihappo; Valproik Asit; Valproinė rūgštis; Valproinsäure; Valproinsav; Valproinsyra; Вальпроевая Кислота.
2-Propylvaleric acid; 2-Propylpentanoic acid.
$C_8H_{16}O_2$=144.2
CAS — 99-66-1.
ATC — N03AG01.
ATC Vet — QN03AG01.
UNII — 614OI1Z5WI.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Valproic Acid). A colourless or very slightly yellow, slightly viscous, clear liquid. Very slightly soluble in water; miscible with alcohol and with dichloromethane. It dissolves in dilute solutions of alkali hydroxides. Store in airtight containers.

USP 36: (Valproic Acid). A colourless to pale yellow, slightly viscous, clear liquid having a characteristic odour. Slightly soluble in water; freely soluble in alcohol, in acetone, in chloroform, in ether, in methyl alcohol, in benzene, in *n*-heptane, and in 1N sodium hydroxide; slightly soluble in 0.1N hydrochloric acid. Store in airtight glass, stainless steel, or polyethylene containers.

Sodium Valproate *(BANM, rINNM)*

Abbott-44090; Natrii Valproas; Natrio valproatas; Natriumvalproaatti; Natriumvalproat; Natrium-valproát; Nátrium-valproát; NIK-240; Sodium, valproate de; Sodyum Valproat; Valproate de Sodium; Valproate Sodium (USAN); Valproato sódico; Натрий Вальпроат.
Sodium 2-propylvalerate; Sodium 2-propylpentanoate.
$C_8H_{15}NaO_2$=166.2
CAS — 1069-66-5.
ATC — N03AG01.
ATC Vet — QN03AG01.
UNII — 5VOM6GYJ0D.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *Jpn.*

Ph. Eur. 8: (Sodium Valproate). A white or almost white, hygroscopic, crystalline powder. It exhibits polymorphism. Very soluble in water; freely soluble in alcohol. Store in airtight containers.

Valproate Pivoxil *(rINN)*

CHF-1504; Valproato de pivoxilo; Valproato pivoxilo; Valproatum Pivoxilum; Вальпроат Пивоксил.
Hydroxymethyl 2-propylvalerate pivalate.
$C_{14}H_{26}O_4$=258.4
CAS — 77372-61-3.
ATC — N03AG01.
ATC Vet — QN03AG01.
UNII — 9F5A05A29T.

Valproate Semisodium *(rINN)*

Abbott-50711; Divalproex Sodium (USAN); Semisodium Valproate (BAN); Valproate Semisodique; Valproato semisódico; Valproatum Seminatricum; Вальпроат Семинатрий.
2-Propylvaleric acid—Sodium 2-propylvalerate (1:1); Sodium hydrogen bis(2-propylvalerate) oligomer.
$C_{16}H_{31}NaO_4$=310.4
CAS — 76584-70-8.
ATC — N03AG01.
ATC Vet — QN03AG01.
UNII — 644VL95AO6.

Pharmacopoeias. In *US.*

USP 36: (Divalproex Sodium). A white to off-white powder. Soluble in acetone; practically insoluble in acetonitrile; very soluble in chloroform; freely soluble in ethyl ether and in methyl alcohol. Store in airtight containers.

Valpromide *(rINN)*

Dipropilacetamida; Dipropylacetamide; Valpromida; Valpromidum; Вальпромид.
2-Propylvaleramide.
$C_8H_{17}NO$=143.2
CAS — 2430-27-5.
ATC — N03AG02.
ATC Vet — QN03AG02.
UNII — RUA6CWU76G.

Uses and Administration

Valproate is an antiepileptic used particularly in the treatment of primary generalised seizures, has notable benefit in absence and myoclonic seizures, and is also used for partial seizures. Its actions are complex and its mode of action in epilepsy is not fully understood. Valproate is also used to treat the acute manic phase of bipolar disorder and for the prophylaxis of migraine.

Forms used include the sodium salts (valproate semisodium and sodium valproate), the amide derivative (valpromide), and valproic acid. Magnesium valproate has also been tried as has calcium valproate. Valproate should preferably be taken with or after food.

In the treatment of **epilepsy** (p. 554.1) the dose should be adjusted to the needs of the individual patient to achieve adequate control of seizures. Plasma concentrations of valproate (see Pharmacokinetics, p. 558.1) are not considered to be a useful index of efficacy and thus their routine monitoring is generally not helpful.

- A suggested initial *oral* daily dose of ***sodium valproate*** is 600 mg given in 2 divided doses. The daily dose may be increased by 200 mg every 3 days to a usual range of 1 to 2 g daily (20 to 30 mg/kg daily); up to a maximum of 2.5 g daily may be necessary if adequate control has not been achieved. Modified-release formulations are available to minimise fluctuations in plasma concentration.
  When oral dosage is not possible, sodium valproate may be given *intravenously* to start therapy or to continue therapy previously given orally. A suggested dose to ***begin*** therapy is up to 10 mg/kg by intravenous injection over 3 to 5 minutes followed by intravenous infusion, as necessary, up to a maximum of 2.5 g daily. To ***continue*** therapy intravenously, doses are the same as the patient's previous oral dose. In the USA, intravenous sodium valproate is given in doses equivalent to those used orally for valproic acid (see below).
- A suggested initial oral dose of ***valproic acid*** is 10 to 15 mg/kg daily increased at one-week intervals by 5 to 10 mg/kg. The maximum recommended dose of valproic acid in the UK is 30 mg/kg daily whereas in the USA it is 60 mg/kg daily. Valproic acid may be given in 2 to 4 divided doses.
- ***Valproate semisodium*** is given orally in doses equivalent to those used for oral valproic acid (see above).
- The amide derivative of valproic acid, ***valpromide***, is also used in some countries. Usual oral doses have ranged from 600 mg to 1.8 g daily, in divided doses.

For details of valproate doses in children, see below.

As with other antiepileptics, withdrawal of valproate or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1.

In the treatment of acute manic episodes of **bipolar disorder** (p. 554.1), the initial oral dose of ***valproate semisodium*** is the equivalent of valproic acid 750 mg daily in 2 or 3 divided doses. Thereafter, the dose is increased as rapidly as possible to achieve the optimal response; the usual range is 1 to 2 g daily with a maximum of up to 60 mg/kg daily. Patients receiving doses higher than 45 mg/kg daily should be carefully monitored. ***Valpromide*** has also been used in some countries for bipolar disorder in doses similar to those for epilepsy (see above).

In the prophylaxis of **migraine** (see Headache, p. 554.2) valproate semisodium is given orally in a dose equivalent to valproic acid 250 mg twice daily; up to 1 g daily may be necessary in some patients.

Action. The actions of valproate are complex and not well understood. As well as enhancing central GABAergic neurotransmission and inhibiting neuronal sodium channels, it affects cellular signalling systems such as the Wnt/β-catenin and extracellular signal-regulated kinase (ERK) pathways, and has actions on inositol and arachidonate metabolism. In addition it has potent effects on transcription of several genes, mediated at least in part by its action as a direct histone deacetylase inhibitor. It is probable that its clinical effects in different disorders depend on a combination of such properties.[1]

1. Rosenberg G. The mechanisms of action of valproate in neuropsychiatric disorders: can we see the forest for the trees? *Cell Mol Life Sci* 2007; **64**: 2090–2103.

Administration in children. Valproate is used as an antiepileptic in children in the treatment of primary generalised seizures, notably for absence and myoclonic seizures, and also for partial seizures. Available forms include the sodium salts (valproate semisodium and sodium valproate) or as valproic acid. The *BNFC* suggests that sodium valproate may also be used for infantile spasms.

A suggested initial *oral* dose of ***sodium valproate*** for children weighing over 20 kg is 400 mg daily (irrespective of weight) in 2 divided doses. This may be gradually increased to a usual dose of 20 to 30 mg/kg daily; up to a maximum of 35 mg/kg daily may be necessary if adequate control has not been achieved. Children weighing under 20 kg may be given 20 mg/kg daily in 2 divided doses, which may be increased to 40 mg/kg daily or more if necessary (but see below). Modified-release formulations are available to minimise fluctuations in plasma concentration. Alternatively the *BNFC* suggests the following *oral* or *rectal* doses, given according to age:

- neonates: initially 20 mg/kg once daily followed by a usual maintenance dose of 10 mg/kg twice daily
- *1 month to 12 years*: initially 5 to 7.5 mg/kg twice daily followed by a usual maintenance dose of 12.5 to 15 mg/kg twice daily; up to 30 mg/kg twice daily may be given for infantile spasms (but see below)
- *over 12 years*: usual adult doses (see above)

When used rectally, the *BNFC* recommends that sodium valproate oral solution may be used and retained for 15 minutes; dilution with water may be required, if necessary.

When oral dosage is not possible, sodium valproate is licensed for use *intravenously* to start therapy or to continue therapy previously given orally. The usual dose is in the range of 20 to 30 mg/kg daily by intravenous injection over 3 to 5 minutes or by infusion; up to 40 mg/kg daily or more may be necessary if adequate control is not achieved (but see below). When switching from oral to intravenous therapy, the intravenous dose should be the same as the established oral dose.

Alternatively, the *BNFC* suggests giving neonates 10 mg/kg twice daily by intravenous injection; those aged from 1 month to 12 years may be given 10 mg/kg initially by intravenous injection, followed by continuous or intermittent infusion, or intravenous injection in 2 to 4 divided doses, up to a usual range of 20 to 40 mg/kg daily, and older children may be given the usual adult doses (see above).

When a dose over 20 mg/kg daily is given, regardless of route, it is recommended that plasma-valproate concentrations should be monitored. If the dose exceeds 40 mg/kg daily, the patient's clinical chemistry and haematological parameters should also be monitored.

The *BNFC* states that children of all ages may be given ***valproic acid*** in doses as for sodium valproate (see above). In the USA, valproic acid is only licensed for children aged 10 years and older, who may be given the adult dose.

In the USA, *valproate semisodium* may also be given to children aged 10 years and over in the usual adult doses (see p. 553.2) for the treatment of epilepsy.

Bipolar disorder. Valproate, usually as valproate semisodium, is increasingly being used as an alternative to lithium in patients with bipolar disorder (p. 397.2).[1-9] Most guidelines consider it to be a first-line alternative to lithium particularly in those who have rapid cycling disease with 4 or more affective episodes a year or in those with mixed or dysphoric states. However, a study[9] failed to show particular benefit in rapid cycling disease, and a systematic review considered that any shift in prescribing practice in favour of valproate was not based on reliable evidence of efficacy,[10] although another concluded it was effective in acute mania.[8] A more recent systematic review[11] concluded that valproate was effective for the relief of depressive symptoms in acute bipolar disorder, and there was no evidence for an increased risk of mania. However, the studies on which this conclusion was based were relatively small, and a large controlled study was advocated.

1. Pope HG, *et al.* Valproate in the treatment of acute mania: a placebo-controlled study. *Arch Gen Psychiatry* 1991; **48**: 62–8.
2. Joffe RT. Valproate in bipolar disorder: the Canadian perspective. *Can J Psychiatry* 1993; **38** (suppl 2): S46–S50.
3. Schaff MR, *et al.* Divalproex sodium in the treatment of refractory affective disorders. *J Clin Psychiatry* 1993; **54**: 380–4.
4. Bowden CL, *et al.* Efficacy of divalproex vs lithium and placebo in the treatment of mania. *JAMA* 1994; **271**: 918–24. Correction. *Ibid.*; 1830.
5. Stoll AL, *et al.* Neurologic factors predict a favorable valproate response in bipolar and schizoaffective disorders. *J Clin Psychopharmacol* 1994; **14**: 311–13.
6. Swann AC, *et al.* Depression during mania: treatment response to lithium or divalproex. *Arch Gen Psychiatry* 1997; **54**: 37–42.
7. Müller-Oerlinghausen B, *et al.* Valproate as adjunct to neuroleptic medication for the treatment of acute episodes of mania: a prospective, randomized, double-blind, placebo-controlled, multicenter study. *J Clin Psychopharmacol* 2000; **20**: 195–203.
8. Macritchie K, *et al.* Valproate for acute mood episodes in bipolar disorder. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 09/06/08).
9. Calabrese JR, *et al.* A 20-month, double-blind, maintenance trial of lithium versus divalproex in rapid-cycling bipolar disorder. *Am J Psychiatry* 2005; **162**: 2152–61.
10. Macritchie K, *et al.* Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder. Available in The Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2001 (accessed 09/06/08).
11. Smith LA, *et al.* Valproate for the treatment of acute bipolar depression: systematic review and meta-analysis. *J Affect Disord* 2010; **122**: 1–9.

Cushing's syndrome. Sodium valproate has been used in the management of Cushing's syndrome (p. 2559.1).

Epilepsy. Valproate is one of the drugs of choice in partial seizures, primary generalised tonic-clonic seizures, absence seizures, and myoclonic seizures (p. 506.1), although evidence for some of these is lacking. It is also the drug of choice in epileptic syndromes such as the Lennox-Gastaut syndrome because of its wide therapeutic spectrum, and it may be useful in tonic or atonic seizures and infantile spasms.

References.

1. Mattson RH, *et al.* A comparison of valproate with carbamazepine for the treatment of complex partial seizures and secondarily generalized tonic-clonic seizures in adults. *N Engl J Med* 1992; **327**: 765–71.
2. Richens A, *et al.* A multicentre trial of sodium valproate and carbamazepine in adult onset epilepsy. *J Neurol Neurosurg Psychiatry* 1994; **57**: 682–7.
3. Verity CM, *et al.* A multicentre comparative trial of sodium valproate and carbamazepine in paediatric epilepsy. *Dev Med Child Neurol* 1995; **37**: 97–108.
4. Beydoun A, *et al.* and the Depakote Monotherapy for Partial Seizures Study Group. Safety and efficacy of divalproex sodium monotherapy in partial epilepsy: a double-blind, concentration-response design clinical trial. *Neurology* 1997; **48**: 182–8.
5. Brodie MJ, Mumford JP. Double-blind substitution of vigabatrin and valproate in carbamazepine-resistant partial epilepsy. *Epilepsy Res* 1999; **34**: 199–205.
6. Posner EB, *et al.* Ethosuximide, sodium valproate or lamotrigine for absence seizures in children and adolescents. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 09/06/08).
7. Guerrini R. Valproate as a mainstay of therapy for pediatric epilepsy. *Paediatr Drugs* 2006; **8**: 113–29.
8. Aldenkamp A, *et al.* Role of valproate across the ages: treatment of epilepsy in children. *Acta Neurol Scand* 2006; **184** (suppl): 1–13.
9. Ben-Menachem E, *et al.* Role of valproate across the ages: treatment of epilepsy in adults. *Acta Neurol Scand* 2006; **184** (suppl): 14–27.
10. Perucca E, *et al.* Role of valproate across the ages: treatment of epilepsy in the elderly. *Acta Neurol Scand* 2006; **184** (suppl): 28–37.
11. Marson AG, *et al.* SANAD Study Group. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. *Lancet* 2007; **369**: 1016–26.
12. Gerstner T, *et al.* Oral valproic acid for epilepsy—long-term experience in therapy and side effects. *Expert Opin Pharmacother* 2008; **9**: 285–92.

Extrapyramidal disorders. Valproate is one of several drugs with GABAergic action that has been tried in the management of tardive dyskinesia (see under Extrapyramidal Disorders, p. 1049.2).

Febrile convulsions. Sodium valproate has been used prophylactically in children thought to be at risk of recurrence of febrile convulsions (p. 511.2), but routine use of antiepileptics is no longer recommended.

References.

1. Newton RW. Randomised controlled trials of phenobarbitone and valproate in febrile convulsions. *Arch Dis Child* 1988; **63**: 1189–91.

Headache. Valproate, as valproate semisodium, may be used for the prophylaxis of *migraine* (p. 670.3) in patients refractory to drugs such as propranolol.[1-7] Valproate has also been shown to be effective and well-tolerated for the prophylaxis of migraine in children aged between 7 and 16 years.[8,9] Intravenous valproate has been tried in the treatment of acute migraine but a review[10] concluded that its use could not be recommended. To date, published studies had mostly been small, open-label, and uncontrolled and had used variable doses. Valproate had not been shown to be superior to other antimigraine drugs and had been inferior to prochlorperazine in one study.

Valproate has also been tried in the prophylaxis of persistent chronic daily headache including *tension-type headache* (p. 671.3) unresponsive to other drugs.[11]

It has also been tried for prevention of *cluster headache* (p. 670.1).

1. Sørensen KV. Valproate: a new drug in migraine prophylaxis. *Acta Neurol Scand* 1988; **78**: 346–8.
2. Hering R, Kuritzky A. Sodium valproate in the prophylactic treatment of migraine: a double-blind study versus placebo. *Cephalalgia* 1992; **12**: 81–4.
3. Coria F, *et al.* Low-dose sodium valproate in the prophylaxis of migraine. *Clin Neuropharmacol* 1994; **17**: 569–73.
4. Mathew NT, *et al.* Migraine prophylaxis with divalproex. *Arch Neurol* 1995; **52**: 281–6.
5. Kaniecki RG. A comparison of divalproex with propranolol and placebo for the prophylaxis of migraine without aura. *Arch Neurol* 1997; **54**: 1141–5.
6. Erdemoglu AK, Ozbakir S. Valproic acid in prophylaxis of refractory migraine. *Acta Neurol Scand* 2000; **102**: 354–8.
7. Freitag FG. Divalproex in the treatment of migraine. *Psychopharmacol Bull* 2003; **37** (suppl 2): 98–115.
8. Caruso JM, *et al.* The efficacy of divalproex sodium in the prophylactic treatment of children with migraine. *Headache* 2000; **40**: 672–6.
9. Ashrafi MR, *et al.* Sodium valproate versus propranolol in paediatric migraine prophylaxis. *Eur J Paediatr Neurol* 2005; **9**: 333–8.
10. Frazee LA, Foraker KC. Use of intravenous valproic acid for acute migraine. *Ann Pharmacother* 2008; **42**: 403–7.
11. Mathew NT, Ali S. Valproate in the treatment of persistent chronic daily headache: an open label study. *Headache* 1991; **31**: 71–4.

Hiccup. Valproic acid may be of value in the treatment of intractable hiccups,[1] especially those of neurogenic origin. For the management of intractable hiccups, see under Chlorpromazine, p. 1046.3.

1. Jacobson PL, *et al.* Treatment of intractable hiccups with valproic acid. *Neurology* 1981; **31**: 1458–60.

HIV infection and AIDS. As mentioned under Precautions, p. 557.1, valproate appears to induce replication of HIV, and this effect has been used to reduce latent, and therefore treatment-resistant, HIV-infection in resting CD4+ T-cells. In a preliminary study,[1] 4 HIV-positive patients on HAART were started on the fusion inhibitor enfuvirtide to intensify their HIV treatment and prevent viral spread due to valproate; oral valproic acid (500 to 750 mg twice daily) was then introduced a few weeks later and continued for 3 months. In 3 of these patients, the frequency of latent infection in resting T-cells significantly declined after enfuvirtide and valproate treatment when compared with pre-treatment values. However, a later study[2] found the levels of latently infected T-cells in 9 HIV-positive patients receiving HAART and oral valproic acid for at least 3 months to be similar to those of patients receiving HAART alone. Other studies[3,4] also suggested the benefits were small or absent. A case report[5] described rapid rebound viraemia occurring in a 54-year-old man when HAART and sodium valproate were stopped after more than 2 years of therapy, suggesting little benefit in eradicating latent infection.

1. Lehrman G, *et al.* Depletion of latent HIV-1 infection in vivo: a proof-of-concept study. *Lancet* 2005; **366**: 549–55.
2. Siliciano JD, *et al.* Stability of the latent reservoir for HIV-1 in patients receiving valproic acid. *J Infect Dis* 2007; **195**: 833–6.
3. Sagot-Lerolle N, *et al.* ANRS EP39 study. Prolonged valproic acid treatment does not reduce the size of latent HIV reservoir. *AIDS* 2008; **22**: 1125–9.
4. Archin NM, *et al.* Valproic acid without intensified antiviral therapy has limited impact on persistent HIV infection of resting CD4+ T cells. *AIDS* 2008; **22**: 1131–5.
5. Steel A, *et al.* No change to HIV-1 latency with valproate therapy. *AIDS* 2006; **20**: 1681–2.

Malignant neoplasms. Valproate appears to have anti-tumour activity, thought to be mediated through the inhibition of cellular histone deacetylase. It has been tried[1-9] usually as an adjunct to other antineoplastics in the treatment of various malignancies, with some reported benefit.

1. Bug G, *et al.* Clinical trial of valproic acid and all-trans retinoic acid in patients with poor-risk acute myeloid leukemia. *Cancer* 2005; **104**: 2717–25.
2. Raffoux E, *et al.* Treatment of elderly acute myeloid leukemia with valproic acid and all-trans retinoic acid. *Haematologica* 2005; **90**: 986–8.
3. Pilatrino C, *et al.* Increase in platelet count in older, poor-risk patients with acute myeloid leukemia or myelodysplastic syndrome treated with valproic acid and all-trans retinoic acid. *Cancer* 2005; **104**: 101–9.
4. Chavez-Blanco A, *et al.* Histone acetylation and histone deacetylase activity of magnesium valproate in tumor and peripheral blood of patients with cervical cancer: a phase I study. *Mol Cancer* 2005; **4**: 22. Full version: http://www.molecular-cancer.com/content/pdf/1476-4598-4-22.pdf (accessed 09/06/08)
5. Münster P, *et al.* Phase I trial of histone deacetylase inhibition by valproic acid followed by the topoisomerase II inhibitor epirubicin in advanced solid tumors: a clinical and translational study. *J Clin Oncol* 2007; **25**: 1979–85.
6. Blum W, *et al.* Phase I study of decitabine alone or in combination with valproic acid in acute myeloid leukemia. *J Clin Oncol* 2007; **25**: 3884–91.
7. Michaelis M, *et al.* Valproic acid as anti-cancer drug. *Curr Pharm Des* 2007; **13**: 3378–93.
8. Duenas-Gonzalez A, *et al.* Valproic acid as epigenetic cancer drug: preclinical, clinical and transcriptional effects on solid tumors. *Cancer Treat Rev* 2008; **34**: 206–22.
9. Bellos F, Mahlknecht U. Valproic acid and all-trans retinoic acid: meta-analysis of a palliative treatment regimen in AML and MDS patients. *Onkologie* 2008; **31**: 629–33.

Migraine. See under Headache, above.

Muscle spasm. The mainstay of management of *spasticity* is physiotherapy and an antispastic drug (see p. 2014.2). Valproate has been tried for its GABAergic activity and case reports[1] of 4 patients with spastic conditions of various aetiologies indicated that the addition of valproate to the existing regimen of antispastic drugs might produce improvements in spasticity and pain; further studies are warranted.

Valproate has also been tried[2] in the management of *stiff-man syndrome* (see under Muscle Spasm, p. 1064.3) unresponsive to diazepam.

1. Zachariah SB, *et al.* Positive response to oral divalproex sodium (Depakote) in patients with spasticity and pain. *Am J Med Sci* 1994; **308**: 38–40.
2. Spehlmann R, *et al.* Improvement of stiff-man syndrome with sodium valproate. *Neurology* 1981; **31**: 1162–3.

Myoclonus. Valproate is used alone or with clonazepam for cortical myoclonus (p. 511.3).

Neuropathic pain. Although carbamazepine is the drug of choice in the treatment of *trigeminal neuralgia* (p. 11.2), sodium valproate is an alternative antiepileptic that may be used in carbamazepine-intolerant patients. Valproate has also been tried, with some success, in painful *diabetic neuropathy*[1] (p. 8.2), *postherpetic neuralgia*[2] (p. 10.3), and neuropathic *cancer pain*[3] (p. 7.1). However, a placebo-controlled study[4] did not find any benefit with valproate therapy in the treatment of pain in diabetic and nondiabetic polyneuropathy.

1. Kochar DK, *et al.* Sodium valproate for painful diabetic neuropathy: randomized double-blind placebo-controlled study. *Q J Med* 2004; **97**: 33–8.
2. Kochar DK, *et al.* Divalproex sodium in the management of post-herpetic neuralgia: a randomized double-blind placebo-controlled study. *Q J Med* 2005; **98**: 29–34.
3. Hardy JR, *et al.* A phase II study to establish the efficacy and toxicity of sodium valproate in patients with cancer-related neuropathic pain. *Pain Symptom Manage* 2001; **21**: 204–9.
4. Otto M, *et al.* Valproic acid has no effect on pain in polyneuropathy: a randomized, controlled trial. *Neurology* 2004; **62**: 285–8.

Psychiatric disorders. Valproate has psychotropic properties and has been used in the management of bipolar disorder (see above) and in some countries as a mood stabiliser for augmentation of antidepressant therapy in the treatment of resistant depression (p. 398.1). Valproate has also been tried in various disorders for the control of symptoms such as agitation, aggression, and rage[1,2] (see Disturbed Behaviour, p. 1030.2). However, a systematic review of the use of valproate for agitation in dementia found no convincing evidence of efficacy at low doses, and adverse effects may be unacceptable at higher doses.[3] Valproate has also been reported[4,5] to be efficacious as adjunctive therapy to antipsychotics, but again, systematic review[6] has thrown doubt upon its efficacy. More recently, a systematic review[7] found no data to support or refute the use of valproate, either alone or as an adjunct to antipsychotics, in the treatment of schizophrenia (p. 1031.3). It has also been tried in anxiety disorders such as panic disorder[8-10] (p. 1029.1), and post-traumatic stress disorder[11,12] (p. 1029.2).

1. Geracioti TD. Valproic acid treatment of episodic explosiveness related to brain injury. *J Clin Psychiatry* 1994; **55**: 416–17.
2. Narayan M, *et al.* Treatment of dementia with behavioral disturbances using divalproex or a combination of divalproex and a neuroleptic. *J Clin Psychiatry* 1997; **58**: 351–4.
3. Lonergan E, Luxenberg J. Valproate preparations for agitation in dementia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2009 (accessed 26/11/09).
4. Wassef AA, *et al.* Randomized, placebo-controlled pilot study of divalproex sodium in the treatment of acute exacerbations of chronic schizophrenia. *J Clin Psychopharmacol* 2000; **20**: 357–61.
5. Grove VE, *et al.* Improvement of Huntington's disease with olanzapine and valproate. *N Engl J Med* 2000; **343**: 973–4.
6. Basan A, *et al.* Valproate as an adjunct to antipsychotics for schizophrenia: a systematic review of randomized trials. *Schizophr Res* 2004; **70**: 33–7.
7. Schwarz C, *et al.* Valproate for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 06/08/09).

8. Primeau F, *et al.* Valproic acid and panic disorder. *Can J Psychiatry* 1990; 35: 248–50.
9. Keck PE, *et al.* Valproate treatment of panic disorder and lactate-induced panic attacks. *Biol Psychiatry* 1993; 33: 542–6.
10. Woodman CL, Noyes R. Panic disorder: treatment with valproate. *J Clin Psychiatry* 1994; 55: 134–6.
11. Fesler FA. Valproate in combat-related posttraumatic stress disorder. *J Clin Psychiatry* 1991; 52: 361–4.
12. Petty F, *et al.* Valproate therapy for chronic, combat-induced posttraumatic stress disorder. *J Clin Psychopharmacol* 2002; 22: 100–101.

Status epilepticus. Valproate has been used in *absence* status epilepticus once the initial attack has been brought under control with intravenous benzodiazepines[1] and has been considered to be the drug of choice to prevent its recurrence.[2] Its place in the management of *convulsive* status epilepticus (p. 510.2) is less clear, but it has been tried, mainly as a second- or third-line drug in benzodiazepine-refractory patients,[3-11] and some centres have included it in management protocols.[3]

1. Bauer J, Elger CE. Management of status epilepticus in adults. *CNS Drugs* 1994; 1: 26–44.
2. Berkovic SF, *et al.* Valproate prevents the recurrence of absence status. *Neurology* 1989; 39: 1294–7.
3. Giroud M, *et al.* Use of injectable valproic acid in status epilepticus: a pilot study. *Drug Invest* 1993; 5: 154–9.
4. Hovinga CA, *et al.* Use of intravenous valproate in three pediatric patients with nonconvulsive or convulsive status epilepticus. *Ann Pharmacother* 1999; 33: 579–84.
5. Campistol J, *et al.* Estado de mal convulsivo en el niño: experiencia con valproato endovenoso, actualización del protocolo de tratamiento. *Rev Neurol* 1999; 29: 359–65.
6. Peters CNA, Pohlmann-Eden B. Intravenous valproate as an innovative therapy in seizure emergency situations including status epilepticus—experience in 102 adult patients. *Seizure* 2005; 14: 164–9.
7. Limdi NA, *et al.* Efficacy of rapid IV administration of valproic acid for status epilepticus. *Neurology* 2005; 64: 353–5.
8. Misra UK, *et al.* Sodium valproate vs phenytoin in status epilepticus: a pilot study. *Neurology* 2006; 67: 340–2.
9. Olsen KB, *et al.* Valproate is an effective, well-tolerated drug for treatment of status epilepticus/serial attacks in adults. *Acta Neurol Scand* 2007; 187 (suppl): 91–4.
10. Agarwal P, *et al.* Randomized study of intravenous valproate and phenytoin in status epilepticus. *Seizure* 2007; 16: 527–32.
11. Mehta V, *et al.* Intravenous sodium valproate versus diazepam infusion for the control of refractory status epilepticus in children: a randomized controlled trial. *J Child Neurol* 2007; 22: 1191–7.

Adverse Effects

The most frequently reported adverse effects associated with valproate therapy are gastrointestinal disturbances, particularly at the start of therapy; enteric-coated formulations, taking doses with meals, and starting with low doses may minimise symptoms. There may be increased appetite, and weight gain is common.

Less common adverse effects include oedema, headache, reversible prolongation of bleeding time, and thrombocytopenia. Leucopenia and bone marrow depression have been reported. Neurological adverse effects including ataxia, tremor, sedation, lethargy, confusion, and more rarely encephalopathy and coma, have occasionally been reported, although these are often associated with too high a starting dose, increasing doses too rapidly, or use with other antiepileptics. Very rare cases of extrapyramidal symptoms or reversible dementia associated with cerebral atrophy have been reported. Increased alertness may occur, which is generally considered beneficial, but occasionally aggression, hyperactivity, and behavioural disturbances have been reported. Hearing loss has been noted. There may occasionally be rashes, and, rarely, hirsutism, acne, toxic epidermal necrolysis and Stevens-Johnson syndrome or erythema multiforme. Transient hair loss, sometimes with regrowth of curly hair, has occurred. Irregular periods, amenorrhoea, and gynaecomastia have been reported rarely.

Liver dysfunction including hepatic failure has occasionally been reported, usually in the first few months of treatment, and requires valproate withdrawal; there have been fatalities. Elevation of liver enzyme values is common but normally transient and dose-related. Hyperammonaemia has occurred, even in the absence of overt hepatic failure, and is sometimes associated with neurological symptoms; hyperglycinaemia has also been reported. Pancreatitis has also been reported rarely, and fatalities have occurred; plasma amylase should be measured if there is acute abdominal pain, although the value of serum amylase as a diagnostic tool has been questioned—see Effects on the Pancreas, p. 556.1. In a few patients there have been reports of reversible defects in renal tubular function (Fanconi's syndrome).

Congenital malformations have been reported in infants born to women who had received antiepileptics including valproate during pregnancy.

Inflammatory reactions and pain have been reported at the injection site after intravenous doses.

Incidence of adverse effects. Adverse effects were present in 71 of 88 children receiving sodium valproate monotherapy[1] and, although average doses in these patients were significantly higher than in the 17 with no adverse effects, no difference in the plasma concentrations was seen between the 2 groups.

- Behavioural alterations seen in 56 included irritability, longer and deeper sleep, superficial sleep, hyperactivity, being more alert, lassitude, drowsiness, being more sociable, calmness, being happier, absent mindedness, being sadder, aggressiveness, being more skillful, and docility; it was emphasised that stimulatory reactions were as frequent as depressant effects
- Digestive disorders occurred in 43 children with anorexia, abdominal pain, and nausea and vomiting being the most frequent; diarrhoea, constipation, an increase in appetite, and a gain in weight also occurred. With the exception of a temporary increase in plasma transaminase concentrations in 2 patients, hepatic or pancreatic dysfunction was not seen
- Neurological changes in the form of tremor, paraesthesia, or ataxia, occurring in only 4 patients, were less frequent than either behavioural or digestive reactions
- Miscellaneous reactions including polydipsia, polyuria, diaphoresis, enuresis, hair loss, change in hair colour or texture, and rash were seen in 23 children
- Of the 71 children having reactions, therapy continued unchanged in 56, was changed in 3 either by altering the pharmaceutical formulation (syrup, tablets, granules), by changing the frequency of dosing, or by reducing the dose in 6, and in the remaining 9 children valproate therapy was stopped

1. Herranz JL, *et al.* Side effects of sodium valproate in monotherapy controlled by plasma levels: a study in 88 pediatric patients. *Epilepsia* 1982; 23: 203–14.

Carnitine deficiency. Carnitine deficiency may occasionally arise during long-term use of valproate; although it is unclear whether carnitine supplementation (p. 2053.3) is of value in children receiving valproate, some neurologists consider it justified in selected cases, including those with, or at risk of, severe acute toxicity such as valproate-induced hepatotoxicity.[1-4]

1. De Vivo DC, *et al.* L-Carnitine supplementation in childhood epilepsy: current perspectives. *Epilepsia* 1998; 39: 1216–25.
2. Lheureux PER, *et al.* Science review: carnitine in the treatment of valproic acid-induced toxicity—what is the evidence? *Crit Care* 2005; 9: 431–40.
3. Russell S. Carnitine as an antidote for acute valproate toxicity in children. *Curr Opin Pediatr* 2007; 19: 206–10.
4. Lheureux PE, Hantson P. Carnitine in the treatment of valproic acid-induced toxicity. *Clin Toxicol* 2009; 47: 101–11.

Effects on the blood. Reports have implicated valproate as a cause of occasional neutropenia,[1-3] leucopenia,[4] and thrombocytopenia.[2] A 1-year prospective study involving 45 patients found that absolute neutropenia developed in 12 and thrombocytopenia in 15, but that the disorders were transient and self-limiting.[2] However, neutropenia has occasionally been sufficiently severe to warrant withdrawal of valproate.[5] A case of delayed-onset neutropenia associated with valproate semisodium has been reported[6] in a 45-year-old man after almost 8 years of therapy; symptoms resolved when the drug was stopped. Red cell aplasia has also been associated with valproate therapy.[7,8] A study[9] involving 30 children indicated that valproate might produce symptoms similar to those of von Willebrand's disease; 19 of the 30 had a history of minor haemorrhage during therapy, and 7 had abnormal bleeding times. Factor VIII therapy might need to be given in patients receiving valproate who underwent surgery or in whom bleeding was severe.

For a discussion of the effects of antiepileptics, including valproate, on serum folate, see under Phenytoin, p. 540.2.

1. Jaeken J, *et al.* Neutropenia during sodium valproate treatment. *Arch Dis Child* 1979; 54: 986–7.
2. Barr RD, *et al.* Valproic acid and immune thrombocytopenia. *Arch Dis Child* 1982; 57: 681–4.
3. Vesta KS, Medina PJ. Valproic acid-induced neutropenia. *Ann Pharmacother* 2003; 37: 819–21.
4. Coulter DL, *et al.* Valproic acid therapy in childhood epilepsy. *JAMA* 1980; 244: 785–8.
5. Symon DNK, Russell G. Sodium valproate and neutropenia. *Arch Dis Child* 1983; 58: 235.
6. Stoner SC, *et al.* Delayed-onset neutropenia with divalproex sodium. *Ann Pharmacother* 2008; 42: 1507–10.
7. MacDougall LG. Pure red cell aplasia associated with sodium valproate therapy. *JAMA* 1982; 247: 53–4.
8. Watts RG, *et al.* Valproic acid-induced cytopenias: evidence for a dose-related suppression of hematopoiesis. *J Pediatr* 1990; 117: 495–9.
9. Kreuz W, *et al.* Induction of von Willebrand disease type I by valproic acid. *Lancet* 1990; 335: 1350–1.

Effects on bone. For the effects of antiepileptics including valproate on bone and on calcium and vitamin D metabolism, see under Phenytoin, p. 540.2.

Effects on the endocrine system. An early study[1] reported that menstrual disturbances were associated more often with valproate than with other antiepileptics among 238 women with epilepsy; 80% of those treated with valproate before 20 years of age had polycystic ovaries or hyperandrogenism. A later study[2] found that the occurrence of polycystic ovaries in 105 epileptic women taking carbamazepine or valproate was no greater than that in the general population, although valproate appeared to increase glucose-stimulated pancreatic insulin secretion. Subsequent studies[3-5] and reviews[6-9] support the association between valproate therapy and reproductive endocrine disorders and metabolic disturbances in female patients with epilepsy. However, a causal link could not be established since epilepsy itself affects the endocrine system. Symptoms such as hyperandrogenism, menstrual disturbances, polycystic ovaries, weight gain, and insulin resistance have been attributed to the development of polycystic ovary syndrome (p. 2253.3) in some patients. Other adverse effects of valproate on the endocrine system include dyslipidaemia, hypocalcaemia, and hypothyroidism.

For mention of the effects of antiepileptics, including valproate, on *sexual function* in male epileptic patients, see under Phenytoin, p. 540.3.

1. Isojärvi JIT, *et al.* Polycystic ovaries and hyperandrogenism in women taking valproate for epilepsy. *N Engl J Med* 1993; 329: 1383–8.
2. Luef G, *et al.* Polycystic ovaries, obesity and insulin resistance in women with epilepsy: a comparative study of carbamazepine and valproic acid in 105 women. *J Neurol* 2002; 249: 835–41.
3. Betts T, *et al.* A study of anticonvulsant medication on ovarian function in a group of women with epilepsy who have only ever taken one anticonvulsant compared with a group of women without epilepsy. *Seizure* 2003; 12: 323–9.
4. Mikkonen K, *et al.* Long-term reproductive endocrine health in young women with epilepsy during puberty. *Neurology* 2004; 62: 445–50.
5. Tan H, *et al.* Valproate-induced insulin resistance in prepubertal girls with epilepsy. *J Pediatr Endocrinol Metab* 2005; 18: 985–9. Correction. *ibid.*: 1134.
6. Morrell MJ. Reproductive and metabolic disorders in women with epilepsy. *Epilepsia* 2003; 44 (suppl 4): 11–20.
7. Rasgon N. The relationship between polycystic ovary syndrome and antiepileptic drugs: a review of the evidence. *J Clin Psychopharmacol* 2004; 24: 322–34.
8. Verrotti A, *et al.* Endocrine and metabolic changes in epileptic patients receiving valproic acid. *J Pediatr Endocrinol Metab* 2005; 18: 423–30.
9. Isojärvi J. Disorders of reproduction in patients with epilepsy: antiepileptic drug related mechanisms. *Seizure* 2008; 17: 111–19.

Effects on the liver. An early review[1] of the hepatotoxicity of valproate included an analysis of 42 cases with fatal hepatitis, 3 cases with a Reye's-like syndrome, and 22 instances of hyperammonaemia:

- In 19 studies the incidence of *abnormal serum aminotransferase* activity ranged from 0 to 44% with an overall incidence of 11% in the 1197 patients monitored; in the non-fatal cases activity was usually between one and three times the upper limit of normal and was not usually, except in the most severe cases, accompanied by rises in serum bilirubin or alkaline phosphatase
- In the 42 cases of *hepatitis* with a fatal outcome the age at presentation ranged from 2.5 months to 34 years with 69% aged 10 years or less. Below the age of 15 years the proportion of males was 62.5% but above this age it was 30%; the disproportionate vulnerability of young individuals, particularly boys, did not appear to be a reflection of prescribing habits in that age group. In more than two-thirds of these patients with a fatal outcome, prodromal symptoms comprised anorexia and vomiting, loss of epilepsy control, impaired consciousness, and ataxia; in about one-third there were signs of liver damage with fever, jaundice, ascites, peripheral oedema, and easy bruising. In all of the patients hepatic coma developed. In 36 patients on whom data were available the onset of hepatic illness in one-third occurred between 1 and 2 months and in only 2 patients did the onset occur after more than 5 months. Of these 42 patients with fatal hepatotoxicity 36 were also given other drugs, mostly antiepileptics
- The 3 children with a *Reye's-like syndrome* all died within 3 weeks of the first occurrence of symptoms as a result of cerebral oedema (2 patients) or aspiration pneumonia (1 patient)
- In the 22 patients with symptomatic *hyperammonaemia*, characterised usually by impaired consciousness and ataxia, but without overt liver disease, withdrawal of valproate resulted in all becoming asymptomatic and biochemical abnormalities returned to normal. Hyperammonaemia has also been reported in asymptomatic patients, and has been stated to occur in the great majority of valproate-treated patients;[2] it is not necessarily related to hepatotoxicity

Hyperammonaemia and encephalopathy may also be precipitated when valproate is used with certain drugs (see Antibacterials, p. 557.2 and Antiepileptics, p. 557.3, under Interactions).

Various hypotheses for the cause of valproate hepatotoxicity have been discussed in detail.[3]

Analysis of deaths in the USA attributed to valproate liver toxicity identified a decline in the incidence of fatalities as use in young children and use with other antiepileptics declined.[4] However, occasional reports still occur in some countries.[5] For the suggestion that carnitine might be useful in the management of valproate hepatotoxicity, see Carnitine Deficiency, above.

1. Powell-Jackson PR, *et al.* Hepatotoxicity to sodium valproate: a review. *Gut* 1984; 25: 673–81.

2. Chicharro AV, *et al.* The measurement of ammonia blood levels in patients taking valproic acid: looking for problems where they do not exist? *Epilepsy Behav* 2007; 11: 361–6.
3. Eadie MJ, *et al.* Valproate-associated hepatotoxicity and its biochemical mechanisms. *Med Toxicol* 1988; 3: 85–106.
4. Dreifuss FE, *et al.* Valproic acid hepatic fatalities: II US experience since 1984. *Neurology* 1989; 39: 201–7.
5. Koenig SA, *et al.* Valproic acid-induced hepatopathy: nine new fatalities in Germany from 1994 to 2003. *Epilepsia* 2006; 47: 2027–31.

Effects on mental function. For a review of the effects of antiepileptic therapy including valproate on *cognition* and *mood* (including the risk of suicidal ideation), see p. 508.3.

Effects on the nervous system. An *extrapyramidal* syndrome of tremor and rigidity, unresponsive to benzatropine or trihexyphenidyl, developed in a 52-year-old man with schizophrenia given a therapeutic trial of sodium valproate 1 to 2 g daily.[1] Giving sodium valproate to a man with dystonic movements of the neck and spine produced a severe subjective and objective deterioration in his symptoms, which returned to their previous severity on withdrawal of the drug.[2] There have also been reports[3,4] of *parkinsonism* associated with valproate antiepileptic therapy; onset was usually insidious and progressive, occurring after several years of good tolerability. A case series[4] also reported *cognitive impairment* in 6 of 10 patients who developed parkinsonism. In most cases symptoms improved on stopping valproate.

Spasmodic dysphonia associated with valproate has been reported;[5] symptoms resolved when the dose of valproate was reduced.

A *stuporous state* associated with EEG abnormalities has been described[6,7] during valproate therapy for complex partial or mixed seizure types and it was suggested that in certain forms of epilepsy valproate may exhibit a paradoxical epileptogenic effect. Other findings[8] have argued against an epileptic origin for valproate-induced stupor.

1. Lautin A, *et al.* Extrapyramidal syndrome with sodium valproate. *BMJ* 1979; 2: 1035–6.
2. Dick DJ, Saunders M. Extrapyramidal syndrome with sodium valproate. *BMJ* 1980; 280: 189.
3. Easterford K, *et al.* Reversible parkinsonism with normal β-CIT-SPECT in patients exposed to sodium valproate. *Neurology* 2004; 62: 1435–7.
4. Masmoudi K, *et al.* Parkinsonism and/or cognitive impairment with valproic acid therapy: a report of ten cases. *Pharmacopsychiatry* 2006; 39: 9–12.
5. Oh J, *et al.* Spasmodic dysphonia induced by valproic acid. *Epilepsia* 2004; 45: 880–1.
6. Marescaux C, *et al.* Stuporous episodes during treatment with sodium valproate: report of seven cases. *Epilepsia* 1982; 23: 297–305.
7. Stecker MM, Kita M. Paradoxical response to valproic acid in a patient with a hypothalamic hamartoma. *Ann Pharmacother* 1998; 32: 1168–72.
8. Aguglia U, *et al.* Negative myoclonus during valproate-related stupor: neurophysiological evidence of a cortical non-epileptic origin. *Electroencephalogr Clin Neurophysiol* 1995; 94: 103–8.

Effects on the pancreas. An early report of 4 cases of pancreatitis associated with valproic acid therapy also reviewed 10 previously published cases.[1] None of the 14 patients, 2 of whom died, suffered other symptoms of a toxic reaction to valproic acid. Pancreatitis was not dose-related and had developed as early as one week and as late as 4.5 years after the introduction of therapy. Symptoms recurred on rechallenge in 6 of 7 patients. However, routine monitoring of serum-amylase concentrations in asymptomatic patients did not seem necessary. In February 1994 the UK CSM commented[2] in a review of drug-induced pancreatitis that they had received 29 reports of pancreatitis, including 2 fatalities, associated with sodium valproate. A later review[3] of 22 children who developed pancreatitis while taking valproate (2 of whom died) found that duration of therapy, dose, serum concentrations, and polytherapy were not risk factors. The authors advised against rechallenge as the rate of relapse is high. Serum amylase concentrations were found to be nondiagnostic in 39% of these patients, and the authors considered that serum lipase concentrations were far more likely to be elevated.

1. Wyllie E, *et al.* Pancreatitis associated with valproic acid therapy. *Am J Dis Child* 1984; 138: 912–14.
2. CSM/MCA. Drug-induced pancreatitis. *Current Problems* 1994; 20: 2–3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024457&RevisionSelectionMethod=LatestReleased (accessed 01/09/08)
3. Werlin SL, Fish DL. The spectrum of valproic acid-associated pancreatitis. *Pediatrics* 2006; 118: 1660–3.

Effects on the skin, hair, and nails. Five of 250 patients developed curly hair during treatment with sodium valproate 1 g daily;[1] in 3 patients this effect followed temporary alopecia. Another report of hair curling in a patient who received sodium valproate in doses up to 3 g daily for 30 months commented that her hair started to revert to the former straight style 9 months after stopping the drug.[2]

Valproate-induced nicotinic-acid deficiency with an associated pellagra-like syndrome has been reported in a young boy;[3] the condition responded dramatically to treatment with nicotinamide.

Reduced serum-zinc concentrations and cutaneous manifestations of zinc deficiency were found in 2 patients receiving antiepileptic drugs.[4] It was thought that deficiency resulted from chelation by sodium valproate, and possibly phenytoin, together with malabsorption and that, in one case, malabsorption was triggered by valproate.

Cutaneous vasculitis has been reported[5] in 2 patients taking sodium valproate. The reaction recurred on rechallenge.

Very rarely, skin rashes occurring with valproate may form part of an antiepileptic hypersensitivity syndrome (see below). Valproate might share the same order of risk as other antiepileptics for the development of Stevens-Johnson syndrome and toxic epidermal necrolysis,[6] although it had previously been regarded as safer in this respect. For a suggestion that skin reactions are less common with valproate than with some other antiepileptics see under Phenytoin, p. 541.1.

Reversible yellow nail pigmentation has been reported[7] in a woman who was taking valproate semisodium.

1. Jeavons PM, *et al.* Valproate and curly hair. *Lancet* 1977; i: 359.
2. Gupta AK. Perming' effects associated with chronic valproate therapy. *Br J Clin Pract* 1988; 42: 75–7.
3. Gillman MA, Sandyk R. Nicotinic acid deficiency induced by sodium valproate. *S Afr Med J* 1984; 65: 986.
4. Lewis-Jones MS, *et al.* Cutaneous manifestations of zinc deficiency during treatment with anticonvulsants. *BMJ* 1985; 290: 603–4.
5. Kamper AM, *et al.* Cutaneous vasculitis induced by sodium valproate. *Lancet* 1991; 337: 497–8.
6. Anonymous. Drugs as risk factors in severe cutaneous diseases. *WHO Drug Inf* 1996; 10: 33–5.
7. Buka R, *et al.* Yellow nail pigmentation following Depakote therapy. *J Drugs Dermatol* 2003; 2: 545–7.

Enuresis. Nocturnal enuresis associated with sodium valproate therapy has been reported[1] in 2 children. Remission of the enuresis was achieved either by reducing or redistributing the doses. Several studies have recorded enuresis as an adverse effect of valproate in children,[2] the frequency being between 1 and 7%. The most likely explanations are that either it is secondary to a central effect on the thirst centre resulting in polydipsia or it is a consequence of the increased depth of sleep associated with valproate.

1. Panayiotopoulos CP. Nocturnal enuresis associated with sodium valproate. *Lancet* 1985; i: 980–1.
2. Choonara IA. Sodium valproate and enuresis. *Lancet* 1985; i: 1276.

Hypersensitivity. An antiepileptic hypersensitivity syndrome, comprising fever, rash, and lymphadenopathy and less commonly lymphocytosis, and liver and other organ involvement, has been associated with some aromatic antiepileptic drugs; however, there have also been case reports[1-3] associated with valproate, a non-aromatic compound. In one case[1] a patient developed these symptoms with carbamazepine but they resolved when the drug was stopped; however, when valproate was started 2 weeks later the symptoms reappeared. Another report[2] described a fatal case occurring in a 2-year-old girl who developed fulminant hepatitis.

1. Arévalo-Lorido JC, *et al.* Antiepileptic drug hypersensitivity syndrome in a patient treated with valproate. *Br J Clin Pharmacol* 2003; 55: 415–16.
2. Huang Y-L, *et al.* Fatal sodium valproate-induced hypersensitivity syndrome with lichenoid dermatitis and fulminant hepatitis. *J Am Acad Dermatol* 2003; 49: 316–19.
3. Roepke S, *et al.* Valproic acid and hypersensitivity syndrome. *Am J Psychiatry* 2004; 161: 579.

Overdosage. A cohort study[1] of valproate poisonings reported to a regional toxicology centre between January 1991 and November 2001 reported 79 cases. Of these, valproate was the only drug taken in 15 cases with a median dose of 15 g; symptoms were mild and included drowsiness (2 patients), vomiting (4), and tachycardia (5). The authors concluded that overdoses of more than 400 mg/kg could cause severe, potentially life-threatening toxicity, but these were uncommon. Symptoms of severe toxicity include significant CNS depression, respiratory insufficiency, and multi-organ failure; fatalities have been reported.[2] Children younger than 2 years of age are considered to be at significant risk for developing fatal valproate-induced hepatotoxicity in overdose; there has been a report of a 26-day-old neonate who died 42 hours after receiving a dose of 75 mg/kg.[3]

1. Isbister GK, *et al.* Valproate overdose: a comparative cohort study of self poisonings. *Br J Clin Pharmacol* 2003; 55: 398–404.
2. Eyer F, *et al.* Acute valproate poisoning: pharmacokinetics, alteration in fatty acid metabolism, and changes during therapy. *J Clin Psychopharmacol* 2005; 25: 376–80.
3. Unal E, *et al.* Fatal valproate overdose in a newborn baby. *Hum Exp Toxicol* 2007; 26: 453–6.

Treatment of Adverse Effects

The value of gastric decontamination for overdose is uncertain since valproic acid and its salts are rapidly absorbed. Activated charcoal may be given orally to adults and children who present within 1 hour of ingesting more than 100 mg/kg: alternatively gastric lavage may be considered in adults within 1 hour of a potentially life-threatening overdose, generally 400 mg/kg or more. Supportive therapy alone may then suffice although haemodialysis and/or haemoperfusion should be considered in very severe poisoning.

Overdosage. Active treatments including forced diuresis, whole bowel irrigation, naloxone, and haemodialysis or haemoperfusion have been advocated for valproate overdose;[1,2] however, supportive measures provided sufficient treatment for a patient who had taken 25 g of sodium valproate.[1] A consensus guideline on out-of-hospital management of valproate poisoning[3] considered that such management was appropriate in patients who had unintentionally ingested up to 50 mg/kg of the drug and were merely somnolent; activated charcoal or, for comatose patients, naloxone, might be given as prehospital management although good evidence to support their use was lacking.

1. Lakhani M, McMurdo MET. Survival after severe self poisoning with sodium valproate. *Postgrad Med J* 1986; 62: 409–10.
2. Sztajnkrycer MD. Valproic acid toxicity: overview and management. *J Toxicol Clin Toxicol* 2002; 40: 789–801. Correction. *ibid.* 2003; 41: 215.
3. Manoguerra AS, *et al.* American Association of Poison Control Centers. Valproic acid poisoning: an evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol* 2008; 46: 661–76.

Precautions

Valproate is contra-indicated in patients with pre-existing liver disease or a family history of severe hepatic dysfunction. Children under 3 years of age and those with congenital metabolic or degenerative disorders, organic brain disease, or severe seizure disorders associated with mental retardation may be at particular risk of hepatotoxicity and the drug should be used with particular caution in these groups. Use with other antiepileptics, which may also increase the risks of liver damage, should be avoided if possible. Liver function tests should be carried out, particularly in those most at risk, before and during the first 6 months of therapy. Raised liver enzymes are not uncommon during treatment and are usually transient or respond to reduction in dosage, but patients should be reassessed clinically and liver function, including prothrombin time, monitored until they return to normal. An abnormally prolonged prothrombin time, particularly in association with other relevant abnormalities, requires treatment to be stopped. If given with salicylates, these should also be stopped. Treatment should also be stopped if pancreatitis is diagnosed.

Patients or their carers should be told how to recognise signs of blood and liver toxicity or pancreatitis, and they should be advised to seek immediate medical attention if symptoms develop.

Patients should be monitored for potential bleeding complications before major elective surgery; some licensed product information suggests regular monitoring before and during therapy.

Valproate should be used with caution if the patient is at risk of SLE.

Patients should be warned of the risk of weight gain and appropriate strategies adopted to minimise the effect.

Care is required when withdrawing valproate therapy — see also Uses and Administration, p. 553.2.

The protein binding of valproate is saturable and thus shows concentration dependency; significant increases in free drug occur at high total plasma concentrations.

Because valproate is partly excreted in the form of ketone bodies, it may cause false positives in urine tests for diabetes mellitus.

Dosage adjustments may be necessary in severe renal impairment in accordance with free serum valproate levels.

Breast feeding. Thrombocytopenic purpura and anaemia occurred in a breast-fed infant whose mother was being treated with valproic acid.[1] The baby recovered when breast feeding was stopped. Low serum-valproate levels were detected[2] in 6 breast-fed infants whose mothers had been taking valproate semisodium post partum; no adverse effects were seen in the infants. Similar results have previously been obtained for patients taking sodium valproate[3] or valproic acid.[4] The American Academy of Pediatrics considers[5] that valproate is, therefore, usually compatible with breast feeding.

For further comment on antiepileptic therapy and breast feeding, see p. 508.3.

1. Stahl MMS, *et al.* Thrombocytopenic purpura and anemia in a breast-fed infant whose mother was treated with valproic acid. *J Pediatr* 1997; 130: 1001–3.
2. Piontek CM, *et al.* Serum valproate levels in 6 breastfeeding mother-infant pairs. *J Clin Psychiatry* 2000; 61: 170–2.
3. Alexander FW. Sodium valproate and pregnancy. *Arch Dis Child* 1979; 54: 240.
4. von Unruh GE, *et al.* Valproic acid in breast milk: how much is really there? *Ther Drug Monit* 1984; 6: 272–6.
5. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 09/06/08)

Driving. For a comment on antiepileptic drugs and driving, see p. 509.2.

HIV infection and AIDS. Limited data from several small *in-vitro* studies have found that valproic acid may induce viral replication of HIV;[1] some clinicians have therefore suggested increased monitoring of viral load in HIV-positive patients treated with valproic acid. For the use of this effect to reduce latent viral load, see under Uses and Administration, p. 554.2.

1. Jennings HR, Romanelli F. The use of valproic acid in HIV-positive patients. *Ann Pharmacother* 1999; 33: 1113–16.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies valproate as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pregnancy. For comments on the management of epilepsy during pregnancy see p. 509.2.

There is an increased risk of neural tube defects in infants exposed *in utero* to antiepileptics including valproate and craniofacial and digital abnormalities and, less commonly, cleft lip and palate have been described, which may form part of a fetal antiepileptic syndrome.[1,2] In an unselected series[3] of 17 infants whose epileptic mothers had received valproate during pregnancy, 9 had minor abnormalities and of these 5 also had major abnormalities, including congenital heart defect in 4. In another series,[4] involving 149 women whose offspring were exposed to valproate monotherapy in the first trimester, 16 infants with major malformations were identified (a relative risk calculated at about 7 times that in the population at large). The abnormalities reported included craniosynostosis, spina bifida, and pulmonary atresia. A population-based study[5] of 2350 births to epileptic women between 1991 and 2000 found that the offspring of mothers who were given valproate, as mono- or polytherapy, in the first trimester had a fourfold increase in risk for congenital malformations compared with untreated mothers; the risk was tenfold in those who were given daily doses of more than 1.5 g. The risk of malformations was not increased in the offspring of mothers taking carbamazepine, oxcarbazepine, or phenytoin as mono- or polytherapy without valproate.

The FDA more recently reported[6] that data from the North American Antiepileptic Drug Pregnancy Registry showed that the rate of major malformations in neonates born to women with epilepsy taking antiepileptic monotherapy was 10.7% in those whose mothers took an average of 1 g of valproic acid daily compared with 2.9% in those whose mothers took other antiepileptic drugs. Major malformations had occurred in 16 of the offspring of 149 women given valproate during pregnancy and included neural tube defects, craniofacial defects, and malformations of cardiovascular and other body systems.

Neonatal bleeding, attributed to fibrinogen depletion and sometimes fatal, has been reported after exposure *in utero* to valproate.[7,8] Hypoglycaemia was recorded[9] in 13 of 22 neonates whose mothers had taken valproate during pregnancy. Valproate-withdrawal symptoms, including irritability, jitteriness, hypertonia, seizures, and feeding problems were also noted.

1. Genton P, *et al.* Valproic acid in epilepsy: pregnancy-related issues. *Drug Safety* 2006; 29: 1–21.
2. Ornoy A. Valproic acid in pregnancy: how much are we endangering the embryo and fetus? *Reprod Toxicol* 2009; 28: 1–10.
3. Thisted E, Ebbesen F. Malformations, withdrawal manifestations, and hypoglycaemia after exposure to valproate in utero. *Arch Dis Child* 1993; 69: 288–91.
4. Wyszynski DF, *et al.* Increased rate of major malformations in offspring exposed to valproate during pregnancy. *Neurology* 2005; 64: 961–5.
5. Artama M, *et al.* Antiepileptic drug use of women with epilepsy and congenital malformations in offspring. *Neurology* 2005; 64: 1874–8.
6. FDA. Information for healthcare professionals: risk of neural tube birth defects following prenatal exposure to valproate (issued 3rd December, 2009). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm192649.htm (accessed 11/01/10)
7. Majer RV, Green PJ. Neonatal afibrinogenaemia due to sodium valproate. *Lancet* 1987; ii: 740–1.
8. Bavoux F, *et al.* Neonatal fibrinogen depletion caused by sodium valproate. *Ann Pharmacother* 1994; 28: 1307.
9. Ebbesen F, *et al.* Neonatal hypoglycaemia and withdrawal symptoms after exposure in utero to valproate. *Arch Dis Child Fetal Neonatal Ed* 2000; 83: F124–F129.

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy. Caution is recommended when giving valproate with other drugs liable to interfere with blood coagulation, such as aspirin or warfarin. Use with other hepatotoxic drugs should be avoided. Use of highly protein bound drugs with valproate may increase free valproate plasma concentrations.

General references.

1. Levy RH, Koch KM. Drug interactions with valproic acid. *Drugs* 1982; 24: 543–56.

Analgesics. The free fraction of valproate was increased eightfold in a 76-year-old man[1] who was also given *aspirin* 325 mg daily, resulting in signs of clinical toxicity. Aspirin displaces valproate from plasma protein binding sites, as well as inhibiting its metabolism by inhibition of beta-oxidation. Similarly, the valproic acid free fraction was reported to be increased, as was the half-life, when aspirin was given in a study in 6 epileptic children.[2] Furthermore, salicylates have been associated with an increased risk of Reye's syndrome (p. 25.3) in children, and combination with another hepatotoxic drug such as valproate is clearly undesirable. In addition, both aspirin and valproate affect blood coagulation and platelet function.

Naproxen has also been reported to produce a slight displacement of protein-bound valproic acid but the effect is probably not sufficiently marked for it to have a clinical effect.[3]

1. Sandson NB, *et al.* An interaction between aspirin and valproate: the relevance of plasma protein displacement drug-drug interactions. *Am J Psychiatry* 2006; 163: 1891–6.
2. Orr JM, *et al.* Interaction between valproic acid and aspirin in epileptic children: serum protein binding and metabolic effects. *Clin Pharmacol Ther* 1982; 31: 642–9.
3. Grimaldi R, *et al.* In vivo plasma protein binding interaction between valproic acid and naproxen. *Eur J Drug Metab Pharmacokinet* 1984; 9: 359–63.

Antibacterials. Raised valproate blood concentrations and symptoms consistent with valproate toxicity have been reported in a patient also given *erythromycin*.[1]

There is a theoretical possibility that carnitine deficiency may be increased in patients receiving *pivampicillin* and valproate. Hyperammonaemic encephalopathy developed in a 72-year-old woman who had been taking valproate for 10 months when she was given *pivmecillinam* for a urinary-tract infection. It was suggested that valproate's propensity to produce hyperammonaemia had been exacerbated by a secondary hyperammonaemia induced by both drugs reducing carnitine concentrations.[2]

Decreases in plasma concentrations of valproate to subtherapeutic levels (and sometimes with loss of seizure control) have been noted in patients during therapy with antibacterial treatment containing *ertapenem*,[3,4] *imipenem*,[5] or *meropenem*.[5-9] Marked reductions in valproate concentrations have also been reported in 3 children given *panipenem* (with betamipron).[10] There is potential for a similar interaction with *doripenem*.[11] The MHRA[12] advises that given the rapid and substantial decrease in valproate concentrations, neither monitoring of sodium valproate concentrations nor making dose adjustments is likely to be of benefit. Therefore, the use of carbapenems with valproic acid/sodium valproate is not recommended.

Increased serum-valproate concentrations resulting in signs of valproate toxicity occurred in a child after beginning therapy with *isoniazid*;[13] the child was a slow acetylator of isoniazid and valproate dosage had to be reduced by about 60% to maintain satisfactory concentrations. When isoniazid was subsequently stopped, valproate dosage had to be increased to its previous value in order to maintain a therapeutic effect.

1. Redington K, *et al.* Erythromycin and valproate interaction. *Ann Intern Med* 1992; 116: 877–8.
2. Lokrantz C-M, *et al.* Hyperammonemic encephalopathy induced by a combination of valproate and pivmecillinam. *Acta Neurol Scand* 2004; 109: 297–301.
3. Lunde JL, *et al.* Acute seizures in a patient receiving divalproex sodium after starting ertapenem therapy. *Pharmacotherapy* 2007; 27: 1202–5.
4. Liao F-F, *et al.* Decrease in serum valproic acid levels during treatment with ertapenem. *Am J Health-Syst Pharm* 2010; 67: 1260–4.
5. Llinares Tello F, *et al.* Interacción farmacocinética entre ácido valproico y antibióticos carbapenémicos: descripción de tres casos. *Farm Hosp* 2003; 27: 258–63.
6. De Turck BJG, *et al.* Lowering of plasma valproic acid concentrations during concomitant therapy with meropenem and amikacin. *J Antimicrob Chemother* 1998; 42: 563–4.
7. Coves-Orts FJ, *et al.* Acute seizures due to a probable interaction between valproic acid and meropenem. *Ann Pharmacother* 2005; 39: 533–7.
8. Fudio S, *et al.* Epileptic seizures caused by low valproic acid levels from an interaction with meropenem. *J Clin Pharm Ther* 2006; 31: 393–6.
9. Spriet I, *et al.* Interaction between valproate and meropenem: a retrospective study. *Ann Pharmacother* 2007; 41: 1130–6.
10. Nagai K, *et al.* Decrease in serum levels of valproic acid during treatment with a new carbapenem, panipenem/betamipron. *J Antimicrob Chemother* 1997; 39: 295–6.
11. Hellwig TR, *et al.* Potential interaction between valproic acid and doripenem. *Curr Drug Saf* 2011; 6: 54–8.
12. MHRA/CHM. Carbapenems: concomitant use with valproic acid not recommended. *Drug Safety Update* 2010; 3(10): 4–5. Available at: http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON081863 (accessed 07/06/10)
13. Jonville AP, *et al.* Interaction between isoniazid and valproate: a case of valproate overdosage. *Eur J Clin Pharmacol* 1991; 40: 197–8.

Antidepressants. As with all antiepileptics, antidepressants may antagonise the antiepileptic activity of valproate by lowering the convulsive threshold.

There have been conflicting reports of the effect of *fluoxetine* on serum concentrations of valproate. While some reported an increase,[1-3] others have reported a decrease[4] in valproate-serum concentrations when the 2 drugs were used together.

For the effect of valproate on *amitriptyline*, see p. 406.2.

1. Sovner R, Davis JM. A potential drug interaction between fluoxetine and valproic acid. *J Clin Psychopharmacol* 1991; 11: 389.
2. Lucena MI, *et al.* Interaction of fluoxetine and valproic acid. *Am J Psychiatry* 1998; 155: 575.
3. Cruz-Flores S, *et al.* Valproic toxicity with fluoxetine therapy. *Mo Med* 1995; 92: 296–7.
4. Droulers A, *et al.* Decrease of valproic acid concentration in the blood when coprescribed with fluoxetine. *J Clin Psychopharmacol* 1997; 17: 139–40.

Antiepileptics. The barbiturate antiepileptic *phenobarbital* is reported to decrease serum-valproate concentrations when given together,[1] apparently by induction of valproate metabolism.[2] This effect is overshadowed, however, by the marked increase in serum-phenobarbital concentrations caused by valproate inhibition of phenobarbital metabolism—see p. 537.2. It has been suggested that phenobarbital may also increase the risk of valproate-induced hyperammonaemic encephalopathy.[3]

Carbamazepine and *phenytoin* are also enzyme-inducing drugs and, as might be expected, are reported to increase the metabolism and decrease the serum concentration of valproate.[4-6] The effect may be clinically significant.[7] The reciprocal effects of valproate on both drugs are complex, with conflicting effects on metabolism and protein binding, and the clinical outcome is difficult to predict. For more details see under Carbamazepine, p. 516.3 and Phenytoin, p. 543.2. An interaction with *oxcarbazepine*, resulting in valproate toxicity, has also been reported.[8]

Serum concentrations of valproic acid were reduced, with considerable interpatient variability, when *ethosuximide*[9] or *mesuximide*[10] was added to the antiepileptic therapy of some patients.

Raised serum concentrations of valproic acid have been reported in patients given *felbamate*.[11]

Reversible hepatic impairment has been reported[12,13] when *topiramate* was added to valproate therapy in patients who had previously tolerated valproate well. Use of valproate with topiramate has also been associated with hyperammonaemia and encephalopathy.[14]

Valproate inhibits the metabolism of *lamotrigine* which may result in serious toxic reactions—see p. 530.1. There is limited evidence that valproic acid may affect the metabolism of *ethosuximide* in some patients—see p. 521.3. Valproate reduces the half-life of *zonisamide*—see p. 561.3.

For interactions with benzodiazepines, see under Diazepam, p. 1069.1.

1. Perucca E. Pharmacokinetic interactions with antiepileptic drugs. *Clin Pharmacokinet* 1982; 7: 57–84.
2. Levy RH, Koch KM. Drug interactions with valproic acid. *Drugs* 1982; 24: 543–56.
3. Segura-Bruna N, *et al.* Valproate-induced hyperammonemic encephalopathy. *Acta Neurol Scand* 2006; 114: 1–7.
4. Panesar SK, *et al.* The effect of carbamazepine on valproic acid disposition in adult volunteers. *Br J Clin Pharmacol* 1989; 27: 323–8.
5. Reunanen MI, *et al.* Low serum valproic acid concentrations in epileptic patients on combination therapy. *Curr Ther Res* 1980; 28: 456–62.
6. Cramer JA, *et al.* Variable free and total valproic acid concentrations in sole- and multi-drug therapy. *Ther Drug Monit* 1986; 8: 411–15.
7. Jann MW, *et al.* Increased valproate serum concentrations upon carbamazepine cessation. *Epilepsia* 1988; 29: 578–81.
8. Xiong GL, *et al.* Toxic interaction between valproate and oxcarbazepine: a case detected by the free valproate level. *J Clin Psychopharmacol* 2008; 28: 472–3.
9. Sälke-Kellermann RA, *et al.* Influence of ethosuximide on valproic acid serum concentrations. *Epilepsy Res* 1997; 26: 345–9.
10. Besag FMC, *et al.* Methsuximide reduces valproic acid serum levels. *Ther Drug Monit* 2001; 23: 694–7.
11. Wagner ML, *et al.* The effect of felbamate on valproic acid disposition. *Clin Pharmacol Ther* 1994; 56: 494–502.
12. Longin E, *et al.* Topiramate enhances the risk of valproate-associated side effects in three children. *Epilepsia* 2002; 43: 451–4.
13. Bumb A, *et al.* Adding topiramate to valproate therapy may cause reversible hepatic failure. *Epileptic Disord* 2003; 5: 157–9.
14. Latour P, *et al.* Drug induced encephalopathy in six epileptic patients: topiramate? valproate? or both? *Hum Psychopharmacol* 2004; 19: 193–203.

Antimalarials. Low serum concentrations of valproate have been reported[1] in patients taking *mefloquine*. Also, mefloquine and *chloroquine* may antagonise the antiepileptic activity of valproate by lowering the convulsive threshold.

1. Anonymous. Mefloquine for malaria. *Med Lett Drugs Ther* 1990; 32: 13–14.

Antineoplastics. A marked reduction in serum-valproate concentration occurred in a 6-year-old child after a high-dose 24-hour infusion of *methotrexate*.[1]

1. Schroder H, Østergaard JR. Interference of high-dose methotrexate in the metabolism of valproate? *Pediatr Hematol Oncol* 1994; 11: 445–9.

Antipsychotics. As with all antiepileptics, antipsychotics may antagonise the antiepileptic activity of valproate by lowering the convulsive threshold. Although a study[1] found that *risperidone* had no significant effect on the pharmacokinetics of valproate, 2 earlier case reports

showed conflicting results; one[2] described increased serum-valproate concentrations, and the other[3] decreased concentrations, when risperidone was added to valproate therapy. For the effect of valproate on *clozapine*, see p. 1061.3.

1. Ravindran A, *et al.* Risperidone does not affect steady-state pharmacokinetics of divalproex sodium in patients with bipolar disorder. *Clin Pharmacokinet* 2004; 43: 733–40.
2. van Wattum PJ. Valproic acid and risperidone. *J Am Acad Child Adolesc Psychiatry* 2001; 40: 866–7.
3. Bertoldo M. Valproic acid and risperidone. *J Am Acad Child Adolesc Psychiatry* 2002; 41: 632.

Antivirals. There have been 2 reports that describe a reduction in plasma-valproate concentrations in HIV-positive patients who were taking valproate for bipolar disorder and were given *efavirenz* in one case[1] and *ritonavir-boosted lopinavir* in another,[2] resulting in mania. However, an earlier study[3] in a small number of HIV-positive patients did not find any clinically significant interactions between these drugs and valproic acid. For the effect of *aciclovir* on valproate, see under Interactions of Phenytoin, p. 544.1.

For the effect of valproate on *zidovudine*, see p. 1026.3.

1. Saraga M, *et al.* Reduced valproate plasma levels possible after introduction of efavirenz in a bipolar patient. *Bipolar Disord* 2006; 8: 415–17.
2. Sheehan NL, *et al.* Possible interaction between lopinavir/ritonavir and valproic acid exacerbates bipolar disorder. *Ann Pharmacother* 2006; 40: 147–50.
3. DiCenzo R, *et al.* Effects of valproic acid coadministration on plasma efavirenz and lopinavir concentrations in human immunodeficiency virus-infected adults. *Antimicrob Agents Chemother* 2004; 48: 4328–31.

Anxiolytics. For interactions between valproate and *benzodiazepines*, see under Diazepam, p. 1069.1. For an interaction between valproate and *zolpidem*, see p. 1117.3.

Calcium-channel blockers. For the effect of sodium valproate on *nimodipine*, see under Nifedipine, p. 1453.3.

Colestyramine. Colestyramine may decrease the absorption of valproate.

Gastrointestinal drugs. Use with an *antacid* (aluminium and magnesium hydroxides) significantly increased the bioavailability of a valproic acid preparation in healthy subjects;[1] other antacids in this study (calcium carbonate and an aluminium magnesium trisilicate mixture) had a lesser, insignificant effect.

Cimetidine significantly increased the half-life and decreased the clearance of sodium valproate in another study;[2] *ranitidine* had no effect on valproate pharmacokinetics.[2]

These interactions have not been reported to be of clinical significance, although the possibility must exist, particularly in patients on high-dose therapy.

1. May CA, *et al.* Effects of three antacids on the bioavailability of valproic acid. *Clin Pharm* 1982; 1: 244–7.
2. Webster LK, *et al.* Effect of cimetidine and ranitidine on carbamazepine and sodium valproate pharmacokinetics. *Eur J Clin Pharmacol* 1984; 27: 341–3.

Ginkgo biloba. For a report of a fatal breakthrough seizure occurring when phenytoin and valproate semisodium were used with ginkgo biloba, see under Phenytoin, p. 545.1.

Sex hormones. A 26-year-old woman who was taking valproate for epilepsy and a combined *oral contraceptive* had lower serum-valproate concentrations and an increase in seizure frequency during the active pill phase when compared with the inactive pill phase.[1] A subsequent study[2] in 9 epileptic women who were taking valproate and a combined oral contraceptive found that the apparent oral clearance of total and unbound valproic acid increased during contraceptive intake compared with the pill-free interval; the authors suggested that this effect was due to the induction of glucuronidation of valproate by ethinylestradiol.

1. Herzog AG, *et al.* Serum valproate levels with oral contraceptive use. *Epilepsia* 2005; 46: 970–1.
2. Galimberti CA, *et al.* Increased apparent oral clearance of valproic acid during intake of combined contraceptive steroids in women with epilepsy. *Epilepsia* 2006; 47: 1569–72.

Pharmacokinetics

Valproic acid and its salts are rapidly and completely absorbed from the gastrointestinal tract; the rate, but not the extent, of absorption is delayed if given with or after food.

Valproic acid is extensively metabolised in the liver, a large part by glucuronidation and the rest by a variety of complex pathways. It does not appear to enhance its own metabolism, but metabolism may be enhanced by other drugs that induce hepatic microsomal enzymes. It is excreted in the urine almost entirely in the form of its metabolites; small amounts are excreted in faeces and expired air.

Valproic acid is extensively bound to plasma proteins. The extent of protein binding is concentration dependent and is stated to be about 90 to 95% at total concentrations of 50 micrograms/mL, falling to about 80 to 85% at 100 micrograms/mL. Reported half-lives for valproic acid have ranged from about 5 to 20 hours; the shorter half-lives have generally been recorded in epileptic patients receiving multiple drug therapy. Clearance is usually higher in children than in adults.

The 'target' range of total plasma-valproic acid is usually quoted as being 40 to 100 micrograms/mL (280 to 700 micromoles/litre) but routine monitoring of plasma concentrations is not generally considered to be of use as an aid to assessing control.

Valproic acid crosses the placental barrier and small amounts are distributed into breast milk.

Valpromide is an amide derivative of valproic acid and its absorption is slower and its bioavailability somewhat less than that of valproic acid. Valpromide is rapidly and almost completely metabolised in the liver to valproic acid.

The pharmacokinetics of valproate are affected by other antiepileptics (see under Interactions, p. 557.3).

References.

1. Zaccara G, *et al.* Clinical pharmacokinetics of valproic acid—1988. *Clin Pharmacokinet* 1988; 15: 367–89.
2. Bialer M. Clinical pharmacology of valpromide. *Clin Pharmacokinet* 1991; 20: 114–22.
3. Cloyd JC, *et al.* Valproic acid pharmacokinetics in children IV: effects of age and antiepileptic drugs on protein binding and intrinsic clearance. *Clin Pharmacol Ther* 1993; 53: 22–9.
4. Yukawa E, *et al.* Population-based investigation of valproic acid relative clearance using nonlinear mixed effects modeling: influence of drug-drug interaction and patient characteristics. *J Clin Pharmacol* 1997; 37: 1160–7.
5. Dutta S, *et al.* Absolute bioavailability and absorption characteristics of divalproex sodium extended-release tablets in healthy volunteers. *J Clin Pharmacol* 2004; 44: 737–42.
6. Dutta S, *et al.* Comparative absorption profiles of divalproex sodium delayed-release versus extended-release tablets: clinical implications. *Ann Pharmacother* 2006; 40: 619–25.
7. Reed RC, *et al.* Every-12-hour administration of extended-release divalproex in patients with epilepsy: impact on plasma valproic acid concentrations. *Epilepsy Behav* 2006; 8: 391–6.
8. Dutta S, *et al.* Valproate protein binding following rapid intravenous administration of high doses of valproic acid in patients with epilepsy. *J Clin Pharm Ther* 2007; 32: 365–71.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Depakene; Exibral; Logical; Valcas; Valcote; Valnar; ***Austral.***: Epilim; Valprease; Valpro; ***Austria***: Convulex; Depakine Chrono; Depakine Chronosphere; Depakine; ***Belg.***: Convulex; Depakine Chrono; Depakine; ***Braz.***: Depacon; Depakene; Depakote; Epilenil; Torval; Valpakine; Valprene; Zyvalprex; ***Canad.***: Depakene; Epival; ***Chile***: Atemperator; Depakene; DI VP; Neuractin; Valcote; ***China***: Depakine (德巴金); Dian Tai (典泰); ***Cz.***: Absenor; Convulex; Depakine Chrono; Depakine Chronosphere; Depakine; Everiden†; Orfiril; ***Denm.***: Delepsine; Deprakine; Orfiril; ***Fin.***: Absenor; Deprakine Depot; Deprakine; Orfiril; ***Fr.***: Depakine Chrono; Depakine; Depakote; Depamide; Micropakine; ***Ger.***: Convulex; Convulsofin; Ergenyl Chrono; Ergenyl Chronosphere†; Ergenyl; Leptilan; Orfiril; Valpro Beta chrono; Valpro Beta; Valpro chrono†; Valpro†; ***Gr.***: Depakine Chrono; Depakine; Depamide; ***Hong Kong***: Epilim; Orlept†; Valpro; ***Hung.***: Convulex; Depakine Chrono; Depakine; Orfiril; ***India***: D-Val; Depakote; Desval; Dicorate; Dilex; Diproex; Disorate; Disoval; Divaa; Divalex-OD; Divalin; Divalprid-OD; Divalpro; Divalrate; Drvel; Elival; Encorate; Epilex Chrono; Epilex; Epival; Eprea; Epsoval; Genval-OD; Kayval; Macorate; Manoval; Navalin; Valcontin; Valparin; Valrate; Valtec; ***Indon.***: Depakene; Depakote; ***Irl.***: Epi-Chrono†; Epilim Chrono; Epilim Chronosphere; Epilim; ***Israel***: Depalept Chrono; Depalept; Orfiril; Valporal; ***Ital.***: Depakin Chrono; Depakin; Depamag; Depamide; ***Jpn***: Depakene; Selenica; ***Malaysia***: Epilim Chrono; Epilim; Orfiril; ***Mex.***: Atemperator; Criam; Depakene; Edorame; Epival; Leptilan; Pimiken; Trankitec; Vematina; ***Neth.***: Depakine Chrono; Depakine; Orfiril; Propymal; ***Norw.***: Deprakine†; Orfiril; ***NZ***: Epilim; ***Philipp.***: Aleptiz; Depacon; Depakene; Depakote; Epival; Valparin XR; ***Pol.***: Absenor; Convulex; Depakine Chrono; Depakine Chronosphere; Depakine; Depamide; Dipromal; Orfiril; Valpro-Ratiopharm Chrono; ValproLek; ***Port.***: Depakine Chrono; Depakine Chronosphere; Depakine; Diplexil-R; Diplexil; ***Rus.***: Apilepsin (Апилепсин)†; Convulex (Конвулекс); Convulsofin (Конвульсофин); Depakine (Депакин); Depakine Chrono (Депакин Хроно); Depakine Chronosphere (Депакин Хроносфера); Encorate (Энкорат); Encorate Chrono (Энкорат Хроно); Valparin XR (Вальпарин XP); ***S.Afr.***: Convulex; Epilim; ***Singapore***: Convulex; Epilim; Orfiril; Valparin; ***Spain***: Depakine Crono; Depakine; Depamide; Milzone†; ***Swed.***: Absenor; Ergenyl Retard; Ergenyl; Orfiril; ***Switz.***: Convulex; Depakine Chrono; Depakine; Orfiril; ***Thai.***: Depakine; Desorate; Encorate; Epiate; Oltril; Valparin; Valrem; ***Turk.***: Convulex; Depakin Chrono; Depakin; ***UAE***: Valopin; ***UK***: Convulex; Depakote; Epilim Chrono; Epilim; Episenta; Orlept; ***Ukr.***: Convulsofin (Конвульсофин); Depakin Chrono; Depakine (Депакин); Valprocom Chrono (Вальпрокома Хроно); ***USA***: Depacon; Depakene; Depakote; Mendatrex; Stavzor; ***Venez.***: Depakine; Valcote; Valpron.

Pharmacopoeial Preparations

BP 2014: Gastro-resistant Sodium Valproate Tablets; Sodium Valproate Oral Solution; Sodium Valproate Tablets;

USP 36: Divalproex Sodium Delayed-Release Capsules; Divalproex Sodium Delayed-Release Tablets; Divalproex Sodium Extended-Release Tablets; Valproate Sodium Injection; Valproic Acid Capsules; Valproic Acid Syrup.

Vigabatrin *(BAN, USAN, rINN)*

4-Amino-5-hexenoic Acid; MDL-71754; RMI-71754; Vigabatrina; Vigabatrine; Vigabatrinum; γ-Vinyl Aminobutyric Acid; γ-Vinyl-GABA; Вигабатрин.

4-Aminohex-5-enoic acid.

$C_6H_{11}NO_2$=129.2

CAS — 60643-86-9.

ATC — N03AG04.

ATC Vet — QN03AG04.

UNII — GR120KRT6K.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Vigabatrin). A white or almost white powder. Freely soluble in water; slightly soluble in methyl alcohol; practically insoluble in dichloromethane.

USP 36: (Vigabatrin). A white or almost white powder. Freely soluble in water; slightly soluble in methyl alcohol; very slightly soluble in alcohol and in chloroform; practically insoluble in dichloromethane; insoluble in hexane and in toluene. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Vigabatrin is an analogue of gamma-aminobutyric acid (GABA) that acts as an irreversible inhibitor of GABA-transaminase, the enzyme responsible for the catabolism of GABA. It is used as an adjunctive antiepileptic in patients with resistant partial epilepsy with or without secondary generalisation, unresponsive to other therapy. It is also used as monotherapy for infantile spasms (as for example in West's syndrome). (See Epilepsy, p. 559.1.)

The recommended initial oral dose of vigabatrin as adjunctive therapy is 1 g daily, increased, according to response and tolerability, in increments of 500 mg at weekly intervals to a maximum of 3 g daily.

Doses may be divided and given twice daily or taken as a single daily dose. Dosage reductions may be required in the elderly and in patients with renal impairment, particularly those with a creatinine clearance of less than 60 mL/min. For further details of doses in renal impairment, see p. 559.1.

For details of doses in children, see below.

As with other antiepileptics, withdrawal of vigabatrin therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1. Licensed product information recommends that the dose of vigabatrin should be gradually reduced over 2 to 4 weeks.

References.

1. Wheless JW, *et al.* Vigabatrin. *Neurotherapeutics* 2007; 4: 163–72.

Administration in children. Vigabatrin is used as an adjunctive antiepileptic in children with resistant partial epilepsy with or without secondary generalisation, unresponsive to other therapy. It is also used as monotherapy for infantile spasms (as for example in West's syndrome).

The recommended initial oral dose of vigabatrin as *adjunctive therapy* is 40 mg/kg daily, as a single dose or in 2 divided doses. Maintenance doses are given according to body-weight as follows:

- 10 to 15 kg: 0.5 to 1 g daily
- 15 to 30 kg: 1 to 1.5 g daily
- 30 to 50 kg: 1.5 to 3 g daily
- over 50 kg: 2 to 3 g daily

Alternatively, the *BNFC* suggests giving the following oral doses according to age:

- neonates to 12 years: initially 15 to 20 mg/kg (maximum of 250 mg) twice daily, increased over 2 to 3 weeks to a usual maintenance dose of 30 to 40 mg/kg twice daily; maximum of 75 mg/kg or 1.5 g twice daily, whichever is less
- 12 to 18 years: initially 250 mg twice daily, increased over 2 to 3 weeks to a usual maintenance dose of 1 to 1.5 g twice daily

Vigabatrin has been given rectally; in the UK, the *BNFC* has suggested that children over 1 month old may be given the same rectal doses, calculated by age, as those used orally (see above). The commercially available oral powder should be dissolved in a small amount of water before use.

For *monotherapy* in infantile spasms, the recommended initial oral dose of vigabatrin is 50 mg/kg daily, adjusted

according to response. Up to 150 mg/kg daily has been used. The *BNFC* suggests starting with 15 to 25 mg/kg twice daily, adjusted according to response over 7 days; the usual maintenance dose is 40 to 50 mg/kg twice daily (maximum of 75 mg/kg twice daily) for neonates and children up to 2 years of age.

Administration in renal impairment. Reduced oral doses of vigabatrin are recommended for patients with renal impairment. US licensed product information recommends the following dose adjustments based on creatinine clearance (CC):

- CC 50 to 80 mL/minute: 25% dose reduction
- CC 30 to 50 mL/minute: 50% dose reduction
- CC 10 to 30 mL/minute: 75% dose reduction

Epilepsy. Vigabatrin is used in the treatment of epilepsy (p. 506.1) as adjunctive therapy for refractory seizures. Reviews[1-4] of vigabatrin have considered it to be most effective in the treatment of complex partial seizures with or without secondary generalisation; it may, however, exacerbate myoclonic or absence seizures. Efficacy as adjunctive therapy in refractory partial seizures was shown by 2 multicentre studies[5,6] involving 228 patients (including 46 children) and a study[7] involving 52 patients being assessed for epilepsy surgery. However, in a follow-up study[8] of 120 patients who had participated in an open-label study of vigabatrin as adjunctive therapy for refractory epilepsy 6 to 8 years earlier, it was considered that vigabatrin had had only marginal benefit on the long-term prognosis of severe refractory epilepsy, despite favourable results from the original study. A later systematic review[9] concluded that although vigabatrin has proven efficacy in the short term for reducing seizure frequency in refractory partial epilepsy, associated adverse effects such as visual field defects are common and can be severe; further study is considered warranted.

Vigabatrin is also of value in infantile spasms (as for example in West's syndrome). In an assessment of vigabatrin as monotherapy in 192 infants with infantile spasms who were followed up for an average of 7.6 months,[10] there was complete cessation of spasms in 131 patients, a decrease in cluster frequency in 37, and no improvement in 24 (including deterioration in 1 infant). A crossover study comparing vigabatrin with corticotropin in 42 infants found that both drugs produced some benefit;[11] a larger multicentre comparison of treatment with prednisolone and tetracosactide versus vigabatrin found that the former produced better initial control, but that the treatments were equivalent after more prolonged follow-up to 12 to 14 months of age.[12] A review of the literature suggested that vigabatrin was particularly effective in infantile spasms associated with tuberous sclerosis;[13] the authors considered that its efficacy might be less in other forms of infantile spasm.[13] A later guideline[14] also tentatively concluded that vigabatrin was effective in the short-term treatment of infantile spasms including those associated with tuberous sclerosis.

1. French JA. Vigabatrin. *Epilepsia* 1999; **40** (suppl 5): S11–S16.
2. Gidal BE, *et al.* Vigabatrin: a novel therapy for seizure disorders. *Ann Pharmacother* 1999; **33**: 1277–86.
3. Lewis H, Wallace SJ. Vigabatrin. *Dev Med Child Neurol* 2001 **43**: 833–5.
4. Willmore LJ, *et al.* Vigabatrin: 2008 update. *Epilepsia* 2009; **50**: 163–73.
5. Dalla Bernadina B, *et al.* Efficacy and tolerability of vigabatrin in children with refractory partial seizures: a single-blind dose-increasing study. *Epilepsia* 1995; **36**: 687–91.
6. French JA, *et al.* A double-blind, placebo-controlled study of vigabatrin three g/day in patients with uncontrolled complex partial seizures. *Neurology* 1996; **46**: 54–61.
7. Malmgren K, *et al.* Cost analysis of epilepsy surgery and of vigabatrin treatment in patients with refractory partial epilepsy. *Epilepsy Res* 1996; **25**: 199–207.
8. Walker MC, *et al.* Long term use of lamotrigine and vigabatrin in severe refractory epilepsy: audit of outcome. *BMJ* 1996; **313**: 1184–5.
9. Hemming K, *et al.* Vigabatrin for refractory partial epilepsy. Available in The Cochrane Database of Systematic Reviews: Issue 3. Chichester: John Wiley; 2008 (accessed 12/08/09).
10. Aicardi J, *et al.* Sabril IS Investigator and Peer Review Groups. Vigabatrin as initial therapy for infantile spasms: a European retrospective survey. *Epilepsia* 1996; **37**: 638–42.
11. Vigevano F, Cilio MR. Vigabatrin versus ACTH as first-line treatment for infantile spasms: a randomized, prospective study. *Epilepsia* 1997; **38**: 1270–4.
12. Lux AL, *et al.* The United Kingdom Infantile Spasms Study (UKISS) comparing hormone treatment with vigabatrin on developmental and epilepsy outcomes to age 14 months: a multicentre randomised trial. *Lancet Neurol* 2005; **4**: 712–17.
13. Hancock E, Osborne JP. Vigabatrin in the treatment of infantile spasms in tuberous sclerosis. *J Child Neurol* 1999; **14**: 71–4.
14. Mackay MT, *et al.* Practice parameter: medical treatment of infantile spasms—report of the American Academy of Neurology and the Child Neurology Society. *Neurology* 2004; **62**: 1668–81.

Metabolic disorders. Vigabatrin, an irreversible inhibitor of GABA-transaminase, has been tried in GABA metabolic disorders, with or without concurrent epilepsy,[1-5] with ambivalent results. Data from 23 case reports of patients with succinic semialdehyde dehydrogenase deficiency indicated that vigabatrin was clinically beneficial in only about one-third of patients.[4]

1. Jaeken J, *et al.* Vigabatrin in GABA metabolism disorders. *Lancet* 1989; **i**: 1074.
2. Gibson KM, *et al.* Vigabatrin therapy in patient with succinic semialdehyde dehydrogenase deficiency. *Lancet* 1989; **ii**: 1105–6.
3. Stephenson JBP. Vigabatrin for startle-disease with altered cerebrospinal-fluid free gamma-aminobutyric acid. *Lancet* 1992; **340**: 430–1.
4. Gibson KM, *et al.* The clinical phenotype of succinic semialdehyde dehydrogenase deficiency (4-hydroxybutyric aciduria): case reports of 23 new patients. *Pediatrics* 1997; **99**: 567–74.
5. Leuzzi V, *et al.* Vigabatrin improves paroxysmal dystonia in succinic semialdehyde dehydrogenase deficiency. *Neurology* 2007; **68**: 1320–1.

Stiff-man syndrome. There have been anecdotal reports[1-3] of improvement of stiff-man syndrome (see under Muscle Spasm, p. 1064.3) with vigabatrin in patients unable to tolerate benzodiazepine therapy.

1. Vermeij FH, *et al.* Improvement of stiff-man syndrome with vigabatrin. *Lancet* 1996; **348**: 612.
2. Preveti MC, *et al.* Improvement of stiff-man syndrome with vigabatrin. *Neurology* 1997; **48**: 1133–4.
3. Sharoqi IA. Improvement of stiff-man syndrome with vigabatrin. *Neurology* 1998; **50**: 833–4.

Withdrawal syndromes. Vigabatrin has been investigated[1,2] with some benefit as an adjunct in the management of *cocaine* and *metamfetamine* dependence; with short-term use no ocular effects were evident.[1]

1. Fechtner RD, *et al.* Short-term treatment of cocaine and/or methamphetamine abuse with vigabatrin: ocular safety pilot results. *Arch Ophthalmol* 2006; **124**: 1257–62.
2. Brodie JD, *et al.* Randomized, double-blind, placebo-controlled trial of vigabatrin for the treatment of cocaine dependence in Mexican parolees. *Am J Psychiatry* 2009; **166**: 1269–77.

Adverse Effects, Treatment, and Precautions

About half of all patients have adverse effects with vigabatrin. The most common are drowsiness and fatigue, although in children excitation and agitation occur more frequently. The incidence of these effects is generally higher at the start of therapy and decreases over time. Other CNS-related adverse effects include dizziness, headache, ataxia, paraesthesia, tremor, impaired concentration, confusion, and memory disturbances. Other reported adverse effects include weight gain, gastrointestinal disturbances, oedema, alopecia, angioedema, urticaria, and skin rash. Haemoglobin and liver enzyme values may be decreased. Rarely, marked sedation, stupor and confusion, with other symptoms suggestive of encephalopathy, have occurred.

About one-third of all patients receiving vigabatrin have developed irreversible visual field defects, ranging from mild to severe and usually occurring after months or years of therapy. Blurred vision, diplopia, or nystagmus are somewhat less common. Retinal disorders such as peripheral retinal atrophy, or very rarely optic neuritis or atrophy have also been reported (see also below). Visual field function should be assessed before beginning treatment and during routine follow-up (ideally at 6-month intervals), and patients should be warned to report any new visual symptoms that develop during therapy. Vigabatrin should not be used in patients with pre-existing visual field defects.

Psychiatric reactions such as agitation, aggression, irritability, nervousness, depression, and paranoid reactions have occurred in patients with or without a psychiatric history; psychosis, hypomania, or mania have been reported rarely. Patients receiving vigabatrin should be observed carefully for any signs of adverse effects on neurological function. Caution is warranted in patients with a history of psychosis, depression, or behavioural problems.

Vigabatrin may exacerbate myoclonic or absence seizures.

Vigabatrin should be given with caution to the elderly and patients with renal impairment.

Care is required when withdrawing vigabatrin therapy—see also Uses and Administration, p. 558.3.

Breast feeding. Licensed product information states that breast feeding is not recommended in women receiving vigabatrin. For comment on antiepileptic therapy and breast feeding, see p. 508.3.

Driving. For a comment on antiepileptic drugs and driving, see p. 509.2.

Particular care should be taken in view of the possible effects of vigabatrin on visual acuity.

Effects on bone. For the effects of antiepileptics, including vigabatrin, on bone and on calcium and vitamin D metabolism, see under Phenytoin, p. 540.2.

Effects on the eyes. A report of 3 patients who developed bilateral severely constricted visual fields 2 to 3 years after vigabatrin was added to their antiepileptic regimens[1] prompted publication of similar anecdotal reports.[2-5] Peripheral retinal atrophy rather than optic nerve damage appeared to be the cause. Symptoms showed no improvement on stopping the drug, although there was no further deterioration. At that time (1997) the manufacturers replied[6] stating that it was a rare occurrence (less than 0.1%) and was being monitored in further clinical studies. The UK CSM subsequently stated[7] (in March 1998) that it had received 41 reports of visual field defects since December 1989, which persisted in most cases despite stopping treatment. The evidence suggested that the onset of symptoms varied from 1 month to several years after starting vigabatrin. In most cases, visual field defects have persisted despite stopping vigabatrin.[8,9] Interim results of a Prescription Event Monitoring Study[10] in the UK stated that vigabatrin was considered to be probably or possibly associated with objective evidence of a visual field defect in 0.2% of patients. However, subsequent evidence appears to have confirmed that the incidence of visual field defects is much higher;[11-14] revised product literature issued in late 1999 indicated that visual field defects occurred in about one-third of all patients receiving vigabatrin. Male patients appear to be at an increased risk of developing defects.[15,16] Whether cumulative dose may be considered a risk factor remains unclear:[16] some have failed to find a correlation[17] whereas a later open-label study noted an increased risk with increasing duration of treatment.[18]

The CSM considered[14] that vigabatrin should only be prescribed by a specialist, and only where all other combination therapies have failed. Ophthalmological consultation and visual field assessment should be undertaken before starting vigabatrin and visual field screening repeated at 6-monthly intervals during treatment. Conventional perimetry is unsuitable in patients under 9 years of age, in whom alternative methods should be employed. Opinion amongst some paediatricians[19] was that the risk of developing visual field defects had to be weighed against the potential benefit of seizure control. In very young patients, in whom monitoring of vision was impossible, the benefits of vigabatrin in the treatment of infantile spasms were felt by some to outweigh this risk.[20]

Vigabatrin should not be used in patients with pre-existing visual field defects.[14,19]

There is some evidence, mainly from studies in *animals* that retinal toxicity may be associated with an induced deficiency of taurine.[21]

1. Eke T, *et al.* Severe persistent visual field constriction associated with vigabatrin. *BMJ* 1997; **314**: 180–1.
2. Wilson EA, Brodie MJ. Severe persistent visual field constriction associated with vigabatrin. *BMJ* 1997; **314**: 1693.
3. Wong ICK, *et al.* Severe persistent visual field constriction associated with vigabatrin. *BMJ* 1997; **314**: 1693–4.
4. Blackwell N, *et al.* Severe persistent visual field constriction associated with vigabatrin. *BMJ* 1997; **314**: 1694.
5. Harding GFA. Severe persistent visual field constriction associated with vigabatrin. *BMJ* 1997; **314**: 1694.
6. Backstrom JT, *et al.* Severe persistent visual field constriction associated with vigabatrin. *BMJ* 1997; **314**: 1694–5.
7. CSM/MCA. Vigabatrin (Sabril) and visual field defects. *Current Problems* 1998; **24**: 1. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2032326&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)
8. Hardus P, *et al.* Long term changes in the visual fields of patients with temporal lobe epilepsy using vigabatrin. *Br J Ophthalmol* 2000; **84**: 788–90.
9. Johnson MA, *et al.* Visual function loss from vigabatrin: effect of stopping the drug. *Neurology* 2000; **55**: 40–5.
10. Wilton LV, *et al.* Interim report on the incidence of visual field defects in patients on long term vigabatrin therapy. *Pharmacoepidemiol Drug Safety* 1999; **8** (suppl): S9–S14.
11. Wilton LV, *et al.* Visual field defect associated with vigabatrin: observational cohort study. *BMJ* 1999; **319**: 1165–6.
12. Kälviäinen R, *et al.* Vigabatrin, a gabaergic antiepileptic drug, causes concentric visual defects. *Neurology* 1999; **53**: 922–6.
13. Lawden MC, *et al.* Visual field defects associated with vigabatrin therapy. *J Neurol Neurosurg Psychiatry* 1999; **67**: 716–22.
14. CSM/MCA. Vigabatrin (Sabril): visual field defects. *Current Problems* 1999; **25**: 13. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023713&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)
15. Kälviäinen R, Nousiainen I. Visual field defects with vigabatrin: epidemiology and therapeutic implications. *CNS Drugs* 2001; **15**: 217–30.
16. Wild JM, *et al.* Vigabatrin and epilepsy: lessons learned. *Epilepsia* 2007; **48**: 1318–27.
17. Kinirons P, *et al.* Vigabatrin retinopathy in an Irish cohort: lack of correlation with dose. *Epilepsia* 2006; **47**: 311–17.
18. Wild JM, *et al.* Visual field loss in patients with refractory partial epilepsy treated with vigabatrin: final results from an open-label, observational, multicentre study. *CNS Drugs* 2009; **23**: 965–82.
19. Appleton RE. Guideline may help in prescribing vigabatrin. *BMJ* 1998; **317**: 1322.
20. Harding GFA. Severe persistent visual field constriction associated with vigabatrin. *BMJ* 1998; **316**: 232–3.
21. Jammoul F, *et al.* Taurine deficiency is a cause of vigabatrin-induced retinal phototoxicity. *Ann Neurol* 2009; **65**: 98–107.

Effects on the liver. Vigabatrin has shown *in-vivo* and *in-vitro* inhibition of plasma-alanine transaminase activity, which may mask signs of early underlying hepatic disease if only transaminase levels are evaluated.[1]

1. Richens A, *et al.* Evidence for both in vivo and in vitro interaction between vigabatrin and alanine transaminase. *Br J Clin Pharmacol* 1997; **43**: 163–8.

Effects on mental function. *Behavioural disturbances* ranging from irritability and confusion to psychotic reactions have been reported in patients receiving vigabatrin.[1-7] An analysis[8] of adverse effect reports from double-blind controlled studies found that the incidence of psychotic reactions was about 2.5% in vigabatrin-treated patients; however, the most common psychiatric reaction was depression, which occurred in 8 to 12% of patients. Symptoms of psychiatric

disturbance were often relatively mild. Psychiatric reactions are generally reversible when doses are reduced or gradually stopped. In 2 patients[9,10] psychosis developed after sudden withdrawal of vigabatrin; mental state improved when the drug was reinstated. It is not clear whether patients with a history of previous psychiatric disturbances are at greater risk when given vigabatrin.[8,11] Also, using low doses of vigabatrin to start therapy did not reduce the incidence of disturbances.[11]

The problems of antiepileptic therapy adversely affecting *cognition* and *mood* (including the risk of suicidal ideation) are discussed on p. 508.3.

1. Sander JWAS, Hart YM. Vigabatrin and behaviour disturbances. *Lancet* 1990; 335: 57.
2. Dam M. Vigabatrin and behaviour disturbances. *Lancet* 1990; 335: 605.
3. Betts T, Thomas L. Vigabatrin and behaviour disturbances. *Lancet* 1990; 335: 605–6.
4. Johnston SJ. Vigabatrin and behaviour disturbances. *Lancet* 1990; 335: 606.
5. Robinson MK, *et al.* Vigabatrin and behaviour disturbances. *Lancet* 1990; 336: 504.
6. Naumann M, *et al.* Bipolar affective psychosis after vigabatrin. *Lancet* 1994; 343: 606–7.
7. Martínez AC, *et al.* Vigabatrin-associated reversible acute psychosis in a child. *Ann Pharmacother* 1995; 29: 1115–17.
8. Levinson DF, Devinsky O. Psychiatric adverse events during vigabatrin therapy. *Neurology* 1999; 53: 1503–11.
9. Ring HA, Reynolds EH. Vigabatrin and behaviour disturbance. *Lancet* 1990; 335: 970.
10. Brodie MJ, McKee PJW. Vigabatrin and psychosis. *Lancet* 1990; 335: 1279.
11. Wong ICK. Retrospective study of vigabatrin and psychiatric behavioural disturbances. *Epilepsy Res* 1995; 21: 227–30.

Effects on the nervous system. Two patients developed disturbances of motor behaviour associated with the addition of vigabatrin to therapy for intractable seizures.[1] Abnormal brain magnetic resonance imaging (MRI) findings have been reported in infants treated with vigabatrin for infantile spasms,[2,3] particularly in young infants given doses of 125 mg/kg daily or more. Although the abnormalities appeared to be transient, resolving in most patients despite continued treatment, their clinical significance is unknown. Movement disorders such as dystonia, dyskinesia, and hypertonia have been associated with the use of vigabatrin for infantile spasms and the MHRA[3] has warned that if any new movement disorders appear during its use, consideration should be given to a dose reduction or a gradual withdrawal of vigabatrin in consultation with specialist advice.

Acute encephalopathy was reported[4] in two patients after starting vigabatrin in addition to carbamazepine; symptoms of stupor, dysphoria, and irritability were present in both and their EEG background activity was slowed. Clinical symptoms could not be related to intoxication with carbamazepine or its epoxide but it was not known whether an interaction between carbamazepine and vigabatrin had caused the acute encephalopathy. Acute encephalopathy was also reported[5] when vigabatrin was given to a 6-month-old girl who was also receiving phenobarbital. Symptoms resolved when vigabatrin was stopped. In another report[6] vigabatrin was associated with the development of encephalopathy in 3 patients already receiving a variety of antiepileptic drugs other than carbamazepine; withdrawal of vigabatrin led to full recovery. The authors suggested that acute encephalopathy after vigabatrin may be related to a pre-existing cerebral abnormality. Other predisposing factors suggested by licensed product information include higher than recommended initial doses, faster dose increases at greater increments than those recommended, and renal failure.

1. Jongsma MJ, *et al.* Reversible motor disturbances induced by vigabatrin. *Lancet* 1991; 338: 893.
2. Wheless JW, *et al.* Magnetic resonance imaging abnormalities associated with vigabatrin in patients with epilepsy. *Epilepsia* 2009; 50: 195–205.
3. MHRA/CHM. Vigabatrin for infantile spasms: risk of movement disorders and MRI abnormalities. *Drug Safety Update* 2009; 3 (4): 4. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON062549&RevisionSelectionMethod=LatestReleased (accessed 13/01/10)
4. Sälke-Kellermann A, Baier H. Acute encephalopathy with vigabatrin. *Lancet* 1993; 342: 185.
5. Haas-Lude K, *et al.* Acute encephalopathy associated with vigabatrin in a six-month-old girl. *Epilepsia* 2000; 41: 628–30.
6. Sharief MK, *et al.* Acute encephalopathy with vigabatrin. *Lancet* 1993; 342: 619.

Interference with diagnostic tests. Vigabatrin can cause changes in the urinary excretion of amino acids which could be potentially misleading in patients undergoing investigation for metabolic disorders.[1,2]

1. Bonham JR, *et al.* Pyroglutamicaciduria from vigabatrin. *Lancet* 1989; i: 1452–3.
2. Shih VE, Tenenbaum A. Aminoaciduria due to vinyl-gaba administration. *N Engl J Med* 1990; 323: 1353.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies vigabatrin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1] There has, however, been a report of a bullous skin eruption in a patient with porphyria cutanea tarda given vigabatrin.[2]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)
2. Hommel L, *et al.* Acute bullous skin eruption after treatment with vigabatrine. *Dermatology* 1995; 191: 181.

Pregnancy. For comments on the management of epilepsy in pregnancy, see p. 509.2.

Little is known of the effects of newer antiepileptics such as vigabatrin on the fetus, although congenital anomalies have been reported in the offspring of some mothers using vigabatrin during pregnancy.

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy.

Antiepileptics. For the effect of vigabatrin on plasma concentrations of other antiepileptics, see under *Carbamazepine*, p. 516.3; *Phenobarbital*, p. 537.2; *Phenytoin*, p. 543.2; and *Primidone*, p. 547.3.

Pharmacokinetics

Vigabatrin is well absorbed after oral doses of the racemate; the inactive *R* (-)-enantiomer is reported to be present at much higher plasma concentrations than the active *S*(+)-enantiomer, perhaps indicating a difference in bioavailability. About 60 to 80% of an oral dose is excreted in urine as unchanged drug. The elimination half-life is reported to be 5 to 8 hours. Vigabatrin is not significantly bound to plasma proteins.

There does not appear to be any correlation between plasma concentrations of vigabatrin and its efficacy or toxicity. Children exhibit a lower area under the concentration-time curve than adults and may need higher doses to achieve therapeutic plasma concentrations.

Vigabatrin crosses the placenta and is distributed into breast milk.

References.

1. Rey E, *et al.* Vigabatrin: clinical pharmacokinetics. *Clin Pharmacokinet* 1992; 23: 267–78.
2. Hoke JF, *et al.* Pharmacokinetics of vigabatrin following single and multiple oral doses in normal volunteers. *J Clin Pharmacol* 1993; 33: 458–62.
3. Elwes RDC, Binnie CD. Clinical pharmacokinetics of newer antiepileptic drugs: lamotrigine, vigabatrin, gabapentin and oxcarbazepine. *Clin Pharmacokinet* 1996; 30: 403–15.
4. Vauzelle-Kervroëdan F, *et al.* Pharmacokinetics of the individual enantiomers of vigabatrin in neonates with uncontrolled seizures. *Br J Clin Pharmacol* 1996; 42: 779–81.
5. Jacqz-Aigrain E, *et al.* Pharmacokinetics of the S(+) and R(-) enantiomers of vigabatrin during chronic dosing in a patient with renal failure. *Br J Clin Pharmacol* 1997; 44: 183–5.
6. Armijo JA, *et al.* Vigabatrin serum concentration to dosage ratio: influence of age and associated antiepileptic drugs. *Ther Drug Monit* 1997; 19: 491–8.
7. Tran A, *et al.* Vigabatrin: placental transfer in vivo and excretion into breast milk of the enantiomers. *Br J Clin Pharmacol* 1998; 45: 409–11.

Preparations

Proprietary Preparations (*details are given in Volume B*)

Single-ingredient Preparations. *Arg.*: Sabril; ***Austral.***: Sabril; ***Austria***: Sabril; ***Belg.***: Sabril; ***Braz.***: Sabril; ***Canad.***: Sabril; ***Chile***: Sabril; ***Cz.***: Sabril; ***Denm.***: Sabrilex; ***Fin.***: Sabrilex; ***Fr.***: Sabril; ***Ger.***: Sabril; ***Gr.***: Sabril; ***Hong Kong***: Sabril; ***Hung.***: Sabril; ***Irl.***: Sabril; ***Israel***: Sabrilan; ***Ital.***: Sabril; ***Mex.***: Sabril; ***Neth.***: Sabril; Sabrilex†; ***Norw.***: Sabrilex; ***NZ***: Sabril; ***Pol.***: Sabril; ***Port.***: Sabril; ***S.Afr.***: Sabril; ***Singapore***: Sabril; ***Spain***: Sabrilex; ***Swed.***: Sabrilex; ***Switz.***: Sabril; ***Turk.***: Sabril; ***UK***: Sabril; ***USA***: Sabril.

Pharmacopoeial Preparations

BP 2014: Vigabatrin Oral Powder; Vigabatrin Tablets.

Zonisamide *(BAN, USAN, rINN)*

AD-810; CI-912; PD-110843; Zonisamida; Zonisamidum; Зонизамид.

1-(1,2-Benzoxazol-3-yl)methanesulphonamide.

$C_8H_8N_2O_3S$=212.2

CAS — 68291-97-4.

ATC — N03AX15.

ATC Vet — QN03AX15.

UNII — 459384H98V.

Pharmacopoeias. In *US.*

USP 36: (Zonisamide). A white to off-white powder. Soluble in methyl alcohol; freely soluble in dimethylformamide.

Stability. An extemporaneously prepared suspension containing zonisamide 10 mg/mL in a mixture of simple syrup was found[1] to be stable for 28 days in plastic amber bottles when stored at room temperature or under refrigeration; when prepared in 0.5% methylcellulose, the suspension was stable for 28 days under refrigeration and for 7 days at room temperature.

1. Abobo CV, *et al.* Stability of zonisamide in extemporaneously compounded oral suspensions. *Am J Health-Syst Pharm* 2009; 66: 1105–9.

Uses and Administration

Zonisamide, a benzisoxazole derivative, is used as an adjunctive antiepileptic in the treatment of partial seizures, with or without secondary generalisation (below); it may also be used as monotherapy in newly diagnosed patients. In some countries, it is also used as an adjunct to levodopa in the management of Parkinson's disease (p. 561.1) when response to standard therapy is inadequate.

For the *adjunctive* treatment of **epilepsy**:

- in the UK, the usual initial oral dose in adults over 18 years of age is 50 mg daily in 2 divided doses, increased after 1 week to 100 mg daily. Thereafter, the dose may be further increased at weekly intervals by increments of up to 100 mg, to a usual dose of 300 to 500 mg daily, although some patients may respond to lower doses. Dose increments at intervals of 2 weeks should be considered in patients with hepatic or renal impairment and in patients who are not receiving CYP3A4 inducers (see also Interactions, p. 561.3). Zonisamide may be given as a single dose or in 2 divided doses after the titration phase
- in the USA, the usual initial oral dose in patients over 16 years of age is 100 mg daily, increased after at least 2 weeks to 200 mg daily, given as a single dose or in 2 divided doses. Thereafter, if necessary, the dose may be further increased at intervals of at least 2 weeks by increments of 100 mg, to a dose of 400 mg daily. Doses of up to 600 mg daily have been used, but there is no current evidence of an increase in response above 400 mg daily; many of the adverse effects of zonisamide are reported to be more frequent at doses of 300 mg daily and above

For *monotherapy*, in the UK, the usual initial oral dose in patients over 18 years of age is 100 mg daily, increased after 2 weeks to 200 mg daily, given as a single dose. Thereafter, the dose may be further increased at intervals of at least 2 weeks by increments of 100 mg, to a usual dose of 300 mg daily, although some patients may require higher doses of up to 500 mg daily.

For details of doses in children, see below.

As with other antiepileptics, withdrawal of zonisamide therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures; UK licensed product information has suggested that the dose may be decreased in steps of 100 mg at weekly intervals. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p. 506.1.

In the management of **Parkinson's disease**, the usual oral dose is 25 mg once daily.

Administration in children. In the UK, zonisamide is licensed as an adjunct in the treatment of partial seizures with or without secondary generalisation in children aged 6 years and over; it is given as a single daily dose. The usual initial oral dose is 1 mg/kg daily for 1 week. Thereafter, the dose may be increased at weekly intervals by increments of 1 mg/kg, to a usual dose of 6 to 8 mg/kg daily in those weighing 20 to 55 kg and 300 to 500 mg daily in heavier children, although some may respond to lower doses. Dose increments at intervals of 2 weeks should be considered in those who are not receiving CYP3A4 inducers (see also Interactions, p. 561.3). Withdrawal of zonisamide therapy should be done gradually: the daily dose should generally be decreased by about 2 mg/kg at weekly intervals.

Bipolar disorder. Zonisamide may have psychotropic properties, and has been tried in the management of bipolar disorder[1-5] (p. 397.2). However, a randomised controlled study[6] did not find statistically significant differences between patients treated with adjunctive zonisamide and those with placebo.

1. Baldassano CF, *et al.* Acute treatment of bipolar depression with adjunctive zonisamide: a retrospective chart review. *Bipolar Disord* 2004; 6: 432–4.
2. Anand A, *et al.* A preliminary open-label study of zonisamide treatment for bipolar depression in 10 patients. *J Clin Psychiatry* 2005; 66: 195–8.
3. McElroy SL, *et al.* Open-label adjunctive zonisamide in the treatment of bipolar disorders: a prospective trial. *J Clin Psychiatry* 2005; 66: 617–24.
4. Ghaemi SN, *et al.* An open prospective study of zonisamide in acute bipolar depression. *J Clin Psychopharmacol* 2006; 26: 385–8.
5. Wilson MS, Findling RL. Zonisamide for bipolar depression. *Expert Opin Pharmacother* 2007; 8: 111–13.
6. Dauphinais D, *et al.* Zonisamide for bipolar disorder, mania or mixed states: a randomized, double blind, placebo-controlled adjunctive trial. *Psychopharmacol Bull* 2011; 44: 5–17.

Epilepsy. Zonisamide is used in the treatment of refractory epilepsy (p. 506.1). Studies in Japan and elsewhere have showed its efficacy mainly as an adjunct in the treatment

of partial seizures with or without secondary generalisation.[1-5] It is also effective as monotherapy.[3,5-10] Efficacy in primary generalised and mixed-seizure epilepsies appears to be more variable, although it may be of value in refractory myoclonic seizures[11,12] and absence seizures.[13] Zonisamide might also be of use in the treatment of epileptic syndromes such as Lennox-Gastaut syndrome,[14] and infantile spasms (as for example in West's syndrome), although only a small number of patients with the latter condition have been studied.[15-17]

1. Chadwick DW, Marson AG. Zonisamide add-on for drug-resistant partial epilepsy. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 09/06/08).
2. Brodie MJ, *et al.* Dose-dependent safety and efficacy of zonisamide: a randomized, double-blind, placebo-controlled study in patients with refractory partial seizures. *Epilepsia* 2005; 46: 31–41.
3. Zaccara G, Specchio LM. Long-term safety and effectiveness of zonisamide in the treatment of epilepsy: a review of the literature. *Neuropsychiatr Dis Treat* 2009; 5: 249–59.
4. Lu Y, *et al.* Efficacy and safety of adjunctive zonisamide in adult patients with refractory partial-onset epilepsy: a randomized, double-blind, placebo-controlled trial. *Clin Drug Investig* 2011; 31: 221–9.
5. Hoy SM. Zonisamide: a review of its use in the management of adults with partial seizures. *Drugs* 2013; 73: 1321–38.
6. Tosches WA, Tisdell J. Long-term efficacy and safety of monotherapy and adjunctive therapy with zonisamide. *Epilepsy Behav* 2006; 8: 522–6.
7. Kothare SV, *et al.* Efficacy and safety of zonisamide monotherapy in a cohort of children with epilepsy. *Pediatr Neurol* 2006; 34: 351–4.
8. Park SP, *et al.* Long-term efficacy and safety of zonisamide monotherapy in epilepsy patients. *J Clin Neurol* 2007; 3: 175–80.
9. Eun S-H, *et al.* Comparative trial of low- and high-dose zonisamide as monotherapy for childhood epilepsy. *Seizure* 2011; 20: 558–63.
10. Baulac M, *et al.* Efficacy and tolerability of zonisamide versus controlled-release carbamazepine for newly diagnosed partial epilepsy: a phase 3, randomised, double-blind, non-inferiority trial. *Lancet Neurol* 2012; 11: 579–88.
11. Kyllerman M, Ben-Menachen E. Zonisamide for progressive myoclonus epilepsy: long-term observations in seven patients. *Epilepsy Res* 1998; 29: 109–14.
12. Vossler DG, *et al.* Zonisamide for the treatment of myoclonic seizures in progressive myoclonic epilepsy: an open-label study. *Epileptic Disord* 2008; 10: 31–4.
13. Wilfong A, Schultz R. Zonisamide for absence seizures. *Epilepsy Res* 2005; 64: 31–4.
14. You SJ, *et al.* Clinical efficacy of zonisamide in Lennox-Gastaut syndrome: Korean multicentric experience. *Brain Dev* 2008; 30: 287–90.
15. Yanai S, *et al.* Treatment of infantile spasms with zonisamide. *Brain Dev* 1999; 21: 157–61.
16. Lotze TE, Wilfong AA. Zonisamide treatment for symptomatic infantile spasms. *Neurology* 2004; 62: 296–8.
17. Yum M-S, Ko T-S. Zonisamide in West syndrome: an open label study. *Epileptic Disord* 2009; 11: 339–44.

Migraine. Zonisamide has been tried with some success in the prophylaxis of migraine (p. 670.3) in patients refractory to, or intolerant of, topiramate.[1-3]

1. Bermejo PE, Dorado R. Zonisamide for migraine prophylaxis in patients refractory to topiramate. *Clin Neuropharmacol* 2009; 32: 103–6.
2. Villani V, *et al.* Zonisamide for migraine prophylaxis in topiramate-intolerant patients: an observational study. *Headache* 2011; 51: 287–91.
3. Mohammadianinejad SE, *et al.* Zonisamide versus topiramate in migraine prophylaxis: a double-blind randomized clinical trial. *Clin Neuropharmacol* 2011; 34: 174–7.

Obesity. Anorexia and weight loss have been associated with zonisamide therapy (see Adverse Effects, below) and it has been tried, with some success, as an adjunct in the treatment of obesity[1-3] (p. 2315.1); it has also been tried in binge-eating disorder associated with obesity.[4,5] Combination with bupropion (p. 408.2) is under investigation.[2]

1. Gadde KM, *et al.* Zonisamide for weight loss in obese adults: a randomized controlled trial. *JAMA* 2003; 289: 1820–5.
2. Gadde KM, *et al.* Combination therapy of zonisamide and bupropion for weight reduction in obese women: a preliminary, randomized, open-label study. *J Clin Psychiatry* 2007; 68: 1226–9.
3. Gadde KM, *et al.* Zonisamide for weight reduction in obese adults: a 1-year randomized controlled trial. *Arch Intern Med* 2012; 172: 1557–64.
4. McElroy SL, *et al.* Zonisamide in the treatment of binge eating disorder with obesity: a randomized controlled trial. *J Clin Psychiatry* 2006; 67: 1897–1906. Correction. *ibid.* 2007; 68: 172.
5. Ricca V, *et al.* Zonisamide combined with cognitive behavioral therapy in binge eating disorder: a one-year follow-up study. *Psychiatry (Edgmont)* 2009; 6: 23–8.

Parkinsonism. The use of zonisamide in the management of Parkinson's disease (p. 889.1) has been reviewed.[1] Preliminary studies have shown that, when used as an adjunct to levodopa, zonisamide improved motor function and was generally well tolerated.

1. Yang LPH, Perry CM. Zonisamide: in Parkinson's disease. *CNS Drugs* 2009; 23: 703–11.

Withdrawal syndromes and abstinence. Zonisamide has been tried with some success in the management of alcohol withdrawal syndrome[1] and dependence[2-4] (p. 1735.1).

1. Rubio G, *et al.* Zonisamide versus diazepam in the treatment of alcohol withdrawal syndrome. *Pharmacopsychiatry* 2010; 43: 257–62.
2. Knapp CM, *et al.* Open label trial of the tolerability and efficacy of zonisamide in the treatment of alcohol dependence. *Am J Drug Alcohol Abuse* 2010; 36: 102–5.
3. Arias AJ, *et al.* Placebo-controlled trial of zonisamide for the treatment of alcohol dependence. *J Clin Psychopharmacol* 2010; 30: 318–22.
4. Rubio G, *et al.* Effects of zonisamide in the treatment of alcohol dependence. *Clin Neuropharmacol* 2010; 33: 250–3.

Adverse Effects

The most common adverse effects reported with adjunctive zonisamide therapy are somnolence, dizziness, and anorexia; decreased serum-bicarbonate concentrations, decreased appetite, and weight loss are most commonly reported with monotherapy. Other common adverse effects have included gastrointestinal disturbances such as abdominal pain, constipation, diarrhoea, dyspepsia, and nausea, ecchymosis, headache, pruritus, peripheral oedema, ataxia, paraesthesia, diplopia, fatigue, insomnia, anxiety, depression, and agitation or irritability.

Zonisamide is a sulfonamide derivative; potentially fatal hypersensitivity reactions and blood dyscrasias associated with sulfonamides (see Sulfamethoxazole, p. 365.3) have also been reported with zonisamide. Severe, sometimes fatal, skin reactions including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have occurred rarely. Other hypersensitivity reactions have been reported, including drug rash with eosinophilia and systemic symptoms (DRESS). The incidence of peripheral oedema, pruritus, Stevens-Johnson syndrome, and drug-induced hypersensitivity syndrome appears to be higher in elderly patients. There have been isolated reports of aplastic anaemia, agranulocytosis, thrombocytopenia, leucopenia, pancytopenia, and leucocytosis.

Decreased serum-bicarbonate concentrations resulting in metabolic acidosis have been associated with zonisamide therapy and usually occurs early in treatment although it can develop at any time; it appears to be dose-dependent but can occur with doses as low as 25 mg daily. The incidence and severity appear to be greater in younger patients.

Other rare adverse effects have included renal calculi (see below), renal impairment, pancreatitis, rhabdomyolysis, abnormal liver function tests, psychosis, psychomotor slowing, reduced concentration, speech or language difficulties, and nystagmus. Reduced sweating with hyperthermia has occurred mainly in children (see below).

Effects on mental function. For a review of the effects of antiepileptic therapy including zonisamide on *cognition* and *mood* (including the risk of suicidal ideation), see p. 508.3.

Hyperthermia. Decreased sweating and hyperthermia have been reported in patients given zonisamide. By the end of December 2001 the manufacturers in the USA were aware of 40 such cases; of these, 38 had occurred in the first 11 years of marketing in Japan and 2 in the first year of marketing in the USA. Many cases were reported after exposure to high ambient temperatures and some progressed to heat stroke, but none had led to death.

The manufacturer noted that children appeared to be at an increased risk of developing these adverse reactions and should be monitored closely for such effects especially during warm or hot weather. Caution was also advised when zonisamide was given with other drugs known to cause similar effects, for example, carbonic anhydrase inhibitors and antimuscarinics.[1]

1. O'Brien C [Elan Pharmaceuticals]. Important drug warning. Available at: http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM171098.pdf (accessed 25/08/10)

Overdosage. A 20-year-old woman who ingested up to 8.7 g of zonisamide in a suicide attempt vomited twice about 3 hours later and presented with nausea, diffuse chest pain, blurred vision, dizziness, and mild headache 5 hours after ingestion;[1] she also had a 5-minute episode of seizure-like activity that recovered spontaneously. Plasma concentrations 5.5 and 48 hours after ingestion were 110 mg/L and 38 mg/L, respectively (the usual therapeutic concentration is 10 to 30 mg/L); half-life was calculated to be 30 hours. Previous case reports,[2,3] one fatal, of zonisamide overdosage were associated with more severe symptoms, however, other drugs had also been ingested.

1. Wightman RS, *et al.* Zonisamide toxicity in a patient with an intentional overdose. *Ann Pharmacother* 2011; 45: 547.
2. Naito H, *et al.* Monitoring plasma concentrations of zonisamide and clonazepam in an epileptic attempting suicide by an overdose of the drugs. *Curr Ther Res* 1988; 43: 463–7.
3. Sztajnkrycer MD, *et al.* Acute zonisamide overdose: a death revisited. *Vet Hum Toxicol* 2003; 45: 154–6.

Renal calculi. Patients treated with zonisamide in the USA and Europe may have had a higher incidence of renal calculi than those treated in Japan. In one US study,[1] 4 of 113 patients (3.5%) receiving long-term treatment with zonisamide developed renal calculi, but a familial relationship was found for 2. In pooled data[2] from earlier studies, renal calculi had been reported in 13 of 700 patients (1.9%) treated in the USA and Europe compared with 2 of 1008 patients (0.2%) in Japan. Another review,[3] involving information from more than 750 patients, considered the risk of renal calculi in zonisamide-treated patients to be 5 to 9 times greater than that in the general population. However, a later study[4] that evaluated all safety data available at the time (from the US and European clinical trial programme and the manufacturer's postmarketing surveillance database) found the prevalence of symptomatic renal calculi to be low. There has been a report[5] of 3 patients who developed renal calculi associated with zonisamide but were able to continue therapy with hydration and/or citrate supplementation.

1. Patsalos PN, Sander JWAS. Newer antiepileptic drugs: towards an improved risk-benefit ratio. *Drug Safety* 1994; 11: 37–67.
2. Peters DH, Sorkin EM. Zonisamide: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in epilepsy. *Drugs* 1993; 45: 760–87.
3. Bennett WM. Risk of kidney stones in patients treated with zonisamide. *Neurology* 2002; 58 (suppl 3): A298–A299.
4. Wroe S. Zonisamide and renal calculi in patients with epilepsy: how big an issue? *Curr Med Res Opin* 2007; 23: 1765–73.
5. Richards KC, *et al.* Continued use of zonisamide following development of renal calculi. *Neurology* 2005; 64: 763–4.

Precautions

Zonisamide is a sulfonamide derivative and is therefore contra-indicated in patients with a history of hypersensitivity to sulfonamides. (For discussion of cross-reactivity in sulfonamides and sulfa drugs see Hypersensitivity under Sulfamethoxazole, p. 365.3.)

It should be used with care in patients with renal impairment; there is no data on safety in those with hepatic impairment. Zonisamide should be used with caution in patients who have risk factors for nephrolithiasis; adequate hydration is recommended to increase urine output, to try to reduce the risk of developing renal calculi, especially in predisposed patients.

Baseline and periodic measurements of serum-bicarbonate concentrations have been recommended during zonisamide treatment. If metabolic acidosis develops or persists, reducing the dose or stopping the drug should be considered. If treatment is continued, alkali therapy should be considered in patients with persistent acidosis. Zonisamide should be used with caution in those who are also taking carbonic anhydrase inhibitors.

Pancreatic lipase and amylase levels should be monitored in patients who develop pancreatitis and consideration should be given to withdrawing zonisamide. Patients who develop severe muscle pain or weakness, with or without fever, should have their serum creatine phosphokinase and aldolase levels assessed; if these are elevated, zonisamide may need to be withdrawn. A dietary supplement or increased food intake may be appropriate in patients who are losing weight or are underweight with zonisamide; withdrawing zonisamide may be warranted in those with substantial undesirable weight loss. Consideration should be given to withdrawing zonisamide in patients who develop unexplained rash.

Care is required when withdrawing zonisamide therapy—see also Uses and Administration p. 560.3.

Breast feeding. Zonisamide is distributed into breast milk;[1] in view of the potential for serious adverse effects in infants from zonisamide, licensed product information recommends that it should only be used in nursing mothers if the benefits outweigh the risks. It is also recommended that breast feeding must not be resumed until 1 month after stopping zonisamide therapy. For comment on antiepileptic therapy and breast feeding, see p. 508.3.

1. Kawada K, *et al.* Pharmacokinetics of zonisamide in perinatal period. *Brain Dev* 2002; 24: 95–7.

Driving. For a comment on antiepileptic drugs and driving, see p. 509.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies zonisamide as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pregnancy. Zonisamide crosses the placenta.[1] For comments on the management of epilepsy during pregnancy, see p. 509.2.

1. Kawada K, *et al.* Pharmacokinetics of zonisamide in perinatal period. *Brain Dev* 2002; 24: 95–7.

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy. Use with drugs that induce or inhibit the cytochrome P450 isoenzyme CYP3A4 may alter plasma concentrations of zonisamide. Carbamazepine, phenytoin, or phenobarbital reduce the half-life of zonisamide; reductions have also been noted with valproate but to a lesser degree.

The use of zonisamide with other drugs that cause nephrolithiasis should be avoided because of the increased risk of developing renal calculi (see under Adverse Effects, p. 561.2). Caution is advised when zonisamide is used with other drugs known to cause heat-related disorders because of the increased risk of developing hyperthermia (see under Adverse Effects, p. 561.2), and with carbonic anhydrase inhibitors because of the increased risk of developing metabolic acidosis (see Precautions, p. 561.3).

References.
1. Sills G, Brodie M. Pharmacokinetics and drug interactions with zonisamide. *Epilepsia* 2007; **48**: 435–41.

Pharmacokinetics

Zonisamide is almost completely absorbed from the gastrointestinal tract and peak plasma concentrations occur within 2 to 6 hours of oral doses. Bioavailability is essentially complete; the presence of food does not affect the bioavailability of zonisamide but the time to reach peak plasma concentrations is delayed. Steady-state concentrations are achieved within 14 days. It is widely distributed into body tissues. Plasma protein binding is low (40 to 50%) but zonisamide is extensively bound to erythrocytes. The plasma elimination half-life is about 63 hours.

Zonisamide undergoes acetylation to *N*-acetylzonisamide and reduction mediated by the cytochrome P450 isoenzyme CYP3A4 to 2-sulfamoylacetylphenol (SMAP); both metabolites are inactive. Excretion is mainly in the urine; about 15 to 30% appearing as unchanged drug, 15% as *N*-acetylzonisamide, and 50% as the glucuronide of SMAP.

Zonisamide crosses the placenta and is distributed into breast milk.

The pharmacokinetics of zonisamide are affected by use with other antiepileptics (see Interactions, p. 561.3).

References.
1. Kochak GM, *et al.* Steady-state pharmacokinetics of zonisamide, an antiepileptic agent for treatment of refractory complex partial seizures. *J Clin Pharmacol* 1998; **38**: 166–71.
2. Mimaki T. Clinical pharmacology and therapeutic drug monitoring of zonisamide. *Ther Drug Monit* 1998; **20**: 593–7.
3. Leppik IE. Zonisamide: chemistry, mechanism of action, and pharmacokinetics. *Seizure* 2004; **13** (suppl 1): S5–S9.
4. Sills G, Brodie M. Pharmacokinetics and drug interactions with zonisamide. *Epilepsia* 2007; **48**: 435–41.
5. Okada Y, *et al.* Population estimation regarding the effects of cytochrome P450 2C19 and 3A5 polymorphisms on zonisamide clearance. *Ther Drug Monit* 2008; **30**: 540–3.
6. Oles KS, Bell WL. Zonisamide concentrations during pregnancy. *Ann Pharmacother* 2008; **42**: 1139–41.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Kinaplase; *Austria*: Zonegran; *Cz.*: Zonegran; *Denm.*: Zonegran; *Fr.*: Zonegran; *Ger.*: Zonegran; *Gr.*: Zonegran; *Hung.*: Zonegran; *Indon.*: Zonegran; *Irl.*: Zonegran; *Ital.*: Zonegran; *Jpn*: Excegran; Trerief; *Malaysia*: Zonegran; *Neth.*: Zonegran; *Norw.*: Zonegran; *Philip.*: Zonegran; *Pol.*: Zonegran; *Port.*: Zonegran; *Spain*: Zonegran; *Swed.*: Zonegran; *Switz.*: Zonegran; *Thai.*: Zonegran; *Turk.*: Excegran; *UK*: Zonegran; *USA*: Zonegran.

Pharmacopoeial Preparations
USP 36: Zonisamide Tablets.

Antifungals

Aspergillosis, p. 563
Blastomycosis, p. 564
Candidiasis, p. 564
Chromoblastomycosis, p. 564
Coccidioidomycosis, p. 565
Cryptococcosis, p. 565
Dermatophytoses, p. 565
Endocarditis, p. 565
Eye infections, p. 565
Histoplasmosis, p. 566
Infections in immunocompromised patients, p. 566
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Mucormycosis, p. 566
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Paracoccidioidomycosis, p. 567
Peritonitis, p. 567
Pityriasis versicolor, p. 567
Pneumocystis pneumonia, p. 567
Protothecosis, p. 567
Respiratory-tract infections, p. 568
Skin infections, p. 568
Sporotrichosis, p. 568
Tinea, p. 569

This chapter describes the drugs that are used mainly in the treatment and prophylaxis of fungal infections (mycoses). They include:

- the azole derivatives, including:
  - imidazoles (such as ketoconazole)
  - triazoles (such as fluconazole, itraconazole, posaconazole, and voriconazole)
- the allylamines (naftifine and terbinafine)
- the echinocandins (such as anidulafungin, caspofungin and micafungin)
- several polyene antibiotics (including amphotericin B and nystatin)
- other antifungal antibiotics (for example griseofulvin)
- other compounds such as amorolfine, ciclopirox olamine, flucytosine, haloprogin, tolnaftate, and undecenoic acid and its salts.

Choice of Antifungal

Fungi may be classified as yeasts or moulds according to their appearance and means of growth. Examples of yeasts are *Candida* and *Cryptococcus* spp., while moulds include *Aspergillus* spp., the dermatophytes, and the Mucorales fungi. Some fungi are termed dimorphic as they appear to be yeast-like in the host, but grow as moulds *in vitro*. Blastomycosis, chromoblastomycosis, coccidioidomycosis, histoplasmosis, paracoccidioidomycosis, and sporotrichosis are examples of diseases caused by dimorphic fungi.

Most fungi that are pathogenic in humans are saprophytic in nature, but cause infection when airborne spores reach the lungs or paranasal sinuses or are inoculated accidentally into the skin or cornea. Most fungal infections are therefore not transmissible between patients, with the exception of ringworm of the scalp. Endemic mycoses such as blastomycosis, coccidioidomycosis, histoplasmosis, and paracoccidioidomycosis are true pathogens and can cause disease in otherwise healthy persons. Other fungi, such as *Aspergillus*, *Candida*, *Cryptococcus*, and *Pneumocystis jirovecii* are of low pathogenicity and require an alteration in the normal defence mechanisms for disease to occur; such disease is called opportunistic. Fungal diseases are classified into 3 groups: the superficial, subcutaneous, and deep or systemic mycoses. **Superficial** infections are confined to the skin, hair, nails, or mucous membranes. **Subcutaneous** infections are largely limited to the subcutaneous tissue but may spread to surrounding bone and skin. **Deep or systemic** infections may involve organs such as the lung, spleen, or brain, or may affect the body as a whole, and tend to occur more frequently in immunocompromised patients. Fungal infections may also be described as **local** when they are restricted to one body area, as **invasive** when there is spread into the tissues, or as **disseminated** when the infection has spread from the primary site to other organs throughout the body.

Ideally antifungal treatment should be chosen after the infecting organism has been identified, but it is often necessary to start empirical treatment before the pathogen can be cultured and identified, especially in immunocompromised patients in whom infections are often rapidly progressive.

The choice of treatment for the important fungal diseases is described below.

Aspergillosis

Aspergillosis[1] is an infection caused by fungi of the genus *Aspergillus*, usually *A. fumigatus*, although *A. flavus*, *A. nidulans*, *A. niger*, and *A. terreus* may occasionally be encountered. Aspergillosis is usually acquired by inhalation and most often causes non-invasive disease of the respiratory tract. Other sites of infection include the eye after trauma or cataract surgery. Tissue invasion adjacent to the site of infection and dissemination to distant organs may occur, mainly in immunocompromised patients. In severely immunocompromised patients aspergillosis usually presents as a severe acute rapidly progressive lung disease. Other organs affected may include the heart (particularly damaged or prosthetic valves), kidneys, bone, brain, liver, and skin.

In general the response of **invasive** aspergillosis to *treatment* is poor and early treatment is essential. Surgical excision may be necessary. High intravenous doses of amphotericin B have traditionally been the antifungal of choice.[2] However, the overall response rate to conventional amphotericin B is reported to be only 30 to 35%; this may be improved by the use of liposomal amphotericin B.[3,4] Studies have shown voriconazole to be better[5-7] than amphotericin B for the treatment of invasive aspergillosis and comparable[8] as empirical therapy for patients with persistent fever and neutropenia. Intravenous or oral voriconazole is now the recommended treatment for invasive pulmonary aspergillosis;[2,9-11] liposomal amphotericin B may be an acceptable first-line alternative for some patients.[9] Favourable responses with caspofungin have been reported in those with invasive disease[12] as well as in patients with persistent fever and neutropenia.[13] In neutropenic patients with prolonged fever despite broad-spectrum antibacterial therapy, empirical treatment with amphotericin B or its lipid formulations, itraconazole, voriconazole, or caspofungin is recommended.[9]

Drugs that may be used for salvage therapy include itraconazole, posaconazole, caspofungin, micafungin, and conventional or (preferably) lipid formulations of amphotericin B.[9] Salvage therapy may also include combination therapy with the initial antifungal drug or combination therapy with antifungal drugs from classes other than that used in the initial treatment regimen.[9] A retrospective review of patients given salvage therapy with voriconazole plus caspofungin or voriconazole alone reported that 3-month survival was greater for the combination than for voriconazole alone.[14] Successful treatment for invasive aspergillosis was also described in 2 patients given caspofungin with itraconazole.[15]

Treatment for invasive pulmonary aspergillosis should be given for a minimum of 6 to 12 weeks; in immunosuppressed patients, it should be continued throughout the period of immunosuppression and until the lesions have cleared.[9] In HIV-infected adults, therapy should continue at least until the CD4+ T lymphocyte count has risen above 200 cells/microlitre, and there is evidence of clinical response.[10]

Antifungal *prophylaxis* with posaconazole is recommended for haematopoietic stem cell transplant recipients with graft-versus-host disease and in patients with acute myeloid leukaemia or myelodysplastic syndromes who are at high risk for invasive aspergillosis. Itraconazole may be useful, but it is not well tolerated.[2,9,16]

Non-invasive forms of aspergillosis include allergic bronchopulmonary aspergillosis, a hypersensitivity reaction to *Aspergillus* usually occurring in asthmatic patients, and aspergilloma, a fungal mass or ball developing within a pre-existing pulmonary cavity or paranasal sinus.

Allergic bronchopulmonary aspergillosis is usually treated with corticosteroids and oral itraconazole.[9,17] A systematic review[18] has concluded that itraconazole modifies the immunological activation associated with allergic bronchopulmonary aspergillosis in asthmatic patients and improves clinical outcome in the first 4 months of treatment.

The treatment of **aspergilloma** depends on the severity of symptoms, and includes conservative management, antifungal therapy, or surgical resection. Treatment with itraconazole, voriconazole, and possibly also posaconazole are considered to have some benefit. Surgical resection and direct intracavitary instillation of antifungals may also be useful in selected patients with a single aspergilloma.[9]

Chronic necrotising pulmonary aspergillosis (CNPA or subacute invasive pulmonary aspergillosis)[19] is a subacute infection seen in patients with an underlying lung disease or systemic risk factors for immunosuppression. Case reports have shown amphotericin B to be successful in about 50% of patients and clinical benefit has also been achieved with intracavitary amphotericin B. Flucytosine has been used with or without amphotericin B. Itraconazole has a reported success rate of 70 to 90%. Voriconazole was also reported to be effective in non-immunocompromised patients with chronic pulmonary aspergillosis,[20] including some with necrotising disease. Evidence therefore supports the use of itraconazole, with voriconazole and possibly also posaconazole as alternatives, for the treatment of CNPA.[9] Treatment needs to be prolonged, so oral antifungals are preferred to parenteral antifungal therapy.

Aspergillosis of the **eye**, like other fungal eye infections, is difficult to treat; antifungals are generally not well absorbed after topical application and infections extending into the vitreous or anterior chamber require subconjunctival, intra-ocular, and/or systemic treatment. Systemic treatment is necessary for ocular manifestations of disseminated disease. Intravenous and intravitreal amphotericin B are recommended for the treatment of *Aspergillus* endophthalmitis; intravitreal or systemic voriconazole may be given as an alternative. For the management of *Aspergillus* keratitis topical antifungal therapy plus systemic antifungal therapy with either amphotericin B, voriconazole, or itraconazole is recommended.[9] For superficial eye infections several drugs including natamycin, amphotericin B, azoles, and sulfadiazine silver have been applied topically alone or as an adjunct to systemic therapy. Surgical excision of infected tissue may be necessary in severe infections.

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Blastomycosis

Blastomycosis (not to be confused with South American blastomycosis, see Paracoccidioidomycosis, p. 567.1) is an infection caused by the fungus *Blastomyces dermatitidis*, which is endemic to much of North America. Inhalation of spores results in pulmonary infection which may be followed in 25 to 40% of patients by dissemination; the skin, skeleton, and genito-urinary system may become infected. While blastomycosis may affect anyone living in an endemic area, disseminated disease (including CNS involvement) is more common in immunocompromised patients.

Acute pulmonary infection may be mild and self-limiting in immunocompetent patients, but treatment should be considered in patients presenting with clinical symptoms. All patients with moderate to severe pneumonia or disseminated disease, and all immunocompromised patients require treatment.[1]

In immunocompetent patients, mild to moderate disease is treated with oral itraconazole; the duration of treatment is at least 6 months for pulmonary disease and 12 months for bone disease. Ketoconazole or fluconazole are less effective alternatives (and ketoconazole is more toxic); the role of voriconazole or posaconazole is not clear,[1] although they may be effective. Patients unable to tolerate azoles or in whom disease progresses should be switched to amphotericin B.[1] Life-threatening disease (either pulmonary or extrapulmonary) should be treated intravenously with a lipid or conventional formulation of amphotericin B; patients are usually switched to oral itraconazole once stabilised.[1] All patients with CNS disease should be given a lipid formulation of amphotericin B intravenously for 4 to 6 weeks, followed by an oral azole; the options for the latter include fluconazole, itraconazole, or voriconazole but some favour the use of voriconazole.[2] Oral treatment should be continued for at least 12 months and until resolution of abnormalities in the CSF.[1]

In patients who are immunosuppressed, the recommended initial treatment is a lipid formulation of amphotericin B given intravenously for 1 to 2 weeks, or until improvement is noted. Once the patient has responded to this initial treatment they may be switched to oral itraconazole, which is continued until at least 12 months of therapy has been given. Life-long itraconazole treatment may be needed in patients in whom immunosuppression cannot be reversed, or in those who relapse despite appropriate therapy (a well-documented phenomenon in immunosuppressed patients).

In pregnant patients presenting with blastomycosis a lipid formulation of amphotericin B is recommended; azoles should be avoided because of possible teratogenicity. If the neonate shows signs of infection, treatment with a conventional (deoxycholate) formulation of amphotericin B is recommended. Children may be treated with amphotericin B or oral itraconazole, depending on the severity of infection; in general, they tolerate conventional amphotericin B better than adults, and lipid formulations may not be needed.

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Candidiasis

Candida spp. are commensal fungi commonly found in the gastrointestinal tract, mouth, and vagina; they may become pathogenic when natural defence mechanisms are impaired. *C. albicans* is the species most commonly associated with infection although infections with other *Candida* spp., notably *C. glabrata* (*Torulopsis glabrata*), *C. krusei*, *C. lusitaniae*, *C. parapsilosis*, and *C. tropicalis*, also occur and together are commonly referred to as non-*albicans* species. Predisposing factors for candidiasis include antibacterial therapy, skin or mucosal breach, abdominal surgery, debility, diabetes mellitus, pregnancy, and neutropenia and T-cell immunodeficiency; candidiasis often occurs in patients with HIV infection.

Candidiasis (or candidosis) may be classified as mucocutaneous (or superficial), invasive (deep-organ), or disseminated.

Mucocutaneous candidiasis includes infections of the oropharynx, genital organs, and skin. Oropharyngeal and vulvovaginal candidiasis are commonly termed thrush. Most superficial infections may be effectively treated with topical antifungals, although the rare chronic mucocutaneous candidiasis syndrome usually requires systemic treatment. The choice of antifungal should be guided by the availability of an appropriate formulation for the site of infection, toxicity, and the duration of treatment.

Oropharyngeal candidiasis may be treated with topical clotrimazole, miconazole, or nystatin, or oral fluconazole. Topical therapy may not be adequate in severely immunocompromised patients or in those with moderate to severe infection, and oral fluconazole generally is preferred in these patients.[1-3] Oral posaconazole or itraconazole solution are suitable alternatives, particularly for fluconazole-refractory infection.[1-3] Oral posaconazole was found to be as effective as oral fluconazole in the treatment of oropharyngeal candidiasis in HIV-infected persons, but more effective than fluconazole in sustaining clinical benefit after treatment was stopped;[4] it is generally better tolerated than itraconazole.[2,3] Oral amphotericin B suspension may also be considered for fluconazole-refractory infection.[1-3] Intravenous amphotericin B, voriconazole, and the echinocandins are usually effective for oropharyngeal candidiasis, but generally are reserved for use when other agents fail or are not tolerated.[1,3]

Oesophageal infections are not normally accessible to topical therapy and oral or intravenous fluconazole[1-3] or oral itraconazole[2,3] are considered to be the drugs of choice. Severe or refractory disease may be treated with oral posaconazole, oral or intravenous voriconazole, an intravenous echinocandin, or intravenous amphotericin B.[1-3]

Vulvovaginal candidiasis responds well to topical antifungal treatment with creams or pessaries. Uncomplicated vaginitis responds to short-course topical therapy with azoles such as butoconazole, clotrimazole, econazole, fenticonazole, isoconazole, miconazole, terconazole, or tioconazole, to topical nystatin, or to oral therapy with fluconazole or itraconazole.[1,5,6] Complicated vulvovaginal candidiasis may occur in up to 10% of cases, and includes disease that is severe, recurrent, caused by non-*albicans* candida, or that occurs in a compromised patient (such as those who are pregnant or have an underlying debilitating medical condition).[1,5,6]

- *Severe* disease will generally require at least 7 to 14 days of treatment with a topical azole[1,5] or high-dose oral fluconazole given twice[5,6] or 3 times[1] at 72 hour intervals. Alternatively, use of a single dose vaginal pessary with a second dose given after 72 hours can be considered.[6]
- For *recurrent* disease (at least 4 symptomatic episodes in a 1-year period) therapy consists of induction, followed by a 6-month maintenance regimen. For induction, 3 doses of high-dose oral fluconazole (given at 72 hour intervals) are recommended; alternatively, 7 to 14 days of topical azole therapy, or 10 to 14 days of oral azole therapy can be used.[1,5,6] Recommended maintenance regimens include high-dose oral fluconazole given once weekly,[1,5,6] oral fluconazole, itraconazole, or ketoconazole given daily,[6] or intermittent topical azoles,[1,5] such as weekly use of a clotrimazole vaginal pessary.[1,6]
- Vulvovaginal candidiasis with non-*albicans* species may not respond to azoles, in which case topical use of nystatin,[6] boric acid,[1,5,6] or flucytosine (alone, or with amphotericin B)[1,6] are often effective; longer treatment courses may be necessary, and 7 to 14 days has been recommended.
- Among *compromised patients* with vulvovaginal candidiasis, a more prolonged (7 to 14 days) conventional antimycotic regimen is again recommended.[5] Treatment regimens for HIV-infected women generally should not differ from those of HIV-uninfected women.[1,5] In pregnancy, topical azoles are recommended[5,6] and appear to be more effective than nystatin;[7] treatment is given for 7 days.

Yogurt preparations containing *Lactobacillus* spp. have been used in the treatment and prevention of vaginal candidiasis in an attempt to restore the natural vaginal flora but evidence to support their use is limited.

Candidal balanitis in men usually responds well to treatment with topical antifungals,[5] generally for 10 to 14 days. Alternatively, a single oral dose of high-dose fluconazole can be considered.

Primary ***prophylaxis*** against mucocutaneous candidiasis is generally not recommended for patients with advanced HIV infection since this may select for resistant *Candida* spp.[2,3] Due to similar concerns, secondary prophylaxis in other patients with mucocutaneous candidiasis is largely restricted to those with frequent or severe recurrences, or those at risk of developing invasive disease, in which case oral fluconazole or itraconazole may be considered.[1,3]

Invasive and disseminated candidiasis require systemic antifungal treatment. Intravenous amphotericin B, with or without flucytosine, has traditionally been regarded as the standard initial treatment in most infections but flucytosine is now infrequently used, except in combination treatment of more serious, invasive infections such as meningitis or endocarditis, because of concerns over its bone-marrow toxicity in AIDS patients. Fluconazole, voriconazole, amphotericin B, and the echinocandins have all been shown to be effective and now offer alternatives for initial antifungal therapy. Either fluconazole or an echinocandin have been suggested for first-line treatment of candidaemia, although the echinocandins may be preferred for more severe infection, those with recent azole exposure, or when infection with *C. glabrata* or *C. krusei* is suspected. Conventional or lipid formulations of amphotericin B are considered appropriate for refractory infections, or where intolerance or resistance limits the use of the more preferred antifungals; it should also be considered for patients suspected to have concomitant candidal meningitis.[1] Neonates with disseminated candidiasis are usually best treated with amphotericin B, although lipid formulations should only be considered where urinary-tract involvement is ruled out. Fluconazole may also be effective.[1,8]

Empirical antifungal therapy may be necessary for persistently febrile neutropenic patients and for non-neutropenic, critically ill patients with unexplained fever and risk factors for invasive candidiasis. Drugs that may be considered for neutropenic patients include caspofungin, amphotericin B (preferably a lipid formulation), or voriconazole. Itraconazole and fluconazole are alternatives, but the latter is considered less suitable due to its restricted antifungal spectrum; azoles should not be used for empirical therapy in patients who have used them for prior prophylaxis.[1] Treatment should generally be continued until signs and symptoms have resolved and the patient is no longer neutropenic. For empirical antifungal treatment in non-neutropenic patients, treatment with fluconazole or an echinocandin has been suggested;[1] echinocandins are preferred where the patient is more seriously ill, recently azole-exposed, or at risk of infection caused by fluconazole-resistant *Candida*. When first-line antifungals are unavailable or ineffective, amphotericin B is a suitable alternative.[1]

Although antifungal ***prophylaxis*** is generally not routinely recommended for non-neutropenic patients, some would consider it appropriate in patients who are at high risk of infection such as patients who are critically ill, neutropenic, or receiving solid organ or bone marrow transplants.[1,9] There is also limited evidence to suggest that prophylactic fluconazole, generally for the first 4 to 6 weeks of life, may reduce the risk of invasive fungal infections (including candidiasis) in very low birth-weight neonates;[10] routine prophylaxis has therefore been recommended by some experts for premature and extremely low birth-weight (less than 1000 g) neonates born in nurseries with a high incidence of invasive candidiasis.[1]

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Chromoblastomycosis

Chromoblastomycosis (chromomycosis) is a chronic fungal infection that affects skin and subcutaneous tissue. It occurs worldwide but is more common in tropical and subtropical climates. Chromoblastomycosis may result from traumatic inoculation of several fungal species including *Fonsecaea compacta* (*Phialophora compacta*), *F. pedrosoi* (*P. pedrosoi*), *Exophiala spinifera*, *E. jeanselmei*, *Phialophora verrucosa*, *Cladosporium carrionii*, and *Rhinocladiella aquaspersa*. In its early stages, when lesions are small, surgical excision or cryotherapy are the treatments of choice, although there is some risk of dissemination during surgery. Many antifungals have been tried but itraconazole and terbinafine, often in high doses and for prolonged periods, have been the most successful. However, recurrence and drug resistance has

been a problem with monotherapy. Itraconazole and terbinafine (given daily on alternate weeks or daily concomitantly for up to 9 months) have been shown to be effective in selected cases of chromoblastomycosis that were unresponsive to monotherapy. Local heat treatment aids healing and may be a useful adjunct.

Coccidioidomycosis

Coccidioidomycosis is an infection caused by inhalation of the spores of *Coccidioides immitis* or *C. posadassi*, fungi found in the soil in arid and semi-desert areas mainly of North, Central, and South America. Common names for the infection include valley fever, desert fever, and desert rheumatism. In endemic areas, coccidioidomycosis is a common opportunistic infection in immunocompromised patients.

Patients with coccidioidomycosis may have acute or chronic lung infections, meningitis, and disseminated disease although many infections are subclinical. In immunocompetent individuals, acute pulmonary disease is usually mild and self-limiting and in 60% of cases resolves without specific chemotherapy. In some patients the infection progresses to chronic pulmonary coccidioidomycosis with granulomatous lesions, fibrosis, and cavitation. Less than 1% of patients develop acute progressive pneumonia (which is commonly fatal if untreated) or disseminated disease (usually involving the skin, bone, meninges, and joints). Severe pulmonary and disseminated infections are more likely in pregnant women, males, certain ethnic groups, diabetics, and immunocompromised patients.

Because the spectrum of disease varies widely, the decision to treat coccidioidomycosis must be individualised, taking into account the severity of infections and risk factors for more serious disease (particularly immunosuppression).[1] If antifungal therapy is given, it is preferably with an oral azole as initial therapy or with intravenous amphotericin B;[1-4] of the azoles, itraconazole and fluconazole are generally preferred,[2,4] while voriconazole[5,6] and posaconazole[6-9] have been reported to be effective in some patients who have not responded to conventional therapy. Amphotericin B is generally used as initial therapy for rapidly progressive non-meningeal disease while azoles are generally preferred for chronic or subacute disease.[1,2] Although combination therapy with an azole and amphotericin B has been used,[1,2] there is no evidence that it is superior to a single antifungal drug.[1] Fluconazole is effective in meningeal infections and is the most frequently recommended antifungal for this indication,[1-3,5] although itraconazole has also produced beneficial responses; intrathecal amphotericin B may also be used, especially in aggressive infections.[1-3] Due to the high incidence of relapse, indefinite suppressive therapy with fluconazole or itraconazole is recommended for patients with coccidioidal meningitis or diffuse pulmonary coccidioidomycosis.[1-3]

Patients with **HIV** infection and **solid organ transplant** recipients who have completed induction therapy should subsequently receive lifelong suppressive fluconazole or itraconazole.[2,10] It may, however, be possible to stop after 12 months total therapy in HIV-infected patients on antiretroviral therapy with sustained CD4+ T lymphocyte counts above 250 cells/microlitre (except in those with meningitis or diffuse pulmonary disease) if there is clinical evidence that the coccidioidal infection is controlled.[2] Primary prophylaxis for HIV-infected adult patients living in coccidioidomycosis-endemic areas is generally only recommended for those with positive IgM or IgG serology and CD4+ T lymphocyte counts below 250 cells/microlitre.[1,2] If prophylaxis is given, it is usually with oral fluconazole.[2] It may also be considered for solid organ transplant recipients who are at risk of coccidioidal infection.[1,10]

The management of **pregnant** women is complicated by the fact that azole antifungals are considered to be teratogenic when given at high doses early in pregnancy (see Pregnancy, under Precautions of Fluconazole, p. 579.3). Recommendations have therefore been published for the management of coccidioidomycosis during pregnancy.[11] Broadly, these are as follows:

- for recent or active non-meningeal infections, amphotericin B based treatment should be given to those in the first trimester; for those in the second or third trimester, azole antifungals or amphotericin B based treatment may be given
- for meningeal infections, intrathecal amphotericin B should be given in the first trimester with azole antifungals being an alternative; for those in the second or third trimester, azole antifungals or intrathecal amphotericin B may be given

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Cryptococcosis

Cryptococcosis is an infection caused by inhalation of the fungi *Cryptococcus neoformans*. or *C. gattii*; it is an important opportunistic infection affecting immunocompromised patients, including those infected with HIV or receiving immunosuppressive drugs, but may rarely afflict apparently immunocompetent individuals. The presentation and severity of cryptococcal disease is often determined by the immune status of the patient and can vary widely, from asymptomatic pulmonary infection to severe CNS or disseminated disease; among HIV-infected individuals, meningitis is the most common presentation.

In immunocompetent and most immunocompromised patients, mild, non-meningeal infections involving a single site such as the lung or skin can generally be ***treated*** with oral fluconazole; for pulmonary infection in immunocompetent patients, itraconazole, voriconazole, and posaconazole are suitable alternatives. Treatment should be continued for 6 to 12 months. In severely immunocompromised individuals, however, mild infections are much more likely to lead to disseminated disease, and therefore should always be treated as severe (see below).[1]

In all patients, severe or disseminated infection and cryptococcal meningitis require a step-wise approach to management that includes induction therapy, followed by consolidation, and then maintenance treatment.

- **Induction therapy** is usually based on amphotericin B and flucytosine.
  - *HIV-infected individuals*[1-3] should generally receive intravenous amphotericin B plus oral or intravenous flucytosine for at least 2 weeks; a lipid formulation is preferred, especially if renal toxicity is a concern.[2] Conventional and lipid formulations of amphotericin B may also be given alone (for 4 to 6 weeks), or with fluconazole (for at least 2 weeks) in patients unable to tolerate flucytosine. Similarly, high-dose fluconazole (see p. 578.3) with flucytosine (for 4 to 6 weeks) may be considered for patients intolerant or refractory to amphotericin B,[1-3] but carries a high risk of toxicity. In some cases fluconazole monotherapy can be considered, but success rates are generally low unless high doses are used.[1]
  - In *solid organ transplant recipients*, lipid formulations of amphotericin B with flucytosine are preferred[1,4,5] due to the high incidence of pre-existing renal dysfunction and frequent use of nephrotoxic medications among such patients.[1,4] Alternatively amphotericin B (lipid or conventional formulation) may be used alone but should be given for at least 4 to 6 weeks.[1]
  - There is less evidence available to guide the choice of induction therapy in *non-HIV infected, non-transplant patients* (including those who are apparently immunocompetent), however, a lipid or conventional formulation of amphotericin B given with flucytosine for at least 4 weeks is usually sufficient;[1] if amphotericin B is given alone, a minimum of two further weeks of therapy should be considered.
- **Consolidation** therapy is required after successful induction therapy in all patients with severe or disseminated cryptococcosis or cryptococcal meningitis, and 8 weeks of oral or intravenous fluconazole is generally recommended.[1-4] Alternatively, oral itraconazole might be considered for HIV-infected patients, but potential drug interactions with antiretrovirals are a concern.[2,3]
- The regimen for **maintenance** therapy in severe disease again depends on the patient's underlying immune status.
  - *Immunocompetent*, and *immunocompromised, non-HIV infected* patients should receive 6 to 12 months of maintenance therapy with oral fluconazole.[1,4]
  - For *HIV-infected patients*, maintenance therapy (secondary prophylaxis) is generally life-long;[1-3] oral fluconazole is preferred but alternatives include oral itraconazole[1,3] or weekly, intravenous amphotericin B.[1] It may be possible to stop maintenance therapy in patients who have received antifungal therapy for at least 12 months,[1] who have shown a sustained response to HAART for more than 6 months,[3] and who remain asymptomatic with regard to cryptococcosis. US guidelines[1-3] recommend restarting secondary prophylaxis if the CD4+ T lymphocyte count falls below 100 to 200 cells/microlitre.

Primary prophylaxis in patients with HIV infection[1-3] or after solid organ transplantation[1,4] is not generally recommended since it has not been shown to be more beneficial than treating cryptococcal infections when they occur and may increase the risk of resistance.

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Dermatophytoses

See under Skin Infections, p. 568.1.

Endocarditis

Infective endocarditis caused by fungi such as *Aspergillus* or *Candida* is much less common than that caused by bacteria (p. 179.2); it most frequently occurs among intravenous drug users, the immunosuppressed,[1,2] or those with a prosthetic heart valve.[1,3]

Mortality due to fungal endocarditis is high. Patients should be treated with antifungal therapy and in most cases surgical removal of the infected heart valve.[1-3] Amphotericin B has commonly been used, usually alone but in some cases combined with flucytosine[1,4-6] or an azole.[2] Alternatives for endocarditis caused by *Candida* spp. are fluconazole or caspofungin. Voriconazole may now be the drug of choice for endocarditis caused by *Aspergillus* spp.[1] Initial treatment regimens should continue for at least 6 weeks, but in many cases considerably longer is needed.[1,3] Since relapse rates of up to 40% have been reported after stopping therapy, secondary prophylaxis is recommended with fluconazole, itraconazole, posaconazole, or voriconazole (depending on the susceptibilities of the infecting organism) for a minimum of 2 years and in some cases for life. Lifelong suppressive therapy is also given to patients who are not suitable candidates for valve replacement.[3-7]

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Eye infections

Fungal infections of the eye are less common than infections with bacteria or viruses, but are usually severe and may lead to loss of vision. Diagnosis may be delayed due to a gradual onset of symptoms and empirical treatment with antibacterials. Patients with impaired host resistance such as diabetics or immunocompromised patients are particularly

at risk. The most common fungi causing eye infections are *Aspergillus, Candida,* and *Fusarium*; others include *Blastomyces, Cryptococcus,* and *Sporothrix*. Corneal infection (keratitis) occurs most frequently, but the orbit, eyelids, lachrymal sacs, conjunctiva, sclera, and intra-ocular structures may also become infected. Infections of the orbit rarely occur spontaneously but are more common with systemic fungal infection or may spread from the adjacent paranasal sinus tissue, as seen in mucormycosis or aspergillosis.[1,2]

Ocular fungal infections are difficult to treat. Diagnosis may be delayed due to a gradual onset of symptoms and empirical treatment with topical antibacterials or corticosteroids. Topical natamycin is generally considered the drug of choice for fungal keratitis due to filamentous fungi, while topical amphotericin B is an alternative. Topical amphotericin B with or without topical flucytosine, is preferred for yeast infections. Azoles have a wide spectrum of activity and clotrimazole, fluconazole, itraconazole, ketoconazole, and miconazole are all used topically; topical posaconazole and voriconazole have also been used in some case reports.

Topical antifungals are not well absorbed and infections extending into the eye require subconjunctival, intra-ocular, or systemic therapy. Systemic treatment may also be indicated when there is a poor response to topical agents, for fungal endophthalmitis, or for ocular manifestations of disseminated fungal disease. When systemic treatment is indicated intravenous amphotericin B is usually given. Azoles may be given for less severe infections or as adjunctive therapy in severe infections. Oral fluconazole and ketoconazole have better penetration into the cornea, aqueous humour, and vitreous humour than itraconazole. Intravitreal injections may be required in infections unresponsive to systemic antifungals.[3,4] For refractory infections, oral posaconazole, systemic voriconazole, and combinations of these with various topical or intravitreal drugs have been effective in some case reports; combination intravenous therapy with voriconazole and caspofungin has also been successfully used.[5]

Surgical debridement or excision may be necessary if the infection progresses despite appropriate antifungal therapy.[1,2]

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Histoplasmosis

Histoplasmosis is a systemic infection caused by *Histoplasma capsulatum*, a fungus found in the soil in endemic areas, particularly at sites with heavy accumulations of bird or bat excrement. Infection is by inhalation of spores. Two types of histoplasmosis occur:

- American histoplasmosis, due to infection with *H. capsulatum* var. *capsulatum*
- African histoplasmosis, due to infection with *H. capsulatum* var. *duboisii*

H. capsulatum var. *capsulatum* is endemic in the central USA where 50 to 90% of the population is infected. Mild infections are generally asymptomatic. However, acute pulmonary infection can occur. Massive infection can be fatal. Chronic pulmonary histoplasmosis can result in lung fibrosis and cavitation. Acute or chronic disseminated infection involving widespread infiltration of the reticuloendothelial system, is mainly seen in immunodeficient or immunocompromised patients.

Histoplasma capsulatum var. *duboisii* is found in Africa and may cause a chronic disseminated form of histoplasmosis with focal lesions mainly in skin and bone.

Antifungal **therapy** for histoplasmosis is necessary in patients with severe acute pulmonary infections, chronic pulmonary disease, or disseminated infection.

Infections which are not life-threatening but not resolving spontaneously may be treated with an oral azole in both immunocompetent and immunocompromised patients.[1,2] Itraconazole is the preferred drug.[1-3] Ketoconazole is moderately effective but more toxic. Fluconazole is less effective than either itraconazole or ketoconazole.[2-4] Posaconazole[3] and voriconazole[2,3] have shown benefit in some cases. Patients with chronic cavitary pulmonary histoplasmosis should be treated with oral itraconazole for a minimum of 1 year.[1]

Patients with moderately severe to severe acute pulmonary histoplasmosis may be treated with intravenous liposomal amphotericin B for 1 to 2 weeks followed by oral itraconazole for a total of 12 weeks. Conventional intravenous amphotericin B may be given as an alternative. The same treatment regimen is recommended for those with progressive disseminated disease; oral itraconazole in these patients should be continued for 12 months.[1-3] Patients with CNS histoplasmosis should be given intravenous liposomal amphotericin B for 4 to 6 weeks, followed by oral itraconazole for a minimum of 1 year.[1-3] Immunocompromised patients with disseminated disease, including those with HIV infection, may need to continue maintenance therapy indefinitely, generally with daily oral itraconazole,[1-3] if immunosuppression cannot be reversed;[1] similar lifelong suppressive therapy should be considered for HIV-infected patients with CNS histoplasmosis,[3] and for patients with disease relapse despite appropriate treatment.[1-3] Intravenous amphotericin B given once weekly has also been suggested for chronic maintenance therapy.[3]

Primary prophylaxis with itraconazole is not recommended routinely but may be considered for adults and adolescents with advanced AIDS at especially high risk of infection due to occupational exposure or residence in a hyperendemic area.[2,3]

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Infections in immunocompromised patients

Immunocompromised patients are at increased risk of infections, including those caused by fungi. Fungi most commonly affecting AIDS patients include *Cryptococcus neoformans, Pneumocystis jirovecii* and *Candida albicans* while those associated with immunosuppressive therapy and cancer are mainly *Aspergillus* and *Candida* spp. Immunocompromised patients are also at increased risk of endemic mycoses, such as coccidioidomycosis, histoplasmosis, and *Penicillium marneffei* as well as a growing number of uncommon fungi reported to cause invasive infections, including *Fusarium, Scedosporium,* and *Trichosporon* species.

Fungal infections in immunocompromised patients are often invasive or disseminated and treatment should start as early as possible. A fungal cause of infection should be considered in patients with persistent febrile neutropenia who have not responded to broad spectrum antibacterials. If the infection has not been identified, **empirical treatment** should be started. Conventional intravenous amphotericin B has been considered first-line empirical therapy and is no less effective than lipid formulations. Fluconazole, itraconazole, voriconazole, and caspofungin appear at least as effective as amphotericin B. For patients with renal impairment lipid formulation of amphotericin B or voriconazole may be given. For patients not responding to an amphotericin B formulation voriconazole, itraconazole, or caspofungin are alternatives. Fluconazole may be considered for low risk patients infected with susceptible *Candida* species.

The benefit and role of **primary prophylaxis** in the management of fungal infections associated with HIV, cancer, and organ transplants is controversial as this may select for resistant isolates and species not susceptible to the antifungals used. This is of particular concern with fluconazole (see Resistance, p. 580.2), one of the drugs most widely used for this purpose. Fluconazole has been shown to be effective as primary prophylaxis against invasive candidiasis but not aspergillosis. Itraconazole, posaconazole, or voriconazole may be preferred for patients at risk of invasive aspergillosis, such as patients being treated for graft-versus-host disease or CMV disease.

Long term suppressive therapy has been recommended for immunocompromised patients with proven or probable invasive aspergillosis or candidiasis. **Secondary prophylaxis** may be stopped when patients are no longer profoundly neutropenic.

Antifungals are also used in selective digestive tract decontamination (see Intensive Care, p. 187.3).

Treatment and prophylaxis of specific fungal infections in immunocompromised patients is discussed under the appropriate headings—see Aspergillosis (p. 563.1), Candidiasis (p. 564.1), Coccidioidomycosis (p. 565.1), Cryptococcosis (p. 565.2), and Histoplasmosis (above), and Pneumocystis Pneumonia (p. 567.2).

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Meningitis

Fungal diseases associated with meningitis include aspergillosis (see p. 563.1), candidiasis (see p. 564.1), coccidioidomycosis (see p. 565.1), cryptococcosis see p. 565.2), and histoplasmosis (see above), although many disseminated fungal infections can involve the CNS, especially in immunocompromised patients. The treatment of each infection is discussed under the appropriate heading, but in general the initial drug of choice in fungal meningitis is intravenous amphotericin B, sometimes with flucytosine.

Mucormycosis

Mucormycosis,[1-4] a rare but invasive and rapidly progressive infection caused by Mucorales fungi, is a form of zygomycosis, a term that is sometimes used synonymously. Mucormycosis usually acquired by inhalation of spores, although trauma and ingestion may also be routes of infection. It usually occurs in immunocompromised patients, or in patients at risk of metabolic acidosis (including those with poorly-controlled diabetes or renal failure). Patients given desferrioxamine may also be at increased risk of infection (see Infection Susceptibility, p. 1547.2). Infections of the mucosa of the respiratory tract or gastrointestinal tract, or of abraded skin, usually with *Rhizopus* or *Rhizomucor* spp., can result in local invasion of deeper tissues including bone and the CNS, with extensive tissue destruction. Disseminated disease may also occur.

The **treatment** of mucormycosis includes a combination of antifungal therapy, surgical debridement when possible, and management of the underlying disease. Invasive or disseminated disease is difficult to treat and is usually fatal. The standard antifungal therapy is relatively high doses of intravenous amphotericin B in standard, or (preferably) lipid formulations: as well as having lower toxicity the latter may produce better response rates.[6] Fluconazole, itraconazole, ketoconazole, or voriconazole are not considered to have a role in the treatment of mucormycosis, although the newer triazoles, posaconazole and ravuconazole, have reported *in-vitro* activity against zygomycete and posaconazole has been tried in patients with refractory disease. Although the echinocandins appear to have no *in-vitro* activity against mucorales fungi, concomitant use of caspofungin was found to improve the response to lipid formulations of amphotericin B in a small study of patients with rhino-orbital-cerebral mucormycosis.[7]

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Mycetoma

Mycetoma[1-4] is a localised infection found worldwide, but most commonly in the tropics and subtropics. Infection mainly results from trauma to the skin, and may spread locally through the lymphatic system to surrounding tissues, progressively destroying connective tissue (fascia) and bone. It is characterised by painless soft-tissue swelling, draining sinus tracts, and discharge of grains composed of large aggregates of filaments (fungal or actinomycete). The foot is most often affected (70 to 80% of cases), less often hand (12%), legs, and knee joints. The term Madura foot is used for mycetoma affecting the foot. Mycetomas may be caused by various organisms; those caused by fungi such as *Madurella mycetomatis, M. grisea,* or *Pseudallescheria boydii* are called eumycetomas. Those caused by the filamentous bacteria, actinomycetes, are called actinomycetomas and are discussed on p. 193.1.

Eumycetomas do not heal spontaneously and are poorly responsive to treatment. They often require both surgical excision and antifungal therapy. Itraconazole or ketoconazole are recommended as first-line antifungals for eumycetomas and the duration of treatment depends on the severity of the infection and ranges from a few months to years. Itraconazole has resulted in good clinical responses and low recurrence rates. Use of oral voriconazole for up to 16 months has also been successful in some case reports.[3-7] Treatment with antifungals before surgery results in lesions that are localised and encapsulated and easier to excise during surgery.[1,2]

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Nail infections

See under Skin Infections, p. 568.1.

Paracoccidioidomycosis

Paracoccidioidomycosis (South American blastomycosis) is caused by an infection with the fungus *Paracoccidioides brasiliensis*. The disease occurs mainly in inhabitants of Central and South America. Infection is thought to be by inhalation and may remain dormant for long periods. While most primary infections are subclinical, some may be progressive and severe, particularly in immunocompromised patients. Paracoccidioidomycosis usually presents as a chronic infection affecting the lungs. Disseminated disease may affect the skin, mucous membranes, gastrointestinal tract, reticuloendothelial system, and adrenals, and may be acute or chronic. Relatively mild cases may be treated with oral itraconazole, or alternatively ketoconazole, for 6 to 12 months or longer.[1] Itraconazole allows shorter treatment courses and lower doses than ketoconazole; relapse rates are also lower. A small open-label study reported that oral voriconazole was as effective as oral itraconazole for long-term treatment of paracoccidioidomycosis.[2] More severe infections or those not responding to azoles are treated with intravenous amphotericin B followed by maintenance azole therapy.[1] Sulfonamides are now used less often since more effective drugs are available. Terbinafine has been used successfully when access to azoles was not possible.[3]

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Peritonitis

Fungal peritonitis may be a complication of peritoneal dialysis, abdominal surgery, or trauma. It is usually caused by yeasts such as *Candida* and rarely moulds such as *Aspergillus*. Fungal peritonitis is associated with considerable mortality and morbidity (including the development of adhesions and other complications that preclude further peritoneal dialysis). Diagnosis and treatment can be difficult.

Amphotericin B is often used to treat fungal peritonitis;[1-4] intravenous dosage has been preferred to intraperitoneal use since the latter route is painful,[4] but intravenous use may lead to poor penetration into the peritoneum.[3] Fluconazole, posaconazole, voriconazole, caspofungin, or flucytosine may also be effective.[3-5] Amphotericin B is often given with flucytosine, particularly for initial empirical therapy,[3] although some prefer to begin treatment with fluconazole alone or with flucytosine, reserving amphotericin B for patients who are immunosuppressed or have significant previous exposure to azoles.[4] Early removal of the peritoneal catheter may reduce the risk of death,[3] and should be rapid if fungal peritonitis is confirmed, although it has been suggested that removal be delayed long enough to allow for vigorous peritoneal lavage with antifungals.[4] Oral continuation therapy with flucytosine and fluconazole has been given after removal of the catheter.[3]

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Pityriasis versicolor

See under Skin Infections, p. 568.1.

Pneumocystis pneumonia

Pneumocystis pneumonia (PCP) is caused by the organism *Pneumocystis jirovecii* (previously named *Pneumocystis carinii* f. sp. *hominis* and at one time considered to be a protozoan). It is an opportunistic pathogen and infection is acquired by inhalation. In persons with normally functioning immune systems infection rarely produces disease, but in immunocompromised patients it may produce interstitial pneumonia which, if untreated, is almost always fatal. In patients with AIDS (p. 957.2) PCP was once a common occurrence, but widespread use of HAART and PCP prophylaxis in many parts of the world has now caused a substantial decline in its incidence; most infections occur in those who have advanced immunosuppression, or who are not receiving appropriate HIV care.

The **treatment** of choice for PCP is:

- intravenous or oral co-trimoxazole[1-4]

Alternative regimens are:[1-4]

- intravenous pentamidine (usually the drug of second choice in severe disease)
- oral or intravenous clindamycin plus oral primaquine
- oral atovaquone
- oral trimethoprim and dapsone
- nebulised pentamidine has occasionally been suggested for mild to moderate infection but is now generally reserved for prophylaxis due to limited treatment efficacy and higher rate of relapse

The recommended duration of treatment is generally 21 days.[1-4]

Intravenous trimetrexate with oral or intravenous folinic acid has been suggested as a possible treatment option for patients who fail to respond to standard first-line drugs.[5]

Adjunctive folinic acid with co-trimoxazole has been associated with an increased risk of therapeutic failure and death in AIDS patients.[3] Combination therapy with co-trimoxazole and pentamidine is not more effective and is potentially more toxic than either drug alone.[6]

Adjunctive treatment with glucocorticosteroids should be given to patients with severe infection[1-4] if they are hypoxic, and treatment should be started as soon as antimicrobial treatment is begun.

Primary **prophylaxis** is indicated for all HIV-positive adolescents and adults (including pregnant women and patients on HAART) with CD4+ T lymphocyte counts lower than 200 cells/microlitre, or a history of oropharyngeal candidiasis.[2,4] It should also be considered for those with a CD4+ T lymphocyte count percentage below 14%, a history of other AIDS-defining illnesses, or in patients with a CD4+ T lymphocyte count less than 250 cells/microlitre for whom routine follow-up counts are not possible.[3] Infants are at increased risk to PCP during their first year of life and, in infants and young children, PCP may occur at higher CD4+ T lymphocyte counts compared with adults. WHO/UNICEF[7] and US guidelines[4] recommend that all infants born to HIV-positive mothers should be given prophylaxis beginning at 4 to 6 weeks of age. Therapy should continue until breast feeding is stopped and the infant is confirmed to be HIV-negative, or for at least 1 year initially. Infants subsequently confirmed to be HIV-positive may need to remain on prophylactic therapy depending on age and CD4+ T lymphocyte cell counts[4,7] or clinical status.[7] In Europe, some clinicians have tended to have a less aggressive approach and only offer prophylaxis once HIV infection is confirmed or opportunistic infections occur.[8] Some recommendations for primary prophylaxis in patients without HIV infection suggest that prophylaxis should be considered for patients with primary immune deficiency, severe protein malnutrition, organ or stem cell transplants, persistent CD4+ T lymphocyte counts lower than 200 cells/microlitre, or patients receiving cytotoxic or immunosuppressive therapy.[2,9,10] In particular, it has been suggested that prophylaxis be considered in adults when the risk of developing PCP exceeds about 3%, as in solid organ transplantation (for the first 6 months after transplantation), allogeneic bone marrow transplantation (for at least the first 6 months, and for the duration of immunosuppression), Wegeners granulomatosis, and acute lymphoblastic leukemia.[11]

Secondary prophylaxis is given to all patients after successful treatment of PCP.[2]

For both primary and secondary prophylaxis[1,3,4] the drug of choice is:

- oral co-trimoxazole; this has the added advantage of also protecting against bacterial infections and toxoplasmosis, a common opportunistic infection in AIDS patients[3,4,7]

Alternative prophylactic regimens[1,2,4] for patients not able to receive co-trimoxazole are:

- oral dapsone (alone, or with oral pyrimethamine if prophylaxis for toxoplasmosis is also required)
- aerosolised pentamidine
- oral atovaquone (alone, or with oral pyrimethamine if prophylaxis for toxoplasmosis is also required)

Other prophylactic regimens include intermittent parenteral administration of pentamidine, pyrimethamine with sulfadoxine, and clindamycin with primaquine, but these are not recommended unless the more usual drugs cannot be used.[4]

In HIV-infected adults, primary and secondary prophylaxis may be discontinued in those who attain a CD4+ T lymphocyte count above 200 cells/microlitre for longer than 3 months on antiretroviral therapy. Primary and secondary prophylaxis should be restarted in adults whose CD4+ T lymphocyte count falls to below 200 cells/microlitre, and in those in whom PCP recurs at a count of greater than 200 cells/microlitre;[4,12] in children, criteria for stopping or restarting prophylaxis vary according to patient age.[4] A study of solid organ transplant recipients[13] suggested that lung transplant recipients are at continued risk of developing PCP and prophylaxis should be continued indefinitely in this group.

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Protothecosis

Protothecosis is an infection with algae of the *Prototheca* spp., usually *P. wickerhamii*. Infection occurs rarely in humans but may follow minor trauma or surgery, leading to a chronic skin lesion and occasionally dissemination. Amphotericin B appears to be the most effective antifungal,[1,2] and has been combined with an oral tetracycline.[2] There are also case reports of itraconazole[3,4] being used successfully and fluconazole has been of benefit in a case unresponsive to itraconazole,[5] but azole therapy has also been associated with treatment failure in some cases.[2] Azole antifungals and

surgery may be considered for patients with more localised disease.[1]

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Respiratory-tract infections

Pathogenic fungi may enter the body by inhalation and colonise the respiratory tract. Fungal infections of the respiratory tract include aspergillosis (see p. 563.1), blastomycosis (see p. 564.1), coccidioidomycosis (see p. 565.1), cryptococcosis (see p. 565.2), histoplasmosis (see p. 566.1), and paracoccidioidomycosis (see p. 567.1). *Pneumocystis jirovecii* is an important cause of pneumonia in HIV-infected patients (see p. 567.2). Other fungi reported to produce respiratory-tract infections mainly in immunocompromised patients include *Candida* spp. (see p. 564.1), *Fusarium* spp., *Penicillium marneffei*, *Pseudoallescheria boydii*, and Zygomycetes such as *Rhizopus arrhizus*. Acute pulmonary fungal infections in immunocompetent individuals are mostly self-limiting conditions that resolve without treatment. Severe, persistent, or progressive infections, or infections in immunocompromised patients, require treatment. Intravenous amphotericin B is usually the drug of choice but mild to moderate infection can be treated with an oral azole such as fluconazole, itraconazole, or ketoconazole. Pulmonary granulomas may require surgical removal. Chronic suppressive treatment is recommended for patients with ongoing immunosuppression due to HIV infection.

Skin infections

The most common fungal skin infections are the dermatophytoses, pityriasis versicolor, and candidiasis. The first two are described here; for candidiasis, see p. 564.1. Other fungal skin infections are discussed under the appropriate headings: blastomycosis (p. 564.1), chromoblastomycosis (p. 564.3), mycetoma (p. 567.1), mucormycosis (p. 566.3), protothecosis (p. 567.3), and sporotrichosis (below). Fungal infections that may involve the skin by dissemination include aspergillosis (p. 563.1), coccidioidomycosis (p. 565.1), cryptococcosis (p. 565.2), histoplasmosis (p. 566.1), and paracoccidioidomycosis (p. 567.1). Less common fungi causing skin infections include *Penicillium marneffei*. Sometimes a fungal infection may affect mucous membranes, nails, or subcutaneous tissue, and there can be spread to deeper tissue and dissemination especially in immunosuppressed patients. The term superficial fungal infections includes those involving the skin, nails, and mucous membranes. Antifungal treatment may be topical or systemic.[1,2]

Dermatophytoses (ringworm, tinea) are infections by dermatophytes, a group of fungi which includes soil-dwelling organisms and human and animal pathogens from 3 genera — *Epidermophyton*, *Microsporum*, and *Trichophyton*. Dermatophytoses are encouraged by hot and humid conditions and poor hygiene and occur throughout tropical and temperate regions of the world.

Dermatophytoses are classified according to the body site affected. They include

- tinea barbae (beard)
- tinea capitis (scalp)
- tinea corporis (body)
- tinea cruris (groin)
- tinea manuum (hand)
- tinea pedis (athlete's foot)
- tinea unguium (nail)

A chronic infection most commonly seen in the tropics is known as favus (tinea favosa) and a variant of tinea corporis known as tinea imbricata (tokelau) is caused by *T. concentricum* and is endemic in parts of the Far East and Central and South America. A severe form of dermatophytosis caused by animal pathogens with deep, suppurant, inflammatory lesions is known as kerion.

Deep infections may occur rarely in immunocompromised patients; they can spread to involve lymph nodes, liver, and brain, and may be fatal.

Mild localised superficial dermatophytoses of hairless skin sites will often respond to *topical* therapy.[3-5] Non-specific agents with a long history of topical use include benzoic acid, methylrosanilinium chloride, selenium sulfide, and salicylic acid. Many of these agents are effective, and while some older preparations such as Compound Benzoic Acid Ointment may be less cosmetically acceptable than modern products, they still have a role in the treatment of minor infections, particularly in the tropics.[6] However, the use of methylrosanilinium chloride is restricted due to fears over possible carcinogenicity (see p. 1762.2). There are many topical antifungals that are active against dermatophytes. The azoles used topically include clotrimazole, econazole, ketoconazole, and miconazole. Ciclopirox olamine[7] and the allylamine antifungals naftifine and terbinafine[8] are also active, and a systematic review[3] considered that allylamines such as terbinafine were slightly more effective than azoles in the treatment of fungal infections of the foot. Chlorphenesin, tolnaftate, and undecenoic acid salts are all effective in uncomplicated dermatophytoses, but there are few comparative studies of their relative efficacy. Amorolfine has also been shown to be effective in skin infections, although its major application is in nail infections (see below).

Infections of some body sites respond poorly to topical therapy, as do extensive infections or those in heavily keratinised areas.[4,8] *Systemic* therapy may be appropriate in these cases as well as in disseminated disease. Griseofulvin, ketoconazole, and itraconazole have been the drugs most widely used, although terbinafine has been reported to be more effective than itraconazole in some forms of tinea[9,10] and also requires only short-duration therapy.[11,12] However, efficacy of terbinafine is reported to depend on the infecting organism.[13] Griseofulvin has proved to have few major toxic effects during long-term therapy and is useful for tinea capitis, extensive or disseminated infections, and nail infections in selected patients. However, since it has a narrow spectrum of activity largely confined to the dermatophytes, accurate diagnosis is essential, particularly before embarking on a prolonged treatment course when no immediate response is anticipated. Ketoconazole has a broader spectrum of activity, but severe adverse effects can occur on prolonged use. Itraconazole appears to produce a rapid response and thus requires shorter treatment periods.[4] Other azoles such as fluconazole may also be effective.[14] Selenium sulfide and povidone-iodine shampoos may be useful adjuncts to oral therapy for tinea capitis to improve efficacy and limit the spread of infection.[15,16] A suitable topical antifungal is used in individuals suspected of carrying infection.[17]

Infections of the **nails (onychomycoses)** are notoriously difficult to treat.[18] Infections of the fingernails take up to 6 months to respond to oral griseofulvin and those of the toenails, a year or longer, but about 60% of nail infections fail to respond or relapse after the initial treatment course. The *oral* antifungals terbinafine, itraconazole, and fluconazole produce persistent antifungal concentrations in the nail more rapidly than griseofulvin.[18,19] Terbinafine and itraconazole have been most widely studied. Both are reported to produce clinical and mycological cures in a high proportion of patients more quickly than griseofulvin, generally after 12 weeks of treatment or less. Long-term follow-up has shown that the response to terbinafine is maintained.[20-22] Terbinafine has been reported to be more effective than itraconazole,[23-26] although neither is effective in all patients. Although *topical* treatments have generally been ineffective in nail infections, ciclopirox nail lacquer has been reported to be effective,[27] but a systematic review[3] noted that cure rates were poor. Amorolfine as a 5% lacquer has also shown benefit,[28] and may be more effective than ciclopirox although evidence is scanty.[3] It has also been used with oral itraconazole[29] or terbinafine[30] with some success. Topical butenafine may also be of benefit.[5] Another approach has been the dissolution of the nail plate with 40% urea paste, usually in combination with topical bifonazole.[31] Guidelines for the treatment of onychomycosis have been published in the UK.[32]

Pityriasis versicolor (tinea versicolor) is a superficial infection caused by the commensal yeast *Malassezia furfur (Pityrosporum orbiculare)*. It is more common in tropical than in temperate latitudes and sun exposure may trigger the infection. Pityriasis versicolor will often respond to topical treatment with an azole antifungal or with selenium sulfide. Topical terbinafine (but not oral) or ciclopirox are alternatives.[33] Immunocompromised patients, including those receiving corticosteroids, may develop extensive infections. In addition, these fungi have caused septicaemia in patients receiving parenteral nutrition.[34] Severe infections require oral treatment with an azole.[35] Griseofulvin is not effective.

Other infections in which *Malassezia* yeasts are implicated include seborrhoeic dermatitis (p. 1689.1) and pityrosporum folliculitis, both of which may present in a more severe form in patients with AIDS. Topical or systemic azole antifungals are effective in these conditions and are the main drugs used. However, relapses are common.[36]

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Sporotrichosis

Sporotrichosis is a disease caused by *Sporothrix schenckii*, a fungus found in soil and vegetation. The infection occurs in the Americas and Africa, and may give rise to cutaneous or extracutaneous disease. The cutaneous form is the more common. It probably follows entry of the organism through skin abrasions and usually presents as a single skin lesion, although infection may spread along lymphatic channels causing a series of skin lesions. Extracutaneous sporotrichosis usually presents as osteoarticular infection. Pulmonary infections are occasionally seen and, rarely, CNS and ocular infections.

Infections rarely heal spontaneously and most patients require **treatment**. Oral potassium iodide has traditionally been used for cutaneous and lymphocutaneous infections although the mode of action is unclear since potassium iodide does not show antifungal activity *in vitro*. Oral itraconazole 200 mg daily for 3 to 6 months is also effective[1-3] and is regarded by some[3,4] as the treatment of choice. The dose of itraconazole may be increased to 200 mg twice daily in non responders; alternatively patients may be given oral terbinafine or a saturated potassium iodide

solution taken orally. Oral fluconazole should only be used in patients who cannot tolerate any of the preferred drugs.[4]

For patients with osteoarticular infections, oral itraconazole 200 mg twice daily for at least 12 months is recommended, with either liposomal or conventional amphotericin B given intravenously as alternatives. Oral itraconazole 200 mg twice daily may be given as maintenance therapy once the patient has responded to the amphotericin B treatment.[4]

Patients with life-threatening pulmonary, disseminated, or meningeal disease should receive treatment for at least 12 months. The drug of choice is intravenous liposomal amphotericin B with conventional amphotericin B given intravenously as an alternative. Oral itraconazole 200 mg twice daily may be given as maintenance therapy. Oral itraconazole may be given in non-life-threatening pulmonary infections and for patients who cannot tolerate amphotericin B.[4]

Lifelong *maintenance* therapy with oral itraconazole 200 mg daily may be beneficial after initial treatment for meningeal or disseminated sporotrichosis in immunocompromised patients, including those with AIDS, if immunosuppression cannot be reversed.[4]

1. Sharkey-Mathis PK, *et al.* Treatment of sporotrichosis with itraconazole. *Am J Med* 1993; **95**: 279–85.
2. Restrepo A, *et al.* Itraconazole therapy in lymphangitic and cutaneous sporotrichosis. *Arch Dermatol* 1986; **122**: 413–17.
3. Anonymous. Antifungal drugs. *Treat Guidel Med Lett* 2005; **3**: 7–14.
4. Kauffman CA, *et al.* Clinical practice guidelines for the management of sporotrichosis: 2007 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2007; **45**: 1255–65. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/522765 (accessed 30/04/08)

Tinea

See under Skin Infections, p. 568.1.

Amorolfine *(BAN, USAN, rINN)*

Amorolfini; Amorolfin; Amorolfina; Amorolfinum; Ro-14-4767/000; Аморольфин.

(±)-*cis*-2,6-Dimethyl-4-[2-methyl-3-(*p*-*tert*-pentylphenyl)propyl]morpholine.

$C_{21}H_{35}NO$=317.5

CAS — 78613-35-1.

ATC — D01AE16.

ATC Vet — QD01AE16.

UNII — AB08HP2FH0.

Amorolfine Hydrochloride *(BANM, rINNM)*

Amorolfina, hidrocloruro de; Amorolfine, Chlorhydrate d'; Amorolfini Hydrochloridum; Hidrocloruro de amorolfina; Ro-14-4767/002; Аморольфина Гидрохлорид.

$C_{21}H_{35}NO,HCl$=354.0

CAS — 78613-38-4.

ATC — D01AE16.

ATC Vet — QD01AE16.

UNII — 741YH7379H.

Uses and Administration

Amorolfine is a morpholine derivative applied topically as the hydrochloride in the treatment of fungal nail and skin infections (p. 568.1). After topical application, systemic absorption of amorolfine is negligible.

For the treatment of nail infections caused by dermatophytes, yeasts, and moulds a lacquer containing the equivalent of 5% amorolfine is painted onto the affected nail once or sometimes twice weekly until the nail has regenerated. Treatment generally needs to be continued for 6 to 12 months.

For skin infections, including dermatophyte infections, a cream containing the equivalent of 0.25% amorolfine is applied once daily for at least 2 to 3 weeks (up to 6 weeks for foot infections) and continued for 3 to 5 days after clinical cure is achieved.

Reviews.

1. Haria M, Bryson HM. Amorolfine: a review of its pharmacological properties and therapeutic potential in the treatment of onychomycosis and other superficial fungal infections. *Drugs* 1995; **49**: 103–20.
2. Flagothier C, *et al.* New insights into the effect of amorolfine nail lacquer. *Mycoses* 2005; **48**: 91–4.

Adverse Effects and Precautions

Skin irritation, presenting as erythema, pruritus, or a burning sensation, and, rarely, more severe skin reactions have been reported after topical application of amorolfine.

Hypersensitivity. A report[1] of allergic contact dermatitis to amorolfine nail lacquer.

1. Pérez-Varela L, *et al.* Dermatitis alérgica de contacto por amorolfina en laca de uñas. *Actas Dermosifiliogr* 2010; **101**: 281–3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies amorolfine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Antimicrobial Action

Amorolfine is a morpholine derivative with antifungal activity. It appears to act by interfering with the synthesis of sterols essential for the functioning of fungal cell membranes.

Amorolfine is active *in vitro* against many pathogenic and opportunistic fungi including dermatophytes, *Blastomyces dermatitidis, Candida* spp., *Histoplasma capsulatum,* and *Sporothrix schenckii.* It also has variable activity against *Aspergillus* spp. However, despite its *in vitro* activity, amorolfine is inactive when given systemically and this limits its use to topical application for superficial infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Laquifun; Loceryl; Micobutina; Micocide A; *Austral.*: Loceryl; *Austria*: Loceryl; *Belg.*: Loceryl; *Braz.*: Loceryl; *Chile*: Loceryl; *China*: Loceryl (罗莫乐); *Cz.*: Loceryl; *Denm.*: Loceryl; *Fin.*: Loceryl; *Fr.*: Curanail; Loceryl; *Ger.*: Amofin; Loceryl; *Gr.*: Loceryl; *Hong Kong*: Loceryl; *Hung.*: Loceryl; *India*: Am-Laqer; Loceryl; *Irl.*: Loceryl; *Israel*: Loceryl; *Ital.*: Locetar; *Jpn*: Pekiron; *Malaysia*: Loceryl; *Mex.*: Loceryl; Onylaq; *Norw.*: Loceryl; *NZ*: Loceryl; *Philipp.*: Locetar; *Pol.*: Loceryl; *Port.*: Locetar; *Rus.*: Loceryl (Лоцерил); *S.Afr.*: Loceryl; *Singapore*: Loceryl; *Spain*: Locetar; Odenil; *Swed.*: Finail; Loceryl; *Switz.*: Curanel; Loceryl; *Thai.*: Loceryl; *UK*: Curanail; Loceryl; Omicur; *Venez.*: Loceryl.

Amphotericin B *(BANM, rINN)*

Amfotericin; Amfotericin B; Amfotericina B; Amfotericinas B; Amfoterisiini; Amfoterisiini B; Amfoterisin; Amfoterisin B; Amfoterycyna b; Amphotericin; Amphotericin B Cholesteryl Sulfate Complex; Amphotericin B Lipid Complex; Amphotericin B Liposome; Amphotericin B Phospholipid Complex; Amphotericin B-Sodium Cholesteryl Sulfate Complex; Amphotéricine B; Amphotericinum; Amphotericinum B; Anfotericina B; Liposomal Amphotericin B; Амфотерицин В.

$C_{47}H_{73}NO_{17}$=924.1

CAS — 1397-89-3.

ATC — A01AB04; A07AA07; G01AA03; J02AA01.

ATC Vet — QA01AB04; QA07AA07; QG01AA03; QJ02AA01.

UNII — 7XU7A7DROE.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int., Jpn,* and *US.*

Ph. Eur. 8: (Amphotericin B; Amphotericin BP 2014). A mixture of antifungal polyenes produced by the growth of certain strains of *Streptomyces nodosus* or by any other means. It consists largely of amphotericin B. It occurs as a yellow or orange, hygroscopic powder. The potency is not less than 750 units per mg with reference to the dried substance. Practically insoluble in water and in alcohol; soluble in dimethyl sulfoxide and in propylene glycol; slightly soluble in dimethylformamide; very slightly soluble in methyl alcohol. Store at 2 degrees to 8 degrees in airtight containers. Protect from light.

USP 36: (Amphotericin B). A yellow to orange, odourless or practically odourless, powder. It contains not less than 750 micrograms of $C_{47}H_{73}NO_{17}$ per mg, and, for material intended for oral or topical use, not more than 15% of amphotericin A, both calculated on the dried substance. Insoluble in water, in dehydrated alcohol, in ether, in benzene, and in toluene; soluble in dimethylformamide, in dimethyl sulfoxide, and in propylene glycol; slightly soluble in methyl alcohol. Store at a temperature not exceeding 8 degrees in airtight containers. Protect from light.

References.

1. Kintzel PE, Smith GH. Practical guidelines for preparing and administering amphotericin B. *Am J Hosp Pharm* 1992; **49**: 1156–64.

Formulation. **Conventional** formulations of amphotericin B injection are typically a complex of amphotericin B and deoxycholate with suitable buffers which form a colloidal dispersion when reconstituted. Nonconventional **'lipid'** formulations of amphotericin B for injection include liposomal amphotericin B, a colloidal dispersion of an amphotericin B and sodium cholesteryl sulfate complex, and a phospholipid complex.

Incompatibility. Because of the wide range of incompatibilities reported with conventional and lipid formulations of amphotericin B, it is generally advisable not to mix them with any other drug. Most incompatibilities are caused by precipitation of amphotericin B due to a change in pH or by the disruption of the colloidal suspension. Precipitation can occur if amphotericin B is added to sodium chloride 0.9% or to electrolyte solutions.

Although heparin is generally reported to be compatible with conventional amphotericin B injection, care should be taken if heparin flush solutions, which are diluted with sodium chloride solution, are used to maintain the patency of intravenous lines in patients receiving amphotericin B. Flushing the intravenous line with 5% glucose solution has been suggested.

Mixtures of conventional amphotericin B in commercial lipid emulsions have been reported to be unstable,[1-3] although others have reported satisfactory stability.[4-6] In one study,[6] vigorous agitation of the mixtures enhanced their stability when compared with gentle mixing.

1. Ericsson O, *et al.* Amphotericin B is incompatible with lipid emulsions. *Ann Pharmacother* 1996; **30**: 298.
2. Ranchère JY, *et al.* Amphotericin B intralipid formulation: stability and particle size. *J Antimicrob Chemother* 1996; **37**: 1165–9.
3. Heide PE. Precipitation of amphotericin B from iv fat emulsion. *Am J Health-Syst Pharm* 1997; **54**: 1449.
4. Lopez RM, *et al.* Stability of amphotericin B in an extemporaneously prepared iv fat emulsion. *Am J Health-Syst Pharm* 1996; **53**: 2724–7.
5. Owens D, *et al.* Stability of amphotericin B 0.05 and 0.5 mg/mL in 20% fat emulsion. *Am J Health-Syst Pharm* 1997; **54**: 683–6.
6. Shadkhan Y, *et al.* The use of commercially available lipid emulsions for the preparation of amphotericin B-lipid admixtures. *J Antimicrob Chemother* 1997; **39**: 635–8. Correction. *ibid.* 1998; **42**: 413.

Preparation of solutions for injection. Recommendations from the manufacturers for preparation of amphotericin solutions are:

- *conventional amphotericin B* formulations for injection are prepared by reconstitution of amphotericin B with sterile water for injection without preservatives, then dilution with glucose injection 5% with a pH above 4.2 to the desired final concentration.
- *liposomal amphotericin B*: injections are prepared by reconstitution with sterile water for injection without a preservative; the required reconstituted amount is then withdrawn and injected via a sterile filter into the desired volume of glucose 5%.
- *amphotericin B-sodium cholesteryl sulfate complex*: injections are prepared by rapidly adding the required amount of water for injection, then further diluting with glucose 5% until the desired final concentration is reached.
- *amphotericin B-phospholipid complex*: before infusion the suspension concentrate must be diluted to the required final concentration with glucose 5%. The required amount of concentrate is injected via a sterile filter into the glucose 5%.

CAUTION: Mixture with sodium chloride injection 0.9% would precipitate amphotericin B.

Stability of oral suspensions. An oral suspension of amphotericin B 100 mg/mL, prepared from a powder of Amphotericin B (USP) and a cherry-flavoured vehicle and maintained at pH 5.3, was found to be stable at 22 to 25 degrees for 93 days.[1]

1. Dentinger PJ, *et al.* Stability of amphotericin B in an extemporaneously compounded oral suspension. *Am J Health-Syst Pharm* 2001; **58**: 1021–4.

Uses and Administration

Amphotericin B is a polyene antifungal antibiotic. It is reported to be fungistatic at concentrations achieved clinically. Amphotericin B is given by intravenous infusion in the treatment of severe *systemic* fungal infections including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis, mucormycosis, paracoccidioidomycosis, and sporotrichosis, and is the usual treatment of choice in fungal endocarditis, meningitis, peritonitis, or severe respiratory-tract infections. Many of these infections are most likely to occur in immunocompromised patients. Amphotericin may be given with flucytosine (p. 581.1) in severe infections.

Amphotericin B is also used for the *local* treatment of superficial candidiasis. It is taken orally for intestinal candidiasis, sometimes as part of regimens for selective decontamination of the digestive tract in patients at special risk of infection, such as those in intensive care (see p. 187.3).

The role of amphotericin B in the treatment of the above systemic and local infections is discussed under Choice of Antifungal, p. 563.1.

Amphotericin B also has antiprotozoal activity. It is used for primary amoebic meningoencephalitis caused by *Naegleria* spp. p. 571.1 and for the treatment of visceral, cutaneous, and mucocutaneous leishmaniasis (see p. 570.3).

Administration and dosage. Amphotericin B is given by *intravenous* infusion conventionally as a colloidal complex with sodium deoxycholate. There is also a liposomal form and other complexes of amphotericin B available for use by infusion when conventional amphotericin B is contra-indicated because of toxicity, especially nephrotoxicity. Before starting therapy with any form of intravenous amphotericin B a test dose is usually advised and the patient observed carefully for about 30 minutes.

Details of intravenous administration and dosage vary according to the formulation being used and it is important not to confuse their dosage regimens; indicative doses for some UK formulations are given below. Therapy has sometimes continued for several months depending on the infection. Doses are expressed in terms of amphotericin B.

- ***Conventional amphotericin B*** *(Fungizone, UK)*. After an initial test dose (1 mg infused over 20 to 30 minutes) treatment usually starts with a daily dose of 250 micrograms/kg, increased gradually to a maximum of 1 mg/kg daily; in seriously ill patients up to 1.5 mg/kg daily or on alternate days may be necessary. If treatment is stopped for longer than 7 days, it should be resumed at a dose of 250 micrograms/kg daily and increased gradually. The daily dose is infused over 2 to 4 hours at a concentration of 100 micrograms/mL in glucose 5%. Slower infusion, over up to 6 hours, may be necessary to reduce the incidence of acute toxic effects.
- ***Liposomal amphotericin B*** *(AmBisome, UK)*. After an initial test dose (1 mg infused over 10 minutes), the usual dose is 1 mg/kg daily, increased gradually to 3 mg/kg if necessary; the *BNF* advises that up to 5 mg/kg daily may be used if required.. The daily dose is infused over 30 to 60 minutes at a concentration of 0.2 to 2 mg/mL in glucose injection.
- ***Amphotericin B-sodium cholesteryl sulfate complex*** *(Amphocil, UK)*. After an initial test dose (2 mg infused over 10 minutes) the usual dose is 1 mg/kg daily, increased gradually to 3 to 4 mg/kg daily if necessary; doses of up to 6 mg/kg daily have been given. The daily dose is infused at a rate of 1 to 2 mg/kg per hour at a concentration of 625 micrograms/mL in glucose 5%.
- ***Amphotericin B-phospholipid complex*** *(Abelcet, UK)*. After an initial test dose (1 mg infused over 15 minutes) the usual dose is 5 mg/kg daily. The daily dose is infused at a rate of 2.5 mg/kg per hour as a diluted suspension containing 1 mg/mL in glucose 5%.

For details of dosing in children, see below.

Conventional amphotericin B may be given by *intrathecal* injection to patients with severe meningitis especially when intravenous therapy has been ineffective. Starting with 25 micrograms, the dose is gradually increased to the maximum that can be tolerated without excessive discomfort. The usual dosage is 0.25 to 1 mg given two to four times each week.

Conventional amphotericin B is also used *orally* as 10-mg lozenges or as a suspension containing 100 mg/mL for oral or perioral candidiasis. The suspension is given in a dose of 1 mL four times daily; it should be retained in the mouth for as long as possible before swallowing. The lozenges are intended to be dissolved in the mouth and are given four times daily, increased to 8 lozenges daily if necessary. Doses of 100 to 200 mg are given four times daily as tablets or suspension to suppress intestinal *Candida*.

Conventional amphotericin B has been given for candiduria as a *continuous bladder irrigation* daily at a suggested concentration of 50 mg in 1000 mL of sterile water. Intermittent irrigation has also been tried.

Conventional amphotericin B has also been given into the lung by nebulised solution, into the eye topically or by subconjunctival or intravitreal injection, to the skin by topical application, into body cavities by instillation, and into joint spaces by intra-articular injection. Liposomal amphotericin B has also been used via inhalation for the prevention of pulmonary aspergillosis (see below).

Administration. *LIPID FORMULATIONS.* Lipid formulations of amphotericin B have been developed in an attempt to minimise renal toxicity and acute toxic reactions. Three lipid-based formulations of amphotericin B available commercially in some countries are:

- liposomes (e.g. *AmBisome*)[1]
- a lipid complex with L-α-dimyristoylphosphatidylcholine and L-α-dimyristoylphosphatidylglycerol (e.g. *Abelcet*)
- a colloidal dispersion with sodium cholesteryl sulfate (e.g. *Amphocil*)

The aim of reducing renal toxicity has largely been achieved, and in some cases patients unable to tolerate conventional amphotericin B have subsequently been successfully treated with one of the lipid-based formulations. Experience with these formulations suggests that they also produce fewer acute toxic reactions. Review articles[2-11] on lipid formulations of amphotericin B generally indicate that clinical studies have been encouraging, and that although they differ in their pharmacodynamics, pharmacokinetics, and dosage, they appear to be clinically at least as effective as amphotericin B.[3,6,11]

1. Barnes RA, *et al.*, eds. AmBisome: an international workshop. *J Antimicrob Chemother* 2002; 49 (suppl S1): 1–86.
2. Coukell AJ, Brogden RN. Liposomal amphotericin B: therapeutic use in the management of fungal infections and visceral leishmaniasis. *Drugs* 1998; 55: 585–612.
3. Brogden RN, *et al.* Amphotericin-B colloidal dispersion: a review of its use against systemic fungal infections and visceral leishmaniasis. *Drugs* 1998; 56: 365–83.
4. Johansen HK, Gøtzsche PC. Amphotericin B lipid soluble formulations versus amphotericin B in cancer patients with neutropenia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2000 (accessed 21/06/05).
5. Dupont B. Overview of the lipid formulations of amphotericin B. *J Antimicrob Chemother* 2002; 49 (Suppl 1): 31–6.
6. Barrett JP, *et al.* A systematic review of the antifungal effectiveness and tolerability of amphotericin B formulations. *Clin Ther* 2003; 25: 1295–320.
7. Herbrecht R, *et al.* The lipid formulations of amphotericin B. *Expert Opin Pharmacother* 2003; 4: 1277–87.
8. Fohrer C, *et al.* Apports des derives lipidiques de l'amphotéricine B dans la prise en charge des infections fongiques. *Therapie* 2006; 61: 235–42.
9. Adler-Moore JP, Proffitt RT. Amphotericin B lipid preparations: what are the differences? *Clin Microbiol Infect* 2008; 14 (suppl 4): 25–36.
10. Bellmann R, *et al.* Clinical roundtable monograph: safety and efficacy of lipid-based amphotericin B. *Clin Adv Hematol Oncol* 2009; 7: 1–8.
11. Moen MD, *et al.* Liposomal amphotericin B: a review of its use as empirical therapy in febrile neutropenia and in the treatment of invasive fungal infections. *Drugs* 2009; 69: 361–92.

INFUSION RATE. Conventional amphotericin B is licensed for use by intravenous infusion over at least 2 hours. A long infusion time is inconvenient for outpatients and often impractical in patients receiving other intravenous medications. This may be overcome by using one of the lipid formulations that can be infused over 30 to 120 minutes. Shorter infusion times have been tried with conventional amphotericin B but although 2 studies[1,2] in small numbers of patients without pre-existing renal impairment found rapid infusion over 1 hour was generally no more toxic than infusion over 4 hours, another[3] found infusion over 45 minutes to be more toxic than a 4-hour infusion during the first 5 to 7 days of treatment. Cardiotoxicity reported in patients receiving rapid infusions includes atrial fibrillation in a patient with pre-existing cardiac disease,[2] ventricular fibrillation associated with hyperkalaemia in a patient with severe renal impairment,[4] and bradycardia[5] and dilated cardiomyopathy[6] in patients without apparent risk factors. Ventricular dysrhythmias were not seen in 27 patients with adequate renal function.[7]

Conversely, continuous infusion of amphotericin B over 24 hours has resulted in fewer adverse effects and a significant reduction in nephrotoxicity compared with infusion over 4 hours.[8] Furthermore, an observational study of 33 patients concluded that a continuous infusion of amphotericin B deoxycholate, started at 1 mg/kg daily and gradually escalated to 2 mg/kg daily was safe and well tolerated by most patients.[9]

1. Oldfield EC, *et al.* Randomized, double-blind trial of 1- versus 4-hour amphotericin B infusion durations. *Antimicrob Agents Chemother* 1990; 34: 1402–6.
2. Cruz JM, *et al.* Rapid intravenous infusion of amphotericin B: a pilot study. *Am J Med* 1992; 93: 123–30.
3. Ellis ME, *et al.* Double-blind randomized study of the effect of infusion rates on toxicity of amphotericin B. *Antimicrob Agents Chemother* 1992; 36: 172–9.
4. Craven PC, Gremillion DH. Risk factors of ventricular fibrillation during rapid amphotericin B infusion. *Antimicrob Agents Chemother* 1985; 27: 868–71.
5. Soler JA, *et al.* Bradycardia after rapid intravenous infusion of amphotericin B. *Lancet* 1993; 341: 372–3.
6. Arswa EL, *et al.* Amphotericin B-induced dilated cardiomyopathy. *Am J Med* 1994; 97: 560–2.
7. Bowler WA, *et al.* Risk of ventricular dysrhythmias during 1-hour infusions of amphotericin B in patients with preserved renal function. *Antimicrob Agents Chemother* 1992; 36: 2542–3.
8. Eriksson U, *et al.* Comparison of effects of amphotericin B deoxycholate infused over 4 or 24 hours: randomised controlled trial. *BMJ* 2001; 322: 579–82.
9. Imhof A, *et al.* Continuous infusion of escalated doses of amphotericin B deoxycholate: an open-label observational study. *Clin Infect Dis* 2003; 36: 943–51.

Administration in children. Conventional and lipid formulations of amphotericin B may be used in children for the treatment of severe systemic fungal infections, and intravenous doses similar to those in adults (see p. 569.3) have been found to be safe and effective. The *BNFC* advises that conventional and liposomal amphotericin B may also be used in neonates; the conventional form may be used in a dose of 1 mg/kg once daily; after a week, the dosing frequency may be reduced to every other day. Daily doses up to 1.5 mg/kg have been tolerated in some studies. The liposomal form may be used in similar doses to adults (see above). Although the most appropriate dose of lipid formulations of amphotericin B for low-birth-weight preterm infants has yet to be firmly established reports suggest that they may be safe and effective at doses similar to those used in adults, relative to body-weight.[1-3]

For all children and neonates, the *BNFC* also advises the use of a weight-based test dose. A dose of 100 micrograms/kg is recommended, to a maximum of 1 mg. For the conventional preparation, the test dose is included as part of the first therapeutic dose. In some countries amphotericin B-sodium cholesteryl sulfate complex is available and it has been suggested that a maximum test dose of 2 mg may be used for this product.

For prophylaxis of neonatal intestinal candidiasis conventional amphotericin B solution 100 mg is given orally once daily.

For information on the pharmacokinetics and doses in children and neonates, see, p. 573.1.

1. Scarcella A, *et al.* Liposomal amphotericin B treatment for neonatal fungal infections. *Pediatr Infect Dis J* 1998; 17: 146–8.
2. Weitkamp J-H, *et al.* Candida infection in very low birth-weight infants: outcome and nephrotoxicity of treatment with liposomal amphotericin B (AmBisome). *Infection* 1998; 26: 11–15.
3. Walsh TJ, *et al.* Amphotericin B lipid complex in pediatric patients with invasive fungal infections. *Pediatr Infect Dis J* 1999; 18: 702–8.

Aspergillosis. While intravenous amphotericin B preparations have a role in the treatment of aspergillosis infections (see p. 563.1), nebulisation may be of value in the prevention of pulmonary disease. In a randomised, placebo-controlled study[1] involving patients with haematological disease where at least 10 days of neutropenia was expected, 12.5 mg liposomal amphotericin B nebulised on 2 consecutive days each week (until neutrophil recovery or a maximum of 12 doses) significantly reduced the incidence of invasive pulmonary aspergillosis.

1. Rijnders BJ, *et al.* Aerosolized liposomal amphotericin B for the prevention of invasive pulmonary aspergillosis during prolonged neutropenia: a randomized, placebo-controlled trial. *Clin Infect Dis* 2008; 46: 1401–8.

Leishmaniasis. The treatment of visceral and mucocutaneous leishmaniasis including the use of amphotericin B is described on p. 923.1 and p. 923.1, respectively.

VISCERAL LEISHMANIASIS. Evidence of declining responsiveness to pentavalent antimonials has led to the evaluation of intravenous amphotericin B as an alternative for first-line therapy. WHO has included liposomal amphotericin B 3 mg/kg daily on each of 5 consecutive days and a sixth dose 6 days later among the regimens suggested for first-line therapy of Mediterranean visceral leishmaniasis in immunocompetent patients,[1] and the drug has been widely adopted as first-line treatment in Europe.[2] Similar doses are recommended by US licensed product information for liposomal amphotericin B (*AmBisome; Gilead, USA*), which recommends 3 mg/kg daily for 5 days with further doses on days 14 and 21. Experience with a short course of 10 mg/kg daily for 2 days was also shown to be effective in 41 immunocompetent children under 14 years, although 1 subsequently relapsed after 5 weeks.[3]

Responses to liposomal amphotericin B have been reported to be slower in immunocompromised patients; relapses occurred in 8 of 11 patients despite treatment with liposomal amphotericin B 1.38 to 1.85 mg/kg daily for 21 days.[4] Increasing the dose to 4 mg/kg daily given on 10 days over a 38-day period did not improve the long-term outcome, although initial responses were good[5] and this regimen is now that recommended by the licensed product information above.

Due to frequent relapse in these patients secondary prophylaxis with intermittent amphotericin B has been considered. An open-label, multicentre study with amphotericin B lipid complex in doses of 3 mg/kg every 21 days for 12 months[6] was effective in 50% of HIV-infected patients. Another cohort study[7] reported that 80% of HIV-infected patients were relapse free at 12 months after receiving an initial treatment course of liposomal amphotericin B in doses of 4 mg/kg daily for 5 consecutive days and then once weekly for 5 weeks, followed by secondary prophylaxis in doses of 5 mg/kg every 3 weeks. However, at 24 months about 45% of the patients had experienced relapses.

Amphotericin B is also being evaluated in other parts of the world. In India, conventional amphotericin B in modest doses (500 micrograms/kg on alternate days) produced good responses both in patients unresponsive to antimonials[8,9] and as first-line therapy.[10] Experience with a higher dose of 1 mg/kg daily for 20 days achieved a 99% cure rate in 938 patients[11] and a dose of 1 mg/kg on alternate days for 30 days is also highly effective.[12] In addition a lower dose regimen of 750 micrograms/kg daily for 15 days was also found to be effective.[13] Liposomal amphotericin B 2 mg/kg daily on 3, 5 or 7 days over a 10-day period all produced clinical cures and minimal toxicity,[14] as did single infusions of 10 mg/kg, 7.5 mg/kg, or 5 mg/kg, or once-daily infusion of 0.75 to 1 mg/kg for 5 days.[15-18] Amphotericin B lipid complex 1, 2, or 3 mg/kg daily for 5 days,[19] or 5 mg/kg given once or twice (5 days apart),[20] has been used successfully although relapses occurred in some patients taking the lower doses in these latter studies. In Brazil, colloidal amphotericin B with sodium cholesteryl sulfate in a dose of 2 mg/kg daily for 5 days produced cures in 10 patients although 1 subsequently relapsed.[21] A study by WHO[22] suggested that more intensive courses of treatment may be needed in Brazil compared with India and Kenya.

MUCOCUTANEOUS LEISHMANIASIS. Amphotericin B is used in mucocutaneous leishmaniasis unresponsive to antimonials. Successful treatment with liposomal amphotericin B has been reported in immunocompetent[23] and immunocompromised[24] patients.

1. Gradoni L, *et al.* Treatment of Mediterranean visceral leishmaniasis. *Bull WHO* 1995; 73: 191–7.

2. Rosenthal E, *et al.* Le traitement de la leishmaniose viscérale en Europe en 2009: place de l'amphotéricine B liposomale. *Med Mal Infect* 2009; **39:** 741–4.
3. Syriopoulou V, *et al.* Two doses of a lipid formulation of amphotericin B for the treatment of Mediterranean visceral leishmaniasis. *Clin Infect Dis* 2003; **36:** 560–6.
4. Davidson RN, *et al.* Liposomal amphotericin B (AmBisome) in Mediterranean visceral leishmaniasis: a multi-centre trial. *Q J Med* 1994; **87:** 75–81.
5. Russo R, *et al.* Visceral leishmaniasis in HIV infected patients: treatment with high dose liposomal amphotericin B (AmBisome). *J Infect* 1996; **32:** 133–7.
6. López-Vélez R, *et al.* Amphotericin B lipid complex versus no treatment in the secondary prophylaxis of visceral leishmaniasis in HIV-infected patients. *J Antimicrob Chemother* 2004; **53:** 540–3.
7. Molina I, *et al.* Efficacy of liposomal amphotericin B for secondary prophylaxis of visceral leishmaniasis in HIV-infected patients. *J Antimicrob Chemother* 2007; **60:** 837–42.
8. Giri OP. Amphotericin B therapy in kala-azar. *J Indian Med Assoc* 1993; **91:** 91–3.
9. Mishra M, *et al.* Amphotericin versus pentamidine in antimony-unresponsive kala-azar. *Lancet* 1992; **340:** 1256–7.
10. Mishra M, *et al.* Amphotericin versus sodium stibogluconate in first-line treatment of Indian kala-azar. *Lancet* 1994; **344:** 1599–1600.
11. Thakur CP, *et al.* Amphotericin B deoxycholate treatment of visceral leishmaniasis with newer modes of administration and precautions: a study of 938 cases. *Trans R Soc Trop Med Hyg* 1999; **93:** 319–23.
12. Sundar S, *et al.* Amphotericin B treatment for Indian visceral leishmaniasis: conventional versus lipid formulations. *Clin Infect Dis* 2004; **38:** 377–83.
13. Sundar S, *et al.* Amphotericin B treatment for Indian visceral leishmaniasis: response to 15 daily versus alternate-day infusions. *Clin Infect Dis* 2007; **45:** 556–61.
14. Thakur CP, *et al.* Comparison of three treatment regimens with liposomal amphotericin B (AmBisome) for visceral leishmaniasis in India: a randomized dose-finding study. *Trans R Soc Trop Med Hyg* 1996; **90:** 319–22.
15. Sundar S, *et al.* Treatment of Indian visceral leishmaniasis with single or daily infusions of low dose liposomal amphotericin B: randomised trial. *BMJ* 2001; **323:** 419–22.
16. Sundar S, *et al.* Single-dose liposomal amphotericin B in the treatment of visceral leishmaniasis in India: a multicenter study. *Clin Infect Dis* 2003; **37:** 800–4.
17. Sundar S, *et al.* Low-dose liposomal amphotericin B in refractory Indian visceral leishmaniasis: a multicenter study. *Am J Trop Med Hyg* 2002; **66:** 143–6.
18. Sundar S, *et al.* Single-dose liposomal amphotericin B for visceral leishmaniasis in India. *N Engl J Med* 2010; **362:** 504–12.
19. Sundar S, *et al.* Short-course, low-dose amphotericin B lipid complex therapy for visceral leishmaniasis unresponsive to antimony. *Ann Intern Med* 1997; **127:** 133–7.
20. Sundar S, *et al.* Treatment of antimony-unresponsive Indian visceral leishmaniasis with ultra-short courses of amphotericin-B-lipid complex. *Ann Trop Med Parasitol* 1998; **92:** 755–64.
21. Dietze R, *et al.* Treatment of kala-azar in Brazil with Amphocil (amphotericin B cholesterol dispersion) for 5 days. *Trans R Soc Trop Med Hyg* 1995; **89:** 309–11.
22. Berman JD, *et al.* Efficacy and safety of liposomal amphotericin B (AmBisome) for visceral leishmaniasis in endemic developing countries. *Bull WHO* 1998; **76:** 25–32.
23. Sampaio RNR, Marsden PD. Mucosal leishmaniasis unresponsive to glucantime therapy successfully treated with AmBisome. *Trans R Soc Trop Med Hyg* 1997; **91:** 77.
24. Amato VS, *et al.* Mucocutaneous leishmaniasis associated with HIV infection treated successfully with liposomal amphotericin B (AmBisome). *J Antimicrob Chemother* 2000; **46:** 341–2.

Primary amoebic meningoencephalitis. Amphotericin B is active *in vitro* against *Naegleria fowleri* and has been recommended for the treatment of primary amoebic meningoencephalitis (p. 920.2) caused by this amoeba. There have been some case reports[1-8] of survival after the use of intravenous and intrathecal amphotericin B. In all cases amphotericin B was combined with other antimicrobials, notably oral rifampicin.

1. Anderson K, Jamieson A. Primary amoebic meningoencephalitis. *Lancet* 1972; **i:** 902–3.
2. Seidel JS, *et al.* Successful treatment of primary amebic meningoencephalitis. *N Engl J Med* 1982; **306:** 346–8.
3. Brown RL. Successful treatment of primary amebic meningoencephalitis. *Arch Intern Med* 1991; **151:** 1201–2.
4. Poungvarin N, Jariya P. The fifth nonlethal case of primary amoebic meningoencephalitis. *J Med Assoc Thai* 1991; **74:** 112–15.
5. Loschiavo F, *et al.* Acute primary meningoencephalitis from entamoeba Naegleria fowleri: report of a clinical case with a favourable outcome. *Acta Neurol (Napoli)* 1993; **15:** 333–40.
6. Wang A, *et al.* Successful treatment of amoebic meningoencephalitis in a Chinese living in Hong Kong. *Clin Neurol Neurosurg* 1993; **95:** 249–52.
7. Jain R, *et al.* Naegleria meningitis: a rare survival. *Neurol India* 2002; **50:** 470–2.
8. Vargas-Zepeda J, *et al.* Successful treatment of Naegleria fowleri meningoencephalitis by using intravenous amphotericin B, fluconazole and rifampicin. *Arch Med Res* 2005; **36:** 83–6.

Adverse Effects

Amphotericin B for intravenous use was originally only available in a conventional colloidal form; lipid formulations have been developed to reduce toxicity. The following adverse effects apply to the **conventional** form. Common adverse effects which occur during or after intravenous infusion of amphotericin B include headache, nausea, vomiting, chills, fever, malaise, muscle and joint pains, anorexia, diarrhoea, and gastrointestinal cramp. Hypertension, hypotension, cardiac arrhythmias including ventricular fibrillation and cardiac arrest, skin rashes, flushing, anaphylactoid reactions including bronchospasm and dyspnoea, blurred vision, tinnitus, hearing loss, vertigo, gastrointestinal bleeding, liver disorders, peripheral neuropathy, and convulsions have been reported occasionally.

Some degree of nephrotoxicity occurs in almost all patients given amphotericin B intravenously. Both tubular and glomerular damage occur; there may be improvement on cessation of therapy, but there is a risk of permanent renal impairment, particularly in patients given large cumulative doses (over 5 g). Renal tubular acidosis without systemic acidosis may develop. Use of amphotericin B is associated with increased urinary excretion of potassium and magnesium resulting in hypokalaemia and hypomagnesaemia respectively. Uric acid excretion is increased and nephrocalcinosis can occur. Limited data indicate that renal toxicity may be associated with sodium depletion; for strategies to improve sodium load see Nephrotoxicity, under Treatment of Adverse Effects, p. 572.1.

A reversible, normocytic, normochromic anaemia develops in most patients given amphotericin B, possibly due to a direct suppressive effect on erythropoietin production. There are rare reports of thrombocytopenia, leucopenia, agranulocytosis, eosinophilia, and coagulation defects.

Leukoencephalopathy has been reported rarely in patients also receiving total body irradiation.

Amphotericin B solutions irritate the venous endothelium and may cause pain and thrombophlebitis at the injection site. Extravasation may cause tissue damage.

After intrathecal injection amphotericin B may also cause irritation of the meninges, neuropathy with pain, impaired vision, and retention of urine.

In general, adverse effects of **lipid** formulations have been similar to those of conventional amphotericin B, but are less frequent and less severe. Brief reversible episodes of renal impairment have occurred but these formulations have been considered to be safe enough to use in patients with renal impairment who could not be given conventional amphotericin B. Anaphylaxis has been reported rarely.

Amphotericin applied **topically** may produce local irritation, pruritus, and skin rash.

Effects on the cardiovascular system. Ventricular arrhythmias in 2 patients, resulting in fatal sudden cardiac arrest in 1, were associated with both conventional and liposomal formulations of amphotericin B at conventional doses and infusion rates,[1] but cardiotoxicity is more common with high doses or rapid infusion rates (see Infusion Rate, under Administration, p. 570.2). Cardiac arrests in 5 infants and children, fatal in 4 cases, were associated[2] with overdoses of conventional amphotericin B of between 3.8 and 40.8 mg/kg. Fatal cardiotoxicity has also been reported in an adult who inadvertently received an overdose (5 mg/kg) of conventional amphotericin B on 2 consecutive days.[3] A case of reversible dilated cardiomyopathy and congestive heart failure has been reported in a 20-year-old male patient after about 2 months of treatment, initially with conventional amphotericin B for 30 days and then with amphotericin B phospholipid complex. Symptoms resolved within 6 weeks of stopping treatment.[4] An increased risk of arrhythmia and cardiac arrest has been reported in patients with evidence of antimony-induced myocardial damage who were switched to amphotericin B treatment for visceral leishmaniasis.[5] A rest period of at least 10 days was advised before beginning amphotericin B in such patients.

Severe hypertension was associated with infusion of phospholipid-amphotericin B complex in 1 patient.[6]

1. Aguado JM, *et al.* Ventricular arrhythmias with conventional and liposomal amphotericin. *Lancet* 1993; **342:** 1239.
2. Cleary JD, *et al.* Amphotericin B overdose in pediatric patients with associated cardiac arrest. *Ann Pharmacother* 1993; **27:** 715–19.
3. Burke D, *et al.* Acute amphotericin B overdose. *Ann Pharmacother* 2006; **40:** 2254–9.
4. Danaher PJ, *et al.* Reversible dilated cardiomyopathy related to amphotericin B therapy. *J Antimicrob Chemother* 2004; **53:** 115–17.
5. Thakur CP. Sodium antimony gluconate, amphotericin, and myocardial damage. *Lancet* 1998; **351:** 1928–9.
6. Rowles DM, Fraser SL. Amphotericin B lipid complex (ABLC)-associated hypertension: case report and review. *Clin Infect Dis* 1999; **29:** 1564–5.

Effects on the eyes. Rapid loss of vision resulting in permanent bilateral blindness occurred in a patient with lupus erythematosus and cryptococcal meningitis after a 1-mg test dose of amphotericin B.[1] Amphotericin B was considered to be the cause as visual disturbances associated with cryptococcal meningitis are usually progressive in nature and acute blindness with normal funduscopic appearance had not previously been reported.

1. Li PKT, Lai KN. Amphotericin B induced ocular toxicity in cryptococcal meningitis. *Br J Ophthalmol* 1989; **73:** 397–8.

Effects on the liver. Amphotericin B has only rarely been associated with adverse effects on the liver. Fatal hepatic failure was reported in a patient after a total dose of 4.82 g given intermittently over 1 year.[1] The patient had been given a potentially incompatible intravenous admixture of amphotericin B and diphenhydramine.

There have been a few reports of abnormal liver-function tests during amphotericin B therapy;[2,3] in such cases amphotericin B should be stopped. Hyperbilirubinaemia associated with amphotericin B has also been reported.[4] An episode of reversible hepatic and renal toxicity has been reported in a child with cystic fibrosis after a cumulative dose of 84 mg of conventional amphotericin B and 168 mg of liposomal amphotericin B.[5]

1. Carnecchia BM, Kurtzke JF. Fatal toxic reaction to amphotericin B in cryptococcal meningo-encephalitis. *Ann Intern Med* 1960; **53:** 1027–36.
2. Miller MA. Reversible hepatotoxicity related to amphotericin B. *Can Med Assoc J* 1984; **131:** 1245–7.
3. Abajo FJ, Carcas AJ. Amphotericin B hepatotoxicity. *BMJ* 1986; **293:** 1243.
4. Olin JL, Spooner LM. Amphotericin B-associated hyperbilirubinemia: case report and review of the literature. *Pharmacotherapy* 2006; **26:** 1011–7.
5. Mohan UR, Bush A. Amphotericin B-induced hepatorenal failure in cystic fibrosis. *Pediatr Pulmonol* 2002; **33:** 497–500.

Effects on the lungs. Reports implicating use of leucocytes[1] or other blood products[2] in the development of pulmonary reactions in patients receiving amphotericin B have been refuted,[3,4] and a report has indicated that amphotericin B can produce pulmonary toxicity in the absence of blood products.[5] An increased incidence of pulmonary symptoms was noted in patients given amphotericin B in lipid emulsion,[6] including acute respiratory distress after starting the infusion. Chest discomfort, including tightness, pain, dyspnoea, and acute hypoxia, has been reported in 3 patients during one-hour infusions of liposomal amphotericin B. The reactions occurred within 5 to 10 minutes of starting the infusion and resolved on stopping the infusion. A slower rate of infusion was subsequently tolerated in 2 patients.[7]

1. Wright DG, *et al.* Lethal pulmonary reactions associated with the combined use of amphotericin B and leukocyte transfusions. *N Engl J Med* 1981; **304:** 1185–9.
2. Haber RH, *et al.* Acute pulmonary decompensation due to amphotericin B in the absence of granulocyte transfusions. *N Engl J Med* 1986; **315:** 836.
3. Forman SJ, *et al.* Pulmonary reactions associated with amphotericin B and leukocyte transfusions. *N Engl J Med* 1981; **305:** 584–5.
4. Bow EJ, *et al.* Pulmonary complications in patients receiving granulocyte transfusions and amphotericin B. *Can Med Assoc J* 1984; **130:** 593–7.
5. Roncoroni AJ, *et al.* Bronchiolis obliterans possibly associated with amphotericin B. *J Infect Dis* 1990; **161:** 589.
6. Schöffski P, *et al.* Safety and toxicity of amphotericin B in glucose 5% or intralipid 20% in neutropenic patients with pneumonia or fever of unknown origin: randomised study. *BMJ* 1998; **317:** 379–84.
7. Johnson MD, *et al.* Chest discomfort associated with liposomal amphotericin B: report of three cases and review of the literature. *Pharmacotherapy* 1998; **18:** 1053–61.

Effects on potassium homoeostasis. In addition to the hypokalaemia known to be associated with amphotericin B and due to increased urinary excretion of potassium, hyperkalaemia has been reported in a patient with severe renal impairment who received a rapid infusion of amphotericin B (see Infusion Rate, under Administration, p. 570.2). Hyperkalaemia also occurred in a 2-year-old child with chronic renal failure after a two-hour infusion of conventional amphotericin B. Hyperkalaemia and fatal cardiac arrest were also reported in a 4-year-old child after 3 infusions of amphotericin B lipid complex.[1]

1. Barcia JP. Hyperkalemia associated with rapid infusion of conventional and lipid complex formulations of amphotericin B. *Pharmacotherapy* 1998; **18:** 874–6.

Hypersensitivity. Anaphylactoid reactions have occurred with conventional amphotericin B, but have also been associated with liposomal amphotericin B,[1-3] including reports of patients who subsequently tolerated conventional formulations.[1,3]

1. Laing RBS, *et al.* Anaphylactic reactions to liposomal amphotericin. *Lancet* 1994; **344:** 682.
2. Torre I, *et al.* Anaphylactic reaction to liposomal amphotericin B in children. *Ann Pharmacother* 1996; **30:** 1036–7.
3. Valdya SJ, *et al.* Anaphylactic reaction to liposomal amphotericin B. *Ann Pharmacother* 2002; **36:** 1480–1.

Red man syndrome. Red man syndrome (see Vancomycin, p. 386.1) occurred in a patient on 2 occasions after a 1-mg test dose of amphotericin B.[1]

1. Ellis ME, Tharpe W. Red man syndrome associated with amphotericin B. *BMJ* 1990; **300:** 1468.

Treatment of Adverse Effects

To reduce febrile reactions antipyretics and antihistamines may be given before the intravenous infusion of conventional amphotericin B. Hydrocortisone given intravenously before or during amphotericin B infusion may also reduce febrile reactions. However, corticosteroids should not be given indiscriminately to patients given amphotericin B (see Interactions, p. 572.2) and dosage should be kept to a minimum. In the UK the advice is to give antipyretics or hydrocortisone prophylactically, but only to patients who have previously had acute adverse reactions and in whom continued treatment with intravenous amphotericin B is essential (see Prophylaxis, p. 572.1). Pethidine has been given intravenously to treat amphotericin B-induced shaking chills. Antiemetics may also be required. Amphotericin B is not removed by haemodialysis. Hypokalaemia and hypomagnesaemia should be corrected, and adequate hydration and sodium supplements may

reduce the severity of renal impairment. Lipid formulations of amphotericin B can be substituted for conventional amphotericin B if the latter cannot be tolerated.

Heparin has been added to conventional amphotericin B infusions to reduce the incidence of thrombophlebitis.

Reference to the management of adverse effects with *lipid* formulations.

1. Craddock C, *et al.* Best practice guidelines for the management of adverse events associated with amphotericin B lipid complex. *Expert Opin Drug Safety* 2010; 9: 139–47.

Anaemia. Amphotericin B appears to produce a normochromic, normocytic anaemia by suppression of erythropoietin production.[1,2] Stopping amphotericin B reverses the suppression but if the anaemia is severe, or treatment with amphotericin B cannot be stopped, blood transfusions may be required. Recombinant erythropoietin may prove an alternative to blood transfusions in patients who need to continue treatment with amphotericin B.

1. MacGregor RR, *et al.* Erythropoietin concentrations in amphotericin B-induced anemia. *Antimicrob Agents Chemother* 1978; 14: 270–3.
2. Lin AC, *et al.* Amphotericin B blunts erythropoietin response to anemia. *J Infect Dis* 1990; 161: 348–51.

Electrolyte disturbances. It has been suggested[1] that amiloride could ameliorate the hypokalaemia and hypomagnesaemia associated with amphotericin B. However, since amiloride may produce sodium depletion and its own associated renal toxicity this strategy is potentially hazardous. Another report[2] has suggested that spironolactone may be a safe and effective method of preventing hypokalaemia.

1. Wazny LD, Brophy DF. Amiloride for the prevention of amphotericin B-induced hypokalemia and hypomagnesemia. *Ann Pharmacother* 2000; 34: 94–7.
2. Ural AU. Comment: spironolactone prevents amphotericin B-induced hypokalemia in neutropenic patients. *Ann Pharmacother* 2000; 34: 1488.

Nephrotoxicity. A review of strategies for limiting the toxicity of amphotericin B concluded that sodium balance should be monitored and sodium replacement implemented if necessary and that, where possible, salt restriction and drugs that potentiate sodium loss or nephrotoxicity should be avoided.[1] Correction of sodium depletion may reverse amphotericin B-induced nephrotoxicity.[2] However, assessment of sodium status and correction of deficiency should precede use of amphotericin B.[3,4] While supplementation with 150 mmol sodium has been recommended for suitable patients,[4] routine prophylactic use of sodium is not advised.[5] However, a randomised study in a small number of patients has suggested that prophylactic sodium supplementation could be beneficial, but that it enhances potassium loss.[6] Diuretics in general should be avoided[7] although there have been suggestions that potassium-sparing diuretics such as amiloride or spironolactone may be useful in preventing hypokalaemia (see Electrolyte Disturbances, above). Use of mannitol as a protective agent is controversial and is not recommended.[3,4,8] Amphotericin B is often given on alternate days although this has never been proven to reduce nephrotoxicity.[3,4]

More recently, lipid formulations have been reported to overcome most problems of chronic nephrotoxicity, even in patients with renal impairment after previous treatment with conventional amphotericin B (see Lipid Formulations, under Administration, p. 570.1).

1. Khoo SH, *et al.* Administering amphotericin B—a practical approach. *J Antimicrob Chemother* 1994; 33: 203–13.
2. Heidemann HT, *et al.* Amphotericin B nephrotoxicity in humans decreased by salt repletion. *Am J Med* 1983; 75: 476–81.
3. Warda J, Barriere SL. Amphotericin B nephrotoxicity. *Drug Intell Clin Pharm* 1985; 19: 25–6.
4. Sabra R, Branch RA. Amphotericin B nephrotoxicity. *Drug Safety* 1990; 5: 94–108.
5. Gardner ML, *et al.* Sodium loading treatment for amphotericin B-induced nephrotoxicity. *DICP Ann Pharmacother* 1990; 24: 940–6.
6. Llanos A, *et al.* Effect of salt supplementation on amphotericin B nephrotoxicity. *Kidney Int* 1991; 40: 302–8.
7. Fisher MA, *et al.* Risk factors for amphotericin B-associated nephrotoxicity. *Am J Med* 1989; 87: 547–52.
8. Bullock WE, *et al.* Can mannitol reduce amphotericin B nephrotoxicity? Double-blind study and description of a new vascular lesion in kidneys. *Antimicrob Agents Chemother* 1976; 10: 555–63.

Prophylaxis. The value of prophylaxis against generalised reactions to amphotericin B infusion was questioned after a retrospective study in 397 patients.[1] The most commonly used drugs were diphenhydramine, corticosteroids, paracetamol, and heparin. It was concluded that patients who had had an adverse reaction after amphotericin B should be given appropriate premedication before subsequent amphotericin B infusions, but that routine premedication was not justified.

1. Goodwin SD, *et al.* Pretreatment regimens for adverse events related to infusion of amphotericin B. *Clin Infect Dis* 1995; 20: 755–61.

Precautions

Although anaphylaxis is rare after intravenous amphotericin B, it is advisable to give a test dose and then to observe the patient carefully for about 30 minutes before starting treatment. Patients with acute toxic reactions in whom treatment is essential may be given prophylactic treatment, as mentioned in Treatment of Adverse Effects, p. 571.3, to ameliorate the reactions. To reduce the risk of vein irritation and infusion-related adverse effects, the rate of intravenous infusion of conventional amphotericin B should be slow (see Infusion Rate, under Administration, p. 570.2). Patients given any parenteral form of amphotericin B should be monitored for changes in renal function, liver function, serum electrolytes, and haematological status. If the BUN or creatinine concentrations increase to clinically significant levels amphotericin B therapy should be interrupted or the dose reduced until renal function improves. Alternatively, a lipid amphotericin B preparation may be substituted. Treatment should be stopped if liver function tests are abnormal. Acute pulmonary reactions have been noted in patients given amphotericin B during or shortly after leucocyte transfusions. Although the association is contested (see Effects on the Lungs, p. 571.3), manufacturers of some amphotericin B products consider it advisable to separate the two and to monitor pulmonary function in these patients.

Care should be taken not to confuse the dosage regimens for individual preparations, and in particular those of conventional and lipid formulations; fatal overdoses have occurred after confusion between the various injectable formulations.

Interference with laboratory tests. Liposomal amphotericin B has been reported to interfere with a specific serum-phosphorus concentration assay;[1,2] when using the Synchron-LX-20 assay (*Beckman Coulter*), falsely elevated readings (as high as 2.5 mg/dL above the normal value) might be expected after around 7 days of therapy with liposomal amphotericin B, until around 5 or 6 days after treatment is stopped.[2]

1. Lane JW, *et al.* Pseudohyperphosphatemia associated with high-dose liposomal amphotericin B therapy. *Clin Chim Acta* 2008; 387: 145–9.
2. Mendoza D, *et al.* Liposomal amphotericin B as a cause of pseudohyperphosphatemia. *Clin Infect Dis* 2008; 46: 645–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies amphotericin B (for systemic use) as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed. Stomatological preparations are classified as not porphyrinogenic; they may be used as drugs of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Pregnancy. There are case reports of conventional amphotericin B having been used successfully to treat fungal infections in pregnant women without any adverse effects on the infant.[1-3] A review[4] of the use of antifungal drugs in pregnancy concluded that parenteral amphotericin B was the drug of first choice in the treatment of serious fungal infections in pregnancy. The safety of the lipid amphotericin formulations in pregnancy is not yet clear, although there are reports of pregnant women with visceral leishmaniasis who were treated in the first or second trimester with a short course of liposomal amphotericin B without adverse effects on the infant.[5,6]

1. Ismail MA, Lerner SA. Disseminated blastomycosis in a pregnant woman. *Am Rev Respir Dis* 1982; 126: 350–3.
2. Peterson CM, *et al.* Coccidioidal meningitis and pregnancy: a case report. *Obstet Gynecol* 1989; 73: 835–6.
3. Dean JL, *et al.* Use of amphotericin B during pregnancy: case report and review. *Clin Infect Dis* 1994; 18: 364–8.
4. Sobel JD. Use of antifungal drugs in pregnancy: a focus on safety. *Drug Safety* 2000; 23: 77–85.
5. Pagliano P, *et al.* Visceral leishmaniasis in pregnancy: a case series and a systematic review of the literature. *J Antimicrob Chemother* 2005; 55: 229–33.
6. Mueller M, *et al.* A comparison of liposomal amphotericin B with sodium stibogluconate for the treatment of visceral leishmaniasis in pregnancy in Sudan. *J Antimicrob Chemother* 2006; 58: 811–5.

Interactions

Most interactions involving amphotericin B have been seen during treatment with conventional formulations. Since lipid formulations appear to be less toxic, it may be anticipated that they will produce fewer serious interactions.

Use of nephrotoxic antibacterials, ciclosporin or other nephrotoxic immunosuppressants, or parenteral pentamidine may lead to an increased risk of nephrotoxicity. If possible, amphotericin B should not be given to patients receiving antineoplastics. Diuretics should generally be avoided in patients taking amphotericin B. If a diuretic has to be given then volume and electrolyte depletion should be monitored carefully. The potassium-depleting effect of amphotericin B may enhance the effects of neuromuscular blocking drugs and may increase the toxicity of digitalis glycosides; corticosteroids may enhance the depletion of potassium and their immunosuppressive effects may be detrimental in patients with severe fungal infections.

Amphotericin B may increase the toxicity of flucytosine, but the combination is nonetheless used in severe infections for its synergistic activity. For information on synergistic and antagonistic effects with other antimicrobials, see under Antimicrobial Action, below. Renal excretion of zalcitabine may be reduced by amphotericin B.

For an increased risk of cardiac arrhythmias and arrest when amphotericin B was given to patients with myocardial damage induced by an antimony compound, see Effects on the Cardiovascular System, under Adverse Effects, p. 571.1.

Antimicrobial Action

Amphotericin B is a polyene antifungal antibiotic that appears to act mainly by interfering with the permeability of the cell membrane of sensitive fungi by binding to sterols, chiefly ergosterol. It is reported to be fungistatic at concentrations achieved clinically. It is active against *Absidia* spp., *Aspergillus* spp., *Basidiobolus* spp., *Blastomyces dermatitidis*, *Candida* spp., *Coccidioides immitis*, *Conidiobolus* spp., *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Mucor* spp., *Paracoccidioides brasiliensis*, *Rhizopus* spp., *Rhodotorula* spp., and *Sporothrix schenckii*. Other organisms that have been reported to be sensitive to amphotericin B include the algal *Prototheca* spp. and the protozoa *Leishmania* and *Naegleria* spp. It is inactive against bacteria (including rickettsia) and viruses.

Some resistant strains of *Candida* have been isolated from immunocompromised patients given prolonged treatment with amphotericin B.

Microbiological interactions. *Azoles.* Although there have been occasional reports of synergy between amphotericin B and the azole antifungals, greater emphasis has been placed on possible antagonism. Studies *in vitro* have supported theoretical concerns that the action of amphotericin B (which depends on binding to ergosterol in the fungal cell membrane) would be antagonised by azoles (which inhibit ergosterol synthesis).[1,2] *Animal* studies appear to have confirmed antagonism between amphotericin B and the imidazole ketoconazole, but not between amphotericin B and the triazoles fluconazole or itraconazole. Available clinical evidence seems to indicate that azoles given with, or as continuation therapy after, induction therapy with amphotericin B, are effective in severe infections, although reduced plasma concentrations of itraconazole have been reported in some patients while being given amphotericin B.[3] However, strains of *Candida albicans* resistant to both amphotericin B and fluconazole have emerged in patients who have received repeated or prolonged courses of fluconazole.[4,5]

1. Martin E, *et al.* Antagonistic effects of fluconazole and 5-fluorocytosine on candidacidal action of amphotericin B in human serum. *Antimicr b Agents Chemother* 1994; 38: 1331–8.
2. Sud IJ, Feingold DS. Effect of ketoconazole on the fungicidal action of amphotericin B in Candida albicans. *Antimicrob Agents Chemother* 198 ; 23: 185–7.
3. Pennick GJ, *et al.* Concomitant therapy with amphotericin B and itraconazole: does this combination affect the serum concentration of itraconazole? *Intersci Conf Antimicrob Agents Chemother* 1994; 34: 9 (A34).
4. Kelly SL, *et al.* Resistance to fluconazole and amphotericin in Candida albicans from AIDS patients. *Lancet* 1996; 348: 1523–4.
5. Nolte FS, *et al.* Isolation and characterization of fluconazole- and amphotericin B-resistant Candida albicans from blood of two patients with leukemia. *Antimicrob Agents Chemother* 1997; 41: 196–9.

Pharmacokinetics

There is little or no absorption of amphotericin B from the gastrointestinal tract. When given intravenously in the *conventional colloidal form* and in the usual increasing dosage regimens, peak plasma concentrations of 0.5 to 4 micrograms/mL have been reported; the average plasma concentration with maintenance doses of 400 to 600 micrograms/kg daily tends to be 500 nanograms/mL. Amphotericin B is highly bound to plasma proteins and is widely distributed, but passes into the CSF only in small quantities. The plasma half-life is about 24 hours; with long-term use the terminal half-life increases to 15 days.

Unchanged amphotericin B is excreted in small amounts slowly in the urine. Traces are present in the serum and urine several weeks after completion of treatment. Amphotericin B is not removed by haemodialysis.

The pharmacokinetics of the lipid formulations differ considerably from the conventional formulation and from each other:

- at clinical doses of 1 to 7.5 mg/kg, *liposomal amphotericin B* produces peak plasma concentrations of around 8 to 80 micrograms/mL, around 20 times those with conventional formulations
- after doses of 0.5 to 8 mg/kg, *amphotericin B-sodium cholesteryl sulfate complex* produces peak plasma concentrations of about 0.7 to 6.2 micrograms/mL
- at a dose of 5 mg/kg daily, *amphotericin B phospholipid complex* produces peak plasma concentrations of about 1.7 micrograms/mL

Studies in *animals* have shown that concentrations in the kidney are several times lower after lipid formulations than with conventional ones.

Children and neonates. There was an inverse relationship between age and total clearance in 12 children aged 4 months to 14 years after the intravenous infusion of *conventional amphotericin B* 0.25 to 1.5 mg/kg daily, suggesting that children older than 9 years may require lower doses.[1] Peak serum concentrations ranged from 0.78 to about 10 micrograms/mL and did not correlate with dose. The elimination half-life was 18.1 ± 6.65 hours. A study in a group of 13 neonates with systemic fungal infections[2] considered that an initial dose of 500 micrograms/kg over 4 to 6 hours was well tolerated and could produce therapeutic serum concentrations more quickly than a regimen which consisted of 100 micrograms/kg on day one increased over 4 to 6 days to 500 micrograms/kg daily. After 5 days of treatment peak serum-amphotericin B concentrations ranged from 0.5 to 4.0 micrograms/mL and this was considered to be the range that could be achieved with the daily maintenance dose of 500 micrograms/kg. The elimination half-life was 14.8 hours. Drug elimination between doses was not detected in 4 of the infants; one was in oliguric renal failure and the other 3 had developed increases in serum-creatinine concentrations. Drug concentrations in CSF of 5 of the neonates were between 40 and 90% of simultaneous serum concentrations.

A comparative study[3] of plasma concentrations of *liposomal amphotericin B* in adults, children, and neonates after a dose of 1 mg/kg daily for 28 days, reported peak concentrations in children and neonates that were significantly lower than in adults. Increases in the mean peak plasma concentrations over days 1 to 28 were: adults, 1.02 to 1.66 micrograms/mL; children aged 1 to 12 years, 0.63 to 1.10 micrograms/mL; and neonates, 0.54 to 0.73 micrograms/mL. This was thought to be due to the greater volume of distribution in the neonates and greater clearance in older children.

The pharmacokinetics of *amphotericin B lipid complex* was studied in a cohort of 6 paediatric cancer patients with hepatosplenic candidiasis receiving a dose of 2.5 mg/kg daily for 6 weeks, to a total dosage of 105 mg/kg.[4] It was noted that the mean plasma concentrations over the dosing interval and area under the curve increased between the first and seventh doses but were similar between doses 7 and 42, suggesting that a steady state was achieved within 1 week of therapy. After the final dose of amphotericin B lipid complex, the mean plasma-amphotericin concentration was noted to be 0.50 micrograms/mL and the maximum concentration in whole blood was 1.69 micrograms/mL.

1. Benson JM, Nahata MC. Pharmacokinetics of amphotericin B in children. *Antimicrob Agents Chemother* 1989; 33: 1989–93.
2. Baley JE, *et al.* Pharmacokinetics, outcome of treatment, and toxic effects of amphotericin B and 5-fluorocytosine in neonates. *J Pediatr* 1990; 116: 791–7.
3. Kotwani RN, *et al.* A comparative study of plasma concentrations of liposomal amphotericin B (L-AMP-LRC-1) in adults, children and neonates. *Int J Pharm* 2002; 238: 11–15.
4. Walsh TJ, *et al.* Safety, tolerance, and pharmacokinetics of amphotericin B lipid complex in children with hepatosplenic candidiasis. *Antimicrob Agents Chemother* 1997; 41: 1944–8.

Distribution. Amphotericin B concentrations in various organs and tissues were determined in 13 cancer patients who had received conventional amphotericin B before death.[1] Concentrations were determined by high-pressure liquid chromatography (HPLC) and bioassay. Mean recovery by HPLC reported as a percentage of total dose given was liver 27.5%, spleen 5.2%, lungs 3.2%, kidney 1.5%, heart 0.4%, brain 0.3%, and pancreas 0.2%; each organ had a specific accumulation pattern. The mean total recovery was 38.8%. Reported median bile concentration was 7.3 micrograms/mL. The drug concentrations obtained by bioassay were much lower than those measured by HPLC. As the HPLC-determined concentrations of amphotericin B were higher than the MICs for the pathogens in patients with candidiasis or aspergillosis, the poor clinical outcome in these patients suggested that amphotericin B in the tissue lacked antifungal activity.

In another study,[2] amphotericin B was not detected in the CSF of 4 AIDS patients with cryptococcal meningitis on intravenous maintenance doses of 350 to 1890 micrograms/kg of the conventional formulation given 1 to 7 times weekly. The clinical success of amphotericin B for this indication could not be explained by measurable CSF drug concentrations.

Concentrations of amphotericin B have been measured in fetal-cord serum in an infant and were 37.5% of maternal serum concentration.[3]

1. Collette N, *et al.* Tissue concentrations and bioactivity of amphotericin B in cancer patients treated with amphotericin B-deoxycholate. *Antimicrob Agents Chemother* 1989; 33: 362–8.
2. Dupont BM, *et al.* Amphotericin B concentrations in cerebrospinal fluid of patients with AIDS and cryptococcal meningitis. *Clin Pharm* 1989; 8: 220–1.
3. Ismail MA, Lerner SA. Disseminated blastomycosis in a pregnant woman. *Am Rev Respir Dis* 1982; 126: 350–3.

Half-life. The terminal half-life for amphotericin B was 15 days in 2 patients on completion of conventional amphotericin B infusion therapy for disseminated histoplasmosis.[1] In another study,[2] the half-life was 21.5 hours (based on the exponential phase of disappearance from the blood) in a 65-year-old patient on a maintenance dose of 500 micrograms/kg of conventional amphotericin B infused over 1 hour every other day. Serum concentrations appeared to plateau at about 600 nanograms/mL 36 to 48 hours after each dose. This suggested that alternate-day dosage might be effective.

1. Atkinson AJ, Bennett JE. Amphotericin B pharmacokinetics in humans. *Antimicrob Agents Chemother* 1978; 13: 271–6.
2. Hoeprich PD. Elimination half-life of amphotericin B. *J Infect* 1990; 20: 173–5.

Lipid formulations. References.

1. Janknegt R, *et al.* Liposomal and lipid formulations of amphotericin B: clinical pharmacokinetics. *Clin Pharmacokinet* 1992; 23: 279–91.
2. Adedoyin A, *et al.* Pharmacokinetic profile of ABELCET (amphotericin B lipid complex injection): combined experience from phase I and phase II studies. *Antimicrob Agents Chemother* 1997; 41: 2201–8.
3. Adedoyin A, *et al.* A pharmacokinetic study of amphotericin B lipid complex injection (Abelcet) in patients with definite or probable systemic fungal infections. *Antimicrob Agents Chemother* 2000; 44: 2900–2.
4. Bekersky I, *et al.* Pharmacokinetics, excretion, and mass balance of liposomal amphotericin B (AmBisome) and amphotericin B deoxycholate in humans. *Antimicrob Agents Chemother* 2002; 46: 828–33.
5. Gubbins PO, *et al.* Pharmacokinetics and buccal mucosal concentrations of a 15 milligram per kilogram of body weight total dose of liposomal amphotericin B administered as a single dose (15 mg/kg), weekly dose (7.5 mg/kg), or daily dose (1 mg/kg) in peripheral stem cell transplant patients. *Antimicrob Agents Chemother* 2009; 53: 3664–74.
6. Lestner JM, *et al.* Pharmacokinetics and pharmacodynamics of amphotericin B deoxycholate, liposomal amphotericin B, and amphotericin B lipid complex in an in vitro model of invasive pulmonary aspergillosis. *Antimicrob Agents Chemother* 2010; 54: 3432–41.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Abelcet; AmBisome; Amphotec; Anfogen†; ***Austral.***: Abelcet; AmBisome; Ampho-cil†; Fungilin; Fungizone†; ***Austria***: Abelcet; AmBisome; Ampho-Moronal; Amphocil; ***Belg.***: Abelcet; AmBisome; Fungizone†; ***Braz.***: Abelcet; AmBisome; Amphocil; Anforicin B; Fungi B; Fungizon; Funtex B; Unianf; ***Canad.***: Abelcet; AmBisome; Amphotec; Fungizone; ***Chile***: Fungizon; ***China***: Amphotec (安泽特克); Fengkesong (锋克松); ***Cz.***: Abelcet; Amphocil; ***Denm.***: Abelcet; AmBisome; Amphocil; Fungizone; ***Fin.***: Abelcet; AmBisome; Fungizone; ***Fr.***: Abelcet; AmBisome; Fungizone; ***Ger.***: Abelcet†; AmBisome; Ampho-Moronal; ***Gr.***: Abelcet; Aglutin; AmBisome; Amphiprol; Amphocil; Fungizone; ***Hong Kong***: AmBisome; Fungizone; ***Hung.***: Abelcet; AmBisome; Amphocil; Fungizone; ***India***: AmBisome; Amfocan; Amfotex; Ampholip; Amphotin-Lip; Amphotin; Amphotret; Fungisome; Fungizone; Mycol; ***Indon.***: Fungizone†; ***Irl.***: Abelcet; AmBisome; Amphocil†; Fungizone; ***Israel***: AmBisome; Amphocil†; Amphotec†; ***Ital.***: Abelcet; AmBisome; Amphocil; Fungilin; Fungizone; ***Jpn***: AmBisome; ***Malaysia***: Amphocil; Fungizone; ***Mex.***: Abelcet; Amfostat; Amphocil; Candipres; Terix; ***Neth.***: Abelcet; AmBisome; Amphocil; Fungizone; ***Norw.***: Abelcet; AmBisome; Fungizone†; ***NZ***: Abelcet; AmBisome; Fungilin; Fungizone†; ***Philipp.***: Ampholip; Amphotret; Fungizone†; ***Pol.***: Abelcet; AmBisome; Amphocil; ***Port.***: Abelcet; AmBisome; Amphocil; Fungizone†; ***Rus.***: AmBisome (АмБизом)†; Amphoglucamin (Амфоглюкамин)†; Fungizone (Фунгизон); ***S.Afr.***: AmBisome; Fungizone; ***Singapore***: Abelcet; AmBisome; Amphocil; Fungizone; ***Spain***: Abelcet; AmBisome; Amphocil; Fungizona†; ***Swed.***: Abelcet; AmBisome; Amphocil†; Fungizone; ***Switz.***: AmBisome; Ampho-Moronal; Fungizone; ***Thai.***: ADPHO†; AmBisome; Amphocil†; Ampholin; Amphotret; Fungizone†; ***Turk.***: Abelcet; AmBisome; Amphocil; Amphotec; Fungizone; ***UK***: Abelcet; AmBisome; Amphocil†; Fungilin†; Fungizone; ***USA***: Abelcet; AmBisome; Amphotec; ***Venez.***: Amphotec; Fungizone.

Multi-ingredient Preparations. ***Austria***: Mysteclin; ***Braz.***: Anfoterin; Gino-Teracin; Novasutin; Talsutin; Tericin AT; Tricocilin B; Vagiklin†; ***Ger.***: Mysteclin; ***Hong Kong***: Talsutin†; ***Indon.***: Talsutin†; ***Philipp.***: Vagimycin†; ***S.Afr.***: Vagmycin†.

Pharmacopoeial Preparations

BP 2014: Amphotericin for Infusion; Amphotericin Lozenges; Amphotericin Oral Suspension;
USP 36: Amphotericin B Cream; Amphotericin B for Injection; Amphotericin B Lotion; Amphotericin B Ointment.

Anidulafungin *(BAN, USAN, rINN)*

Anidulafungina; Anidulafungine; Anidulafunginum; LY-303366; V-Echinocandin; Анидулафунгин.

(4*R*,5*R*)-4,5-Dihydroxy-*N*^{2}-[[4″-(pentyloxy)-*p*-terphenyl-4-yl]carbonyl]-L-ornithyl-L-threonyl-*trans*-4-hydroxy-L-prolyl-(*S*)-4-hydroxy-4-(*p*-hydroxyphenyl)-L-threonyl-L-threonyl-(3*S*,4*S*)-3-hydroxy-4-methyl-L-proline cyclic (6→1)-peptide; 1-[(4*R*,5*R*)-4,5-Dihydroxy-*N*^{2}-[[4″-(pentyloxy)(1,1′:4′,1″-terphenyl)-4-yl]carbonyl]-L-ornithine]-echinocandin B.

$C_{58}H_{73}N_7O_{17}$=1140.3

CAS — 166663-25-8.

ATC — J02AX06.
ATC Vet — QJ02AX06.
UNII — 9HLM53094I.

Uses and Administration

Anidulafungin is an echinocandin antifungal active against *Aspergillus* and *Candida* spp. It is used in the treatment of candidaemia, oesophageal candidiasis, and other forms of invasive candidiasis.

Anidulafungin is given by intravenous infusion, the rate of which should not exceed 1.1 mg/minute. For candidaemia and other invasive candidiasis a loading dose of 200 mg is given on the first day followed by 100 mg daily thereafter. For oesophageal candidiasis the loading dose is 100 mg followed by 50 mg daily.

For details of doses in children, see below.

Reviews.

1. Murdoch D, Plosker GL. Anidulafungin. *Drugs* 2004; 64: 2249–58.
2. Vazquez JA, Sobel JD. Anidulafungin: a novel echinocandin. *Clin Infect Dis* 2006; 43: 215–22.
3. Menichetti F. Anidulafungin, a new echinocandin: effectiveness and tolerability. *Drugs* 2009; 69 (suppl 1): 95–7.

Administration in children. Although anidulafungin is not licensed for use in children, a small study[1] found that neonates and infants given an intravenous loading dose of 3 mg/kg followed by 1.5 mg/kg daily thereafter had overall drug exposures similar to older children receiving the same weight-adjusted dosage and adult patients receiving 100 mg daily; no serious drug-related adverse effects were reported in this study. The American Academy of Pediatrics[2] suggests that an intravenous loading dose of 1.5 to 3 mg/kg may be given on the first day followed by 0.75 to 1.5 mg/kg daily thereafter for susceptible *Candida* infections.

1. Cohen-Wolkowiez M, *et al.* Safety and pharmacokinetics of multiple-dose anidulafungin in infants and neonates. *Clin Pharmacol Ther* 2011; 89: 702–7.
2. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Adverse Effects and Precautions

As for Caspofungin, see p. 575.1.

Dose adjustments are not required in patients with hepatic or renal impairment.

Interactions

Few drug interactions are expected with anidulafungin, as it is not metabolised by the hepatic cytochrome P450 system and almost no renal clearance occurs.

Antimicrobial Action

As for Caspofungin, see p. 575.2.

References.

1. Morace G, *et al.* Anidulafungin, a new echinocandin: in vitro activity. *Drugs* 2009; 69 (suppl 1): 91–4.

Pharmacokinetics

Steady state plasma concentrations of anidulafungin occur after the first loading dose; systemic clearance is about 1 litre/hour and the terminal elimination half-life is 40 to 50 hours. Anidulafungin is 84% bound to plasma proteins and the volume of distribution is 30 to 50 litres. It is not metabolised, but undergoes slow chemical degradation to inactive peptide degradants. Less than 10% of the intact drug is eliminated in the faeces and less than 1% is excreted in the urine.

References.

1. Dowell JA, *et al.* Population pharmacokinetic analysis of anidulafungin, an echinocandin antifungal. *J Clin Pharmacol* 2004; 44: 590–8.
2. Benjamin DK, *et al.* Safety and pharmacokinetics of intravenous anidulafungin in children with neutropenia at high risk for invasive fungal infections. *Antimicrob Agents Chemother* 2006; 50: 632–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ecalta; ***Austral.***: Eraxis; ***Austria***: Ecalta; ***Belg.***: Ecalta; ***Braz.***: Ecalta; ***Canad.***: Eraxis; ***Chile***: Ecalta; ***Cz.***: Ecalta; ***Denm.***: Ecalta; ***Fr.***: Ecalta; ***Ger.***: Ecalta; ***Gr.***: Ecalta; ***Hong Kong***: Eraxis; ***Hung.***: Ecalta; ***Irl.***: Ecalta; ***Israel***: Eraxis; ***Ital.***: Ecalta; ***Malaysia***: Eraxis; ***Neth.***: Ecalta; ***Norw.***: Ecalta; ***Philipp.***: Eraxis; ***Pol.***: Ecalta; ***Port.***: Ecalta; ***Singapore***: Eraxis; ***Spain***: Ecalta; ***Swed.***: Ecalta; ***Switz.***: Ecalta; ***Thai.***: Eraxis; ***Turk.***: Eraxis; ***UK***: Ecalta; ***Ukr.***: Eraxis (Эракспс); ***USA***: Eraxis.

Bifonazole *(BAN, USAN, rINN)*

Bay-h-4502; Bifonatsoli; Bifonazol; Bifonazolas; Bifonazolum; Бифоназол.

1-(α-Biphenyl-4-ylbenzyl)imidazole.

The symbol † denotes a preparation no longer actively marketed

$C_{22}H_{18}N_2$=310.5.
CAS — 60628-96-8.
ATC — D01AC10.
ATC Vet — QD01AC10.
UNII — QYJ305Z91O.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn*.

Ph. Eur. 8: (Bifonazole). A white or almost white crystalline powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in dehydrated alcohol.

Profile

Bifonazole is an imidazole antifungal with a broad spectrum of activity; sensitive fungi include dermatophytes, *Malassezia furfur*, and *Candida* spp. It also has some antibacterial activity.

Bifonazole is mainly used by topical application in the treatment of fungal skin and nail infections (p. 568.1). It is applied once daily as a 1% cream, powder, solution, or gel. Treatment is usually continued for 2 to 4 weeks. More prolonged treatment is necessary for nail infections and bifonazole may be applied initially with a 40% urea paste to soften the nail.

Local reactions including burning and itching have been reported.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3.

References.

1. Lackner TE, Clissold SP. Bifonazole: a review of its antimicrobial activity and therapeutic use in superficial mycoses. *Drugs* 1989; **38**: 204–25.
2. Bonifaz A, Ibarra G. Onychomycosis in children: treatment with bifonazole-urea. *Pediatr Dermatol* 2000; **17**: 310–314.
3. Watanabe S, *et al.* A comparative clinical study between 2 weeks of luliconazole 1% cream treatment and 4 weeks of bifonazole 1% cream treatment for tinea pedis. *Mycoses* 2006; **49**: 236–41. Correction. *ibid.*: 441.
4. Linder N, *et al.* Association of high-dose bifonazole administration during early pregnancy and severe limb reduction defects in the newborn. *Birth Defects Res A Clin Mol Teratol* 2010; **88**: 201–4.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies bifonazole as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Bimicot; Micosol; Sinamida Atleta; Sinamida Plus; ***Austral.***: Canesten Once Daily; Mycospor; ***Austria***: Canesten Bifonazol; ***Belg.***: Canestene Derm Bifonazole; ***Braz.***: Mycospor; ***Chile***: Multifung; Mycosporan; ***China***: Bayclear Plus (金美克); Bi Fu (必伏); Fu Kang (孚康); Fu Ning (孚宁); Fu Qi (孚琪); FuKang (孚康); Hui Fu De (惠复得); Lie He Suo (列合素); Mycospor (美克); ***Cz.***: Canespor; Mycospor; ***Fr.***: Amycor; ***Ger.***: Antifungol Extra†; Bifomyk; Bifon; Canesten Extra; Mycospor; ***Gr.***: Aeroderma; Bifized; Bifon; Compaser; Fungiderm; Gloryskin; Helpovion; Kavaderm; Myco-flusemidon; Mycospor; Neltolon; Ofniforte; Poulmycin; Rye; ***Hong Kong***: Canesten Extra; Mycospor†; ***Hung.***: Canesten Plus; Mycospor†; ***India***: Mycospor; ***Indon.***: Mycospor; ***Israel***: Agispor; ***Ital.***: Azolmen; Bifazol†; Canesten Unidie; ***Mex.***: Mycospor; ***Neth.***: Mycospor; ***Pol.***: Mycospor; ***Port.***: Mycospor; Topical; ***Rus.***: Bifosin (Бифосин); Mycospor (Микоспор); ***S.Afr.***: Mycospor; ***Singapore***: Mycospor; ***Spain***: Bifokey; Canespie Bifonazol; Levelina; Mycospor; ***Swed.***: Mycosporan†; ***Turk.***: Mycospor; ***Ukr.***: Bifonal (Бифонал); Canespor (Канеспор); Mycospor (Микоспор); ***Venez.***: Mycospor.

Multi-ingredient Preparations. *Arg.*: Empecid Pie; Piecidex NF; ***Austria***: Canesten Bifonazol comp; ***Cz.***: Mycospor Sada na Nehty; ***Fr.***: Amycor Onychoset; ***Ger.***: Canesten Extra Nagelset; ***Hung.***: Canespro; ***Israel***: Agispor Onychoset; Comagis; Keratospor; ***Mex.***: Mycospor Onicoset; ***Pol.***: Mycospor Onychoset; ***Rus.***: Mycospor (Микоспор); ***S.Afr.***: Mycospor Onycho-set†; ***Spain***: Mycospor Onicoset; ***Turk.***: Mycospor; ***Ukr.***: Canespor Set (Канеспор Набор); Mycospor Kit (Микоспор Набор)†; ***Venez.***: Mycospor Onicoset.

Bromochlorosalicylanilide

Bromchlorsalicylanilidum; Bromisalisyylikloorianilidi; Bromoclorosalicilanilida; Bromsalicylkloranilid; Бромохлоросалицилианилин.
5-Bromo-4′-chlorosalicylanilide; 5-Bromo-*N*-(4-chlorophenyl)-2-hydroxybenzamide.
$C_{13}H_9BrClNO_2$=326.6
CAS — 3679-64-9.
ATC — D01AE01.
ATC Vet — QD01AE01.

Profile

Bromochlorosalicylanilide is a bromsalan antifungal that has been applied topically. Photosensitivity may occur. See also Bromsalans, p. 1741.2.

Butenafine Hydrochloride *(BANM, USAN, rINNM)*

Butenafiinihydrokloridi; Butenafina, hidrocloruro de; Buténafine, Chlorhydrate de; Butenafinhydroklorid; Butenafini Hydrochloridum; Hidrocloruro de butenafina; KP-363; Бутенафина Гидрохлорид.
N-(*p*-*tert*-Butylbenzyl)-*N*-methyl-1-naphthalenemethylamine hydrochloride; 4-*tert*-Butylbenzyl(methyl)(1-naphthalenemethyl)amine hydrochloride.
$C_{23}H_{27}N,HCl$=353.9
CAS — 101828-21-1 (butenafine); 101827-46-7 (butenafine hydrochloride).
ATC — D01AE23.
ATC Vet — QD01AE23.
UNII — R8XA2029ZI.

Profile

Butenafine is a benzylamine antifungal with actions similar to those of the allylamine antifungal terbinafine (p. 593.3). The hydrochloride is used topically as a 1% cream for the treatment of superficial dermatophyte infections (see Skin Infections, p. 568.1).

Reviews.

1. McNeely W, Spencer CM. Butenafine. *Drugs* 1998; **55**: 405–12.
2. Singal A. Butenafine and superficial mycoses: current status. *Expert Opin Drug Metab Toxicol* 2008; **4**: 999–1005.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Ingebut†; ***Braz.***: Tefin; ***Chile***: Dermacom; ***China***: Fu Da Jing (孚答静); Jia Rui (嘉瑞); Te Li Da (特利达); ***India***: Butop; Fintop; ***Israel***: Mentax; ***Jpn***: Mentax; ***Mex.***: Derfina; Lexoderil; ***Philipp.***: Funcid†; ***USA***: Lotrimin Ultra; Mentax.

Butoconazole Nitrate *(BANM, USAN, rINNM)*

Butoconazol, nitrato de; Butoconazole, Nitrate de; Butoconazoli Nitras; Nitrato de butoconazol; RS-35887-00-10-3; RS-35887; Бутоконазола Нитрат.
1-[4-(4-Chlorophenyl)-2-(2,6-dichlorophenylthio)butyl]imidazole mononitrate.
$C_{19}H_{17}Cl_3N_2S,HNO_3$=474.8
CAS — 64872-76-0 (butoconazole); 64872-77-1 (butoconazole nitrate).
ATC — G01AF15.
ATC Vet — QG01AF15.
UNII — 4805237NP5.

Pharmacopoeias. In *US*.

USP 36: (Butoconazole Nitrate). A white to off-white crystalline powder. Practically insoluble in water; slightly soluble in acetone, in acetonitrile, in dichloromethane, and in tetrahydrofuran; very slightly soluble in ethyl acetate; sparingly soluble in methyl alcohol. Protect from light.

Uses and Administration

Butoconazole is an imidazole antifungal used locally as the nitrate in the treatment of vulvovaginal candidiasis (p. 564.1). It is given intravaginally as a 100-mg pessary or as 5 g of a 2% cream for 3 consecutive nights; a single application of the cream has also been used.

Adverse Effects and Precautions

Local reactions including burning and irritation and pelvic or abdominal pain or cramping may occur when butoconazole is applied vaginally.

Intravaginal preparations of butoconazole may damage latex contraceptives and additional contraceptive measures are therefore necessary during local application.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3.

Effects on the blood. Severe reversible thrombocytopenia was associated with treatment with intravaginal butoconazole.[1] The patient had previously had a drop in white cell count after treatment with intravaginal clotrimazole, suggestive of an idiosyncratic reaction to imidazoles.

1. Maloley PA, *et al.* Severe reversible thrombocytopenia resulting from butoconazole cream. *DICP Ann Pharmacother* 1990; **24**: 143–4.

Antimicrobial Action

Butoconazole is an imidazole antifungal with antimicrobial activity similar to that of ketoconazole (p. 587.2) including activity against *Candida* spp.

Pharmacokinetics

About 5% of a dose of butoconazole is absorbed after vaginal use. The plasma half-life is 21 to 24 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Gynazole; ***Belg.***: Gynomyk; ***Braz.***: Gynazole; ***Canad.***: Gynazole; ***China***: Gynazole (妇娜宁); ***Fr.***: Gynomyk†; ***Hung.***: Gynazol; ***Indon.***: Gynofor; ***Malaysia***: Gynofort; ***Mex.***: Gynafem†; ***Neth.***: Gynomyk; ***Pol.***: Gynazol; ***Rus.***: Gynofort (Гинофорт); ***Singapore***: Gynofort; ***Switz.***: Gynazole†; ***Ukr.***: Gynofort (Гинофорт); ***USA***: Gynazole†; Mycelex-3†.

Pharmacopoeial Preparations
USP 36: Butoconazole Nitrate Vaginal Cream.

Caspofungin Acetate

(BANM, USAN, rINNM)

Acetato de caspofungina; Caspofungina, acetato de Caspofungine, Acétate de; Caspofungini Acetas; Kaspofungiiniasetaatti; Kaspofunginacetat; L-743873; MK-0991; Каспофунгина Ацетат.
(4*R*,5*S*)-5-[(2-Aminoethyl)amino]-*N*^{2}-(10,12-dimethyltetradecanoyl)-4-hydroxy-L-ornithyl-L-threonyl-*trans*-4-hydroxy-L-prolyl-(*S*)-4-hydroxy-4-(*p*-hydroxyphenyl)-L-threonyl-*threo*-3-hydroxy-L-ornithyl-*trans*-3-hydroxy-L-proline cyclic (6→1)-peptide diacetate.
$C_{52}H_{88}N_{10}O_{15}.2C_2H_4O_2$=1213.4
CAS — 179463-17-3.
ATC — J02AX04.
ATC Vet — QJ02AX04.
UNII — VUW370O5QE.

Uses and Administration

Caspofungin is an echinocandin antifungal used in the treatment of invasive aspergillosis (p. 563.1) in patients who are refractory to, or intolerant of, other therapy. It is also used in the treatment of invasive candidiasis (and in some countries for oesophageal candidiasis) and as empirica therapy for presumed fungal infections in febrile neutropenic patients.

Caspofungin is used as the acetate but doses are expressed in terms of the base; caspofungin acetate 77.7 mg is equivalent to about 70 mg of caspofungin. It is given by slow intravenous infusion over about 1 hour. A loading dose of 70 mg is given on the first day and is followed by 50 mg daily; a loading dose is not used in those being treated for oesophageal candidiasis. In adult patients weighing more than 80 kg, and in patients taking hepatic enzyme-inducing drugs who fail to respond, a daily dose of 70 mg is recommended. Doses may need to be reduced in patients with hepatic impairment (see p. 575.1).

Extemporaneously prepared 0.5% caspofungin acetate eye drops have been used to treat fungal eye infections (see p. 575.1).

Reviews.

1. Letscher-Bru V, Herbrecht R. Caspofungin: the first representative of a new antifungal class. *J Antimicrob Chemother* 2003; **51**: 513–21.
2. Deresinski SC, Stevens DA. Caspofungin. *Clin Infect Dis* 2003; **36**: 1445–57.
3. Morris MI, Villmann M. Echinocandins in the management of invasive fungal infections, part 1. *Am J Health-Syst Pharm* 2006; **63**: 1693–1703.
4. Morris MI, Villmann M. Echinocandins in the management of invasive fungal infections, part 2. *Am J Health-Syst Pharm* 2006; **63**: 1813–20.
5. Falagas ME, *et al.* Caspofungin for the treatment of fungal infections: a systematic review of randomized controlled trials. *Int J Antimicrob Agents* 2007; **29**: 136–43.
6. Hope WW, *et al.* The pharmacology and clinical use of caspofungin. *Expert Opin Drug Metab Toxicol* 2007; **3**: 263–74.
7. Waters L, Nelson M. The use of caspofungin in HIV-infected individuals. *Expert Opin Invest Drugs* 2007; **16**: 899–908.
8. Lichtenstern C, *et al.* Efficacy of caspofungin in invasive candidiasis and candidemia—de-escalation strategy. *Mycoses* 2008; **51** (suppl 1): 35–46.
9. Heinz WJ, Einsele H. Caspofungin for treatment of invasive aspergillus infections. *Mycoses* 2008; **51** (suppl 1): 47–57.
10. Mu XD, *et al.* Caspofungin in salvage treatment of severe pneumocystis pneumonia: case report and literature review. *Chin Med J (Engl)* 2009; **122**: 996–9.
11. Colombo AL, *et al.* Caspofungin use in patients with invasive candidiasis caused by common non-albicans Candida species: review of the caspofungin database. *Antimicrob Agents Chemother* 2010; **54**: 1864–71.
12. Holt SL, Drew RH. Echinocandins: addressing outstanding questions surrounding treatment of invasive fungal infections. *Am J Health-Syst Pharm* 2011; **68**: 1207–20.
13. Chen SC-A, *et al.* Echinocandin antifungal drugs in fungal infections: a comparison. *Drugs* 2011; **71**: 11–41.

Administration in children. Use of caspofungin appears to be effective and well tolerated in paediatric patients.[1-6] In

the UK, it is licensed for use in children from 12 months of age for the treatment of invasive aspergillosis in those who are refractory to, or intolerant of other therapy. It is also licensed for treatment of invasive candidiasis, and for empirical therapy of presumed fungal infection in those with febrile neutropenia. In the USA, caspofungin is licensed for use in similar indications in children as young as 3 months; it is also licensed for use in oesophageal candidiasis. (The *BNFC* also suggests that children 3 months to 1 year of age may receive caspofungin treatment.)

Doses are based on body-surface and given by intravenous infusion over about 1 hour. For all indications, a 70 mg/m² loading dose is given on the first day, followed by 50 mg/m² once daily thereafter; the maintenance dose may be increased to 70 mg/m² where the standard dose has been well tolerated, but led to inadequate clinical response. Single doses for infants and children should not exceed 70 mg.

Although unlicensed, the use of caspofungin in neonates has been studied. A case series[4] of 10 neonates (9 preterm) with invasive candidiasis not responsive to amphotericin B and/or fluconazole reported that *Candida* spp. were cleared from the blood in all patients in a mean of 4.3 days after starting caspofungin therapy. Nine neonates were given an initial dose of 1 mg/kg daily for the first 2 days followed by 2 mg/kg daily for 15 to 21 days; the other was given a lower dose. UK licensed product information and the *BNFC* both suggest that neonates and infants less than 3 months of age may be given a dose of 25 mg/m² once daily.

1. Lehrnbecher T, Groll AH. Experiences with the use of caspofungin in paediatric patients. *Mycoses* 2008; **51** (suppl 1): 58–64.
2. Franklin JA, *et al.* Retrospective study of the safety of caspofungin in immunocompromised pediatric patients. *Pediatr Infect Dis J* 2003; **22**: 747–9.
3. Groll AH, *et al.* Treatment with caspofungin in immunocompromised paediatric patients: a multicentre survey. *J Antimicrob Chemother* 2006; **57**: 527–35.
4. Odio CM, *et al.* Caspofungin therapy of neonates with invasive candidiasis. *Pediatr Infect Dis J* 2004; **23**: 1093–7.
5. Zaoutis TE, *et al.* A prospective, multicenter study of caspofungin for the treatment of documented Candida or Aspergillus infections in pediatric patients. *Pediatrics* 2009; **123**: 877–84.
6. Garnock-Jones KP, Keam SJ. Caspofungin: in pediatric patients with fungal infections. *Paediatr Drugs* 2009; **11**: 259–69.

Administration in hepatic impairment. Patients with mild hepatic impairment do not require dosage adjustment. In patients with moderate hepatic impairment (Child-Pugh score of 7 to 9), a daily dose of caspofungin 35 mg should be used after the initial dose of 70 mg; appropriate doses for patients with severe hepatic impairment have not been established.

Fungal eye infections. Fungal keratitis caused by *Candida albicans* was successfully treated with extemporaneously prepared 0.5% caspofungin acetate eye drops after the patient failed to respond to one-months' treatment with topical and oral voriconazole. The eye drops were initially applied hourly for one week followed by a progressive decrease in the dose over a further 3 weeks.[1] Caspofungin acetate 0.5% eye drops have also been used with intrastromal caspofungin acetate 0.5% plus topical, oral, and intrastromal voriconazole for the treatment of a patient with atypical *Alternaria* keratitis.[2]

Caspofungin acetate 0.5% eye drops are prepared aseptically by reconstituting a 50-mg vial of caspofungin acetate with 10.5 mL of normal saline[1] or water for injection.[2,3] A stability study[3] found that the solution was stable under refrigerated conditions (at about 4 degreesC) for 4 weeks and at room temperature (about 25 degreesC) for 3 days.

1. Hurtado-Sarrió M, *et al.* Successful topical application of caspofungin in the treatment of fungal keratitis refractory to voriconazole. *Arch Ophthalmol* 2010; **128**: 941–2.
2. Neoh CF, *et al.* Treatment of Alternaria keratitis with intrastromal and topical caspofungin in combination with intrastromal, topical, and oral voriconazole. *Ann Pharmacother* 2011; **45**: e24.
3. Neoh CF, *et al.* Stability of extemporaneously prepared 0.5-percent caspofungin eye drops: a potential cost-savings exercise. *Antimicrob Agents Chemother* 2012; **56**: 3435–7.

Adverse Effects and Precautions

Adverse effects reported with caspofungin have included diarrhoea, nausea and vomiting, flushing, headache, fever, tachycardia, and venous complications around the infusion site. Possible histamine-mediated symptoms have been rash, facial swelling, pruritus, sensation of warmth, or bronchospasm. Hypokalaemia and decreased red and white blood cell counts are common. Anaphylaxis has occurred.

Raised liver enzyme values are common and there have been isolated cases of hepatotoxicity; patients who develop abnormal liver function tests should be monitored for deterioration in hepatic function. Caspofungin may need to be given in reduced doses to patients with hepatic impairment (see above).

Breast feeding. Caspofungin is excreted in the breast milk of lactating *animals* but the risk to breast-fed infants is suggested to be low. Recommendations in licensed product information vary: in the UK it recommends against use in women who are breast feeding, while in the USA caution is advised.

Effects on the skin. Severe toxic epidermal necrolysis, which progressed and was eventually fatal despite systemic hydrocortisone and diphenhydramine, developed in an elderly man given a dose of caspofungin for disseminated candidal infection.[1] The patient had developed transient rash, responsive to corticosteroid and antihistamine treatment, after a previous dose.

1. Lee M-C, *et al.* Caspofungin-induced severe toxic epidermal necrolysis. *Ann Pharmacother* 2010; **44**: 1116–18.

Hypersensitivity. Cross-sensitivity to caspofungin has been reported[1] in a patient hypersensitive to micafungin.

1. Patel S, *et al.* Immediate cross-hypersensitivity between micafungin and caspofungin: a case report. *J Oncol Pharm Pract* 2009; **15**: 187–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies caspofungin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Pregnancy. Caspofungin has been shown to cross the placenta in *animal* studies and was shown to be embryotoxic in *rats* and *rabbits*; it was noted that there were no adequate and well-controlled studies in human pregnancy. Caspofungin is generally only recommended in pregnancy if the benefits to the mother are considered to outweigh the risks to the fetus.

Interactions

Although caspofungin is not appreciably metabolised by the hepatic cytochrome P450 system, drugs that induce hepatic enzymes may increase its clearance. Such effects have been noted with carbamazepine, dexamethasone, efavirenz, nevirapine, phenytoin, and rifampicin, and an increase in the dose of caspofungin should be considered in patients who are also taking these drugs and who are not clinically responding (see Uses and Administration, p. 574.3).

When caspofungin has been given with ciclosporin, an increase in the area under the concentration-time curve for caspofungin, as well as increases in hepatic enzymes, were seen and use of the two drugs together should be avoided unless the potential benefit outweighs the risk.

Caspofungin has resulted in decreased blood concentrations of tacrolimus and therapeutic drug monitoring and appropriate dosage adjustments to tacrolimus are recommended.

Antimicrobial Action

Caspofungin inhibits the synthesis of β-1,3-D-glucan, an essential component of the cell wall of many fungi. Caspofungin shows *in-vitro* activity against many *Aspergillus* spp. and is fungicidal against *Candida* spp. including non-albicans strains.

Pharmacokinetics

Plasma concentrations of caspofungin decline in a polyphasic manner after intravenous infusion. The initial short α-phase occurs immediately post-infusion and is followed by a β-phase with a half-life of 9 to 11 hours; an additional longer γ-phase also occurs with a half-life of 40 to 50 hours. Plasma clearance is dependent on distribution rather than on biotransformation or excretion. Caspofungin is highly bound to plasma protein. There is slow metabolism of caspofungin by hydrolysis and *N*-acetylation and excretion in faeces and urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cancidas; ***Austral.***: Cancidas; ***Austria***: Cancidas; ***Belg.***: Cancidas; ***Braz.***: Cancidas; ***Canad.***: Candidas; ***Chile***: Candidas; ***China***: Candidas (科赛斯); ***Cz.***: Candidas; ***Denm.***: Candidas; ***Fin.***: Candidas; ***Fr.***: Candidas; ***Ger.***: Candidas; ***Gr.***: Candidas; ***Hong Kong***: Candidas; ***Hung.***: Candidas; ***India***: Candidas; ***Irl.***: Candidas; ***Israel***: Candidas; ***Ital.***: Candidas; ***Jpn***: Candidas; ***Malaysia***: Candidas; ***Neth.***: Candidas; ***Norw.***: Candidas; ***NZ***: Candidas; ***Philipp.***: Candidas; ***Pol.***: Candidas; ***Port.***: Candidas; ***Rus.***: Candidas (Кансидас); ***S.Afr.***: Candidas; ***Singapore***: Candidas; ***Spain***: Candidas; ***Swed.***: Candidas; ***Switz.***: Candidas; ***Thai.***: Candidas; ***Turk.***: Candidas; ***UK***: Candidas; ***Ukr.***: Candidas (Кансидас); ***USA***: Candidas; ***Venez.***: Candidas.

Chlormidazole Hydrochloride *(BANM, rINNM)*

Chlormidazole, Chlorhydrate de; Chlormidazoli Hydrochloridum; Clomidazole Hydrochloride; Clormidazol, hidrocloruro de; *Hidrocloruro de clormidazol*; *Хлормидазола Гидрохлорид*.

1-(4-Chlorobenzyl)-2-methylbenzimidazole hydrochloride.

$C_{15}H_{13}ClN_2.HCl$=293.2

CAS — 3689-76-7 (chlormidazole); 54118-67-1 (chlormidazole hydrochloride).

ATC — D01AC04.

ATC Vet — QD01AC04.

UNII — 0RH29TB951.

Profile

Chlormidazole hydrochloride is an imidazole antifungal used topically as the hydrochloride in the treatment of fungal infections of the skin.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Pol.***: Unifungicid†.

Multi-ingredient Preparations. ***Pol.***: Polfungicid.

Chlorphenesin *(BAN, pINN)*

Chlorphénésine; Chlorphenesinum; Clorfenesina; Kloorifenesiini; Klorfenesin; *Хлорфенезин*.

3-(4-Chlorophenoxy)propane-1,2-diol.

$C_9H_{11}ClO_3$=202.6

CAS — 104-29-0.

ATC — D01AE07.

ATC Vet — QD01AE07.

UNII — I670DAL4SZ.

Profile

Chlorphenesin has antifungal and antibacterial properties. It has been applied locally in mild uncomplicated dermatophyte and other cutaneous infections and in vaginal infections.

Chlorphenesin carbamate (p. 2022.2) is used as a skeletal muscle relaxant.

Adverse effects. References.

1. Brown VL, Orton DI. Two cases of facial dermatitis due to chlorphenesin in cosmetics. *Contact Dermatitis* 2005; **52**: 48–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Dermicil.

Multi-ingredient Preparations. ***Austral.***: ZSC; ***Braz.***: Oto-Betnovate; ***India***: Derby Cool; Exomega.

Ciclopirox *(BAN, USAN, rINN)*

Ciclopiroxum; Ciklopiroksas; Ciklopiroxi; Hoe-296b; Siklopiroksi; *Циклопирокс*.

6-Cyclohexyl-1-hydroxy-4-methyl-2-pyridone.

$C_{12}H_{17}NO_2$=207.3

CAS — 29342-05-0.

ATC — D01AE14; G01AX12.

ATC Vet — QD01AE14; QG01AX12.

UNII — 19W019ZDRJ.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Ciclopirox). A white or yellowish-white, crystalline powder. Slightly soluble in water; freely soluble in alcohol and in dichloromethane. Protect from light.

USP 36: (Ciclopirox). A white to slightly yellowish white, crystalline powder. Slightly soluble in water; freely soluble in dehydrated alcohol and in dichloromethane; soluble in ether. Store at a temperature of 15 degrees to 30 degrees. Protect from light.

Ciclopirox Olamine *(BANM, USAN, rINNM)*

Ciclopirox-Olamin; Ciclopirox olamina; Ciclopirox olaminum; Ciclopiroxi Olaminum; Ciclopiroxolamine; Ciclopiroxum Olaminum; Ciklopiroksas olaminas; Ciklopirox olamin; Ciklopiroxolamin; Ciklopirox-olamin; Hoe-296; Siklopiroksiolamiini; Sikloproks Olamin; *Циклопирокс Оламин*.

The 2-aminoethanol salt of 6-cyclohexyl-1-hydroxy-4-methyl-2-pyridone.

$C_{12}H_{17}NO_2.C_2H_7NO$=268.4

CAS — 41621-49-2.

ATC — D01AE14; G01AX12.
ATC Vet — QD01AE14; QG01AX12.
UNII — 50MD4SB4AP.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Ciclopirox Olamine). A white or pale yellow crystalline powder. It exhibits polymorphism. Slightly soluble in water; very soluble in alcohol and in dichloromethane; slightly soluble in ethyl acetate; practically insoluble in cyclohexane. A 1% solution in water has a pH of 8.0 to 9.0. Protect from light.

USP 36: (Ciclopirox Olamine). A white to slightly yellowish-white, crystalline powder. Slightly soluble in water; very soluble in alcohol and in dichloromethane; practically insoluble in cyclohexane. pH of a 1% solution in water is between 8.0 and 9.0. Store in airtight containers at a temperature of 5 degrees to 25 degrees. Protect from light.

Uses and Administration

Ciclopirox is an antifungal that is applied topically in the treatment of fungal skin and nail infections, including cutaneous candidiasis (p. 564.1), dermatophytosis, pityriasis versicolor (see Skin Infections, p. 568.1), and seborrhoeic dermatitis (p. 1689.1). It has also been used in the treatment of vaginal candidiasis.

It is applied twice daily for skin infections, as a cream, gel, suspension, solution, or powder; both the base and the olamine salt have been used, with products containing the equivalent of 0.77% ciclopirox base.

A lacquer containing 8% ciclopirox base is applied once daily for nail infections.

A shampoo containing 1% ciclopirox base is used twice weekly for the treatment of seborrhoeic dermatitis.

References.

1. Gupta AK, Skinner AR. Ciclopirox for the treatment of superficial fungal infections: a review. *Int J Dermatol* 2003; **42** (suppl 1): 3–9.
2. Gupta AK, Nicol KA. Ciclopirox 1% shampoo for the treatment of seborrheic dermatitis. *Int J Dermatol* 2006; **45**: 66–9.

Adverse Effects

Irritation and pruritus have been reported after topical application of ciclopirox.

Antimicrobial Action

Ciclopirox has a wide spectrum of antifungal activity. It inhibits most *Candida*, *Epidermophyton*, *Microsporum*, and *Trichophyton* spp. and is also active against *Malassezia furfur*. It has some antibacterial activity.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Loprox; Micopirox; Mycosten†; Stieprox; *Austral.*: Stieprox; *Austria*: Batrafen; Kitonail; Stieprox; *Belg.*: Mycosten; *Braz.*: Celamina; Derm Prox; Fungirox; Gino-Loprox; Loprox; Micolamina; Mupirox; Stiprox; *Canad.*: Loprox; Penlac; Stieprox; *Chile*: Batrafen; Fungopirox; Micopirox; Stiprox; *China*: Batrafen (巴特芬); Dafnegin (得凡尼金); Huanli (环利); Sai Jie (赛洁); *Cz.*: Batrafen; Dafnegin; Polinail; Stieprox; *Denm.*: Mycofen; Sebiprox; *Fin.*: Sebiprox†; *Fr.*: Mycosquam†; Mycoster; Onytec; Sebiprox; Stiprox; *Ger.*: Batrafen; Ciclocutan; Ciclopoli; Inimur Myko†; Nagel Batrafen; Sebiprox; *Gr.*: Batrafen; Candimyc; Dafnegin; Kitonail; Myclopir; Mycolacil; Mycomycen; Neo-botacreme; Neo-mycodermol; Rozolam; Stieprox; *Hong Kong*: Batrafen; Stieprox; *Hung.*: Batrafen; *India*: Batrafen; Olamin; Onylac; *Indon.*: Batrafen; Loprox; *Irl.*: Batrafen†; Oilatum Scalp Treatment†; Stieprox; *Israel*: Batrafen; Cicloderm; Ciclopoli; Punginail; Mycoster; *Ital.*: Batrafen; Bioginal; Brumixol; Ciclopoli; Dafnegin; Miclast; Micomicen; Micoxolamina; Roxolac; Sebiprox; Stiprox; *Malaysia*: Stieprox; *Mex.*: Funamix; Loprox; Stiprox; *Neth.*: Batrafen; Loprox; Sebiprox†; *Norw.*: Sebiprox; Stieprox†; *NZ*: Batrafen; Stieprox; *Philipp.*: Stieprox; *Pol.*: Batrafen; Dafnegin; Hascofungin; Mycosten; Pirolam; Polinail; Stieprox; *Port.*: Batrafen†; Mycoster; Sebiprox; *Rus.*: Batrafen (Батрафен); Dafnegin (Дафнеджин); *Singapore*: Stieprox; *Spain*: Ciclochem; Fungowas; Miclast; Ony-Tec; Sebiprox; *Swed.*: Sebiprox; *Switz.*: Batrafen†; Ciclocutan; Ciclopoli; Dafnegil Neo†; Dafnegil; Mycoster; Sebiprox; *Thai.*: Loprox; Stieprox; *Turk.*: Canolen; Nibulen; *UK*: Oilatum Scalp Treatment; *USA*: Ciclodan; Loprox; Pedipirox; Penlac; *Venez.*: Batrafen.

Multi-ingredient Preparations. *Arg.*: Derm's; Piroctol; Pityrum; Stieproxal; *Fr.*: Kelual DS; Stiproxal; Trigopax; *India*: Flucort-C; Fluticare-C; Olamin-F; *Israel*: Cicloderm-C; *UK*: Oilatum Scalp Intensive; *USA*: CNL Nail Kit.

Pharmacopoeial Preparations

USP 36: Ciclopirox Olamine Cream; Ciclopirox Olamine Topical Suspension; Ciclopirox Topical Solution.

Climbazole *(BAN, rINN)*

Bay-e-6975; Climbazol; Climbazolum; MEB-6401; Климбазол.

1-(*p*-Chlorophenoxy)-1-imidazol-1-yl-3,3-dimethyl-2-butanone.

$C_{15}H_{17}ClN_2O_2$=292.8

CAS — 38083-17-9.

UNII — 9N42CW7I54.

NOTE. The name Crinipan AD has been used as a trade mark for climbazole.

Profile

Climbazole is an azole antifungal included in preparations for the topical treatment of seborrhoeic dermatitis.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Mencogrin; Micocert; Micodual; *Chile*: Eucerin Shampoo Anticaspa†; Eucerin Shampoo para el Tratamiento de la Caspa; Micodual; Node DS†; Shampoo Anticaspa†; *Fr.*: Node DS; Node P†; Sebosquam†; Squaphane E; Squaphane P; Squaphane S; Squaphane; Squaphane; *Ital.*: Cue Soluzione Otologica; Pitiren; *Port.*: Efluvium Anticaspa†; *Venez.*: Node DS; Sensibio DS.

Clotrimazole *(BAN, USAN, rINN)*

Bay-5097; Clotrimazol; Clotrimazolum; FB-5097; Klotrimatsoli; Klotrimazol; Klotrimazolas; Klotrymazol; Клотримазол.

1-(α-2-Chlorotrityl)imidazole.

$C_{22}H_{17}ClN_2$=344.8

CAS — 23593-75-1.

ATC — A01AB18; D01AC01; G01AF02.

ATC Vet — QA01AB18; QD01AC01; QG01AF02; QJ02AB90.

UNII — G07GZ97H65.

NOTE. Compounded preparations of clotrimazole may be represented by the following names:

- Co-climasone (*PEN*)—clotrimazole and betamethasone dipropionate.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Clotrimazole). A white or pale yellow crystalline powder. Practically insoluble in water; soluble in alcohol and in dichloromethane. Protect from light.

USP 36: (Clotrimazole). A white to pale yellow, crystalline powder. Practically insoluble in water; freely soluble in alcohol, in acetone, in chloroform, and in methyl alcohol. Store in airtight containers.

Uses and Administration

Clotrimazole is an imidazole antifungal used topically in superficial candidiasis (p. 564.1), and in the skin infections pityriasis versicolor and dermatophytosis (see Skin Infections, p. 568.1).

Clotrimazole is applied topically two or three times daily for 2 to 4 weeks as a 1% cream, lotion, spray, or solution in the treatment of fungal skin infections; a 1% powder may be used with the cream or solution and has been applied to prevent re-infection. The 1% solution is also used topically for fungal otitis externa. Clotrimazole is given as pessaries in dosage regimens of 100 mg for 6 days, 200 mg for 3 days, or a single dose of 500 mg in the treatment of vulvovaginal candidiasis; similar doses are given as a 1, 2, or 10% vaginal cream. It may be necessary to treat balanitis in male partners concurrently.

For the treatment of oropharyngeal candidiasis one 10-mg lozenge of clotrimazole is dissolved in the mouth five times daily for 14 days. For the prophylaxis of oropharyngeal candidiasis in patients receiving immunosuppressant therapy the dose is one 10-mg lozenge three times daily for the duration of the immunosuppressant treatment. Clotrimazole has also been given orally but has now been largely superseded by other azole drugs.

Sickle-cell disease. Oral clotrimazole has been investigated for the treatment of sickle-cell disease (p. 1123.2).

1. Brugnara C, *et al.* Therapy with oral clotrimazole induces inhibition of the Gardos channel and reduction of erythrocyte dehydration in patients with sickle cell disease. *J Clin Invest* 1996; **97**: 1227–34.

Adverse Effects and Precautions

Nausea, vomiting, unpleasant mouth sensations, and pruritus have been reported after the use of oral clotrimazole lozenges. Raised liver enzyme values have also occurred. Local reactions including irritation and a burning sensation may occur in patients treated topically; contact allergic dermatitis has been reported.

Intravaginal preparations of clotrimazole may damage latex contraceptives and additional contraceptive measures are therefore necessary during local application.

Gastrointestinal disturbance, elevation of liver enzymes, dysuria, and mental depression have been reported after oral clotrimazole (although this route is no longer used). For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies clotrimazole (for gynaecological use) as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients. Dermatological preparations are classified as probably not porphyrinogenic; they may be used as drugs of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Antimicrobial Action

Clotrimazole is an imidazole antifungal with antimicrobial activity similar to that of ketoconazole (p. 587.2).

Pharmacokinetics

When applied topically clotrimazole penetrates the epidermis but there is little if any systemic absorption. Absorption of 3 to 10% of a dose has been reported after vaginal use. Clotrimazole is metabolised in the liver to inactive compounds and excreted in the faeces and urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Aflorix; Clotri-Q; Clotrix; Dr Scholl's; Empecid; Eximius; Fiasole; Fungocop Premium; Ikolan; Klomazole; Livomonil; Medifungol; Micoclin; Miccmax†; Micomazol Deo; Micomazol; Micosep B; Micosep; Miccotrim; Mycanden; Otrix; Panmicol; Permykot; Sinamida Gyno; Sinfung; Trimazol; *Austral.*: Canesten; Chemists Own Clozole; Clofeme†; Clonea; Femizol†; Tinaderm Extra†; Topizol†; *Austria*: Candibene; Canesten; Imazol; Myko Cordes†; Pedikurol; *Belg.*: Canestene; *Braz.*: ABC; Antimicotico Martel†; Canesten; Clomazen; Clomazol; Clotigen†; Clotren; Clotriderm; Clotrigel; Clotrizan†; CTL; Dermo-Trimazen; Dermobene; Dermotrizol; Gino-Canesten; Gino-Clotrimix†; Gino-Trimazen; Kinasten†; Miclonazol; Micotrat†; Neo Clotrimazyl; Trimazen; *Canad.*: Canesten; Clotrimaderm; *Chile*: Arnela; Axasol; Canesten; Clotrimin; Cotrisan; Creminem; Dermicin; Fungos; Funzal; Gynocanesten; Konifungil; Novacetol; Telugren; *China*: Gyno Canesten (凯妮汀); Lin Guan (林冠); Noah Smearing Film (诺亚涂膜); Zhengmeiting (正美汀); *Cz.*: Aknecolor; Baycuten†; Candibene; Candimax; Canesten; Canifug; Clotricyd; Imazol; Jenamazol; *Denm.*: Canesten; Canvag; *Fin.*: Canesten; *Fr.*: MycoHydralin; *Ger.*: Antifungol†; Canesten; Canifug; Cloderm; Clotri OPT; Clotrigalen; cutistad; Fungiderm†; Fungizid; Gilt; KadeFungin; Mycofug; Myko Cordes; Mykofungin; Mykohaug; SD-Hermal; Uromykol; *Gr.*: Canesten; Factodin; *Hong Kong*: Aristen; Can Vag†; Canasderm†; Candinox†; Canesten; Clocreme; Clotri-Denk; Clozole; Cotren; Fungesten†; Gyne-Lotremin; Gyne-Zole†; Kamicin; Lotremin; Mycoril; Synesten†; Tricloderm†; *Hung.*: Candibene; Canesten; Canifug†; *India*: Antican; Calcrem; Canazole; Cancap-VT; Candasia; Candiclo; Candid; Candinil; Canesten; Canfem VG; Canison; Cansoft; Cazol; Clenorush Torche; Cloben; Clocip; Clogen; Clomax; Clotrin-V; Clozol; CTM; CTZole; Decand; Demazole; Endid; Fungimac; Gynostatum; Imidil; Intramol-V6; Kundo-V; Leozole; Lotril; Lotrim; Mycocid; Mycoclear; Mycoderm-C; Nifugal; Nuforce Dust Powder; Nuforce Mouth Paint; Nuforce V6; Oraloz; Ortho Applicator; Surfaz; *Indon.*: Bernesten; Canesten Clonitia†; Fungiderm†; Gyne-Lotremin†; Kranos; Lotremin Medisten†; Trimadan†; *Irl.*: Canazole Clotrimazole†; Canesten *Israel*: Agisten; Clothree; Clotrimaderm; Fungicare; Myco-Hermal; Oralten; *Ital.*: Antimicotico; Canesten; Cangil; Gyno Canesten; *Malaysia*: Candazole; Candid: Canesten; Clomazole†; Fungicip; Gyne-Lotremin; Lotremin; Taraten; *Mex.*: Altenal†; Candimon; Candiphen; Canesten; Clocan; Clomacin; Dermasten; Euroderm; Liferzol; Lodirtrem; Lomecan V†; Lotrimin, Rangyn†; Tenescan; Toczol; Traxelan; *Neth.*: Canesten; Imazol; Parvemaxol†; *Norw.*: Canesten; *NZ*: Canesten; Clocreme†; Clomazol; Clotrihexal†; Clourimaderm; *Philipp.*: Candid V6; Candiva; Canesten; Canison; Clorifort; Cloxy; Gixaderm; Gynesol; Vaff; Vagizol; Yeastazol; *Pol.*: Canesten†; Imazol; *Port.*: Canesten; Diomicete; Gino-Canesten; Gino-Lotremine†; Lotremine; Micolysin; Nalbix; Pan-Fungex; *Rus.*: Amyclon (Амиклон); Antifungol (Антифунгол)†; Candibene (Кандибене); Candid (Кандид); Candid V6 (Кандид В6); Candizole (Кандизол); Canesten (Канестен); Canison (Канизон); Imidil (Имидил); *S.Afr.*: A-Por; Canalba; Candaspor; Candizole; Canesten; Canex; Clomaderm; Closcript; Covospor; Dynaspor; Fungispor; Gynezol; Gyno-Trimaze; Innospore; Medaspor; Micomisan; Mycoban; Mycohexal†; Normospor; Pinaspor; Stiemazol†; Trimaze; Xerasport†; *Singapore*: Candazole; Candid; Canesten; Cotren; Cristan; Myco-Hermal; Mycoril; Sastid Anti-Fungal; *Spain*: Canesmed; Canespie Clotrimazol; Canesten; Fungidermo; Gine Canesten; *Swed.*: Canesten; *Switz.*: Acneco-

lor; Aknecolor; Canestene; Corisol; Fungotox; Gromazol; Gyno-Canestene; Imazol; Undex au clotrimazole; ***Thai.***: Caginal; Canasone; Canazol; Candazole; Candex; Candid; Candinox; Canesten; Cenecon; Chingazol; Clomaz; Clotri; Clotricin; Clotrimed; Comat†; Comazol; Cotren; CST†; Defungo; Dermaten; Dermizole; Fadae†; Fango Cream; Fungi; Fungicon; Fungiderm; Gynebo; Gynestin 200; Gyno-Clotrin; Gynosten; Hofra B; Hofra; Kanezin†; Kenet; Klamacin; Lamazone; Lyma; Manomazole; Mycoda; Mycoderm-C; Mycoril; Mycotopic; Mycozole; Myda; Nestic; P-Gyzole; RanoTroc†; Taraten; Vagizole; Vamazole; Vanesten; Zema; ***Turk.***: Canesten; Clozol; Fungosten†; Gyno-Canesten; ***UK***: Canesten Combi; Canesten; Fungederm; ***Ukr.***: Candibene (Кандибене); Candid (Кандид); Imazol (Имазол); ***USA***: Fungi Cure Intensive; Gyne-Lotrimin; Lotrimin AF; Lotrimin; Mycelex-7; Mycelex; ***Venez.***: Canesten; Clotilen; Clotrizol; Fugolin; Ginolotricomb; Gyno Canesten; Imazol; Ipalat; Micozol; Polik.

Multi-ingredient Preparations. ***Arg.***: Becortin; Calmurid; Cortispec; Dicasone Complex; Empecid Cort; Gentacort Plus; Hongal; Lotricomb; Micomazol B; Quadriderm; Quiacort G Plus; Vagisan Compuesto; Vitacortil; ***Austral.***: Canesoral Duo; Femazole Duo; Hydrozole; VagiClear Duo; ***Austria***: Imazol Duo; Myko Cordes†; ***Belg.***: Lotriderm; ***Braz.***: Baycuten; ***Canad.***: Canesoral Combi-Pak; Lotriderm; ***Chile***: B-Laboterol; Baycuten; Clotrimin-B; Creminem-B; Cutanil; Dermicin B; Donomix; Locrim; Lotriderm; Novadrel; Novarnela; Telugren Plus; Tribesona; ***China***: Clotrasone (荷洛松); Shan Qing (山庆); Shuang Zuo Tai (双唑泰); ***Cz.***: Imacort; Imazol Plus; ***Denm.***: Clotrason; ***Ger.***: Antifungol†; Baycuten HC; Fungidexan; Imazol comp; Imazol Plus; Imazol; Lotricomb; Myko Cordes Plus; ***Gr.***: Lotriderm; ***Hong Kong***: Candacort; Canesten HC; Clobert-G†; Clobeta-G; Clotrim-B†; Clotrinolon; Cobetsol†; Dermacloft†; Derzid-C; Lozopin†; Synco-CFN†; Triderm; Tridewel†; Uni-Quaderm†; ***India***: Adcort; Advin-NC; Aliderma; Alvi; Arima; Atasol; Baclasia-CG; Baclasia-CN; BC-Zole; BC-Zole; Beclasone-C; Beclocid-G; Beclocid; Beclocin-O; Beclolab-CG; Beclolab-NC; Beclotis-C; Beclotis-CG; Becmet-CG; Becmet-CG; Bectop; Benda; Bestec; Bestonim C; Bestopic-N; Bugderm; Caltec; Candasia-B; Candibiotic; Candid B; Candid Ear Drops; Candid-CL; Candid-TV; Candiderma +; Candiderma; Candigen-BG; Candikit-N; Candivate; Canesten-S; Canison-B; Canison-BN; Canison-C; Canoderma; Cazol-B; CBL; Ceflox-CF; Cezel-PT; Ciprolar-FC; CLCD; Clenorush; Clevyx; Clima-V; Clingen Plus; Clingen; Cloat-V; Cloben-G; Cloben; Clobiotic; Clocain; Clocip B; Clocip NB; Clodaz-V6; Clofung GM; Clofung-G; Clofung-N; Clofung; Clomax BN; Clomax-B; Clomax-BG; Clomycin†; Clorid-B; Clovar-V; Clozed; CNB; Convoy; Corge-C; Cuticare; Cutgard; Dandruff Plus; Decand B; Decand BG; Dermaspan; Derminol; Diprogen; Drep; Drocort; Eligao; Epicort-GC; Everbate; Evergum; Excan; Flucocip; Fourderm AF; Fubac; Fungi-BC; Fungidrops; GCB; Gentacort-MF; Gentalene Plus; Gentalene-C; Ginal-V; Ginal-V; Ginlac-V; Hill-V; Hydrozole; IFB; Ifyclo-G; Imidil B; Imidil Plus; Imidil-CV; Infabact; Itchasia; Itchicos; Itchicure; Itchipol; Lamonte-BG; LBC; Leobet-NC; Leozole-B; Lotriderm; Lotril-B; Lotril-BG; Lotril-LB; Mycoderm; Myconip-C; Myconorm; Mycotic; Naderm RF; NC Derm; Neobate; Neocip FC; Nifugal-B; Nivate-NC; Nuforce-CD; Nuforce-GM; Olotic; Onderm; Otek-AC Plus; Otichek; Otiden; Otiderm; Otiflox; Otocin-O; Otocin; Otocos; Otosym; Sigmaderm; Sofradex-F; Surfaz-SN; Surfaz; Translipo-Triple; ***Indon.***: Baycuten-N; Heltiskin†; Lotriderm; ***Irl.***: Canesten HC; Lotriderm; ***Israel***: Agisten 1; Agisten with Aloe Vera; Clotrisone; Hydroagisten; Polycutan; Tevacutan; Triderm; ***Ital.***: Desamix Effe; Meclon; ***Malaysia***: Baycuten N†; Betamethasone Clo; Candacort; Candid B; Triderm-C; ***Mex.***: Barmicil Compuesto; Baycuten N; Baycuten; Beclogen; Beclotrin; Betrigen; Clotricina; Gelmicin; Miclobet; Prubagen; Quadriderm NF; Qudermin; Triderm; Xyloderm; ***Neth.***: Imazol Duo; ***NZ***: Canesten Duo; ***Philipp.***: Baycuten; Candacort; Candibec; Clotrasone; Combiderm; Triderm; ***Pol.***: Imazol Plus; Lotriderm; Triderm; ***Port.***: Baycuten; Beta-Micoter; Flotiran; Quadriderme; ***Rus.***: Akriderm GK (Акридерм ГК); Candibiotic (Кандибиотик); Candid B (Кандид Б); Candiderm (Кандидерм); Canison Plus (Канизон Плюс); Metrogyl Plus (Метрогил Плюс); Triderm (Тридерм); ***S.Afr.***: Lotriderm; ***Singapore***: Candacort; Canesten HC; Combiderm; Gentriderm; Gentrisone; Modaderm; Neoderm; Saerogenta-A; Triderm; ***Spain***: Beta Micoter; Clotrasone; ***Switz.***: Imacort; Imazol; Triderm; ***Thai.***: Bacda-B; Canasone CB; Canazol-BE; Candacort; Candex Plus; Chingazone; Derzid-C; Fada-B; Fango-B; Fungicon; Fungiderm-B; Gynesten-B†; Gynestin; Mycosone-B; Mycozole-B; Myda-B; Myrazole-B; Sema-X; Twina; Zema B†; ***Turk.***: Imazol; ***UK***: Canesten HC; ***Ukr.***: Candibiotic (Кандибиотик); Candid B (Кандид-Б); Candiderm (Кандидерм); Clotrex (Клотрекс); Clotrisal (Клотрисал); Imacort (Имакорт); Triacutan (Триакутан); Triderm (Тридерм); Vagiklin (Вагиклин); ***USA***: Lotrisone; ***Venez.***: Baycuten N; Lotricomb; Lotrisone; Triderm.

Pharmacopoeial Preparations

BP 2014: Clotrimazole Cream; Clotrimazole Pessaries;

USP 36: Clotrimazole and Betamethasone Dipropionate Cream; Clotrimazole Cream; Clotrimazole Lotion; Clotrimazole Lozenges; Clotrimazole Topical Solution; Clotrimazole Vaginal Tablets.

Cloxiquine *(rINN)*

5-Chloro-8-hydroxyquinoline; Cloxiquina; Cloxiquinum; Cloxyquin; Cloxyquin (USAN); Клоксихин.

5-Chloroquinolin-8-ol.

C_9H_6ClNO=179.6

CAS — 130-16-5.

UNII — BPF36H1G6S.

Profile

Cloxiquine has been included in preparations used topically for the treatment of fungal and bacterial skin infections. It is a component of halquinol, p. 309.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Decoderm trivalent†; ***Indon.***: Decoderm 3.

Croconazole Hydrochloride *(rINNM)*

Cloconazole Hydrochloride; Croconazol, Chlorhydrate de; Croconazol, hidrocloruro de; Croconazoli Hydrochloridum; Hidrocloruro de croconazol; 710674-S (croconazole); Кроконазола Гидрохлорид.

1-[(1-[*o*-[(*m*-Chlorobenzyl)oxy]phenyl)vinyl]imidazole hydrochloride.

$C_{18}H_{15}ClN_2O.HCl$=347.2

CAS — 77175-51-0 (croconazole).

UNII — I0WFH323HZ.

Pharmacopoeias. In *Jpn*.

Profile

Croconazole is an imidazole antifungal used topically in the treatment of superficial cutaneous candidiasis, dermatophytosis, and pityriasis versicolor. It is applied as a 1% cream or gel containing the hydrochloride.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Pilzcin†.

Eberconazole Nitrate *(rINNM)*

Eberconazole, Nitrate de; Eberconazoli Nitras; Nitrato de eberconazol; Эберконазола Нитрат.

(±)-1-(2,4-Dichloro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)imidazole nitrate.

$C_{18}H_{14}Cl_2N_2.NO_3$=391.2

CAS — 128326-82-9 (eberconazole).

ATC — D01AC17.

ATC Vet — QD01AC17.

Profile

Eberconazole nitrate is an imidazole antifungal used topically as a 1% cream in the treatment of superficial fungal infections of the skin.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3.

References.

1. del Palacio A, *et al.* A double-blind randomized comparative trial: eberconazole 1% cream versus clotrimazole 1% cream twice daily in Candida and dermatophyte skin infections. *Mycoses* 2001; **44**: 173–80.
2. Repiso Montero T, *et al.* Eberconazole 1% cream is an effective and safe alternative for dermatophytosis treatment: multicenter, randomized, double-blind, comparative trial with miconazole 2% cream. *Int J Dermatol* 2006; **45**: 600–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Ebernet; ***Spain***: Ebermac; Ebernet; Ebertop; ***Turk.***: Ebernet.

Econazole *(BAN, USAN, rINN)*

Econazol; Econazole; Econazolum; Ekonatsoli; Ekonazol; Ekonazolas; Эконазол.

1-[2,4-Dichloro-β-(4-chlorobenzyloxy)phenethyl]imidazole.

$C_{18}H_{15}Cl_3N_2O$=381.7

CAS — 27220-47-9.

ATC — D01AC03; G01AF05.

ATC Vet — QD01AC03; QG01AF05.

UNII — 6Z1Y2V4A7M.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Econazole). A white or almost white powder. M.p. 88 degrees to 92 degrees. Practically insoluble in water; very soluble in alcohol and in dichloromethane. Protect from light.

Econazole Nitrate *(BANM, USAN, rINNM)*

C-C2470; Econazol, nitrato de; Econazole, nitrate d'; Econazoli Nitras; Econazolnitrat; Ekonatsolinitraatti; Ekonazolnitrat; Ekonazol-nitrat; Ekonazolo nitratas; Nitrato de econazol; R-14827; SQ-13050; Эконазола Нитрат.

(±)-1-[2,4-Dichloro-β-(4-chlorobenzyloxy)phenethyl]imidazole nitrate.

$C_{18}H_{15}Cl_3N_2O.HNO_3$=444.7

CAS — 24169-02-6 (econazole nitrate); 68797-31-9 ((±)-econazole nitrate).

ATC — D01AC03; G01AF05.

ATC Vet — QD01AC03; QG01AF05.

UNII — H438WYN10E.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Econazole Nitrate). A white or almost white crystalline powder. Very slightly soluble in water; slightly soluble in alcohol; sparingly soluble in dichloromethane; soluble in methyl alcohol. Protect from light.

USP 36: (Econazole Nitrate). A white or practically white, crystalline powder, with not more than a slight odour. Very slightly soluble in water and in ether; slightly soluble in alcohol; sparingly soluble in chloroform; soluble in methyl alcohol. Protect from light.

Uses and Administration

Econazole is an imidazole antifungal used topically in the treatment of superficial candidiasis (see p. 564.1) and in dermatophytosis and pityriasis versicolor (see Skin Infections, p. 568.1).

Econazole nitrate is applied topically up to 3 times daily as a 1% cream, lotion, powder, or solution in the treatment of fungal skin infections. Treatment is continued for 2 to 4 weeks. It is also used in the treatment of vaginal candidiasis as pessaries of 150 mg once daily at bedtime for 3 consecutive nights; a single dose of 150 mg in a long-acting formulation has also been used. Intravaginal use of 5 g of a 1% cream once daily at night has been given for 2 weeks. A 1% cream may be used concurrently for the treatment of vulval infections or for the treatment of balanitis in a male partner.

In the treatment of fungal infections of the nails, a 1% cream or lotion is applied once daily and covered with an occlusive dressing.

Econazole nitrate has also been used as eye or ear drops.

Econazole sulfosalicylate has also been used.

Adverse Effects and Precautions

Local reactions including burning and irritation may occur when econazole nitrate is applied topically. Contact dermatitis has been reported rarely.

Intravaginal preparations of econazole may damage latex contraceptives and additional contraceptive measures are therefore necessary during local application.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies econazole (for gynaecological use) as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients. Dermatological preparations are classified as probably not porphyrinogenic; they may be used as drugs of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Antimicrobial Action

Econazole is an imidazole antifungal with antimicrobial activity similar to that of ketoconazole (p. 587.2).

Pharmacokinetics

Absorption is not significant when econazole nitrate is applied to the skin or vagina.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dermocitran; Excelentia Antimicotico; Micocide; Micolis; Micotex; Nomicon; Novo Paramicon; Sinamida Econazol; ***Austral.***: Dermazole†; Pevaryl; ***Austria***: Gyno-Pevaryl; Pevaryl; ***Belg.***: Pevaryl†; ***Braz.***: Dermazol; Micostyl; ***Chile***: Micolis; ***China***: Confort (康妇特); ***Cz.***: Gyno-Pevaryl; Pevaryl; ***Denm.***: Pevaryl†; ***Fin.***: Pevaryl†; ***Fr.***: Dermazol; Pongeryl†; Pongileine; Gyno-Pevaryl; Mycoapaisyl; Mycosedermyl; Myleugyn; Pevaryl; ***Ger.***: Epi-Pevaryl Pv; Epi-Pevaryl; Gyno-Pevaryl; ***Gr.***: Bismulin; Fungistat; Mycobacter; Nectarmidin; Penicomb; Pevaryl; Unifungin; ***Hong Kong***:

Ecomi; Econite†; Ecosone†; Ecozol; Heads Shampoo†; ***Hung.***: Gyno-Pevaryl; Pevaryl; ***India***: Ecanol; ***Irl.***: Ecostatin†; Gyno-Pevaryl; ***Israel***: Gyno-Pevaryl; Pevaryl†; ***Ital.***: Dermazol†; Ecodergin; Ecomesol; Ecomi; Ecorex; Ecosteril; Ganazolo; Ifenec; Micos; Pevaryl; Polinazolo; ***Malaysia***: Gyno-Pevaryl; ***Mex.***: Arecolex; Micostyl; Pevaryl; ***Neth.***: Pevaryl; ***Norw.***: Pevaryl; ***NZ***: Ecreme†; Pevaryl; ***Philipp.***: Pevaryl; ***Pol.***: Gyno-Pevaryl; Pevaryl; Pevazol; ***Port.***: Gyno-Pevaryl; Pevaryl; ***Rus.***: Ecalin (Экалин)†; Ecodax (Экодакс); Gyno-Pevaryl (Гино-Певарил); Ifenec (Ифенек); ***S.Afr.***: Ecoderm†; Econal-C†; Gyno-Pevaryl; Pevaryl; ***Singapore***: Gyno-Pevaryl; Pevaryl; ***Spain***: Ecotam; Micoespec†; ***Swed.***: Pevaryl; ***Switz.***: Gyno-Pevaryl; Pevaryl; ***Thai.***: Econ; ***UK***: Ecostatin†; Gyno-Pevaryl; Pevaryl; ***Ukr.***: Ecodax (Екодакс); ***USA***: Ecoza; Spectazole; ***Venez.***: Gyno-Pevaryl; Miconax; Pevaryl.

Multi-ingredient Preparations. ***Arg.***: Diflunazol; Filoderma Plus; Griseocrem; Griseoplus; ***Austria***: Pevisone; ***Belg.***: Pevisone†; ***China***: Fu Yan Ning (扶严宁); Ji Bai Pu (吉佰美); Pevisone (派瑞松); YiFuQing (益富清); Zhaohuile (朝晖乐); ***Denm.***: Pevison; Pevisone†; ***Fin.***: Pevisone; ***Fr.***: Pevisone; ***Ger.***: Epipevisone; ***Gr.***: Pevison; ***Hong Kong***: Ecocort; Pevisone; Triamecon; Triconazole; ***India***: Bestopic; Cobederm-H†; Ecodax-G; Halog-E; Mediron; ***Israel***: Pevisone†; ***Ital.***: Pevisone; ***Malaysia***: Aecoras; Ecocort; Econazine; Endix; Kifugan; ***Norw.***: Pevisone; ***Philipp.***: Nizolex; Pevaryl HP†; Pevisone; ***Pol.***: Pevisone; ***Port.***: Pevisone; ***S.Afr.***: Pevisone; ***Singapore***: Ecocort; Econazine; Epiderm; Pevisone; ***Swed.***: Pevisone; ***Switz.***: Pevisone; ***Thai.***: Ecocort; Ecoderm; Econazine; Tricozole; ***UK***: Econacort†.

Pharmacopoeial Preparations
BP 2014: Econazole Cream; Econazole Pessaries.

Enilconazole *(BAN, USAN, rINN)*

Enilconazol; Enilconazole; Enilconazolum; Enilkonatsoli; Enilkonazol; R-23979; Энилконазол.
(±)-1-(β-Allyloxy-2,4-dichlorophenethyl)imidazole.
$C_{14}H_{14}Cl_2N_2O$=297.2
CAS — 35554-44-0.
ATC Vet — QD01AC90.
UNII — 6K0NOF3XQ6.

Pharmacopoeias. In *Eur.* (see p. vii) for veterinary use only.

Ph. Eur. 8: (Enilconazole for Veterinary Use; Enilconazole BP(Vet) 2014). A clear, yellowish, oily liquid or solid mass. Very slightly soluble in water; freely soluble in alcohol, in methyl alcohol, and in toluene. Store in airtight containers. Protect from light.

Profile

Enilconazole is an imidazole antifungal used topically in veterinary medicine for the treatment of fungal skin infections in cattle, horses, and dogs. It is also used by inhalation for the treatment of aspergillosis in ostriches.

Fenticonazole Nitrate

(BANM, USAN, rINNM)

Fenticonazol, nitrato de; Fenticonazole, Nitrate de; Fenticonazoli Nitras; Fenticonazolnitrat; Fentikonatsolinitraatti; Fentikonazolnitrat; Fentikonazol-nitrát; Fentikonazolo nitratas; Nitrato de fenticonazol; Rec-15/1476; Фентиконазола Нитрат.
(±)-1-[2,4-Dichloro-β-[[*p*-(phenylthio)benzyl]oxy]phenethyl] imidazole mononitrate.
$C_{24}H_{20}Cl_2N_2OS.HNO_3$=518.4
CAS — 72479-26-6 (fenticonazole); 73151-29-8 (fenticonazole nitrate).
ATC — D01AC12; G01AF12.
ATC Vet — QD01AC12; QG01AF12.
UNII — 8V4JGC8YRF.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Fenticonazole Nitrate). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; freely soluble in dimethylformamide and in methyl alcohol. Protect from light.

Uses and Administration

Fenticonazole is an imidazole antifungal used locally as the nitrate in the treatment of vulvovaginal candidiasis (p. 564.1). A 200-mg pessary is inserted into the vagina at bedtime for 3 nights or a 600-mg pessary is inserted once only at bedtime. It is also available as a 2% vaginal cream; 5 g is inserted into the vagina twice daily for 3 days. Fenticonazole nitrate is also applied topically as a 2% cream or solution for the treatment of fungal skin infections.

Reviews.

1. Veraldi S, Milani R. Topical fenticonazole in dermatology and gynaecology: current role in therapy. *Drugs* 2008; 68: 2183–94.

Adverse Effects and Precautions

Burning and itching have been reported after the application of fenticonazole nitrate.

Intravaginal preparations of fenticonazole may damage latex contraceptives and additional contraceptive measures are therefore necessary during local application.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3.

Antimicrobial Action

Fenticonazole is an imidazole antifungal active against a range of organisms including dermatophyte pathogens, *Malassezia furfur*, and *Candida albicans*.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Lomexin; ***Belg.***: Gynoxin; ***Braz.***: Fentizol; Lomexin; ***Cz.***: Lomexin; ***Fr.***: Lomexin; Terlomexin; ***Ger.***: Fenizolan; Lomexin†; ***Gr.***: Lomexin; ***Hung.***: Gynoxin; Lomexin; ***Irl.***: Gynoxin; Lomexin; ***Ital.***: Falvin; Lomexin; Lorenil; ***Mex.***: Lomexin; ***Neth.***: Gynoxin; ***Pol.***: Gynoxin; ***Port.***: Lomexin; ***Rus.***: Lomexin (Ломексин); ***S.Afr.***: Lomexin; ***Spain***: Laurimic; Lomexin; ***Turk.***: Gyno-Lomexin; ***UK***: Gynoxin; ***Ukr.***: Lomexin (Ломексин); ***Venez.***: Mycofentin.

Fluconazole *(BAN, USAN, rINN)*

Fluconazol; Fluconazolum; Flukonatsoli; Flukonazol; UK-49858; Флуконазол.
2-(2,4-Difluorophenyl)-1,3-bis(1*H*-1,2,4-triazol-1-yl)propan-2-ol.
$C_{13}H_{12}F_2N_6O$=306.3
CAS — 86386-73-4.
ATC — D01AC15; J02AC01.
ATC Vet — QD01AC15; QJ02AC01.
UNII — 8VZV102JFY.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Fluconazole). A white or almost white, hygroscopic, crystalline powder. It exhibits polymorphism. Slightly soluble in water; freely soluble in methyl alcohol; soluble in acetone. Store in airtight containers.

USP 36: (Fluconazole). A white or almost white, crystalline powder. Slightly soluble in water; soluble in alcohol and in acetone; sparingly soluble in chloroform and in isopropyl alcohol; freely soluble in methyl alcohol; very slightly soluble in toluene. Store in airtight containers at a temperature below 30 degrees.

Incompatibility and stability. References.

1. Lor E, *et al.* Visual compatibility of fluconazole with commonly used injectable drugs during simulated Y-site administration. *Am J Hosp Pharm* 1991; 48: 744–6.
2. Couch P, *et al.* Stability of fluconazole and amino acids in parenteral nutrient solutions. *Am J Hosp Pharm* 1992; 49: 1459–62.
3. Hunt-Fugate AK, *et al.* Stability of fluconazole in injectable solutions. *Am J Hosp Pharm* 1993; 50: 1186–7.
4. Ishisaka DY. Visual compatibility of fluconazole with drugs given by continuous infusion. *Am J Hosp Pharm* 1994; 51: 2290 and 2292.
5. Dotson B, Churchwell MD. Physical compatibility of 4% sodium citrate with 23.4% sodium chloride, fluconazole, and micafungin. *Am J Health-Syst Pharm* 2011; 68: 377–8.

Uses and Administration

Fluconazole is a triazole antifungal used for superficial mucosal (oropharyngeal, oesophageal, or vaginal) candidiasis and for fungal skin infections. It is also given for systemic infections including systemic candidiasis, coccidioidomycosis, and cryptococcosis, and has been tried in blastomycosis, histoplasmosis, and sporotrichosis. The place of fluconazole in the treatment of fungal infections is discussed in the various sections under Choice of Antifungal, p. 563.1. Fluconazole has also been used for the treatment of cutaneous leishmaniasis, for details see p. 579.2.

Fluconazole is given orally or by intravenous infusion in similar doses. For intravenous infusion it is given as a solution containing 2 mg/mL at a rate of 5 to 10 mL/minute (300 to 600 mL/hour). In the USA, a maximum infusion rate of 100 mL/hour is recommended.

For **superficial mucosal candidiasis** (other than genital candidiasis), the usual oral dose of fluconazole in the UK is 50 mg daily, although 100 mg daily may be given if necessary. Treatment usually continues for 7 to 14 days in *oropharyngeal* candidiasis (except in severely immunocompromised patients), for 14 days in *atrophic oral candidiasis* associated with dentures, and for 14 to 30 days in other mucosal candidal infections including *oesophagitis*.

Higher doses are recommended in the USA where an initial dose of fluconazole 200 mg is followed by 100 mg once daily and where the minimum treatment period is 14 days for oropharyngeal infection, or a minimum of 21 days and at least 14 days after resolution of symptoms for oesophageal infections; doses of up to 400 mg daily may be used for oesophageal candidiasis if necessary.

Fluconazole 150 mg as a single oral dose may be used for **genital candidiasis** (vaginal candidiasis or candidal balanitis).

Dermatophytosis, pityriasis versicolor, and *Candida* **infections of the skin** may be treated with fluconazole 50 mg orally once daily for up to 6 weeks.

Systemic candidiasis, cryptococcal meningitis, and **other cryptococcal infections** may be treated with fluconazole orally or by intravenous infusion; the initial dose is 400 mg followed by a maintenance dose of 200 to 400 mg once daily. Duration of therapy is based on clinical and mycological response, but is usually at least 6 to 8 weeks in cryptococcal meningitis; in the USA, treatment for 10 to 12 weeks after the CSF cultures become negative is recommended. Fluconazole may also be used in daily doses of 100 to 200 mg orally or intravenously to prevent relapse after a primary course of antifungal treatment for acute cryptococcal meningitis in patients with AIDS.

In *immunocompromised patients* at risk of fungal infection, fluconazole may be given **prophylactically** in a dose of 50 to 400 mg daily orally or by intravenous infusion, although long-term prophylaxis has been associated with the emergence of resistant organisms (see under Intermittent Doses, below).

For details of doses used in children and in those with renal impairment, see p. 579.1.

Reviews.

1. Grant SM, Clissold SP. Fluconazole: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in superficial and systemic mycoses. *Drugs* 1990; 39: 877–916. Correction. *ibid.* 40: 862.
2. Kowalsky SF, Dixon DM. Fluconazole: a new antifungal agent. *Clin Pharm* 1991; 10: 179–94.
3. Goa KL, Barradell LB. Fluconazole: an update of its pharmacodynamic and pharmacokinetic properties and therapeutic use in major superficial and systemic mycoses in immunocompromised patients. *Drugs* 1995; 50: 658–90.
4. Charlier C, *et al.* Fluconazole for the management of invasive candidiasis: where do we stand after 15 years? *J Antimicrob Chemother* 2006; 57: 384–410.

Administration. *HIGH DOSES.* Doses higher than those in licensed product information for fluconazole have been tried, and in some cases are routinely recommended, for patients with some life-threatening fungal infections. For **cryptococcal meningitis** in *HIV-infected* patients, oral fluconazole doses of 800 mg to 2 g daily have been used in some second-line induction regimens. In the USA, some experts[1] have suggested:

- 800 mg daily when used with amphotericin B
- at least 800 mg, and preferably 1.2 g daily when used with flucytosine
- 800 mg to 2 g daily, preferably 1.2 g daily or more, when fluconazole is used alone

Daily oral doses of up to 800 mg have also been used in consolidation treatment of *non-HIV infected* patients with cryptococcal meningitis,[1] and 800 mg daily has been suggested for **CNS blastomycosis.**[2] For the treatment of **CNS coccidioidomycosis**, some experts[3] suggest initial oral doses of 800 mg to 1 g fluconazole daily; for disseminated disease, up to 2 g daily has been used. Intravenous doses of 10 mg/kg daily have been tried in **disseminated candidiasis,**[4] and US guidelines[5] suggest up to 12 mg/kg daily if fluconazole is to be used for CNS infection. When used for treatment of disseminated neonatal candidiasis, a dose of 12 mg/kg daily has also been suggested.[5]

1. Perfect JR, *et al.* Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2010; 50: 291–322. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/649858 (accessed 16/08/10)
2. Chapman SW, *et al.* Clinical practice guidelines for the management of blastomycosis: 2008 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2008; 46: 1801–12. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/588300 (accessed 16/08/10)
3. Galgiani JN, *et al.* Infectious Diseases Society of America. Coccidioidomycosis. *Clin Infect Dis* 2005; 41: 1217–23. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/496991 (accessed 16/08/10)
4. Graninger W, *et al.* Treatment of Candida albicans fungaemia with fluconazole. *J Infect* 1993; 26: 133–46.
5. Pappas PG, *et al.* Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009; 48: 503–35. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/596757 (accessed 16/08/10)

INTERMITTENT DOSES. Concern has been expressed about the increasingly widespread use of fluconazole[1] and, in particular, about the impact of continuous fluconazole therapy in immunocompromised patients on the development of resistance (see under Antimicrobial Action, p. 580.2). Nevertheless, fluconazole remains popular for primary and secondary prophylaxis. Some investigators have suggested the use of intermittent doses[2,3] although this could further increase the risk of infections with resistant organisms.

Once-weekly treatment with fluconazole has been tried in onychomycosis[4] and tinea capitis.[5] In HIV-infected patients with oropharyngeal candidiasis, a single 750-mg oral dose of fluconazole has been reported to be as effective

and well tolerated as a standard, 2 week course of fluconazole 150 mg orally once daily.[6]

1. Mangino JE, *et al.* When to use fluconazole. *Lancet* 1995; **345:** 6–7.
2. Singh N, *et al.* Low-dose fluconazole as primary prophylaxis for cryptococcal infection in AIDS patients with CD4 cell counts of ≤ 100/mm³: demonstration of efficacy in a prospective, multicenter trial. *Clin Infect Dis* 1996; **23:** 1282–6.
3. Schuman P, *et al.* Weekly fluconazole for the prevention of mucosal candidiasis in women with HIV infection: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1997; **126:** 689–96.
4. Scher RK, *et al.* Once-weekly fluconazole (150 mg, 300 mg, or 450 mg) in the treatment of distal subungual onychomycosis of the toenail. *J Am Acad Dermatol* 1998; **38:** S77–S86.
5. Gupta AK, *et al.* Once weekly fluconazole is effective in children in the treatment of tinea capitis: a prospective, multicentre study. *Br J Dermatol* 2000; **142:** 965–8.
6. Hamza OJ, *et al.* Single-dose fluconazole versus standard 2-week therapy for oropharyngeal candidiasis in HIV-infected patients: a randomized, double-blind, double-dummy trial. *Clin Infect Dis* 2008; **47:** 1270–6.

Administration in children. Fluconazole may be used in neonates and children for the treatment of candidiasis and cryptococcal infections (including meningitis), as well as for prevention of fungal infection in those who are immunocompromised; in children, it may also be used for the treatment of fungal skin infections. Fluconazole may be given orally, or by intravenous infusion at a rate not exceeding 5 to 10 mL/min.

For children from 4 weeks of age, the following licensed doses have been recommended, to a maximum of 400 mg daily; the duration of treatment is generally as for adults (see Uses and Administration, p. 578.2):

- **mucosal candidiasis**: 3 to 6 mg/kg initially, followed by 3 mg/kg once daily
- **systemic candidiasis** and **cryptococcal infections**: 6 to 12 mg/kg once daily
- **prevention of fungal infections** if immunocompromised: 3 to 12 mg/kg once daily

Neonates may be given the same doses as older children, but the dosing interval must be extended due to slower excretion of fluconazole. For neonates less than 2 weeks of age, UK licensed product information suggests doses should be given every 72 hours, for those between 2 and 4 weeks of age doses should be given every 48 hours.

Additionally, the *BNFC* makes the following unlicensed recommendations for children from 1 month of age:

- treatment of **tinea corporis, cruris, and pedis infections, pityriasis versicolor, and dermal candidiasis**: 3 mg/kg orally (maximum 50 mg) once daily for up to 6 weeks
- treatment of **tinea capitis** infection: 6 mg/kg orally (maximum 300 mg) once daily for 2 to 4 weeks
- **prevention of relapse of cryptococcal meningitis in AIDS patients** after completion of primary therapy: 6 mg/kg (maximum 200 mg) orally or intravenously once daily

The use of fluconazole for prophylaxis in neonatal intensive care has been reviewed.[1-7] There is some evidence to suggest that prophylactic systemic fluconazole, generally for the first 4 to 6 weeks of life, may reduce the risk of invasive fungal infections in **very low birth-weight** (less than 1500 g) neonates.[8] Doses that have been tried in some studies are:

- 3 mg/kg every third day for the first two weeks, then every second day during the third and fourth weeks, then daily during the fifth and sixth weeks
- 3 or 6 mg/kg every second day until 30 days after birth or until 45 days in infants of birth-weight less than 1000 g
- 6 mg/kg every third day for the first week, then every day until 4 weeks
- 3 mg/kg twice weekly for six weeks

1. Isaacs D. Fungal prophylaxis in very low birth weight neonates: nystatin, fluconazole or nothing? *Curr Opin Infect Dis* 2008; **21:** 246–50.
2. Kaufman DA. Fluconazole prophylaxis: can we eliminate invasive Candida infections in the neonatal ICU? *Curr Opin Pediatr* 2008; **20:** 332–40.
3. Healy CM, Baker CJ. Fluconazole prophylaxis in the neonatal intensive care unit. *Pediatr Infect Dis J* 2009; **28:** 49–52.
4. Manzoni P, *et al.* The use of fluconazole in neonatal intensive care units. *Arch Dis Child* 2009; **94:** 983–7.
5. McGuire W, Clerihew L. The effect of fluconazole prophylaxis in very low birthweight infants is overestimated by before-after studies. *Arch Dis Child Fetal Neonatal Ed* 2010; **95:** F182–F187.
6. Reed BN, *et al.* Fluconazole prophylaxis in high-risk neonates. *Ann Pharmacother* 2010; **44:** 178–84.
7. Kaufman DA. Epidemiology and prevention of neonatal candidiasis: fluconazole for all neonates? *Adv Exp Med Biol* 2010; **659:** 99–119.
8. Clerihew L, *et al.* Prophylactic systemic antifungal agents to prevent mortality and morbidity in very low birth weight infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 18/01/12).

Administration in renal impairment. Patients with renal impairment may require dosage reduction. Normal loading or initial doses of oral and parenteral formulations of fluconazole should be given on the first day of treatment and subsequent doses should be adjusted according to creatinine clearance (CC):

- CC more than 50 mL/minute: 100% of the standard recommended dose
- CC less than 50 mL/minute and not receiving dialysis: 50% of the standard recommended dose
- patients on regular haemodialysis: 100% of the standard recommended dose after each dialysis session

No dosage adjustment is needed in patients with renal impairment given single-dose therapy.

A review[1] of antimicrobial dosing in renal replacement therapy has recommended that critically ill patients undergoing intermittent haemodialysis should receive a dose of 200 to 400 mg every 48 to 72 hours, or 100 to 200 mg every 24 hours (after dialysis on dialysis days). The authors also recommend that those undergoing continuous renal replacement therapy (CRRT) receive a loading dose of 400 to 800 mg, with the following maintenance doses depending on the type of CRRT:

- continuous venovenous haemofiltration (CVVH): 200 to 400 mg every 24 hours
- continuous venovenous haemodialysis (CVVHD): 400 to 800 mg every 24 hours
- continuous venovenous haemodiafiltration (CVVHDF): 800 mg every 24 hours

1. Heintz BH, *et al.* Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 2009; **29:** 562–77.

Leishmaniasis. Fluconazole has been tried in the treatment of cutaneous leishmaniasis (p. 922.1) caused by *Leishmania major*. In a randomised, double-blind, placebo-controlled study,[1] 80 patients received a six-week course of oral fluconazole 200 mg daily, of whom 63 had complete healing of lesions after 3 months, compared with 22 of 65 patients who received placebo. However, others[2] have reported a response rate not significantly different from placebo. High-dose oral fluconazole has also been tried for the treatment of cutaneous leishmaniasis due to *L. braziliensis*. A small study[3] of 28 patients reported a cure rate of 75% for those patients who took a daily dose of 5 mg/kg for 4 to 12 weeks (mean 7.6 weeks) and a cure rate of 100% for those who took a daily dose of 8 mg/kg for 4 to 5 weeks (mean 4.2 weeks).

1. Alrajhi AA, *et al.* Fluconazole for the treatment of cutaneous leishmaniasis caused by Leishmania major. *N Engl J Med* 2002; **346:** 891–5.
2. Morizot G, *et al.* Healing of Old World cutaneous leishmaniasis in travelers treated with fluconazole: drug effect or spontaneous evolution? *Am J Trop Med Hyg* 2007; **76:** 48–52. Correction. *ibid.*; 791.
3. Sousa AQ, *et al.* High-dose oral fluconazole therapy effective for cutaneous leishmaniasis due to Leishmania (Vianna) braziliensis. *Clin Infect Dis* 2011; **53:** 693–5.

Adverse Effects

Adverse effects reported with fluconazole most commonly affect the gastrointestinal tract and include abdominal pain, diarrhoea, flatulence, nausea and vomiting, and taste disturbance. Other adverse effects include headache, dizziness, leucopenia, thrombocytopenia, hyperlipidaemias, and raised liver enzyme values. Serious hepatotoxicity has been reported in patients with severe underlying disease such as AIDS or malignancy. Anaphylaxis and angioedema have been reported rarely.

Skin reactions are rare but exfoliative cutaneous reactions such as toxic epidermal necrolysis and Stevens-Johnson syndrome have occurred, more commonly in patients with AIDS.

Alopecia. Alopecia has occasionally been reported in patients receiving fluconazole, especially during prolonged use.[1,2]

1. Weinroth SE, Tuazon CU. Alopecia associated with fluconazole treatment. *Ann Intern Med* 1993; **119:** 637.
2. Pappas PG, *et al.* Alopecia associated with fluconazole therapy. *Ann Intern Med* 1995; **123:** 354–7.

Effect on electrolyte balance. Hypokalaemia was associated with fluconazole in 3 patients with acute myeloid leukaemia.[1]

1. Kidd D, *et al.* Hypokalaemia in patients with acute myeloid leukaemia after treatment with fluconazole. *Lancet* 1989; **i:** 1017.

Effects on the heart. Prolonged QT interval and torsade de pointes have been reported rarely in patients receiving fluconazole.[1-5]

1. Wassmann S, *et al.* Long QT syndrome and torsade de pointes in a patient receiving fluconazole. *Ann Intern Med* 1999; **131:** 797.
2. Tholakanahalli VN, *et al.* Fluconazole-induced torsade de pointes. *Ann Pharmacother* 2001; **35:** 432–4.
3. Khazan M, Mathis AS. Probable case of torsades de pointes induced by fluconazole. *Pharmacotherapy* 2002; **22:** 1632–7.
4. Pham CP, *et al.* Long QTc interval and torsade de pointes caused by fluconazole. *Ann Pharmacother* 2006; **40:** 1456–61.
5. McMahon JH, Grayson ML. Torsades de pointes in a patient receiving fluconazole for cerebral cryptococcosis. *Am J Health-Syst Pharm* 2008; **65:** 619–23.

Effects on the liver. Although severe hepatic reactions to fluconazole are rare they have been reported, especially in patients with severe underlying diseases or hepatic dysfunction.[1,2] Elevated liver enzymes are commonly found and there have been reports of jaundice.[3,4] Hepatic necrosis has been seen rarely post mortem in patients with severe underlying disease who had received fluconazole. In one such patient, hepatotoxicity was concluded to be dose-dependent.[5]

1. Wells C, Lever AML. Dose-dependent fluconazole hepatotoxicity proven on biopsy and rechallenge. *J Infect* 1992; **24:** 111–12.
2. Jacobson MA, *et al.* Fatal acute hepatic necrosis due to fluconazole. *Am J Med* 1994; **96:** 188–90.
3. Holmes J, Clements D. Jaundice in HIV positive haemophiliac. *Lancet* 1989; **i:** 1027.
4. Franklin IM, *et al.* Fluconazole-induced jaundice. *Lancet* 1990; **336:** 565.
5. Bronstein J-A, *et al.* Fatal acute hepatic necrosis due to dose-dependent fluconazole hepatotoxicity. *Clin Infect Dis* 1997; **25:** 1266–7.

Hypersensitivity. Desensitisation has been successfully carried out in a patient with AIDS who had hypersensitivity to both fluconazole and itraconazole.[1] Gradually increasing oral doses of fluconazole (starting at 5 mg daily) were given over 7 days; thereafter dosage was maintained at 400 mg daily. No adverse reactions were seen during desensitisation or in the 3 months up to the publication of the report.

1. Takahashi T, *et al.* Desensitization to fluconazole in an AIDS patient. *Ann Pharmacother* 2001; **35:** 642–3.

Precautions

Fluconazole should be used with caution in patients with impaired hepatic or renal function. Abnormalities in haematological, hepatic, and renal-function tests have been noted in patients with serious underlying diseases such as AIDS or malignancy. Cases of torsade de pointes and QT prolongation have been reported rarely and caution is advised when giving fluconazole to patients with proarrhythmic conditions.

Teratogenicity has occurred in *animals* given high doses of fluconazole and its use is not recommended in pregnancy (see Pregnancy, below).

Breast feeding. Fluconazole is distributed into breast milk, achieving concentrations similar to those found in maternal plasma,[1] and its use in women who are breast feeding is not recommended by licensed product information.

In one report,[2] no untoward effects, other than a slight increase in lactase dehydrogenase level, were seen in an infant who was exposed to fluconazole in breast milk for 6 weeks.

The American Academy of Pediatrics considers that the use of fluconazole is usually compatible with breast feeding.[3]

1. Force RW. Fluconazole concentrations in breast milk. *Pediatr Infect Dis J* 1995; **14:** 235–6.
2. Bodley V, Powers D. Long-term treatment of a breastfeeding mother with fluconazole-resolved nipple pain caused by yeast: a case study. *J Hum Lact* 1997; **13:** 307–11.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 21/06/05)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fluconazole as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Pregnancy. High (toxic) doses of *fluconazole, itraconazole,* and *ketoconazole* have been reported to be teratogenic in *rodents*. Although there is little information about the use of these drugs in human pregnancy, there is a report of a woman who took fluconazole 400 mg daily throughout pregnancy and who gave birth to an infant with severe craniofacial and limb abnormalities.[1] The abnormalities resembled those associated with the Antley-Bixler syndrome, a genetic disorder, but a teratogenic effect could not be excluded. Although prescription-event-monitoring studies of fluconazole did not reveal adverse effects on the fetus,[2-5] congenital abnormalities have occurred in infants whose mothers were given high doses of fluconazole for 3 months or more. In August 2011 the FDA issued a drug safety communication to draw attention to the fact that use of long-term, high-dose fluconazole (400 to 800 mg daily) during most or all of the first trimester of pregnancy may be associated with a rare and distinct set of birth defects in infants. These features include brachycephaly, abnormal facial features and calvarial development, cleft palate, femoral bowing, thin ribs and long bones, muscle weaknesses, joint deformities, and congenital heart disease.[6] However, they also stated that a single dose of fluconazole (150 mg) used to treat vaginal candidiasis during pregnancy does not appear to be associated with the birth defects.[6] Data collected by the manufacturer,[7] relating to 198 women exposed to itraconazole during the first trimester of pregnancy, indicated that the malformation rate for both exposed women and matched controls was within the expected baseline risk for the general population; a prospective cohort study[8] involving 206

women with first-trimester exposure to itraconazole also found no difference in the rate of congenital abnormalities between exposed and unexposed infants, although a possible increased rate of spontaneous abortion was suggested. Nevertheless, the manufacturers recommend that fluconazole, itraconazole, and ketoconazole should be avoided during pregnancy.

Licensed product information states that doses of *voriconazole* equivalent to those used therapeutically have been shown to be teratogenic and embryotoxic in *rodents*. It therefore recommends that voriconazole should be avoided during pregnancy and that women of child-bearing potential should use effective contraception during treatment. Similar recommendations have been made for *posaconazole*.

Other azole antifungals including butoconazole, clotrimazole, econazole, miconazole, sulconazole, terconazole, and tioconazole are reported to be embryotoxic but not teratogenic in *rodents* given high doses. Many of these drugs are used topically or intravaginally and the systemic absorption from these routes of administration varies. While these drugs may not necessarily be contra-indicated in pregnancy, consideration should be given to these potential risks when choosing antifungal therapy for such patients.

1. Lee BE, *et al.* Congenital malformations in an infant born to a woman treated with fluconazole. *Pediatr Infect Dis J* 1992; 11: 1062–4.
2. Rubin PC, *et al.* Fluconazole and pregnancy: results of a prescription event-monitoring study. *Int J Gynecol Obstet* 1992; 37 (suppl): 25–7.
3. Inman W, *et al.* Safety of fluconazole in the treatment of vaginal candidiasis: a prescription-event monitoring study, with special reference to the outcome of pregnancy. *Eur J Clin Pharmacol* 1994; 46: 115–18.
4. Sørensen HT, *et al.* Risk of malformations and other outcomes in children exposed to fluconazole in utero. *Br J Clin Pharmacol* 1999; 48: 234–8.
5. Nørgaard M, *et al.* Maternal use of fluconazole and risk of congenital malformations: a Danish population-based cohort study. *J Antimicrob Chemother* 2008; 62: 172–6.
6. FDA. FDA drug safety communication: use of long-term, high-dose Diflucan (fluconazole) during pregnancy may be associated with birth defects in infants (issued 3rd August, 2011). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm266030.htm (accessed 17/01/12)
7. Bar-Oz B, *et al.* Pregnancy outcome after in utero exposure to itraconazole: a prospective cohort study. *Am J Obstet Gynecol* 2000; 183: 617–20.
8. De Santis M, *et al.* First-trimester itraconazole exposure and pregnancy outcome: a prospective cohort study of women contacting teratology information services in Italy. *Drug Safety* 2009; 32: 239–44.

Renal impairment. For dose adjustments in renal impairment, see Administration in Renal Impairment, under Uses and Administration, p. 579.1.

Interactions

In general, fewer interactions are considered to occur with fluconazole than with either itraconazole or ketoconazole.

Use of rifampicin with fluconazole results in reduced plasma concentrations of fluconazole. Use of hydrochlorothiazide and fluconazole has resulted in clinically insignificant increases in plasma-fluconazole concentrations.

Fluconazole may interfere with the metabolism of some other drugs, mainly through inhibition of the cytochrome P450 isoenzymes CYP3A4 and CYP2C9. This may account for the reported increases in plasma concentrations of bosentan, ciclosporin, midazolam, nevirapine, amitriptyline, nortriptyline, phenytoin, rifabutin, sulfonylurea hypoglycaemics and nateglinide, selective cyclo-oxygenase-2-inhibitors such as celecoxib and parecoxib, tacrolimus, triazolam, warfarin, and zidovudine; fluconazole may inhibit the formation of a toxic metabolite of sulfamethoxazole.

Increases in terfenadine concentrations after high doses of fluconazole have been associated with ECG abnormalities. A similar effect may be anticipated with astemizole. Use of fluconazole with cisapride could result in increased cisapride concentrations and associated toxicity. The use of fluconazole with astemizole, cisapride, or terfenadine should therefore be avoided because of the risk of cardiac arrhythmias. Syncope attributed to increased amitriptyline concentrations has occurred when amitriptyline was given with fluconazole.

Fluconazole may also reduce the clearance of theophylline. The concentration of contraceptive steroids has been reported to be both increased and decreased in patients receiving fluconazole and the efficacy of oral contraceptives may be affected.

For further information on interactions between drugs metabolised by the cytochrome P450 isoenzyme CYP3A and azoles, see under Itraconazole, p. 585.1.

Antineoplastics. For the effect of azole antifungals on *cyclophosphamide* metabolism, see p. 773.3.

Fluoroquinolones. Both *levofloxacin* and fluconazole can cause a prolonged QT interval. The simultaneous use of intravenous levofloxacin and fluconazole resulted in an episode of torsade de pointes in a patient on haemodialysis.[1]

1. Gandhi PJ, *et al.* Fluconazole- and levofloxacin-induced torsades de pointes in an intensive care unit patient. *Am J Health-Syst Pharm* 2003; 60: 2479–83.

Nitrofurans. For a report of pulmonary and hepatic toxicity due to a possible interaction between *nitrofurantoin* and fluconazole, see p. 332.3.

Antimicrobial Action

Fluconazole is a triazole antifungal drug that in sensitive fungi inhibits cytochrome P450-dependent enzymes, resulting in impairment of ergosterol synthesis in fungal cell membranes. It is active against *Blastomyces dermatitidis*, *Candida* spp., *Coccidioides immitis*, *Cryptococcus neoformans*, *Epidermophyton* spp., *Histoplasma capsulatum*, *Microsporum* spp., and *Trichophyton* spp.

Resistance has developed in some *Candida* spp. following long-term prophylaxis with fluconazole, and cross-resistance with other azoles has been reported.

Microbiological interactions. A synergistic antifungal effect was seen *in vitro* with terbinafine and fluconazole against strains of *Candida albicans*.[1] For effects on the antifungal activity of fluconazole when given with amphotericin B, see p. 572.3.

1. Barchiesi F, *et al.* In vitro activities of terbinafine in combination with fluconazole and itraconazole against isolates of Candida albicans with reduced susceptibility to azoles. *Antimicrob Agents Chemother* 1997; 41: 1812–14.

Resistance. The emergence of strains of *Candida* spp. resistant to fluconazole has become increasingly important, particularly in immunocompromised patients receiving long-term prophylaxis with fluconazole.[1,2] In addition to resistance in *C. albicans*,[3-5] infections caused by *C. dubliniensis*,[5] *C. glabrata*, and *C. krusei*, all of which may be less sensitive to fluconazole than *C. albicans*, have been noted in these patients,[6,7] and more recently the non-albicans species have emerged as a prominent cause of candidiasis in immunocompromised patients.[8] Secondary resistance of *C. glabrata* has also been reported during fluconazole therapy.[9,10] Resistance to fluconazole has been reported to occur more frequently than resistance to either ketoconazole or itraconazole and may be related to the widespread use of this drug.[4,7] Cross-resistance with other azoles[11,12] and with amphotericin B[13,14] has been reported.

Fluconazole resistance has also been reported in *Cryptococcus neoformans*[15] and *Histoplasma capsulatum*.[16] Histoplasmosis developed during treatment with fluconazole in a patient with HIV infection.[17] Fluconazole-resistant *C. neoformans* has been isolated from an immunocompetent patient who had not been exposed to azole antifungals previously.[18]

1. Rex JH, *et al.* Resistance of Candida species to fluconazole. *Antimicrob Agents Chemother* 1995; 39: 1–8.
2. Brion LP, *et al.* Risk of resistance associated with fluconazole prophylaxis: systematic review. *J Infect* 2007; 54: 521–9.
3. Sandven P, *et al.* Susceptibilities of Norwegian Candida albicans strains to fluconazole: emergence of resistance. *Antimicrob Agents Chemother* 1993; 37: 2443–8.
4. Johnson EM, *et al.* Emergence of azole drug resistance in Candida species from HIV-infected patients receiving prolonged fluconazole therapy for oral candidosis. *J Antimicrob Chemother* 1995; 35: 103–14.
5. Ruhnke M, *et al.* Development of simultaneous resistance to fluconazole in Candida albicans and Candida dubliniensis in a patient with AIDS. *J Antimicrob Chemother* 2000; 46: 291–5.
6. Price MF, *et al.* Fluconazole susceptibilities of Candida species and distribution of species recovered from blood cultures over a 5-year period. *Antimicrob Agents Chemother* 1994; 38: 1422–4.
7. Odds FC. Resistance of yeasts to azole-derivative antifungals. *J Antimicrob Chemother* 1993; 31: 463–71.
8. Kanafani ZA, Perfect JR. Resistance to antifungal agents: mechanisms and clinical impact. *Clin Infect Dis* 2008; 46: 120–8.
9. Hitchcock CA, *et al.* Fluconazole resistance in Candida glabrata. *Antimicrob Agents Chemother* 1993; 37: 1962–5.
10. Miyazaki H, *et al.* Fluconazole resistance associated with drug efflux and increased transcription of a drug transporter gene, PDH1, in Candida glabrata. *Antimicrob Agents Chemother* 1998; 42: 1695–1701.
11. Martinez-Suarez JV, Rodriguez-Tudela JL. Patterns of in vitro activity of itraconazole and imidazole antifungal agents against Candida albicans with decreased susceptibility to fluconazole from Spain. *Antimicrob Agents Chemother* 1995; 39: 1512–16.
12. Goldman M, *et al.* Does long-term itraconazole prophylaxis result in in vitro azole resistance in mucosal Candida albicans isolates from persons with advanced human immunodeficiency virus infection? *Antimicrob Agents Chemother* 2000; 44: 1585–7.
13. Kelly SL, *et al.* Resistance to fluconazole and amphotericin in Candida albicans from AIDS patients. *Lancet* 1996; 348: 1523–4.
14. Nolte FS, *et al.* Isolation and characterization of fluconazole- and amphotericin B-resistant Candida albicans from blood of two patients with leukemia. *Antimicrob Agents Chemother* 1997; 41: 196–9.
15. Venkateswarlu K, *et al.* Fluconazole tolerance in clinical isolates of Cryptococcus neoformans. *Antimicrob Agents Chemother* 1997; 41: 748–51.
16. Wheat J, *et al.* Hypothesis on the mechanism of resistance to fluconazole in Histoplasma capsulatum. *Antimicrob Agents Chemother* 1997; 41: 410–14.
17. Pottage JC, Sha BE. Development of histoplasmosis via human immunodeficiency virus infected patient receiving fluconazole. *J Infect Dis* 1991; 164: 622–3.
18. Omi-Wasserlauf R, *et al.* Fluconazole-resistant Cryptococcus neoformans isolated from an immunocompetent patient without prior exposure to fluconazole. *Clin Infect Dis* 1999; 29: 1592–3.

Pharmacokinetics

Fluconazole is well absorbed after oral doses, bioavailability from the oral route being 90% or more of that from the intravenous route. Mean peak plasma concentrations of 6.72 micrograms/mL have occurred in healthy subjects after a 400-mg oral dose. Peak concentrations occur within 1 to 2 hours of oral doses. Plasma concentrations are proportional to the dose over a range of 50 to 400 mg. Multiple dosing leads to increases in peak plasma concentrations; steady-state concentrations are reached in 5 to 10 days but may be attained on day 2 if a loading dose is given.

Fluconazole is widely distributed and the apparent volume of distribution is close to that of total body water. Concentrations in breast milk, joint fluid, saliva, sputum, vaginal fluids, and peritoneal fluid are similar to those achieved in plasma. Concentrations in the CSF range from 50 to 90% of plasma concentrations, even in the absence of meningeal inflammation. Protein binding is only about 12%.

About 80% of a dose is excreted unchanged in the urine and about 11% as metabolites. The elimination half-life of fluconazole is about 30 hours and is increased in patients with renal impairment. Fluconazole is removed by dialysis.

Reviews.

1. Debruyne D, Ryckelynek J-P. Clinical pharmacokinetics of fluconazole. *Clin Pharmacokinet* 1993; 24: 10–27.
2. Debruyne D. Clinical pharmacokinetics of fluconazole in superficial and systemic mycoses. *Clin Pharmacokinet* 1997; 33: 52–77.
3. Pittrow L, Penk A. Special pharmacokinetics of fluconazole in septic obese and burn patients. *Mycoses* 1999; 42 (suppl 2): 87–90.
4. Silling G. Fluconazole: optimized antifungal therapy based on pharmacokinetics. *Mycoses* 2002; 45 (suppl 3): 39–41.

Burns. The mean half-life of fluconazole was decreased to 24.4 hours in 9 patients with burns.[1] Fluconazole clearance was 27.5 mL/minute, which was 30% higher than that reported in healthy subjects.

1. Boucher BA, *et al.* Fluconazole pharmacokinetics in burn patients. *Antimicrob Agents Chemother* 1998; 42: 930–3.

Children and neonates. References.

1. Saxén H, *et al.* Pharmacokinetics of fluconazole in very low birth weight infants during the first two weeks of life. *Clin Pharmacol Ther* 1993; 54: 269–77.
2. Nahata MC, Brady MT. Pharmacokinetics of fluconazole after oral administration in children with human immunodeficiency virus infection. *Eur J Clin Pharmacol* 1995; 48: 291–3.

Distribution. Salivary concentrations of fluconazole after oral doses should be adequate for the treatment of oropharyngeal and oesophageal candidiasis[1,2] even in patients with AIDS who may have decreased salivation.[3] Treatment failures are more likely to be due to inadequate dosage or resistant organisms than to decreased salivary secretion.[3]

Pharmacologically active concentrations of fluconazole have been detected in scalp hair[4] and nails[5] after oral treatment with conventional daily doses and with once-weekly dosage.

1. Force RW, Nahata MC. Salivary concentrations of ketoconazole and fluconazole: implications for drug efficacy in oropharyngeal and esophageal candidiasis. *Ann Pharmacother* 1995; 29: 10–15.
2. Koks CHW, *et al.* Pharmacokinetics of fluconazole in saliva and plasma after administration of an oral suspension and capsules. *Antimicrob Agents Chemother* 1996; 40: 1935–7.
3. García-Hermoso D, *et al.* Fluconazole concentrations in saliva from AIDS patients with oropharyngeal candidosis refractory to treatment with fluconazole. *Antimicrob Agents Chemother* 1995; 39: 656–60.
4. Yeates R, *et al.* Accumulation of fluconazole in scalp hair. *J Clin Pharmacol* 1998; 38: 138–43.
5. Faergemann J. Pharmacokinetics of fluconazole in skin and nails. *J Am Acad Dermatol* 1999; 40 (suppl): S14–S20.

HIV-infected patients. Plasma clearance of fluconazole may be lower in patients with HIV infection than in immunocompetent patients, and the half-life may be prolonged.[1,2]

1. Tett S, *et al.* Pharmacokinetics and bioavailability of fluconazole in two groups of males with human immunodeficiency virus (HIV) infection compared with those in a group of males without HIV infection. *Antimicrob Agents Chemother* 1995; 39: 1835–41.
2. McLachlan AJ, Tett SE. Pharmacokinetics of fluconazole in people with HIV infection: a population analysis. *Br J Clin Pharmacol* 1996; 41: 291–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Antimicon; Candimicol; Damicol; Femixol; Flucoginkan; Flucolaf; Fluconovag; Fluzol; Fungicil; Fungocina; Fungototal; Honguil Plus; Klonarizol; Klonazol†; Micolis Novo; Micoral Fluco; Mutum; Naxo C; Nifurtox; Nimic; Niofen; Periplum; Ponaris; Proseda F; Triflucan; *Austral.*: Canesoral; Di-Con One; Diflucan; Dizole; Flufeme; Fluzole; Ozole; *Austria*: Diflucan; Difluzol; Flucosept; Fungata; *Belg.*: Candizole; Diflucan; Fungimed; *Braz.*: Candix†; Candizol; Floltec; Flucanil; Flucazol; Flucocin; Flucodan; Flucol; Flucomed; Fluconal; Fluconeo; Fluconid; Flucoton; Flucozen; Flusan; Fluxilase; Fungnon; Glyflucan; Helmicin; Pantec; Riconazol; Triazol; Unizol; Zelix; Zolanix†; Zolmic; Zoltec; Zoltren; *Canad.*: Diflucan; *Chile*: Diflucan; Felcar; Felsol; Flucoxan; Fluctin; Fungimax; Ibarin; Microvaccin; Plusgin; Tavor; *China*: Bin Li (滨力); Conquer (酵达); Diflucan (大扶康); Fu Da (扶达);

Fu Kang (扶亢); Fupengxing (芙艿星); Hao Kang (昊康); Hong Xu Guang (弘旭光); Hu Qi (护齐); Hua Shi Xin (华士欣); Jin Zhou (金周); Kai Xing (凯兴); Kang Li Yin (康立因); Ke Da Kang (科达康); Lai Kang (莱抗); Li Xing (力星); Luo Rui (罗瑞); Medoflucon (麦道氟康); Mei Di Ke (美狄克); Qian De (仟德); QianYi (乾意); Qu Er Man Duo (曲尔曼多); Ru Ning (汝宁); Sai Ke Lu Ding (赛可路丁); Shuai Ke Feng (帅克风); Shuang Wei Du Qing (双威独青); Sunvecon (三维康); Tai Ning (泰宁); Wei Ke Hen (维可衡); Wen Qing (文清); Xinlizuo (信利唑); Yi Li Kang (依利康); Yi Qi Fu (易启扶); Yi Zhen Shi (益真施); You Ni An (尤尼安); Cz.: Diflazon†; Diflucan; Fluco†; Forcan; Mycomax; Mycosyst; Mykohexal; ***Denm.***: Diflucan; Fluconastad; Generazole†; Lozanoc; Stadanazol; ***Fin.***: Canesoral; Diflucan; ***Fr.***: Beagyne; Triflucan; ***Ger.***: Canifug Fluco†; Diflucan; Flucobeta; Flucoderm; FlucoLich; Flunazul; Fungata; ***Gr.***: Azoflu; Azzol-S; Dalrich; Diflucan; Falipan; Farviron; Figalol; Flucalit; Flucanid; Flucocaps; Flucodrug; Flucofin; Fluconapen; Flucoran; Flucovein; Flucozol; Flukatril; Flusenil; Fluzomic; Fumecal; Funadel; Fungo; Fungram; Fungustatin; Fungusteril; Fuxilidin; Gynosant; Hadlinol; Medoflucon; Mycazole; Neomycol†; Novoflon; Opumyk; Rifagen; Stabilanol; Tierlite; Varmec; Zidonil; ***Hong Kong***: Diflazon; Diflucan; Flucoric; Flucozal; Fludicon; Forcan†; Lucon; Nofung; Stalene; Vick-Flucan; ***Hung.***: Dermyc; Diflucan; Flucohexal; Fluconer; Flucoric†; Mycosyst; Nofung; ***India***: Adcon; Adecon; AF; Aglocon; Alfa Tab; Alfucoz; Alicon; Alsflu; Antican-O; Aviflu; Cancap; Candicon; Cinflu; Clozole; Conclze; Conflu; Cyflu; E-Flu; Endida; Excan; F-Con; F-Zole; Fabizol; Fantizole; Fasicon; FCN; Fiscon; Fixit; Flecon; Flori; Flozol; Fluact; Flubit; Fluc; Flucalup; Flucan; Flucare; Flucoat; Flucolab; Flucomet; Flucoric; Flucos; Flucoside; Flucovar; Flucozed; Fludia; Flufact; Flufung; Fluka; Flukamep; Flumed; Flumicon; Flunaz; Flunec; Flunif; Flunova; Fluol; Flusta; Flustate; Flusyst; Flutaur; Flutel; Flutrox; Fluzart; Fluzeet; Fluzide; Fluzole; Fluzon; Foflu; Forcan; Ful; Fumac; Fumycin; Funcan; Funesta; Fungal-F; Fungard; Fungazol; Fungdor; Fungiban; Fungicon; Fungid; Fungina; Fungisan-F; Fungo; Funspor; Fusys; Futiza; GFlu; Glenflu; Gocan; Gusnil; Hif; Indcon; Kairflu; Kit; Kon; Koni; Kozole; Leecon; Lido; Logican; Lozic; Lucoz; M-Fluk; Myconorm-F; Mycorest; Mycosure; Myzole; NBOzole; Neocon; Nipcan; Nuforce; Odicon; One Can; Optican; Ozus; Syscan; ***Indon.***: Cancid†; Candipar; Candizol†; Cryptal; Diflucan; Flucess†; Flucoral; Fludis; Funzela; Govazol; Kifluzol; Zemyc; ***Irl.***: ByFluc; CanOral; Diflazole; Diflucan; Flucandid†; Flucol; ***Israel***: Diflucan; Flucanol; Stabilanol; Trican; Triflucan; ***Ital.***: Alozol; Aviflucox; Canazol; Diflucan; Dizolo; Elazor; Flukimex; Flumicon; Flumos; Fluores; Fungus; Klaider; Lefunzol; Miconix; Riflax; Trimikos; Winch; Zerfun; Zoloder; ***Jpn***: Diflucan; ***Malaysia***: Avezol; Biozole; Diflucan; Difluvid; Flucess; Flucon; Fluconol; Flucoric; Flugal; Fukole; Medoflucon; Odaft; Stalene; ***Zolstan; Mex.***: Afungil; Bioxel; Candizol; Diflucan; Difusel; Fectrin; Fharder; Fleridux; Flucoxan; Fludisol; Fluhexal†; Flukezol; Fluxes; Fluxicap; Fluzor†; Fucandyl; Funser; Lanfluzol; Menifar; Neofomiral; Ongicil; Oxifungol; Ranflu†; Solarisol†; Terplex; Trifuncan; Zilrin; Zoldicam; ***Neth.***: Diflucan; Flucoderm†; ***Norw.***: Diflucan; ***NZ***: Canesten Fluconazole; Diflucan; Flucasten; Flucazole; ***Philipp.***: Diflucan; Dyzolor; Exomax; Flucandia; Flucon; Flucoral; Fluzocan; Pukole; Funzela; Odaft; Reflucan; Syscan; ***Pol.***: Diflucan; Flucolast; Fluco-LEK†; Fluconazin; Flucorta; Flumycon; Mycomax; Mycosyst; ***Port.***: Azoflune†; Diflucan; Fludocel; Maxflin†; Reforce; Supremase; ***Rus.***: Diflazon (Дифлазон); Diflucan (Дифлюкан); Flucomabol (Флукомабол); Flucostat (Флюкостат); Flucozan (Флукозан); Flucozyd (Флукозид); Flukonorm (Флуконорм); Flumicon (Флюмикон)†; Forcan (Форкан); Fungolon (Фунголон)†; Funzole (Фунзол); Medoflucon (Медофлюкон); Mycoflucan (Микофлюкан); Mycomax (Микомакс); Mycosyst (Микосист); Nofung (Нофунг); Procanazol (Проканазол); Syscan (Цискан); ***S.Afr.***: Diflucan; Difluzole; Exomax; Flucoric; Fluzol; Mycorest; ***Singapore***: Diflucan; Medoflucon; Mycorest; Omastin; Stalene†; ***Spain***: Acandix; Candifix; Citiges; Diflucan; Lavisa; Loitin; ***Swed.***: Diflucan; ***Switz.***: Diflucan; Flucazol; Flucoderm; Fluconax; Flunizol†; ***Thai.***: Biozole; Diflucan; Flucozole; Fludizol; Flunco; Fluzoral; Funa; Kyrin; Stalene; ***Turk.***: Biocanol†; Candidin; Flucan; Flurit; Fluzole; Fulurit; Fungan; Funolteva; Kandizol; Lumen; Triflucan; Trizol; Zolax; ***UAE***: Oramax; ***UK***: Canesten Oral; Diflucan; ***Ukr.***: Diflazon (Дифлазон); Diflucan (Дифлюкан); Difluzol (Дифлюзол); Flucoric (Флюкорик); Flunol (Флунол)†; Fluzamed (Флузамед); Mycomax (Микомакс); Mycosyst (Микосист); ***USA***: Diflucan; ***Venez.***: Aflumicort; Albesin; Diflucan; Flucess; Flucon; Flunal; Fluval; Fugin; Fungomax; Funizol; Micoflux; Mutum.

Multi-ingredient Preparations. ***Arg.***: Gynerium UD; ***Austral.***: Canesoral Duo; Femazole Duo; VagiClear Duo; ***Canad.***: Canesoral Combi-Pak; ***India***: AF-Kit; Azintra-3; Azithral XP; Azostat; Cancap-Kit; Eradikit; Eve Kit; Fas-3 Kit; FC-Kit; Fiscon Tab; Flucos-TZ; Flucoti; Flunec Combikit; Flutini Kit; Fluzon-T; Forcan TZ; Fulkit; Fungid-OR; Fusys-TZ; Fygek-AS; Gyn-3; Gynotrim Kit; Hif-AS; Kit-3D; Myconor-4; Nuforce Kit; Nuforce-3 Kit; Od-Kit; Orflaz Kit; Saf Kit; ***Mex.***: Afumix; ***NZ***: Canesten Duo; ***Rus.***: Safocid (Сафоцид); ***Ukr.***: Ginekit (Гинекит).

Pharmacopoeial Preparations

USP 36: Fluconazole for Oral Suspension; Fluconazole Injection; Fluconazole Tablets.

Flucytosine *(BAN, USAN, rINN)*

5-FC; Flucitosina; Flucitozin; Fluctozinas; Flucytosin; Flucytosinum; Flucytozyna; Flusitozin; Flusytosiini; Ro-2-9915; Флуцитозин.

5-Fluorocytosine; 4-Amino-5-fluoropyrimidin-2(1*H*)-one.

$C_4H_4FN_3O$=129.1

CAS — 2022-85-7.

ATC — D01AE21; J02AX01.

ATC Vet — QD01AE21; QJ02AX01.

UNII — D83282DT06.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Flucytosine). A white or almost white crystalline powder. Sparingly soluble in water; slightly soluble in dehydrated alcohol. Protect from light.

USP 36: (Flucytosine). A white to off-white crystalline powder, odourless or with a slight odour. Sparingly soluble in water; slightly soluble in alcohol; practically insoluble in chloroform and in ether. Store in airtight containers. Protect from light.

Stability. A solution of flucytosine for intravenous infusion should be stored between 18 degrees and 25 degrees. Precipitation may occur at lower temperatures and decomposition, with the formation of fluorouracil, at higher temperatures.

Uses and Administration

Flucytosine is a fluorinated pyrimidine antifungal used in the treatment of systemic fungal infections, the treatments for which are discussed under Choice of Antifungal, p. 563.1. It is mainly used with amphotericin B or fluconazole in the treatment of severe systemic candidiasis and cryptococcal meningitis. It has also been tried in other infections due to susceptible fungi including chromoblastomycosis.

Flucytosine is given by *intravenous infusion* as a 1% solution over 20 to 40 minutes. The usual dose is 200 mg/kg daily in 4 divided doses; a dose of 100 to 150 mg/kg daily may be sufficient in some patients. Dosage should be adjusted to produce trough plasma concentrations of 25 to 50 micrograms/mL. This is particularly important in patients with AIDS who are at increased risk of bone marrow toxicity. Parenteral treatment is rarely given for more than 7 days, except for cryptococcal meningitis when it is continued for at least 4 months. For intravenous doses to be used in patients with renal impairment, see below.

Flucytosine is given *orally* in usual doses of 50 to 150 mg/kg daily in 4 divided doses. Again, blood concentrations should be monitored and dosage adjusted in patients with renal impairment to avoid accumulation of the drug.

For details of doses in children, see below.

Flucytosine has been used *topically* for azole-refractory vaginitis caused by *Candida* spp., but such use may increase problems of resistance.

Reviews.

1. Viviani MA. Flucytosine—what is its future? *J Antimicrob Chemother* 1995; **35**: 241–4.
2. Summers KK, *et al.* Therapeutic drug monitoring of systemic antifungal therapy. *J Antimicrob Chemother* 1997; **40**: 753–64.
3. Vermes A, *et al.* Flucytosine: a review of its pharmacology, clinical indications, pharmacokinetics, toxicity and drug interactions. *J Antimicrob Chemother* 2000; **46**: 171–9.

Administration in children. Flucytosine may be given to neonates and children for the treatment of systemic fungal infections, including as an adjunct to amphotericin B in the management of severe infections, including cryptococcal meningitis or severe systemic candidiasis. The following doses, given orally or by intravenous infusion over 20 to 40 minutes, are recommended by the *BNFC*:

- neonates: 50 mg/kg every 12 hours
- children from 1 month of age: 50 mg/kg every 6 hours: 25 to 37.5 mg/kg every 6 hours may be sufficient for infections caused by very susceptible fungi. As an adjunct in cryptococcal meningitis, 25 mg/kg every 6 hours is recommended.

Administration in renal impairment. Flucytosine is mainly excreted by the kidneys and the dose must be adjusted in patients with renal impairment.

Dose intervals for intravenous flucytosine should be adjusted according to creatinine clearance (CC):

For intravenous use,

- CC 20 to 40 mL/minute: 50 mg/kg every 12 hours
- CC 10 to 20 mL/minute: 50 mg/kg every 24 hours
- CC less than 10 mL/minute: 50 mg/kg then further doses should be based on plasma concentrations which should not exceed 80 micrograms/mL

Initial oral doses should be at the lower end of the recommended range (see above) and dosage should be adjusted subsequently to avoid accumulation.

Adverse Effects

Adverse effects of flucytosine include nausea, vomiting, diarrhoea, and skin rashes. Less frequently reported adverse effects include confusion, hallucinations, convulsions, headache, sedation, and vertigo, and also allergic reactions, toxic epidermal necrolysis, and cardiotoxicity. Alterations in liver function tests are generally dose-related and reversible; hepatotoxicity may also occur. Hypokalaemia may occur. There have been a few reports of peripheral neuropathy.

Bone-marrow depression, especially leucopenia and thrombocytopenia, is associated with blood concentrations of flucytosine greater than 100 micrograms/mL, with concurrent use of amphotericin B, and with renal impairment. Fatal agranulocytosis and aplastic anaemia have been reported.

Effects on the blood. Bone marrow toxicity associated with flucytosine has been attributed to its conversion to fluorouracil, possibly by intestinal flora.[1] A pilot study[2] of 6 patients given intravenous flucytosine found that the amounts of fluorouracil in serum samples were undetectable, whereas flucytosine could be detected in the samples. This might be because intravenous dosage did not allow the conversion of flucytosine to fluorouracil by intestinal microflora. However, one patient still developed thrombocytopenia and another leucocytopenia and the authors hypothesised that toxicity might be due to flucytosine and not the metabolite.

1. Pirmohamed M, *et al.* The role of active metabolites in drug toxicity. *Drug Safety* 1994; **11**: 114–44.
2. Vermes A, *et al.* 5-fluorocytosine-related bone-marrow depression and conversion to fluorouracil: a pilot study. *Fundam Clin Pharmacol* 2002; **16**: 39–47.

Precautions

Flucytosine should be given with great care to patients with renal impairment, or with blood disorders or bone marrow depression. Renal and hepatic function and blood counts should be monitored during therapy (at least weekly in patients with renal impairment or blood disorders). In patients with renal impairment, doses should be reduced and trough blood concentrations of flucytosine should be checked regularly from blood samples taken just before an injection of flucytosine (see under Uses, above). Care should be taken in patients given radiation therapy or other drugs which depress bone marrow.

Flucytosine is teratogenic in *rats*.

AIDS. Frequent bone marrow toxicity has been reported in patients with AIDS during flucytosine therapy.[1] However, in a study in 381 patients, no additional haematotoxicity was reported in patients given amphotericin B plus flucytosine compared with those given amphotericin B alone.[2] The toxicity could be minimised by monitoring serum concentrations[3] and the British Society for Antimicrobial Chemotherapy has suggested that these should be maintained within 25 to 50 micrograms/mL in patients with AIDS.[4]

1. Chuck SL, Sande MA. Infections with Cryptococcus neoformans in the acquired immunodeficiency syndrome. *N Engl J Med* 1989; **321**: 794–9.
2. van der Horst CM, *et al.* Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. *N Engl J Med* 1997; **337**: 15–21.
3. Viviani MA. Flucytosine—what is its future? *J Antimicrob Chemother* 1995; **35**: 241–4.
4. British Society for Antimicrobial Chemotherapy Working Party. Antifungal chemotherapy in patients with acquired immunodeficiency syndrome. *Lancet* 1992; **340**: 648–51.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies flucytosine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Pregnancy. Teratogenicity has been reported in some *animal* models and licensed product information recommends that flucytosine should only be used if the benefit justifies that possible risk to the fetus. The congenital defects are thought to be as a result of the conversion of flucytosine to fluorouracil by the intestinal microflora. However, there are some case reports of pregnant patients receiving flucytosine (with or without amphotericin B) in the second[1-4] and third[5] trimesters with no reports of abnormalities in the infants.

1. Philpot CR, Lo D. Cryptococcal meningitis in pregnancy. *Med J Aust* 1972; **2**: 1005–7.
2. Schönebeck J, Segerbrand E. Candida albicans septicaemia during first half of pregnancy successfully treated with 5-fluorocytosine. *BMJ* 1973; **4**: 337–8.
3. Curole DN. Cryptococcal meningitis in pregnancy. *J Reprod Med* 1981; **26**: 317–19.
4. Chotmongkol V, Siricharoensang S. Cryptococcal meningitis in pregnancy: a case report. *J Med Assoc Thai* 1991; **74**: 421–2.
5. Chen C-P, Wang K-G. Cryptococcal meningitis in pregnancy. *Am J Perinatol* 1996; **13**: 35–6.

Interactions

Flucytosine is commonly used with amphotericin B. Amphotericin B can cause a deterioration in renal function,

which can result in raised flucytosine blood concentrations and increased toxicity. However, the two drugs are generally regarded as having synergistic antifungal activity. Cytarabine has been claimed to reduce blood concentrations of flucytosine and to antagonise its antifungal activity, although the evidence is limited.

Antimicrobial Action

Flucytosine is a fluorinated pyrimidine antifungal. In susceptible fungi it is converted by cytosine deaminase to fluorouracil which is then incorporated in place of uracil into fungal RNA and disrupts protein synthesis. The activity of thymidilate synthetase is also inhibited and this effect interferes with fungal DNA synthesis.

Flucytosine is active against *Candida* spp., *Cryptococcus neoformans*, *Cladosporium* spp., and *Fonsecaea* spp. Some *Aspergillus* spp. have also been reported to be sensitive. There is synergy between flucytosine and amphotericin B against *Candida* spp. and *Cryptococcus neoformans*.

There is a high incidence of primary resistance to flucytosine among isolates of *Candida* spp. and *Cryptococcus neoformans*. Resistance also develops during treatment with flucytosine and has been reported rarely from combination therapy with flucytosine and amphotericin B.

Pharmacokinetics

Flucytosine is absorbed rapidly and almost completely from the gastrointestinal tract. Bioavailability is 78 to 89%. After oral doses of 37.5 mg/kg every 6 hours, peak plasma concentrations of 70 to 80 micrograms/mL occur within 2 hours; similar concentrations occur, but more rapidly, after an intravenous dose. The plasma-flucytosine concentration for optimum response is 25 to 50 micrograms/mL. Flucytosine is widely distributed through the body tissues and fluids; concentrations in the CSF are 65 to 90% of those in serum. About 2 to 4% of flucytosine is protein bound.

About 90% of a dose is excreted unchanged by glomerular filtration; a small amount of flucytosine may be metabolised to fluorouracil. The small amount of an oral dose of flucytosine not absorbed from the gastrointestinal tract is eliminated unchanged in the faeces. The elimination half-life is 2.5 to 6 hours in patients with normal renal function but increases with decreasing renal function. Flucytosine is removed by haemodialysis or peritoneal dialysis.

References[1-3] to the pharmacokinetics of flucytosine. A study[3] reviewing flucytosine concentrations in serum, blood, or plasma from 233 patients, including 33 neonates, found that they were within the therapeutic range in only about 20% of cases; of the remainder, 40% were low (5% undetectable) and 40% were excessive (potentially toxic in about 10% of the samples). The results emphasised the importance of therapeutic drug monitoring.

1. Daneshmend TK, Warnock DW. Clinical pharmacokinetics of systemic antifungal agents. *Clin Pharmacokinet* 1983; **8**: 17–42.
2. Baley JE, *et al.* Pharmacokinetics, outcome of treatment, and toxic effects of amphotericin B and 5-fluorocytosine in neonates. *J Pediatr* 1990; **116**: 791–7.
3. Pasqualotto AC, *et al.* Flucytosine therapeutic monitoring: 15 years experience from the UK. *J Antimicrob Chemother* 2007; **59**: 791–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Ancotil†; *Austral.*: Ancotil; *Austria*: Ancotil; *Denm.*: Ancotil; *Fr.*: Ancotil; *Ger.*: Ancotil; *Gr.*: Ancotil; *Hong Kong*: Ancobon; Ancotil†; *Irl.*: Ancotil; *Ital.*: Ancotil; *Neth.*: Ancotil; *NZ*: Ancotil†; *Pol.*: Ancotil; *Rus.*: Ancotyl (Анкотил); *Singapore*: Ancotil†; *Swed.*: Ancotil; *Switz.*: Ancotil; *UK*: Ancotil; *USA*: Ancobon.

Pharmacopoeial Preparations
BP 2014: Flucytosine Tablets;
USP 36: Flucytosine Capsules; Flucytosine Oral Suspension.

Flutrimazole *(BAN, rINN)*

Flutrimatsoli; Flutrimazol; Flutrimazolas; Flutrimazolum; UR-4056; Флутримазол.
1-[o-Fluoro-α-(*p*-fluorophenyl)-α-phenylbenzyl]imidazole; (*RS*)-1-(2,4′-Difluorotrityl)imidazole.
$C_{22}H_{16}F_2N_2$=346.4.
CAS — 119006-77-8.
ATC — D01AC16; G01AF18.
ATC Vet — QD01AC16; QG01AF18.
UNII — 7765OUP252.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Flutrimazole). A white or almost white powder. Practically insoluble in water; soluble in methyl alcohol; freely soluble in tetrahydrofuran. Protect from light.

Profile

Flutrimazole is an imidazole antifungal used topically as a 1% cream, gel, powder, or solution in the treatment of superficial fungal infections.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3.

References.
1. Rigopoulos D, *et al.* Flutrimazole shampoo 1% versus ketoconazole shampoo 2% in the treatment of pityriasis versicolor. A randomised double-blind comparative trial. *Mycoses* 2007; **50**: 193–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Micetal; *Braz.*: Micetal; *Chile*: Micetal; *Cz.*: Micetal; *Gr.*: Topiderm; *Hung.*: Micetal; *Ital.*: Micetal; *Mex.*: Micetal; *Pol.*: Micetal; *Port.*: Flutrim†; *Spain*: Flusporan; Gine Micetal†; Micetal.

Fosfluconazole *(BAN, rINN)*

Fosfluconazol; Fosfluconazolum; UK-292663; Фосфлуконазол.
1-(2,4-Difluorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)-1-[(1*H*-1,2,4-triazol-1-yl)methyl]ethyl dihydrogen phosphate.
$C_{13}H_{13}F_2N_6O_4P$=386.3
CAS — 194798-83-9.
UNII — 3JU299EWH.

Profile

Fosfluconazole is a phosphate prodrug of fluconazole that is used for the treatment of systemic fungal infections, including oral candidiasis and recurrent cryptococcal meningitis in AIDS patients.

References.
1. Takahashi D, *et al.* Fosfluconazole for antifungal prophylaxis in very low birth weight infants. *Int J Pediatr* 2009; **2009**: 274768.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Prodif.

Griseofulvin *(BAN, rINN)*

Curling Factor; Griseofulviini; Griseofulvina; Griséofulvine; Griseofulvinum; Grizeofulvin; Grizeofulvinas; Gryzeofulwina; Гризеофульвин.
(2*S*,4′*R*)-7-Chloro-2′,4,6-trimethoxy-4′-methylspiro[benzofuran-2(3*H*),3′-cyclohexene]-3,6′-dione.
$C_{17}H_{17}ClO_6$=352.8
CAS — 126-07-8.
ATC — D01AA08; D01BA01.
ATC Vet — QD01AA08; QD01BA01.
UNII — 32HRV3E3D5.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Griseofulvin). An antifungal substance produced by the growth of certain strains of *Penicillium griseofulvum*, or by any other means. It is a white or yellowish-white powder. The particles of the powder are generally up to 5 micrometres in maximum dimension, though larger particles, which may occasionally exceed 30 micrometres, may be present. It contains 97 to 102% of $C_{17}H_{17}ClO_6$, calculated on the dried substance.

Practically insoluble in water; slightly soluble in dehydrated alcohol and in methyl alcohol; freely soluble in dimethylformamide and in tetrachloroethane.

USP 36: (Griseofulvin). A white to creamy-white, odourless powder, in which particles of the order of 4 micrometres in diameter predominate. It has a potency of not less than 900 micrograms of $C_{17}H_{17}ClO_6$ per mg. Very slightly soluble in water; sparingly soluble in alcohol; soluble in acetone, in chloroform, and in dimethylformamide. Store in airtight containers.

Uses and Administration

Griseofulvin is an antifungal used orally in the treatment of dermatophyte infections. It is generally given when such infections involve the scalp, hair, nails, and skin and do not respond to topical treatment (see Skin Infections, p. 568.1); infections of the soles of the feet, the palms of the hands, and the nails respond slowly.

The usual dose of griseofulvin has been 0.5 to 1 g daily in single or divided doses; these doses are for preparations of griseofulvin of reduced particle size, sometimes known as microcrystalline or microsize griseofulvin. Doses have been reduced by about one-quarter when preparations, available in some countries, containing ultramicrocrystalline or ultramicrosize griseofulvin are used. Griseofulvin should be given with or after meals.

For details of doses in children, see below.

The duration of treatment depends on the thickness of the keratin layer: 2 to 8 weeks for infections of the hair and skin, up to 6 months for infections of the fingernails, and 12 months or more for infections of the toenails.

Griseofulvin has also been used as a 1% topical spray in tinea pedis.

Reviews.
1. Fleece D, *et al.* Griseofulvin versus terbinafine in the treatment of tinea capitis: a meta-analysis of randomized, clinical trials. *Pediatrics* 2004; **114**: 1312–15.
2. Gupta AK, *et al.* Meta-analysis: griseofulvin efficacy in the treatment of tinea capitis. *J Drugs Dermatol* 2008; **7**: 369–72.

Administration in children. Griseofulvin may be given orally to children for the treatment of dermatophyte infections where topical therapy has failed or is inappropriate. For children from 1 month of age, 10 to 20 mg/kg daily (to a maximum of 1 g) of the microcrystalline preparation, given once daily or in divided doses, has been recommended by the *BNFC* and the American Academy of Pediatrics (AAP);[1] for ultramicrocrystalline preparations, the AAP recommends a dose of 5 to 15 mg/kg once daily (to a maximum of 750 mg). For tinea capitis caused by *Trichophyton tonsurans*, the *BNFC* suggests microcrystalline griseofulvin 15 to 20 mg/kg daily (to a maximum of 1 g) once daily or in divided doses.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases.* 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Non-infective skin disorders. Lichen planus is usually treated with corticosteroids or retinoids (see p. 1685.2) but griseofulvin has been suggested as an alternative to topical corticosteroids in erosive disease.[1] However, some researchers have found it to be of no value.[2]

Dramatic responses of pigmented purpuric dermatoses to griseofulvin 500 to 750 mg daily have been reported in 5 patients.[3]

1. Lamey P-J, Lewis MAO. Oral medicine in practice: white patches. *Br Dent J* 1990; **168**: 147–52.
2. Bagan JV, *et al.* Treatment of lichen planus with griseofulvin. *Oral Surg Oral Med Oral Pathol* 1985; **60**: 608–10.
3. Tamaki K, *et al.* Successful treatment of pigmented purpuric dermatosis with griseofulvin. *Br J Dermatol* 1995; **132**: 159–60.

Adverse Effects

Adverse effects are usually mild and transient and consist of headache, skin rashes and urticaria, dry mouth, an altered sensation of taste, and gastrointestinal disturbances. Angioedema, erythema multiforme, toxic epidermal necrolysis, proteinuria, leucopenia and other blood dyscrasias, oral candidiasis, peripheral neuropathy, photosensitisation, and severe headache have been reported occasionally. Depression, confusion, dizziness, impaired coordination, insomnia, and fatigue have also been reported. Griseofulvin may precipitate or aggravate SLE.

There have been a few reports of hepatotoxicity attributed to griseofulvin.

Effects on the skin. Fatal toxic epidermal necrolysis in a 19-year-old woman[1] was attributed to griseofulvin that she had taken for 6 days; she had also taken metronidazole for 1 day. There are also reports[2,3] of erythema multiforme in 4 patients occurring within 10 days of starting griseofulvin. The precipitation or aggravation of SLE is a known complication of griseofulvin. Most cases are said to be characterised by prominent skin manifestations and absence of renal disease although the nephrotic syndrome has been described[4] in a 16-year-old male after 2 single doses of griseofulvin taken 3 weeks apart.

1. Mion G, *et al.* Fatal toxic epidermal necrolysis after griseofulvin. *Lancet* 1989; **ii**: 1331.
2. Rustin MHA, *et al.* Erythema multiforme due to griseofulvin. *Br J Dermatol* 1989; **120**: 455–8.
3. Thami GP, *et al.* Erythema multiforme due to griseofulvin with positive re-exposure test. *Dermatology* 2001; **203**: 84–5.
4. Bonilla-Felix M, *et al.* Nephrotic syndrome related to systemic lupus erythematosus after griseofulvin therapy. *Pediatr Nephrol* 1995; **9**: 478–9.

Hypersensitivity. A serum sickness-like reaction has been reported in a 5-year-old child being treated for tinea capitis with griseofulvin.[1] About 3 weeks after starting treatment the child developed fever, rash on his legs and back, swelling of his toes and fingers, and leg pain. Symptoms resolved after griseofulvin was stopped.

1. Colton RL, *et al.* Serum sickness-like reaction associated with griseofulvin. *Ann Pharmacother* 2004; **38**: 609–11.

Precautions

Griseofulvin is contra-indicated in patients with severe liver disease or SLE.

Griseofulvin is embryotoxic and teratogenic in *rats* and there have been isolated cases of conjoined twins after its use during the first trimester of pregnancy. It is therefore

contra-indicated in pregnancy and women should not become pregnant during, or within 1 month of stopping therapy. Griseofulvin may reduce the efficacy of oral contraceptives and additional contraceptive precautions should be used during treatment. Data from *in-vitro* and *in-vivo* studies using mammalian cells, which showed aneuploidy, have led to the warning that men taking griseofulvin should not father children within 6 months of treatment.

Griseofulvin may impair the ability to drive or operate machinery, and has been reported to enhance the effects of alcohol.

Porphyria. Although griseofulvin has not been classified in the Drug Database for Acute Porphyria compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden,[1] both Porphyria South Africa[2] and the European Porphyria Network[3] classify griseofulvin as unsafe and it should be avoided in patients with porphyria.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 2/11/11)
2. Porphyria South Africa. Available at: http://web.uct.ac.za/depts/porphyria/ (accessed 2/11/11)
3. European Porphyria Network. Available at: http://www.porphyria-europe.com (accessed 2/11/11)

Interactions

Phenobarbital has been reported to decrease the gastrointestinal absorption of griseofulvin. Plasma concentrations of griseofulvin have also been reported to be reduced by drugs that induce metabolising enzymes.

Griseofulvin may increase the rate of metabolism and diminish the effects of some drugs such as coumarin anticoagulants and oral contraceptives.

Griseofulvin may enhance the effects of alcohol.

Alcohol. In addition to reports of griseofulvin enhancing the effects of alcohol, a severe disulfiram-like reaction to alcohol has been reported in a patient taking griseofulvin.[1]

1. Fett DL, Vukov LF. An unusual case of severe griseofulvin-alcohol interaction. *Ann Emerg Med* 1994; 24: 95–7.

Bromocriptine. For a report that griseofulvin can block the response to bromocriptine, see p. 899.1.

Salicylates. Griseofulvin has been reported to reduce plasma concentrations of salicylate in a patient taking aspirin, see p. 26.3.

Antimicrobial Action

Griseofulvin is a fungistatic antibiotic that inhibits fungal cell division by disruption of the mitotic spindle structure. It may also interfere with DNA production. It is active against the common dermatophytes, including some species of *Epidermophyton, Microsporum,* or *Trichophyton.*

Pharmacokinetics

Absorption of griseofulvin from the gastrointestinal tract is variable and incomplete, but is enhanced by reducing the particle size or when given with a fatty meal. Peak plasma concentrations occur within 4 hours and are maintained for 10 to 20 hours.

Griseofulvin is about 84% bound to plasma proteins. It is deposited in keratin precursor cells and is concentrated in the stratum corneum of the skin and in the nails and hair, thus preventing fungal invasion of newly formed cells. Concentrations of 12 to 25 micrograms/g are maintained in skin during long-term use, while plasma concentrations remain at about 1 to 2 micrograms/mL. Griseofulvin has an elimination half-life of 9 to 24 hours, and is metabolised by the liver mainly to 6-demethylgriseofulvin and its glucuronide conjugate which are excreted in the urine. A large amount of a dose of griseofulvin of reduced particle size appears unchanged in the faeces; less than 1% is excreted unchanged in the urine; some is excreted in the sweat.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Grisovin; *Austral.*: Grisovin; *Braz.*: Fulcin; Sporostatin; *Fr.*: Grisefuline; *Ger.*: Griseo; Likuden M†; *Gr.*: Grisenova; *Hong Kong*: CP-Griseo†; Grisuvin; *India*: Dermonorm; Fluvin; Fungal; Fungivin; Geovin; Griderm; Gris-OD; Grisactin; Grisomed; Grisonorm; Grisoral; Grisovin; Idifulvin; Microfulvin; Myconorm; Nufulvin; Walavin; *Indon.*: Fulcin; Fungistop; Griseofort; Grivin; Mycostop†; Rexavin; *Irl.*: Grisol; *Israel*: Grifulin†; *Ital.*: Fulcin; Grisovina FP; *Malaysia*: Grisuvin; Grivin; Krisovin; *Mex.*: Fulcin; Fulsivin†; Grisovin; *Philipp.*: Grisovin; *Port.*: Grisovin†; *S.Afr.*: Microcidal; *Singapore*: Hexene; Krisovin; SP-Grevin; *Spain*: Fulcin; *Thai.*: Aofen; Fulvin; Fungivin; Fusovin; Grifulvin; Griseo-Med; Grisflavin; Grisin; Grisovex; Grivin; KB Vinecin; Mycovin; Mycoxyl; Neofulvin; Trivanex; *Turk.*: Gefulvin; Grisovin; *UK*: Fulsovin†; Grisol; *USA*: Grifulvin V; Gris-PEG; *Venez.*: Grisovin.

Multi-ingredient Preparations. *Arg.*: Griseoplus.

Pharmacopoeial Preparations
BP 2014: Griseofulvin Tablets;
USP 36: Griseofulvin Capsules; Griseofulvin Oral Suspension; Griseofulvin Tablets; Ultramicrosize Griseofulvin Tablets.

Isoconazole *(BAN, USAN, rINN)*

Isoconazol; Isoconazolum; Isokonatsoli; Isokonazol; Izokonazol; Izokonazolas; Изоконазол.

1-[2,4-Dichloro-β-(2,6-dichlorobenzyloxy)phenethyl]imidazole.

$C_{18}H_{14}Cl_4N_2O$=416.1

CAS — 27523-40-6.

ATC — D01AC05; G01AF07.

ATC Vet — QD01AC05; QG01AF07.

UNII — GRI7WFR424.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Isoconazole). A white or almost white powder. Practically insoluble in water; freely soluble in alcohol; very soluble in methyl alcohol. Protect from light.

Isoconazole Nitrate *(BANM, rINNM)*

Isoconazol, nitrato de; Isoconazole, bitrate d'; Isoconazole, Nitrate d'; Isoconazoli Nitras; Isoconazolnitrat; Isokonatsolini-traatti; Isokonazolnitrat; Isokonazol-nitrát; Izokonazol Nitrat; Izokonazol-nitrát; Izokonazolo nitratas; Nitrato de isoconazol; R-15454; Изоконазола Нитрат.

$C_{18}H_{14}Cl_4N_2O,HNO_3$=479.1

CAS — 24168-96-5 (Isoconazole mononitrate); 40036-10-0 (isoconazole nitrate).

ATC — D01AC05; G01AF07.

ATC Vet — QD01AC05; QG01AF07.

UNII — 5AS8P3N30X.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Isoconazole Nitrate). A white or almost white powder. Very slightly soluble in water; slightly soluble in alcohol; soluble in methyl alcohol. Protect from light.

Uses and Administration

Isoconazole is an imidazole antifungal used locally as the nitrate in the treatment of vaginal mycoses, particularly due to *Candida* spp. (p. 564.1) and in fungal skin infections (p. 568.1). For vaginal infections it is usually given as pessaries in a single dose of 600 mg or 300 mg daily for 3 days, or as a 1% vaginal cream daily for 7 days. For skin infections a 1% or 2% cream or other topical formulation has been used.

Adverse Effects and Precautions

Local reactions including burning or itching may occur after application of isoconazole.

Intravaginal preparations of azole antifungals may damage latex contraceptives and additional contraceptive measures are therefore necessary during local application.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3.

Antimicrobial Action

Isoconazole is an imidazole antifungal active against a wide spectrum of fungi including *Candida* spp., dermatophytes, and *Malassezia furfur.* It is also active against some Gram-positive bacteria.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Isomicol; Mupaten; *Austria*: Gyno-Travogen; Travogen; *Belg.*: Travogen; *Braz.*: Gino-Isomax†; Ginotrax; Gyno-Icaden; Icaden; Isomax†; Micaden; Mycel Gyno†; Neo Isocaden; *Chile*: Ufarin; *Fr.*: Fazol G; Fazol; *Gr.*: Travogen; *Hong Kong*: Travogen; *Israel*: Isogen; *Ital.*: Abimono; Isogyn; Travogen; *Malaysia*: Travogen; *Mex.*: Icaden; Nocazin; *Philipp.*: Travogen; *Pol.*: Gyno-Travogen†; Travogen; *Port.*: Gino-Travogen; *Rus.*: Gyno-Travogen (Гино-травоген); Travogen (Травоген); *Singapore*: Gyno-Travogen; Travogen; *Switz.*: Gyno-Travogen; Travogen; *Thai.*: Travogen; *Turk.*: Gyno-Travogen; Travogen; *Ukr.*: Gyno-Travogen (Гино-Травоген); Travogen (Травоген); *Venez.*: Icaden; Noginox.

Multi-ingredient Preparations. *Arg.*: Scheriderm; *Austria*: Travocort; *Belg.*: Travocort; *Ger.*: Travocort; *Gr.*: Travocort; *Hong Kong*: Travocort; *Indon.*: Travocort; *Irl.*: Travocort; *Israel*: Isocort; Tevaderm; *Ital.*: Travocort; *Malaysia*: Isoradin; Travocort; *Mex.*: Scheriderm; *Philipp.*: Travocort; *Pol.*: Travocort; *Port.*: Travocort; *Rus.*: Travocort (Травокорт); *S.Afr.*: Maxaderm; Travocort; *Singapore*: Travocort; *Switz.*: Travocort; *Thai.*: Travocort; *Turk.*: Travazol; Travocort; *Ukr.*: Travocort (Травокорт).

Pharmacopoeial Preparations
BP 2014: Isoconazole Pessaries.

Itraconazole *(BAN, USAN, rINN)*

Itraconazol; Itraconazolum; Itrakonatsoli; Itrakonazol; Itrakonazolas; Oriconazole; R-51211; Итраконазол.

(±)-2-sec-Butyl-4-[4-(4-[4-[(2*R**,4*S**)-2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-ylmethoxy]phenyl]-piperazin-1-yl)phenyl]-2,4-dihydro-1,2,4-triazol-3-one.

$C_{35}H_{38}Cl_2N_8O_4$=705.6

CAS — 84625-61-6.

ATC — J02AC02.

ATC Vet — QJ02AC02.

UNII — 304NUG5GF4.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn,* and *US.*

Ph. Eur. 8: (Itraconazole). A white or almost white powder. Practically insoluble in water; very slightly soluble in alcohol; freely soluble in dichloromethane. Protect from light.

USP 36: (Itraconazole). A white or almost white powder. Practically insoluble in water; very slightly soluble in alcohol; freely soluble in dichloromethane; sparingly soluble in tetrahydrofuran. Store in airtight containers. Protect from light.

Uses and Administration

Itraconazole is a triazole antifungal given orally for the treatment of oropharyngeal and vulvovaginal candidiasis, for pityriasis versicolor, for dermatophytoses unresponsive to topical treatment, for onychomycosis, and for systemic infections including aspergillosis, blastomycosis, candidiasis, chromoblastomycosis, coccidioidomycosis, cryptococcosis, histoplasmosis, paracoccidioidomycosis, and sporotrichosis. It is also given for the prophylaxis of fungal infections in immunocompromised patients. The place of itraconazole in the treatment of fungal infections is discussed in the various sections under Choice of Antifungal, p. 563.1. Itraconazole has also been used in the management of some protozoal infections including acanthamoeba keratitis (p. 584.2), leishmaniasis (p. 584.2), and trypanosomiasis (p. 584.2).

Doses of itraconazole oral liquid and capsules are not equivalent and may not be used interchangeably.

In the UK, itraconazole *oral liquid* is licensed for use in *oral* and *oesophageal candidiasis* in a dose of 200 mg daily for 1 week; it may be taken as a single daily dose, or, preferably, in 2 divided doses, the liquid being retained in the mouth for 20 seconds before swallowing. If there is no response after a week, treatment may be continued for a further week. In the USA, a similar regimen is licensed for *oropharyngeal candidiasis,* but in oesophageal candidiasis an alternative regimen of 100 mg daily for at least 3 weeks is preferred, although the dose may be increased to 200 mg daily if necessary.

For patients with *fluconazole-resistant infections* the dose in the UK is 100 to 200 mg twice daily for 2 weeks; if there is no response, treatment may be given for a further 2 weeks. In the USA the recommended dose is 100 mg twice daily.

Itraconazole oral liquid is also licensed in the UK for prophylaxis of susceptible fungal *infections in immunocompromised patients,* in doses of 5 mg/kg daily, in 2 divided doses.

The following oral doses all apply to itraconazole *capsules.*

- the dose in *oropharyngeal candidiasis* is 100 mg (or 200 mg in patients with AIDS or neutropenia) daily for 15 days
- *vulvovaginal candidiasis* may be treated with itraconazole 200 mg twice daily for 1 day
- *pityriasis versicolor* may be treated with itraconazole 200 mg daily for 7 days
- for dermatophytoses the dose is 100 mg daily for 15 days or 200 mg daily for 7 days in *tinea corporis* or *tinea cruris;* doses are 100 mg daily for 30 days or 200 mg twice daily for 7 days in *tinea pedis* or *tinea manuum*
- for *nail infections* the dose is 200 mg daily for 3 months or pulse therapy with 200 mg twice daily for 7 days repeated once (for fingernails) or twice (for toenails) after drug-free intervals of 21 days
- For *systemic infections,* itraconazole capsules are given in usual doses of 100 to 200 mg once daily, increased to 200 mg twice daily for invasive or disseminated infections, including cryptococcal meningitis.

  In life-threatening infections a loading dose of 200 mg three times daily for 3 days has been given. A dose of 200 mg daily is used for primary or secondary prophylaxis in neutropenic patients or those with AIDS. Absorption may be impaired in these patients and monitoring of plasma concentrations is advised with an increase in dose to 200 mg twice daily if necessary. This

higher dose is recommended routinely by some authorities in the USA such as the CDC.

Itraconazole may also be given by **intravenous infusion** in a dose of 200 mg given twice daily over 1 hour for two days, then 200 mg daily thereafter.

It has been suggested that a daily dose of 200 mg should not be exceeded when itraconazole is to be **co-administered** with ritonavir-boosted HIV-protease inhibitors.

For details of doses in children, see below.

Reviews.

1. Haria M, *et al.* Itraconazole: a reappraisal of its pharmacological properties and therapeutic use in the management of superficial fungal infections. *Drugs* 1996; 51: 585–620.
2. Pierard GE, *et al.* Itraconazole. *Expert Opin Pharmacother* 2000; 1: 287–304.
3. Stevens DA (ed). Managing fungal infections in the 21st century: focus on itraconazole. *Drugs* 2001; 61 (suppl 1): 1–56.
4. Slain D, *et al.* Intravenous itraconazole. *Ann Pharmacother* 2001; 35: 720–9.
5. Boogaerts M, Maertens J. Clinical experience with itraconazole in systemic fungal infections. *Drugs* 2001; 61 (suppl 1): 39–47.
6. Maertens J, Boogaerts M. The place for itraconazole in treatment. *J Antimicrob Chemother* 2005; 56 (suppl 1): i33–i38.
7. Potter M. Strategies for managing systemic fungal infection and the place of itraconazole. *J Antimicrob Chemother* 2005; 56 (suppl 1): i49–i54.
8. Korting HC, Schöllmann C. The significance of itraconazole for treatment of fungal infections of skin, nails and mucous membranes. *J Dtsch Dermatol Ges* 2009; 7: 11–20.

Administration. *HIGH DOSES.* Doses of itraconazole 600 mg daily in two divided doses for 3 to 16 months were used in 8 patients with systemic mycoses resistant to conventional therapy.[1] Two patients with AIDS and cryptococcal meningitis failed to respond and 2 who responded initially later relapsed or developed progressive disease when the dose was reduced. The main adverse effects were hypokalaemia, hypertension, and oedema possibly associated with adrenal suppression.

In a patient with cerebral aspergillosis, itraconazole 800 mg daily for 5 months then 400 mg daily for a further 4½ months produced complete resolution of cerebral lesions.[2]

1. Sharkey PK, *et al.* High-dose itraconazole in the treatment of severe mycoses. *Antimicrob Agents Chemother* 1991; 35: 707–13.
2. Sánchez C, *et al.* Treatment of cerebral aspergillosis with itraconazole: do high doses improve the prognosis? *Clin Infect Dis* 1995; 21: 1485–7.

Administration in children. A review of the use of itraconazole in children[1] considered oral itraconazole to be safe and effective against most fungal organisms causing superficial infections.

Itraconazole was given to 2 premature infants with disseminated candidiasis in a dose of 10 mg/kg daily in two divided doses for 3 or 4 weeks without adverse effects.[2] Treatment was successful in both infants.

Although itraconazole oral liquid is not licensed for use in children in the UK, and the capsules are only licensed from 12 years of age, the *BNFC* suggests the following daily *oral* doses; unlike in adults (p. 583.3) it makes no distinction between doses of the oral liquid and the capsules. Doses are given as a single dose (unless otherwise specified):

for **oropharyngeal candidiasis**:
- 1 month to 12 years of age, 3 to 5 mg/kg (to a maximum of 100 mg) daily for 15 days; up to 200 mg daily may be given to patients with neutropenia or AIDS
- 12 to 18 years of age, 100 mg (200 mg in those with neutropenia or AIDS) daily for 15 days

for **dermatophyte infections**:
- 1 month to 12 years of age, 3 to 5 mg/kg daily; this is given to a maximum of 200 mg daily for 7 days (pityriasis versicolor), to a maximum of 100 mg daily for 15 days (tinea corporis and tinea cruris), to a maximum of 100 mg daily for 30 days (tinea pedis and tinea manuum), or to a maximum of 200 mg daily for 2 to 6 weeks (tinea capitis)
- 12 to 18 years of age, 200 mg daily for 7 days (pityriasis versicolor); 100 mg daily for 15 days or as in pityriasis (tinea corporis and tinea cruris); or 100 mg daily for 30 days or 200 mg *twice* daily for 7 days (tinea pedis and tinea manuum); or up to a maximum of 200 mg daily for 2 to 6 weeks (tinea capitis)

for **onychomycosis**, from 1 year of age:
- 1 to 12 years, courses of 5 mg/kg (to a maximum of 200 mg) daily for 7 days, repeated after intervals of 21 days to a total of 2 courses for infections of the fingernails and 3 courses for toenail infections
- 12 to 18 years, either 200 mg daily for 3 months, or courses of 200 mg *twice* daily for 7 days, repeated after intervals of 21 days to a total of 2 courses for infections of the fingernails and 3 courses for toenail infections

for **histoplasmosis** or for **systemic fungal infections** such as aspergillosis, candidiasis, and cryptococcosis (including cryptococcal meningitis) where other antifungal drugs are inappropriate or ineffective:
- from 1 month of age to 18 years, 5 mg/kg (to a maximum of 200 mg) once or twice daily; the *twice* daily dose should be used in invasive or disseminated disease or cryptococcal meningitis. For intravenous doses, see below

for **maintenance in AIDS patients** to prevent relapse of underlying fungal infection, or for **prophylaxis in neutropenia** when standard therapy is inappropriate:
- from 1 month of age to 18 years, 5 mg/kg (to a maximum of 200 mg) daily, increased to *twice* daily if plasma-itraconazole concentrations are low

for **prophylaxis in haematological malignancy or bone marrow transplantation** (in patients expected to become neutropenic), where standard therapy is inappropriate the *oral liquid* may be given as follows:
- from 1 month of age to 18 years, 2.5 mg/kg *twice* daily, starting before transplantation or chemotherapy and continued until the neutrophil count recovers

As for the oral liquid, the intravenous product is not licensed in children in the UK; the *BNFC* suggests the following *intravenous* doses by infusion in children with **systemic fungal infections**:
- from 1 month of age to 18 years, 2.5 mg/kg (to a maximum of 200 mg) every 12 hours for 2 days, then the same dose once daily for a maximum of 12 days. Doses should be given by diluting 250 mg as the intravenous concentrate in 50 mL of sodium chloride 0.9% and infusing over 60 minutes

1. Gupta AK, *et al.* Efficacy and safety of itraconazole use in children. *Dermatol Clin* 2003; 21: 521–35.
2. Bhandari V, Narang A. Oral itraconazole therapy for disseminated candidiasis in low birth weight infants. *J Pediatr* 1992; 120: 330.

Amoebic infections. Topical and oral itraconazole has been tried for *Acanthamoeba* keratitis (p. 919.3).

Leishmaniasis. When systemic therapy is required for the treatment of leishmaniasis (p. 922.1), pentavalent antimonials are generally most commonly used. The successful use of itraconazole has been reported in some patients[1-5] with **cutaneous** disease (p. 922.1) and a systematic review[6] reported that for *L. tropica* infections there was reasonable evidence that itraconazole (200 mg daily) for 6 weeks was more effective than placebo. Infections with *Leishmania aethiopica* may not respond.[7] In a study of patients in Kuwait with cutaneous leishmaniasis, combination therapy with oral itraconazole (100 mg twice daily) and topical imiquimod 5% cream (applied 3 times a week) was found to produce better cure rates than treatment with itraconazole alone.[8]

Although a pilot study[9] in patients with **mucocutaneous** leishmaniasis (p. 923.1) reported benefit with itraconazole this was not confirmed in another study[10] where the response was only transient in the majority of patients. Similarly, itraconazole with terbinafine has been found to be ineffective in post kala-azar dermal leishmaniasis.[11]

1. Albanese G, *et al.* Cutaneous leishmaniasis: treatment with itraconazole. *Arch Dermatol* 1989; 125: 1540–2.
2. Plaloux G, *et al.* Cutaneous leishmaniasis in an AIDS patient: cure with itraconazole. *J Infect Dis* 1990; 162: 1221–2.
3. Dogra J, Saxena VN. Itraconazole and leishmaniasis: a randomised double-blind trial in cutaneous disease. *Int J Parasitol* 1996; 26: 1413–15.
4. Consigli J, *et al.* Cutaneous leishmaniasis: successful treatment with itraconazole. *Int J Dermatol* 2006; 45: 46–9.
5. Baroni A, *et al.* Cutaneous leishmaniasis treated with itraconazole. *Dermatol Ther* 2009; 22 (suppl 1): S27–S29.
6. González U, *et al.* Interventions for Old World cutaneous leishmaniasis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 31/03/09).
7. Akuffo H, *et al.* The use of itraconazole in the treatment of leishmaniasis caused by Leishmania aethiopica. *Trans R Soc Trop Med Hyg* 1990; 84: 532–4.
8. Al-Mutairi N, *et al.* Treatment of Old World cutaneous leishmaniasis with dapsone, itraconazole, cryotherapy, and imiquimod, alone and in combination. *Int J Dermatol* 2009; 48: 862–9.
9. Amato VS, *et al.* Use of itraconazole in the treatment of mucocutaneous leishmaniasis: a pilot study. *Int J Infect Dis* 2000; 4: 153–7.
10. Calvopina M, *et al.* Itraconazole in the treatment of New World mucocutaneous leishmaniasis. *Int J Dermatol* 2004; 43: 659–63.
11. Khalil EAG, *et al.* Failure of a combination of two antifungal drugs, terbinafine plus itraconazole, in Sudanese post kala-azar dermal leishmaniasis. *Trans R Soc Trop Med Hyg* 1996; 90: 187–8.

Trypanosomiasis. Itraconazole, alone or with allopurinol, may produce beneficial responses in American trypanosomiasis (p. 925.3).

Adverse Effects

The most common adverse effects associated with itraconazole include dyspepsia, abdominal pain, nausea, vomiting, constipation, diarrhoea, headache, and dizziness. Others include allergic reactions such as pruritus, rash, urticaria, angioedema, and photosensitivity. Isolated cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, exfoliative dermatitis, and leucocytoclastic vasculitis have also been associated with itraconazole.

An increase in liver enzyme values has occurred in some patients and cases of hepatitis and cholestatic jaundice have been seen, especially in those treated for more than one month. There have been rare cases of liver failure and death.

Heart failure and pulmonary oedema have been reported rarely and serious cardiovascular events including arrhythmias and sudden death have been attributed to drug interactions in patients receiving itraconazole (see Interactions, p. 585.1). Blood disorders including leucopenia, neutropenia, and thrombocytopenia have also occurred.

Alopecia, oedema, and hypokalaemia have also been associated with prolonged use. Menstrual disorders and peripheral neuropathy, as well as visual disorders, tinnitus, and transient or permanent hearing loss, have been reported in a few patients.

Incidence of adverse effects. Itraconazole 50 to 400 mg daily for a median of 5 months was considered to be well tolerated in 189 patients with systemic fungal infections.[1] Of 86 patients with underlying disease, including 49 with AIDS, 16 with diabetes, and 23 with malignancy, nausea and vomiting occurred in 19 patients, hypertriglyceridaemia in 16, hypokalaemia in 11, and elevated liver enzyme values in 13. The role of itraconazole in hypertriglyceridaemia could not be assessed because all the samples were not drawn in the fasting state and hypertriglyceridaemia is a complication of HIV infection. Gynaecomastia occurred in 2 patients, 1 of whom also took spironolactone. Rash occurred in 4 patients.

Of 49 patients taking itraconazole 100 to 400 mg daily for up to 39 months, 23 had no adverse effects during treatment,[2] while 6 had nausea and vomiting, 5 developed oedema, and 2 developed hypertension; 3 of the patients who developed oedema and 1 who became hypertensive were diabetic. Three patients stopped itraconazole, 1 due to vomiting, 1 to leucopenia, and 1 to nephrotic syndrome. The patient with nephrotic syndrome had pre-existing oedema and hypertension; the syndrome cleared when itraconazole was stopped.

1. Tucker RM, *et al.* Adverse events associated with itraconazole in 189 patients on chronic therapy. *J Antimicrob Chemother* 1990; 26: 561–6.
2. Graybill JR, *et al.* Itraconazole treatment of coccidioidomycosis. *Am J Med* 1990; 89: 282–90.

Effects on the heart. Between September 1992, when itraconazole was approved in the USA, and April 2001, the FDA had received 58 reports of potential cases of heart failure associated with itraconazole.[1] There had been 28 patients admitted to hospital, and 13 had died. However, a causal relationship was difficult to prove. Overall, 43 patients had risk factors or diseases which might confound an association between the use of itraconazole and development of heart failure. Unpublished studies in *dogs* and humans had suggested a negative inotropic effect with intravenous itraconazole.

In August 2001, the UK CSM published a similar alert.[2] By this time, about 67 million patients worldwide had received itraconazole and there had been 75 spontaneously reported cases of suspected heart failure and an additional 63 reports of oedema suggestive of heart failure associated with oral formulations; there had been only 1 report of suspected heart failure in the UK. The CSM considered that the risk of heart failure with itraconazole was low, especially in young healthy patients receiving short courses of treatment (e.g. for vulvovaginal candidiasis). However, the risks appeared to be higher for older patients, patients with pre-existing heart disease or risk factors for heart failure, and for those receiving high doses and longer treatment courses (e.g. for onychomycosis).

The CSM[2] therefore advised caution when prescribing itraconazole to patients at risk of heart failure, whereas the FDA[1] contra-indicated it for the treatment of onychomycosis in patients with evidence of ventricular dysfunction.

1. Ahmad SR, *et al.* Congestive heart failure associated with itraconazole. *Lancet* 2001; 357: 1766–7.
2. CSM. Cardiodepressant effect of itraconazole (Sporanox). *Current Problems* 2001; 27: 11–12. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007456&RevisionSelectionMethod=LatestReleased (accessed 04/06/06)

Precautions

Itraconazole has caused abnormalities in fetal development in *rodents* and is therefore contra-indicated in pregnancy. For further information, see Pregnancy, under Precautions of Fluconazole, p. 579.3.

Itraconazole is not recommended in patients with raised liver enzyme values, active liver disease, or a history of drug-induced hepatotoxicity; liver function should be monitored in patients with pre-existing liver function abnormalities and testing should be considered for all patients using itraconazole. Treatment should be stopped if signs or symptoms of hepatitis occur.

Dose adjustments may also be required in some patients with renal impairment. Licensed product information warns that the use of intravenous preparations of itraconazole formulated with hydroxypropylbetadex is contra-indicated in patients with a creatinine clearance of less than 30 mL/minute.

Itraconazole should be stopped if neuropathy develops.

Itraconazole should not be used for the treatment of less severe fungal infections such as onychomycosis in patients with evidence of, or a history of, ventricular dysfunction such as heart failure.

Hypochlorhydria, which may be present in patients with AIDS, can reduce absorption of itraconazole. In this case absorption may be improved by giving itraconazole with an acidic drink, such as a cola beverage.

Breast feeding. Licensed product information does not recommend breast feeding while receiving itraconazole although only small amounts of itraconazole are distributed into breast milk.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies itraconazole as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 14/10/11)

Interactions

Enzyme-inducing drugs such as carbamazepine, isoniazid, nevirapine, phenobarbital, phenytoin, rifabutin, rifampicin, or St John's wort may *decrease* plasma concentrations of itraconazole sufficiently to reduce its efficacy. Conversely, enzyme inhibitors such as clarithromycin, erythromycin, HIV-protease inhibitors, including ritonavir-boosted HIV-protease inhibitors, may *increase* plasma concentrations of itraconazole. Use of drugs that reduce stomach acidity, such as antimuscarinics, antacids, proton pump inhibitors, and histamine H_2-receptor antagonists, may reduce the absorption of itraconazole.

Like other triazole antifungals, itraconazole is a potent inhibitor of the cytochrome P450 isoenzyme CYP3A4, and may increase plasma concentrations of other drugs reliant upon it for their metabolism. This increases the risk of adverse effects and such combinations should be given with caution and careful monitoring, if at all. Drugs so affected may include:

- *antiarrhythmics* such as disopyramide, dofetilide and quinidine
- *antidepressants* such as reboxetine
- *antiepileptics* such as carbamazepine (which in turn decreases the concentration of the antifungal, see above)
- *antihistamines* such as astemizole, mizolastine, and terfenadine
- *antimalarials* such as halofantrine
- *antimigraine drugs* such as dihydroergotamine, ergometrine, ergotamine, methylergometrine, and eletriptan
- the *antimycobacterial* rifabutin (which again also decreases antifungal concentrations)
- *antineoplastics* such as busulfan, docetaxel, trimetrexate, and the vinca alkaloids
- *antipsychotics* such as pimozide and sertindole
- *anxiolytics and sedatives* such as buspirone
- *benzodiazepines* such as alprazolam, brotizolam, diazepam, midazolam, and triazolam
- *calcium-channel blockers* such as bepridil, verapamil, and the dihydropyridines felodipine, nifedipine, and nisoldipine (see also below)
- some *corticosteroids* such as budesonide, dexamethasone, fluticasone and methylprednisolone
- the *coumarin anticoagulant* warfarin
- the *gastrointestinal prokinetic* cisapride
- *HIV-protease inhibitors* such as indinavir, ritonavir, and saquinavir (concentrations of the antifungal may be increased in turn by indinavir, ritonavir, or co-formulated lopinavir-ritonavir, but not by saquinavir)
- *immunosuppressants* such as ciclosporin, sirolimus, and tacrolimus
- *opioids* such as alfentanil, fentanyl, and levacetylmethadol
- some *oral hypoglycaemics* such as repaglinide
- the *phosphodiesterase type-5 inhibitors* sildenafil and vardenafil and the *phosphodiesterase type-3 inhibitor* cilostazol
- *statins* (HMG Co-A reductase inhibitors) such as atorvastatin, lovastatin, and simvastatin
- *vasopressin receptor antagonists* such as conivaptan and tolvaptan

Itraconazole is also an inhibitor of p-glycoprotein, and may increase plasma concentrations of substrates such as digoxin.

Where drugs metabolised via CYP3A4 also prolong the QT interval, the risk of serious cardiovascular effects such as torsade de pointes means that the combination should be avoided; this includes astemizole, bepridil, cisapride, dofetilide, levacetylmethadol, mizolastine, pimozide, quinidine, sertindole, and terfenadine. Other drugs that should not be used with itraconazole due to the risk of unacceptable toxicity include eletriptan, the ergotamine derivatives, and the benzodiazepines midazolam and triazolam; additionally, UK licensed product information advises that halofantrine and disopyramide be avoided when oral pulse regimens of itraconazole are used. Care is also required with calcium-channel blockers, which may increase the risk of congestive heart failure if given together, and nisoldipine in particular is considered contra-indicated. Use with the statins is also best avoided because of the risk of muscle damage.

Reviews of drug interactions with azole antifungals.

1. Baciewicz AM, Baciewicz FA. Ketoconazole and fluconazole drug interactions. *Arch Intern Med* 1993; 153: 1970–6.
2. Lomaestro BM, Piatek MA. Update on drug interactions with azole antifungal agents. *Ann Pharmacother* 1998; 32: 915–28.
3. Venkatakrishnan K, *et al.* Effects of the antifungal agents on oxidative drug metabolism: clinical relevance. *Clin Pharmacokinet* 2000; 38: 111–80.

Immunosuppressants. Fatal hepatitis occurred in a 68-year-old woman[1] after 2 months of use of itraconazole and *leflunomide*. The authors suggested that the combined hepatotoxicity of both drugs might have accounted for this.

1. Legras A, *et al.* Fatal hepatitis with leflunomide and itraconazole. *Am J Med* 2002; 113: 352–3.

Metal ions. Didanosine in a formulation containing aluminium and magnesium ion buffering agents could reduce the absorption of itraconazole due to the resultant increase in gastric pH.[1]

1. Moreno P, *et al.* Itraconazole-didanosine excipient interaction. *JAMA* 1993; 269: 1508.

Antimicrobial Action

Itraconazole is a triazole antifungal drug that in sensitive fungi inhibits cytochrome P450-dependent enzymes resulting in impairment of ergosterol synthesis in fungal cell membranes. It has a slightly wider spectrum of activity than ketoconazole. It is active against *Aspergillus* spp., *Blastomyces dermatitidis*, *Candida* spp., *Coccidioides immitis*, *Cryptococcus neoformans*, *Epidermophyton* spp., *Histoplasma capsulatum*, *Malassezia furfur*, *Microsporum* spp., *Paracoccidioides brasiliensis*, *Sporothrix schenckii*, and *Trichophyton* spp. Itraconazole also has some antiprotozoal activity against *Leishmania* spp.

Acquired resistance to itraconazole is rare but ketoconazole-resistant strains of *Candida albicans* have been found to be cross resistant to itraconazole.

Microbiological interactions. Synergistic antifungal effects were seen *in vitro* with terbinafine and itraconazole against strains of *Candida albicans*[1] and *Scedosporium prolificans*.[2] For effects on the antifungal activity of azoles when given with amphotericin B, see p. 572.3.

1. Barchiesi F, *et al.* In vitro activities of terbinafine in combination with fluconazole and itraconazole against isolates of Candida albicans with reduced susceptibility to azoles. *Antimicrob Agents Chemother* 1997; 41: 1812–14.
2. Meletiadis J, *et al.* In vitro interaction of terbinafine with itraconazole against clinical isolates of Scedosporium prolificans. *Antimicrob Agents Chemother* 2000; 44: 470–2.

Resistance. For a discussion of increasing resistance of *Candida* spp. to azoles, see under Antimicrobial Action of Fluconazole, p. 580.2. Decreased susceptibility to itraconazole and cross-resistance to fluconazole has been reported in *C. albicans* isolated from patients with AIDS given long-term prophylaxis with itraconazole.[1] *Aspergillus fumigatus* resistant to itraconazole has also been seen.[2,3]

1. Goldman M, *et al.* Does long-term itraconazole prophylaxis result in in vitro azole resistance in mucosal Candida albicans isolates from persons with advanced human immunodeficiency virus infection? *Antimicrob Agents Chemother* 2000; 44: 1585–7.
2. Denning DW, *et al.* Itraconazole resistance in Aspergillus fumigatus. *Antimicrob Agents Chemother* 1997; 41: 1364–8.
3. Dannaoui E, *et al.* Acquired itraconazole resistance in Aspergillus fumigatus. *J Antimicrob Chemother* 2001; 47: 333–340.

Pharmacokinetics

Itraconazole is absorbed from the gastrointestinal tract when given orally either as capsules containing itraconazole coated onto sugar spheres or as an oral liquid formulated with hydroxypropylbetadex. Absorption from the capsule formulation is enhanced by an acidic gastric environment and is greatest when doses are taken with food; absorption from the oral liquid is not dependent on an acid environment, and absorption is greatest in the fasting state. Peak plasma concentrations occur between 1.5 and 5 hours after a dose of either formulation, and steady state is reached within 15 days during daily dosing. Peak plasma concentrations at steady state of about 2 micrograms/mL have been reported after daily doses of 200 mg.

Bioavailability increases with doses of 100 to 400 mg in such a manner as to suggest that itraconazole undergoes saturable metabolism. Itraconazole is highly protein bound; only 0.2% circulates as free drug. Itraconazole is widely distributed but only small amounts diffuse into the CSF. Concentrations attained in the skin, sebum, pus, and many organs and tissues are several times higher than simultaneous plasma concentrations. Therapeutic concentrations of itraconazole remain in the skin and mucous membranes for 1 to 4 weeks after the drug is stopped. Small amounts are distributed into breast milk.

Itraconazole is metabolised in the liver mainly by cytochrome P450 isoenzyme CYP3A4. The major metabolite, hydroxyitraconazole, has antifungal activity comparable with that of itraconazole. Itraconazole is also excreted as inactive metabolites in the bile or urine; 3 to 18% is excreted in the faeces as unchanged drug. Small amounts are eliminated in the stratum corneum and hair. Itraconazole is not removed by dialysis.

The elimination half-life after a single 100-mg dose has been reported as 20 hours, increasing to 30 to 40 hours with continued use.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Itrac; Micotenk; Nitridazol; Panastat; Salimidin; Sporanox; ***Austral.***: Sporanox; ***Austria***: Itrabene; Sporanox; ***Belg.***: Sporanox; ***Braz.***: Estiranox; Fungonax; Itraconol†; Itracotan; Itrahexal; Itralex; Itraspor; Itrazol; Neo Itrax; Sporanox; Spozol; Traconal; Tracozon†; Tratzol; Traxonol; ***Canad.***: Sporanox; ***Chile***: Itodal; Sporanox; Teramic; ***China***: Mei Fu (美扶); Sporanox (斯皮仁诺); Yi Qi Kang (易启康); Cz.: Cladostad; Prokanazol; Sporanox; ***Denm.***: Itrastad; Niddazol; Sporanox; ***Fin.***: Sporanox; ***Fr.***: Sporanox; ***Ger.***: Itracol†; Itraconbeta; Itraderm; Sempera; Siros; ***Gr.***: Assosept-S; Bevonazole; Brovicton; Deratil; Etrel; Fansidol; Flunol; Fungonazol; Fungospor; Idranox; Inrozol; Isoflon; Itrabest; Itracon; Itraconal; Itralfa; Itraproton; Itraspor; Itraviron; Itrazol; Laverio; Lorenzol; Mesmor; Micronazol; Mycodrox; Neo-Candimyk; Prominox; Soprazon; Sporanox; Sporizole; Stas; Sterginox; Zetilox; ***Hong Kong***: Aranox; Inox; Itracon; Itranstad; Quali-itrazole; Sporacid†; Sporanox; ***Hung.***: Cladostad; Itraconep; Itragen; Omicral; Orungal; ***India***: Biospore; Candistat; Canditral; Fulcover; Fungicap; Itaspor; Itra; Itracan; Itrazen; Itrole; ***Indon.***: Forcanox; Fungitrazol; Furolnok†; Itzol; Mycotrazol; Nufatrac; Petrazole; Sporacid; Sporanox; Sporax; Spyrocon; Trachon; Tracor; Unitrac; Zitrazol†; ***Irl.***: Sporanox; ***Israel***: Itranol; Sporanox; ***Ital.***: Sporanox; Tranizolo; Trazer; Triasporin; ***Jpn***: Itrizole; ***Malaysia***: Canditral; Inox; Itracon; Sporanox; Unitrac; ***Mex.***: Carexan†; Conamed; Congox; Derusil; Ergospharma†; Fitocyd; Fuzoltec; Imazol†; Iqcona; Isóporum; Isox; Itracosid; Itranax; Lozartil; Rixtal; Seritral; Silicsan; Sinozol; Solmavin; Sporanox; Steitraz; Trax; Z-Fin; Zitriasol; Zolken; Zotril; ***Neth.***: Trisporal; ***Norw.***: Sporanox; ***NZ***: Itcozol; Itrazole; Sporanox; ***Philipp.***: Inox; Sporanox; ***Pol.***: ItraGen; ItraMerck; Orungal; Trioxal; ***Port.***: Fungizol; Itracic; Sporanox; Unisens; ***Rus.***: Canditral (Кандитрал); Irunine (Ируния); Itramicol (Итрамикол); Itrazol (Итразол); Miconihol (Микониxол); Orungal (Оруngал); Orungamin (Оруngамин); Orunit (Орунит); Rumycoz (Румикоз); Teknazol (Текназол); ***S.Afr.***: Adco-Sporozole; Sporanox; Trisporal; ***Singapore***: Canditral; Hitrazole; Sporanox; Unitrac; ***Spain***: Canadiol; Hongoseril; Oromic†; Sporanox; ***Swed.***: Sporanox; ***Switz.***: Gosegyne G; Itraderm; Sporanox; ***Thai.***: Canditral†; Icona†; Itra; Itracon; Itrasix; Itrazole; Norspor; Spazol; Sporal; Sporlab†; Spornar; ***Turk.***: Funit; Itraspor; Sporanox; Sporex; ***UK***: Sporanox; ***Ukr.***: Funit (Фунит); Itracon (Итракон); Itral (Итрал); Orunzol (Орунзол)†; Sporagal (Споргал); Trioxal (Триоксал)†; ***USA***: Onmel; Sporanox; ***Venez.***: Fungosin; Sporanox.

Multi-ingredient Preparations. ***Mex.***: Gitrasek; Sepia; Sporasec; ***Venez.***: Sporasec.

Ketoconazole *(BAN, USAN, rINN)*

Ketoconazol; Kétoconazole; Ketoconazolum; Ketokonatsoli; Ketokonazol; Ketokonazolas; R-41400; Кетоконазол.

(±)-*cis*-1-Acetyl-4-[4-[2-(2,4-dichlorophenyl)-2-imidazol-1-ylmethyl-1,3-dioxolan-4-ylmethoxy]phenyl]piperazine.

$C_{26}H_{28}Cl_2N_4O_4$=531.4

CAS — 65277-42-1.

ATC — D01AC08; G01AF11; J02AB02.

ATC Vet — QD01AC08; QG01AF11; QJ02AB02.

UNII — R9400W927I.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US*.

Ph. Eur. 8: (Ketoconazole). A white or almost white powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane; soluble in methyl alcohol. Protect from light.

Uses and Administration

Ketoconazole is an imidazole antifungal used topically or orally. However, the risk of liver damage and adrenal gland problems (see Effects on the Liver p. 587.1 and Effects on Endocrine Function, p. 586.3, respectively) with *oral* use is considered by some licensing authorities to outweigh any benefits: the EMEA states that oral ketoconazole should not be used to treat fungal infections, while the FDA states it should not be given as first-line treatment but may be considered for the treatment of life-threatening infections when other effective antifungal drugs are not available or tolerated. It has been given for the prophylaxis of fungal infections in immunocompromised patients, although

fluconazole or itraconazole are usually preferred. It has been recommended that, because of its erratic absorption and slow therapeutic response, ketoconazole should not be used for the treatment of life-threatening fungal infections, including fungal meningitis, or for severe infections in immunocompromised patients.

The place of ketoconazole in the treatment of fungal infections is discussed in the various sections under Choice of Antifungal, p. 563.1. Ketoconazole has also been used in the treatment of some protozoal infections, including acanthamoeba infections and leishmaniasis. It has also been used in the management of acute respiratory distress syndrome, hypercalcaemia, and certain endocrine disorders and malignancies. For further information see below.

The usual oral dose for treatment and prophylaxis of fungal infections is 200 mg once daily taken with food. This may be increased to 400 mg daily if an adequate response is not obtained; in some infections even higher doses have been used. Treatment should usually be continued until symptoms have cleared and cultures have become negative. Some infections may require several months of treatment and giving ketoconazole for such prolonged periods may increase the risk of hepatotoxicity.

It has been suggested that daily doses of 200 mg should not be exceeded when ketoconazole is given with ritonavir-boosted HIV-protease inhibitors.

For details of doses in children, see below.

Ketoconazole is applied topically as a 2% cream in the treatment of candidal or dermatophyte infections of the skin, or in the treatment of pityriasis versicolor. It is used once or twice daily and continued for at least a few days after the disappearance of symptoms. A foam containing 2% ketoconazole applied twice daily for 4 weeks may be used in the treatment of seborrhoeic dermatitis. A shampoo containing 1 or 2% ketoconazole is also used; it is applied twice weekly for 2 to 4 weeks (or occasionally longer) in the treatment of dandruff or seborrhoeic dermatitis. The 2% shampoo is used once daily for up to 5 days in pityriasis versicolor. For prophylaxis of seborrhoeic dermatitis the 2% shampoo is used once every 1 to 2 weeks; for prophylaxis of pityriasis versicolor it may be used once daily for a maximum of 3 days before exposure to sunshine.

Administration in children. In infants and children, ketoconazole may be used topically for the treatment of fungal skin infections similarly to in adults. Oral use should be restricted to situations where other antifungals cannot be used due to resistance or intolerance.

In the UK, an oral dose of 100 mg once daily is recommended for children weighing from 15 to 30 kg; children weighing more than 30 kg may be dosed as for adults (see p. 585.3). Alternatively, in the USA, the American Academy of Pediatrics[1] has recommended an oral dose of 3.3 to 6.6 mg/kg once daily for children from 2 years of age.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Acanthamoeba infections. Although there is currently no established treatment for granulomatous amoebic encephalitis, ketoconazole may have some activity against the *Acanthamoeba* spp. responsible for this infection and has been applied topically to skin lesions. Ketoconazole has also been suggested for *Acanthamoeba* keratitis (p. 919.3), when it has been given orally with topical miconazole.

Acute respiratory distress syndrome. In two small double-blind, controlled studies,[1,2] the development of acute respiratory distress syndrome (ARDS—p. 1599.3) and mortality rates were lower in high-risk patients given ketoconazole than in those given placebo. An accompanying editorial[3] commented that adequate blood concentrations appeared to be essential. The mode of action could be associated with inhibition of leukotriene and thromboxane synthesis.[2,3] Nevertheless, in a study in 234 patients,[4] ketoconazole failed to reduce mortality or improve clinical outcomes when given early in the course of ARDS. Some centres have developed guidelines for ketoconazole prophylaxis in patients at risk of ARDS.[5]

1. Slotman GJ, *et al.* Ketoconazole prevents acute respiratory failure in critically ill surgical patients. *J Trauma* 1988; **28**: 648–54.
2. Yu M, Tomasa G. A double-blind, prospective, randomized trial of ketoconazole, a thromboxane synthetase inhibitor, in the prophylaxis of the adult respiratory distress syndrome. *Crit Care Med* 1993; **21**: 1635–42.
3. Slotman GJ. Ketoconazole: maybe it isn't the magic potion, but... *Crit Care Med* 1993; **21**: 1642–4.
4. The ARDS Network Authors. Ketoconazole for early treatment of acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2000; **283**: 1995–2002.
5. Sinuff T, *et al.* Development, implementation, and evaluation of a ketoconazole practice guideline for ARDS prophylaxis. *J Crit Care* 1999; **14**: 1–6.

Blastomycosis. Ketoconazole has largely been replaced by itraconazole as the azole of choice in the treatment of blastomycosis (p. 564.1) because of its higher incidence of adverse effects, and lower efficacy. If used as an alternative it is given in doses of 400 to 800 mg daily.[1]

1. Chapman SW, *et al.* Clinical practice guidelines for the management of blastomycosis: 2008 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2008; **46**: 1801–12. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/588300 (accessed 03/07/08)

Endocrine disorders and malignant neoplasms. Ketoconazole has been reported to impair steroid hormone synthesis[1] and to blunt the response of cortisone to adrenocorticotrophic hormone (ACTH)[2] and has been tried in the management of some endocrine disorders.

In **Cushing's syndrome** (p. 2559.1), ketoconazole in doses of up to 1200 mg daily has been used successfully as an alternative or adjuvant to definitive therapies such as surgery or radiotherapy.[3-6]

Treatment of **hirsutism** is usually with an anti-androgen (see under Cyproterone, p. 2262.1), but ketoconazole has been tried in small numbers of women at a dose of 300 mg daily[7] or 400 mg daily,[8,9] with variable results.

Ketoconazole has been reported to produce a beneficial response in some forms of **precocious puberty** (p. 2254.1) that do not generally respond to gonadorelin analogues; cessation of menstruation and regression of pubertal signs in girls[10] and reduced testosterone secretion and increase in adult height in boys[11-13] has been noted in small numbers of patients studied.

The anti-androgenic effects of ketoconazole have also been found useful in the management of **prostatic cancer** (p. 712.3) in selected patients,[14-16] although there have been some concerns about its tolerability,[17] and it is not generally used as a first-line treatment.

Ketoconazole was ineffective in suppressing **postoperative erection** in patients undergoing penile reconstructive surgery;[19] it has been tried with prednisone for the management of recurrent ischaemic **priapism**.[20]

1. Pont A, *et al.* Ketoconazole blocks adrenal steroid synthesis. *Ann Intern Med* 1982; **97**: 370–2.
2. White MC, Kendall-Taylor P. Adrenal hypofunction in patients taking ketoconazole. *Lancet* 1985; **i**: 44–5.
3. Winquist EW, *et al.* Ketoconazole in the management of paraneoplastic Cushing's syndrome secondary to ectopic adrenocorticotropin production. *J Clin Oncol* 1995; **13**: 157–64.
4. Estrada J, *et al.* The long-term outcome of pituitary irradiation after unsuccessful transsphenoidal surgery in Cushing's disease. *N Engl J Med* 1997; **336**: 172–7.
5. Berwaerts JJ, *et al.* Corticotropin-dependent Cushing's syndrome in older people: presentation of five cases and therapeutical use of ketoconazole. *J Am Geriatr Soc* 1998; **46**: 880–4.
6. Chou SC, Lin JD. Long-term effects of ketoconazole in the treatment of residual or recurrent Cushing's disease. *Endocr J* 2000; **47**: 401–6.
7. Venturoli S, *et al.* A prospective randomized trial comparing low dose flutamide, finasteride, ketoconazole, and cyproterone acetate-estrogen regimens in the treatment of hirsutism. *J Clin Endocrinol Metab* 1999; **84**: 1304–10.
8. Sonino N, *et al.* Low-dose ketoconazole treatment in hirsute women. *J Endocrinol Invest* 1990; **13**: 35–40.
9. Venturoli S, *et al.* Ketoconazole therapy for women with acne and/or hirsutism. *J Clin Endocrinol Metab* 1990; **71**: 335–9.
10. Syed FA, Chalew SA. Ketoconazole treatment of gonadotropin independent precocious puberty in girls with McCune-Albright syndrome: a preliminary report. *J Pediatr Endocrinol Metab* 1999; **12**: 81–3.
11. Bertelloni S, *et al.* Long-term outcome of male-limited gonadotropin-independent precocious puberty. *Horm Res* 1997; **48**: 235–9.
12. Soriano-Guillén L, *et al.* Adult height after ketoconazole treatment in patients with familial male-limited precocious puberty. *J Clin Endocrinol Metab* 2005; **90**: 147–51.
13. Almeida MQ, *et al.* Long-term treatment of familial male-limited precocious puberty (testotoxicosis) with cyproterone acetate or ketoconazole. *Clin Endocrinol (Oxf)* 2008; **69**: 93–98.
14. Lowe FC, Bamberger MH. Indications for use of ketoconazole in management of metastatic prostate cancer. *Urology* 1990; **36**: 541–5.
15. Mahler C, *et al.* Ketoconazole and liarozole in the treatment of advanced prostatic cancer. *Cancer* 1993; **71**: 1068–73.
16. Small EJ, *et al.* Ketoconazole retains activity in advanced prostate cancer patients with progression despite flutamide withdrawal. *J Urol (Baltimore)* 1997; **157**: 1204–7.
17. Bok RA, Small EJ. The treatment of advanced prostate cancer with ketoconazole: safety issues. *Drug Safety* 1999; **20**: 451–8.
18. Pettaway CA, *et al.* Neoadjuvant chemotherapy and hormonal therapy followed by radical prostatectomy: feasibility and preliminary results. *J Clin Oncol* 2000; **18**: 1050–7.
19. DeCastro BJ, *et al.* Oral ketoconazole for prevention of postoperative penile erection: a placebo controlled, randomized, double-blind trial. *J Urol (Baltimore)* 2008; **179**: 1930–2.
20. Abern MR, Levine LA. Ketoconazole and prednisone to prevent recurrent ischemic priapism. *J Urol (Baltimore)* 2009; **182**: 1401–6.

Hypercalcaemia. Ketoconazole has been used[1-3] in the treatment of hypercalcaemia (p. 1778.1). It acts to reduce 1,25-dihydroxycholecalciferol concentrations by inhibiting cytochrome P450-dependent 1α-hydroxylation of vitamin D. For the treatment of infantile hypercalcaemia initial doses have ranged from 3 to 9 mg/kg daily, depending on the severity of the disease; the dose has then been progressively decreased, and finally stopped when the urinary calcium/creatinine ratio decreased below the upper limits of normal.[3]

1. Yavuz H. Familiar drugs for the treatment of hypercalcemia. *J Pediatr* 1998; **133**: 311.
2. Young C, *et al.* Hypercalcaemia in sarcoidosis. *Lancet* 1999; **353**: 374.
3. Nguyen M, *et al.* Infantile hypercalcemia and hypercalciuria: new insights into a vitamin D-dependent mechanism and response to ketoconazole treatment. *J Pediatr* 2010; **157**: 296–302.

Leishmaniasis. Ketoconazole has been tried as an alternative to conventional first- and second-line therapy for **visceral** leishmaniasis (p. 923.1),[1,2] although reports of treatment have not all been favourable.[3,4]

It has also been tried in **cutaneous** leishmaniasis (p. 922.1). A cure rate of 70% was reported in over 100 patients with *Leishmania major* infections treated with oral ketoconazole 200 to 400 mg daily for 4 to 6 weeks. Ketoconazole was not considered to be effective in infections due to *L. tropica*, *L. aethiopica*,[5] or *L. guyanensis*.[6] Ketoconazole 600 mg daily for 28 days has produced similar results to sodium stibogluconate intramuscularly for 20 days in patients with cutaneous leishmaniasis due to *L. panamensis*.[7] A further comparative study[8] of 96 patients being treated for cutaneous leishmaniasis, caused mainly by *L. major* or *L. tropica*, found ketoconazole given in doses of 600 mg in adults or 10 mg/kg in children for 30 days to be more effective than 6 to 8 bi-weekly intralesional injections of meglumine antimonate. In another study,[9] ketoconazole was less effective than sodium stibogluconate when cutaneous leishmaniasis was due to *L. braziliensis*, but more effective when *L. mexicana* was the cause.

1. Wali JP, *et al.* Ketoconazole in treatment of visceral leishmaniasis. *Lancet* 1990; **336**: 810–11.
2. Wali JP, *et al.* Ketoconazole in the treatment of antimony- and pentamidine-resistant Kala-azar. *J Infect Dis* 1992; **166**: 215–16.
3. Sundar S, *et al.* Ketoconazole in visceral leishmaniasis. *Lancet* 1990; **336**: 1582–3.
4. Rashid JR, *et al.* The efficacy and safety of ketoconazole in visceral leishmaniasis. *East Afr Med J* 1994; **71**: 392–5.
5. Weinrauch L, *et al.* Ketoconazole in cutaneous leishmaniasis. *Br J Dermatol* 1987; **117**: 666–7.
6. Dedet J-P, *et al.* Failure to cure Leishmania braziliensis guyanensis cutaneous leishmaniasis with oral ketoconazole. *Trans R Soc Trop Med Hyg* 1986; **80**: 176.
7. Saenz RE, *et al.* Efficacy of ketoconazole against Leishmania braziliensis panamensis cutaneous leisbmaniasis. *Am J Med* 1990; **89**: 147–55.
8. Salmanpour R, *et al.* Comparative study of the efficacy of oral ketoconazole with intra-lesional meglumine antimoniate (Glucantime) for the treatment of cutaneous leishmaniasis. *J Dermatol Treat* 2001; **12**: 159–62.
9. Navin TR, *et al.* Placebo-controlled clinical trial of sodium stibogluconate (Pentostam) versus ketoconazole for treating cutaneous leishmaniasis in Guatemala. *J Infect Dis* 1992; **165**: 528–34.

Adverse Effects

Gastrointestinal disturbances are the most frequently reported adverse effect after the oral use of ketoconazole. Nausea and vomiting have been reported in about 3% of patients, and abdominal pain in about 1%. These adverse effects are dose-related and may be minimised by giving ketoconazole with food. Asymptomatic, transient elevations in serum concentrations of liver enzymes may occur in about 10% of patients. Hepatitis has been reported and the risk appears to increase if treatment with ketoconazole is continued for longer than 2 weeks; it is usually reversible on stopping ketoconazole but fatalities have occurred. Ketoconazole interferes with steroid biosynthesis and adverse endocrine effects include gynaecomastia, oligospermia, menstrual irregularities, and adrenal cortex suppression, especially at high doses.

Other adverse effects include allergic reactions such as urticaria and angioedema, and rare cases of anaphylaxis after the first dose have been reported. Pruritus, rash, alopecia, headache, dizziness, impotence, and somnolence may also occur. Thrombocytopenia, paraesthesia, raised intracranial pressure, photophobia, and photosensitivity have been reported rarely.

After topical use of ketoconazole, irritation, dermatitis, or a burning sensation has occurred.

Effects on the blood. A case of fatal aplastic anaemia was reported[1] in a 23-year-old woman who had taken oral ketoconazole for 4 days for the treatment of vaginal discharge.

1. Duman D, *et al.* Fatal aplastic anemia during treatment with ketoconazole. *Am J Med* 2001; **111**: 737.

Effects on endocrine function. Oral ketoconazole blocks testosterone synthesis and adrenal response to corticotropin, resulting in azospermia and oligospermia, gynaecomastia, impotence and decreased libido, and adrenal insufficiency.[1-3] As an inhibitor of steroid production, ketoconazole is valuable in controlling hypercortisolism and is used therapeutically in some endocrine disorders and prostatic cancer. For further discussion see under Uses and Administration, above.

1. DePellce R, *et al.* Gynecomastia with ketoconazole. *Antimicrob Agents Chemother* 1981; **19**: 1073–4.
2. Pont A, *et al.* High-dose ketoconazole therapy and adrenal and testicular function in humans. *Arch Intern Med* 1984; **144**: 2150–3.
3. White MC, Kendall-Taylor P. Adrenal hypofunction in patients taking ketoconazole. *Lancet* 1985; **i**: 44–5.
4. Dandona P, *et al.* Non-suppression of cortisol secretion by long term treatment with ketoconazole in patients with acute leukaemia. *J Clin Pathol* 1985; **38**: 677–8.

5. Pillans PI, *et al.* Hyponatraemia and confusion in a patient taking ketoconazole. *Lancet* 1985; I: 821–2.
6. McCance DR, *et al.* Acute hypoadrenalism and hepatotoxicity after treatment with ketoconazole. *Lancet* 1987; I: 573.
7. Best TR, *et al.* Persistent adrenal insufficiency secondary to low-dose ketoconazole therapy. *Am J Med* 1987; 82: 676–80.
8. Khosla S, *et al.* Adrenal crisis in the setting of high-dose ketoconazole therapy. *Arch Intern Med* 1989; 149: 802–4.

Effects on the liver. Hepatic adverse reactions to oral ketoconazole are well known.[1-4] Transient minor elevations of liver enzymes without clinical signs or symptoms of hepatic disease occur in about 10% of patients and may occur at any stage of treatment. Although this reaction is not usually clinically important it may signal the onset of more serious hepatic injury and indicates the need for close monitoring of liver function. Symptomatic hepatic reactions are much rarer (less than 0.1% of patients) but are potentially fatal. There is usually a hepatocellular pattern of damage and sometimes cholestasis. Patients at increased risk of hepatic injury include those with a history of liver disease, those aged over 50, especially women, and those requiring prolonged treatment. It is important to monitor liver function during treatment as well as to limit the length of treatment. If liver enzyme values continue to rise or jaundice or hepatitis occur, ketoconazole should be withdrawn immediately since fatalities have occurred in patients who continued treatment after signs of hepatic injury developed.

1. Janssen PA, Symoens JE. Hepatic reactions during ketoconazole treatment. *Am J Med* 1983; 74: 80–5.
2. Lewis JH, *et al.* Hepatic injury associated with ketoconazole therapy. *Gastroenterology* 1984; 86: 503–13.
3. Lake-Bakaar G, *et al.* Hepatic reactions associated with ketoconazole in the United Kingdom. *BMJ* 1987; 294: 419–21.
4. García Rodríguez LA, *et al.* A cohort study on the risk of acute liver injury among users of ketoconazole and other antifungal drugs. *Br J Clin Pharmacol* 1999; 48: 847–52.

Precautions

Since ketoconazole has been reported to cause hepatotoxicity it should not be given to patients with pre-existing liver disease. Patients given ketoconazole should be monitored for symptoms of hepatitis; also, liver function tests should be performed before starting oral treatment with ketoconazole lasting for more than 14 days and then at least monthly throughout therapy. Adrenal function should be monitored in patients with actual or borderline adrenal insufficiency, those under prolonged periods of physiological stress, or those on prolonged therapy showing signs or symptoms suggestive of adrenal insufficiency.

Ketoconazole has been shown to be teratogenic in *animal* studies and its use is generally not recommended during pregnancy. For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3.

Hypochlorhydria, which may be present in patients with AIDS, can reduce absorption of ketoconazole. In this case absorption may be improved by giving ketoconazole with an acidic drink, such as a cola beverage.

Breast feeding. Ketoconazole is excreted in breast milk and licensed product information states that oral use should be avoided during breast feeding. However, no adverse effects were seen in a breast-fed infant whose mother was receiving ketoconazole;[1] it was calculated that the infant was exposed to about 0.4% of the usual therapeutic dose of ketoconazole for this age group. The American Academy of Pediatrics considers[2] that use of ketoconazole is therefore usually compatible with breast feeding.

1. Moretti ME, *et al.* Disposition of maternal ketoconazole in breast milk. *Am J Obstet Gynecol* 1995; 173: 1625–6.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/06/05)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ketoconazole for systemic use as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients. Dermatological preparations are classified as possibly porphyrinogenic; they should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Interactions

Use of drugs that reduce stomach acidity, such as antimuscarinics, antacids, histamine H_2-antagonists, and proton pump inhibitors, may reduce the absorption of ketoconazole. Absorption of ketoconazole may also be reduced by sucralfate. Enzyme-inducing drugs such as rifampicin, isoniazid, efavirenz, nevirapine, or phenytoin may reduce plasma-ketoconazole concentrations. Concentrations of isoniazid and rifampicin may also be reduced by ketoconazole.

Ketoconazole inhibits certain hepatic oxidase enzymes, especially the cytochrome P450 isoenzyme CYP3A4, in a similar way to itraconazole (p. 585.1) and similar care should be taken to avoid adverse effects due to increased plasma concentrations of the interacting drugs.

A disulfiram-like reaction may occur in patients taking ketoconazole after drinking alcohol. The efficacy of oral contraceptives may be reduced.

For reviews of drug interactions with azole antifungals, see Itraconazole, p. 585.2.

Antimicrobial Action

Ketoconazole is an imidazole antifungal that interferes with ergosterol synthesis and therefore alters the permeability of the cell membrane of sensitive fungi. It is reported to be fungistatic at concentrations achieved clinically. Ketoconazole has a wide spectrum of antimicrobial activity including activity against *Blastomyces dermatitidis, Candida* spp., *Coccidioides immitis, Epidermophyton floccosum, Histoplasma capsulatum, Malassezia* spp., *Microsporum canis, Paracoccidioides brasiliensis, Trichophyton mentagrophytes,* and *T. rubrum.* Some strains of *Aspergillus* spp., *Cryptococcus neoformans,* and *Sporothrix schenckii* are sensitive.

Ketoconazole has activity against some Gram-positive bacteria and some antiprotozoal activity against *Leishmania* spp.

There are rare reports of *Candida albicans* acquiring resistance to ketoconazole.

Microbiological interactions. For the effect of imidazoles and amphotericin B on each other's antimicrobial activity, see Amphotericin B, p. 572.3.

Resistance. For a discussion of increasing resistance of *Candida* spp. to azoles see Fluconazole, Antimicrobial Action, p. 580.2.

Pharmacokinetics

The absorption of ketoconazole from the gastrointestinal tract is variable and increases with decreasing stomach pH. Mean peak plasma concentrations of about 3.5 micrograms/mL occur about 2 hours after an oral dose of 200 mg. Systemic absorption after topical or vaginal application in healthy subjects is minimal. Ketoconazole is more than 90% bound to plasma proteins, mainly albumin. It is widely distributed and appears in breast milk. Penetration into the CSF is poor. The elimination of ketoconazole is reported to be biphasic, with an initial half-life of 2 hours and a terminal half-life of about 8 hours.

Ketoconazole is metabolised in the liver to inactive metabolites. It is excreted as metabolites and unchanged drug chiefly in the faeces; some is excreted in the urine.

References.

1. Daneshmend TK, Warnock DW. Clinical pharmacokinetics of ketoconazole. *Clin Pharmacokinet* 1988; 14: 13–34.
2. Lelawongs P, *et al.* Effect of food and gastric acidity on absorption of orally administered ketoconazole. *Clin Pharm* 1988; 7: 228–35.
3. Lake-Bakaar G, *et al.* Gastropathy and ketoconazole malabsorption in the acquired immunodeficiency syndrome (AIDS). *Ann Intern Med* 1988; 109: 471–3.
4. Daneshmend TK. Diseases and drugs but not food decrease ketoconazole 'bioavailability'. *Br J Clin Pharmacol* 1990; 29: 783–4.
5. Hurwitz A, *et al.* Gastric function in the elderly: effects on absorption of ketoconazole. *J Clin Pharmacol* 2003; 43: 996–1002.
6. Pitch WL, *et al.* Revisiting the metabolism of ketoconazole using accurate mass. *Drug Metab Lett* 2009; 3: 191–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: C-86; Cetonil; Eumicel; Faction; Fangan; Fitonal; Grenfung; Keduo; Ketogeno; Ketolef; Ketonazol; Micoespec; Micoral; Otifungal; Perative; Pitylis; Quadion; Sinamida Accion Caspa; Socosep; Tikl; Triatop; *Austral.*: Hexal Konazol Shampoo†; Nizoral; Sebizole; *Austria*: Fungoral; Nizoral; *Belg.*: Docketoral†; Nizoral; Pelikair†; *Braz.*: Aciderm†; Arcolan; Candiderm; Candoral; Cetoconalab; Cetoderm; Cetohexal; Cetomed; Cetomizol; Cetonax; Cetoneo; Cetonil; Cetonin; Cetozan; Cetozol; Clearlop; Conazol; Dermitrat; Ketonazol; Lozan; Miconan; Micoral; Nizonazol; Nizoral; Nizoretic†; Noriderm; Noronal; Zanoc; Zolmicol; *Canad.*: Ketoderm; Nizoral; Nu-Ketocon†; *Chile*: Arcolane; Biogel; Fungarest; Fungium; Soridermal; TKC; *China*: 999 Xuanling (999 选灵); Gold Daktarin (金达克宁); Jing Yu (敬宇); Kexin (可欣); Nizoral (里素芬); Pikangwang (皮康王); Triatop (采乐); Xian Ke Xin (显克欣); Zhuolixin (卓立欣); *Cz.*: Asquam†; Nizoral; *Denm.*: Nizoral; Samkol; *Fin.*: Konact; Nizoral; *Fr.*: Ketoderm; Ketolium†; Nizoral†; *Ger.*: Nizoral; Terzolin; *Gr.*: Abba; Adenosan; Aquarius; Botaderm; Cezolin; Ebersept; Flidaphen; Fungoral; Ilgem; Libroman; Lovegin; Mycofebrin; Neo-egmol; Nyoxep; Reprol; Scalpin; Sostatin; Tonsil; Vafluson; Zemidral; *Hong Kong*: CP-Keto†; Dezor; Diazon; Fluzoral†; Fungazol†; Funginox†; Ketocon; Ketovid; Ketozol; Ketozole; Larry; Nizoral; Pristine; Pristinex; Stada K†; Synizoral†; Ziconal†; *Hung.*: Ketospor; Nizoral; *India*: Arclone; Arcolane; Dandoff; Dandrex; Danfree; Danruf; Denfast; Derm-Keta; Emcon; Finazole; Fulkit; Funazole†; Fungicide; Funginoc; Fungizole; Hyphoral; Jacanzole; Jcanzole; K to Z; Ke-Toza; Kenazol; Ketafung; Keto; Ketocare; Ketoco; Ketocure; Ketonex; Ketopil; Ketovate; Ketoz; Ketozoe; Ketozole; Kezole; Kiton; Koiz; KZ; KZL; Nizol; Nizral; Novale; Ocona; *Indon.*: Anfuhex†; Dermaral; Dexazol; Dysfungal†; Fexazol; Formyco; Funet; Fungasol; Fungoral; Grazol; Interzol; Ketomed; Lusanoc; Micoticum†; Muzoral; Mycoderm; Mycoral; Mycozid; Nizol; Nizoral; Nofung; Picamic; Profungal; Solinfec; Sporex; Thicazol; Wizol; Zoloral; Zoralin; Zumazol†; *Irl.*: Ketopine; Ketozol; Nizoral; *Israel*: Ketozol; Nizoral; *Ital.*: Asquam; Nizoral; Triatop; *Malaysia*: Dezor; Diazon; Fungazol; Funginox; Ketozotan; Kezoral; Larry; Nizoral; Pristine; Pristinex; Yucomy; *Mex.*: Akorazol†; Biozoral; Conazol; Cremosan; Ergomicon; Eurolat; Fomiral; Fungipar; Fungoral; Fungosine†; Hispazzon†; Honzil; Ketofar; Ketomed; Ketomizol; Ketoril; Konaderm; Konaturil; Lizovag; Messelzol; Mi-Ke-Sons; Micoser; Micozol; Mycocil; Mycodib; Nastil; Nazolfarm; Nazoltec; Nizoral; Onofin-K; Prenalon; Remecon; Strizole†; Termizol; Tiniasil; Tiniazol; Toconal; Tolcrem; Tomiko; Triatop; *Neth.*: Nizoral; *Norw.*: Fungoral; Konazal†; *NZ*: Daktagold; Ketopine; Nizoral; Sebizole; *Philipp.*: Conatab†; Dezor; Donaxene; Fungizol; Ketovid; Konazole; Kozec; Nizoral; Reduff; *Pol.*: Fungores†; Nizoral; Noeli; Zoxinat; *Port.*: Farmorol; Nizale; Nizoral; Tedol; *Rus.*: Fungistab (Фунгистаб); Livarole (Ливарол); Mycoket (Микокет); Mycosoral (Микозорал); Nizoral (Низорал); Oronazol (Оронязол); Perkhotal (Перхотал); Sebozole (Себозол); *S.Afr.*: Adco-Dermed; Ketazol; Kez; Nizcreme; Nizoral; Nizorelle†; Nizovules†; Nizshampoo; *Singapore*: Antanazol; Beatoconazole; Dezor; Diazon; Formyco; Ketozole†; Kezoral†; Mycoral; Nicozone; Ninazol; Nitozol; Nizoral; Phytoral; Pristine; Pristinex; Sebizole; Sunazol; Yucomy; *Spain*: Fungarest; Fungo Farmasierra†; Fungo Zeus; Keto-Cure; Ketoisdin; Medezol; Micoticum†; Panfungol; *Swed.*: Fundan†; Fungoral; Ketoson†; Kezol†; *Switz.*: Keto-med; Ketozol; Lur; Nizoral; Terzolin; *Thai.*: AC-FA; Chintaral; Chintoral; Dandril; Dezor; Diazon; Fungazol; Fungiderm-K; Funginox; Fungizin; Kandex; Kara; Katsin; Kazinal; Kenalyn†; Kenazol; Kenoral; Ketazon; Ketocine; Ketolan; Ketomed; Ketonazole; Ketopac; Ketoral; Ketosil†; Ketozal; Kezole; Kezon; Konaz; Konazol; Lama†; Larry; Liquimed; Manoketo; Masarol; Mizoco; Mizoron; Mycella; Myco-shampoo; Myco; Mycoral; Nazole; Ninazol; Nizoral; Nora; Pasalen; SP-Keto; Sporaxyl; Sporoxyl; *Turk.*: Fungoral; Keto; Ketoderm; Ketoral; Konazol; Nizoral; *UK*: Daktarin Gold; Dandrazol; Dandrid; Nizoral; *Ukr.*: Kenazole (Кенязол); Ketodin (Кетодин); Ketozoral (Кетозорал); Livarol (Ливарол); Nizoral (Низорал); *USA*: Extina; Ketodan; Nizoral; Xolegel; *Venez.*: Arcolane; Freetop; Kenazol; Ketazol; Ketomed; Nizoral.

Multi-ingredient Preparations. *Arg.*: Bactisona†; Butimerin Complex; Ciprocort; Colposan; Dercotex; Dermoperative; Gentacler; Gynerium; Linfol Dermico; Magicrem; Microsona C; Ovogin; Torgyn Duo; Tricur; Tridermal; *Braz.*: Betacortazol; Betazol Cort†; Betricort; Candicort; Capel; Celocort; Cetobeta; Cetocort; Cetocorten; Cimecort; Conacort; Cortifungin; Dermocorte; Emscort; Naderm; Novacort; Trok-N; Trok; *China*: Baolongkang (保龙慷); Bi Liang (必亮); Compound Ketoconazole (复方酮康唑); *India*: Apodruff; Clinhair; Cotar-K; Danclear; Dancure; Emvate; Everzple; Flakefree; Fungicide; Hyphoral; Kekona; Ketosis; Ketotar; Ketz; Koiz; Konaz; KTC; Nazcare; Nazz; Nuforce Shampoo; Ocona-CT; Ocona-Z; Scalpe; *Ital.*: Keto Z; Ketomousse; *Malaysia*: Ketoplus; *Mex.*: Femisan; Loffymix†; Trexen Duo; *Philipp.*: Scalpex; *Rus.*: Keto Plus (Кето Плюс); *Thai.*: Nizoral Cool; *Ukr.*: Keto Plus (Кето Плюс); *USA*: Xolegel CorePak; Xolegel Duo.

Pharmacopoeial Preparations

USP 36: Ketoconazole Oral Suspension; Ketoconazole Tablets.

Lanoconazole *(rINN)*

Lanoconazol; Lanoconazolum; Latoconazole; NND-318; TJN-318; Ланоконазол.

(±)-α-[(*E*)-4-(*o*-Chlorophenyl)-1,3-dithiolan-2-ylidene]imidazole-1-acetonitrile.

$C_{14}H_{10}ClN_3S_2$=319.8

CAS — 101530-10-3.

UNII — 4E7858311F.

Profile

Lanoconazole is an imidazole antifungal used topically in the treatment of fungal skin infections as a 1% cream, ointment, or solution, applied once daily. For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3.

Hypersensitivity. For reports of cross-sensitivity between lanoconazole and luliconazole, see p. 588.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Astat.

Liranaftate *(rINN)*

Liranaftato; Liranaftatum; M-732; Piritetrate; Лиранафтат.
O-5,6,7,8-Tetrahydro-2-naphthyl 6-methoxy-*N*-methylthio-2-pyridinecarbamate.
$C_{18}H_{20}N_2O_2S$=328.4
CAS — 88678-31-3.
UNII — 5253IGO5X3.

Profile

Liranaftate is an antifungal related to tolnaftate (p. 596.1) and is applied once daily as a 2% cream or solution in the treatment of superficial dermatophyte infections (p. 568.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Ao Shu Zhi (澳舒旨); Dang Zhi (当止); Fu An (扶安); Jia Yi (嘉益); Li Wei Kang (利维康); Liang Qi (良奇); Sheng Fu Shuang (圣夫爽); Sifulin (斯芙林); Yi Fu Ping (一孚平); Yi Shen (易神); *Jpn*: Zefnart.

Luliconazole *(USAN, rINN)*

Luliconazol; Luliconazolum; NND-502; PR-2699; Луликоназол.
(-)-(*E*)-[(4*R*)-4-(2,4-Dichlorophenyl)-1,3-dithiolan-2-ylidene](1*H*-imidazol-1-yl)acetonitrile.
$C_{14}H_9Cl_2N_3S_2$=354.3
CAS — 187164-19-8.
UNII — RE91AN4S8G.

Profile

Luliconazole is an imidazole antifungal that is applied topically, as a 1% solution or cream, in the treatment of fungal skin infections.

Hypersensitivity. Two patients who had allergic contact dermatitis to luliconazole were found on patch testing to be cross-sensitive to lanoconazole but not to several other imidazole antifungals.[1,2]

1. Shono M. Allergic contact dermatitis from luliconazole. *Contact Dermatitis* 2007; **56**: 296–7.
2. Tanaka T, *et al.* Allergic contact dermatitis from luliconazole: implication of the dithioacetal structure. *Acta Derm Venereol* 2007; **87**: 271–2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Lulicon.

Mepartricin *(BAN, USAN, rINN)*

Mepartricina; Mépartricine; Mepartricinum; Methylpartricin; SN-654; SPA-S-160; Менартрицин.
CAS — 11121-32-7.
ATC — A01AB16; D01AA06; G01AA09; G04CX03.
ATC Vet — QA01AB16; QD01AA06; QG01AA09; QG04CX03.
UNII — B7FBW3Y74G.

Profile

Mepartricin is a mixture of the methyl esters of 2 related polyene antibiotics that may be obtained from a strain of *Streptomyces aureofaciens*. It has antifungal and antiprotozoal activity and has been used in vaginal candidiasis and trichomoniasis as pessaries or as a vaginal cream. A cream is also available for the treatment of superficial candidiasis. An oral form of mepartricin sodium laurilsulfate is also used. Oral mepartricin 40 mg daily is used in the treatment of some prostate disorders.

Prostate disorders. Studies[1,2] have shown that mepartricin given orally is effective in the treatment of *benign prostatic hyperplasia* (see p. 2347.1 for the more usual treatments); a dose of 40 mg daily is commonly used.[2] Mepartricin is thought to reduce cholesterol, oestrogen, and androgen binding to the prostate. Similarly, another study[3] has shown that the same dose of mepartricin provides symptomatic improvement in the management of *chronic prostatitis/chronic pelvic pain syndrome* (see Prostatitis, p. 2350.2).

1. Tosto A, *et al.* A double-blind study of the effects of mepartricin in the treatment of obstruction due to benign prostatic hyperplasia. *Curr Ther Res* 1995; **56**: 1270–75.
2. Denis L, *et al.* Double-blind, placebo-controlled trial to assess the efficacy and tolerability of mepartricin in the treatment of BPH. *Prostate* 1998; **37**: 246–52.
3. De Rose AF, *et al.* Role of mepartricin in category III chronic nonbacterial prostatitis/chronic pelvic pain syndrome: a randomized prospective placebo-controlled trial. *Urology* 2004; **63**: 13–16.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Iperplasin†; *Cz.*: Ipertrofan; *Ital.*: Ipertrofan; Tricandil; *Philipp.*: Ipertrofan†; *Pol.*: Ipertrofan; *Port.*: Iperplasin; Ipertrofan; Tricandil; *Rus.*: Ipertrofan (Ипертрофан).

Multi-ingredient Preparations. *Braz.*: Tricangine.

Micafungin Sodium *(BANM, USAN, rINNM)*

FK-463; Micafungina sódica; Micafungine Sodique; Natrii Micafunginum; Натрий Микафунгин.
5-((15,25)-2-[(2*R*,6*S*,9*S*,11*R*,12*R*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*)-20-[(1*R*)-3-Amino-1-hydroxy-3-oxopropyl]-2,11,12,15-tetrahydroxy-6-[(1*R*)-1-hydroxyethyl]-16-methyl-5,8,14,19,22,25-hexaoxo-9-[[4-[5-[4-(pentyloxy)phenyl]isoxazol-3-yl]benzoyl]amino]tetracosahydro-1*H*-dipyrrolo[2,1-*c*:2′,1′-*l*][1,4,7,10,13,16]hexaazacyclohenicosin-23-yl)-1,2-dihydroxyethyl)-2-hydroxyphenyl sodium sulfate.
$C_{56}H_{70}N_9NaO_{23}S$=1292.3
CAS — 235114-32-6 (micafungin); 208538-73-2 (micafungin sodium).
ATC — J02AX05.
ATC Vet — QJ02AX05.
UNII — IS1UP79R56.

Uses and Administration

Micafungin is an echinocandin antifungal with general properties similar to those of caspofungin (p. 575.1). It is used for the treatment and prophylaxis of candidiasis and, in some countries, for the treatment of aspergillosis. It is given as the sodium salt by intravenous infusion in doses of 50 mg once daily for candidiasis. For the treatment of oesophageal candidiasis the recommended dose is 150 mg daily. For invasive candidiasis, including candidaemia or disseminated infection, a dose of 100 mg once daily is recommended; if clinical response is inadequate, the dose may be increased to 200 mg once daily. For aspergillosis 50 to 150 mg is given once daily. Doses up to 300 mg daily have been used in severe or refractory disease. A dose of 50 mg daily is used for prophylaxis of candidiasis in patients undergoing haematopoietic stem cell transplantation, or in those expected to have neutropenia for 10 days or more.

For details of doses in children, see below. UK licensed product information advises that adults weighing 40 kg or less should also be dosed as for children.

Reviews.
1. Denning DW. Echinocandin antifungal drugs. *Lancet* 2003; **362**: 1142–51.
2. Jarvis B, *et al.* Micafungin. *Drugs* 2004; **64**: 969–84.
3. Carver PL. Micafungin. *Ann Pharmacother* 2004; **38**: 1707–21.
4. van Burik JA, *et al.* Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. *Clin Infect Dis* 2004; **39**: 1407–16.
5. Chandrasekar PH, Sobel JD. Micafungin: a new echinocandin. *Clin Infect Dis* 2006; **42**: 1171–8.
6. Fritz JM, *et al.* Micafungin for the prophylaxis and treatment of Candida infections. *Expert Rev Anti Infect Ther* 2008; **6**: 153–62.
7. Cross SA, Scott LJ. Micafungin: a review of its use in adults for the treatment of invasive and oesophageal candidiasis, and as prophylaxis against Candida infections. *Drugs* 2008; **68**: 2225–55.
8. Horn DL, *et al.* Factors related to survival and treatment success in invasive candidiasis or candidemia: a pooled analysis of two large, prospective, micafungin trials. *Eur J Clin Microbiol Infect Dis* 2010; **29**: 223–9.
9. Bormann AM, Morrison VA. Review of the pharmacology and clinical studies of micafungin. *Drug Des Devel Ther* 2009; **3**: 295–302.

Administration in children. In the UK, micafungin is licensed for use in neonates and children for the treatment of invasive candidiasis, and the prophylaxis of candida infection in patients undergoing haematopoietic stem cell transplantation or those expected to have neutropenia for 10 days or more. In those 16 years of age and older, it may also be used for treatment of oesophageal candidiasis. The following doses are recommended based on body weight, and given by intravenous infusion over 1 hour:

- for treatment of invasive candidiasis: 2 mg/kg once daily; if adequate clinical response does not occur, the dose may be doubled
- for oesophageal candidiasis: 3 mg/kg once daily
- for prophylaxis of candidiasis: 1 mg/kg once daily

For children weighing more than 40 kg, adult doses (see above) should be used.

References.
1. Carter NJ, Keating GM. Micafungin: a review of its use in the prophylaxis and treatment of invasive Candida infections in pediatric patients. *Paediatr Drugs* 2009; **11**: 271–91.
2. Lehrnbecher T, Groll AH. Micafungin: a brief review of pharmacology, safety, and antifungal efficacy in pediatric patients. *Pediatr Blood Cancer* 2010; **55**: 229–32.

Adverse Effects

As for Caspofungin, p. 575.1. Rare cases of haemolysis, including acute intravascular haemolysis and haemolytic anaemia have been reported in patients given micafungin. Serious hepatic dysfunction has occurred after micafungin use, including fatalities. Children less than 1 year old may be more prone to liver injury. Isolated cases of renal dysfunction or acute renal failure have also occurred in patients taking micafungin.

Hypersensitivity. For reference to cross-sensitivity to caspofungin in a patient hypersensitive to micafungin see p. 575.2.

Precautions

Patients who develop abnormal liver- or renal-function tests while taking micafungin should be monitored for deterioration in hepatic or renal function respectively. Liver tumours have occurred in *rats* given micafungin for 3 months or more. Although the risk to humans is unknown, micafungin should be used with caution in patients with pre-existing risk of malignancy due to severe liver function impairment or chronic liver disease, or in those also using hepatotoxic or genotoxic medications.

Interactions

Micafungin may increase the area under the concentration-time curve for conventional amphotericin B, itraconazole, nifedipine, and sirolimus.

Antimicrobial Action

As for Caspofungin, p. 575.2.

Pharmacokinetics

Micafungin is absorbed from the gastrointestinal tract after oral doses. It is more than 99% bound to plasma proteins, mainly albumin.

Micafungin is metabolised by arylsulfatase to its catechol form and further metabolised to the methoxy form by catechol-*O*-methyltransferase. Some hydroxylation to micafungin via cytochrome P450 isoenzymes also occurs.

After 28 days about 71% of a dose is recovered in the faeces and 12% in the urine. Mean half-lives of 14.0 to 17.2 hours have been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Mycamine; *Braz.*: Mycamine; *Canad.*: Mycamine; *China*: Mycamine (米开民); *Cz.*: Mycamine; *Denm.*: Mycamine; *Fr.*: Mycamine; *Ger.*: Mycamine; *Gr.*: Mycamine; *Hong Kong*: Mycamine; *Hung.*: Mycamine; *Indon.*: Mycamine; *Irl.*: Mycamine; *Ital.*: Mycamine; *Jpn*: Funguard; *Neth.*: Mycamine; *Norw.*: Mycamine; *Philipp.*: Mycamine; *Pol.*: Mycamine; *Port.*: Mycamine; *Rus.*: Micamin (Микамин); *Spain*: Mycamine; *Swed.*: Mycamine; *Switz.*: Mycamine; *Thai.*: Mycamine; *UK*: Mycamine; *Ukr.*: Micamin (Микамин); *USA*: Mycamine.

Miconazole *(BAN, rINN)*

Miconazol; Miconazolum; Mikonatsoli; Mikonazol; Mikonazolas; R-18134; Миконазол.
1-[2,4-Dichloro-β-(2,4-dichlorobenzyloxy)phenethyl]imidazole.
$C_{18}H_{14}Cl_4N_2O$=416.1
CAS — 22916-47-8.
ATC — A01AB09; A07AC01; D01AC02; G01AF04; J02AB01; S02AA13.
ATC Vet — QA01AB09; QA07AC01; QD01AC02; QG01AF04; QJ02AB01; QS02AA13.
UNII — 7NNO0D7S5M.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Miconazole). A white or almost white powder. It exhibits polymorphism. M.p. 83 degrees to 87 degrees. Very slightly soluble in water; soluble in alcohol; freely soluble in methyl alcohol. Protect from light.

USP 36: (Miconazole). A white to pale cream powder. It may exhibit polymorphism. M.p. 78 degrees to 88 degrees. Insoluble in water; soluble 1 in 9.5 of alcohol, 1 in 2 of chloroform, 1 in 15 of ether, 1 in 4 of isopropyl alcohol, 1 in 5.3 of methyl alcohol, and 1 in 9 of propylene glycol; freely soluble in acetone and in dimethylformamide. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Miconazole Nitrate (BANM, USAN, rINNM)

Miconazol, nitrato de; Miconazole, Nitrate de; Miconazoli Nitras; Miconazolnitrat; Mikonatsolinitraatti; Mikonazol Nitrat; Mikonazolnitrat; Mikonazol-nitrát; Mikonazolo nitratas; Mikonazolu azotan; Nitrato de miconazol; R-14889; Миконазола Нитрат.

$C_{18}H_{14}Cl_4N_2O,HNO_3$=479.1

CAS — 22832-87-7.

ATC — A01AB09; A07AC01; D01AC02; G01AF04; J02AB01; S02AA13.

ATC Vet — QA01AB09; QA07AC01; QD01AC02; QG01AF04; QJ02AB01; QS02AA13.

UNII — VW4H1CYW1K.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Miconazole Nitrate). A white or almost white powder. Very slightly soluble in water; slightly soluble in alcohol; sparingly soluble in methyl alcohol. Protect from light.

USP 36: (Miconazole Nitrate). A white or practically white, crystalline powder, with not more than a slight odour. Soluble 1 in 6250 of water, 1 in 312 of alcohol, 1 in 75 of methyl alcohol, 1 in 525 of chloroform, 1 in 1408 of isopropyl alcohol, 1 in 119 of propylene glycol; freely soluble in dimethyl sulfoxide; soluble in dimethylformamide; insoluble in ether. Protect from light.

Uses and Administration

Miconazole is an imidazole antifungal used as miconazole base or nitrate in the treatment of superficial candidiasis (p. 564.1), and of the skin infections dermatophytosis and pityriasis versicolor (p. 568.1). It has also been given intravenously by infusion in the treatment of disseminated fungal infections, but other azoles are now more commonly used.

Miconazole may be given orally as a gel containing 20 mg/g (24 mg/mL) for the treatment and prevention of oropharyngeal and intestinal candidiasis. The usual adult dose is 5 to 10 mL four times daily (equivalent to a total of about 15 mg/kg daily). For the treatment of oral lesions the oral gel is applied directly. Miconazole may also be given once daily as a muco-adhesive buccal tablet (containing 50 mg miconazole) for the treatment of oropharyngeal candidiasis in immunocompromised patients.

Miconazole nitrate is usually applied twice daily as a 2% cream, lotion, or powder in the treatment of fungal infections of the skin including candidiasis, dermatophytosis, and pityriasis versicolor; it may be applied once or twice daily to treat fungal nail infections. In the treatment of vaginal candidiasis, 5 g of a 2% intravaginal cream is inserted into the vagina once daily for 10 to 14 days or twice daily for 7 days. Miconazole nitrate pessaries may be inserted in dosage regimens of 100 mg once daily for 7 or 14 days, 100 mg twice daily for 7 days, 200 or 400 mg daily for 3 days, or in a single dose of 1200 mg.

For details of miconazole use in children, see below.

Administration in children. Miconazole may be used in children for the treatment and prevention of oropharyngeal and intestinal candidiasis. In the UK, the oral gel (containing miconazole 20 mg/g) may be given to children from 4 months of age for oral infections in the following licensed doses:

- 4 months to 2 years of age: 1.25 mL 4 times daily
- from 2 years of age: 2.5 mL 4 times daily

Although unlicensed for use in younger children, the *BNFC* suggests that a dose of 1.25 mL 4 times daily may also be used in children as young as 1 month; for neonates, a dose of 1 mL 2 to 4 times daily is recommended.

For **intestinal infections** in children from 4 months of age miconazole oral gel is given in a daily dose of 20 mg/kg (to a maximum of 1 g) in 4 divided doses.

Miconazole nitrate may be used topically to treat fungal skin and nail infections in neonates and children similarly to adults (see above).

Acanthamoeba keratitis. Miconazole has been applied topically in *Acanthamoeba* keratitis (p. 919.3).

Skin disorders. Topical preparations containing an imidazole such as ketoconazole or miconazole, usually with hydrocortisone, are used in the management of *seborrhoeic dermatitis* (p. 1689.1). A cream containing miconazole nitrate 2% and benzoyl peroxide 5% has been used topically in the treatment of *acne* (p. 1682.2).

Adverse Effects

After oral use of miconazole, nausea and vomiting have been reported, and also diarrhoea (usually on long-term treatment). There have been allergic reactions, rarely, and isolated reports of hepatitis.

Local irritation and sensitivity reactions may occur when miconazole nitrate is used topically; contact dermatitis has been reported.

After the intravenous infusion of miconazole, phlebitis, nausea, vomiting, diarrhoea, anorexia, pruritus, rash, febrile reactions, flushes, drowsiness, and hyponatraemia have been reported. Other effects include hyperlipidaemia, aggregation of erythrocytes, anaemia, and thrombocytosis. Transient tachycardia and other cardiac arrhythmias have followed the rapid intravenous injection of miconazole (but see also Effects on the Heart, below). Rare adverse effects include acute psychosis, arthralgia, and anaphylaxis. Many of these adverse effects have been associated with the injection vehicle, which contains polyoxyl castor oil (p. 2202.3).

Effects on the heart. Bradycardia, progressing to fatal ventricular fibrillation and cardiac arrest, occurred in a heart transplant patient during intravenous infusion of miconazole for an invasive fungal infection.[1]

1. Coley KC, Crain JL. Miconazole-induced fatal dysrhythmia. *Pharmacotherapy* 1997; 17: 379–82.

Overdosage. A report[1] of a generalised tonic-clonic convulsion that occurred in an infant 10 to 15 minutes after the inadvertent infusion of miconazole 500 mg instead of 50 mg.

1. Coulthard K, *et al.* Convulsions after miconazole overdose. *Med J Aust* 1987; 146: 57–8.

Precautions

Systemic use of miconazole should be avoided in patients with hepatic impairment;

Intravaginal preparations of miconazole may damage latex contraceptives and additional contraceptive measures are therefore necessary during local application.

Miconazole has been fetotoxic at high doses in *animals* and its use is generally not recommended during *pregnancy*. For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies miconazole (for dermatological use) as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed. Stomatological preparations are classified as not porphyrinogenic; they may be used as drugs of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Interactions

Miconazole can inhibit the metabolism of drugs metabolised by the cytochrome P450 isoenzymes CYP3A4 and CYP2C9, and may thus have effects similar to those of fluconazole (p. 580.1). Miconazole may enhance the activity or serum concentrations of oral anticoagulants, sulfonylurea hypoglycaemics, or phenytoin. Adverse effects have been reported when miconazole was given with carbamazepine.

There is a risk of cardiac arrhythmias if oral miconazole is used with substrates of CYP3A4 that may prolong the QT interval, such as, astemizole, cisapride, dofetilide, halofantrine, mizolastine, pimozide, quinidine, sertindole, or terfenadine and such combinations should be avoided.

Anticoagulants. The anticoagulant activity of coumarin anticoagulants can be potentiated by miconazole given orally,[1] intravaginally,[2] or topically.[3] As of December 2002 the Australian Adverse Drug Reactions Advisory Committee had received 18 reports of significant increases in the INR of patients previously stabilised on warfarin within 1 to 2 weeks of starting treatment with miconazole oral gel.[4]

1. Ortín M, *et al.* Miconazole oral gel enhances acenocoumarol anticoagulant activity: a report of three cases. *Ann Pharmacother* 1999; 33: 175–7.
2. Lansdorp D, *et al.* Potentiation of acenocoumarol during vaginal administration of miconazole. *Br J Clin Pharmacol* 1999; 47: 225–26.
3. Devaraj A, *et al.* Interaction between warfarin and topical miconazole cream. *BMJ* 2002; 325: 77.
4. Australian Adverse Drug Reactions Advisory Committee (ADRAC). Miconazole oral gel elevates INR—a reminder. *Aust Adverse Drug React Bull* 2002; 21: 14. Available at: http://www.tga.gov.au/adr/aadrb/aadr0212.pdf (accessed 28/06/05)

Antimicrobial Action

Miconazole is an imidazole antifungal with similar antimicrobial activity to that of ketoconazole (p. 587.2). It also has some activity against *Aspergillus* spp., *Cryptococcus neoformans*, *Pseudallescheria boydii*, and some Gram-positive bacteria including staphylococci and streptococci.

References.

1. Barasch A, Griffin AV. Miconazole revisited: new evidence of antifungal efficacy from laboratory and clinical trials. *Future Microbiol* 2008; 3: 265–9.

Microbiological interactions. A study *in vitro* indicating antimicrobial synergism of miconazole and benzoyl peroxide against *Staphylococcus* spp. and *Propionibacterium acnes*.[1]

For the effect on antifungal activity of giving azoles and amphotericin B together, see p. 572.3.

1. Vanden Bossche H, *et al.* Synergism of the antimicrobial agents miconazole and benzoyl peroxide. *Br J Dermatol* 1982; 107: 343–8.

Pharmacokinetics

Miconazole is incompletely absorbed from the gastrointestinal tract. Peak plasma concentrations of 1 microgram/mL occur about 4 hours after a dose of 1 g daily. Over 90% is reported to be bound to plasma proteins.

Miconazole is metabolised in the liver to inactive metabolites. From 10 to 20% of an oral dose is excreted in the urine, mainly as metabolites, within 6 days. About 50% of an oral dose may be excreted unchanged in the faeces. The elimination pharmacokinetics of miconazole have been described as triphasic, with a biological half-life of about 24 hours.

Very little miconazole is removed by haemodialysis.

There is little absorption through skin or mucous membranes when miconazole nitrate is applied topically.

Reviews.

1. Daneshmend TK, Warnock DW. Clinical pharmacokinetics of systemic antifungal drugs. *Clin Pharmacokinet* 1983; 8: 17–42.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Daktarin; Deralbine; Gynotran; Miconol; Micopul; Micotgez; Micotral; Micotrim P; Monizol; Nedis; ***Austral.***: Daktarin; Hairscience Anti-Dandruff; Resolve Thrush; Resolve Tinea; Resolve; ***Austria***: Daktarin; ***Belg.***: Daktarin; Gyno-Daktarin; Tibozole; ***Braz.***: Amicozol; Anfugitarin; Ciconazol; Colpadak; Dakgran†; Daktarin; Daktazol; Dermalina; Ginedak†; Gino Mizonol; Gino-Daczol; Ginotarin; Gyno Daknax; Gyno-Daktarin; Micofim; Micogyn; Micotarin†; Micotrin†; Micozen; Mizonol; Mycosin†; Vodol; ***Canad.***: Micatin; Micozole; Monistat-Derm; Monistat; ***Chile***: Daktarin; ZeaSorb AF†; ***China***: Ao Xian Ning (澳先宁); Bai Ni Duo (拜尼多); Beikang (倍康); Daktarin (达克宁); Le Wei (乐唯); Qingkun (清坤); Wu Mei (吾玫); ***Cz.***: Loramyc; ***Denm.***: Brentan; ***Fin.***: Daktarin; Gyno-Daktarin; Loramyc†; ***Fr.***: Daktarin; Gyno-Daktarin; Loramyc; ***Ger.***: Castellani mit Miconazol; Daktar; Derma-Mykotral†; Fungur M†; Gyno-Daktar; Gyno-Mykotral; InfectoSoor; Loramyc; Micobeta†; Micotar; Mykoderm Mund-Gel; Mykoderm; Mykotin; Vobamyk; ***Gr.***: Crimak; Daktarin; Fantersol; Gnostoderm; Gyno-Daktarin; Iristop; Medacter; Mezolitan; Untano; ***Hong Kong***: BF-Micozo†; Daktarin; Dermon; Funga†; Micrutin†; Tinazol†; Uni-Mizole†; Zarin†; ***India***: Candistat; Candizole; Canticid; Daktarin; Decanazole; Emiconazole; Fungitop; Gyno-Daktarin; Micogel; Miconit; Micoptic; Micoson; Mizole; Zole; ***Indon.***: Daktarin; Daktazol; Fungares; Funtas; Micoskin; Micrem; Moladerm; Mycorine; Sporend; Zolagel; ***Irl.***: Daktarin; Gyno-Daktarin; ***Israel***: Daktarin; Fungiderm; Gyno-Daktarin; Pitrion; Zimycan†; ***Ital.***: Daktarin; Miconal; Micotef; Miderm†; Nizacol; Prilagin; ***Jpn***: Florid; ***Malaysia***: Antifungal; Becarin; Daktarin; Decozol; Dermon; Resolve; Zarin; ***Mex.***: Aloid; Biodantyl-C; Daktarin; Dermifun; Falernol; Fucoderm; Fungicrem†; Fungiquim; Ginazol†; Gyno-Daktarin; Hipo Femune; K-Mizol; Lotrimin AF; Micoffen; Nacomic; Neomicol; Nimicon; Niscamil; Oz Crema; Vigasil; ***Neth.***: Daktarin; Dermacure; Gyno-Daktarin; Kruidvat Antischimmelcreme; Kruidvat Antischimmelpoeder; Loramyc; Zimycan†; ***Norw.***: Daktar; ***NZ***: Daktarin; Fungo†; Micozole; Micreme; Monistat; ***Philipp.***: Daktarin; De-Ol; Defungin†; Emizole; Fungtopic; Micoson; Micotran; Monistat; ***Pol.***: Daktarin; Gyno-Femidazol; Loramyc; Miconal; ***Port.***: Daktarin; Gyno-Daktarin; Zimycan†; ***Rus.***: Daktarin (Дактарин)†; Gynezol (Гинезол); Micoson (Микозон); ***S.Afr.***: Covarex; Daktarin; Dermazole; Gyno-Daktarin; Gynospor†; Micmat; ***Singapore***: Antifungal; Candiplas; Daktarin; Decozol; Guardian Antifungal; Liconar; Micon; Minazol; Mycoban; Resolve; SP-Micozol; Tinazol; Zarin; ***Spain***: Daktarin; Fungisdin; Pasedon†; ***Swed.***: Daktar; ***Switz.***: Daktarin; Monistat; Sebolox; ***Thai.***: Daktarin; Dermon†; Funcort; Funga; Fungi-M; Fungisil; Mic†; Micazin; Mysocort; Nikarin; Noxtraxin; Podakrin; Ranozol; Skindure; Tara; ***Turk.***: Funguci; Micon; Minazol; Mycoban; Resolve; SP-Micozol; Tinazol; Zarin; ***Spain***: Daktarin; Fungisdin; Pasedon†; ***Swed.***: Daktar; ***Switz.***: Daktarin; Monistat; Sebolox; ***Thai.***: Daktarin; Dermon†; Funcort; Funga; Fungi-M; Fungisil; Mic†; Micazin; Mysocort; Nikarin; Noxtraxin; Podakrin; Ranozol; Skindure; Tara; ***Turk.***: Funguci; Lotrimin; Miko-Penetran; ***UAE***: Gyno-Mikozal; Mikozal; ***UK***: Daktarin; Gyno-Daktarin; Loramyc; ***Ukr.***: Micogel (Микогель); ***USA***: Aloe Vesta; Azolen; Baza Antifungal; Critic-Aid Clear AF; Cruex; Desenex Liquid Spray†; Desenex Powder; Femizol-M†; Fungoid; Lotrimin AF; M-Zole†; Micatin; Micro-Guard†; Miranel AF; Monistat; Neosporin AF†; Oravig; Podactin; Prescription Strength Desenex†; Ting; Triple Paste AF; Vagistat-3; ZeaSorb AF†; ***Venez.***: Daktarin; Gyno-Daktarin.

Multi-ingredient Preparations. ***Arg.***: Adenil; Betacort Plus; Blamy; Ciprocort; Colpofilin Max; Cuta Crema; Daktozin; Delisan; Denvercrem; Dermizol Trio; Dermosona; Factor Dermico; Fangan Plus; Genamic†; Gentasol; Ginal Cent; Ginkan; Gynormal; Hifamonil Crema; Ladylen; Lazar-Cort Complex; Lichensa; Linfol Cicatrizante; Macril; Mailen; Miklogen; Monizol Cort Crema; Monizol Cort; Neo Pelvicillin; Ovufem; Ovumix; Pentol; Protiderm; Septigyn; Triblocort; Tricifa; Triliver; Triplex; Vagicural Plus; ***Austral.***: Daktozin; Resolve Nappy Rash; Resolve Plus; Resolve Tinea; Resolve; ***Austria***: Acne Plus; Vobaderm; ***Belg.***: Acneplus; Daktacort; Daktozin; ***Braz.***: Amplium-G; Anfu-

gine; Daktozin†; Facyl M; Gino-Colon; Gino-Pletil; Ginosutin-M†; Limpele Ginecologico; Trinizol M; *Chile*: Doxifen; Exomicol; Famidal; Ginecopast Dual; Ginecopast; Ginedazol Dual; Ginedazol; Medidos; Mizonase; Tinidazol Compuesto; *China*: Dapule (达替乐); *Cz.*: Klion-D; *Denm.*: Brentacort; *Fin.*: Daktacort; *Fr.*: Squaphane E; Squaphane P; Squaphane S; Squaphane; Squaphane; *Ger.*: Acne Plus; Decoderm tri; Infecto-Soor; Micotar ZP; Vobaderm; *Gr.*: Antimycotic; Catrigel; Combi; Conazol; Daktodor; Decoderm Trivalente-N; Domycotin; Edmudo; Expectein; Feminella; Finicort; Flenazole; Flumicomplex; Fluniprol; Flunovon; Fosemyk; Fumicon; Ifleric; Micoflup; Micogen; Mifler†; Milfer; Oxigon; Panderm; Panmyk; Sarmel; Verdal; *Hong Kong*: Axcel Fungicort†; Conazole; Daktacort; Fungo Soothing Balm†; Hydro-Funga†; Micosone; Uni-Mizole-HC†; Zaricort†; *Hung.*: Klion-D; Mycosolon; *India*: Alclos-GM; Atderm; Beclasone-GM; Beclex-GM; Beclomin; Beclomin; Beclozen; Becmet-GM; Betamil-GM; Betamil-M; Betanate GM; Betanate M; Betaspi-GM; Betnederm GM; Betnovate-GM; Betnovate-M; Betzee-GM; Betzee-M; Candifem; Candizole-T†; CGM; Clobact-GM; Clobaderm-GM; Clobasia-GM; Clobecos-GM; Clobequad; Cloberis-GM; Clobesym-GM; Clobeta-CP; Clobquad; Cloby; Cloderm-GM; Clodip-GM; Clofung GM; Clogem; Clomic-M; Clomic-ZM; Clonate-GM; Clop-M; Clop-MG; Clos-GM; Clotof-GM; Clotof-M; Cortiderm-GM; Cosvate-GM; Cutasol-GM; Daktacort; Daktarin-T; Dandrid; Dermocrat Plus; Dermonit; Dermotel; Dermotriad; Dermotyl-M; Dermowin-GM; Drez-V; E-Derm; Eclospan; Ecziclo-GM; Elderm; Enderm-GM; Etan-GM; Eumosone-M; Excel-M; Flual-M; Flucort-MZ; Flucreme-NM; Flunec; Fungifite; Fungitop-F; Gemiderm; Gentacort-FC; GMF; Halostrol-M; Hyton; Kloryl-M; Labosol-GM; Leobet-GM; Leta-GM; Lobate-GM; Lobate-M; Losweat; Lozee-GM; Lozee-M; Lupiderm-GM; Lupiderm-M; Metazole; Miclogenta; Micocort-G; Micogel F; Micogram; Micolon; Mictop-F; Nazo-F; Stecort-NM†; Tenovate M; Valbet; Zole-F; *Indon.*: Benoson M; Brentan; Daktarin Diaper; Thecort; Zolacort; Zolagel Diaper; *Irl.*: Daktacort; *Israel*: Daktacort; *Ital.*: Acnidazil; Decoder Micoflu; *Malaysia*: Daktacort; Decocort; Neo-Penotran; Zaricort; *Mex.*: Bebektin; Daktacort; Gynotran; *Neth.*: Acnecare; Daktacort; *Norw.*: Cortimyk†; Daktacort; *NZ*: Daktacort; Micreme H; Resolve Plus; *Philipp.*: Acne Plus†; Daktacort; Neo-Penotran; *Pol.*: Mycosolon; *Port.*: Daktacort; Zacne†; *Rus.*: Klion-D (Клион-Д); Mycosolon (Микозолон); Neo-Penotran (Нео-Пенотран); *S.Afr.*: Acneclear†; Acnidazil†; Daktacort; Elozart; Trialone†; *Singapore*: Axcel Fungicort; Conazole; Daktacort; Decocort; Micon-H; Neo-Penotran; Tri-Micon; Zaricort; *Spain*: Bexicortil†; Blastoestimulina; Brentan; Nutracel; *Swed.*: Cortimyk; Daktacort; *Switz.*: Acne Creme Plus; Daktacort; Decoderm bivalent; *Thai.*: Daktacort; Decocort†; Fungisil-T; Kelaplus; Ladocort; Lymarin; Tara-Plus; Timi; Trimicon; *Turk.*: Ekze-Mant; Gynotran; Neo-Penotran; Nidazol-M; Pers-Mant; *UK*: Acorvio Plus; Daktacort HC; Daktacort; *Ukr.*: Klion-D (Клион-Д); Mycosolon (Микозолон)†; Neo-Penotran (Нео-Пенотран); Neotrizol (Неотризол); *USA*: Fungoid HC; Vusion; *Venez.*: Daktozin.

Pharmacopoeial Preparations
BP 2014: Miconazole and Hydrocortisone Acetate Cream; Miconazole and Hydrocortisone Cream; Miconazole and Hydrocortisone Ointment; Miconazole Cream; Miconazole Oromucosal Gel;
USP 36: Miconazole Injection; Miconazole Nitrate Cream; Miconazole Nitrate Topical Powder; Miconazole Nitrate Vaginal Suppositories.

Naftifine Hydrochloride *(BANM, USAN, rINNM)*

AW-105-843; Hidrocloruro de naftifina; Naftifin Hidroklorür; Naftifina, hidrocloruro de; Naftifine, Chlorhydrate de; Naftifini Hydrochloridum; Naftifungin Hydrochloride; SN-105-843 (naftifine); Нафтифина Гидрохлорид.
(*E*)-*N*-Cinnamyl-*N*-methyl(1-naphthylmethyl)amine hydrochloride.
$C_{21}H_{21}N,HCl=323.9$
CAS — 65472-88-0 (naftifine); 65473-14-5 (naftifine hydrochloride).
ATC — D01AE22.
ATC Vet — QD01AE22.
UNII — 25UR9N9041.

Pharmacopoeias. In *US.*

USP 36: (Naftifine Hydrochloride). Store in airtight containers.

Profile

Naftifine hydrochloride is an allylamine derivative (see Terbinafine, p. 593.3) which is fungicidal against dermatophytes, but only fungistatic against *Candida* spp.

Naftifine hydrochloride 1 or 2% is applied topically for fungal nail and skin infections, particularly dermatophytosis (see Skin Infections, p. 568.1).

Local reactions such as burning or stinging may occur.

Reviews.

1. Gupta AK, *et al.* Naftifine: a review. *J Cutan Med Surg* 2008; **12:** 51–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Exoderil; *Canad.*: Naftin†; *China*: Fang Di (芳迪); Xin Xin (欣欣); *Cz.*: Exoderil; *Ger.*: Exoderil†; *Gr.*: Exoderil; *Hong Kong*: Exoderil; *Hung.*: Exoderil; *Indon.*: Exoderil; *Israel*: Exoderil; *Ital.*: Suadian; *Malaysia*: Exoderil; *Pol.*: Exoderil; *Rus.*: Exoderil (Экзодерил); *Spain*: Micosona†; *Turk.*: Exoderil; *Ukr.*: Exoderil (Экзодерил); *USA*: Naftin.

Multi-ingredient Preparations. *China*: Bi Liang (必亮).

Pharmacopoeial Preparations
USP 36: Naftifine Hydrochloride Cream; Naftifine Hydrochloride Gel.

Natamycin *(BAN, USAN, pINN)*

Antibiotic A-5283; CL-12625; E235; Natamicina; Natamycine; Natamycinum; Natamycyna; Natamysiini; Pimaricin; Pimarisin; Натамицин.
$C_{33}H_{47}NO_{13}=665.7$
CAS — 7681-93-8.
ATC — A01AB10; A07AA03; D01AA02; G01AA02; S01AA10.
ATC Vet — QA01AB10; QA07AA03; QD01AA02; QG01AA02; QS01AA10.
UNII — 8O0C852CPO.

Pharmacopoeias. In *Jpn, Pol.*, and *US.*

USP 36: (Natamycin). An off-white to cream-coloured powder. It may contain up to 3 moles of water. Practically insoluble in water; soluble in glacial acetic acid and in dimethylformamide; slightly soluble in methyl alcohol. A 1% suspension in water has a pH of 5.0 to 7.5. Store in airtight containers. Protect from light.

Uses and Administration

Natamycin is a polyene antifungal antibiotic produced by the growth of *Streptomyces natalensis*. It is used for the local treatment of candidiasis (p. 564.1) and fungal keratitis (see Eye Infections, p. 565.3). It has also been used in vaginal trichomoniasis (p. 925.1).

A 5% ophthalmic suspension or a 1% ointment of natamycin is used in the treatment of blepharitis, conjunctivitis, or keratitis due to susceptible fungi, including *Fusarium solani*.

Natamycin lozenges are used for the treatment of oral candidiasis in a dose of 10 mg every 4 to 6 hours. Tablets have been given orally for the treatment of intestinal candidiasis. Natamycin has also been used topically for fungal skin infections and for candidal and trichomonal infections of the vagina.

Adverse Effects and Precautions

Gastrointestinal disturbances have occurred after oral use of natamycin. Local application has sometimes produced irritation.

Antimicrobial Action

Natamycin is a polyene antifungal active against *Candida* and *Fusarium* spp. In addition it is active against the protozoan *Trichomonas vaginalis*.

Pharmacokinetics

Natamycin is poorly absorbed from the gastrointestinal tract. It is not absorbed through the skin or mucous membranes when applied topically. After ocular use, natamycin is present in therapeutic concentrations in corneal stroma but not in intra-ocular fluid; systemic absorption does not usually occur.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Natacyn; *China*: Natezhen (那特真); *Cz.*: Pimafucin; *Fin.*: Pimafucin; *Ger.*: Infectomyk; Pima Biciron N†; Pimafucin†; *Hong Kong*: Natacyn†; *Hung.*: Pimafucin; *India*: Elmycin; Natadrops; Natam; Natamet; Natoptic; *Indon.*: Fukricin; *Malaysia*: Natacyn; *Mex.*: Miconacina; *Neth.*: Pimafucin; *Pol.*: Pimafucin; *Rus.*: Pimafucin (Пимафуцин); *S.Afr.*: Natacyn; *Singapore*: Natacyn; *Thai.*: Natacyn; *Turk.*: Pimafucin; *Ukr.*: Pimafucin (Пимафуцин); *USA*: Natacyn.

Multi-ingredient Preparations. *Cz.*: Pimafucort; *Fin.*: Pimafucort; *Hung.*: Pimafucort; *Neth.*: Pimafucort; *NZ*: Pimafucort; *Pol.*: Pimafucort; *Port.*: Pimafucort; *Rus.*: Pimafucort (Пимафукорт); *Ukr.*: Pimafucort (Пимафукорт).

Pharmacopoeial Preparations
USP 36: Natamycin Ophthalmic Suspension.

Neticonazole Hydrochloride *(rINNM)*

Hidrocloruro de neticonazol; Neticonazol, hidrocloruro de; Néticonazole, Chlorhydrate de; Neticonazoli Hydrochloridum; SS-717; Нетиконазола Гидрохлорид.
(*E*)-1-[2-(Methylthio)-1-[*o*-(pentyloxy)phenyl]vinyl]imidazole hydrochloride.
$C_{17}H_{22}N_2OS,HCl=338.9$
CAS — 130726-68-0 (neticonazole); 130773-02-3 (neticonazole hydrochloride).
UNII — PKF582ZH6P.

Profile

Neticonazole is an imidazole antifungal that has been used topically in preparations containing 1% of the hydrochloride in the treatment of superficial fungal infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Atolant.

Nifuroxime *(rINN)*

CCRIS-1180; NF-6; Nifuroxima; Nifuroximum; Nitrofuroxime; Нифуроксим.
5-Nitro-2-furaldehyde oxime.
$C_5H_4N_2O_4=156.1$
CAS — 6236-05-1.
UNII — 465N7P5U85.

NOTE. The names carbilquinone and carbazylquinone have been (possibly erroneously) applied to nifuroxime; however, carbazilquinone is a synonym for the antineoplastic carboquone, and care should be taken to avoid confusion.

Profile

Nifuroxime is a nitrofuran antimicrobial that has been used with furazolidone to treat vaginal candidiasis and trichomoniasis.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Mex.*: Reuginal.

Nystatin *(BAN, USAN, rINN)*

Fungicidin; Nistatin; Nistatina; Nistatinas; Nisztatin; Nystatiini; Nystatine; Nystatinum; Nystatyna; Нистатин.
CAS — 1400-61-9.
ATC — A07AA02; D01AA01; G01AA01.
ATC Vet — QA07AA02; QD01AA01; QG01AA01.
UNII — BDF1O1C72E (nystatin); W1LX4T91WI (nystatin A_1).

Pharmacopoeias. In *Eur.* (see p. vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 8: (Nystatin). An antifungal substance obtained by fermentation using certain strains of *Streptomyces noursei*. It contains mainly tetraenes, the principal component being nystatin A_1. The potency is not less than 4400 units/mg and not less than 5000 units/mg if intended for oral use, calculated with reference to the dried substance. It is a yellow or slightly brownish hygroscopic powder. Practically insoluble in water and in alcohol; freely soluble in dimethylformamide and in dimethyl sulfoxide; slightly soluble in methyl alcohol. Store in airtight containers. Protect from light.

USP 36: (Nystatin). A substance, or a mixture of two or more substances, produced by the growth of *Streptomyces noursei* (Streptomycetaceae). It has a potency of not less than 4400 units/mg, or, where intended for use in extemporaneous preparation of oral suspensions, not less than 5000 units/mg. A yellow to light tan, hygroscopic powder, with an odour suggestive of cereals; it is affected by long exposure to light, heat, and air. Practically insoluble in water and in alcohol; insoluble in chloroform and in ether; freely soluble in dimethylformamide and in dimethyl sulfoxide; slightly to sparingly soluble in methyl alcohol, in *n*-butyl alcohol, and in *n*-propyl alcohol. A 3% suspension in water has a pH of 6.0 to 8.0. Store in airtight containers. Protect from light.

Uses and Administration

Nystatin is a polyene antifungal antibiotic used for the prophylaxis and treatment of candidiasis of the skin and mucous membranes (see p. 564.1). It has been used with antibacterials in various regimens to suppress the overgrowth of gastrointestinal flora and as part of selective decontamination regimens (see Intensive Care, p. 187.3).

For the treatment of intestinal or oesophageal candidiasis, nystatin is given in oral doses of 500 000 or 1 000 000 units, as a tablet or capsule, 3 or 4 times daily.

For the treatment of lesions of the mouth, pastilles or a suspension may be given in a dosage of 100 000 units 4 times daily. The formulation should be kept in contact with the affected area for as long as possible, and patients should avoid taking food or drink for one hour after a dose. In the USA, doses of 400 000 to 600 000 units 4 times daily of the suspension, or 200 000 to 400 000 units 4 or 5 times daily as lozenges, are used.

For prophylaxis of intestinal candidiasis in patients given broad-spectrum antibacterials, tablets to a total dose of 1 000 000 units daily may be given.

For details of doses in children, see below.

For the treatment of vaginal infections, nystatin is given in a dosage of 100 000 to 200 000 units daily for 14 days or longer as pessaries or vaginal cream. For cutaneous lesions, ointment, gel, cream, or dusting powder containing *100 000 units/g may be applied 2 to 4 times daily.*

A liposomal formulation of nystatin for *parenteral* use is under investigation.

Administration in children. Nystatin may be used orally in infants and children for the prevention and treatment of candida infections of the mucous membranes. It may also be used topically for candidiasis of the skin.

For the treatment of intestinal candidiasis, an oral dose of 100 000 units 4 times daily is recommended. Nystatin oral suspension is used locally for the treatment of oral lesions: UK licensed product information recommends a dose of 100 000 units be applied 4 times daily for infants and children; in the USA, 200 000 units for infants, or 400 000 to *600 000 units for older children, may be given 4 times daily.* The formulation should be kept in contact with the affected areas for as long as possible.

For prophylaxis of oral infection in infants born to mothers with vaginal candidiasis, nystatin 100 000 units once daily is recommended. Oral nystatin has also been studied for the prevention of invasive fungal infections, such as candidiasis, in very premature or very low birthweight infants;[1] typically doses of 100 000 units 3 times daily have been used.

1. Austin N, *et al.* Prophylactic oral/topical non-absorbed antifungal agents to prevent invasive fungal infection in very low birth weight infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 01/12/09).

Candidiasis. A systematic review[1] of 14 studies (12 of prophylaxis, 2 of treatment) considered that nystatin could not be recommended for prophylaxis or treatment of *Candida* infections in patients with immunosuppression. In practice, fluconazole is usually preferred in such patients (see p. 564.1). Despite this, it has been suggested that nystatin may be a better choice for prophylaxis in very low birth-weight infants[2] (those weighing below 1.5 kg at birth).

1. Getzsche PC, Johansen HK. Nystatin prophylaxis and treatment in severely immunodepressed patients. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 28/06/05).
2. Isaacs D. Fungal prophylaxis in very low birth weight neonates: nystatin, fluconazole or nothing? *Curr Opin Infect Dis* 2008; 21: 246–50.

Adverse Effects

Nausea, vomiting, and diarrhoea have occasionally been reported after oral use of nystatin. Oral irritation or sensitisation may occur. Rashes, including urticaria, have occurred and Stevens-Johnson syndrome has been reported rarely. Irritation may occur rarely after the topical use of nystatin.

Effects on the skin. Generalised pustular eruptions were reported in 3 patients after oral nystatin.[1] Subsequent sensitivity testing revealed delayed (type IV) hypersensitivity to nystatin.

1. Küchler A, *et al.* Acute generalized exanthematous pustulosis following oral nystatin therapy: a report of three cases. *Br J Dermatol* 1997; 137: 808–11.

Precautions

Some intravaginal preparations of nystatin may damage latex contraceptives and additional contraceptive precautions may be necessary during treatment.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nystatin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Antimicrobial Action

Nystatin is a polyene antifungal antibiotic that interferes with the permeability of the cell membrane of sensitive fungi by binding to sterols, chiefly ergosterol. Its main action is against *Candida* spp.

Pharmacokinetics

Nystatin is poorly absorbed from the gastrointestinal tract. It is not absorbed through the skin or mucous membranes when applied topically.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Candermil; Candidias; Dipni; Micostatin; Neostatin; Nistagrand; Nistamed; Nistat; *Austral.*: Mycostatin; Nilstat; *Austria*: Candio; Mycostatin; Nystaderm†; *Belg.*: Nilstat; *Braz.*: Albistin; Bebex N; Canditrat; Inofungin; Kandistatt†; Micostat†; Micostalab; Micostatin; Neo Mistatin; Neostatin; Nicostat; Nidazolin; Nistagyn†; Nistatec; Nistatin†; Nistaval; Nistomic; Nistrazin; Tricocet; Vagistatina; *Canad.*: Mycostatin†; Nyaderm; *Chile*: Micostatin; Nistoral; *China*: Fukangning (健康宁); Mycostatin (米可定); *Cz.*: Fungicidin; *Denm.*: Mycostatin; *Fin.*: Mycostatin; *Fr.*: Mycostatine; *Ger.*: Adicair; Biofanal; Candio-Hermal; Lederlind; Moronal; Mykoderm Heilsalbe; Mykundex mono; Mykundex; Nystaderm; *Gr.*: Mycostatin; Nystamysyn; *Hong Kong*: Christatin†; Lystin; Mycostatin†; *India*: Mycostatin; *Indon.*: Candistin; Cazetin; Enystin; Fungatin; Fustin; Kandistatin; Mycostatin; Nymiko; Nystin; *Irl.*: Mycostatin; *Ital.*: Mycostatin; *Malaysia*: Mikostat; Mycostatin; Uphastatin; *Mex.*: Aponistan; Bistatin; Mibesan-S; Micostatin; Nistan; Nistaquim; Nizin-V; *Norw.*: Mycostatin; *NZ*: Mycostatin; Nilstat; *Philipp.*: Afunginal; Maicostat; Mycostatin†; Mycosyl; Orastin; Stanys; *Port.*: Mycostatin; *S.Afr.*: Candacide; Canstat; Mycostatin; Nystacid; *Singapore*: Candistatin; Mycostatin; *Spain*: Mycostatin; *Swed.*: Mycostatin; *Switz.*: Multilind; Mycostatine; *Thai.*: Mycostatin†; Tystatin; *Turk.*: Fungostatin; Mikostatin; *UAE*: Mikostat; *UK*: Nystan; *USA*: Mycostatin; Nilstat; Nystop; Pedi-Dri; pediaderm AF; *Venez.*: Micostatin.

Multi-ingredient Preparations. *Arg.*: Bacticort Complex; Bexon; Biotaer Nebulizable; Dermadex NN; Farm-X Duo; Fasigyn Nistatina; Flagystatin; Kenacomb; Linfol; Linfol; Metanis; Mini O; Naxo TV; Nistinol†; O-Biol P†; O-Biol; Pelvicillin NF; Polygynax; Tratomax; Tratomax; Vagilen; *Austral.*: Kenacomb; Otocomb Otic; *Austria*: Mycostatin-Zinkoxid; *Belg.*: Mycolog; *Braz.*: Alivbaby; Babyneo; Benzevit; Bio-Vagin; Colpagex-N†; Colpatrin; Colpist; Colpistar; Colpistatin; Colpolase†; Dermodex; Dermokin†; Dermostatin; Donnagel; Flagyl Nistatina; Fungimax; Ginec; Ginestatin†; Gynax-N; Kolpitrat; Londerm-N†; Mud; Naxogin Composto; Neolon D; Omcilon-A M; Oncibel; Oncileg; Onciplus†; Oxyderme; Poliginax; Pratiderm; Tricolpex; Tricomax; Trinodazol Nistatina; Trinodazol; Trivagel N; Vagi Biotic; Vagimax†; Vagitrin-N; *Canad.*: Flagystatin; ratio-Triacomb; Viaderm-KC; *Chile*: Multilind; Naxogin Compositum†; Nistaglos; *China*: Kenacomb (复方康纳乐霜); Lang Yi (朗依); Shui Qing (水青); *Cz.*: Macmiror Complex; Polygynax; *Denm.*: Kenalog Comp med Mycostatin†; *Fin.*: Flagyl Comp; *Fr.*: Auricularum; Polygynax Virgo; Polygynax; Tergynan; *Ger.*: Candio-Hermal Plus; Lokalison-antimikrobiell Creme N†; Moronal V†; Multilind; Mykoproct sine†; Mykundex Heilsalbe; Nystaderm comp; Nystalocal; Nystatin Softpaste; Volonimat Plus N†; *Gr.*: Auricularum; Beclomycin; Bioderm; Dermochrom; Kenacomb; *Hong Kong*: Anlina†; Centacomb; Clonetin†; Dermawell†; Inquadeicren; Kenacomb†; Macmiror Complex; Neoclobet†; Polygynax; Triacomb†; Uni-Quaderm†; *India*: Kenacomb; *Indon.*: Fasigyn-Nystatin†; Fladystin; Flagystatin; Gynoxa; Myco-Z; Naxogin Complex; Neo Gynoxa; New Kenacomb†; Provagin; Trichostatic; Vagistin; *Irl.*: Kenacomb†; Nystaform†; Timodine; Tinaderm-M†; *Israel*: Dermacombin; *Ital.*: Assocort†; Fasigin N; Inimur Complex; Macmiror Complex; *Malaysia*: Kenacomb; *Mex.*: Acenil; Bidrozil†; Decadron con Nistatina; Dermalog-C; Flagystatin V; Kenacomb; Macmiror Complex V; Metrofur†; Micostatin Baby; Novageon; Nysmosons-V; Promibasol-Plus†; Vagitrol-V; *Neth.*: Mycolog†; *NZ*: Kenacomb; Viaderm-KC; *Philipp.*: Dermovate-NN; Flagystatin; Kenacomb†; Lidex NGN; Oticom; *Pol.*: Macmiror Complex; Triacomb; *Port.*: Dafnegil; *Rus.*: Gyterna (Гитерна); Macmiror Complex (Макмирор Комплекс); Polygynax (Полижинакс); Tergynan (Тержинан); *S.Afr.*: Hiconcil-NS†; Kenacomb†; Riostatin†; Tetrex-F†; *Singapore*: Flagystatin; Polygynax; *Spain*: Interderm; Positon; *Swed.*: Kenacombin Novum†; *Switz.*: Multilind; Mycolog N; Nystalocal; Topsym polyvalent; *Thai.*: Dermacombin; Gynecon-T; Gynecon; Gynocot†; Gynova†; Gyonep; Gyracon; Kenacomb†; Nystin; Quinradon-N†; Vagicin; VG Med; *Turk.*: Macmiror Complex; *UAE*: Mikostat Baby Ointment; Panderm; *UK*: Dermovate-NN†; Nystaform-HC; Nystaform; Timodine; Tinaderm-M†; Trimovate; *Ukr.*: Macmiror Complex (Макмирор Комплекс); Micogynax (Микожинакс); Polygynax (Полижинакс); Tergynan (Тержинан); *USA*: First Duke's Mouthwash; First Mary's Mouthwash; Myco-Biotic II; Myco-Triacet II; Mycogen II; Mycolog-II; Myconel; NGT; Tri-Statin II; *Venez.*: Halcicomb; Kenacomb.

Pharmacopoeial Preparations

BP 2014: Nystatin Ointment; Nystatin Oral Suspension; Nystatin Pastilles; Nystatin Pessaries; Nystatin Tablets;

USP 36: Nystatin and Triamcinolone Acetonide Cream; Nystatin and Triamcinolone Acetonide Ointment; Nystatin Cream; Nystatin for Oral Suspension; Nystatin Lotion; Nystatin Lozenges; Nystatin Ointment; Nystatin Oral Suspension; Nystatin Tablets; Nystatin Topical Powder; Nystatin Vaginal Suppositories; Nystatin Vaginal Tablets; Nystatin, Neomycin Sulfate, Gramicidin, and Triamcinolone Acetonide Cream; Nystatin, Neomycin Sulfate, Gramicidin, and Triamcinolone Acetonide Ointment; Oxytetracycline and Nystatin Capsules; Oxytetracycline and Nystatin for Oral Suspension; Tetracycline Hydrochloride and Nystatin Capsules.

Omoconazole Nitrate *(USAN, rINNM)*

10-80-07; Nitrato de omoconazol; Omoconazol, nitrato de; Omoconazole, Nitrate d'; Omoconazoli Nitras; Омоконазола Нитрат.

(*Z*)-1-[2,4-Dichloro-β-[2-(*p*-chlorophenoxy)ethoxy]-α-methylstyryl]imidazole nitrate.

$C_{20}H_{17}Cl_3N_2O_2,HNO_3$=486.7

CAS — 74512-12-2 (omoconazole); 83621-06-1 (omoconazole nitrate).

ATC — D01AC13; G01AF16.

ATC Vet — QD01AC13; QG01AF16.

UNII — 15LTY5STY6.

Profile

Omoconazole is an imidazole antifungal used locally for fungal skin infections (p. 568.1) and for vaginal candidiasis (p. 564.1). It is applied topically as the nitrate as a 1% cream, powder, or solution in the treatment of cutaneous candidiasis, dermatophytosis, and pityriasis versicolor. For vaginal candidiasis, omoconazole nitrate is given as pessaries in doses of 150 mg daily for 6 days, 300 mg daily for 3 days, or 900 mg as a single dose.

Intravaginal preparations of azoles may damage latex contraceptives.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Fongamil; Fongarex; *Gr.*: Afongan; Fongamil; *Hung.*: Mikogal; *Mex.*: Afongan†; *Port.*: Fongamil; *Rus.*: Mikogal (Микогал); *Ukr.*: Micogal (Микогал).

Oxiconazole Nitrate *(BANM, USAN, rINNM)*

Nitrato de oxiconazol; Oxiconazol, nitrato de; Oxiconazole, Nitrate d'; Oxiconazoli Nitras; Ro-13-8996; Ro-13-8996/000 (oxiconazole); Ro-13-8996/001; SGD-301-76; ST-813; Оксиконазола Нитрат.

2′,4′-Dichloro-2-imidazol-1-ylacetophenone (*Z*)-*O*-(2,4-dichlorobenzyl)oxime mononitrate.

$C_{18}H_{13}Cl_4N_3O,HNO_3$=492.1

CAS — 64211-45-6 (oxiconazole); 64211-46-7 (oxiconazole nitrate).

ATC — D01AC11; G01AF17.

ATC Vet — QD01AC11; QG01AF17.

UNII — RQ8UL4C17S.

Profile

Oxiconazole is an imidazole antifungal applied topically as the nitrate as a cream, solution, or powder equivalent to oxiconazole 1% in the treatment of fungal infections of the skin (p. 568.1). It is also given as a pessary in a single dose equivalent to 600 mg of oxiconazole in the treatment of vaginal candidiasis (p. 564.1).

Local reactions including burning and itching have been reported. Intravaginal preparations of azoles may damage latex contraceptives.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3.

Reviews.

1. Jegasothy BV, Pakes GE. Oxiconazole nitrate: pharmacology, efficacy, and safety of a new imidazole antifungal agent. *Clin Ther* 1991; 13: 126–41.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Oxistat†; *Austria*: Lidermant†; *Braz.*: Micotin; Oceral; Oxipelle; *Cz.*: Myfungar; *Fr.*: Fonx; *Ger.*: Myfungar†; *Mex.*: Myfungar; Oxistat; *Rus.*: Myfungar (Мифунгар); *Spain*: Salongo; *Switz.*: Oceral; *Turk.*: Oceral; *Ukr.*: Myfungar (Мифунгар)†; *USA*: Oxistat.

Multi-ingredient Preparations. *India*: Zoderm.

Parconazole Hydrochloride *(USAN, rINNM)*

Hidrocloruro de parconazol; Parconazol, hidrocloruro de; Parconazole, Chlorhydrate de; Parconazoli Hydrochloridum; R-39500; Парконазола Гидрохлорид.

cis-1-[[2-(2,4-Dichlorophenyl)-4-[(2-propynyloxy)methyl]-1,3-dioxolan-2-yl]methyl]-1*H*-imidazole hydrochloride.

$C_{17}H_{16}Cl_2N_2O_3$, HCl=403.7

CAS — 61400-59-7 (parconazole); 68685-54-1 (parconazole); 62973-77-7 (parconazole hydrochloride).

UNII — 8IF7HES548.

Profile

Parconazole is an antifungal that has been used as the hydrochloride in the treatment of gastrointestinal candidiasis in veterinary medicine.

Pentamycin

Fungichromin; Lagosin; Pentamicina; Пентамицин.

$C_{35}H_{58}O_{12}$=670.8

CAS — 6834-98-6.

ATC — G01AA11.

ATC Vet — QG01AA11.

UNII — 1JB340D58S.

NOTE. The name FemiFect has been used as a trade mark for pentamycin.

Profile

Pentamycin is a polyene antifungal antibiotic obtained from *Streptomyces pentaticus*. It has been used in the treatment of vaginal candidiasis and for the protozoal infection trichomoniasis.

References.

1. Frey Tirri B, *et al.* Safety, tolerability and pharmacokinetics of intravaginal pentamycin. *Chemotherapy* 2010; **56**: 190–6.

Posaconazole *(BAN, USAN, rINN)*

Posaconazol; Posaconazolum; Sch-56592; Позаконазол.

4-[4-[4-[4-[[(3*R*,5*R*)-5-(2,4-Difluorophenyl)tetrahydro-5-(1*H*-1,2,4-triazol-1-ylmethyl)-3-furyl]methoxy]phenyl]-1-piperazinyl]phenyl]-1-[(1*S*,2*S*)-1-ethyl-2-hydroxypropyl]-Δ^2-1,2,4-triazolin-5-one.

$C_{37}H_{42}F_2N_8O_4$=700.8

CAS — 171228-49-2.

ATC — J02AC04.

ATC Vet — QJ02AC04.

UNII — 6TK1G07BHZ.

Uses and Administration

Posaconazole is an oral triazole antifungal used in the treatment of oropharyngeal candidiasis. It is also indicated in the treatment of invasive aspergillosis, chromoblastomycosis, coccidioidomycosis, fusariosis, or mycetoma infections in patients who are resistant to, or intolerant of, other antifungals. Posaconazole is also given for the prophylaxis of fungal infections in patients who are at high risk for invasive fungal disease due to prolonged neutropenia.

Posaconazole is given orally as a suspension; doses should be given with a meal, or a nutritional supplement in those who cannot tolerate food, in order to enhance oral absorption and ensure adequate exposure.

For the treatment of **oropharyngeal candidiasis** posaconazole is given in a loading dose of 200 mg on the first day, followed by 100 mg daily for 13 days. In patients with oropharyngeal candidiasis refractory to itraconazole and/or fluconazole, posaconazole is given at a dose of 400 mg twice daily.

In patients with refractory **invasive systemic fungal infections**, it is given at a dose of 400 mg twice daily. Patients not tolerating food or nutritional supplements should take 200 mg four times daily.

In the **prophylaxis** of invasive fungal infections, the recommended dose is 200 mg three times daily. Treatment is continued until recovery from neutropenia or immunosuppression. In patients undergoing cytotoxic chemotherapy for haematological malignancies, or haematopoietic stem-cell transplantation, treatment should begin several days before the anticipated onset of neutropenia and continue for 7 days after the neutrophil count rises above 500 cells/mm^3.

References.

1. Herbrecht R. Posaconazole: a potent, extended-spectrum triazole anti-fungal for the treatment of serious fungal infections. *Int J Clin Pract* 2004; **58**: 612–24.
2. Segal BH, *et al.* Posaconazole as salvage therapy in patients with chronic granulomatous disease and invasive filamentous fungal infection. *Clin Infect Dis* 2005; **40**: 1684–8.
3. Keating GM. Posaconazole. *Drugs* 2005; **65**: 1553–67.
4. Raad II, *et al.* Safety of long-term oral posaconazole use in the treatment of refractory invasive fungal infections. *Clin Infect Dis* 2006; **42**: 1726–34.
5. Nagappan V, Deresinski S. Posaconazole: a broad-spectrum triazole antifungal agent. *Clin Infect Dis* 2007; **45**: 1610–7.
6. Frampton JE, Scott LJ. Posaconazole: a review of its use in the prophylaxis of invasive fungal infections. *Drugs* 2008; **68**: 993–1016.
7. Rachwalski EJ, *et al.* Posaconazole: an oral triazole with an extended spectrum of activity. *Ann Pharmacother* 2008; **42**: 1429–38.
8. Morris MI. Posaconazole: a new oral antifungal agent with an expanded spectrum of activity. *Am J Health-Syst Pharm* 2009; **66**: 225–36.
9. Cornely OA, *et al.* Current experience in treating invasive zygomycosis with posaconazole. *Clin Microbiol Infect* 2009; **15** (suppl 5): 77–81.
10. Bhattacharya M, *et al.* Posaconazole. *J Postgrad Med* 2010; **56**: 163–7.

Trypanosomiasis. For mention of posaconazole being tried in American trypanosomiasis see p. 925.3

Adverse Effects

The most commonly reported adverse effects with posaconazole are headache and nausea. Other common adverse effects include abdominal pain, anorexia, asthenia, back pain, diarrhoea, dyspepsia, dizziness, dry mouth, dry skin, fatigue, fever, flatulence, hot flushes, insomnia, neutropenia, paraesthesia, pruritus, rash, somnolence, and vomiting. Increased liver enzyme values, and rarely more severe hepatotoxicity (including fatal cases), have occurred in some patients, especially in those with serious underlying disease. Hypersensitivity and allergic reactions, including Stevens-Johnson syndrome, have occurred rarely.

Precautions

Some azoles have been associated with QT interval prolongation and licensed product information therefore advises that posaconazole should be used with caution in patients with potentially proarrhythmic conditions. Patients who develop abnormal liver function tests while being treated with posaconazole should be routinely monitored for the development of more serious liver injury.

Breast feeding. Breast feeding while taking posaconazole is not recommended by UK licensed product information.

Pregnancy. Posaconazole has been shown to be teratogenic and embryotoxic in *animal* studies and its use is generally not recommended during pregnancy. For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3. UK licensed product information recommends that women of child-bearing potential should use effective contraception during treatment with posaconazole.

Interactions

Posaconazole is metabolised by the uridine diphosphate glucuronosyltransferase UGT1A4, and is a substrate for p-glycoprotein. The use of drugs that either inhibit (for example, clarithromycin, erythromycin, ciclosporin, and verapamil) or induce (see below) enzymes in this pathway may increase or decrease plasma-posaconazole concentrations, respectively. Rifabutin and phenytoin have been shown to decrease plasma-posaconazole concentrations and a similar effect may be expected with rifampicin, carbamazepine, primidone, and phenobarbital. Concentrations of posaconazole are reduced by cimetidine possibly due to reduced absorption of posaconazole as a result of decreased acid production and reduced posaconazole concentrations may also be expected with other H_2-antagonists and proton pump inhibitors.

Posaconazole is an inhibitor of the cytochrome P450 isoenzyme CYP3A4 and concentrations of other drugs that are metabolised by this enzyme pathway may be increased by posaconazole. Increased plasma concentrations of astemizole, cisapride, halofantrine, pimozide, quinidine, and terfenadine could be expected and concomitant use is contra-indicated because of the risk of cardiac arrhythmias including torsade de pointes. Use with ergot alkaloids such as ergotamine and dihydroergotamine is also contra-indicated because of the possible risk of ergotism. In the UK, HMG-CoA reductase inhibitors such as atorvastatin, lovastatin, and simvastatin are contra-indicated as concomitant use has been associated with rhabdomyolysis; US licensed product information, however, suggests that use may be possible if consideration is given to lowering the statin dose. Increased plasma concentrations of ciclosporin, sirolimus, and tacrolimus have been noted. Doses of ciclosporin and tacrolimus may need to be reduced and concentrations monitored, although use of sirolimus with posaconazole should generally be avoided. Close monitoring of blood glucose is necessary if posaconazole is used with oral hypoglycaemics such as the sulfonylureas. Dose reductions may be needed for calcium-channel blockers, digoxin, vinca alkaloids, and some benzodiazepines (such as alprazolam, midazolam, and triazolam). It is expected that posaconazole will increase the concentrations of HIV-protease inhibitors and NNRTIs.

Interactions may occur where both posaconazole and the other drug are affected. Examples are ciclosporin (where concentrations of both posaconazole and ciclosporin are increased) and rifabutin (where concentrations of posaconazole are reduced but those of rifabutin are increased).

For further information on interactions between drugs metabolised by the cytochrome P450 isoenzyme CYP3A4 and azoles, see under Itraconazole, p. 585.1.

For reviews of drug interactions with azole antifungals, see Itraconazole, p. 585.2.

Antimicrobial Action

Posaconazole is a triazole antifungal drug that in sensitive fungi inhibits the enzyme lanosterol 14α-demethylase (CYP51) resulting in the impairment of ergosterol synthesis in fungal cell membranes. Posaconazole has activity against *Candida* spp., *Aspergillus* spp., *Coccidioides immitis*, *Fonsecaea pedrosoi*, and some species of *Fusarium* and zygomycetes.

Reports of breakthrough fungal infections in patients treated empirically or prophylactically with posaconazole [1-3]

1. Rieger C, *et al.* Breakthrough infection of Trichosporon asahii during posaconazole treatment in a patient with acute myeloid leukaemia. *Infect J Clin Microbiol Infect Dis* 2007; **26**: 843–5.
2. Kishel JJ, Sivik J. Breakthrough invasive fungal infection in an immunocompromised host while on posaconazole prophylaxis: an omission in patient counseling and follow-up. *J Oncol Pharm Pract* 2008; **14**: 189–93.
3. Lekakis LJ, *et al.* Fatal rhizopus pneumonia in allogeneic stem cell transplant patients despite posaconazole prophylaxis: two cases and review of the literature. *Biol Blood Marrow Transplant* 2009; **15**: 991–5.

Pharmacokinetics

Posaconazole has linear pharmacokinetics after single and multiple doses with a high fat meal. No further increases in plasma concentration are seen with doses above 800 mg daily. It is slowly absorbed from the gastrointestinal tract and has a large volume of distribution. Peak plasma concentrations occur about 5 hours after an oral dose. Steady state plasma-posaconazole concentrations occur after 7 to 10 days of multiple dosage. Plasma protein binding is over 98%.

Metabolism plays only a minor role in the elimination of posaconazole; most circulating metabolites are glucuronide conjugates with only small amounts of oxidative metabolites. Posaconazole is slowly eliminated with a mean elimination half-life of 35 hours. The main elimination route of posaconazole is via the faeces (77%) where 66% of a dose is excreted unchanged. About 14% of a dose is excreted in the urine with only trace amounts excreted unchanged.

Reviews.

1. Courtney R, *et al.* Pharmacokinetics, safety, and tolerability of oral posaconazole administered in single and multiple doses in healthy adults. *Antimicrob Agents Chemother* 2003; **47**: 2788–95.
2. Krishna G, *et al.* Posaconazole plasma concentrations in juvenile patients with invasive fungal infection. *Antimicrob Agents Chemother* 2007; **51**: 812–8.
3. Dodds Ashley ES, *et al.* Pharmacokinetics of posaconazole administered orally or by nasogastric tube in healthy volunteers. *Antimicrob Agents Chemother* 2009; **53**: 2960–4.
4. Moton A, *et al.* Pharmacokinetics of a single dose of the antifungal posaconazole as oral suspension in subjects with hepatic impairment. *Curr Med Res Opin* 2010; **26**: 1–7.
5. Li Y, *et al.* Pharmacokinetic/pharmacodynamic profile of posaconazole. *Clin Pharmacokinet* 2010; **49**: 379–96.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Noxafil; ***Austral.***: Noxafil; ***Austria***: Noxafil; ***Belg.***: Noxafil; ***Canad.***: Posanol; ***Chile***: Noxafil; ***Cz.***: Noxafil; ***Denm.***: Noxafil; ***Fr.***: Noxafil; ***Ger.***: Noxafil; ***Gr.***: Noxafil; ***Hung.***: Noxafil; ***Irl.***: Noxafil; ***Israel***: Noxafil; ***Ital.***: Noxafil; ***Malaysia***: Noxafil; ***Mex.***: Spriafil; ***Neth.***: Noxafil; ***Norw.***: Noxafil; ***NZ***: Noxafil; ***Pol.***: Noxafil; ***Port.***: Noxafil; ***Rus.***: Noxafil (Нокспфил); ***Singapore***: Noxafil; ***Spain***: Noxafil; ***Swed.***: Noxafil; ***Switz.***: Noxafil; ***Thai.***: Noxafil; ***Turk.***: Noxafil; ***UK***: Noxafil; ***Ukr.***: Noxafil (Нокспфил); ***USA***: Noxafil.

Propionic Acid

Ácido propiónico; E280; E283 (potassium propionate); Kwas propionowy; Propanoico, ácido; Пропионовая Кислота.

Propanoic acid.

$C_2H_5CO_2H$=74.08

CAS — 79-09-4.

UNII — JHU490RVYR.

Pharmacopoeias. In *Fr.* Also in *USNF.*

USNF 31: (Propionic Acid). An oily liquid having a slight pungent, rancid odour. Miscible with water, with alcohol, and with various other organic solvents. Store in airtight containers.

Calcium Propionate

E282; Пропионат Кальция.

Calcium propanoate.

$(C_3H_5O_2)_2Ca$=186.2
CAS — 4075-81-4 (anhydrous calcium propionate); 56744-45-7 (calcium propionate monohydrate).
UNII — 8AI80040KW.

Pharmacopoeias. In *USNF*.

USNF 31: (Calcium Propionate). A white, crystalline solid. Soluble 1 in 3 of water. A 10% solution in water has a pH of 7.5 to 10.5. Store in airtight containers.

Sodium Propionate

E281; Natrii propionas; Natrio propionatas; Natriumpropionaatti; Natriumpropionat; Nátrium-propionát; Propionan sodný; Propionato de sodio; Sodium, propionate de; Пропионат Натрия.
Sodium propanoate.
$C_3H_5NaO_2$=96.06
CAS — 137-40-6 (anhydrous sodium propionate); 6700-17-0 (sodium propionate hydrate).
ATC — S01AX10.
ATC Vet — QA16QA02; QS01AX10.
UNII — DK6Y9P42IN.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Sodium Propionate). Slightly hygroscopic colourless crystals or white or almost white powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in dichloromethane. A 2% solution in water has a pH of 7.8 to 9.2. Store in airtight containers.

USNF 31: (Sodium Propionate). Colourless transparent crystals or a granular crystalline powder; odourless or with a faint acetic-butyric odour. Deliquescent in moist air. Soluble 1 in 1 of water, 1 in 0.65 of boiling water, and 1 in 24 of alcohol; practically insoluble in chloroform and in ether. Store in airtight containers.

Profile

Propionic acid and its salts are antifungals. Calcium and sodium propionate have been used topically, usually with other antimicrobials for the treatment of dermatophyte infections. Eye drops containing sodium propionate have also been used.

Propionic acid and its calcium, sodium, and potassium salts are used in the baking industry as inhibitors of moulds.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Propionat.

Multi-ingredient Preparations. *Arg.*: Cicatrol; Farm-X; Fungicida; Hipoglos Cicatrizante; Novo Miconol†; *Austral.*: Mycoderm; *Austria*: Dermowund†; *Braz.*: Andriodermol; Andriodermol; Colpagex-N†; Gynax-N; Vagitrin-N; *Chile*: Fittig Antimicotico; *Fr.*: Angispray; Dermacide; *Gr.*: Buccasept†; Dermacide; *Indon.*: Decyline; Decyline; *Israel*: Otomycin; *Malaysia*: Mycoderm†; *S.Afr.*: Neopan; *USA*: Amino-Cerv; Prophyllin.

Pyrrolnitrin *(USAN, rINN)*

52230; NSC-107654; Pirrolnitrina; Pyrrolnitrine; Pyrrolnitrinum; Пирролнитрин.
3-Chloro-4-(3-chloro-2-nitrophenyl)pyrrole.
$C_{10}H_6Cl_2N_2O_2$=257.1
CAS — 1018-71-9.
ATC — D01AA07.
ATC Vet — QD01AA07.
UNII — N0P24B6EDQ.

Pharmacopoeias. In *Jpn*.

Profile

Pyrrolnitrin is an antifungal antibiotic isolated from *Pseudomonas pyrrocinia* and has been applied topically in the treatment of superficial fungal infections.

Ravuconazole *(pINN)*

BMS-207147; ER-30346; Ravuconazol; Ravuconazolum; Равуконазол.
4-[2-[(1*R*,2*R*)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-4-thiazolyl]-benzonitrile.
$C_{22}H_{17}F_2N_5OS$=437.5
CAS — 182760-06-1.
UNII — 95YH599JWV.

Profile

Ravuconazole is a triazole antifungal said to possess a broader spectrum of activity than fluconazole or itraconazole. It is under investigation for the treatment of systemic fungal infections. A prodrug of ravuconazole, E-1224, is also being studied for the treatment of American trypanosomiasis.

References.
1. Urbina JA, *et al.* In vitro and in vivo activities of ravuconazole on Trypanosoma cruzi, the causative agent of Chagas disease. *Int J Antimicrob Agents* 2003; 21: 27–38.
2. Gupta AK, *et al.* A phase I/II randomized, double-blind, placebo-controlled, dose-ranging study evaluating the efficacy, safety and pharmacokinetics of ravuconazole in the treatment of onychomycosis. *J Eur Acad Dermatol Venereol* 2005; 19: 437–43.
3. Pasqualotto AC, *et al.* Novel triazole antifungal drugs: focus on isavuconazole, ravuconazole and albaconazole. *Curr Opin Investig Drugs* 2010; 11: 165–74.

Sertaconazole Nitrate *(BANM, rINNM)*

Nitrato de sertaconazol; Sertaconazol, nitrato de; Sertaconazole, Nitrate de; Sertaconazoli Nitras; Sertaconazolnitrat; Sertakonatsollnitraatti; Sertakonazol Nitrat; Sertakonazolnitrat; Sertakonazol-nitrát; Sertakonazolo nitratas; Szertakonazol-nitrát; Сертаконазола Нитрат.
(±)-1-[2,4-Dichloro-β-[[7-chlorobenzo[*b*]thien-3-yl)methoxy]phenethyl]imidazole nitrate.
$C_{20}H_{15}Cl_3N_2OS,HNO_3$=500.8
CAS — 99592-32-2 (sertaconazole); 99592-39-9 (sertaconazole nitrate).
ATC — D01AC14.
ATC Vet — QD01AC14.
UNII — 1DV05410M5.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Sertaconazole Nitrate). A white or almost white powder. Practically insoluble in water; sparingly soluble in alcohol and in dichloromethane; soluble in methyl alcohol. Protect from light.

Profile

Sertaconazole is an imidazole antifungal used topically as the nitrate as a 2% cream, gel, solution, or powder in the treatment of superficial candidiasis, dermatophytosis, seborrhoeic dermatitis, and pityriasis versicolor. In the treatment of vaginal candidiasis it is used as a 2% vaginal cream daily for 7 or 8 days or as a single dose of a 300-mg or 500-mg pessary.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3. Intravaginal preparations of azole antifungals may damage latex contraceptives.

References.
1. Croxtall JD, Plosker GL. Sertaconazole: a review of its use in the management of superficial mycoses in dermatology and gynaecology. *Drugs* 2009; 69: 339–59.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Zalain; *Braz.*: Gyno Zalain; Zalain†; *Chile*: Tromderm; Zalain; *China*: Li Ling Qi (立灵奇); Zalain (卓兰); *Ger.*: Mykosert; Zalain; *Gr.*: Fuganol; *Hong Kong*: Zalain; *Hung.*: Zalain; *India*: Onabet; *Indon.*: Dermofix†; *Ital.*: Sertacream; Sertaderm; Sertadie; Sertagyn; *Mex.*: Ertaczo; *Mon.*: Monazol; *Philipp.*: Zalain; *Port.*: Dermofix; Sertopic; *Rus.*: Zalain (Залаин); *Singapore*: Zalain; *Spain*: Dermofix; Dermoseptic; Gine Zalain†; Ginedermofix; Zalain; *Thai.*: Zalain; *Turk.*: Zalain; *Ukr.*: Zalain (Залаин); *USA*: Ertaczo; *Venez.*: Zalain.

Siccanin *(rINN)*

Sicanina; Siccanine; Siccaninum; Сикканин.
(13a*S*)-1,2,3,4,4aβ,5,6,6a,11bβ,13bβ-Decahydro-4-4-6aβ,9-tetramethyl-13*H*-benzo[*a*]furo[2,3,4-*mn*]xanthen-11-ol.
$C_{22}H_{30}O_3$=342.5
CAS — 22733-60-4.
UNII — L702S858Z6.

Pharmacopoeias. In *Jpn*.

Profile

Siccanin is obtained from *Helminthosporium siccans*, a parasitic organism of rye grass It has antifungal activity and has been used topically as a 1% ointment for dermatophyte infections.

Sodium Parachlorobenzoate

Sodium *p*-Chlorobenzoate; Натрий Парахлорбензоат.
$C_7H_4ClNaO_2$=178.5
CAS — 3686-66-6.

Profile

Sodium parachlorobenzoate has antifungal activity and is used as a 4% powder in the treatment of fungal skin infections (p. 568.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Hung.*: Mycosid.

Sulconazole Nitrate *(BANM, USAN, rINNM)*

Nitrato de sulconazol; RS-44872-00-10-3; RS-44872; Sulconazol, nitrato de; Sulconazole, Nitrate de; Sulconazoli Nitras; Sulkonazol Nitrat; Сульконазола Нитрат.
1-[2,4-Dichloro-β-(4-chlorobenzyl)thiophenethyl]imidazole nitrate.
$C_{18}H_{15}Cl_3N_2S,HNO_3$=460.8
CAS — 61318-90-9 (sulconazole); 61318-91-0 (sulconazole nitrate).
ATC — D01AC09.
ATC Vet — QD01AC09.
UNII — 1T89100D5U.

Pharmacopoeias. In *Fr.* and *US*.

USP 36: (Sulconazole Nitrate). A white to off-white crystalline powder. Soluble 1 in 3333 of water, 1 in 100 of alcohol, 1 in 130 of acetone, 1 in 333 of chloroform, 1 in 286 of dichloromethane, 1 in 2000 of dioxan, 1 in 71 of methyl alcohol, 1 in 10 of pyridine, and 1 in 2000 of toluene. Protect from light.

Uses and Administration

Sulconazole is an imidazole antifungal used topically as the nitrate once or twice daily as a 1% cream or solution in the treatment of fungal skin infections including dermatophyte infections and pityriasis versicolor (see Skin Infections, p. 568.1), and candidiasis (p. 564.1).

Adverse Effects and Precautions

Local reactions including blistering, burning, itching, and erythema have been reported after sulconazole use.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3.

Antimicrobial Action

Sulconazole is an imidazole antifungal with activity against dermatophytes, *Candida* spp., and *Malassezia furfur*.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Antifungal; *Belg.*: Myk-1; *China*: Ge Xuan (革选); *Fr.*: Myk†; *Gr.*: Suldisyn; *Neth.*: Myk-1; *Turk.*: Exelderm; *UK*: Exelderm†; *USA*: Exelderm.

Terbinafine *(BAN, USAN, rINN)*

SF-86-327; SF-86327; Terbinafiini; Terbinafin; Terbinafina; Terbinafinum; Тербинафин.
(*E*)-6,6-Dimethylhept-2-en-4-ynl(methyl)-(1-naphthylmethyl) amine.
$C_{21}H_{25}N$=291.4
CAS — 91161-71-6.
ATC — D01AE15; D01BA02.
ATC Vet — QD01AE15; QD01BA02.
UNII — G7RIW8S0XP.

Terbinafine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de terbinafina; Terbinafiinihydrokloridi; Terbinafin Hidroklorür; Terbinafina, hidrocloruro de; Terbinafine, Chlorhydrate de; Terbinafinhydrochlorid; Terbinafin-hydrochlorid; Terbinafinhydroklorid; Terbinafini Hydrochloridum; Terbinafiny chlorowodorek; Тербинафина Гидрохлорид.
$C_{21}H_{26}ClN$=327.9
CAS — 78628-80-5.
ATC — D01AE15; D01BA02.
ATC Vet — QD01AE15; QD01BA02.
UNII — 012CT1ZU6G.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Terbinafine Hydrochloride). A white or almost white powder. Very slightly or slightly soluble in water; freely soluble in dehydrated alcohol and in methyl alcohol; slightly soluble in acetone. Protect from light.

USP 36: (Terbinafine Hydrochloride). A white or off-white powder. Very slightly or slightly soluble in water; freely

soluble in dehydrated alcohol and in methyl alcohol; slightly soluble in acetone; Protect from light.

Uses and Administration

Terbinafine is an allylamine antifungal given orally as the hydrochloride in the treatment of dermatophyte infections of the skin and nails (p. 568.1). Oral doses are stated in terms of the base. Terbinafine hydrochloride 1.13 g is equivalent to about 1 g of terbinafine. It is also applied, as the hydrochloride, to the skin in dermatophytoses, in pityriasis versicolor (see Skin Infections, p. 568.1), and in cutaneous candidiasis (p. 564.1).

An oral dose of 250 mg is given once daily for 2 to 4 weeks for tinea cruris; treatment may be continued for up to 6 weeks for tinea pedis infections; a 4-week course is used in tinea corporis infections. A cream, gel, or solution containing 1% terbinafine hydrochloride is applied once or twice daily for 1 to 2 weeks to treat tinea corporis and tinea cruris; a 1-week course is recommended for tinea pedis. A 2-week course of treatment is used in cutaneous candidiasis and pityriasis versicolor.

Dermatophyte infections of the nails are treated with the equivalent of terbinafine 250 mg orally once daily for 6 to 12 weeks although longer treatment may be necessary in toe-nail infections.

Dosage should be reduced in patients with renal impairment (see below).

References.
1. Balfour JA, Faulds D. Terbinafine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in superficial mycoses. *Drugs* 1992; 43: 259–84.
2. Abdel-Rahman SM, Nahata MC. Oral terbinafine: a new antifungal agent. *Ann Pharmacother* 1997; 31: 445–56.
3. McClellan KJ, *et al.* Terbinafine: an update of its use in superficial mycoses. *Drugs* 1999; 58: 179–202.
4. Darkes MJ, *et al.* Terbinafine: a review of its use in onychomycosis in adults. *Am J Clin Dermatol* 2003; 4: 39–65.
5. Fleece D, *et al.* Griseofulvin versus terbinafine in the treatment of tinea capitis: a meta-analysis of randomized, clinical trials. *Pediatrics* 2004; 114: 1312–15.
6. Gupta AK, *et al.* The use of terbinafine in the treatment of onychomycosis in adults and special populations: a review of the evidence. *J Drugs Dermatol* 2005; 4: 302–8.
7. Revankar SG, *et al.* Use of terbinafine in rare and refractory mycoses. *Future Microbiol* 2008; 3: 9–17.
8. Krishnan-Natesan S. Terbinafine: a pharmacological and clinical review. *Expert Opin Pharmacother* 2009; 10: 2723–33.

Administration in children. Although terbinafine is not currently licensed in the UK for use in children, the *BNFC* suggests the following oral doses for the treatment of dermatophyte infections of the skin and nails in children over 1 year of age:

- in those weighing 10 to 20 kg: the equivalent of terbinafine 62.5 mg once daily
- in those weighing 20 to 40 kg: 125 mg once daily
- in those weighing over 40 kg: 250 mg once daily

Treatment is usually given for 4 weeks for tinea capitis, 2 to 4 weeks for tinea cruris, 4 weeks for tinea corporis, and may be continued for up to 6 weeks in tinea pedis. Infections of the nails are treated for 6 weeks to 3 months, although longer treatment may occasionally be required for toe-nail infections.

Similar regimens have been suggested by the American Academy of Pediatrics[1] and also reported in the literature.[2,3] A review on the use of terbinafine in children considered it both safe and effective in the management of tinea capitis and onychomycosis.[4]

Children with renal impairment may need lower doses (see below).

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases.* 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.
2. Jones TC. Overview of the use of terbinafine (Lamisil) in children. *Br J Dermatol* 1995; 132: 683–9.
3. Fuller LC, *et al.* A randomized comparison of 4 weeks of terbinafine vs 8 weeks of griseofulvin for the treatment of tinea capitis. *Br J Dermatol* 2001; 144: 321–7.
4. Gupta AK, *et al.* The efficacy and safety of terbinafine in children. *J Eur Acad Dermatol Venereol* 2003; 17: 627–40.

Administration in renal impairment. Although UK licensed product information does not recommend the use of oral terbinafine in patients with renal impairment, the *BNF* and *BNFC* suggest that the usual recommended oral doses for adults (see above) and children (see above) should be reduced by half if the estimated glomerular filtration rate is less than 50 mL/min per 1.73 m².

Leishmaniasis. An inadvertent beneficial response has been reported[1] in an HIV-positive patient with cutaneous leishmaniasis (p. 922.1) who was taking terbinafine 250 mg daily for tinea corporis and onychomycosis. Beneficial results were also reported in a pilot study[2] in which patients with cutaneous leishmaniasis took either terbinafine 125 mg twice daily (those aged 5 to 15 years), or terbinafine 250 mg twice daily (those over 15 years), for 4 weeks.

1. González-Rupérez J, *et al.* Remission of localized cutaneous leishmaniasis in a HIV-positive patient using systemic terbinafine. *Dermatology* 1997; 194: 85–6.
2. Bahamdan KA, *et al.* Terbinafine in the treatment of cutaneous leishmaniasis: a pilot study. *Int J Dermatol* 1997; 36: 59–60.

Non-dermatophyte fungal infections. Beneficial responses to oral terbinafine have been reported in candidal infections of the nails and mouth,[1-3] aspergillosis, chromoblastomycosis, paracoccidioidomycosis, and sporotrichosis.[3,4]

1. Nolting S, *et al.* Terbinafine in onychomycosis with involvement by non-dermatophytic fungi. *Br J Dermatol* 1994; 130 (suppl 43): 16–21.
2. Segal R, *et al.* Treatment of Candida nail infection with terbinafine. *J Am Acad Dermatol* 1996; 35: 958–61.
3. Pérez A. Terbinafine: broad new spectrum of indications in several subcutaneous and systemic and parasitic diseases. *Mycoses* 1999; 42 (suppl 2): 111–4.
4. Francesconi G, *et al.* Terbinafine (250 mg/day): an effective and safe treatment of cutaneous sporotrichosis. *J Eur Acad Dermatol Venereol* 2009; 23: 1273–6.

Seborrhoeic dermatitis. Terbinafine has been tried in the treatment of seborrhoeic dermatitis (p. 1689.1). In one study, 60 patients were randomised to receive oral terbinafine 250 mg daily or a placebo cream applied twice daily for 4 weeks.[1] Clinical improvement, maintained 8 weeks after completing treatment, in the terbinafine group led the investigators to conclude that oral terbinafine is an effective treatment for seborrhoeic dermatitis, and to suggest that this might be due to its activity against *Malassezia ovalis* (*Pityrosporum ovale*) as well as to some anti-inflammatory action. However, the methodology of this study has been questioned[2] and further investigation is needed. A further, uncontrolled, study[3] of 661 patients who received oral terbinafine 250 mg daily for 12 days each month for 3 months concluded that intermittent oral terbinafine could be effective for seborrhoeic dermatitis, at least in severe or recalcitrant forms. It has also been tried topically as a 1% cream.[4]

1. Scaparro E, *et al.* Evaluation of the efficacy and tolerability of oral terbinafine (Daskil) in patients with seborrhoeic dermatitis: a multicentre, randomized, investigator-blinded, placebo-controlled trial. *Br J Dermatol* 2001; 144: 854–7.
2. Faergemann J. Treatment of seborrhoeic dermatitis with oral terbinafine? *Lancet* 2001; 358: 170.
3. Cassano N, *et al.* Oral terbinafine for the treatment of seborrheic dermatitis in adults. *Int J Dermatol* 2002; 41: 821–2.
4. Gündüz K, *et al.* Efficacy of terbinafine 1% cream on seborrhoeic dermatitis. *J Dermatol* 2005; 32: 22–5.

Adverse Effects

The most frequent adverse effects after oral use of terbinafine hydrochloride are gastrointestinal disturbances such as nausea, diarrhoea, and mild abdominal pain. Loss or disturbance of taste may occur and occasionally may be severe enough to lead to anorexia and weight loss. Other frequent adverse effects include headache and skin reactions, including rash or urticaria, sometimes with arthralgia or myalgia. Severe skin reactions including angioedema, photosensitivity, Stevens-Johnson syndrome, and toxic epidermal necrolysis have occurred rarely. Allergic reactions, including anaphylaxis, have been reported. Liver dysfunction with isolated reports of cholestasis, hepatitis, and jaundice, has occurred and there have also been rare cases of hepatic failure, sometimes leading to death or needing liver transplantation, in patients both with and without pre-existing liver disease. Other rare adverse effects include paraesthesia, hypoaesthesia, dizziness, malaise, fatigue, alopecia, impaired hearing, tinnitus, rhabdomyolysis, and vasculitis. Smell disturbances, including loss of smell, have also been reported; these may resolve when treatment is stopped but may also be prolonged or permanent. Haematological disorders including neutropenia, thrombocytopenia, agranulocytosis, and pancytopenia have occurred. Psychiatric disturbances such as depression and anxiety, and precipitation or exacerbation of cutaneous and systemic lupus erythematosus, and psoriasis have been reported very rarely.

There may be local reactions after topical use of terbinafine.

Incidence of adverse effects. Postmarketing surveillance of about 10 000 patients[1] suggested the following incidences of adverse effects to oral terbinafine: gastrointestinal symptoms, 4.7%; dermatological effects, 3.3%; CNS symptoms (commonly headache), 1.8%; taste disturbances, 0.6%; and transient disturbances in liver function, 0.1%. Serious adverse effects possibly or probably related to terbinafine included angioedema, bronchospasm, erythema multiforme, extended stroke, and unilateral leg oedema. Combined data from 25 884 patients from this and 3 further studies[2] generally confirmed these results. Overall, adverse effects were reported in 10.5% of patients and caused treatment to be stopped in 5.3%. Serious adverse effects probably or possibly related to terbinafine occurred in 12 patients (0.046%).

1. O'Sullivan DP, *et al.* Postmarketing surveillance of oral terbinafine in the UK: report of a large cohort study. *Br J Clin Pharmacol* 1996; 42: 559–6.
2. O'Sullivan DP. Terbinafine: tolerability in general medical practice. *Br J Dermatol* 1999; 141 (suppl 56): 21–5.

Effects on the blood. Up to August 2006, the Australian Adverse Drug Reactions Advisory Committee had received 16 reports of blood dyscrasias attributed to oral terbinafine including agranulocytosis (7 reports), neutropenia (reports), and pancytopenia (2 reports).[1] The reactions generally occurred within 4 to 6 weeks of starting therapy. Eleven patients recovered, 4 within one week of stopping treatment. However, a 79-year-old patient who developed agranulocytosis about 2 months after starting terbinafine died from septic shock.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Life threatening blood dyscrasias with oral terbinafine. *Aust Adverse Drug React Bull* 2006; 25: 15. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0608.pdf (accessed 02/05/08)

Effects on the eyes. The US manufacturer has noted that changes in the lens and retina of the eye have sometimes been associated with oral terbinafine, although the significance of these changes is unknown.

Effects on the salivary glands. Bilateral parotid swelling was associated with terbinafine in a 38-year-old man. Information from the manufacturer and the UK CSM indicated that this effect had occurred in other patients but was very rare. More recently, severe sialadenitis as a complication of drug reaction with eosinophilia and systemic complications (DRESS—a type of hypersensitivity reaction) was reported in an 80-year-old woman treated with terbinafine.[2] She also had severe xerostomia, lachryma gland swelling, dry eyes, and keratitis.

1. Torrens JK, McWhinney PH. Parotid swelling and terbinafine. *BMJ* 1998; 316: 440–1.
2. Abecassis S, *et al.* Severe sialadenitis: a new complication of drug reaction with eosinophilia and systemic symptoms. *J Am Acad Dermatol* 2004; 51: 827–30.

Effects on the skin. Serious skin reactions are occasionally reported in patients receiving terbinafine and have included erythema multiforme,[1,2] erythroderma,[1] severe urticaria,[1] pityriasis rosea,[1] worsening of pre-existing psoriasis,[1,3] acrodermatitis continua of Hallopeau,[4] bullous pemphigoid,[5] acute generalised exanthematous pustulosis,[6,7] and lupus erythematosus.[8-11] Several of these patients had a history of auto-immune disease[2,10] and it has been suggested that this could be a risk factor for developing severe reactions.[2] Photo-allergic reactions have also been reported.[12]

1. Gupta AK, *et al.* Cutaneous adverse effects associated with terbinafine therapy: 10 case reports and a review of the literature. *Br J Dermatol* 1998; 138: 529–32.
2. Goeteyn V, *et al.* Is systemic autoimmune disease a risk factor for terbinafine-induced erythema multiforme? *Br J Dermatol* 2000; 142: 578–9.
3. Wilson NJE, Evans S. Severe pustular psoriasis provoked by oral terbinafine. *Br J Dermatol* 1998; 139: 168.
4. Nishiwaki F, *et al.* Acrodermatitis continua of Hallopeau due to oral terbinafine. *Br J Dermatol* 2007; 157: 1073–4.
5. Aksakal BA, *et al.* Oral terbinafine-induced bullous pemphigoid. *Ann Pharmacother* 2003; 37: 1625–7.
6. Beltraminelli HS, *et al.* Acute generalized exanthematous pustulosis induced by the antifungal terbinafine: case report and review of the literature. *Br J Dermatol* 2005; 152: 780–3.
7. Ibrahimi OA, *et al.* Terbinafine-induced acute generalized exanthematous pustulosis (AGEP) responsive to high dose intravenous corticosteroid. *Dermatol Online J* 2009; 15 (9): 8.
8. Murphy M, Barnes L. Terbinafine-induced lupus erythematosus. *Br J Dermatol* 1998; 138: 708–9.
9. Brooke R, *et al.* Terbinafine-induced subacute cutaneous lupus erythematosus. *Br J Dermatol* 1998; 139: 1132–3.
10. Holmes S, Kemmett D. Exacerbation of systemic lupus erythematosus induced by terbinafine. *Br J Dermatol* 1998; 139: 1133.
11. Hill VA, *et al.* Subacute lupus erythematosus-like eruption due to terbinafine: report of three cases. *Br J Dermatol* 2003; 148: 1056.
12. Spiewak R. Systemic photoallergy to terbinafine. *Allergy* 2010; 65: 1071–2.

Effects on taste. Disturbance and loss of taste have been reported in about 0.6% of patients taking terbinafine. While this usually resolves gradually once the drug is withdrawn, persistent impairment of taste has been reported.[1,2]

1. Bong JL, *et al.* Persistent impairment of taste resulting from terbinafine. *Br J Dermatol* 1998; 139: 747–8.
2. Duxbury AJ, *et al.* Persistent impairment of taste associated with terbinafine. *Br Dent J* 2000; 188: 295–6.

Precautions

Terbinafine should not be used in patients with existing liver disease and liver function tests should be performed in all patients before starting oral therapy. Terbinafine should be stopped if clinical or biochemical evidence of hepatotoxicity develops. It should also be stopped if any progressive skin rash occurs and should be used with caution in patients with psoriasis.

Licensed product information advises that the use of terbinafine in patients with renal impairment is not recommended, however, dosing guidance has been issued by some authorities (see Administration in Renal Impairment, under Uses and Administration, p. 594.1).

Breast feeding. Terbinafine is excreted in breast milk and licensed product information states that it should be avoided during breast feeding.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies terbinafine (for systemic use) as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients. Topical preparations for dermatological use are classified as probably not porphyrinogenic; they may be used as drugs of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Interactions

Plasma concentrations of terbinafine may be increased by drugs that inhibit its metabolism by cytochrome P450, such as cimetidine, and decreased by drugs that induce cytochrome P450 enzymes, such as rifampicin. Menstrual disturbances including breakthrough bleeding have been reported in patients taking oral contraceptives and terbinafine.

Terbinafine has been shown to inhibit metabolism mediated by the cytochrome P450 isoenzyme CYP2D6. Hence it may affect the plasma concentrations of drugs mainly metabolised by this enzyme such as tricyclic antidepressants, antiarrhythmics (such as flecainide and propafenone), beta blockers, SSRIs, and type B MAOIs.

For the effects of terbinafine on some other drugs, see caffeine (p. 1206.2), carbamazepine (p. 517.1), ciclosporin (p. 1956.3), tricyclic antidepressants (p. 406.3), theophylline (p. 1235.1), and warfarin (p. 1532.1).

Antimicrobial Action

Terbinafine is an allylamine derivative reported to have a broad spectrum of antifungal activity. It is considered to act through inhibition of fungal sterol synthesis. Terbinafine is fungicidal against dermatophytes, moulds, and certain dimorphic fungi and some yeasts.

Microbiological interactions. Additive and synergistic activity was reported with terbinafine plus fluconazole or itraconazole against strains of *Candida albicans* that had reduced susceptibility to azoles *in vitro*.[1] Terbinafine was also reported to enhance the activity of azoles against *Scedosporium prolificans*[2] and against the protozoan *Leishmania braziliensis*.[3]

1. Barchiesi F, *et al.* In vitro activities of terbinafine in combination with fluconazole and itraconazole against isolates of Candida albicans with reduced susceptibility to azoles. *Antimicrob Agents Chemother* 1997; **41**: 1812–14.
2. Meletiadis J, *et al.* In vitro interaction of terbinafine with itraconazole against clinical isolates of Scedosporium prolificans. *Antimicrob Agents Chemother* 2000; **44**: 470–2.
3. Rangel H, *et al.* Naturally azole-resistant Leishmania braziliensis promastigotes are rendered susceptible in the presence of terbinafine: comparative study with azole-susceptible Leishmania mexicana promastigotes. *Antimicrob Agents Chemother* 1996; **40**: 2785–91. Correction. *ibid.* 1997; **41**: 496.

Pharmacokinetics

Terbinafine hydrochloride is well absorbed from the gastrointestinal tract. The bioavailability is about 40% because of first-pass hepatic metabolism. Mean peak plasma concentrations of about 1 microgram/mL occur within 2 hours of a single oral dose of 250 mg. Steady state concentrations are about 25% higher than those seen after a single dose and occur in 10 to 14 days. Terbinafine is extensively bound to plasma proteins. Terbinafine is distributed into the stratum corneum of the skin, the nail plate, and hair where it reaches concentrations considerably higher than those found in plasma. It appears in breast milk.

Terbinafine is metabolised in the liver to inactive metabolites which are excreted mainly in the urine. A plasma elimination half-life varying from 17 to 36 hours has been reported and a terminal elimination half-life of up to 400 hours in patients given prolonged therapy, probably representing elimination from skin and adipose tissue. Fungicidal concentrations in nails are maintained for several weeks after therapy is stopped. The elimination rate may be altered in patients with liver or kidney disease. Less than 5% of a topical dose of terbinafine hydrochloride is absorbed.

References.

1. Kovarik JM, *et al.* Multiple-dose pharmacokinetics and distribution in tissue of terbinafine and metabolites. *Antimicrob Agents Chemother* 1995; **39**: 2738–41.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Fungueal; Lamisil; Maditez; Piecidex NF; Repliderm; Sinamida Terbinafina; Tacna; TerbiDerm; Terekol; Terfin; *Austral.*: Lamisil; SolvEasy; Tamsil; Terbihexal; Tinasil; Zabel; *Austria*: Amisan; Amykal; Daskil†; Lamisil; Myconafin†; Myconormin; Pedibene; Terbiderm; Terbinac†; *Belg.*: Fungster; Lamisil; *Braz.*: Funtyl; Lamisil; Lamisilate; Lorentil; Micosil; Terbinacol; *Canad.*: Lamisil; *Chile*: Dermoxyl; Dicil; Donter; Elater; Farbicil; Pinex; Lamisil; Micoset; Mucivil; Terfex; Terfin; *China*: Dingke (丁克); Fusu (扶苏); Futeshu (芙特抒); Kang Ning (康宁); Lamisil (兰美抒); Mujonal (采特); Pi Fu Te (披孚特); *Cz.*: Atifan†; Lamisil; Mycodekan†; Onychon†; Tefinet†; Terbihexal†; Terbisil†; Terbistad; Terfimed; Verbinaf†; Zonesist†; *Denm.*: Finigen; Funginix†; Lamisil; Tefin; Terbisil; Terbistad; Terimed†; *Fin.*: Fungis; Fungorin; Lamisil; Terbistada; *Fr.*: Fungster; Lamisil; Lamisilate; LamisilDermgel; *Ger.*: Amiada; Dermatin; Fungizid Extra; Lamisil; Myconormin; Octosan†; Onymax†; Terbiderm; Terbigalen; Terbina-Q†; *Gr.*: Anaplas; Chemiderm; Demsil; Drogenil; Ealk; Flixid; Frezylin; Funger; Fungitherapy; Fungster; Lamiderm; Lamigen; Lamisil; Mycutol; Optimus; Pavlinox; Pro-Misil; Romiver; Seralon; Soluterb; Teranfis; Terbafin; Terbigram; Terbin; Terbiprol; Terbiskin; Terbisol; Terfinil; Terfinor; Termisil; Ternafinol; Thateron; Vifaderm; Zakofin; *Hong Kong*: Interbi; Lamisil; Orlasil; Tebinisil; Terbifin; *Hung.*: Lamigard; Lamisil; Myconafine; Terbigen; Terbiner; Terbisil; Terfin; Tineal; *India*: Daskil; Dermafine; Exifine; Fin; Fungotek; Lamisil; Mycofem; Terbifin†; *Indon.*: Interbi; Lamisil; Termisil; *Irl.*: Fungafine; Fungasil; Lamater; Lamisil; Lanafine; Nailderm; Terbasil; Ternaf; *Israel*: Dermasil; Lamisil; Patir; *Ital.*: Daskil; Lamisil; Onymax; *Malaysia*: Camisan; Dermafin; Exifine; Lamisil; Lisim†; *Mex.*: Binafex; Erbitrax; Fyterdin; Lamisil; Losil; Mycelvan; Sebifin†; Unasal; Xilatril; *Neth.*: Atifan; Binanidda; Finanidda†; Lamisil; Niddafin; Niddavita†; Terbiderm; Terbinavita†; Vitabin; *Norw.*: Lamisil; *NZ*: Lamisil; Terbafin†; *Philipp.*: Lamifen; Lamisil; *Pol.*: Afugin†; Dermogen; Erfin; Lamisil; Lamisilatt; Myconafine; Onymax; Tenasil; Terbiderm; TerbiGen; Terbisil; Undofen Max; Verbinaf; Zelefion; *Port.*: Arrolina; Daskyl; Fungil; Fungster; Lamisil; Termycol; *Rus.*: Atifin (Атифин); Binafin (Бинафин); Cidocan (Цидокан); Exifine (Экзифин); Fungoterbine (Фунготербин); Lamican (Ламикан); Lamisil (Ламизил); Lamitel (Ламитель); Medofloran (Медофлоран); Miconorm (Миконорм); Onychon (Онихон); Terbifin (Тербифин); Terbinox (Тербинокс); Terbised (Тербизед); Terbisil (Тербизил); Terbix (Тербикс); Termicon (Термикон); *S.Afr.*: Dermax; Finderm; Lamisil; Lamispor; Nafin; Terbane; Terbicil; Terbiclear; *Singapore*: Lamisil; *Spain*: Fungicare†; Isis; Lamicosil; Lamisil; Talixane†; Tighum†; *Swed.*: Funginix; Lamisil; Terbisil; *Switz.*: Fungster†; Helvepedin; Lamisil; Myconormin; Onymax†; Terbifil; Terbinax; Tineafine; *Thai.*: EU 2000; Lamisil; *Turk.*: Corbinal; Laminox; Lamisil; Mikonafin; Mycocur; Myconaf; Tekfin; Terafin; Terbin; Terbisil; Terbonile; Terinateva; Terminus; Tigal; *UAE*: Negafen; *UK*: Boots Athlete's Foot Cream; Lamisil; *Ukr.*: Exifine (Экзифин); Fungoterbine (Фунготербин); Lamicon (Ламикон); Lamifen (Ламифен); Lamisil (Ламизил); Mycofin (Микофин); Myconorm (Миконорм)†; Terbisil (Тербизил); *USA*: DesenexMax; Lamisil; Terbinex; *Venez.*: Lamisil; Nafina; Terfex.

Multi-ingredient Preparations. *India*: Cutivate-GT; Cutizone-T; Mecloma-T; Mezo-T; Momoz-T.

Pharmacopoeial Preparations
USP 36: Terbinafine Oral Suspension; Terbinafine Tablets.

Terconazole *(BAN, USAN, rINN)*

R-42470; Terconazol; Terconazolum; Terkonatsoli; Terkonazol; Terkonazolas; Triaconazole; Терконазол.
1-[4-[[2-(2,4-Dichlorophenyl)-*r*-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-*c*-4-yl]methoxy]phenyl]-4-isopropylpiperazine.
$C_{26}H_{31}Cl_2N_5O_3$=532.5
CAS — 67915-31-5.
ATC — G01AG02.
ATC Vet — QG01AG02.
UNII — 0KJ2VE664U.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Terconazole). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol; soluble in acetone; freely soluble in dichloromethane. Protect from light.

USP 36: (Terconazole). A white to off-white powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane; soluble in acetone. Protect from light.

Uses and Administration

Terconazole is a triazole antifungal used in the local treatment of vulvovaginal candidiasis (p. 564.1). Intravaginal dosage regimens are terconazole 40 mg (as 0.8% vaginal cream) or 80 mg (as a pessary) at bedtime for 3 nights or 20 mg (as 0.4% cream) at bedtime for 7 nights.

Adverse Effects

Local reactions including burning and itching have been reported with vaginal use of terconazole. Other adverse effects have included dysmenorrhoea and genital, body, and abdominal pain. A flu-like syndrome with headache, fever, chills, and hypotension has been reported in some patients and may be more prevalent with vaginal pessaries providing doses larger than 80 mg.

Flu-like syndrome. References.

1. Moebius UM. Influenza-like syndrome after terconazole. *Lancet* 1988; **ii**: 966–7.

Precautions

Intravaginal preparations of terconazole may damage latex contraceptives and additional contraceptive measures are therefore necessary during local application.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3.

Antimicrobial Action

Terconazole is a triazole derivative that is thought to disrupt normal fungal cell membrane permeability. Terconazole is active *in vitro* against *Candida* spp. and other fungi. It has some antibacterial activity *in vitro* but not against usual vaginal flora such as lactobacilli.

Pharmacokinetics

After intravaginal use, 5 to 16% of terconazole is absorbed. Systemically absorbed drug is metabolised by the liver and excreted in urine and faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Gyno-Fungix; Tecomax; Terconan; *Canad.*: Terazol; *India*: Gyno-Terazol; *Mex.*: Fungistat; *S.Afr.*: Terazol†; *USA*: Terazol; Zazole†; *Venez.*: Fungistat.

Multi-ingredient Preparations. *Mex.*: Gynoclin-V.

Tioconazole *(BAN, USAN, rINN)*

Tioconazol; Tioconazolum; Tiokonatsoli; Tiokonazol; Tiokonazolas; UK-20349; Тиоконазол.
1-[2,4-Dichloro-β-(2-chloro-3-thenyloxy)phenethyl]imidazole.
$C_{16}H_{13}Cl_3N_2OS$=387.7
CAS — 65899-73-2.
ATC — D01AC07; G01AF08.
ATC Vet — QD01AC07; QG01AF08.
UNII — S57Y5X1117.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Tioconazole). A white or almost white crystalline powder. Very slightly soluble in water; freely soluble in alcohol; very soluble in dichloromethane. Protect from light.

USP 36: (Tioconazole). Store in airtight containers.

Uses and Administration

Tioconazole is an imidazole antifungal used in the treatment of superficial candidiasis (p. 564.1), and dermatophytoses and pityriasis versicolor (see Skin Infections, p. 568.1).

For vaginal candidiasis it is used as pessaries or vaginal ointment usually as a single 300-mg dose.

It has been used topically as a 1% cream, lotion, or powder in the treatment of superficial fungal infections. Tioconazole has also been used for nail infections as a 28% w/w topical solution, although systemic treatment is generally preferred.

Adverse Effects and Precautions

Local reactions to tioconazole including burning, itching, and erythema have been reported.

Intravaginal preparations of tioconazole may damage latex contraceptives and additional contraceptive measures are therefore necessary during local application.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3.

Hypersensitivity. Tioconazole, an imidazole antifungal widely used in Finland, appeared to be an important cause of contact allergy in that country, since an incidence of more than 1% was reported in patients undergoing routine patch testing.[1] There may be cross-reactivity with other commonly used imidazole derivatives.

1. Heikkilä H, *et al.* A study of 72 patients with contact allergy to tioconazole. *Br J Dermatol* 1996; **134**: 678–80.

Antimicrobial Action

Tioconazole is an imidazole antifungal with a broad spectrum of activity including action against dermatophytes, *Malassezia furfur*, and *Candida albicans*. Tioconazole is active *in vitro* against some Gram-positive bacteria.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Honguil; Niofen; Tiomicol; Trosyd; ***Austria***: Trosyd; ***Braz.***: Gino Conazol†; Gino Tralen†; Neo Tionazol; Tioconax; Tionazen; Tralen; ***Chile***: Telset; ***Fin.***: Gyno-Trosyd; Trosyd; ***Fr.***: Gyno-Trosyd; Trosyd; ***Ger.***: Mykontral; ***Gr.***: Cotinazin; Infester; Lakafin; ***Hong Kong***: Gyno-Trosyd; Trosyd; ***Indon.***: Prodermal; Trosyd; ***Irl.***: Trosyl; ***Ital.***: Trosyd; ***Malaysia***: Gyno-Trosyd; Trosyd; ***Philipp.***: Trosyd; ***Port.***: Gino-Trosyd; Trosyd; ***S.Afr.***: Gyno-Trosyd†; Trosyd; ***Singapore***: Gyno-Trosyd; Trosyd; ***Spain***: Onicozol†; Sernax; Trosderm; Trosid; ***Switz.***: Trosyd†; ***Thai.***: Trosyd; ***Turk.***: Dermo-Rest; Dermo-Trosyd; Gyno-Trosyd; Tiocan; Tiocell; Tioderma; ***UK***: Trosyl; ***USA***: Vagistat-1; ***Venez.***: Gino-Tralen; Tralen.

Multi-ingredient Preparations. ***Braz.***: Cartrax; Duozol; Gynben; Gynomax; Gynopac; Seczol; Takil; Tinin; Tiotrax; Travogyn; Vulnagen; ***Fin.***: Trosycort; ***Mex.***: Fasigyn VT; ***Turk.***: Gynomax.

Pharmacopoeial Preparations
BP 2014: Tioconazole Cream; Tioconazole Nail Solution.

Tolciclate *(USAN, rINN)*

K-9147; KC-9147; Tolciclato; Tolciclatum; Тольциклат.
O-(1,2,3,4-Tetrahydro-1,4-methano-6-naphthyl) *m,N*-dimethylthiocarbanilate.
$C_{20}H_{21}NOS$=323.5
CAS — 50838-36-3.
ATC — D01AE19.
ATC Vet — QD01AE19.
UNII — T3TZ02X2AZ.

Profile

Tolciclate is an antifungal with activity against *Epidermophyton*, *Microsporum*, and *Trichophyton* spp. It is used topically as a 1% cream or lotion, or as a 0.5% powder in the treatment of various dermatophyte infections and in pityriasis versicolor.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Tolmicil; ***NZ***: Tolmicen†; ***Rus.***: Tolmicen (Тольмицен).

Tolnaftate *(BAN, USAN, rINN)*

Sch-10144; Tolnaftaatti; Tolnaftat; Tolnaftát; Tolnaftatas; Tolnaftato; Tolnaftatum; Тольнафтат.
O-2-Naphthyl *m,N*-dimethylthiocarbanilate; *O*-Naphthalen-2-yl methyl(3-methylphenyl)carbamothioate.
$C_{19}H_{17}NOS$=307.4
CAS — 2398-96-1.
ATC — D01AE18.
ATC Vet — QD01AE18.
UNII — 06KB629TKV.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Tolnaftate). A white or yellowish-white powder. Practically insoluble in water; very slightly soluble in alcohol; freely soluble in acetone and in dichloromethane. Protect from light.

USP 36: (Tolnaftate). A white to creamy-white, fine powder, with a slight odour. Practically insoluble in water; slightly soluble in alcohol; freely soluble in acetone and in chloroform; sparingly soluble in ether. Store in airtight containers.

Uses and Administration

Tolnaftate is an antifungal used topically as a 1% gel, solution, powder, ointment, or cream in the treatment or prophylaxis of superficial dermatophyte infections and of pityriasis versicolor (see Skin Infections, p. 568.1). Tolnaftate is applied twice daily for 2 to 6 weeks. Repeat treatment may be required.

Adverse Effects

Skin reactions occur rarely with tolnaftate and include irritation and contact dermatitis.

Antimicrobial Action

Tolnaftate inhibits the growth of the dermatophytes *Epidermophyton*, *Microsporum*, *Trichophyton* spp., and *Malassezia furfur*, but is not active against *Candida* spp. or bacteria.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Curatin†; Ringworm Ointment; Tinaderm; Tineafax; ***Canad.***: Absorbine Jr Antifungal; Athlete's Foot; Avon Footworks; Dr Scholl's Athlete's Foot; Fungicure; Pitrex; Proclearz; Tinactin; ZeaSorb AF†; ***Chile***: Tinaderm†; ***Fr.***: Sporiline; ***Ger.***: Tinatox; ***Gr.***: Tinaderm; ***Hung.***: Chinofungin; Digifungin; ***India***: Tinaderm; Tolnaderm†; ***Indon.***: Naftate†; ***Irl.***: Mycil; Scholl Athlete's Foot; Tinaderm; ***Israel***: Athletes Foot; Pitrex; Tinasol†; ***Malaysia***: Dermoplex Antifungal; Myco-Aid; Tolnaderm; ***Mex.***: Excelsior; Tinaderm; Tinoxal; ***Philipp.***: Tinactin; Tolnaderm; ***Port.***: Tinaderme; ***S. Afr.***: Tinaderm; ***Singapore***: Creobic; Naftate; Scholl Athlete's Foot; Tolnaderm; ***Thai.***: Ezon-T; Tonaf; Tonof†; ***Turk.***: Mikoderm†; Tinactin; ***UK***: Mycil; Scholl Athlete's Foot; Tinaderm; ***USA***: Aftate†; Blis-To-Sol; Dr Scholl's Athlete's Foot; Genasport†; Lamisil AF Defense; Mycocide NS; Podactin; Quinsana Plus†; Tinactin; Ting; ***Venez.***: Tinaderm; Tolnaftan.

Multi-ingredient Preparations. ***Arg.***: Bacticort Complex; Cevaderm; ***Austral.***: Mycil Healthy Feet; Mycil Healthy Feet; ***Braz.***: Cremederme; Permut; Polideims; Quadribeta; Quadriderm; Quadrihexal; Quadrikin†; Quadrilon; Quadriplus†; Qualiderm; Tetraderm; ***Gr.***: Helpogen; ***Hong Kong***: Alox†; Alphate†; Aselan†; Dermafacte†; Ezon-T; Mycil†; Mycostop†; Quadriderm; Triditol-G; ***India***: ABC Derm; Alcoderm; Darederm; Dermitop; Esgiderm; Fourderm; Quiss; Surfaz-SN; ***Irl.***: Mycil; Mycil; Tinaderm-M†; ***Israel***: Phytoderm Compositum; ***Malaysia***: Elan-Forte; ***Philipp.***: Quadriderm; Quadrotopic; ***S.Afr.***: Quadriderm; ***Spain***: Cuatroderm; ***Switz.***: Undex; ***Thai.***: Alber T; Dermaheu; Dertec; Ezon-T; Quadriderm; Spectroderm; ***UK***: Mycil; Mycil; Tinaderm-M†; ***USA***: Dermasept Antifungal.

Pharmacopoeial Preparations
USP 36: Tolnaftate Cream; Tolnaftate Gel; Tolnaftate Topical Aerosol; Tolnaftate Topical Powder; Tolnaftate Topical Solution.

Triacetin *(rINN)*

E1518; Glicerin-triacetát; Glycerol Triacetate; Glycerolum Triacetas; Glyceryl Triacetate; Triacetato de glicerilo; Triacetina; Triacetinas; Triacétine; Triacetinum; Triacetyna; Triasetiini; Триацетин.
1,2,3-Propanetriol triacetate.
$C_9H_{14}O_6$=218.2
CAS — 102-76-1.
UNII — XHX3C3X673.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Triacetin). A clear, colourless, slightly viscous, oily liquid. Soluble in water; miscible with dehydrated alcohol and with toluene. Store in well-filled containers.

USP 36: (Triacetin). A colourless, somewhat oily liquid with a slight, fatty odour. Soluble in water; slightly soluble in carbon disulfide; miscible with alcohol, with chloroform, and with ether. Store in airtight containers.

Profile

Triacetin is reported to possess fungistatic properties based on the liberation of acetic acid. It has been applied topically in the treatment of superficial dermatophyte infections. It has also been used as a plasticiser in oral preparations.

Triacetin may destroy rayon fabric. It should not come into contact with metals.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Hong Kong***: Ezon-T; ***Thai.***: Alber T; Ezon-T.

Trimetrexate Glucuronate *(BANM, USAN, rINNM)*

CI-898 (trimetrexate); Glucuronato de trimetrexato; JB-11 (trimetrexate); NSC-249008 (trimetrexate); NSC-328564 (trimetrexate); NSC-352122; Trimétrexate, Glucuronate de; Trimetrexati Glucuronatum; Trimetrexato, glucuronato de; Триметрексата глюкуронат.
5-Methyl-6-(3,4,5-trimethoxyanilinomethyl)quinazolin-2,4-diyldiamine mono-D-glucuronate.
$C_{19}H_{23}N_5O_3.C_6H_{10}O_7$=563.6
CAS — 52128-35-5 (trimetrexate); 82952-64-5 (trimetrexate glucuronate).
ATC — P01AX07.
UNII — L137U4A79K.

Profile

Trimetrexate is a dihydrofolate reductase inhibitor with general properties similar to those of methotrexate (p. 822.2). It has been used in a regimen with folinic acid in the management of moderate to severe pneumocystis pneumonia in immunocompromised patients, notably patients with AIDS, where other therapy has proved ineffective (see also p. 567.2). At therapeutic doses the selective transport of trimetrexate, but not folinic acid, into *Pneumocystis jirovecii* allows folinic acid to protect normal host cells from the cytotoxicity of trimetrexate without inhibiting its antifungal activity. It has also been tried as an antineoplastic in the management of various solid tumours.

Trimetrexate has been given as the glucuronate but doses are stated in terms of trimetrexate. Trimetrexate glucuronate 1.53 mg is equivalent to about 1 mg of trimetrexate. It is given by intravenous infusion, over 60 to 90 minutes. The schedule in pneumocystis pneumonia is 45 mg/m² daily for 21 days, with folinic acid rescue for 24 days; for details of the folinic acid dose regimen, see Uses and Administration of Folinic Acid, p. 2067.1. The dosage of trimetrexate and folinic acid should be adjusted according to the results of blood tests, which should be performed at least twice a week during therapy. Renal and hepatic function and haemoglobin values should also be monitored. Treatment with zidovudine and other myelosuppressive drugs should be interrupted to allow full doses of trimetrexate to be given.

References.
1. Fulton B, *et al.* Trimetrexate: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in the treatment of Pneumocystis carinii pneumonia. *Drugs* 1995; **49**: 563–76.
2. Short CE, *et al.* Trimetrexate and folinic acid: a valuable salvage option for Pneumocystis jirovecii pneumonia. *AIDS* 2009; **23**: 1287–90.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Neutrexin; ***Thai.***: Neutrexin

Undecenoic Acid

Acide Undécylénique; Ácido undecenoico; Acidum undecylenicum; 10-Hendecenoic Acid; Kyselina undecylenová; Undecilénico, ácido; Undecileno rūgštis; Undecilénsav; Undecylenic Acid; Undecylensäure; Undecylensyra; Undesenoatlar; Undesilenatlar; Undesyleenihappo; Ундеценовая Кислота.
Undec-10-enoic acid.
$C_{11}H_{20}O_2$=184.3
CAS — 112-38-9.
ATC — D01AE04.
ATC Vet — QD01AE04.
UNII — K3D86KJ24N.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Undecylenic Acid; Undecenoic Acid BP 2014). A colourless or pale yellow liquid or a white or very pale yellow crystalline mass. Practically insoluble in water; freely soluble in alcohol and in fatty and essential oils. Store in nonmetallic containers. Protect from light.

USP 36: (Undecylenic Acid). A clear, colourless to pale yellow liquid with a characteristic odour. Practically insoluble in water; miscible with alcohol, with chloroform, with ether, with benzene, and with fixed and volatile oils. Store in airtight containers. Protect from light.

Calcium Undecenoate

Calcium Undecylenate (USAN); Undecenoato de calcio; Undecilenato de calcio; Ундециленат Кальция.
Calcium di(undec-10-enoate).
$(C_{11}H_{19}O_2)_2Ca$=406.6
ATC — D01AE04.
ATC Vet — QD01AE04.
UNII — 77YW1RTU8V.

Pharmacopoeias. In *US*.

USP 36: (Calcium Undecylenate). A fine white powder with a characteristic odour and no grit. Practically insoluble in water, in cold alcohol, in acetone, in chloroform, and in ether; slightly soluble in hot alcohol.

Zinc Undecenoate

Cinko undecilenatas; Çinko Undesilenat; Cink-undecilenát; Sinkkiundesylenaatti; Undecenoato de zinc; Undecilenato de zinc; Undecilinato de Zinco; Undecylenan zinečnatý; Zinc Undecylenate; Zinc, undécylénate de; Zinci undecylenas; Zinkundecylenat; Ундециленат Цинка.
Zinc di(undec-10-enoate).
$(C_{11}H_{19}O_2)_2Zn$=431.9
CAS — 557-08-4.

ATC — D01AE04.
ATC Vet — QD01AE04.
UNII — 388VZ25OUR.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Zinc Undecylenate; Zinc Undecenoate BP 2014). A fine white or almost white powder. Practically insoluble in water and in alcohol. Protect from light.

USP 36: (Zinc Undecylenate). A fine, white powder. Practically insoluble in water and in alcohol.

Uses and Administration

Undecenoic acid and its zinc salt are applied topically in the prophylaxis and treatment of superficial dermatophytoses, particularly tinea pedis (see Skin Infections, p. 568.1). Typical concentrations are undecenoic acid 2 to 5% and zinc undecenoate 20%. They are used in creams, ointments, solutions, or powders, often with each other. Calcium undecenoate is used as a 10 or 15% powder.

Several other salts and derivatives of undecenoic acid including methyl, phenyl, and propyl undecenoate, disodium sulfosuccinated undecenoic acid monoethanolamide, and undecenoic acid monoethanolamide and diethanolamide have been used similarly.

A systematic review[1] of topical treatments for fungal skin or nail infections considered undecenoates to be effective, although comparative studies with other classes of topical antifungal were largely lacking.

1. *Crawford F, Hollis S.* Topical treatments for fungal infections of the skin and nails of the foot. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 07/07/08).

Adverse Effects

Irritation may rarely occur after the topical application of undecenoic acid or its salts.

Antimicrobial Action

Undecenoic acid and its derivatives are active against some pathogenic fungi, including the dermatophytes *Epidermophyton*, *Trichophyton*, and *Microsporum*spp.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Bentophyto; Sinamida Pies; Umasam; *Austria*: Crino Cordes; Pelsana Med; *Canad.*: Desenex†; *Cz.*: Mykoseptin; *Fr.*: Mycodecyl; Mycodecyl; Mycodecyl; *Hung.*: Lubex; *Indon.*: Decyline; Topix†; Undecyl; *Irl.*: Caldesene; Desenex; *Israel*: Undecyl; *Mex.*: Derman; *Pol.*: Mykodermina; Mykodermina; Unguentum Undecylenicum; *Rus.*: Mykoseptin (Микосептин); *S.Afr.*: Mycota; *Switz.*: Lubex; Turexan Creme†; Turexan Douche†; *Turk.*: Undo-Pate; Utalk†; *UK*: Mycota; *Ukr.*: Mykoseptin (Микосептин); *USA*: Blis-To-Sol; Cruex; Cruex; Decylenes; Desenex; DiabetiDerm; Elon Dual Defense; Fungi Cure; Protectol; Undelenic.

Multi-ingredient Preparations. *Arg.*: Bentophyto; Bifena; Champuacid; Cicatrol; Dettonjab; Farm-X; Fungicida; Fungocop; Hipoglos Cicatrizante; Laurinol Plus; Novo Miconol†; Zinc-S Plus; *Austral.*: Pedoz; Sebitar; *Austria*: Mycopol; Pelsana Med; *Braz.*: Andriodermol; Andriodermol; *Canad.*: Feet Athletes Foot and Antifungal†; *Chile*: Pittig Antimicotico; NP-27; NP-27; *Fr.*: Paps†; *Ger.*: Skinman Soft; *Gr.*: Ekzegamma; Hemorrocort; Undex; *Hong Kong*: Sebitar; *Hung.*: Pedimed; Pelsano Med; Squa-med; *Indon.*: Decyline; Decyline; Mikorex†; Skintex†; *Irl.*: Pedamed; *Israel*: Acti Talc Fungimon; Pedisol†; Pitrisan†; *Ital.*: Foot Zeta; Genisol; Micofoot; Propast; Sideck Shampoo Antiforfora; *Malaysia*: Sebitar; *Mex.*: Micotex; *NZ*: Grans Remedy; Sebitar; *Pol.*: Undofen; *Port.*: Micaveen†; *S.Afr.*: AF; *Singapore*: Sebitar; Vetic; *Switz.*: Crimanex; Ederphyt†; Pelsano; Pruri-med; Undex†; Undex; *Turk.*: Fungecyl; Undo-Talk; *UK*: Ceanel; Healthy Feet; Mycota; *USA*: Breezee Mist Foot Powder; Dermasept Antifungal; Gordochom; Phicon-F.

Pharmacopoeial Preparations
USP 36: Compound Undecylenic Acid Ointment.

Voriconazole *(BAN, USAN, rINN)*

UK-109496; Voriconazol; Voriconazolum; Vorikonazol; Вориконазол.

(2*R*,3*S*)-2-(2,4-Difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1,2,4-triazol-1-yl)butan-2-ol.

$C_{16}H_{14}N_5F_3O$=349.3

CAS — 137234-62-9.

ATC — J02AC03.
ATC Vet — QJ02AC03.
UNII — JFU09I87TR.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Voriconazole). A white or almost white powder. Very slightly soluble in water; freely soluble in acetone and in dichloromethane. If the substance is sterile, store in airtight containers.

USP 36: (Voriconazole). A white to almost white powder. Very slightly soluble in water; freely soluble in acetone and in dichloromethane.

Uses and Administration

Voriconazole is a triazole antifungal used mainly in immunocompromised patients for the treatment of invasive aspergillosis (p. 563.1), candidaemia (p. 564.1) in non-neutropenic patients, fluconazole-resistant serious invasive candidiasis, oesophageal candidiasis, and serious fungal infections due to *Scedosporium* and *Fusarium* spp.

Voriconazole may be given orally or intravenously. It has also been used topically, usually as a 1% eye drop, in the treatment of certain fungal and protozoal eye infections (see below).

Oral doses as film-coated tablets should be taken at least 1 hour before, or 1 hour after a meal; oral suspensions should be taken at least 1 hour before, or 1 to 2 hours after a meal.

The following *oral loading doses* of voriconazole are given every 12 hours for the first 24 hours:
- adults and adolescents weighing more than 40 kg: 400 mg
- under 40 kg: 200 mg

Subsequent *oral maintenance doses* are:
- adults and adolescents over 40 kg: 200 mg twice daily, increased to 300 mg twice daily if the response is inadequate
- under 40 kg: 100 mg twice daily, increased to 150 mg twice daily if the response is inadequate

Intravenous loading doses of voriconazole are:
- adults and adolescents: 6 mg/kg every 12 hours for the first 24 hours

Intravenous maintenance doses are:
- adults and adolescents: 4 mg/kg twice daily; a lower dose of 3 mg/kg twice daily may be suitable for candidaemia in non-neutropenic patients or for deep tissue *Candida* infections, or for patients unable to tolerate the higher dose

Intravenous infusions should be given at a maximum rate of 3 mg/kg per hour over 1 to 2 hours. UK licensed product information recommends that intravenous therapy should not be given for longer than 6 months.

Doses of voriconazole may need to be modified in patients with hepatic or renal impairment (see below).

The dose of voriconazole may also need to be adjusted for the management of significant drug interactions. Increased oral maintenance doses of 400 mg, and 350 mg twice daily have been suggested when voriconazole must be used with phenytoin or rifabutin respectively; for patients weighing less than 40 kg, a dose of 200 mg twice daily is recommended. For intravenous voriconazole, the maintenance dose should be increased to 5 mg/kg twice daily. When given with efavirenz, the maintenance dose of voriconazole should be increased to 400 mg twice daily; the dose of efavirenz must also be adjusted, for details, see Uses and Administration of Efavirenz, p. 975.1.

For details of doses in children, see below.

Reviews.
1. Muijsert RBR, *et al.* Voriconazole: in the treatment of invasive aspergillosis. *Drugs* 2002; 62: 2655–64.
2. Johnson LB, Kauffman CA. Voriconazole: a new triazole antifungal agent. *Clin Infect Dis* 2003; 36: 630–7.
3. Pearson MM, *et al.* Voriconazole: a new triazole antifungal agent. *Ann Pharmacother* 2003; 37: 420–32.
4. Gothard P, Rogers TR. Voriconazole for serious fungal infections. *Int J Clin Pract* 2004; 58: 74–80.
5. Donnelly JP, De Pauw BE. Voriconazole—a new therapeutic agent with an extended spectrum of antifungal activity. *Clin Microbiol Infect* 2004; 10 (suppl 1): 107–17.
6. Scott LJ, Simpson D. Voriconazole: a review of its use in the management of invasive fungal infections. *Drugs* 2007; 67: 269–98.
7. Ta M, *et al.* The role of voriconazole in the treatment of central nervous system blastomycosis. *Ann Pharmacother* 2009; 43: 1696–700.
8. Thompson GR, Lewis JS. Pharmacology and clinical use of voriconazole. *Expert Opin Drug Metab Toxicol* 2010; 6: 83–94.

Administration in children. In the UK, voriconazole is licensed for use in children for the treatment of invasive aspergillosis, candidaemia in non-neutropenic patients, serious fluconazole-resistant invasive candidiasis, and serious infections caused by *Scedosporium* or *Fusarium* spp. Children from 2 years of age, and young adolescents (12 to 14 years of age) weighing less than 50 kg should be treated with intravenous voriconazole initially and then switched to oral treatment only if clinically appropriate. The following doses are suggested:
- for intravenous use: a loading dose of 9 mg/kg twice daily for the first 24 hours, followed by a maintenance dose of 8 mg/kg twice daily; the infusion rate should not exceed 3 mg/kg per hour
- for oral use: 9 mg/kg (to a maximum of 350 mg) twice daily of the oral suspension; doses should be taken at least one hour before, or two hours after a meal

Adult doses are suggested for young adolescents (12 to 14 years of age) weighing 50 kg or more, and for adolescents aged 15 to 17 years (see above).

In the USA, voriconazole is not licensed for use in children; however, the American Academy of Pediatrics[1] suggests it may be given orally or intravenously from 2 years of age; recommended doses are similar to those for the UK.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Administration in hepatic impairment. No dosage adjustment is necessary when voriconazole is given to patients with acute hepatic impairment but doses should be modified in patients with chronic disease. Patients with mild to moderate hepatic cirrhosis (Child-Pugh category A and B) should receive the standard loading doses of oral or intravenous voriconazole (see Uses and Administration, above) but maintenance doses should be halved. Doses for patients with severe hepatic cirrhosis (Child-Pugh category C) have not been established.

Administration in obese patients. Although the ideal voriconazole dose regimen in obese patients has not been determined, it has been suggested that an intravenous dose regimen based on the adjusted body-weight will give a voriconazole area under the curve similar to a non-obese patient.[1] On the other hand, a study that evaluated the steady-state plasma pharmacokinetics of oral voriconazole in a small number of healthy subjects with class II obesity or greater concluded that adjustment of oral doses does not appear to be necessary on the basis of body weight.[2]

1. Dickmeyer NJ, Kiel PJ. Dosing voriconazole in an obese patient. *Clin Infect Dis* 2011; 53: 745.
2. Pai MP, Lodise TP. Steady-state plasma pharmacokinetics of oral voriconazole in obese adults. *Antimicrob Agents Chemother* 2011; 55: 2601–5.

Administration in renal impairment. No dose adjustment is needed for oral voriconazole in patients with renal impairment. Patients with a creatinine clearance less than 50 mL/minute should receive oral voriconazole instead of intravenous voriconazole, as accumulation of the intravenous vehicle, sulfobutyl ether beta-cyclodextrin sodium (SBECD), may occur. When intravenous voriconazole is considered justified in such patients, serum creatinine should be closely monitored and consideration given to changing to the oral route if increases occur. A retrospective, observational study[1] in a small number of patients treated with either oral or intravenous voriconazole for a minimum of 3 consecutive days and with a creatinine clearance of less than 50 mL/minute, found that the route of administration and/or baseline renal function were not predictors of worsening renal dysfunction after 3 to 7 days of consecutive treatment. The strongest predictors for renal dysfunction were reported to be underlying disease, baseline liver impairment, and the concomitant use of other drugs such as penicillins, fluoroquinolones, and immunosuppressants; treatment with fluconazole within 30 days of starting voriconazole treatment was also identified as a major risk factor for renal dysfunction by day 3.

Although voriconazole is haemodialysed, no dose adjustment is required for patients on haemodialysis.

1. *Neofytos D, et al.* Administration of voriconazole in patients with renal dysfunction. *Clin Infect Dis* 2012; 54: 913–21.

Eye infections. Topical voriconazole, either alone or combined with other therapy, has been investigated for the treatment of various types of fungal eye infection.[1] Voriconazole 1% eye drops were found to be successful as first-line treatment in a patient with keratitis caused by *Candida albicans*.[2] Effective salvage treatment of *Scedosporium apiospermum* keratitis has also been reported with topical voriconazole in a patient who relapsed after treatment with topical natamycin.[3] Additionally, the use of topical plus oral voriconazole has been effective for *Aspergillus fumigatus* keratitis refractory to treatment with topical natamycin, topical amphotericin B, and systemic ketoconazole.[4]

Topical voriconazole has also been tried as an adjunctive treatment for *Acanthamoeba* keratitis unresponsive to standard treatment with chlorhexidine and hexamidine.[5] Of three eyes additionally treated with voriconazole 1% eye drops, 2 had clinical resolution of disease. Recurrent disease in one eye was successfully treated with voriconazole by intrastromal injection.

1. Hariprasad SM, *et al.* Voriconazole in the treatment of fungal eye infections: a review of current literature. *Br J Ophthalmol* 2008; 92: 871–8.
2. Al-Badriyeh D, *et al.* Successful use of topical voriconazole 1% alone as first-line antifungal therapy against Candida albicans keratitis. *Ann Pharmacother* 2009; 43: 2103–7.
3. Al-Badriyeh D, *et al.* Successful salvage treatment of Scedosporium apiospermum keratitis with topical voriconazole after failure of natamycin. *Ann Pharmacother* 2009; 43: 1139–42.
4. Mehta H, *et al.* Voriconazole for the treatment of refractory Aspergillus fumigatus keratitis. *Indian J Ophthalmol* 2008; 56: 243–5.
5. Bang S, *et al.* Treatment with voriconazole in 3 eyes with resistant Acanthamoeba keratitis. *Am J Ophthalmol* 2010; 149: 66–9.

Fusariosis. The results of a retrospective study[1] suggest that voriconazole may have a role in the treatment of disseminated *Fusarium* infection in severely immunocompromised patients; in the study of 73 immunocompromised patients with invasive fusariosis, 47% had complete or partial response to voriconazole therapy after a median of 57 days of therapy. Most patients had failed prior antifungal therapy.

1. Lortholary O, *et al.* International retrospective analysis of 73 cases of invasive fusariosis treated with voriconazole. *Antimicrob Agents Chemother* 2010; 54: 4446–50.

Adverse Effects

The most commonly reported adverse effects with voriconazole are visual disturbances, fever, rashes, nausea, vomiting, diarrhoea, abdominal pain, headache, sepsis, respiratory disorders, and peripheral oedema. There have been some serious hepatic reactions including fatalities. Skin reactions have included rare cases of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Photosensitivity reactions may occur and are more likely during long-term treatment; some patients with phototoxic skin reactions while on long-term voriconazole treatment have gone on to develop melanoma or squamous cell carcinoma of the skin (risk factors include skin phototype, cumulative exposure to sunlight, and immunosuppression, particularly of a chronic nature).

Other adverse effects reported as being common during treatment with voriconazole include: chills, flu-like syndrome, asthenia, back pain, chest pain, injection site reactions, facial oedema, hypotension, sinusitis, altered liver function tests, jaundice, cheilitis, blood disorders, hypokalaemia, hypoglycaemia, dizziness, hallucinations, confusion, depression, anxiety, tremor, agitation, paraesthesia, pruritus, alopecia, exfoliative dermatitis, acute renal failure, and haematuria. Hypersensitivity reactions, including anaphylaxis, have occurred rarely.

Effects on the blood. Fever and leucocytosis with eosinophilia in one patient has been attributed to voriconazole treatment.[1]

1. Vishnubhotla P, *et al.* Fever and eosinophilia associated with voriconazole. *Ann Pharmacother* 2004; 38: 900–901.

Effects on plasma-fluoride concentration. Voriconazole contains 16.3% fluorine by weight and cases of elevated plasma fluoride concentrations have been reported in transplant patients taking normal doses of oral voriconazole for longer than 6 months. Long-term use of oral voriconazole has also been associated with painful periostitis and exostoses; plasma fluoride levels decreased and symptoms improved on stopping voriconazole.[1]

1. Wermers RA, *et al.* Fluoride excess and periostitis in transplant patients receiving long-term voriconazole therapy. *Clin Infect Dis* 2011; 52: 604–11.

Effects on the heart. Bradycardia with a prolonged QT interval and asymptomatic episodes of torsade de pointes occurred in a 15-year-old patient, after 3 weeks of voriconazole therapy at usual doses.[1] All drug treatment was stopped but the effects recurred on rechallenge with a small dose of voriconazole.

Arrhythmia also occurred in an elderly patient after 40 days of treatment with oral voriconazole at usual doses.[2] Voriconazole treatment was stopped and the patient's QTc returned to baseline with supportive treatment (see p. 1537.1). However, 2 days later oral voriconazole was re-started at the same dose and the patient developed episodes of torsade de pointes. Voriconazole was again stopped but the next day the patient developed a fatal polymorphic ventricular tachycardia despite serum-voriconazole concentrations being below the lower limit of detection. The authors considered that repeat doses of voriconazole may have led to the accumulation of active compounds that predisposed to arrhythmia or that a drug interaction with the proton pump inhibitor lansoprazole could have inhibited the metabolism of voriconazole (see also under Interaction, below).

1. Alkan Y, *et al.* Voriconazole-induced QT interval prolongation and ventricular tachycardia: a non-concentration-dependent adverse effect. *Clin Infect Dis* 2004; 39: e49–e52.
2. Tsubokura M, *et al.* Fatal dysrhythmia following initiation of lansoprazole during a long-term course of voriconazole. *J Clin Pharmacol* 2011; 51: 1488–90.

Effects on the liver. A patient who developed hepatotoxicity (liver enzyme values > 10 times the upper limit of normal) and a severe cutaneous reaction during high-dose oral treatment with voriconazole for aspergillosis was subsequently treated with high-dose intravenous voriconazole without recurrence of toxicity.[1] The authors considered that oral use might have led to higher concentrations of potentially toxic metabolites, due to a first-pass effect, although alternative explanations were possible.

1. Alffenaar JW, *et al.* Intravenous voriconazole after toxic oral administration. *Antimicrob Agents Chemother* 2010; 54: 2741–2.

Effects on the lungs. Cases of interstitial pneumonia have been reported in a few elderly patients after the use of intravenous voriconazole. The condition resolved after voriconazole treatment was stopped; some patients were also treated with corticosteroids.[1]

1. Japanese Pharmaceuticals and Medical Devices Safety Information no. 284 (issued October 2011). Available at: http://www.pmda.go.jp/english/service/pdf/precautions/PMDSI-284.pdf (accessed 23/04/12)

Effects on mental function. There have been reports[1,2] of patients having hallucinations (auditory or visual) during treatment with voriconazole. In one study 18 of 415 patients (4.3%) given voriconazole had visual hallucinations compared with 2 of 422 (0.5%) given amphotericin B.[1]

1. Walsh TJ, *et al.* Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. *N Engl J Med* 2002; 346: 225–34.
2. Agrawal AK, Sherman LK. Voriconazole-induced musical hallucinations. *Infection* 2004; 32: 293–5.

Precautions

Acute renal failure may occur with voriconazole and renal function should be monitored during treatment. Liver function should also be monitored before and during treatment with voriconazole. It should be used with caution in patients with hepatic impairment and doses may need to be adjusted (see under Uses and Administration, p. 597.3). Visual disturbances may occur and patients affected should not drive or operate hazardous machinery. In addition, all patients, whether affected by visual disturbances or not, should not drive at night, and should have their visual function monitored if they are receiving voriconazole for more than 28 days. Voriconazole has been associated with QT interval prolongation and should therefore be given with caution to patients with potentially pro-arrhythmic conditions. Any electrolyte disturbances should be corrected, if necessary before starting treatment with voriconazole; the intravenous form must not be given simultaneously with concentrated electrolyte infusions or blood products, even by separate lines. To minimise the risk of phototoxicity, direct sun exposure should be avoided and suitable clothing and sunscreen worn. Treatment periods should be as short as possible, and long-term treatment (> 6 months) should be considered only where the benefits clearly outweigh the risks.

Voriconazole has been shown to be teratogenic and embryotoxic in *animal* studies and its use is generally not recommended during pregnancy. For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p. 579.3. Licensed product information recommends that women of child-bearing potential should use effective contraception during treatment with voriconazole.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies voriconazole as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Interactions

Voriconazole is metabolised by cytochrome P450 isoenzymes CYP2C19, CYP2C9, and CYP3A4. Use of drugs that either inhibit or induce these isoenzymes may increase or decrease plasma concentrations of voriconazole, respectively. Rifampicin has been shown to decrease voriconazole plasma concentrations and a similar effect may be expected with carbamazepine, phenobarbital, or St John's wort; use of voriconazole with these drugs is therefore contra-indicated.

Concentrations of other drugs that are metabolised by CYP2C19, CYP2C9, or CYP3A4 may be increased by voriconazole. Increased plasma concentrations of astemizole, cisapride, pimozide, quinidine, and terfenadine could be expected and concomitant use is contra-indicated because of the risk of cardiac arrhythmias including torsade de pointes. Use with ergot alkaloids such as ergotamine and dihydroergotamine is also contra-indicated because of the possible risk of ergotism. Increased plasma concentrations of ciclosporin, sirolimus, and tacrolimus have been noted; use with sirolimus is contra-indicated, although ciclosporin or tacrolimus may be used providing doses are reduced and concentrations monitored. Likewise, monitoring and possible dose reductions of some opioid analgesics (such as alfentanil, fentanyl, hydrocodone, methadone, oxycodone, and sufentanil) may be needed during concomitant use. Concentrations of oral anticoagulants may be affected and increased prothrombin time has occurred with warfarin; monitoring should therefore be carried out. Close monitoring of blood glucose is necessary if voriconazole is used with oral hypoglycaemics such as the sulfonylureas. Dose reductions may be needed for some statins, calcium channel blockers, NSAIDs, vinca alkaloids, and some benzodiazepines (such as alprazolam, midazolam, and triazolam) if their plasma concentrations are increased.

Interactions may occur where both voriconazole and the other drug are affected. Examples are phenytoin and rifabutin (where concentrations of voriconazole are reduced but those of phenytoin or rifabutin are increased). If it is essential to give either drug with voriconazole, then an increase in the dose of voriconazole is recommended (see Uses and Administration, p. 597.2). With omeprazole, the plasma concentration of both drugs may be increased and a reduced dose of omeprazole is recommended (see under Interactions of Omeprazole, p. 1874.1). Similar effects may be noted between other proton pump inhibitors and voriconazole.

Voriconazole may inhibit metabolism of non-nucleoside reverse transcriptase inhibitors and they in turn may either inhibit the metabolism of voriconazole (e.g. delavirdine) or induce the metabolism of voriconazole (e.g. efavirenz and nevirapine); if co-administration of voriconazole and efavirenz cannot be avoided, an increase in the dose of voriconazole and a decrease in the dose of efavirenz is recommended. Similarly, voriconazole may inhibit metabolism of HIV-protease inhibitors (e.g. saquinavir, amprenavir, and nelfinavir) while they may in turn inhibit the metabolism of voriconazole. High doses of ritonavir (400 mg twice daily) significantly decrease plasma concentrations of voriconazole and co-administration is contra-indicated. Similar effects have been seen with low doses of ritonavir (100 mg twice daily) and use with voriconazole should be avoided where possible. Indinavir, however, does not appear to interact with voriconazole.

For further information on interactions between drugs metabolised by the cytochrome P450 isoenzyme CYP3A4 and azoles, see under Itraconazole, p. 585.1.

For reviews of drug interactions with azole antifungals, see Itraconazole, p. 585.2.

Antimicrobial Action

Voriconazole is a triazole antifungal that in sensitive fungi inhibits cytochrome P450-dependent enzymes resulting in the impairment of ergosterol synthesis in fungal cell membranes. Voriconazole has a broad spectrum of activity against all *Candida* species, including fluconazole-resistant strains, as well as *Aspergillus* spp., *Scedosporium* spp., and *Fusarium* spp.

Reports of breakthrough zygomycosis and other fungal infections in immunocompromised patients treated empirically or prophylactically with voriconazole.[1-6]

1. Marty FM, *et al.* Breakthrough zygomycosis after voriconazole treatment in recipients of hematopoietic stem-cell transplants. *N Engl J Med* 2004; 350: 950–2.
2. Siwek GT, *et al.* Invasive zygomycosis in hematopoietic stem cell transplant recipients receiving voriconazole prophylaxis. *Clin Infect Dis* 2004; 39: 584–7.
3. Imhof A, *et al.* Breakthrough fungal infections in stem cell transplant recipients receiving voriconazole. *Clin Infect Dis* 2004; 39: 743–6.
4. Oren I, Breakthrough zygomycosis during empirical voriconazole therapy in febrile patients with neutropenia. *Clin Infect Dis* 2005; 40: 770–1.
5. Vigouroux S, *et al.* Zygomycosis after prolonged use of voriconazole in immunocompromised patients with hematologic disease: attention required. *Clin Infect Dis* 2005; 40: e35–e37.
6. Trifilio S, *et al.* Breakthrough fungal infections after allogeneic hematopoietic stem cell transplantation in patients on prophylactic voriconazole. *Bone Marrow Transplant* 2007; 40: 451–6.

Pharmacokinetics

Voriconazole has non-linear pharmacokinetics due to saturable metabolism. It is rapidly and almost completely absorbed from the gastrointestinal tract. Peak plasma concentrations occur about 1 to 2 hours after an oral dose. Plasma protein binding of voriconazole is about 58%. Voriconazole diffuses into CSF.

Voriconazole is metabolised by hepatic cytochrome P450 isoenzyme CYP2C19; the major metabolite is the inactive *N*-oxide. Metabolism via isoenzymes CYP2C9 and CYP3A4 has also been shown *in vitro*. About 80% of voriconazole is excreted in the urine.

References.

1. Purkins L, *et al.* Pharmacokinetics and safety of voriconazole following intravenous- to oral-dose escalation regimens. *Antimicrob Agents Chemother* 2002; 46: 2546–53.
2. Johnston A. The pharmacokinetics of voriconazole. *Br J Clin Pharmacol* 2003; 56 (suppl 1): 1.
3. Walsh TJ, *et al.* Pharmacokinetics and safety of intravenous voriconazole in children after single- or multiple-dose administration. *Antimicrob Agents Chemother* 2004; 48: 2166–72.
4. Theuretzbacher U, *et al.* Pharmacokinetic/pharmacodynamic profile of voriconazole. *Clin Pharmacokinet* 2006; 45: 649–63.
5. Brüggemann RJ, *et al.* Therapeutic drug monitoring of voriconazole. *Ther Drug Monit* 2008; 30: 403–11.
6. Berge M, *et al.* Voriconazole pharmacokinetic variability in cystic fibrosis lung transplant patients. *Transpl Infect Dis* 2009; 11: 211–9.
7. Scholz I, *et al.* Pharmacokinetics, metabolism and bioavailability of the triazole antifungal agent voriconazole in relation to CYP2C19 genotype. *Br J Clin Pharmacol* 2009; 68: 906–15.
8. Johnson RJ, *et al.* Voriconazole pharmacokinetics in liver transplant recipients. *Antimicrob Agents Chemother* 2010; 54: 852–9.

9. Neely M, *et al.* Voriconazole pharmacokinetics and pharmacodynamics in children. *Clin Infect Dis* 2010; **50**: 27–36.
10. Pasqualotto AC, *et al.* Voriconazole therapeutic drug monitoring: focus on safety. *Expert Opin Drug Safety* 2010; **9**: 125–37.
11. Walsh TJ, *et al.* Pharmacokinetics, safety, and tolerability of voriconazole in immunocompromised children. *Antimicrob Agents Chemother* 2010; **54**: 4116–23.
12. Han K, *et al.* Bioavailability and population pharmacokinetics of voriconazole in lung transplant recipients. *Antimicrob Agents Chemother* 2010; **54**: 4424–31.
13. Michael C, *et al.* Voriconazole pharmacokinetics and safety in immunocompromised children compared to adult patients. *Antimicrob Agents Chemother* 2010; **54**: 3225–32.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Vfend; *Austral.*: Vfend; *Austria*: Vfend; *Belg.*: Vfend; *Braz.*: Vfend; *Canad.*: Vfend; *Chile*: Vfend; *China*: Pinup (匹纳普); Vfend (威凡); *Cz.*: Vfend; *Denm.*: Vfend; *Fin.*: Vfend; *Fr.*: Vfend; *Ger.*: Vfend; *Gr.*: Vfend; *Hong Kong*: Vfend; *Hung.*: Vfend; *Indon.*: Vfend; *Irl.*: Vfend; *Israel*: Vfend; *Ital.*: Vfend; *Malaysia*: Vfend; *Mex.*: Vfend; *Neth.*: Vfend; *Norw.*: Vfend; *NZ*: Vfend; *Philipp.*: Vfend; *Pol.*: Vfend; *Port.*: Vfend; *Rus.*: Vfend (Вифенд); *S.Afr.*: Vfend; *Singapore*: Vfend; *Spain*: Vfend; *Swed.*: Vfend; *Switz.*: Vfend; *Thai.*: Vfend; *Turk.*: Vfend; *UK*: Vfend; *Ukr.*: Vfend (Вифенд); *USA*: Vfend; *Venez.*: Vorcum.

Antigout Drugs

This chapter deals with the treatment of gout and hyperuricaemia and the drugs used mainly for these disorders.

Gout and hyperuricaemia

Uric acid is the final product of the metabolism of endogenous and exogenous purine in man. An excess of uric acid, measured in the plasma as sodium urate, constitutes **hyperuricaemia**. A patient is usually considered to be hyperuricaemic when plasma-urate concentrations exceed

- 0.42 mmol/litre (7 mg per 100 mL) in men and postmenopausal women
- 0.36 mmol/litre (6 mg per 100 mL) in premenopausal women.

Hyperuricaemia may be caused by an overproduction of urate (e.g. due to excessive dietary purine intake, certain cancers or their treatment, or, more rarely, enzyme defects of purine metabolism), or reduced urate excretion due to renal disease, hypertension, or the intake of certain drugs such as thiazide diuretics and some immunosuppressants (such as ciclosporin and tacrolimus). Other factors contributing to hyperuricaemia include hyperlipidaemia, obesity, alcohol consumption, and lead exposure.

At hyperuricaemic concentrations there is a risk of crystals of monosodium urate monohydrate being formed and deposited in synovial fluid and various tissues. The presence of urate crystals in the synovial fluid leads to an inflammatory response in the affected joint, commonly at the base of the big toe (podagra). The ensuing exquisite pain, tenderness, erythema, and swelling constitute the clinical manifestations of **acute inflammatory gouty arthritis**. Repeated acute attacks may be associated with a visible or palpable build up of crystal deposits (**tophi**) at various sites including in and around the affected joint. Tophi release urate crystals into the synovial fluid after various stimuli and so cause further acute attacks, leading to **chronic tophaceous gout**. Intra-articular and peri-articular tophi may cause gradual joint erosion, which, without treatment, results in disabling **chronic gouty arthritis**. Rarely, the kidney can be affected by urate deposits producing a gouty nephropathy or by uric acid calculi or stones (uric acid nephrolithiasis or urolithiasis).

Treatment aims to:

- alleviate the acute attack
- prevent future attacks
- lower plasma-urate concentration.

Plasma-urate concentrations may be reduced by control of obesity and modification of diet and alcohol intake. Drug treatment can relieve the pain of acute attacks but more prolonged therapy for hyperuricaemia is generally only considered if there are recurrent attacks of gout or there is renal involvement (see under Chronic Gout, below).

Acute gout. An attack of acute inflammatory gouty arthritis is best treated as soon as possible with an NSAID. Aspirin or other salicylates are not suitable since they may increase plasma-urate concentrations. Treatment is started with high doses of an NSAID, the doses being reduced as the patient responds. Usually treatment can be withdrawn within 1 to 2 weeks. Colchicine is an effective alternative; it may be used alone, or with an NSAID. Another alternative to NSAIDs or colchicine, for example in those for whom these drugs are contra-indicated, is an oral or intramuscular corticosteroid. Intra-articular corticosteroids are effective in acute monoarticular gout, or when used adjunctively in patients with polyarticular gout; infection of joints should be excluded before injection. Canakinumab, a recombinant human monoclonal interleukin-1β antibody, may be used for the treatment of frequent attacks when NSAIDs, colchicine, and repeated courses of corticosteroids are inappropriate or ineffective. Intravenous, intramuscular, or subcutaneous corticotropin has also been used, alone or adjunctively. Other therapies for acute gout include adjunctive analgesics and topical ice. Drugs used for chronic gout (allopurinol or the uricosurics) should not be started during an acute attack since they can exacerbate and prolong it (see below).

Chronic gout. If the patient suffers frequent acute attacks or develops tophaceous gout, or has renal complications as a result of urate overproduction, then long-term treatment of hyperuricaemia may be needed. Such **urate-lowering therapy** should not be started during an acute attack, or for 2 to 3 weeks thereafter, as fluctuations in urate concentration may prolong the existing attack or trigger a new one. Treatment involves inhibiting the production of uric acid or enhancing its urinary excretion, in order to maintain a serum urate concentration at or below 0.3 or 0.36 mmol/litre. Hyperuricaemia due to *overproduction* of urate is treated with allopurinol, which inhibits the enzyme xanthine oxidase, involved in purine metabolism. Hyperuricaemia associated with *underexcretion* of uric acid can be treated with either allopurinol or a uricosuric such as probenecid or sulfinpyrazone.

Allopurinol is most commonly given as first-line therapy, but may be combined with or replaced by uricosurics if treatment fails. Allopurinol should also be used for patients with renal urate deposits or with uric acid renal calculi as it reduces urolithiasis. Febuxostat is an alternative xanthine oxidase inhibitor for those patients who cannot take allopurinol.

With either treatment there is mobilisation of urate crystals from established tophi, as the plasma-urate concentration falls, which can trigger further acute attacks of gout. Patients are thus also given **prophylaxis** with an NSAID or colchicine from the start of urate-lowering treatment until at least a month after the plasma-urate has been reduced to an acceptable concentration; up to 6 months of prophylactic cover has been recommended.

Once the hyperuricaemia is corrected, the patient continues to receive therapy with allopurinol or uricosurics indefinitely. If an acute attack occurs during such maintenance therapy, this therapy should be continued to avoid fluctuations in urate concentration, and the acute attack treated in its own right. For chronic gout that is refractory to conventional urate-lowering therapy, pegloticase, a recombinant form of urate oxidase, may be tried.

Surgery may have to be considered for patients severely affected by chronic tophaceous gout.

References to gout and its management are given below.[1-14]

1. Anonymous. Gout in primary care. *Drug Ther Bull* 2004; 42: 37–40.
2. Schlesinger N. Management of acute and chronic gouty arthritis: present state-of-the-art. *Drugs* 2004; 64: 2399–2416.
3. Wortmann RL. Recent advances in the management of gout and hyperuricemia. *Curr Opin Rheumatol* 2005; 17: 319–24.
4. Underwood M. Gout. *Clin Evid* 2005; 13: 1435–44.
5. Suresh E. Diagnosis and management of gout: a rational approach. *Postgrad Med J* 2005; 81: 572–9.
6. Teng GG, *et al.* Pathophysiology, clinical presentation and treatment of gout. *Drugs* 2006; 66: 1547–63.
7. Underwood M. Diagnosis and management of gout. *BMJ* 2006; 332: 1315–19.
8. Zhang W, *et al.* EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2006; 65: 1312–24.
9. Jordan KM, *et al.* British Society for Rheumatology and British Health Professionals in Rheumatology Standards, Guidelines and Audit Working Group (SGAWG). British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of gout. *Rheumatology (Oxford)* 2007; 46: 1372–4. Also available at: http://rheumatology.oxfordjournals.org/cgi/reprint/46/8/1372 (accessed 22/04/08)
10. Tausche A-K, *et al.* Gout—current diagnosis and treatment. *Dtsch Arztebl Int* 2009; 106: 549–55.
11. Underwood M, Adebajo A. Gout, hyperuricaemia and crystal arthritis. In: Adebajo A, ed. *ABC of rheumatology*. 4th ed. Chichester: Wiley-Blackwell, 2010: 59–64.
12. Richette P, Bardin T. Gout. *Lancet* 2010; 375: 318–28.
13. Wilson JF. In the clinic. Gout. *Ann Intern Med* 2010; 152: ITC2-2–ITC2-14. Correction. *ibid.*; 479–80.
14. Bhansing KJ, *et al.* Gout: a clinical syndrome illustrated and discussed. *Neth J Med* 2010; 68: 352–9.

Allopurinol *(BAN, USAN, rINN)*

Allopürinol; Allopurinoli; Allopurinolo; Allopurinolum; Allopurynol; Alopurinol; Alopurinolis; BW-56-158; HPP; NSC-1390; Аллопуринол.

$C_5H_4N_4O$=136.1

CAS — 315-30-0 (allopurinol); 17795-21-0 (allopurinol sodium).

ATC — M04AA01.

ATC Vet — QM04AA01.

UNII — 63CZ7GJN5I.

Description. Allopurinol is a tautomeric mixture of 1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ol and 1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Allopurinol). A white or almost white powder. Very slightly soluble in water and in alcohol; dissolves in dilute solutions of alkali hydroxides.

USP 36: (Allopurinol). A fluffy white to off-white powder having only a slight odour. Very slightly soluble in water and in alcohol; practically insoluble in chloroform and in ether; soluble in solutions of potassium and sodium hydroxides.

Incompatibility. Allopurinol sodium as a 3 mg/mL solution in 0.9% sodium chloride was visually incompatible with amikacin sulfate, amphotericin B, carmustine, cefotaxime sodium, chlormethine hydrochloride, chlorpromazine hydrochloride, cimetidine hydrochloride, clindamycin phosphate, cytarabine, dacarbazine, daunorubicin hydrochloride, diphenhydramine hydrochloride, doxorubicin hydrochloride, doxycycline hyclate, droperidol, floxuridine, gentamicin sulfate, haloperidol lactate, hydroxyzine hydrochloride, idarubicin hydrochloride, imipenem with cilastatin sodium, methylprednisolone sodium succinate, metoclopramide hydrochloride, minocycline hydrochloride, nalbuphine hydrochloride, netilmicin sulfate, ondansetron hydrochloride, pethidine hydrochloride, prochlorperazine edisilate, promethazine hydrochloride, sodium bicarbonate, streptozocin, tobramycin sulfate, and vinorelbine tartrate.[1]

1. Trissel LA, Martinez JF. Compatibility of allopurinol sodium with selected drugs during simulated Y-site administration. *Am J Hosp Pharm* 1994; 51: 1792–9.

Uses and Administration

Allopurinol is used to treat hyperuricaemia (above) associated with chronic gout, acute uric acid nephropathy, recurrent uric acid stone formation, certain enzyme disorders, or cancer and its treatment (see Tumour Lysis Syndrome, p. 730.2). It is not used for asymptomatic hyperuricaemia. Allopurinol is also used in the management of renal calculi caused by the deposition of calcium oxalate (in the presence of hyperuricosuria) and of 2,8-dihydroxyadenine (see Renal Calculi, p. 602.1). It may have the potential to reduce oxidative stress by blocking the production of free radicals and is an ingredient of kidney preservation solutions. In addition allopurinol has antiprotozoal activity and has been used in leishmaniasis and American trypanosomiasis.

Allopurinol is used in **gout and hyperuricaemia** to inhibit the enzyme xanthine oxidase, thus preventing the oxidation of hypoxanthine to xanthine and xanthine to uric acid. The urinary purine load, normally almost entirely uric acid, is thereby divided between hypoxanthine, xanthine, and uric acid, each with its independent solubility. This results in the reduction of urate and uric acid concentrations in plasma and urine, ideally to such an extent that deposits of monosodium urate monohydrate or uric acid are dissolved or prevented from forming. At low concentrations allopurinol acts as a competitive inhibitor of xanthine oxidase and at higher concentrations as a non-competitive inhibitor. However, most of its activity is due to the metabolite oxipurinol which is a non-competitive inhibitor of xanthine oxidase.

Allopurinol is used in *chronic gout* to correct hyperuricaemia, reduce the likelihood of acute attacks, and prevent the sequelae of chronic gout. Initially, it may increase plasma-concentrations of urate and uric acid by dissolving deposits. This can trigger or exacerbate acute attacks, so allopurinol should not be started until an acute attack has completely subsided, and treatment should be started with a low dose and increased gradually; an NSAID (but not aspirin or salicylates) or colchicine should also be given for at least 1 month after hyperuricaemia is corrected. It may take several months to deplete the uric acid level sufficiently to control acute attacks.

A suggested oral starting dose of allopurinol is 100 mg daily, gradually increased by 100 mg for example at weekly intervals until the concentration of urate in plasma is reduced to 0.36 mmol/litre (6 mg per 100 mL) or less. A daily dose range of 100 to 300 mg may be adequate for those with mild gout and up to 600 mg for those with moderately severe tophaceous gout. The maximum recommended daily dose is 800 mg in the USA and 900 mg in the UK. Up to 300 mg may be taken as a single daily dose; larger amounts should be taken in divided doses to reduce the risk of gastric irritation. Taking allopurinol after food will also minimise gastric irritation. Patients should maintain an adequate fluid intake to prevent renal xanthine deposition.

Doses of allopurinol should be reduced in patients with renal impairment (see p. 601.1)

When used for the *prevention of uric acid nephropathy associated with cancer therapy* 600 to 800 mg may be given daily, generally for 2 or 3 days before starting the cancer treatment. A high fluid intake is essential. Maintenance doses of allopurinol in patients with hyperuricaemia secondary to cancer or cancer chemotherapy are similar to those used in gout and are given according to the response.

Allopurinol sodium has been given by intravenous infusion in sodium chloride 0.9% or glucose 5% to patients (usually cancer patients) unable to take allopurinol orally. The recommended dose in adults is the equivalent of allopurinol 200 to 400 mg/m² daily up to a maximum of 600 mg daily. Allopurinol sodium 116.2 mg is equivalent to about 100 mg of allopurinol.

The oral dose of allopurinol recommended for the management of recurrent calcium oxalate renal calculi in patients with hyperuricosuria is 200 to 300 mg daily, adjusted on the basis of subsequent 24-hour urinary urate excretion.

For doses in children, see Administration in Children, below.

Administration in children. The main use of allopurinol in children is for hyperuricaemia associated with cancer or cancer chemotherapy or with enzyme disorders. The dosage used may vary: in the UK an oral dose of 10 to 20 mg/kg daily, up to a maximum of 400 mg daily, is recommended for children under 15 years of age, while in the USA the dose is 150 mg daily for children under 6 years of age and 300 mg daily for those aged 6 to 10 years, adjusted if necessary after 48 hours.

Administration in hepatic impairment. UK licensed product information recommends that reduced oral doses of allopurinol be used in patients with hepatic impairment, and that liver function should be periodically monitored in the early stages of therapy.

Administration in renal impairment. Excretion of allopurinol and its active metabolite oxipurinol is mainly via the kidneys and therefore the dosage should be reduced in renal impairment according to creatinine clearance (CC).

In the USA the following doses are suggested for oral and intravenous use:

- CC 10 to 20 mL/minute: 200 mg daily
- CC less than 10 mL/minute: no more than 100 mg daily
- CC less than 3 mL/minute: consider also a longer dosage interval

In the UK a maximum initial oral daily dosage of 100 mg is recommended for those with renal impairment, increased only if the response is inadequate. Doses less than 100 mg daily or 100 mg at intervals longer than 1 day are recommended for those with severe renal insufficiency. Because of the imprecision of low creatinine clearance values, it is suggested that, if facilities are available for monitoring, the allopurinol dose should be adjusted to maintain plasma-oxipurinol concentrations below 100 micromoles/litre (15.2 micrograms/mL). A suggested alternative dose for patients requiring dialysis two or three times weekly is 300 to 400 mg allopurinol immediately after dialysis only.

The difficulties of maintaining an appropriate dose in such patients were illustrated by a study[1] in New Zealand involving 227 allopurinol-treated patients. The guidelines used suggested maintenance doses based on CC as follows:

- less than 10 mL/minute: 100 mg every 3 days
- 10 mL/minute: 100 mg every 2 days
- 20 mL/minute: 100 mg daily
- 40 mL/minute: 150 mg daily
- 60 mL/minute: 200 mg daily

The recommended dose or less was used in the majority of cases (183 of 227). However, of 214 patients for whom serum-uric acid concentrations were available, only 48 achieved values of 0.36 mmol/litre or less. The proportion of patients achieving acceptable serum-uric acid concentrations was higher (38%) in patients given higher than recommended doses than in those on doses recommended by the guidelines (19%). Although guidelines might be useful for initial dosing, longer term use could lead to inadequate control of hyperuricaemia.

1. Dalbeth N, *et al.* Dose adjustment of allopurinol according to creatinine clearance does not provide adequate control of hyperuricemia in patients with gout. *J Rheumatol* 2006; 33: 1646–50.

Angina pectoris. Allopurinol has been investigated for its apparent anti-ischaemic effects in angina (p. 1254.3). A randomised study[1] in 60 subjects with chronic stable angina found that high-dose allopurinol significantly improved exercise tolerance compared with placebo. A proposed mechanism was enhanced myocardial oxygen and ATP balance, possibly supplemented by improved coronary blood flow and reduced left ventricular afterload.

1. Noman A, *et al.* Effect of high-dose allopurinol on exercise in patients with chronic stable angina: a randomised, placebo controlled crossover trial. *Lancet* 2010; 375: 2161–7.

Bipolar disorder. A double-blind study was conducted in 141 adults with bipolar disorder (p. 397.2), diagnosed as being acutely manic with or without psychotic features. Patients received lithium and were randomised to either oral allopurinol 600 mg daily, oral dipyridamole, or placebo. Improvements in mania were significant for those randomised to allopurinol, and were associated with decreasing uric acid concentrations, suggesting a role for purinergic system dysfunction in mania.[1]

1. Machado-Vieira R, *et al.* A double-blind, randomized, placebo-controlled 4-week study on the efficacy and safety of the purinergic agents allopurinol and dipyridamole adjunctive to lithium in acute bipolar mania. *J Clin Psychiatry* 2008; 69: 1237–45.

Diagnosis and testing. Deficiency of the enzyme ornithine carbamoyltransferase can result in severe CNS dysfunction or even in death, and identification of women at risk of being carriers of this genetic enzyme deficiency has been described.[1] The enzyme deficiency causes carbamoyl phosphate to accumulate, which stimulates the synthesis of orotidine. The test relies on giving a single dose of allopurinol, which will, in carriers, greatly increase the urinary excretion of orotidine. However, mutation analysis is now more usually used to establish the diagnosis.

1. Hauser ER, *et al.* Allopurinol-induced orotidinuria. *N Engl J Med* 1990; 322: 1641–5. Correction. *ibid.* 1997; 336: 1335.

Epilepsy. Reduction in the frequency of seizures has been described in some patients with severe or intractable epilepsy (p. 506.1) when allopurinol was added to their existing antiepileptic therapy.[1-4] Although the mode of action was unknown it was noted that the patients were not hyperuricaemic and that allopurinol did not affect plasma concentrations of existing antiepileptics.[1] However, others[3] have seen no benefit.

1. DeMarco P, Zagnoni P. Allopurinol and severe epilepsy. *Neurology* 1986; 36: 1538–9.
2. Tada H, *et al.* Clinical effects of allopurinol on intractable epilepsy. *Epilepsia* 1991; 32: 279–83.
3. Zagnoni PG, *et al.* Allopurinol as an add-on therapy in refractory epilepsy—a double-blind placebo-controlled randomised study. *Epilepsia* 1994; 35: 107–12.
4. Togha M, *et al.* Allopurinol as adjunctive therapy in intractable epilepsy: a double-blind and placebo-controlled trial. *Arch Med Res* 2007; 38: 313–16.
5. Coppola G, Pascotto A. Double-blind, placebo-controlled, cross-over trial of allopurinol as add-on therapy in childhood refractory epilepsy. *Brain Dev* 1996; 18: 50–2.

Hypertension. Hypertension (p. 1251.1) may be associated with hyperuricaemia. Thirty adolescents with mild hypertension and a serum uric acid concentration of 6 mg per 100 mL or more, and not on any antihypertensive therapy, were randomised to oral allopurinol 200 mg twice daily or placebo for 4 weeks in a double-blind, crossover study. Allopurinol treatment was associated with a significant decrease in systolic and diastolic blood pressure.[1]

1. Feig DI, *et al.* Effect of allopurinol on blood pressure of adolescents with newly diagnosed essential hypertension: a randomized trial. *JAMA* 2008; 300: 924–32.

Organ and tissue transplantation. Allopurinol 25 mg on alternate days has been added to the immunosuppressive treatment for renal transplantation,[1] and is reported to reduce the frequency of acute rejection. One possible explanation for this effect is allopurinol's ability to suppress the production of free radicals (see Oxidative Stress, below). Organ and tissue transplantation, and the more usual drugs used in immunosuppressive regimens are discussed on p. 1936.2. It should be noted that allopurinol interacts with azathioprine (see Immunosuppressants, under Interactions, p. 603.2) and ciclosporin (p. 1957.1).

1. Chocair P, *et al.* Low-dose allopurinol plus azathioprine/cyclosporin/prednisolone, a novel immunosuppressive regimen. *Lancet* 1993; 342: 83–4.

Oxidative stress. Allopurinol, through its inhibition of xanthine oxidase, can block the development of superoxide free radicals during reperfusion after an ischaemic episode. Consequently, the ability of allopurinol to reduce oxidative stress has been investigated in a number of clinical situations.

In a small study[1] of patients with idiopathic dilated cardiomyopathy, short-term intracoronary allopurinol improved myocardial efficiency by decreasing the oxygen demand of left ventricular contraction.

In patients undergoing coronary artery bypass graft surgery, perioperative allopurinol reduced hospital mortality, the incidence of arrhythmias, the number of ischaemic events, and the need for inotropic support, although the findings were not consistent in all studies.[2]

Improved endothelial dysfunction has been found in patients with chronic heart failure given allopurinol.[3,4]

A large study[5] in neonates undergoing cardiac surgery found that allopurinol caused a reduction in seizures and cardiac events in those with hypoplastic left heart syndrome. No benefit was found in neonates with less severe forms of congenital heart disease, considered to be at lower risk of adverse surgical outcome or reperfusion injury. Allopurinol also failed to reduce the incidence of periventricular leucomalacia (thought to represent ischaemic infarction of the developing brain) in preterm infants compared with placebo in a large study.[6] Similarly, allopurinol did not reduce the incidence of infarct extension in patients with acute myocardial infarction,[7] nor did it improve cerebrovascular reactivity in a small study in patients who had recently had subcortical stroke,[8] despite earlier results suggesting improvements in inflammatory indices.[9]

A pilot study using allopurinol showed a beneficial effect on free radical formation, cerebral blood volume, and electrical brain activity in severely asphyxiated newborns.[10] However, a systematic review[11] of this and 2 other studies in such infants was unable to determine whether allopurinol produced clinically important benefits.

Women in labour with signs of fetal distress were given intravenous allopurinol in a study to determine whether treatment would reduce free radical formation in the fetus, leading to a reduction of the neurodevelopmental consequences of fetal hypoxia.[12] Allopurinol was found to cross the placenta, although concentrations of allopurinol and its metabolite oxipurinol were lower in the umbilical cord compared with concentrations measured after an equivalent dose of oral allopurinol to mothers in uncomplicated labour. Newborns with therapeutic allopurinol and/or oxipurinol concentrations in cord blood had lower concentrations of the brain injury marker S-100B.

The possibility that allopurinol limits the production of free radicals has also led to allopurinol sodium being included as an ingredient of the University of Wisconsin solution [UW Solution; Belzer UW Solution (commercially available as *Viaspan*)], which is used for the preservation of organs for transplantation.[13]

For evidence that allopurinol may be of value in angina pectoris see above.

1. Cappola TP, *et al.* Allopurinol improves myocardial efficiency in patients with idiopathic dilated cardiomyopathy. *Circulation* 2001; 104: 2407–11.
2. Weimert NA, *et al.* Allopurinol as a cardioprotectant during coronary artery bypass graft surgery. *Ann Pharmacother* 2003; 37: 1708–11.
3. Doehner W, *et al.* Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricaemic patients with chronic heart failure: results from 2 placebo-controlled studies. *Circulation* 2002; 105: 2619–24.
4. Farquharson CAJ, *et al.* Allopurinol improves endothelial dysfunction in chronic heart failure. *Circulation* 2002; 106: 221–6.
5. Clancy RR, *et al.* Allopurinol neurocardiac protection trial in infants undergoing heart surgery using deep hypothermic circulatory arrest. *Pediatrics* 2001; 108: 61–70.
6. Russell GAB, Cooke RWI. Randomised controlled trial of allopurinol prophylaxis in very preterm infants. *Arch Dis Child Fetal Neonatal Ed* 1995; 73: F27–F31.
7. Parmley LF, *et al.* Allopurinol therapy of ischemic heart disease with infarct extension. *Can J Cardiol* 1992; 8: 280–6.
8. Dawson J, *et al.* The effect of allopurinol on the cerebral vasculature of patients with subcortical stroke: a randomized trial. *Br J Clin Pharmacol* 2009; 68: 662–8.
9. Muir SW, *et al.* Allopurinol use yields potentially beneficial effects on inflammatory indices in those with recent ischemic stroke: a randomized, double-blind, placebo-controlled trial. *Stroke* 2008; 39: 3303–7.
10. Van Bel F, *et al.* Effect of allopurinol on postasphyxial free radical formation, cerebral haemodynamics, and electrical brain activity. *Pediatrics* 1998; 101: 185–93.
11. Chaudhari T, McGuire W. Allopurinol for preventing mortality and morbidity in newborn infants with suspected hypoxic-ischaemic encephalopathy. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 14/07/08).
12. Torrance HL, *et al.* Maternal allopurinol during fetal hypoxia lowers cord blood levels of the brain injury marker S-100B. *Pediatrics* 2009; 124: 350–7. Also available at: http://pediatrics.aappublications.org/cgi/reprint/124/1/350 (accessed 05/01/11)
13. Southard JH, Belzer FO. Organ preservation. *Annu Rev Med* 1995; 46: 235–47.

Prostatitis. Although allopurinol has been reported to be of benefit[1] in a small study in patients with chronic prostatitis (p. 2350.2), a systematic review[2] found no other satisfactory evidence of benefit, and considered that the clinical relevance of the original study results was unclear.

1. Persson BE, *et al.* Ameliorative effect of allopurinol on nonbacterial prostatitis: a parallel double-blind controlled study. *J Urol (Baltimore)* 1996; 155: 961–4.
2. McNaughton Collins M, Wilt T. Allopurinol for chronic prostatitis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 18/05/06).

Protozoal infections. Allopurinol has been widely used as an adjunct to pentavalent antimonials in the treatment[1,2] of Old World *visceral leishmaniasis* (p. 923.1), particularly where resistance to antimony alone is likely, although the degree of benefit has been called into question.[3] It has also been used with other drugs such as pentamidine[4] or azole antifungals,[5-8] including in transplant patients[7] or those with AIDS,[5] or in whom antimonials were otherwise poorly tolerated.[8] Allopurinol has also been tried alone[9,10] or with other drugs in both Old World[11-13] and New World[14-16] *cutaneous* (p. 922.1) or *mucocutaneous leishmaniasis*; (p. 923.1) results, particularly in the latter, have been variable. Allopurinol is usually given in oral doses of 15 to 20 mg/kg daily in 3 divided doses for leishmaniasis, and treatment lasts about 30 days.[3,4,11,12]

Beneficial results have been noted in some[17-20] but not all[21] studies using allopurinol in indeterminate and chronic Chagas' disease (*American trypanosomiasis*, p. 925.3). It may be less effective and have more adverse effects than itraconazole. Allopurinol 8.5 mg/kg daily is typically given orally for about 60 days;[17,19,20] higher doses (900 mg daily) were ineffective for chronic disease.[21]

The selective antiparasitic action of allopurinol is believed to be due to its incorporation into the protozoal, but not the mammalian, purine salvage pathway. This leads to the formation of 4-aminopyrazolopyrimidine ribonucleotide triphosphate, a highly toxic analogue of adenosine triphosphate, that is incorporated into ribonucleic acid. This action of allopurinol is shared by allopurinol riboside, one of the minor metabolites in man, but not by oxipurinol, the major human metabolite. Thus, some studies have been conducted with allopurinol riboside, rather than allo-

purinol, in an attempt to enhance activity by avoiding host-mediated inactivation.[22]

1. di Martino L, *et al.* Low dosage combination of meglumine antimoniate plus allopurinol as first choice treatment of infantile visceral leishmaniasis in Italy. *Trans R Soc Trop Med Hyg* 1990; 84: 534–5.
2. Gradoni L, *et al.* Treatment of Mediterranean visceral leishmaniasis. *Bull WHO* 1995; 73: 191–7.
3. Singh NKP, *et al.* Combination therapy in kala-azar. *J Assoc Physicians India* 1995; 43: 319–20.
4. Das VNR, *et al.* A randomized clinical trial of low dosage combination of pentamidine and allopurinol in the treatment of antimony unresponsive cases of visceral leishmaniasis. *J Assoc Physicians India* 2001; 49: 609–13.
5. Raffi F, *et al.* Use of an itraconazole/allopurinol combination for the treatment of visceral leishmaniasis in a patient with AIDS. *Clin Infect Dis* 1995; 21: 1338–9.
6. Torrus D, *et al.* Fluconazole plus allopurinol in treatment of visceral leishmaniasis. *J Antimicrob Chemother* 1996; 37: 1042–3.
7. Hueso M, *et al.* The renal transplant patient with visceral leishmaniasis who could not tolerate meglumine antimoniate-cure with ketoconazole and allopurinol. *Nephrol Dial Transplant* 1999; 14: 2941–3.
8. Kuyucu N, *et al.* Successful treatment of visceral leishmaniasis with allopurinol plus ketoconazole in an infant who developed pancreatitis caused by meglumine antimoniate. *Pediatr Infect Dis J* 2001; 20: 455–7.
9. Halbert AR, *et al.* Allopurinol for Old World cutaneous leishmaniasis. *Pediatr Dermatol* 1995; 12: 287–8.
10. D'Oliveira A, *et al.* Evaluating the efficacy of allopurinol for the treatment of cutaneous leishmaniasis. *Int J Dermatol* 1997; 36: 938–40.
11. Esfandiarpour I, Alavi A. Evaluating the efficacy of allopurinol and meglumine antimoniate (Glucantime) in the treatment of cutaneous leishmaniasis. *Int J Dermatol* 2002; 41: 521–4.
12. Momeni AZ, Aminjavaheri M. Successful treatment of non-healing cases of cutaneous leishmaniasis, using a combination of meglumine antimoniate plus allopurinol. *Eur J Dermatol* 2003; 13: 40–3.
13. Esfandiarpour I, Dabiri SR. Treatment of cutaneous leishmaniasis recidivans with a combination of allopurinol and meglumine antimoniate: a clinical and histologic study. *Int J Dermatol* 2007; 46: 848–52.
14. Velez I, *et al.* Inefficacy of allopurinol as monotherapy for Colombian cutaneous leishmaniasis: a randomized, controlled trial. *Ann Intern Med* 1997; 126: 232–6.
15. Martinez S, *et al.* Treatment of cutaneous leishmaniasis with allopurinol and stibogluconate. *Clin Infect Dis* 1997; 24: 165–9.
16. Llanos-Cuentas A, *et al.* Efficacy of sodium stibogluconate alone and in combination with allopurinol for treatment of mucocutaneous leishmaniasis. *Clin Infect Dis* 1997; 25: 677–84.
17. Apt W, *et al.* Treatment of chronic Chagas' disease with itraconazole and allopurinol. *Am J Trop Med Hyg* 1998; 59: 133–8.
18. Amato Neto V. Etiological treatment for infection by Trypanosoma cruzi. *Rev Inst Med Trop Sao Paulo* 1999; 41: 211–3.
19. Apt W, *et al.* Itraconazole or allopurinol in the treatment of chronic American trypanosomiasis: the regression and prevention of electrocardiographic abnormalities during 9 years of follow-up. *Ann Trop Med Parasitol* 2003; 97: 23–9.
20. Apt W, *et al.* Itraconazole or allopurinol in the treatment of chronic American trypanosomiasis: the results of clinical and parasitological examinations 11 years post-treatment. *Ann Trop Med Parasitol* 2005; 99: 733–41.
21. Rassi A, *et al.* Specific treatment for Trypanosoma cruzi: lack of efficacy of allopurinol in the human chronic phase of Chagas disease. *Am J Trop Med Hyg* 2007; 76: 58–61.
22. Shapiro TA, *et al.* Pharmacokinetics and metabolism of allopurinol riboside. *Clin Pharmacol Ther* 1991; 49: 506–14.

Renal calculi. In conjunction with a reduced dietary purine intake, high fluid intake, and potassium citrate, allopurinol may be used to prevent the recurrence of calcium oxalate renal calculi (p. 2350.3) in patients with hyperuricosuria.[1,2] Allopurinol is also advocated for the management of 2,8-dihydroxyadenine (2,8-DHA) renal stones associated with deficient activity of the enzyme adenine phosphoribosyltransferase.

1. Ettinger B, *et al.* Randomized trial of allopurinol in the prevention of calcium oxalate calculi. *N Engl J Med* 1986; 315: 1386–9.
2. Sorensen CM, Chandhoke PS. Hyperuricosuric calcium nephrolithiasis. *Endocrinol Metab Clin North Am* 2002; 31: 915–25.

Sarcoidosis. Although corticosteroids remain the mainstay of drug therapy for sarcoidosis (p. 1612.2), and other drugs are very much second line, there are reports[1-3] of benefit in cutaneous disease from the use of allopurinol.

1. Brechtel B, *et al.* Allopurinol: a therapeutic alternative for disseminated cutaneous sarcoidosis. *Br J Dermatol* 1996; 135: 307–9.
2. Antony F, Layton AM. A case of cutaneous acral sarcoidosis with response to allopurinol. *Br J Dermatol* 2000; 142: 1052–3.
3. Bregnhoej A, Jemec GB. Low-dose allopurinol in the treatment of cutaneous sarcoidosis: response in four of seven patients. *J Dermatol Treat* 2005; 16: 125–7.

Schizophrenia. Involvement of purinergic neurotransmission has been hypothesised to play some role in schizophrenia (p. 1031.3), and allopurinol has been investigated as a possible adjunctive treatment, with some evidence of benefit, especially in patients with refractory positive symptoms.[1]

1. Buie LW, *et al.* Allopurinol as adjuvant therapy in poorly responsive or treatment refractory schizophrenia. *Ann Pharmacother* 2006; 40: 2200–4.

Skin disorders. Reactive perforating collagenosis (RPC) is a condition in which altered collagen is eliminated through the epidermis; it may be inherited or acquired. In 3 of 4 patients with RPC refractory to antibacterials and oral and topical corticosteroids, significant improvement was seen with allopurinol, in terms of reduction of new lesions, improvement of existing lesions, and reduction of pruritus. The fourth patient died from unrelated causes before review.[1]

1. Hoque SR, *et al.* Acquired reactive perforating collagenosis: four patients with a giant variant treated with allopurinol. *Br J Dermatol* 2006; 154: 759–62.

Adverse Effects

The most common adverse effect of allopurinol is rash. Rashes are generally maculopapular or pruritic, sometimes purpuric, but more serious hypersensitivity reactions may occur and include exfoliative rashes, the Stevens-Johnson syndrome, and toxic epidermal necrolysis. It is therefore recommended that allopurinol be withdrawn immediately if a rash occurs (see Precautions, below). Further symptoms of hypersensitivity include fever and chills, lymphadenopathy, leucopenia or leucocytosis, eosinophilia, arthralgia, and vasculitis leading to renal and hepatic damage and, very rarely, seizures. These hypersensitivity reactions may be severe, even fatal, and patients with hepatic or renal impairment are at special risk.

Hepatotoxicity and signs of altered liver function may also be found in patients who are not hypersensitive. Haematological effects include thrombocytopenia, aplastic anaemia, agranulocytosis, and haemolytic anaemia.

Many other adverse effects have been noted rarely and include paraesthesia, peripheral neuropathy, alopecia, gynaecomastia, hypertension, taste disturbances, nausea, vomiting, abdominal pain, diarrhoea, headache, malaise, drowsiness, vertigo, and visual disturbances.

Patients with gout may have an increase in acute attacks on beginning treatment with allopurinol, although attacks usually subside after several months.

Incidence of adverse effects. A Boston Collaborative Drug Surveillance Program involving 29 524 hospitalised patients found that, with the exception of skin reactions, 33 of 1835 patients treated with allopurinol (1.8%) had adverse effects. These effects were dose-related and the most frequent were haematological (11 patients, 0.6%), diarrhoea (5 patients, 0.3%), and drug fever (5 patients, 0.3%). Hepatotoxicity was reported in 3 patients (0.2%). Two patients developed possible hypersensitivity reactions to allopurinol.[1]

A further analysis involving 1748 outpatients indicated no instances of acute blood disorders, skin diseases, or hypersensitivity that warranted hospital treatment. Liver disease, although found, was not considered to be associated with allopurinol. There were only 2 patients in whom renal disease could possibly have been caused by allopurinol.[2]

1. McInnes GT, *et al.* Acute adverse reactions attributed to allopurinol in hospitalised patients. *Ann Rheum Dis* 1981; 40: 245–9.
2. Jick H, Perera DR. Reactions to allopurinol. *JAMA* 1984; 252: 1411.

Effects on the blood. In addition to the haematological abnormalities of leucopenia, thrombocytopenia, haemolytic anaemia, and clotting abnormalities noted in the Boston Collaborative Drug Surveillance Program,[1] aplastic anaemia has also been reported, sometimes in patients with renal impairment.[2] Pure red cell aplasia has also been reported.[3,4]

1. McInnes GT, *et al.* Acute adverse reactions attributed to allopurinol in hospitalised patients. *Ann Rheum Dis* 1981; 40: 245–9.
2. Anonymous. Allopurinol and aplastic anaemia. *WHO Drug Inf* 1989; 3: 26.
3. Lin Y-W *et al.* Acute pure red cell aplasia associated with allopurinol therapy. *Am J Hematol* 1999; 61: 209–11.
4. Chao S-C, *et al.* Hypersensitivity syndrome and pure red cell aplasia following allopurinol therapy in a patient with chronic kidney disease. *Ann Pharmacother* 2005; 39: 1552–6.

Effects on the eyes. Some case reports have suggested an association between allopurinol use and the development of cataracts,[1] but a detailed ophthalmological survey involving 51 patients who had taken allopurinol failed to confirm this.[2] However, a large retrospective case-control study in elderly patients concluded that long-term, or high-dose, allopurinol therapy did increase the risk of cataract extraction.[3]

1. Fraunfelder FT, *et al.* Cataracts associated with allopurinol therapy. *Am J Ophthalmol* 1982; 94: 137–40.
2. Clair WK, *et al.* Allopurinol use and the risk of cataract formation. *Br J Ophthalmol* 1989; 73: 173–6.
3. Garbe E, *et al.* Exposure to allopurinol and the risk of cataract extraction in elderly patients. *Arch Ophthalmol* 1998; 116: 1652–6.

Effects on the skin. Skin reactions are the most common adverse effects of allopurinol.

One report calculated that of 215 adverse effects noted over a 16-year period 188 (87.4%) were related to the skin or mucous membranes.[1] An analysis by the Boston Collaborative Drug Surveillance Program of data on 15 438 patients hospitalised between 1975 and 1982 detected 6 allergic skin reactions attributed to allopurinol among 784 recipients of the drug.[2] Desensitisation protocols[3] and alternative drugs[4] have been used after cutaneous reactions to allopurinol.

Serious skin reactions to allopurinol may occur as part of a generalised hypersensitivity reaction (see also Hypersensitivity, below). A review of the literature between 1970 and the end of 1990 revealed 101 cases of allopurinol hypersensitivity syndrome, 94 of which involved the skin.[5] Skin reactions included erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, or a diffuse maculopapular or exfoliative dermatitis; 27 of the 101 patients died. The relative risk of toxic epidermal necrolys s or Stevens-Johnson syndrome occurring with allopurinol was high (calculated to be 5.5) in a case-control stud y including 13 patients with these cutaneous reactions wh o had received allopurinol.[6] This risk was not constant ove r time, being higher during the first 2 months of treatmen . During these 2 months the estimated excess risk was 1. 5 cases per million users per week. Another case-contr l study,[7] involving 379 patients with Stevens-Johnso n syndrome or toxic epidermal necrolysis, found tha t allopurinol was the drug most frequently associated wit h these reactions. The risk again appeared to be restricted t o short-term use (less than 8 weeks) and was greater i n patients taking 200 mg or more daily.

1. Vinciullo C. Allopurinol hypersensitivity. *Med J Aust* 1984; 141: 449–5 .
2. Bigby M, *et al.* Drug-induced cutaneous reactions. *JAMA* 1986; 25 : 3358–63.
3. Fam AG, *et al.* Efficacy and safety of desensitization to allopurin l following cutaneous reactions. *Arthritis Rheum* 2001; 44: 231–8.
4. Fam AG. Difficult gout and new approaches for control of hyperuricemi in the allopurinol-allergic patient. *Curr Rheumatol Rep* 2001; 3: 29–35.
5. Arellano F, Sacristán JA. Allopurinol hypersensitivity syndrome: review. *Ann Pharmacother* 1993; 27: 337–43.
6. Roujeau J-C, *et al.* Medication use and the risk of Stevens-Johnso syndrome or toxic epidermal necrolysis. *N Engl J Med* 1995; 333: 1600 1607.
7. Halevy S, *et al.* EuroSCAR Study Group. Allopurinol is the most commo cause of Stevens-Johnson syndrome and toxic epidermal necrolysis i Europe and Israel. *J Am Acad Dermatol* 2008; 58: 25–32.

Hypersensitivity. Skin reactions to allopurinol are com mon (see Effects on the Skin, above), and may occur a part of a hypersensitivity reaction. A DRESS syndrom (drug rash with eosinophilia and systemic symptoms characterised by exfoliative dermatitis with eosinophilia complicated by symptoms such as hepatitis and interstitia nephritis, has been described.[1-3] Pathogenesis of th syndrome is not entirely clear, but may relate to the accu mulation of the metabolite oxipurinol. Risk factors include renal impairment and use with thiazide diuretics.[1] Patients who developed this syndrome have been success fully treated by immediate withdrawal of allopurinol an use of corticosteroids.[1,2]

1. Tausche A-K, *et al.* The Janus faces of allopurinol—allopurino hypersensitivity syndrome. *Am J Med* 2008; 121: e3–e4.
2. Markel A. Allopurinol hypersensitivity and DRESS syndrome. *Am J Me* 2008; 121: e25.
3. Calogiuri GF, *et al.* Therapeutic alternatives in a patient with DRESS syndrome induced by allopurinol. *J Investig Allergol Clin Immunol* 2009 19: 333–4.
4. Dewan AK, Quinonez RA. Allopurinol-induced DRESS syndrome in an adolescent patient. *Pediatr Dermatol* 2010; 27: 270–3.
5. Yang DC, Chang CM. Allopurinol-induced drug reaction with eosinophilia and systemic symptoms syndrome with recurrence. *J Am Geriatr Soc* 2010; 58: 2043–4.

Precautions

Allopurinol should not be used for the treatment of an acute attack of gout; additionally, allopurinol therapy should not be begun for any purpose during an acute attack. However, allopurinol is continued when acute attacks occur in patients already receiving the drug, and the acute attack is treated separately.

Treatment should be stopped immediately if any skin reactions or other signs of hypersensitivity develop:

- cautious reintroduction at a low dose may be attempted after resolution of *mild skin reactions* (see Effects on the Skin, above)
- allopurinol should not be reintroduced in those patients who have had *other forms of hypersensitivity* reaction

Dosage should be reduced in renal or hepatic impairment. Care is advised in patients being treated for hypertension or cardiac insufficiency, who may also have renal impairment.

To reduce the risk of renal xanthine deposition an adequate fluid intake (2 to 3 litres daily) is required. In addition, a neutral or slightly alkaline urine may be desirable.

Breast feeding. Allopurinol and its metabolite, oxipurinol, are distributed into breast milk, and licensed product information recommends that allopurinol should be used with caution in breast-feeding women. Although oxipurinol was detected in the plasma of a breast-fed infant, no adverse effects were noted in the infant during 6 weeks of maternal treatment with allopurinol.[1] The last available guidance from the American Academy of Pediatrics noted that there had been no documented problems with allopurinol and its use was considered to be usually compatible with breast feeding.[2]

1. Kamilli I, Gresser U. Allopurinol and oxypurinol in human breast milk. *Clin Investig* 1993; 71: 161–4.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/05/04)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies allopurinol as

probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 08/07/11)

Interactions

Drugs that can increase uric acid concentrations may decrease the efficacy of allopurinol. Aspirin and the salicylates possess this activity and should generally be avoided in hyperuricaemia and gout. An increase in hypersensitivity reactions, and possibly also other adverse effects, has been reported in patients taking allopurinol with ACE inhibitors or thiazide diuretics, particularly in patients with renal impairment.

The metabolism of azathioprine and mercaptopurine is inhibited by allopurinol and their doses should be markedly reduced when either of them is given with allopurinol to avoid potentially life-threatening toxicity. There have also been reports of allopurinol enhancing the activity of, and possibly increasing the toxicity of, several other drugs including some antibacterials, some anticoagulants, some other antineoplastics, ciclosporin, some sulfonylurea antidiabetics, theophylline, and vidarabine.

ACE inhibitors. An apparent interaction between allopurinol and *captopril* has been reported in patients with chronic renal failure. Development of fatal Stevens-Johnson syndrome after the introduction of allopurinol in 1 case was thought to be due to potentiation by captopril.[1] In another patient hypersensitivity, characterised by fever, arthralgia, and myalgia, occurred and was believed to be due to captopril, or one of its metabolites, potentiated by the addition of allopurinol.[2] Care is advised if allopurinol is used with captopril, especially in patients with chronic renal failure.

1. Pennell DJ, *et al.* Fatal Stevens-Johnson syndrome in a patient on captopril and allopurinol. *Lancet* 1984; i: 463.
2. Samanta A, Burden AC. Fever, myalgia, and arthralgia in a patient on captopril and allopurinol. *Lancet* 1984; i: 679.

Antacids. Allopurinol failed to reduce blood-uric-acid concentrations when given at the same time as *aluminium hydroxide* in 3 patients on chronic haemodialysis. However, if allopurinol was given 3 hours before aluminium hydroxide the expected decrease in uric acid concentration did occur.[1]

1. Weissman I, Krivoy N. Interaction of aluminium hydroxide and allopurinol in patients on chronic hemodialysis. *Ann Intern Med* 1987; 107: 787.

Antibacterials. There may be an increased incidence of rash when allopurinol is used with *ampicillin* or *amoxicillin*. For further details, see Ampicillin, p. 219.2.

Anticoagulants. For the effect of allopurinol on *dicoumarol, phenprocoumon,* or *warfarin,* see Warfarin, p. 1532.2.

Antiepileptics. For a report of allopurinol possibly inhibiting the metabolism of *phenytoin,* see under Antigout Drugs, p. 543.3.

Antigout drugs. Uricosuric drugs are likely to increase the renal elimination of oxipurinol (the major active metabolite of allopurinol). For example, *benzbromarone* lowered plasma concentrations of oxipurinol by about 40% when used with allopurinol, although plasma concentrations of allopurinol itself were not affected.[1] The interaction was not of concern, since the combination was more effective than allopurinol alone in lowering serum concentrations of uric acid. Licensed product information recommends reassessing the dosage of allopurinol on an individual basis when a uricosuric drug is added.

Probenecid has been reported to decrease the clearance of oral allopurinol riboside.[2] In a pharmacokinetic study in healthy subjects,[3] giving allopurinol and probenecid together significantly reduced oxipurinol concentrations; again, however, this combination had a greater hypouricaemic effect than either drug given alone.

1. Müller FO, *et al.* The effect of benzbromarone on allopurinol/oxypurinol kinetics in patients with gout. *Eur J Clin Pharmacol* 1993; 44: 69–72.
2. Were JBO, Shapiro TA. Effects of probenecid on the pharmacokinetics of allopurinol riboside. *Antimicrob Agents Chemother* 1993; 37: 1193–6.
3. Stocker SL, *et al.* Pharmacokinetic and pharmacodynamic interaction between allopurinol and probenecid in healthy subjects. *Clin Pharmacokinet* 2008; 47: 111–18.

Antineoplastics. Allopurinol inhibits the metabolism of *mercaptopurine* and marked dosage reduction of this drug to one-quarter to one-third of the usual dose is required if it is used with allopurinol. Deliberate use of the effects of allopurinol on mercaptopurine metabolism has been investigated (see p. 821.3).

There are also reports of interactions between allopurinol and other antineoplastics. Mild chronic allopurinol-induced hepatotoxicity has been reported in a male patient to have been exacerbated by *tamoxifen.*[1] Hypersensitivity vasculitis resulting in the death of a patient receiving allopurinol and *pentostatin* has been described. Although it could not be ascertained whether this effect was due to one of the drugs alone or to an interaction it was believed that this combination should not be used.[2]

For a report of an increased incidence of bone-marrow toxicity in patients given allopurinol with *cyclophosphamide,* see p. 773.2.

1. Shah KA, *et al.* Allopurinol hepatotoxicity potentiated by tamoxifen. *N Y State J Med* 1982; 82: 1745–6.
2. Steinmetz JC, *et al.* Hypersensitivity vasculitis associated with 2-deoxycoformycin and allopurinol therapy. *Am J Med* 1989; 86: 499.

Antivirals. For the effect of allopurinol on *didanosine,* see p. 973.3.

Immunosuppressants. Allopurinol inhibits the metabolism of mercaptopurine, the metabolite of *azathioprine,* and marked dosage reduction of azathioprine to one-quarter to one-third of the usual dose is required if it is used with allopurinol. Similar caution is also required with mercaptopurine itself (see Antineoplastics, above). The effects of allopurinol on *ciclosporin* concentrations (a marked increase) are reported on p. 1957.1.

Xanthines. For the effect of allopurinol on the pharmacokinetics of *caffeine* and *theophylline,* see p. 1206.2 and p. 1235.2 respectively.

Pharmacokinetics

Up to 90% of an oral dose of allopurinol is rapidly absorbed from the gastrointestinal tract; its plasma half-life is about 1 to 2 hours. Allopurinol's major metabolite is oxipurinol (alloxanthine), which is also an inhibitor of xanthine oxidase with a plasma half-life of about 15 or more hours in patients with normal renal function, although this is greatly prolonged by renal impairment. Both allopurinol and oxipurinol are conjugated to form their respective ribonucleosides. Allopurinol and oxipurinol are not bound to plasma proteins.

Excretion is mainly through the kidney, but it is slow since oxipurinol undergoes tubular reabsorption. About 70% of a daily dose may be excreted in the urine as oxipurinol and about 10% as allopurinol. The remainder of the dose is excreted in the faeces. Allopurinol and oxipurinol have also been detected in breast milk. Allopurinol has been found to cross the placenta.

References.

1. Murrell GAC, Rapeport WG. Clinical pharmacokinetics of allopurinol. *Clin Pharmacokinet* 1986; 11: 343–53.
2. Turnheim K, *et al.* Pharmacokinetics and pharmacodynamics of allopurinol in elderly and young subjects. *Br J Clin Pharmacol* 1999; 48: 501–9.
3. Day RO, *et al.* Clinical pharmacokinetics and pharmacodynamics of allopurinol and oxypurinol. *Clin Pharmacokinet* 2007; 46: 623–44.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Alfadiman; Colpuril A; Puritenk; *Austral.*: Allohexal†; Allosig; Progout; Zyloprim; *Austria*: Allostad; Gewapurol†; Gichtex; Purinol; Urosin; Zyloric; *Belg.*: Alpuric†; Docalloput†; Zyloric; *Braz.*: Lopurax; Zilopur†; Zyloric; *Canad.*: Alloprin; Novo-Purol; Zyloprim; *Chile*: Talol; Urogotan A; Zyloric; *China*: Ao Mai Bi Li (奥迈必利); Lu Bi Li (路必利); Valeric (维洛林); Yi Da Tong (易达通); Cz.: Milurit; Purinol; *Denm.*: Hexanurat; *Fin.*: Allonol; Apurin; Zyloric; *Fr.*: Zyloric; *Ger.*: Allo†; Allobeta; Bleminol†; Cellidrin†; Epidropal; Foligan†; Remid; Uribenz†; Zyloric; *Gr.*: Arsol; Gealgica; Petrazyc; Purigan; Soluric; Stradumel; Zylapour; Zyloric; *Hong Kong*: Allopin†; Arnol†; Marinol†; Milurit; Progout; Purinol†; Synpurinol†; Zyloric†; *Hung.*: Milurit; *India*: Aligout; Allgoric; Aloric; Aloriv; Alur; Alurid; Ciploric; Edorin; Gurik; Lodiric; Logout; Orlu; Zyloric; *Indon.*: Algut†; Alluric; Benoxuric; Hycemia†; Isoric; Licoric; Llanol†; Nilapur; Panuric; Pritanol; Puricemia; Reucid; Rinolic; Sinoric; Tylonic; Urica; Uricnol; Xanturic; Zyloric; *Irl.*: Alopur; Purinol; Tipuric; Zyloric; *Israel*: Alloril; *Ital.*: Alluril; Zyloric; *Malaysia*: Zyloric; *Mex.*: Acyprin†; Alzoprim; Atisuril; Bionol; Darzune; Etindrax; Unizuric; Zyloprim; *Neth.*: Acepurin; Zyloric; *Norw.*: Allopur; Zyloric; *NZ*: Allohexal†; Allorin; Progout†; *Philipp.*: AL; Allocor; Allurase; Alpurase; Elavil; Llanol; Lopric; Loricid; Prinol; Purinase; Purispec; Puristen†; Synol; Trianol; Urinol; Xanurace; Zyloprim; *Pol.*: Allupol; Milurit; Zyloric; *Port.*: Alosfar†; Uriprim; Zurim; Zyloric; *Rus.*: Purinol (Пуринол); *S.Afr.*: Lonol; Puricos; Redurate; Urinol†; Zyloprim; *Singapore*: Progout; Zyloric; *Spain*: Zyloric; *Swed.*: Zyloric; *Switz.*: Allopur; Cellidrine†; Mephanol; Uriconorm; Zyloric; *Thai.*: Alinol; Allo; Allonol; Allopin; Alloric; Apnol; Apronol; Apurol†; Chinnol; Loporic; Medoric†; Puride; Uricad; Valeric; Xandase; Xanol; Zylic; Zyloric; *Turk.*: Allo-Urik; Allogut; Urikoliz†; *UK*: Caplenal; Cosuric; Rimapurinol; Zyloric; *Ukr.*: Allohexal (Аллогексал)†; *USA*: Aloprim; Zyloprim; *Venez.*: Aluron; Zyloric.

Multi-ingredient Preparations. *Arg.*: Artrex; Colpuril; Xuric-A; *Austria*: Allobenz; Gichtex plus; *China*: Allo Comp (通益风宁); *Ger.*: Allo.comp.†; *India*: Aluno-A; *Malaysia*: Lanolone; *Philipp.*: Allomaron; *Thai.*: Allomaron.

Pharmacopoeial Preparations

BP 2014: Allopurinol Oral Suspension; Allopurinol Tablets;
USP 36: Allopurinol Oral Suspension; Allopurinol Tablets.

The symbol † denotes a preparation no longer actively marketed

Benzbromarone *(BAN, USAN, rINN)*

Bensbromaron; Bentsbromaroni; Benzbromaron; Benzbromarona; Benzbromaronas; Benzbromaronum; L-2214; MJ-10061; Бензбромарон.

3,5-Dibromo-4-hydroxyphenyl 2-ethylbenzofuran-3-yl ketone.

$C_{17}H_{12}Br_2O_3$=424.1

CAS — 3562-84-3.

ATC — M04AB03.

ATC Vet — QM04AB03.

UNII — 4POG0RL69O.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.*

Ph. Eur. 8: (Benzbromarone). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in acetone and in dichloromethane. Protect from light.

Uses and Administration

Benzbromarone is a uricosuric drug that reduces plasma concentrations of uric acid by blocking renal tubular reabsorption. It has been suggested that benzbromarone may also increase the intestinal elimination of uric acid. It has been used to treat hyperuricaemia including that associated with chronic gout (p. 600.1) although it has been withdrawn in many countries due to reports of hepatotoxicity. Some countries restrict its use to those patients in whom allopurinol is contra-indicated.

Benzbromarone is not used to treat acute attacks of gout and may exacerbate and prolong them if given during an attack; treatment should not start therefore until an acute attack has subsided.

The usual oral dose has been 50 to 200 mg daily. An NSAID or colchicine should be given initially to reduce the risk of precipitating acute gout. An adequate fluid intake should be maintained. Lower doses of benzbromarone (20 mg) have also been used in the form of a combination product with allopurinol.

References.

1. Hanvivadhanakul P, *et al.* Efficacy of benzbromarone compared to allopurinol in lowering serum uric acid level in hyperuricemic patients. *J Med Assoc Thai* 2002; 85 (suppl 1): S40–S47.
2. Kumar S, *et al.* Benzbromarone therapy in management of refractory gout. *N Z Med J* 2005; 118: U1528.
3. Lee M-HH, *et al.* A benefit-risk assessment of benzbromarone in the treatment of gout. Was its withdrawal from the market in the best interest of patients? *Drug Safety* 2008; 31: 643–65.
4. Reinders MK, *et al.* Efficacy and tolerability of uricate-lowering drugs in gout: a randomised controlled trial of benzbromarone versus probenecid after failure of allopurinol. *Ann Rheum Dis* 2009; 68: 51–6.

Adverse Effects

Benzbromarone may cause gastrointestinal adverse effects, especially diarrhoea. It may precipitate an acute attack of gout and cause uric acid renal calculi and renal colic. Hepatotoxicity, sometimes fatal, has occurred and monitoring of liver function has been recommended.

Effects on the liver. Benzbromarone-induced liver damage, sometimes fatal, has been reported.[1-4]

1. Van Der Klauw MM, *et al.* Hepatic injury caused by benzbromarone. *J Hepatol* 1994; 20: 376–9.
2. Anonymous. Benzbromarone and hepatitis. *WHO Drug Inf* 2000; 14: 29.
3. Wagayama H, *et al.* Fatal fulminant hepatic failure associated with benzbromarone. *J Hepatol* 2000; 32: 874.
4. Arai M, *et al.* Fulminant hepatic failure associated with benzbromarone treatment: a case report. *J Gastroenterol Hepatol* 2002; 17: 625–6.

Effects on the lungs. Benzbromarone has been associated with the development of drug-induced eosinophilic pneumonia and pulmonary alveolar haemorrhage.[1] Symptoms resolved on stopping the drug and treatment with corticosteroids.

1. Hara A, *et al.* Drug-induced eosinophilic pneumonia with pulmonary alveolar hemorrhage caused by benzbromarone. *Intern Med* 2010; 49: 435–8.

Precautions

Benzbromarone should be avoided in patients with liver impairment, severe renal impairment, in those with uric acid renal calculi, and in those with urinary uric acid excretion rates of greater than 700 mg per 24 hours. Like other uricosurics, treatment with benzbromarone should not be started during an acute attack of gout. Similarly, an adequate fluid intake should be maintained to reduce the risk of uric acid renal calculi; additionally, alkalinisation of the urine may be considered.

Interactions

Aspirin and other salicylates antagonise the effect of benzbromarone. Pyrazinamide, sulfinpyrazone, and thiazide diuretics can also inhibit the uricosuric effect of benzbromarone. Benzbromarone may increase the anticoagulant activity of coumarin oral anticoagulants (see under Interactions of Warfarin, p. 1532.2).

Antigout drugs. For mention of the effects of benzbromarone on the clearance of oxipurinol, the major active metabolite of *allopurinol*, and the view that this was not clinically significant, see under Interactions of Allopurinol, p. 603.1.

Pharmacokinetics

Benzbromarone is only partially absorbed from the gastrointestinal tract, reaching peak plasma concentrations about 2 to 4 hours after an oral dose. Benzbromarone is extensively bound to plasma proteins. It is metabolised in the liver, and is excreted mainly in the faeces; a small amount appears in the urine.

References.
1. Maurer H, Wollenberg P. Urinary metabolites of benzbromarone in man. *Arzneimittelforschung* 1990; **40**: 460–2.
2. Walter-Sack I, *et al.* Variation of benzbromarone elimination in man—a population study. *Eur J Clin Pharmacol* 1990; **39**: 173–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Narcaricina; *China*: Er Tong Shu (尔同舒); Narcaricin (立加利仙/步利仙); You Nuo (尤诺); *Jpn*: Urinorm; *Neth.*: Desuric; *Spain*: Urinorm; *Thai.*: Benarone.

Multi-ingredient Preparations. *Austria*: Allobenz; Gichtex plus; *China*: Allo Comp (通益风宁); *Ger.*: Allo.comp.†; *Malaysia*: Lanolone; *Philipp.*: Allomaron; *Thai.*: Allomaron.

Colchicine

Colchicin; Colchicina; Colchicinum; Kolchicin; Kolchicinas; Kolşisin; Kolkicin; Kolkisiini; Колхицин.

(*S*)-*N*-(5,6,7,9-Tetrahydro-1,2,3,10-tetramethoxy-9-oxobenzo[a]heptalen-7-yl)acetamide.

$C_{22}H_{25}NO_6$=399.4

CAS — 64-86-8.

ATC — M04AC01.

ATC Vet — QM04AC01.

UNII — SML2Y3J35T.

Description. Colchicine is an alkaloid obtained from various *Colchicum* spp.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*. *Chin.* also has a monograph for colchicine amide.

Ph. Eur. 8: (Colchicine). A yellowish-white amorphous or crystalline powder. Very soluble in water, rapidly recrystallising from concentrated solutions as the sesquihydrate; freely soluble in alcohol and in chloroform. Protect from light.

USP 36: (Colchicine). An alkaloid obtained from various *Colchicum* spp. and other genera. Pale yellow to pale greenish-yellow amorphous scales, or powder or crystalline powder. Is odourless or nearly so, and darkens on exposure to light. Soluble 1 in 25 of water and 1 in 220 of ether; freely soluble in alcohol and in chloroform. Store in airtight containers. Protect from light.

Uses and Administration

Colchicine is used for the relief of acute gout (p. 600.1) and for the prophylaxis of acute attacks, particularly during the first few months of treatment with allopurinol or uricosurics. Colchicine produces a dramatic response in acute gout, probably by reducing the inflammatory reaction to urate crystals; this effect might be due to several actions including decreased lactic acid production by leucocytes. It is not an analgesic and has no effect on blood concentrations of uric acid, or on the excretion of uric acid. Colchicine also appears to inhibit β-tubulin polymerisation, inhibiting the activation, degranulation and migration of neutrophils, which may mediate some gout symptoms.

Colchicine is used for the treatment of familial Mediterranean fever and has also been used in several other conditions including amyloidosis, Behçet's syndrome, pericarditis, primary biliary cirrhosis, and pyoderma gangrenosum.

If colchicine is used for *acute attacks* of **gout**, then treatment should be started as soon as possible and an effect may be expected within 12 hours. The recommended oral dose in the UK is 1 mg initially, then 500 micrograms every 2 to 3 hours until pain relief is obtained or gastrointestinal adverse effects occur (but see also Administration, below). The total dose should not exceed 6 mg. At least 3 days should elapse before another course is given. In the USA the oral dose is 1.2 mg initially followed by 600 micrograms one hour later. The maximum total dose for an acute attack is 1.8 mg over 1 hour. This dose may also be used (in the USA) for treatment of a gout flare while the patient is taking colchicine for prophylaxis (see below); the prophylactic dose may be resumed 12 hours after treatment.

Colchicine is also used for the *prophylaxis* of gout; oral doses are 500 micrograms two or three times daily in the UK whereas in the USA 600 micrograms may be given once or twice daily, to a maximum of 1.2 mg daily.

Although no longer licensed in many countries, colchicine was formerly given intravenously for *acute attacks* of gout in a usual treatment dose of 2 mg over 2 to 5 minutes with additional doses of 500 micrograms every 6 hours as required to a total dose of not more than 4 mg in 24 hours; once this amount of colchicine has been given further doses should not then be given by any route for at least 7 days. Colchicine has also been given intravenously for *prophylaxis*, usually in doses of 500 micrograms to 1 mg once or twice daily; however, the oral route is preferable. For the view that the intravenous route should be avoided, see Administration, below.

For **familial Mediterranean fever**, US licensed product information for colchicine recommends an oral dose of 1.2 to 2.4 mg daily (which can be given in 2 divided doses); doses can be increased or decreased as needed within this range in increments of 300 micrograms daily.

Although colchicine is not licensed in the UK for familial Mediterranean fever, the *BNF* suggests an oral dose of 500 micrograms to 2 mg once daily as prophylaxis.

For dose recommendations in children, patients with hepatic or renal impairment, or when colchicine is used with other drugs, see below.

References.
1. Lange U, *et al.* Current aspects of colchicine therapy: classical indications and new therapeutic uses. *Eur J Med Res* 2001; **6**: 150–60.
2. Schlesinger N, *et al.* Colchicine for acute gout. Available in The Cochrane Database of Systematic Reviews: Issue 4. Chichester: John Wiley; 2006 (accessed 21/04/08).
3. Nuki G. Colchicine: its mechanism of action and efficacy in crystal-induced inflammation. *Curr Rheumatol Rev* 2008; **10**: 218–27.
4. Yang LPH. Oral colchicine (Colcrys): in the treatment and prophylaxis of gout. *Drugs* 2010; **70**: 1603–13.
5. Richette P, Bardin T. Colchicine for the treatment of gout. *Expert Opin Pharmacother* 2010; **11**: 2933–8.

Administration. Although colchicine 1 mg **orally**, followed by 500 micrograms every 2 to 3 hours, is recommended in the UK for the treatment of acute gout, many rheumatologists consider this excessive; a low-dose regimen of 500 micrograms no more than 3 times daily has been advocated in preference.[1] In the USA, a total oral dose of 1.8 mg is recommended, as studies found low-dose (1.2 mg followed by a single dose of 600 micrograms) and high-dose (1.2 mg followed by 600 micrograms every hour for 6 hours) colchicine regimens to have similar efficacy, but considerably fewer adverse effects were seen with the low-dose schedule.[2,3]

The safety of **intravenous** colchicine has been questioned, and it has been suggested that, although undoubtedly effective, it should not be used because of the risk of severe or fatal adverse effects.[4,5] For reports of fatalities with intravenous colchicine during unlicensed use, see Inappropriate Administration, p. 606.1.

1. Morris I, *et al.* Colchicine in acute gout. *BMJ* 2003; **327**: 1275–6.
2. FDA. Information for healthcare professionals: new safety information for colchicine (marketed as Colcrys) (issued 30th July, 2009). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm174382.htm (accessed 10/09/09)
3. Terkeltaub RA, *et al.* High versus low dosing of oral colchicine for early acute gout flare: twenty-four-hour outcome of the first multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison colchicine study. *Arthritis Rheum* 2010; **62**: 1060–8.
4. Morris I, *et al.* Colchicine in acute gout. *BMJ* 2004; **328**: 289.
5. Schlesinger N. Reassessing the safety of intravenous and compounded injectable colchicine in acute gout treatment. *Expert Opin Drug Safety* 2007; **6**: 625–9.

Administration in children. In the USA, colchicine is licensed for use in children for the treatment of familial Mediterranean fever. It is given orally in the following daily doses according to age:

- 4 to 6 years: 300 micrograms to 1.8 mg
- 6 to 12 years: 900 micrograms to 1.8 mg
- over 12 years: adult doses are given, see above

Administration in hepatic impairment. The clearance of colchicine may be significantly reduced and plasma half-life prolonged in patients with chronic hepatic impairment, compared with healthy subjects.

When colchicine is used for the *treatment* of acute **gout**, licensed product information in the USA considers dose reduction is not necessary for patients with hepatic impairment, but suggests that they should be monitored closely for adverse effects. Treatment courses should not be repeated more often than once every 2 weeks in patients with severe impairment, and alternative therapy considered in those patients who require repeated courses.

When used for *prophylaxis* of gout flares, US licensed product information states that no dose adjustment is recommended for patients with mild to moderate hepatic impairment, although patients should be monitored closely for adverse effects. Dose reduction should be considered in patients with severe hepatic impairment.

Patients with hepatic impairment who are given colchicine prophylaxis should not be treated with colchicine for acute gout flares.

In **familial Mediterranean fever**, US licensed product information suggests that patients with mild to moderate hepatic impairment are monitored closely for adverse effects. Dose reduction may be considered for patients with severe hepatic impairment.

Colchicine should not be used in patients with hepatic impairment who are taking P-glycoprotein inhibitors, strong cytochrome P450 isoenzyme CYP3A4 inhibitors, or HIV-protease inhibitors.

Administration in renal impairment. When oral colchicine is used for the *treatment* of acute **gout**, licensed product information in the UK suggests a dose reduction or an increased interval between doses in patients with a creatinine clearance (CC) of 10 to 50 mL/min, and contra-indicates its use in patients with severe renal impairment (CC less than 10 mL/min), or those on dialysis. In the USA, no dose reduction is considered necessary in patients with mild to moderate renal impairment (CC 30 to 80 mL/min), although patients should be monitored closely for adverse effects. Patients with severe renal impairment (CC less than 30 mL/min) also do not require a dose reduction, but treatment courses should not be repeated more than once every 2 weeks; alternative therapy should be considered in those patients who require repeated courses. In dialysis patients, the total recommended dose for acute gout should be reduced to a single oral dose of 600 micrograms, not repeated more than once every 2 weeks.

When used for *prophylaxis* of gout flares, US licensed product information states that dose reduction is not considered necessary in those patients with mild to moderate renal impairment (CC 30 to 80 mL/min), although patients should be monitored closely for adverse effects. For patients with severe renal impairment (CC less than 30 mL/min), however, the initial dose should be 300 micrograms daily and any increase done with close monitoring. In patients on dialysis, 300 micrograms can be given twice weekly, with close monitoring.

Patients with renal impairment who are given colchicine prophylaxis should not be treated with colchicine for acute gout flares.

In **familial Mediterranean fever**, US licensed product information suggests that patients with mild to moderate renal impairment (30 to 80 mL/min) should be monitored closely; a reduction in colchicine dose may be necessary. For patients with severe renal impairment (CC less than 30 mL/min) or dialysis patients, an initial oral dose of colchicine 300 micrograms daily is recommended, with close monitoring after any dose increases.

Colchicine should **not** be used in patients with renal impairment who are taking P-glycoprotein inhibitors, strong cytochrome P450 isoenzyme CYP3A4 inhibitors, or HIV-protease inhibitors.

Administration with other drugs. Use of colchicine with drugs that inhibit cytochrome P450 isoenzyme CYP3A4 or P-glycoprotein increases the risk of colchicine toxicity. In the USA, if no alternative is available, licensed product information recommends adjustment of the colchicine dose when it is used with these drugs, or if these drugs have been taken within 14 days of colchicine. Patients with renal or hepatic impairment should not be given colchicine with these drugs. Patients receiving colchicine prophylactically who are given CYP3A4 inhibitors should not be treated with colchicine for gout flares.

When used for the **treatment of gout flares**, oral colchicine doses are reduced from the usual dose (see Uses and Administration, above) as follows:

- with strong CYP3A4 inhibitors: a single dose of colchicine 600 micrograms, followed by 300 micrograms 1 hour later
- with moderate CYP3A4 inhibitors: a single dose of colchicine 1.2 mg
- with P-glycoprotein inhibitors: a single dose of 600 micrograms
- with HIV-protease inhibitors (except unboosted fosamprenavir, see below): a single dose of colchicine 600 micrograms, followed by 300 micrograms 1 hour later
- with fosamprenavir (when given alone and not with ritonavir): a single dose of colchicine 1.2 mg

Treatment courses should not be repeated within 3 days.

When used for the **prophylaxis of gout flares**, if the original *intended* oral dose of colchicine would have been 600 micrograms *twice* daily (see Uses and Administration above), the following colchicine doses are recommended:

- with strong CYP3A4 inhibitors: 300 micrograms once daily
- with moderate CYP3A4 inhibitors: 300 micrograms twice daily, or 600 micrograms once daily
- with P-glycoprotein inhibitors: 300 micrograms once daily

- with HIV-protease inhibitors (except unboosted fosamprenavir, see below): 300 micrograms once daily
- with fosamprenavir (when given alone and not with ritonavir): 300 micrograms twice daily, or 600 micrograms once daily

When used for the prophylaxis of gout flares, if the original *intended* oral dose of colchicine would have been 600 micrograms *once* daily (see Uses and Administration, p. 604.1), the following colchicine doses are recommended:

- with strong CYP3A4 inhibitors: 300 micrograms once every other day
- with moderate CYP3A4 inhibitors: 300 micrograms once daily
- with P-glycoprotein inhibitors: 300 micrograms once every other day
- with HIV-protease inhibitors (except unboosted fosamprenavir, see below): 300 micrograms once every other day
- with fosamprenavir (when given alone and not with ritonavir): 300 micrograms once daily

When used in the management of **familial Mediterranean fever**, the maximum daily dose of oral colchicine (given as a single dose or in 2 divided doses) is as follows:

- with strong CYP3A4 inhibitors: 600 micrograms
- with moderate CYP3A4 inhibitors: 1.2 mg
- with P-glycoprotein inhibitors: 600 micrograms
- with HIV-protease inhibitors (except unboosted fosamprenavir, see below): 600 micrograms
- with fosamprenavir (when given alone and not with ritonavir): 1.2 mg

Amyloidosis. Colchicine is well known to have a useful role in amyloidosis (p. 819.3) secondary to familial Mediterranean fever, where results have suggested the possibility of reversing nephropathic changes due to renal amyloid deposition (see below). However, combination therapy with melphalan and prednisone was found to be more effective than colchicine alone in primary amyloidosis,[1] and a later study[2] found no benefit in adding colchicine to the standard therapy. The mechanism of the anti-amyloid effect of colchicine is not clear.

1. Skinner M, *et al.* Treatment of 100 patients with primary amyloidosis: a randomised trial of melphalan, prednisone, and colchicine versus colchicine only. *Am J Med* 1996; **100**: 290–8.
2. Kyle RA, *et al.* A trial of three regimens for primary amyloidosis: colchicine alone, melphalan and prednisone, and melphalan, prednisone, and colchicine. *N Engl J Med* 1997; **336**: 1202–7.

Behçet's syndrome. Behçet's syndrome (p. 1601.1) has been treated with many drugs. Where possible, topical treatment of local lesions should be tried before starting systemic therapy. Corticosteroids are favoured for systemic treatment in many countries, but colchicine has also been widely used. Beneficial responses have been described for most of the symptoms including the arthritic, ocular, and cutaneous manifestations, although a systematic review has questioned colchicine's efficacy.[1] The mechanism of action in this condition is believed to be based on the effect on polymorphonuclear leucocytes and other cellular effects.[2] Colchicine has also been used with corticosteroids for acute exacerbations, followed by colchicine maintenance;[3] colchicine with aspirin has also been recommended in acute disease,[4] and colchicine with benzathine benzylpenicillin has been tried.[5]

1. Saenz A, *et al.* Pharmacotherapy for Behcet's syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1998 (accessed 27/04/05).
2. Schattner A. Colchicine—expanding horizons. *Postgrad Med J* 1991; **67**: 223–6.
3. Rakover Y, *et al.* Behcet disease: long-term follow-up of three children and review of the literature. *Pediatrics* 1989; **83**: 986–92.
4. Wechsler B, Piette JC. Behçet's disease. *BMJ* 1992; **304**: 1199–1200.
5. Çalgüneri M, *et al.* Effect of prophylactic benzathine penicillin on mucocutaneous symptoms of Behçet's disease. *Dermatology* 1996; **192**: 125–8.

Familial Mediterranean fever. Familial Mediterranean fever (recurrent or paroxysmal polyserositis; periodic disease) is an inherited disorder that mainly affects Sephardic Jews or persons of Arab, Armenian, or Turkish ancestry.[1,2] It is characterised by attacks of acute abdominal pain, fever, and signs of peritonitis, which resolve spontaneously, usually in 24 to 48 hours. Pleuritic chest pain, arthritis, rash, pericarditis, and headache may occur. The most dangerous complication, however, is type AA amyloidosis (see also p. 819.3), which can lead to nephrotic syndrome, renal failure, and death.

Familial Mediterranean fever is managed with colchicine.[1-3] Colchicine cannot stop an established attack, but, given prophylactically, it reduces the frequency of attacks, prevents amyloidosis and reverses proteinuria. Attacks are usually treated with NSAIDs[1,3] or, in severe cases, opioids.[3] Anecdotal evidence has suggested that prazosin may also be of benefit,[4] but initial reports of improvement with interferon alfa have not been borne out.[1] Anakinra has also been investigated.[5]

1. Drenth JPH, van der Meer JWM. Hereditary periodic fever. *N Engl J Med* 2001; **345**: 1748–57.
2. Ben-Chetrit E, Touitou I. Familial Mediterranean fever in the world. *Arthritis Rheum* 2009; **61**: 1447–53.
3. Kallinich T, *et al.* Colchicine use in children and adolescents with familial Mediterranean fever: literature review and consensus statement. *Pediatrics* 2007; **119**: e474–e483. Also available at: http://pediatrics.aappublications.org/cgi/reprint/119/2/e474 (accessed 21/04/08)
4. Kataoka H, *et al.* Treating familial Mediterranean fever with prazosin hydrochloride. *Ann Intern Med* 1998; **129**: 424–5.
5. Roldan R, *et al.* Anakinra: new therapeutic approach in children with Familial Mediterranean Fever resistant to colchicine. *Joint Bone Spine* 2008; **75**: 504–5.

Interstitial lung disease. Colchicine has been used in patients with idiopathic pulmonary fibrosis (see Interstitial Lung Disease, p. 1607.1). However, studies have generally shown no evidence of survival benefit, and it is not recommended.

Pericarditis. Mild cases of recurrent pericarditis may be treated with colchicine, as an adjunct to NSAID therapy.[1-3] It may also provide effective prophylaxis, allowing the tapering of corticosteroids, which are usually reserved for the treatment of severe acute attacks.[2,3] The drug has also been used successfully in children.[4] In an open-label study, colchicine added to conventional therapy with aspirin or prednisone significantly decreased the recurrence rate in patients with a first episode of recurrent pericarditis, compared with conventional therapy alone.[5] Another open-label study had similar results using adjunctive colchicine for the first episode of acute pericarditis.[6] In patients with two or more relapses of acute pericarditis, colchicine was found to be highly effective in preventing recurrence.[7] The proportion of patients with relapses during or after colchicine therapy was significantly higher, and the duration of colchicine therapy significantly longer, in those who had pretreatment with corticosteroids.

Colchicine has also been investigated in the prevention of post-pericardiotomy syndrome, a complication of cardiac surgery characterised by fever, pleuritic chest pain, and evidence of pleural effusion and new or worsening pericardial effusion. A multicentre double-blind study[8] found that oral colchicine 1 mg twice daily on the first day and then 500 micrograms twice daily for one month (or half these doses in patients weighing under 70 kg or intolerant to the higher dose) markedly reduced incidence of the syndrome at 12 months compared with placebo; the condition was diagnosed in 16 of 180 patients given colchicine versus 38 of 180 in the placebo group. Secondary end-points of disease-related hospitalisation, cardiac tamponade, constrictive pericarditis, or recurrent pericarditis occurred in 9 of the placebo group versus 1 patient given colchicine. No serious adverse effects occurred, although about 10% of patients taking colchicine developed diarrhoea.

1. Millaire A, *et al.* Treatment of recurrent pericarditis with colchicine. *Eur Heart J* 1994; **15**: 120–4.
2. Adler Y, *et al.* Colchicine treatment for recurrent pericarditis: a decade of experience. *Circulation* 1998; **97**: 2183–5.
3. Oakley CM. Myocarditis, pericarditis and other pericardial diseases. *Heart* 2000; **84**: 449–54.
4. Yazigi A, *et al.* Colchicine for recurrent pericarditis in children. *Acta Paediatr Scand* 1998; **87**: 603–4.
5. Imazio M, *et al.* Colchicine as first-choice therapy for recurrent pericarditis: results of the CORE (COlchicine for REcurrent pericarditis) trial. *Arch Intern Med* 2005; **165**: 1987–91.
6. Imazio M, *et al.* Colchicine in addition to conventional therapy for acute pericarditis: results of the COlchicine for acute PEricarditis (COPE) trial. *Circulation* 2005; **112**: 2012–16.
7. Artom G, *et al.* Pretreatment with corticosteroids attenuates the efficacy of colchicine in preventing recurrent pericarditis: a multi-centre all-case analysis. *Eur Heart J* 2005; **26**: 723–7.
8. Imazio M, *et al.* COPPS Investigators. COlchicine for the Prevention of the Post-pericardiotomy Syndrome (COPPS): a multicentre, randomized, double-blind, placebo-controlled trial. *Eur Heart J* 2010; **31**: 2749–54.

Peyronie's disease. Beneficial effects have been reported with colchicine in men with Peyronie's disease. Small studies show colchicine to be most effective in reducing pain during penile erection.[1] A combination of vitamin E and colchicine has also been suggested as an alternative in early disease.[2]

1. Kadioğlu A, *et al.* Treatment of Peyronie's disease with oral colchicine: long-term results and predictive parameters of successful outcome. *Int J Impot Res* 2000; **12**: 169–75.
2. Prieto Castro RM, *et al.* Combined treatment with vitamin E and colchicine in the early stages of Peyronie's disease. *BJU Int* 2003; **91**: 522–4.

Primary biliary cirrhosis. Primary biliary cirrhosis (p. 2638.3) is a chronic progressive liver disease with no specific treatment, and in general drug therapy has been poor or largely ineffective. Reviewers have noted[1-3] that several studies have been conducted with colchicine, and, although biochemical parameters were improved, a beneficial effect on clinical symptoms or liver histology was not found. A comparative study of colchicine and methotrexate showed that while both drugs improved biochemical test results and symptoms, the response to methotrexate was greater.[4] Some consider that combination therapy with colchicine, methotrexate, and ursodeoxycholic acid may be more promising than monotherapy.[2]

1. Heathcote EJ. Evidence-based therapy of primary biliary cirrhosis. *Eur J Gastroentrol Hepatol* 1999; **11**: 607–15.
2. Holtmeier J, Leuschner U. Medical treatment of primary biliary cirrhosis and primary sclerosing cholangitis. *Digestion* 2001; **64**: 137–50.
3. Gong Y, Gluud C. Colchicine for primary biliary cirrhosis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 27/04/05).
4. Kaplan MM, *et al.* A prospective trial of colchicine and methotrexate in the treatment of primary biliary cirrhosis. *Gastroenterology* 1999; **117**: 1173–80.

Pyoderma gangrenosum. Pyoderma gangrenosum (p. 1688.3) associated with inflammatory bowel disease has been successfully treated with colchicine in 2 patients.[1,2] Colchicine was also of benefit in 3 patients with pyoderma associated with familial Mediterranean fever.[3] Other isolated reports include the use of low-dose colchicine in idiopathic pyoderma gangrenosum.[4]

1. Paolini O, *et al.* Treatment of pyoderma gangrenosum with colchicine. *Lancet* 1995; **345**: 1057–8.
2. Rampal P, *et al.* Colchicine in pyoderma gangrenosum. *Lancet* 1998; **351**: 1134–5.
3. Lugassy G, Ronnen M. Severe pyoderma associated with familial Mediterranean fever: favourable response to colchicine in three patients. *Am J Med Sci* 1992; **304**: 29–31.
4. Kontochristopoulos GJ, *et al.* Treatment of pyoderma gangrenosum with low-dose colchicine. *Dermatology* 2004; **209**: 233–6.

Retroperitoneal fibrosis. There are reports[1-3] of success with colchicine, with or without corticosteroids, in the treatment of retroperitoneal fibrosis (p. 1612.1).

1. Vega J, *et al.* Treatment of idiopathic retroperitoneal fibrosis with colchicine and steroids: a case series. *Am J Kidney Dis* 2009; **53**: 628–37.
2. de Socio G, *et al.* Association between familial Mediterranean fever and retroperitoneal fibrosis: retroperitoneal fibrosis regression after colchicine therapy. *Int J Immunopathol Pharmacol* 2009; **22**: 521–4.
3. de Socio G, *et al.* Effectiveness of colchicine therapy in 4 cases of retroperitoneal fibrosis associated with autoinflammatory diseases. *J Rheumatol* 2010; **37**: 1971–2.

Adverse Effects and Treatment

Colchicine has a narrow therapeutic margin, and overdosage may be serious (see p. 606.1). The most frequent adverse effects of oral colchicine are those involving the gastrointestinal tract and may be associated with its antimitotic action. Diarrhoea, nausea, vomiting, and abdominal pain are often the first signs of toxicity and are usually an indication that colchicine therapy should be stopped or the dose reduced. Larger doses may cause profuse diarrhoea, gastrointestinal haemorrhage, rashes, and renal and hepatic damage.

Rarely, bone marrow depression with agranulocytosis, thrombocytopenia, and aplastic anaemia have occurred on prolonged treatment as have peripheral neuropathy, myopathy, rashes, disseminated intravascular coagulation, and alopecia. Fatal pancytopenia has been reported.

Adverse effects after intravenous use include cardiac arrhythmias and local reactions such as thrombophlebitis and neuritis. Extravasation may cause tissue necrosis.

Effects on the neuromuscular system. Colchicine-induced myoneuropathy may be a common but unrecognised condition in patients with *reduced* renal function who receive usual doses of colchicine.[1] Although both skeletal muscles and peripheral nerves are affected, myopathy is most prominent and associated axonal neuropathy is mild. The condition usually presents with proximal muscle weakness and is always accompanied by elevations in serum creatine kinase concentrations. Withdrawal of colchicine leads to spontaneous remission of these symptoms within a few weeks but resolution of the polyneuropathy is slow. Examination of proximal muscles shows marked abnormal spontaneous activity and, because of the features of the condition, it is often initially misdiagnosed as probable polymyositis or uraemic myopathy. A literature review[2] identified renal impairment as the primary risk factor for the development of colchicine-induced myopathy; dosage adjustment is advised in these patients.

There have been reports suggesting colchicine-induced myopathy may develop in patients who have *normal* renal function.

A patient with normal renal function but chronic alcohol-induced liver disease developed an unusual form of myoneuropathy after receiving only a short course of colchicine. This patient was also taking tolbutamide, the microsomal enzyme-inhibiting activity of which may have exacerbated the toxicity of colchicine.[3] A teenager with familial Mediterranean fever who had normal renal and hepatic function developed toxic myopathy due to colchicine use. Myopathy improved after colchicine was stopped and recurred when it was restarted at a lower dose.[4]

Rhabdomyolysis has also been reported.[5,6]

1. Kunel RW, *et al.* Colchicine myopathy and neuropathy. *N Engl J Med* 1987; **316**: 1562–8.
2. Wilbur K, Makowsky M. Colchicine myotoxicity: case reports and literature review. *Pharmacotherapy* 2004; **24**: 1784–92.
3. Besana C, *et al.* Colchicine myoneuropathy. *Lancet* 1987; **ii**: 1271–2.

4. Sayarlioglu M, *et al.* Colchicine-induced myopathy in a teenager with familial Mediterranean fever. *Ann Pharmacother* 2003; 37: 1821–4.
5. Chattopadhyay I, *et al.* Colchicine induced rhabdomyolysis. *Postgrad Med J* 2001; 77: 191–2.
6. Boomershine KH. Colchicine induced rhabdomyolysis. *Ann Pharmacother* 2002; 36: 824–6.

Effects on the reproductive system. UK licensed product information states that colchicine may adversely affect spermatogenesis under certain conditions of therapy. *Animal* data have shown that colchicine in high doses may arrest spermatogenesis and lead to azoospermia. However, in clinical practice male infertility does not seem to be common in patients given colchicine, and may be related in some cases to the underlying disease rather than the drug.[1] Similarly, although colchicine is not recommended in the first trimester of pregnancy, it may improve fertility in women with familial Mediterranean fever, and results in women who have been taking colchicine at conception and during pregnancy have been relatively reassuring[1] (see also under Pregnancy, below).

1. Mijatovic V, *et al.* Familial Mediterranean fever and its implications for fertility and pregnancy. *Eur J Obstet Gynecol Reprod Biol* 2003; 108: 171–6.

Inappropriate administration. Intravenous use of colchicine is associated with a risk of severe or fatal adverse effects (see Administration, p. 604.2). Although unlicensed either orally or parenterally for use in back pain, intravenous colchicine has apparently been used in alternative medicine for this indication. As of February 2008, the FDA had received reports of 50 adverse events, including 23 deaths, associated with the unapproved use of intravenous colchicine. Three of the reported deaths were associated with compounded colchicine that, due to preparation errors, was 8 times more potent than the amount stated on the label. Potentially fatal effects include neutropenia, thrombocytopenia, pancytopenia, acute renal failure, and congestive heart failure.[1,2]

1. FDA. FDA takes action to stop the marketing of unapproved injectable drugs containing colchicine (issued 6th February 2008). Available at: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01791.html (accessed 21/04/08)
2. FDA. Questions and answers about FDA's enforcement action against unapproved injectable colchicine products (issued 6th February 2008). Available at: http://www.fda.gov/cder/drug/unapproved_drugs/colchicine_qa.htm (accessed 21/04/08)

Overdosage. Colchicine has a narrow therapeutic index and is extremely toxic in overdose;[1] it has been associated with serious and fatal toxicity.[1–7] Patients at particular risk of toxicity are those with renal or hepatic impairment, gastrointestinal or cardiac disease, and the very young or very old.[1]

There is often a delay of up to 6 hours before toxicity is apparent; some features may be delayed up to 1 week or longer. Early features (which occur up to 1 day after ingestion) include nausea, vomiting, abdominal pain, and diarrhoea. Diarrhoea may be profuse and bloody, causing electrolyte disturbances and hypovolaemic shock. Features occurring after 1 to 7 days include confusion, decreased cardiac output, cardiac arrhythmias, renal and hepatic impairment, respiratory distress, hyperpyrexia, and bone marrow depression. These can progress in severe cases to multiple organ damage with bone marrow aplasia, convulsions, coma, rhabdomyolysis, and disseminated intravascular coagulation.[1] Alopecia and rebound leucocytosis can occur.[3,8] A toxic epidermal necrolysis-like reaction has also been reported.[6]

The lethal dose varies: 7 mg has caused death,[8] yet recovery has occurred after much larger doses.[9–11]

In acute overdosage, the UK National Poisons Information Service (NPIS) states that the value of gut decontamination is uncertain. Oral activated charcoal 50 g can be considered for adults who have ingested more than 100 micrograms/kg within 1 hour; children who have ingested any amount of colchicine within 1 hour may be given activated charcoal 1 g/kg. Doses may be repeated every 4 hours in both adults and children, for those who have ingested more than 300 micrograms/kg, provided they are not vomiting. Gastric lavage may be an alternative in adults who present within 1 hour of a potentially life-threatening overdose. Management is mainly symptomatic and supportive, with attention given to pulse, blood pressure, and cardiac rhythm; fluid and electrolyte imbalances should be corrected. Patients are monitored for at least 6 hours after ingestion, or 12 hours if they have taken more than 300 micrograms/kg. Asymptomatic patients may then be discharged, with advice to return if gastrointestinal symptoms appear. Haemodialysis and haemoperfusion are of no benefit as they do not enhance colchicine elimination; blood and urine concentrations are of no use diagnostically.

1. MHRA/CHM. Colchicine: reminder on risk of serious and fatal toxicity in overdose. *Drug Safety Update* 2009; 3 (issue 4): 5. Available at: http://www.mhra.gov.uk/home/groups/pl-p/documents/publication/con062549.pdf (accessed 05/01/11)
2. McIntyre IM, *et al.* Death following colchicine poisoning. *J Forensic Sci* 1994; 39: 280–6.
3. Milne ST, Meek PD. Fatal colchicine overdose: report of a case and review of the literature. *Am J Emerg Med* 1998; 16: 603–8.
4. Kubler PA. Fatal colchicine toxicity. *Med J Aust* 2000; 172: 498–9.
5. Mullins ME, *et al.* Fatal cardiovascular collapse following acute colchicine ingestion. *J Toxicol Clin Toxicol* 2000; 38: 51–4.
6. Arroyo MP, *et al.* Toxic epidermal necrolysis-like reaction secondary to colchicine overdose. *Br J Dermatol* 2004; 150: 581–8.
7. Miller MA, *et al.* Colchicine-related death presenting as an unknown case of multiple organ failure. *J Emerg Med* 2005; 28: 445–8.
8. Hood RL. Colchicine poisoning. *J Emerg Med* 1994; 12: 171–7.
9. Baud FJ, *et al.* Brief report: treatment of severe colchicine overdose with colchicine-specific Fab fragments. *N Engl J Med* 1995; 332: 642–5.
10. Critchley JAJH, *et al.* Granulocyte-colony stimulating factor in the treatment of colchicine poisoning. *Hum Exp Toxicol* 1997; 16: 229–32.
11. Harris R, *et al.* Colchicine-induced bone marrow suppression: treatment with granulocyte colony-stimulating factor. *J Emerg Med* 2000; 18: 435–40.

Precautions

Colchicine should be given with great care to elderly or debilitated patients who may be particularly susceptible to cumulative toxicity. It should also be used with caution in patients with cardiac, hepatic, renal, or gastrointestinal disease. Colchicine should be avoided in patients with blood disorders. It should also generally be avoided in pregnancy since it is known to be teratogenic in *animals* and there have also been some suggestions of a risk of fetal chromosome damage in humans.

Colchicine should not be given by subcutaneous or intramuscular injection as it causes severe local irritation.

Breast feeding. Colchicine is distributed into breast milk,[1–3] and some have recommended waiting for 8 hours[2] or 12 hours[3] after a dose before breast feeding to minimise exposure of the infant. However, since no adverse effects on the infant have been noted in these reports, the last available guidance from the American Academy of Pediatrics considered its use to be usually compatible with breast feeding.[4]

1. Milunsky JM, Milunsky A. Breast-feeding during colchicine therapy for familial Mediterranean fever. *J Pediatr* 1991; 119: 164.
2. Guillonneau M, *et al.* Colchicine is excreted at high concentrations in human breast milk. *Eur J Obstet Gynecol Reprod Biol* 1995; 61: 177–8.
3. Ben-Chetrit E, *et al.* Colchicine in breast milk of patients with familial Mediterranean fever. *Arthritis Rheum* 1996; 39: 1213–17.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/05/04)

Pregnancy. Colchicine is contra-indicated in pregnancy because of *animal* teratogenicity. However, it has been used during pregnancy in women with familial Mediterranean fever (see under Uses, p. 605.1). There was no increase in abnormality rate of the newborns and no problems were detected in 130 offspring.[1]

1. Rabinovitch O, *et al.* Colchicine treatment in conception and pregnancy: two hundred thirty-one pregnancies in patients with familial Mediterranean fever. *Am J Reprod Immunol* 1992; 28: 245–6.

Interactions

Colchicine is a substrate for P-glycoprotein and the cytochrome P450 isoenzyme CYP3A4. Inhibitors of these may increase colchicine blood concentrations and the potential for toxicity; life-threatening or fatal drug interactions have been reported when colchicine was given with clarithromycin, erythromycin, ciclosporin, or calcium channel antagonists such as verapamil and diltiazem. If treatment with a P-glycoprotein inhibitor, CYP3A4 inhibitors, or HIV-protease inhibitors is required in patients with normal renal and hepatic function, the colchicine dose may need to be adjusted (see Administration with Other Drugs, p. 604.3). Such combinations should be avoided in patients with renal or hepatic impairment.

Cases of myopathy and rhabdomyolysis have been reported in patients taking colchicine with statins, fibrates, ciclosporin, or digoxin.

Thiazide diuretics may increase serum uric acid and interfere with the activity of colchicine. Colchicine may impair the absorption of vitamin B_{12}.

Cardiovascular drugs. Muscle toxicity is a known adverse effect of both colchicine and statins, and there may be an increased risk if they are given together, particularly if renal function is impaired. Acute myopathy has been reported in patients with chronic renal impairment given colchicine with *fluvastatin*,[1] *pravastatin*,[2] or *simvastatin*,[3,4] while a patient[5] with nephrotic syndrome but normal renal function developed rhabdomyolysis when *atorvastatin* was added to long-standing colchicine therapy. Another patient with normal renal function developed myopathy when *lovastatin* was added to colchicine.[6] Since many statins are metabolised by the cytochrome P450 isoenzyme CYP3A4, as is colchicine, this has been proposed as one possible mechanism.[1,2,6] However, fluvastatin and pravastatin are cleared through different isoenzymes. Alternative proposed mechanisms are synergistic myopathy[1,4] or interference with transport mediated by P-glycoprotein.[2,5]

Tetraparesis developed in a patient who took colchicine with *verapamil*; this was considered to be due to a pharmacokinetic interaction which increased serum and CSF concentrations of colchicine.[7]

1. Atasoyu EM, *et al.* Possible colchicine rhabdomyolysis in a fluvastatin-treated patient. *Ann Pharmacother* 2005; 39: 1368–9.
2. Alayli G, *et al.* Acute myopathy in a patient with concomitant use of pravastatin and colchicine. *Ann Pharmacother* 2005; 39: 1358–61.
3. Hsu W-C, *et al.* Colchicine-induced acute myopathy in a patient with concomitant use of simvastatin. *Clin Neuropharmacol* 2002; 25: 266–8.
4. Baker SK, *et al.* Cytoskeletal myotoxicity from simvastatin and colchicine. *Muscle Nerve* 2004; 30: 799–802.
5. Tufan A, *et al.* Rhabdomyolysis in a patient treated with colchicine and atorvastatin. *Ann Pharmacother* 2006; 40: 1466–9.
6. Torgovnick J, *et al.* Colchicine and HMG Co-A reductase inhibitors induced myopathy—a case report. *Neurotoxicology* 2006; 27: 1126–7.
7. Tröger U, *et al.* Tetraparesis associated with colchicine is probably due to inhibition by verapamil of the P-glycoprotein efflux pump in the blood-brain barrier. *BMJ* 2005; 331: 613. Correction. *ibid.* 2006; 332: 88.

Ciclosporin. There is a need for caution if colchicine is used with ciclosporin. Myopathies or rhabdomyolysis[1] may be a problem, especially in transplant patients or those with renal impairment.[3] In addition, increased blood-ciclosporin concentrations and nephrotoxicity developed in a renal transplant patient after the introduction of colchicine therapy.[4]

1. Arellano F, Krupp P. Muscular disorders associated with cyclosporin. *Lancet* 1991; 337: 915.
2. Simkin PA, Gardner GC. Colchicine use in cyclosporine treated transplant recipients: how little is too much? *J Rheumatol* 2000; 27: 1334–7.
3. Rumpf KW, Henning HV. Is myopathy in renal transplant patients induced by cyclosporin or colchicine? *Lancet* 1990; 335: 800–1.
4. Menta R, *et al.* Reversible acute cyclosporin nephrotoxicity induced by colchicine administration. *Nephrol Dial Transplant* 1987; 2: 380–1.

Grapefruit juice. Near-fatal colchicine toxicity occurred in an 8-year-old girl with familial Mediterranean fever who was also drinking large quantities of grapefruit juice daily.[1]

1. Goldbart A, *et al.* Near fatal acute colchicine intoxication in a child: a case report. *Eur J Pediatr* 2000; 159: 895–7.

Macrolides. Life-threatening or fatal colchicine toxicity has been reported with use of colchicine and clarithromycin[1,2] or erythromycin.[3] A FDA analysis of safety data found that about half of the reported deaths associated with therapeutic oral doses of colchicine involved patients who were also taking clarithromycin.[4] A retrospective study in 116 patients given both drugs concluded that clarithromycin increased the risk of colchicine toxicity, especially in those patients with renal impairment, and that the two drugs should not be used together.[5]

1. Dogukan A, *et al.* Acute fatal colchicine intoxication in a patient on continuous ambulatory peritoneal dialysis (CAPD): possible role of clarithromycin administration. *Clin Nephrol* 2001; 55: 181–2.
2. Rollot F, *et al.* Acute colchicine intoxication during clarithromycin administration. *Ann Pharmacother* 2004; 38: 2074–7.
3. Caraco Y, *et al.* Acute colchicine intoxication—possible role of erythromycin administration. *J Rheumatol* 1992; 19: 494–6.
4. FDA. Information for healthcare professionals: new safety information for colchicine (marketed as Colcrys) (issued 30th July, 2009). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm174382.htm (accessed 10/09/09)
5. Hung IFN, *et al.* Fatal interaction between clarithromycin and colchicine in patients with renal insufficiency: a retrospective study. *Clin Infect Dis* 2005; 41: 291–300.

Tolbutamide. For a suggestion that tolbutamide may have exacerbated the toxicity of colchicine in a patient with liver disease, see under Effects on the Neuromuscular System, p. 605.3.

Pharmacokinetics

Peak plasma concentrations of colchicine occur within 2 hours of oral use. Absolute bioavailability is reported to be about 45%. The absorption of colchicine from the gastrointestinal tract is thought to be limited by its expulsion by P-glycoprotein, for which colchicine is a substrate. Absorbed colchicine is found in high concentrations in the kidney, liver, and spleen. It is demethylated in the liver via the cytochrome P450 isoenzyme CYP3A4 to 2 primary metabolites, 2-*O*-demethylcolchicine and 3-*O*-demethylcolchicine (2-DMC and 3-DMC, respectively), and 1 minor metabolite, 10-*O*-demethylcolchicine (also known as colchiceine). Plasma concentrations of metabolites are minimal. Enterohepatic recycling occurs. The main route of elimination is hepatobiliary excretion in the faeces. Renal excretion accounts for 10 to 20% of colchicine elimination in patients with normal renal function. The mean elimination half-life is about 28 hours. Colchicine crosses the placenta and is distributed into breast milk.

References.

1. Rochdi M, *et al.* Pharmacokinetics and absolute bioavailability of colchicine after iv and oral administration in healthy human volunteers and elderly subjects. *Eur J Clin Pharmacol* 1994; 46: 351–4.
2. Ferron GM, *et al.* Oral absorption characteristics and pharmacokinetic of colchicine in healthy volunteers after single and multiple doses. *J Clin Pharmacol* 1996; 36: 874–83.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Xuric; ***Austral.***: Colgout; Lengout; ***Braz.***: Cixin; Cocichimil; Colchin; Colchis; Colcitrat; Colzuric; ***Hong Kong***: Colcina; Colgout; CP-Colchi; ***Hung.***: Colchicum-Dispert; ***India***: Colchicindon; Coljoy; Goutnil; ***Indon.***: Recolfar; ***Mex.***: Colchiquim; Sixol; Ticolcin; ***NZ***: Colgout; ***Philipp.***: Goutnil; ***Thai.***: Cochic; Colchily; Colcine; Colcitex; Gouti-chine; Koji; Prochic; Tolchicine; Zoric; ***Turk.***: Colchicum-Dispert; Kolsin; ***USA***: Colcrys.

Multi-ingredient Preparations. ***Arg.***: Artrex; Colchimax; Colpuril; Xuric-A; ***Fr.***: Colchimax; ***Mex.***: Butayonacol; ***Spain***: Colchimax; ***USA***: ColBenemid.

Homoeopathic Preparations. ***Ger.***: Anore rheumat; Cefarheumin S†.

Pharmacopoeial Preparations
BP 2014: Colchicine Tablets;
USP 36: Colchicine Injection; Colchicine Tablets; Probenecid and Colchicine Tablets.

Colchicum

Colchico; Colchique; Безвременник.
UNII — 7SUW9D360K.

Profile

Colchicum, the dried ripe seeds or dried corm of the meadow saffron, *Colchicum autumnale*, contains colchicine (p. 604.1) and has been used similarly for the prophylaxis and relief of acute gout.

It is also included in several herbal preparations.

Homoeopathy

Colchicum has been used in homoeopathic medicines under the following names: Colchicinum; Colchicum autumnale; Colchicum, tuber; Colch. at.

Poisoning. *Colchicum autumnale* is quite similar to a species of garlic *Allium ursinum*, especially in leaf appearance, and both plants grow in the same areas at the same time of year. There are reports of colchicine poisoning, some of them fatal, after accidental ingestion of *C. autumnale*.[1-6] Colchicine poisoning should be considered in patients with gastroenterocolitis after a wild plant meal.

1. Brnčić N, *et al.* Accidental plant poisoning with Colchicum autumnale: report of two cases. *Croat Med J* 2001; **42:** 673–5.
2. Sannohe S, *et al.* Colchicine poisoning resulting from accidental ingestion of meadow saffron (Colchicum autumnale). *J Forensic Sci* 2002; **47:** 1391–6.
3. Gabrscek L, *et al.* Accidental poisoning with autumn crocus. *J Toxicol Clin Toxicol* 2004; **42:** 85–8.
4. Brvar M, *et al.* Case report: fatal poisoning with Colchicum autumnale. *Crit Care* 2004; **8:** R56–R59.
5. Brvar M, *et al.* Acute poisoning with autumn crocus (Colchicum autumnale L.). *Wien Klin Wochenschr* 2004; **116:** 205–8.
6. Sundov Z, *et al.* Fatal colchicine poisoning by accidental ingestion of meadow saffron-case report. *Forensic Sci Int* 2005; **149:** 253–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Colchysat.

Multi-ingredient Preparations. ***Chile***: Uroknop; ***Ger.***: Unguentum lymphaticum†; ***Neth.***: Diarrheel S; ***Venez.***: Linfoderm.

Homoeopathic Preparations. ***Austria***: Colchicum Med Complex; Daram; Pulsatilla Med Complex; ***Canad.***: Arnica-Heel Comp†; Arthflex; Homeo-Form AR†; Hyalgesic LBP†; Indigestion†; Renelix; ***Chile***: Arnica Compuesta; Artroplex; ***Fr.***: Basilicum Complexe No 96; Berberis Complexe No 83; L 8; Ledum Complexe No 81; Momordica Complexe No 109†; Rhus Toxicodendron Complexe No 80; Uranthone; ***Ger.***: Alho-Arthrosan N; Arthrorell N; Berberis N Oligoplex; Colchicum Complex; Doloject; G1-Injektopas; Gelenk Albin; Girheulit HM†; Girheulit HOM; Harnsauretropfen F; Hewerheum N†; Lymphdiaral; Poly-Arthrisan M; Rheucostan R; rheuma-loges; Rheuma-Pasc; Rheuma-Pasc; Rheumodoron 2; Uro Albin; ***Neth.***: Apo-Rheum†; Apo-STOM; Reudol; ***Rus.***: Rhus-Plus (Рус-Плюс); ***Ukr.***: Homvio-Reuman (Хомвио-Ревман).

Febuxostat *(BAN, USAN, rINN)*

Febuxostatum; TMX-67; Фебуксостат.
2-[3-Cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid.
$C_{16}H_{16}N_2O_3S$=316.4
CAS — 144060-53-7.
ATC — M04AA03.
ATC Vet — QM04AA03.
UNII — 101V0R1N2E.

Uses and Administration

Febuxostat is a non-purine, selective inhibitor of xanthine oxidase. It is used for the treatment of hyperuricaemia in patients with chronic gout. In the EU, the recommended oral dose is 80 mg once daily. If the serum uric acid is above 6 mg per 100 mL after 2 to 4 weeks, the dose may be increased to 120 mg once daily. In the USA, febuxostat 40 mg once daily is given initially; if the serum uric acid is 6 mg per 100 mL or above after 2 weeks, the dose may be increased to 80 mg once daily.

Initially, febuxostat may increase plasma concentrations of urate and uric acid, and treatment should not be started until an acute attack of gout has completely subsided; an NSAID or colchicine should be given for at least 6 months after starting febuxostat.

For dosage recommendations in hepatic and renal impairment, see below.

Administration in hepatic impairment. Exposure to febuxostat did not change significantly in patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment compared with subjects with normal hepatic function.[1] EU licensed product information states that the recommended oral dose of febuxostat in patients with mild hepatic impairment is 80 mg daily. No dose recommendations are given for moderate impairment; efficacy and safety of febuxostat has not been studied in those with severe (Child-Pugh class C) hepatic impairment. In the USA, no dosage adjustment is considered necessary for mild or moderate hepatic impairment; caution is advised in severe impairment due to a lack of data.

1. Khosravan R, *et al.* The effect of mild and moderate hepatic impairment on pharmacokinetics, pharmacodynamics, and safety of febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase. *J Clin Pharmacol* 2006; **46:** 88–102.

Administration in renal impairment. In patients with mild, moderate, or severe renal impairment, peak plasma concentrations of febuxostat did not alter, relative to those with normal renal function; however, the mean area under the concentration-time curve was increased in those with severe renal impairment. EU and US licensed product information state that no dosage adjustments are considered necessary in those with mild or moderate renal impairment, but that efficacy and safety have not been evaluated in those with severe renal impairment (creatinine clearance of less than 30 mL/min).

A study[1] found that although exposure to febuxostat and its metabolites was generally higher in subjects with increasing degrees of renal impairment, decreases in uric acid were comparable regardless of renal function.

1. Mayer MD, *et al.* Pharmacokinetics and pharmacodynamics of febuxostat, a new non-purine selective inhibitor of xanthine oxidase in subjects with renal impairment. *Am J Ther* 2005; **12:** 22–34.

Gout. The use of febuxostat in gout has been reviewed.[1-4] Studies have shown febuxostat to be more effective than allopurinol at lowering the serum uric acid concentration; however, the dose of allopurinol was fixed and not titrated, so the efficacy of febuxostat compared with optimal use of allopurinol is unknown.[5] While febuxostat has generally been well tolerated,[6] it has been associated with more gout flares when compared with allopurinol, despite prophylaxis, leading to more withdrawals from treatment.[5] Concerns have also been raised about elevations in liver enzyme concentrations and a trend towards a higher rate of death and cardiovascular events compared with allopurinol therapy.[6] An international position paper[6] and NICE[7] both recommend that the use of febuxostat be restricted to those patients who are intolerant of allopurinol or for whom allopurinol is either contra-indicated or ineffective.

1. Bruce SP. Febuxostat: a selective xanthine oxidase inhibitor for the treatment of hyperuricemia and gout. *Ann Pharmacother* 2006; **40:** 2187–94.
2. Hair PI, *et al.* Febuxostat. *Drugs* 2008; **68:** 1865–74.
3. Ernst ME, Fravel MA. Febuxostat: a selective xanthine-oxidase/xanthine-dehydrogenase inhibitor for the management of hyperuricemia in adults with gout. *Clin Ther* 2009; **31:** 2503–18.
4. Schlesinger N. New agents for the treatment of gout and hyperuricemia: febuxostat, puricase, and beyond. *Curr Rheumatol Rep* 2010; **12:** 130–4.
5. Anonymous. Febuxostat for gout. *Drug Ther Bull* 2010; **48:** 78–82.
6. Jansen TL, *et al.* International position paper on febuxostat. *Clin Rheumatol* 2010; **29:** 835–40.
7. NICE. Febuxostat for the management of hyperuricaemia in people with gout (TA164, issued December 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA164Guidance.pdf (accessed 07/01/09)

Adverse Effects

The most common adverse effects of febuxostat are liver function abnormalities, diarrhoea, headache, nausea, and rashes. Liver function should be monitored periodically; hepatitis and gallstones have also been reported. Less commonly reported effects include gastrointestinal adverse effects such as abdominal pain and constipation, fatigue, oedema, thirst, hemiparesis, Guillain-Barré syndrome, agitation, depression, flushing, dizziness, paraesthesia, somnolence, insomnia, altered taste, tinnitus, vertigo, hearing loss, blurred vision, hypersensitivity, herpes zoster infection, electrolyte disturbances, hyperglycaemia, hyperlipidaemia, diabetes mellitus, renal failure, nephrolithiasis, haematuria, urinary frequency, dermatitis, urticaria, pruritus, altered skin pigmentation, photosensitivity, and musculoskeletal effects such as arthralgia and myalgia. Blood disorders include anaemia, leucopenia, and thrombocytopenia. Abnormal coagulation tests have occurred. Thromboembolic events such as myocardial infarction and stroke have been reported, as have arrhythmias, angina, hypotension, hypertension, and palpitations. Respiratory adverse effects include cough, bronchitis, dyspnoea, and upper respiratory-tract infections. Erectile dysfunction, breast pain, and gynaecomastia have occurred. Alterations in hair colour and growth pattern have been reported, as has alopecia.

Precautions

Febuxostat therapy should not be started during an acute attack of gout; however treatment is usually continued when acute attacks occur in patients already receiving the drug, and the acute attack is treated separately. Febuxostat is not recommended for the control of hyperuricaemia secondary to malignant disease or cancer chemotherapy. Treatment in patients with ischaemic heart disease or congestive heart failure is not recommended.

Interactions

Inhibition of xanthine oxidase is known to increase concentrations of mercaptopurine or azathioprine, so use of febuxostat with these drugs is not recommended. Similarly, caution is advised when febuxostat is given with theophylline, and theophylline concentrations should be monitored.

Febuxostat is metabolised via the uridine diphosphate glucuronosyltransferase enzyme system, and inhibitors or inducers of this system might affect exposure to febuxostat. Serum uric acid should be monitored 1 to 2 weeks after starting treatment with a potent inducer of glucuronidation.

Pharmacokinetics

Febuxostat is rapidly and well absorbed after oral doses. Although dosage with a high-fat meal decreases peak plasma concentration and exposure, this is not thought clinically significant, and febuxostat may be taken with or without food. Plasma protein binding is about 99%. Febuxostat is extensively metabolised by conjugation via the uridine diphosphate glucuronosyltransferase (UDPGT) enzyme system, and by oxidation via the cytochrome P450 isoenzyme system; active metabolites are formed mainly by UGT1A1, UGT1A8, UGT1A9, and by CYP1A1, CYP1A2, CYP2C8, or CYP2C9. Febuxostat has a mean terminal half-life of about 5 to 8 hours. About half of a dose is excreted via the urine, and the other half via the faeces.

References.

1. Khosravan R, *et al.* Pharmacokinetics, pharmacodynamics and safety of febuxostat, a non-purine selective inhibitor of xanthine oxidase, in a dose escalation study in healthy subjects. *Clin Pharmacokinet* 2006; **45:** 821–41.
2. Khosravan R, *et al.* The effect of age and gender on pharmacokinetics, pharmacodynamics, and safety of febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase. *J Clin Pharmacol* 2008; **48:** 1014–24.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Adenuric; ***Canad.***: Uloric; ***Cz.***: Adenuric; ***Fr.***: Adenuric; ***Ger.***: Adenuric; ***Gr.***: Adenuric; ***Irl.***: Adenuric; ***Ital.***: Adenuric; ***Jpn***: Feburic; Uloric†; ***Neth.***: Adenuric; ***Port.***: Adenuric; ***Spain***: Adenuric; ***UK***: Adenuric; ***USA***: Uloric.

Probenecid *(BAN, rINN)* ⊗

Probenecidas; Probénécide; Probenecidum; Probenesid; Probenesidi; Пробенецид.
4-(Dipropylsulphamoyl)benzoic acid.
$C_{13}H_{19}NO_4S$=285.4
CAS — 57-66-9.
ATC — M04AB01.
ATC Vet — QM04AB01.
UNII — PO572Z7917.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Probenecid). A white or almost white crystalline powder or small crystals. Practically insoluble in water; sparingly soluble in dehydrated alcohol; soluble in acetone.

USP 36: (Probenecid). A white or practically white, fine, practically odourless, crystalline powder. Practically insoluble in water and in dilute acids; soluble in alcohol, in acetone, in chloroform, and in dilute alkali.

Uses and Administration

Probenecid is a uricosuric drug used to treat hyperuricaemia (p. 600.1) associated with chronic gout; it has also been used to treat hyperuricaemia caused by diuretic therapy. It is also used as an adjunct to some antibacterials to reduce their renal tubular excretion and is given with the antiviral cidofovir to reduce nephrotoxicity.

Probenecid is used in **chronic gout and hyperuricaemia** to inhibit the renal tubular reabsorption of uric acid so increasing the urinary excretion of uric acid, lowering plasma-urate concentrations, and eventually reducing urate deposits in the tissues. Probenecid is therefore of value in hyperuricaemia caused by decreased uric acid excretion rather than increased urate production, and is not used for hyperuricaemia associated with cancer or cancer therapy.

Probenecid has no analgesic or anti-inflammatory action and is of no value in acute gout. Initially it may increase plasma concentrations of urate and uric acid by dissolving deposits. This can trigger or exacerbate acute attacks, hence probenecid should not be started until an acute attack has completely subsided, and an NSAID or colchicine may be given during the first few months.

It is usual to start treatment for gout with oral doses of 250 mg twice daily increased after a week to 500 mg twice daily and later, if the therapeutic effects are inadequate, by increments of 500 mg every 4 weeks, up to 2 g daily. Probenecid may not be effective in chronic renal impairment particularly when the glomerular filtration rate is less than 30 mL/minute. An adequate fluid intake is required to reduce the risk of uric acid renal calculi.

When the patient has been free from acute attacks for at least 6 months, and provided that the plasma-urate concentration is within acceptable limits, the daily dose may be gradually reduced, by 500 mg every 6 months, to the lowest effective maintenance dose which is then given indefinitely.

Probenecid may also be used as an **adjunct to antibacterial therapy** particularly when treating severe or resistant infections. It reduces the tubular excretion of penicillins and most cephalosporins and may increase their plasma concentrations up to fourfold. The usual dosage for reducing tubular excretion of penicillins and cephalosporins is 500 mg four times daily, or less in elderly patients with suspected renal impairment. When renal impairment is sufficient to retard the excretion of antibacterials, probenecid should not be given.

For doses in children, see Administration in Children, below.

Single oral doses of probenecid 1 g are given with a suitable oral antibacterial, or at least 30 minutes before an injected antibacterial, in the single-dose treatment of gonorrhoea (p. 204.2).

Doses of probenecid to be used with cidofovir are given on p. 970.1.

Administration in children. For children aged 2 years of age or older and weighing 50 kg or less, the recommended oral dose of probenecid is 25 mg/kg (or 700 mg/m²) initially, followed by 40 mg/kg (or 1.2 g/m²) daily, given in 4 divided doses. For children weighing more than 50 kg, the usual adult dose is recommended (see Uses and Administration, above).

Adverse Effects and Treatment

Probenecid may cause nausea, vomiting, anorexia, headache, sore gums, flushing, alopecia, dizziness, anaemia, and urinary frequency. Hypersensitivity reactions, with fever, dermatitis, pruritus, urticaria, and, rarely, anaphylaxis, and Stevens-Johnson syndrome have occurred. There have been reports of leucopenia, hepatic necrosis, nephrotic syndrome, and aplastic anaemia. Haemolytic anaemia has also occurred, and may be associated with G6PD deficiency.

When used in chronic gout, and particularly during the first few months of therapy, probenecid may precipitate acute attacks. Uric acid renal calculi, with or without haematuria, costovertebral pain and renal colic may occur.

In massive overdosage probenecid causes stimulation of the CNS, with convulsions and death from respiratory failure. Severe overdosage should be managed by lavage and symptomatic treatment.

Precautions

Probenecid therapy should not be started during an acute attack of gout; however treatment is usually continued when acute attacks occur in patients already receiving the drug, and the acute attack is treated separately. Probenecid is also unsuitable for the control of hyperuricaemia secondary to cancer or cancer chemotherapy. Probenecid should not be given to patients with a history of uric acid renal calculi or blood disorders. It should be used with caution in patients with a history of peptic ulceration. Probenecid should not be used as an antibacterial adjunct in patients with known renal impairment, and it is ineffective in gout in patients with severe renal impairment.

To reduce the risk of uric acid renal calculi in patients with gout an adequate fluid intake (2 to 3 litres daily) is required, and, if necessary, especially during the first few months of treatment, sodium bicarbonate or potassium citrate may be given to render the urine alkaline.

A reducing substance has been found in the urine of some patients taking probenecid, and may give false positive results with some tests for glucose in the urine. Probenecid reduces the excretion of some iodinated contrast media and may interfere with laboratory tests by decreasing the excretion of aminohippuric acid, phenolsulfonphthalein, and sulfobromophthalein.

Abuse. It has been alleged that some athletes using banned anabolic steroids have taken probenecid in an attempt to inhibit the urinary excretion of steroid metabolites in order to avoid detection by urine screening tests.[1] The World Anti-Doping Agency includes probenecid among substances prohibited for use by athletes in and out of competition.

1. Anonymous. Does probenecid mask steroid use? *Pharm J* 1987; 239: 299.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies probenecid as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 08/07/11)

Interactions

The dose of probenecid may need to be increased if patients are also given drugs, such as diuretics or pyrazinamide, that increase the blood concentration of uric acid. Salicylates, including aspirin, and probenecid are mutually antagonistic and should not be given together.

Probenecid may also affect many other drugs. By inhibiting renal tubular secretion, it has the potential to increase the toxicity and/or to enhance the therapeutic efficacy of drugs excreted by that route. In some instances a reduction in dose is essential to counteract an increase in toxicity, as is the case with methotrexate. Some combinations, such as that with ketorolac, should be avoided. Conversely, probenecid may be given with some antibacterials such as the penicillins and cephalosporins to increase their effects.

Altered excretion may also increase serum concentrations of other antibacterials (aminosalicylic acid, conjugated sulfonamides, dapsone, meropenem, some quinolones, rifampicin), some antivirals (aciclovir, ganciclovir, zalcitabine, zidovudine, and possibly famciclovir), some benzodiazepines (adinazolam, lorazepam, and nitrazepam), some ACE inhibitors (captopril and enalapril), some NSAIDs (diflunisal, indometacin, ketoprofen, meclofenamate, naproxen), paracetamol, and sulfonylurea hypoglycaemic drugs. The clinical significance of such interactions is not entirely clear although the possibility of the need for a reduction in dosage of these drugs should be borne in mind.

It has been reported that patients receiving probenecid require lower doses of thiopental for induction of anaesthesia. Probenecid may increase the speed of induction of anaesthesia with midazolam.

Reducing the urinary concentration of some drugs could diminish their activity in certain diseases as might happen with nitrofurantoin or some quinolones in urinary-tract infections and penicillamine in cystinuria.

Allopurinol. Probenecid may increase the clearance of allopurinol despite an increased hypouricaemic effect when these 2 drugs are given together (see Antigout Drugs, under Allopurinol, p. 603.1).

Pharmacokinetics

Probenecid is completely absorbed from the gastrointestinal tract and peak plasma concentrations occur 2 to 4 hours after a dose. It is extensively bound to plasma proteins (85 to 95%). The plasma half-life is dose-dependent and ranges from less than 5 to more than 8 hours. Probenecid crosses the placenta. It is metabolised by the liver, and excreted in the urine mainly as metabolites. Excretion of unchanged probenecid is increased in alkaline urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Pro-Cid; *Canad.*: Benuryl; *Fr.*: Benemide; *Gr.*: Benemid†; *India*: Bencid; *Mex.*: Benecid; *Norw.*: Probecid; *S.Afr.*: Proben; *Swed.*: Probecid; *Switz.*: Santuril; *Thai.*: Benacid; Bencid; Benecid; Benemid; *USA*: Benemid†.

Multi-ingredient Preparations. *China*: Zhuo Tong (卓彤); *India*: Alcephin-LA; Ampilong; Cefalong-DS; Ceff-LA; Dax-LA; Himox Plus; *USA*: ColBenemid.

Used as an adjunct in:. *Braz.*: Emicilin; Gonol; *China*: Ai Luo Di (艾罗迪); En Pu Luo (恩普洛); *India*: Moxylong; Mydrox.

Pharmacopoeial Preparations

BP 2014: Probenecid Tablets;

USP 36: Ampicillin and Probenecid for Oral Suspension; Probenecid and Colchicine Tablets; Probenecid Tablets.

Sulfinpyrazone *(BAN, rINN)*

G-28315; Sulfinpirazona; Sulfinpirazonas; Sulfinpyratsoni; Sulfinpyrazon; Sulfinpyrazonum; Sulphinpyrazone; Sulphoxyphenylpyrazolidine; Szulfinpirazon; Сульфинпиразон.

1,2-Diphenyl-4-(2-phenylsulphinylethyl)pyrazolidine-3,5-dione.

$C_{23}H_{20}N_2O_3S$=404.5

CAS — 57-96-5.

ATC — M04AB02.

ATC Vet — QM04AB02.

UNII — V6OFU47K3W.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Sulfinpyrazone). A white or almost white powder. Very slightly soluble in water; sparingly soluble in alcohol; dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 36: (Sulfinpyrazone). A white to off-white powder. Practically insoluble in water and in petroleum spirit; soluble in alcohol and in acetone; sparingly soluble in dilute alkali.

Uses and Administration

Sulfinpyrazone is a uricosuric drug used to treat hyperuricaemia associated with chronic gout (p. 600.1). It also has some antiplatelet activity and has been used in thromboembolic disorders.

Sulfinpyrazone inhibits the renal tubular reabsorption of uric acid so increasing the urinary excretion of uric acid, lowering plasma-urate concentrations, and eventually reducing urate deposits in the tissues. It is therefore used in hyperuricaemia caused by decreased uric acid excretion rather than increased urate production and is not suitable for hyperuricaemia associated with cancer or cancer therapy.

Sulfinpyrazone has little analgesic or anti-inflammatory action and is of no value in acute gout. Initially, it may increase plasma concentrations of urate and uric acid by dissolving deposits. This can trigger or exacerbate acute attacks, hence sulfinpyrazone should not be given until an acute attack has completely subsided, and an NSAID or colchicine may be given during the first few months.

The initial oral dose of sulfinpyrazone in the UK is 100 to 200 mg daily, taken with meals or milk. This may be gradually increased over 2 to 3 weeks until a daily dosage of 600 mg is reached; up to 800 mg daily may be given if necessary. After the plasma-urate concentration has been controlled, the daily maintenance dose may be reduced to as low as 200 mg. An adequate fluid intake is required to prevent formation of uric acid renal calculi.

Adverse Effects, Treatment, and Precautions

The most frequent adverse effects of sulfinpyrazone involve the gastrointestinal tract, and include nausea, vomiting, diarrhoea and abdominal pain. It may cause gastric bleeding or aggravate existing peptic ulcers. Rashes have been reported, and may be associated with a hypersensitivity reaction. Aplastic anaemia, agranulocytosis, leucopenia, and thrombocytopenia have been reported rarely as have raised liver enzyme values, jaundice, and hepatitis, renal impairment, salt and water retention, and acute renal failure.

Sulfinpyrazone should not be started during an acute attack of gout; however, treatment is usually continued when acute attacks occur in patients already receiving the drug, and the acute attack is treated separately. When used in chronic gout, particularly during the first few months of treatment, sulfinpyrazone may precipitate acute attacks and there is a risk of uric acid renal calculi developing. To reduce the risk of uric acid renal calculi an adequate fluid intake (2 to 3 litres daily) is required; alkalinising the urine with sodium bicarbonate or potassium citrate may also be considered.

Sulfinpyrazone should be given with care to patients with renal impairment or heart failure and is contra-indicated in those with severe renal or hepatic impairment. It is also contra-indicated in patients with blood dyscrasias or blood coagulation disorders, and in patients with uric acid renal calculi or peptic ulcer disease or a history of such disorders. It is recommended that patients

have periodic full blood counts to detect any haematological abnormalities.

Sulfinpyrazone should not be given to patients hypersensitive to it or to other pyrazole derivatives such as phenylbutazone; nor should it be given to patients in whom hypersensitivity reactions (including bronchospastic reactions in asthmatics) have been provoked by aspirin or by other drugs with prostaglandin-synthetase inhibiting activity.

Renal-function tests involving aminohippuric acid or phenolsulfonphthalein may be invalidated.

Interactions

Doses of sulfinpyrazone may need to be increased if it is given with other drugs, such as diuretics or pyrazinamide, that increase uric acid concentrations. Sulfinpyrazone and salicylates including aspirin are mutually antagonistic and should not be used together. There may also be an increased risk of bleeding when sulfinpyrazone is used with other drugs such as aspirin that inhibit platelet function.

Sulfinpyrazone's renal tubular secretion is inhibited by probenecid although with little clinical effect. Since sulfinpyrazone, like probenecid, inhibits the tubular secretion of weak organic acids, interactions can be expected with penicillins although the effect is not considered to be clinically useful.

Sulfinpyrazone can potentiate the action of some drugs. The most significant interaction of this type involves warfarin, acenocoumarol, and possibly other coumarin anticoagulants (p. 1532.2). Patients receiving sulfinpyrazone and such an anticoagulant should have their prothrombin times monitored and the anticoagulant dosage reduced as appropriate. Similarly, sulfinpyrazone may potentiate the effects of phenytoin (see Antigout Drugs, p. 543.3), and possibly some sulfonamides and sulfonylureas.

In contrast, sulfinpyrazone may increase the metabolism of theophylline (p. 1235.2) and diminish its activity.

Pharmacokinetics

Sulfinpyrazone is readily absorbed from the gastrointestinal tract. It is about 98% bound to plasma proteins and has a plasma half-life of about 2 to 4 hours. Sulfinpyrazone is partly metabolised in the liver and some of the metabolites are active. On long-term therapy, sulfinpyrazone induces its own metabolism. Unchanged drug and metabolites are mainly excreted in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Eryfrace; *Ital.*: Enturen; *Philipp.*: Sulfin; *Thai.*: Sulfin; *UK*: Anturan†; *USA*: Anturane†.

Pharmacopoeial Preparations
BP 2014: Sulfinpyrazone Tablets;
USP 36: Sulfinpyrazone Capsules; Sulfinpyrazone Tablets.

Tisopurine *(rINN)*

MPP; Thioallopurinol; Thiopurinol; Tisopurina; Tisopurinum; Тизопурин.
1*H*-Pyrazolo[3,4-*d*]pyrimidine-4-thiol.
$C_5H_4N_4S$=152.2
CAS — 5334-23-6.
ATC — M04AA02.
ATC Vet — QM04AA02.
UNII — 79F9I2R16M.

Profile

Tisopurine, an analogue of allopurinol, is an inhibitor of uric acid synthesis. It is used orally in the treatment of disorders associated with hyperuricaemia (p. 600.1), including gout, in doses of 100 to 400 mg daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Exuracid.

Urate Oxidase

CB-8129; Urato oxidasa; Uricasa; Uricase; Уратоксидаза.
CAS — 9002-12-4.
ATC — M04AX01.
ATC Vet — QM04AX01.

Pegloticase *(USAN, rINN)*

Pegloticasa; Pégloticase; Pegloticasum; Пэглотиказа.
CAS — 885051-90-1.
ATC — M04AX02.
ATC Vet — QM04AX02.
UNII — R581OT55EA.

Rasburicase *(BAN, USAN, rINN)*

Rasburicasa; Rasburicasum; Rasburikaasi; Rasburikas; Rasburikaz; SR-29142; Разбуриказа.
CAS — 134774-45-1.
ATC — V03AF07.
ATC Vet — QV03AF07.
UNII — 08GY9K1EUO.

Description. Rasburicase is a recombinant form of the enzyme urate oxidase.

Uses and Administration

Rasburicase is a recombinant form of the enzyme urate oxidase, which oxidises uric acid to allantoin. It is used in the treatment and prophylaxis of severe hyperuricaemia (p. 600.1) associated with the treatment of malignancy. Rasburicase is diluted to a final volume of 50 mL with sodium chloride 0.9%, and given by intravenous infusion over 30 minutes. The recommended dose is 200 micrograms/kg as a single daily dose. Duration of treatment may vary from 5 to 7 days.

For doses in children, see Administration in Children, below.

Pegloticase is a recombinant, pegylated form of the enzyme urate oxidase. It is used for the treatment of chronic gout that is refractory to conventional urate-lowering therapy. Pegloticase is diluted in 250 mL of sodium chloride (0.45 or 0.9%) and given by intravenous infusion over not less than 2 hours. The recommended dose is 8 mg every 2 weeks.

The native form of urate oxidase has also been used.

Administration in children. Rasburicase is used in children for the treatment and prophylaxis of severe hyperuricaemia associated with treatment of malignancy in the same dose as for adults (see Uses and Administration, above). For further discussion of its use in children with tumour lysis syndrome, see below.

Gout. Rasburicase has been used successfully to treat gout in patients allergic to allopurinol.[1,2] Pegloticase has also successfully reduced plasma-urate concentrations in patients with treatment-resistant disease,[3,4] although more evidence is needed to assess its risks and benefits.[5]

1. Vogt B. Urate oxidase (rasburicase) for treatment of severe tophaceous gout. *Nephrol Dial Transplant* 2005; 20: 431–3.
2. Richette P, Bardin T. Successful treatment with rasburicase of a tophaceous gout in a patient allergic to allopurinol. *Nat Clin Pract Rheumatol* 2006; 2: 338–42.
3. Sundy JS, *et al.* Pegloticase Phase 2 Study Investigators. Reduction of plasma urate levels following treatment with multiple doses of pegloticase (polyethylene glycol-conjugated uricase) in patients with treatment-failure gout: results of a phase II randomized study. *Arthritis Rheum* 2008; 58: 2882–91.
4. Reinders MK, Jansen TL. New advances in the treatment of gout: review of pegloticase. *Ther Clin Risk Manag* 2010; 6: 543–50.
5. Anderson A, Singh JA. Pegloticase for chronic gout. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2010 (accessed 10/05/10).

Tumour lysis syndrome. The tumour lysis syndrome (p. 730.2) represents a biochemical disturbance after massive release of cellular breakdown products from tumour cells sensitive to therapy; hyperuricaemia is a cardinal feature. Rasburicase was effective in the prophylaxis or treatment of hyperuricaemia in children and young adults with leukaemia or lymphoma who either presented with abnormally high plasma concentrations of uric acid or had large tumour cell burdens.[1] Treatment was mostly well tolerated; one patient developed nausea and vomiting and one experienced bronchospasm and hypoxaemia 3 hours after infusion. Antibodies to rasburicase were seen in 17 of 121 assessable patients. Safety and efficacy were confirmed in further studies of children[2] and adults[2,3] considered to be at particularly high risk of tumour lysis syndrome. In children[4] with haematologic malignancies at high risk for tumour lysis, rasburicase given intravenously achieved more rapid control and lower levels of plasma uric acid than oral allopurinol. No antibodies to rasburicase were detected at day 14. In 3 children with acute lymphoblastic leukaemia, hyperuricaemia was reportedly controlled with oral allopurinol and a single dose of rasburicase, although subclinical tumour lysis was apparent.[5] Rasburicase has also been used for tumour lysis syndrome in neonates. One infant was given a single dose of rasburicase after 2 days of induction chemotherapy for neuroblastoma; started on day 21 of life; serum urate normalised and chemotherapy was completed without further incident. A second infant, with acute lymphoblastic leukaemia and renal dysfunction, presented with tumour lysis syndrome, and had 6 doses of intravenous rasburicase plus aggressive supportive therapy, but died of complications on day 7 of life.[6] Reviews[7,8] have concluded that rasburicase is highly effective at decreasing uric acid concentrations rapidly and thoroughly; there is some suggestion that shorter durations of treatment (between 1 and 3 days as opposed to 5 days) may be sufficient even in high-risk patients.

1. Pui C-H, *et al.* Recombinant urate oxidase for the prophylaxis or treatment of hyperuricemia in patients with leukaemia or lymphoma. *J Clin Oncol* 2001; 19: 697–704.
2. Pui C-H, *et al.* Recombinant urate oxidase (rasburicase) in the prevention and treatment of malignancy-associated hyperuricemia in pediatric and adult patients: results of a compassionate-use trial. *Leukemia* 2001; 15: 1505–9.
3. Coiffier B, *et al.* Efficacy and safety of rasburicase (recombinant urate oxidase) for the prevention and treatment of hyperuricemia during induction chemotherapy of aggressive non-Hodgkin's lymphoma: results of the GRAAL1 (Groupe d'Etude des Lymphomes de l'Adulte Trial on Rasburicase Activity in Adult Lymphoma) study. *J Clin Oncol* 2003; 21: 4402–6.
4. Goldman SC, *et al.* A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis. *Blood* 2001; 97: 2998–3003.
5. Lee ACW, *et al.* Treatment of impending tumor lysis with single-dose rasburicase. *Ann Pharmacother* 2003; 37: 1614–17.
6. McNutt DM, *et al.* Rasburicase for the management of tumor lysis syndrome in neonates. *Ann Pharmacother* 2006; 40: 1445–50.
7. Bessmertny O, *et al.* Rasburicase: a new approach for preventing and/or treating tumor lysis syndrome. *Curr Pharm Des* 2005; 11: 4177–85.
8. Oldfield V, Perry CM. Rasburicase: a review of its use in the management of anticancer therapy-induced hyperuricaemia. *Drugs* 2006; 66: 529–45.

Adverse Effects and Treatment

The most serious adverse effects of rasburicase involve hypersensitivity reactions, including anaphylaxis, rashes, bronchospasm, rhinitis, urticaria, hypotension, dyspnoea, arthralgia, peripheral oedema, and chest pain and tightness. Haemolysis and methaemoglobinaemia have also been reported. Rasburicase can interfere with uric acid measurements. Other adverse effects are nausea, vomiting, abdominal pain, constipation, diarrhoea, headache, fever, respiratory distress, sepsis, and mucositis. Pulmonary haemorrhage, arrhythmias, and coronary artery disorders have also been reported.

Hypersensitivity reactions including anaphylaxis due to pegloticase can be serious. Infusion reactions, despite pretreatment with corticosteroids and antihistamines, are common. Gout flares can occur, especially upon starting therapy, and prophylaxis with an NSAID or colchicine is recommended, starting 1 week before pegloticase and continuing for at least 6 months, unless contra-indicated or not tolerated. Exacerbation of congestive cardiac failure has been reported. Other adverse effects include gastrointestinal disturbances, and chest pain.

Precautions

Treatment with rasburicase should be immediately and permanently stopped if hypersensitivity reactions, methaemoglobinaemia, or haemolysis develop. Rasburicase is contra-indicated in patients with G6PD deficiency or other cellular metabolic disorders known to cause haemolytic anaemia; hydrogen peroxide, which is produced during oxidation of uric acid to allantoin, can induce haemolytic anaemia in these patients. Patients at higher risk of having G6PD deficiency should be screened before receiving rasburicase.

The risk for anaphylaxis and infusion reactions in patients given pegloticase is higher in those whose uric acid concentration increases to above 6 mg per 100 mL, especially if two consecutive readings above this concentration are seen; serum uric acid should be monitored and treatment possibly stopped if increases above this level occur. Patients should be pretreated with antihistamines and corticosteroids, and pegloticase infused slowly over no less than 2 hours. Caution is recommended when treating patients with congestive cardiac failure.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies rasburicase as not porphyrinogenic: it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 08/07/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Fasturtec; *Austria*: Fasturtec; *Belg.*: Fasturtec; *Braz.*: Fasturtec; *Canad.*: Fasturtec; *Cz.*: Fasturtec; *Denm.*: Fasturtec; *Fin.*: Fasturtec; *Fr.*: Fasturtec; *Ger.*: Fasturtec; *Gr.*: Fasturtec; *Hong Kong*: Fasturtec; *Hung.*: Fasturtec; *Irl.*: Fasturtec; *Ital.*: Fasturtec; *Neth.*: Fasturtec; *Norw.*: Fasturtec; *NZ*: Fasturtec; *Pol.*: Fasturtec; *Port.*: Fasturtec; *Singapore*: Fasturtec; *Spain*: Fasturtec; *Swed.*: Fasturtec; *Switz.*: Fasturtec; *Turk.*: Fasturtec; *UK*: Fasturtec; *USA*: Elitek; Krystexxa; *Venez.*: Fasturtec.

Antihistamines

Uses of Antihistamines, p. 610
Anaesthesia, p. 610
Anaphylaxis, p. 611
Angioedema, p. 611
Asthma, p. 611
Conjunctivitis, p. 611
Coughs and colds, p. 611
Food allergy, p. 611
Hay fever, p. 611
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Ménière's disease, p. 611
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Nausea and vomiting, p. 611
Otitis media, p. 612
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Rhinitis, p. 612
Urticaria and angioedema, p. 612
Vertigo, p. 612
Adverse Effects of Antihistamines, p. 613
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Interactions of Antihistamines, p. 614

The peripheral effects of histamine are chiefly mediated by 2 sets of receptors termed H_1 and H_2. Effects mediated by the H_1 receptors include the contraction of smooth muscle and the dilatation and increased permeability of the capillaries. The effects of histamine on vascular smooth muscle are mediated by H_2 as well as H_1 receptors. Other effects that are mediated by H_2 receptors include cardiac accelerating effects and, in particular, the stimulating action of histamine on the secretion of gastric acid. An H_3 receptor has also been identified in several systems including the CNS and peripheral nerves. It is thought that H_3 receptors are involved in the autoregulation of the release of histamine and other neurotransmitters from neurones. More recently, a H_4-receptor has been discovered.

The term 'antihistamines' is normally reserved for histamine H_1-antagonists and this is the convention used in *Martindale*. H_2-antagonists, typified by cimetidine (p. 1830.1), are described in the chapter on Gastrointestinal Drugs. H_3-antagonists are under investigation.

The older antihistamines are associated with troublesome sedative and antimuscarinic effects, and are often termed 'sedating antihistamines'. The newer antihistamines, which are essentially devoid of these effects, are correspondingly termed 'non-sedating antihistamines' and include acrivastine, cetirizine, and loratadine.

On the basis of their chemical structure most antihistamines can be classified into one of 6 groups:

- *Alkylamines:* drugs within this group typically possess significant sedative actions, although paradoxical stimulation can occur, especially in children. They are highly potent H_1-antagonists. Brompheniramine and chlorphenamine are typical alkylamines; acrivastine is a non-sedating alkylamine antihistamine.
- *Monoethanolamines:* monoethanolamine derivatives have pronounced sedative and antimuscarinic actions but a low incidence of gastrointestinal effects. Examples include clemastine and diphenhydramine.
- *Ethylenediamines:* these antihistamines are selective H_1-antagonists. They cause moderate sedation (despite having weak CNS effects), gastric disturbances, and skin sensitisation. Antazoline and mepyramine are examples.
- *Phenothiazines:* phenothiazine antihistamines have significant sedative, and pronounced antiemetic and antimuscarinic effects. Photosensitivity reactions have occurred. Promethazine is a typical phenothiazine.
- *Piperazines:* this group of antihistamines possesses moderate sedative and significant antiemetic actions. Piperazine derivatives include cetirizine, cyclizine, and hydroxyzine. Cetirizine causes less sedation than other members of this group.
- *Piperidines:* piperidines cause moderate or low sedation and are highly selective for H_1 receptors. Examples include azatadine, cyproheptadine, and the non-sedating antihistamine loratadine.

Although characteristic pharmacological properties have been described for members of each group it should be noted that many of the effects of antihistamines vary as much with each patient as with each drug and that, in particular, some of the newer non-sedating antihistamines may share the chemical structure of a group in which the other members have sedative effects.

References.
1. Hill SJ, *et al.* International Union of Pharmacology. XIII. Classification of histamine receptors. *Pharmacol Rev* 1997; 49: 253–78.
2. Esbenshade TA, *et al.* The histamine H_3 receptor: an attractive target for the treatment of cognitive disorders. *Br J Pharmacol* 2008; 154: 1166–81.
3. Huang JF, Thurmond RL. The new biology of histamine receptors. *Curr Allergy Asthma Rep* 2008; 8: 21–7.
4. Thurmond RL, *et al.* The role of histamine H1 and H4 receptors in allergic inflammation: the search for new antihistamines. *Nat Rev Drug Discov* 2008; 7: 41–53.

Hypersensitivity. Hypersensitivity may be defined as an exaggerated or inappropriate immune response causing tissue damage. Hypersensitivity reactions are generally classified into 4 types (types I to IV) although this may be considered an over simplification and more than one type can often be postulated for a patient's hypersensitivity. In each of the 4 types, prior sensitisation of the patient to the specific antigen is required. The term *'allergy'* by definition originally covered all types of hypersensitivity reactions as well as the induction of immunity in an individual. Nowadays, the term is more commonly applied to type I hypersensitivity reactions.

Type I, immediate hypersensitivity reactions occur after exposure to an antigen (the allergen) in a sensitised subject; that is, one in whom the initial exposure to the antigen has caused the production of specific antibodies, mainly IgE (immunoglobulin E), which are bound to the surface of mast cells and basophils. At subsequent exposure, antigen binds to antibody resulting in degranulation of mast cells and basophils with release of mediators. These include preformed mediators such as histamine and chemotactic factors, and newly synthesised mediators such as leukotrienes, platelet-activating factor, and prostaglandins. Although type I reactions are usually described as being acute and short-lived, clinically there may often also be a late-phase and more prolonged reaction affecting the skin and bronchi. Examples of type I hypersensitivity reactions include allergic conjunctivitis (p. 611.1), allergic rhinitis (p. 612.1), urticaria and angioedema (p. 612.3), and anaphylactic shock (p. 611.1).

Type II, cell-surface hypersensitivity reactions are caused by the interaction of circulating antibodies, mainly IgG (immunoglobulin G) and IgM (immunoglobulin M), with antigens that are on the surface of specific cells or tissues. This interaction results in activation of complement and of phagocytic and killer cells leading to cell damage or lysis. Type II reactions are responsible for blood transfusion reactions, some drug-induced blood disorders, and many auto-immune disorders.

Type III, immune complex hypersensitivity reactions, are caused by the interaction of fixed or circulating antigens with circulating antibodies, mainly IgG and IgM (either soluble or particulate), resulting in formation of immune complexes. The immune complexes trigger a variety of inflammatory processes including complement activation, mediator release from mast cells and basophils, and platelet aggregation. Examples of type III reactions include serum sickness, some auto-immune and neoplastic disorders, type 2 lepra reactions (see Leprosy, p. 188.3), and reactions, particularly in the lung, to some particulate antigens such as micro-organisms.

Type IV, cell-mediated or delayed hypersensitivity reactions, are caused by interaction of an antigen with sensitised T-lymphocytes; lymphokines are released by T-lymphocytes and inflammation ensues. Type IV reactions usually occur at least 24 hours after contact with the antigen. A type IV reaction is responsible for tuberculin reactions used for sensitivity testing, contact dermatitis, and some reactions to chronic infectious disease for example type 1 lepra reactions (p. 188.3).

An **anaphylactoid** (pseudoallergic) reaction produces similar symptoms to those of anaphylaxis (see p. 611.1), but is caused by direct release of histamine provoked by an unclear, non-immune mechanism. There is thus no requirement for prior exposure to the triggering factor, commonly a drug.

Uses of Antihistamines

The activation of histamine H_1 receptors by histamine results in vasodilatation, increased capillary permeability, flare and itch reactions in the skin, and, to some extent, contraction of smooth muscle in the bronchi and gastrointestinal tract. Histamine H_1-antagonists (termed 'antihistamines' in *Martindale*) reduce or abolish the major actions of histamine in the body by competitive, reversible blockade of histamine H_1-receptor sites on tissues; they do not inactivate histamine or prevent its synthesis, nor, in most cases, its release (although some are claimed to have mast-cell stabilising properties).

Many *sedating antihistamines may* also possess antimuscarinic, adrenaline-antagonising, serotonin-antagonising, and local anaesthetic effects. Some have calcium-channel blocking activity.

Antihistamines are used mainly for the alleviation of conditions such as urticarial **rashes** and **nasal allergy** that are characterised by type I hypersensitivity (see above), but by virtue of their associated pharmacological actions they are also used to alleviate the symptoms of many other conditions (such as pruritus and nausea and vomiting).

The antihistamines can improve or relieve the symptoms of **seasonal allergic rhinitis** ('hay fever') in many patients. They alleviate rhinorrhoea and sneezing (and ocular symptoms such as conjunctivitis) but may be less effective for nasal congestion. The relief obtained is dependent on the severity and nature of the symptoms, being greater in the milder stages. The *non-sedating antihistamines* are preferred for daytime control, but a *sedating antihistamine* may be preferred at night. Antihistamines may also be of value in **vasomotor rhinitis**, despite the fact that this is not mainly an allergic condition. *Sedating antihistamines* are widely marketed, often with a decongestant, in compound preparations for the symptomatic treatment of coughs and **colds** although there is little evidence of value.

Antihistamines are of value in preventing **urticaria** and are used to treat urticarial rashes and mild **angioedema**. They are also used as adjuncts to adrenaline in the emergency treatment of **anaphylaxis** and severe angioedema. However, the use of an antihistamine is not appropriate for the control of blood transfusion reactions caused by ABO incompatibility.

The *sedating antihistamines* are of value in the alleviation of **pruritus** both of allergic and of non-allergic origin; they have a major role in pruritus associated with atopic eczema. The *non-sedating antihistamines* do not alleviate pruritus of non-allergic origin owing to their poor penetration of the blood-brain barrier.

Sedating antihistamines have marked antiemetic activity and are used to control **nausea and vomiting** caused by a variety of vestibular disorders. In the case of motion sickness a sedating antihistamine, such as dimenhydrinate or promethazine, is used if severe drowsiness (or even sleep) is not considered undesirable, but generally a less sedative antihistamine, such as cyclizine, cinnarizine, or meclozine may be preferred. Sedating antihistamines are similarly used to control the vertigo and nausea associated with **Ménière's disease** and related conditions, with cinnarizine promoted as a specific treatment. Sedating antihistamines also have an important role in the alleviation of the nausea and vomiting of **migraine**, and buclizine or cyclizine are marketed in some countries in a combination preparation for this purpose; cyproheptadine, which has serotonin antagonist and calcium-channel blocking activity, may be of value in the prophylaxis of migraine. Sedating antihistamines have a very limited role in the short-term management of vomiting of pregnancy but are no longer considered appropriate for nausea alone. *Sedating antihistamines* have also been used in anaesthetic practice for **premedication** and the prevention of postoperative nausea and vomiting.

Some of the antihistamines with very pronounced sedative effects, such as diphenhydramine and promethazine, have been marketed for treatment of occasional **insomnia** but their long duration of action can cause hangover effects. Some antihistamines are also available as preparations for topical application for the alleviation of **insect bites**, but there is little evidence of any real value and such use may be associated with sensitisation.

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Anaesthesia

Phenothiazine antihistamines have been used for anaesthetic premedication (p. 1899.1) and to relieve anxiety

during surgical and obstetric procedures, but benzodiazepines are now used more routinely. However, sedating antihistamines such as promethazine and cyclizine do have a role in the control of postoperative vomiting (below). Alimemazine is licensed for premedication in children, although when given alone it may cause postoperative restlessness if pain is present.

Anaphylaxis

Anaphylaxis is commonly a type I (immediate) hypersensitivity reaction (see p. 610.1) to various allergens such as drugs, foods, and insect venoms. A clinically identical reaction can, however, be provoked by some other immune mechanisms, or by non-immune mechanisms (previously termed anaphylactoid reactions). Symptoms include erythema, pruritus, urticaria, and angioedema; respiratory obstruction may result from oedema of the larynx or epiglottis. Gastrointestinal disturbances, bronchospasm, hypotension, and coma can occur in severe reactions.

Anaphylaxis is a medical emergency and requires prompt treatment with adrenaline. (see Anaphylaxis and Anaphylactic Shock, p. 1293.2). The use of antihistamines in the management of anaphylaxis has been a matter of some debate. During acute treatment they are unlikely to be life-saving, and should never be used alone. However, an intramuscular or slow intravenous injection of an H_1-antagonist such as chlorphenamine or diphenhydramine may be given after adrenaline and repeated over the next 24 to 48 hours to counter histamine-mediated vasodilatation and bronchoconstriction. The use of antihistamines in treating the symptoms of milder forms of hypersensitivity is discussed under individual symptoms such as Pruritus (p. 612.1) and Urticaria and Angioedema (p. 612.3).

Angioedema

See under Urticaria and Angioedema, p. 612.3.

Asthma

Antihistamines appear to have no place in the treatment of asthma (p. 1195.2). A meta-analysis[1] of double-blind randomised placebo-controlled studies published since 1980 did not support the use of antihistamines in the treatment of asthma, although the quality of the studies was generally considered to be poor.

1. Van Gesse E, *et al.* Effects of antihistamines in adult asthma: a meta-analysis of clinical trials. *Eur Respir J* 1997; 10: 2216–24.

Conjunctivitis

Allergic conjunctivitis is a type I hypersensitivity reaction (p. 610.1). It is usually seasonal but perennial attacks due to allergens such as house dust mites can occur. Itching, tears, and burning are common symptoms and frequently rhinitis (p. 612.1) will co-exist. Conjunctivitis can also be caused by pathogenic micro-organisms (see Eye Infections, p. 182.1).

Avoidance of unnecessary exposure to aeroallergens is of prime importance in the management of allergic conjunctivitis. Since a large number of inflammatory mediators are involved in its pathogenesis no single drug will be completely effective. Systemic sedating and non-sedating antihistamines are effective in reducing allergic symptoms and preventing attacks; the choice of drug depends on the degree of sedation required. Ophthalmic antihistamine preparations such as antazoline, azelastine, emedastine, levocabastine, and olopatadine may also be used for acute attacks. Ophthalmic corticosteroids may reduce inflammation, but should be restricted to severe cases only and limited to 5 to 7 days of use because of the risk of local adverse effects such as cataract or raised intra-ocular pressure. Mast-cell stabilisers including ketotifen, lodoxamide, nedocromil, and sodium cromoglicate have been widely used for prophylaxis; some antihistamines also have mast-cell stabilising properties. Diclofenac and ketorolac eye drops are available for the treatment of allergic conjunctivitis. Combined preparations of astringents such as zinc sulfate and sympathomimetics or other conjunctival decongestants such as naphazoline may also be used for symptomatic relief.

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Coughs and colds

Sedating antihistamines are frequently used in combination preparations for the treatment of coughs and colds (p. 1651.2 and p. 951.1 respectively). The mechanism of their antitussive action may involve reduction in cholinergic nerve transmission or may simply result from their sedative effects; reduction of nasal secretions may be of value in treating cough caused by postnasal drip. Antihistamines should not be used to treat productive coughs because reduction in bronchial secretions may cause formation of viscid mucus plugs. The sedative effects of antihistamines may prove troublesome for daytime use but may be a short-term advantage for night coughs.

Cough and cold preparations containing antihistamines should be used with caution in children, and generally avoided in young children (for details see p. 614.1). However, antihistamines may be useful in the management of children with an acute allergic cough in the pollen season. They may also be used, with allergen avoidance and intranasal corticosteroids, in children with a chronic throat clearing type of cough and signs of allergic rhinitis.[1]

1. Shields MD, *et al.* British Thoracic Society Cough Guideline Group. Recommendations for the assessment and management of cough in children. *Thorax* 2008; 63 (suppl III): iii1–iii15. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Cough/Guidelines/cough_in_children.pdf (accessed 01/08/08)

Food allergy

The term food allergy (food hypersensitivity) should be reserved for instances in which an immune mechanism for the reaction is proven, as may occur, for example, with nuts; food intolerance is used to describe a non-immune reaction. Food allergy may be the result of a type I (immediate), or possibly a type III (immune complex), hypersensitivity reaction (see p. 610.1). Management revolves around the identification of the provoking food allergen and its subsequent avoidance. Individualised diets are designed and patients are educated about possible hidden sources of the allergen. Drug therapy has a very limited role in the prevention of food allergy; oral sodium cromoglicate has been used but efficacy has not been unequivocally established.

Inadvertent exposure to an allergen resulting in anaphylaxis (p. 1293.2) requires immediate treatment with adrenaline. Milder symptoms may be controlled by antihistamines and corticosteroids. Allergen immunotherapy (p. 2435.1) plays no role in the routine management of food allergy.

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Hay fever

Hay fever is a seasonal form of allergic rhinitis in which symptoms of conjunctivitis are also present. Management is symptomatic and therapies used are discussed under Conjunctivitis, above and Rhinitis, p. 612.1.

Insomnia

Some of the older sedating antihistamines including diphenhydramine and promethazine, have been promoted to the public for occasional insomnia (p. 1033.2), although their long duration of action may cause hangover effects. Promethazine was formerly popular for children but the use of hypnotics in this age group is not usually justified. Moreover a possible association between phenothiazines and sudden infant death syndrome (see under the Adverse Effects of Promethazine, p. 639.1) contributed to the recommendation that such antihistamines should not be used in young children.

Ménière's disease

Ménière's disease is a disorder of the labyrinth (the inner ear) characterised by recurrent attacks of vertigo, progressive hearing loss, and worsening tinnitus (p. 1994.1). It usually presents in middle age and may equally affect men and women. The main pathological feature is an excess of endolymph fluid producing an increase in pressure in the membranous labyrinth (endolymphatic hydrops). Attacks occur in clusters over a few weeks with periods of remission lasting weeks or months.

The aims of treatment are to alleviate symptoms and preserve hearing if possible. It is therefore important to assess how far the disease has progressed, particularly in terms of hearing loss. In addition to conventional hearing tests, cochlear dysfunction may be assessed pharmacologically. Hypertonic glycerol has been given orally to reduce the endolymphatic fluid volume by osmotic diuresis, any temporary improvement in hearing indicating reversible impairment. However, this test is associated with adverse effects that some consider unacceptable. Urea has been used as an alternative to glycerol. Intravenous acetazolamide has been used diagnostically to increase endolymphatic pressure temporarily in order to produce transient hearing loss in patients in the reversible stages of the disease.

Acute attacks of vertigo in the early stages may be treated with the same drugs used for vertigo of any cause (see p. 612.3).

Vasodilators have been advocated for maintenance treatment because ischaemia of the labyrinth has been postulated as a factor in the aetiology. Betahistine, a histamine analogue, is used. Restriction of dietary sodium and administration of diuretics, such as chlortalidone, furosemide, and hydrochlorothiazide, has also been used traditionally to reduce the amount of fluid in the endolymphatic spaces.

As the disease progresses, vestibular ablation with aminoglycosides may be indicated. Systemic streptomycin has been used but the risk of further hearing loss and other serious adverse effects has limited its use. Intratympanic use of gentamicin is now preferred, and can improve vertigo in up to 90% of patients, although exacerbation of hearing loss is still a risk, albeit at a lower incidence than that with systemic streptomycin.

Surgical treatment remains an option for patients with Ménière's disease refractory to medical interventions.

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Migraine

Antihistamines have several uses in the management of migraine (p. 670.3). Those with antiemetic activity such as buclizine and cyclizine are used to alleviate the nausea and vomiting associated with migraine; they are common ingredients of compound analgesic preparations given for the initial treatment of migraine.

Those antihistamines with antiserotonin actions, including cyproheptadine and flunarizine, have been used for the prophylaxis of migraine.

Nausea and vomiting

The management of various types of nausea and vomiting is discussed in detail on p. 1814.3.

The older antihistamines such as cinnarizine, cyclizine, dimenhydrinate, meclozine, and promethazine are among the principal drugs used for **motion sickness**. They are all of similar efficacy but may differ in onset and duration of action and in the extent of adverse effects such as drowsiness. If a sedative effect is desired dimenhydrinate and promethazine are useful, otherwise a slightly less sedating antihistamine such as cinnarizine, cyclizine, or meclozine may be preferred. The aim is prevention of motion sickness since antiemetics are more effective for prophylaxis than for treatment; intramuscular promethazine may be effective as a treatment if injection is feasible. Antihistamines may be slightly less effective against motion sickness than the antimuscarinic hyoscine (p. 1848.3), but are often better tolerated. Non-sedating antihistamines, which penetrate poorly into the CNS, do not appear to be effective against motion sickness.

Diphenhydramine has been included in antiemetic regimens for the control of nausea and vomiting associated with **cancer chemotherapy** to reduce the extrapyramidal reactions associated with metoclopramide; it may also improve overall antiemetic control. Cyclizine is used as an antiemetic in **palliative care**.

Cyclizine is given as a supplement to opioids for premedication and has been effective prophylactically as well as in established **postoperative nausea and vomiting**. Promethazine has also been used for the

prevention and treatment of postoperative nausea and vomiting, but has marked sedative effects. Dimenhydrinate is also effective for prophylaxis.

Nausea in the first trimester of **pregnancy** does not usually require drug therapy, but on rare occasions if vomiting is severe an antihistamine such as promethazine may be required pending specialist advice. A combination preparation containing doxylamine and pyridoxine is also available for use during early pregnancy in women who have not responded to conservative management. See under Precautions for Antihistamines, p. 614.2, for a discussion of the risks of antiemetic therapy during pregnancy.

Otitis media

Acute otitis media (p. 195.2) and otitis media with effusion may resolve without treatment although antibacterials are often given. Antihistamines and decongestants, alone or in combination, have been widely given to children for symptomatic management of acute otitis media and associated respiratory symptoms, but studies have failed to show benefit and their use is not recommended.[1] Indeed in one study,[2] adjunctive treatment with chlorphenamine was found to prolong the duration of middle ear effusion.

1. Griffin G, *et al.* Antihistamines and/or decongestants for otitis media with effusion (OME) in children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 07/03/07).
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Pruritus

The sedating antihistamines are commonly used to relieve pruritus (itching) (p. 1687.3) from a variety of causes. They are effective in relieving pruritus associated with urticaria (below) but are also used for itching associated with dermatoses such as atopic eczema (p. 1684.1), where the degree of benefit is less certain. They are given in the latter to control nocturnal itching and for severe pruritus associated with relapse.

The exact pathophysiology of itching remains unclear.[1-3] Although histamine release is associated with itching in atopic eczema different inflammatory mediators are involved in other dermatoses. The CNS is also thought to play a part in the perception of itch. Hence, the relative roles of CNS sedation and peripheral histamine-receptor blockade in the mode of action of antihistamines in these conditions is a matter of debate. Although sedation has generally been considered the more important, the benefits of sedating antihistamines appear to be less in eczema than in urticaria. In addition, clemastine has been reported to provide no antipruritic benefit, yet it induces significant sedation. Studies with non-sedating antihistamines have been inconclusive; most found no benefit in pruritus associated with atopic eczema, although one early study has shown a slight benefit from the addition of acrivastine or terfenadine to treatment with a topical corticosteroid and an emollient.[4] Some have questioned whether any antihistamine offers much benefit in pruritus.[5]

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Rhinitis

Rhinitis may be allergic or non-allergic in origin. Allergic rhinitis is a type I hypersensitivity reaction (see p. 610.1); both early (sneezing, rhinorrhoea, and nasal congestion) and late (nasal congestion) reactions may be provoked. It may be seasonal (as in hay fever) or perennial and, in some patients, will frequently co-exist with conjunctivitis (p. 611.1). Non-allergic rhinitis may be divided into eosinophilic non-allergic rhinitis or non-eosinophilic non-allergic rhinitis. The term vasomotor rhinitis has been used to describe the latter although its use is best avoided since no vasomotor dysfunction has been clearly identified.

In the management of **allergic rhinitis**, avoidance of unnecessary exposure to aeroallergens is of prime importance. However, in most sufferers this is not possible and some form of drug therapy will be necessary. A large number of inflammatory mediators are involved in the pathogenesis of rhinitis and no single drug is completely effective in the alleviation of symptoms.

- Some antihistamines may nonetheless be useful in reducing secretions, nasal itching, sneezing, and ocular symptoms such as conjunctivitis, but are less effective for relief of nasal congestion. Non-sedating oral antihistamines such as acrivastine, cetirizine, ebastine, fexofenadine, loratadine, and mizolastine are now considered the first-choice treatment for mild and/or intermittent allergic rhinitis. They are also used for the management of breakthrough symptoms in those sufferers using prophylactic intranasal corticosteroids or sodium cromoglicate (see below). Since the maximum effect of antihistamines occurs several hours after peak serum concentrations have been obtained, they should be given in anticipation of a reaction to achieve the maximum response. Most antihistamines are unsuitable for topical use in the nose or eye since they are generally ineffective at the concentrations suitable for local therapy; also there is the potential for sensitisation. However, the antazoline salts, azelastine and levocabastine have been used topically in the nose for control of symptoms and are an alternative to oral antihistamines. Such preparations are considered less effective than intra-nasal corticosteroids but probably more effective than cromoglicate.
- The actions of topical corticosteroids in allergic rhinitis include relief of inflammation, a decrease in capillary permeability and in mucus production, and vasoconstriction; they inhibit both the early and late response to allergen exposure. Corticosteroids are first-line treatment for the prophylaxis of moderate to severe and/or persistent allergic rhinitis. In seasonal allergic rhinitis, they should be started at least 2 weeks before the pollen season and taken regularly throughout the season. Those applied intranasally include beclometasone, budesonide, flunisolide, fluticasone, mometasone, and triamcinolone. At recommended dosage, local adverse effects are mild and transient, and systemic effects are not a risk; aqueous sprays may cause less local effects than pressurised aerosols. Treatment of allergic rhinitis with oral or parenteral corticosteroids has been reserved for short-term treatment in special circumstances only, although some have contested even this practice.
- Mast-cell stabilisers such as ketotifen, nedocromil, and sodium cromoglicate are thought to act mainly by preventing release of inflammatory mediators from sensitised mast cells through stabilisation of mast-cell membranes. They are an alternative to corticosteroids in the prophylactic treatment of allergic rhinitis and may be preferred for therapy in children. They may also be useful in controlling mild to moderate symptoms.
- The leukotriene receptor antagonist montelukast has produced benefits comparable to those seen with antihistamines, and is licensed in some countries for management of seasonal allergic rhinitis.
- Intranasal sympathomimetics such as phenylephrine, naphazoline, oxymetazoline, and xylometazoline may be useful for short-term treatment of allergic rhinitis to relieve severe nasal congestion which can be painful and may impede delivery of sodium cromoglicate or a corticosteroid to the mucosal surfaces. Oral sympathomimetic decongestants such as pseudoephedrine and phenylpropanolamine are less effective than topical sympathomimetics and adverse effects may be troublesome.
- Ipratropium bromide given intranasally may be useful as adjunctive therapy in patients with rhinorrhoea as it has a localised parasympathetic blocking action which reduces watery hypersecretion from nasal mucosa.

Allergen immunotherapy (p. 2435.1) is generally only indicated in severe allergic rhinitis when sensitivity testing shows sensitivity to one allergen and when exposure to the allergen is unavoidable or symptomatic treatment has failed.

The management of **non-allergic rhinitis** is similar to that of allergic rhinitis despite different mechanisms being involved in its aetiology. Topical corticosteroids are often first-line therapy especially if nasal congestion is a dominant feature. The role of antihistamines is more limited; sedating antihistamines are useful in reducing nasal secretions because of their antimuscarinic actions; however, non-sedating antihistamines are relatively ineffective. In patients in whom rhinorrhoea is a particular problem, intranasal ipratropium is of value. Although intranasal sympathomimetics have also been used they should generally be avoided because of the risk of rebound congestion. Oral sympathomimetics are largely ineffective.

Other therapies tried include topical capsaicin, to induce local desensitisation, and nasal douching with a saline and sodium bicarbonate solution.

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Urticaria and angioedema

Most patients with urticaria or angioedema (p. 1689.2) derive some benefit from oral antihistamines, especially in relief of pruritus. However, patients who are severely affected, particularly those with laryngeal oedema, are allergic emergencies and require immediate treatment with adrenaline (see Anaphylaxis and Anaphylactic Shock, p. 1293.2). Also, large doses of antihistamines are sometimes required and urticarias with a type I immunological origin and iatrogenic urticarias respond better than physical urticarias. If attacks of urticaria are frequent, antihistamines may be given prophylactically. Sedating antihistamines such as chlorphenamine and diphenhydramine have been widely used in the treatment of urticaria but non-sedating antihistamines are now generally preferred. Hydroxyzine has been used particularly in dermographism and cholinergic urticaria. Cyproheptadine has generally been considered the drug of choice for cold urticaria, although appetite stimulation may be a problem.

Some drugs with both H_1-antagonist and mast-cell stabilising actions, such as ketotifen, oxatomide, and azatadine have shown efficacy in the treatment of urticaria; the role of mast-cell stabilisation is unknown.

Topical treatment is rarely effective except for cases of mild urticaria; topical antihistamines carry a risk of sensitisation.

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Vertigo

Vertigo is a symptom of vestibular disorders. It is characterised by a sensation of rotation of the surroundings or of movement of static objects. Dizziness is considered to be a wider term, although sometimes it is used as a synonym for vertigo.

A variety of disorders may affect the vestibular system and produce vertigo, including cerebrovascular disorders, epilepsy, head injury, malignant neoplasms, Ménière's disease, migraine, multiple sclerosis, and infections. Motion sickness can induce vertigo. Ototoxic drugs may also cause vestibular damage and precipitate vertigo.

Patients suffering from vertigo should undergo thorough investigations to identify any underlying cause. Simple measures to improve the integration of sensory input from visual, proprioceptive, and vestibular receptors may prove effective, especially in the elderly, in whom the inappropriate prescribing of drugs for postural instability needs to be avoided. Such measures include improving visual acuity, balance exercises, and the use of walking aids.

The most widely used drugs for acute vertigo are the antihistamines. They may have a direct action on the inner ear besides acting centrally. Antimuscarinic actions may contribute to their activity; antimuscarinics, especially hyoscine, have a long history of use in vertigo. Antihistamines used in the treatment of vertigo include buclizine, cyclizine, dimenhydrinate, diphenhydramine, meclozine, and promethazine. Cinnarizine and flunarizine are also used for vertigo although they are devoid of any significant antimuscarinic actions; their activity may be due to calcium-channel blockade. Phenothiazines such as prochlorperazine are also used to control any associated vomiting. Benzodiazepines including diazepam have been given in acute

severe attacks. However, their prolonged use in those with chronic symptoms is of questionable value.

Vasodilators may be of benefit in the treatment of vertigo of vascular aetiology. Parenteral or sublingual histamine was formerly widely used, and betahistine is still advocated especially for vertigo associated with Ménière's disease. Nicotinyl alcohol has also been used.

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Adverse Effects of Antihistamines

The most common adverse effect of the *sedating antihistamines* is CNS depression, with effects varying from slight drowsiness to deep sleep, and including lassitude, dizziness, and incoordination (although paradoxical stimulation may occasionally occur, especially at high doses and in children or the elderly). These sedative effects, when they occur, may diminish after a few days of treatment. *Non-sedating antihistamines* generally cause little or no drowsiness (but see Sedation, below).

Other adverse effects that are more common with the *sedating antihistamines* include headache, psychomotor impairment, and antimuscarinic effects, such as dry mouth, thickened respiratory-tract secretions, blurred vision, urinary difficulty or retention, constipation, and increased gastric reflux. Most *non-sedating antihistamines* have little or no antimuscarinic effect.

Occasional gastrointestinal adverse effects of antihistamines include nausea, vomiting, diarrhoea, or epigastric pain. Those with antiserotonin actions, such as cyproheptadine, may cause an increase in appetite with resultant weight gain, whereas anorexia has been reported with some other antihistamines.

Palpitations and arrhythmias have been reported occasionally with most antihistamines, but a particular disadvantage of the *non-sedating antihistamines* astemizole and terfenadine was the rare occurrence of hazardous ventricular arrhythmias which led to important restrictions on their use (see Precautions, below).

Antihistamines sometimes cause rashes and hypersensitivity reactions (including bronchospasm, angioedema, and anaphylaxis) and cross-sensitivity to related drugs may occur. Photosensitivity can be a problem, particularly with the phenothiazine antihistamines.

Blood disorders, including agranulocytosis, leucopenia, haemolytic anaemia, and thrombocytopenia, although rare, have been reported. Jaundice has also been seen, particularly with the phenothiazine antihistamines.

Other adverse effects that have been reported with the antihistamines include convulsions, sweating, myalgia, paraesthesias, extrapyramidal effects, tremor, sleep disturbances, depression, confusion, tinnitus, hypotension, and hair loss.

Despite reports suggesting a possibility of human fetal abnormalities resulting from the use of some antihistamines, especially the piperazine derivatives, a causal relationship has largely been rejected; for details see Pregnancy, under Precautions, p. 614.2.

Some antihistamines have been abused for their CNS effects.

Antihistamines available as preparations for application to the skin may occasionally cause skin sensitisation; systemic adverse effects have been reported after topical application to large areas of the skin.

Overdosage with *sedating antihistamines* is associated with antimuscarinic, extrapyramidal, and CNS effects. When CNS stimulation predominates over CNS depression, which is more likely in children or the elderly, it causes ataxia, excitement, tremors, psychoses, hallucinations, and convulsions; hyperpyrexia may also occur. Deepening coma and cardiorespiratory collapse may follow. In adults, CNS depression is more common with drowsiness, coma, and convulsions, progressing to respiratory failure and cardiovascular collapse. In the case of the *non-sedating antihistamines*, antimuscarinic effects are less marked, but hazardous ventricular arrhythmias (below) have been a particular problem with astemizole and terfenadine, even in modest overdoses, and led to restrictions on their use.

Reviews.

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Arrhythmias. Ventricular arrhythmias have been reported rarely with astemizole and terfenadine particularly in association with increased blood concentrations. For full details and specific warnings see under Astemizole, p. 616.2, and Terfenadine, p. 640.3.

The suspicion that such life-threatening arrhythmias may be a class effect of the non-sedating antihistamines has so far proven unfounded. Data[1] from the WHO adverse drug reaction database showed that cardiac events had been reported with the 5 most widely prescribed non-sedating antihistamines at that time (acrivastine, astemizole, cetirizine, loratadine, and terfenadine), and an attempt to quantify the risk[2] suggested that use of these drugs was associated overall with a fourfold increase in likelihood of developing ventricular arrhythmias, although the absolute risk remained low. However, other centres[3] have argued that definitive causality has only been proven for astemizole and terfenadine. In addition, a possible mechanism for drug-induced cardiac toxicity has only been found with astemizole and terfenadine;[4] both drugs have been shown to block cardiac potassium channels *in vitro*, a phenomenon that results in prolongation of the QT interval, which is a risk factor for developing ventricular arrhythmias. Studies[5] with loratadine and cetirizine have found that neither drug blocked potassium channels *in vitro*, and a similar lack of activity might be expected with desloratadine and levocetirizine; however, there is some evidence that mizolastine can block potassium channels at high concentrations *in vitro*[6] (although a small study in healthy subjects noted no adverse effects on cardiac conduction at doses up to 4 times those normally given).[7] A case report[8] of arrhythmias in a patient with pre-existing QT-prolongation given fexofenadine, did not appear to be associated with blocking of potassium channels.[9]

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Reye's syndrome. For criticism of a suggested link in children between antihistamines and Reye's syndrome, see p. 25.3.

Sedation. CNS depression is a common adverse effect of the *sedating antihistamines* and sedative effects can range from slight drowsiness to deep sleep. Daytime sedation can be a problem especially for those who have to drive or operate machinery. When sedative effects do occur they are most apparent at the start of treatment and often diminish after a few days despite continued use. Sedation caused by alcohol or other CNS depressants is enhanced. Many studies have attempted to quantify and compare the sedative effects of the older antihistamines, but results vary widely and classifications are difficult to make. Theoretically, the onset, degree, and persistence of sedation depend on factors such as penetration of the blood-brain barrier and on the relative affinity for central and peripheral histamine H_1 receptors. In general, antihistamines of the monoethanolamine and phenothiazine classes cause the most sedation.

In view of these problems, *non-sedating antihistamines* have been developed. These compounds have poor penetration into the CNS and/or higher affinity for peripheral rather than central histamine H_1 receptors. Studies with acrivastine,[1] astemizole,[2] fexofenadine,[3] loratadine,[4] and terfenadine[5] have generally indicated a lower incidence of sedation and related CNS effects than that seen with older antihistamines and comparable with that of placebo; prescription-event monitoring suggested that sedation was lower with fexofenadine and loratadine than with acrivastine or cetirizine, although the risk was low with all 4 drugs.[6] In a study[7] to compare the effects of acrivastine, terfenadine, and diphenhydramine on driving performance, terfenadine had no significant effect on driving performance. Acrivastine's effects were dose-related, but with little effect at the normal therapeutic dose, whereas diphenhydramine profoundly impaired all the measures of driving performance. In another study,[8] the effects of fexofenadine on driving performance were comparable with placebo. Studies with terfenadine[9] suggest that the incidence of sedation does not increase significantly with increased dose or duration of administration. Cetirizine appears to be more sedating than loratadine or terfenadine but less sedating than older antihistamines; the effect appears to be dose dependent.[9] Limited data with azelastine[10] indicate a similar incidence of drowsiness to that with terfenadine. An incidence of sedation comparable with that caused by terfenadine has also been seen for mequitazine when given in the recommended dosage of 5 mg twice daily.[5] Sedation has, however, occurred after doses of 10 mg twice daily.[11] Other newer antihistamines claimed to produce no troublesome sedation include ebastine, epinastine, mizolastine, and setastine.

A review[12] of studies in drivers divided antihistamines into:

- first-generation (such as clemastine, diphenhydramine, and triprolidine), which produced significant impairment of driving ability
- second-generation (acrivastine, cetirizine, ebastine, emedastine, loratadine, mizolastine, and terfenadine), which produced more modest degrees of impairment; higher doses than normal produced significant impairment
- third-generation (levocetirizine, fexofenadine), which seemed to produce little or no impairment

Several studies have indicated that the non-sedating antihistamines do not seem to enhance the effects of alcohol and other CNS depressants.

A few patients treated with non-sedating antihistamines have experienced drowsiness. Therefore it is prudent to exercise caution before driving or operating machinery; the effect of a drug on a particular patient can be ascertained after the first few doses.

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Precautions for Antihistamines

Drowsiness is a major problem with the *sedating antihistamines* and those affected should not drive or operate machinery; alcohol should be avoided. In the case of *non-sedating antihistamines*, although drowsiness is rare, it can occur and may affect the performance of skilled tasks.

Because of their antimuscarinic actions the *sedating antihistamines* should be used with care in conditions such as angle-closure glaucoma, urinary retention, prostatic hyperplasia, or pyloroduodenal obstruction; antimuscarinic adverse effects are not a significant problem with the *non-sedating antihistamines*.

Occasional reports of convulsions in patients taking antihistamines suggest a need for caution in patients with epilepsy.

Many antihistamines are excreted in the urine in the form of active metabolites so that dosage reduction may be necessary in renal impairment (see individual monographs for specific advice). Caution is also needed in hepatic impairment, notably with phenothiazine antihistamines (for further details, see Effects on the Liver, under Chlorpromazine, p. 1049.1) and, above all, with the *non-sedating antihistamines*, astemizole and terfenadine (hazardous ventricular arrhythmias may occur in the presence of excessive blood concentrations). Other important cautions for astemizole and terfenadine include avoidance of use with drugs liable to interfere with their hepatic metabolism or otherwise increase the risk of arrhythmias, and contra-indication in patients with cardiac disease, known or suspected prolongation of the QT interval, or hypokalaemia or other electrolyte imbalances. For full details see under Astemizole, p. 616.2, and Terfenadine, p. 640.3.

Antihistamines should not be given to neonates because the latter are more susceptible to antimuscarinic effects. It has also been recommended that antihistamines should be

avoided in young children (see Children, below, and under Promethazine, p. 639.2, and Alimemazine, p. 615.2). Elderly patients are also more susceptible to many of the adverse effects of antihistamines and, in particular, their inappropriate use for postural giddiness should be avoided (see Vertigo, p. 612.3).

Topical preparations containing antihistamines should not be used on broken or eczematous skin.

Several large studies have failed to find any strong associations between fetal abnormalities and antihistamines taken during pregnancy (see under Pregnancy, below).

Asthma. Antihistamines are not considered effective in the management of asthma[1] and their use has often been contra-indicated in patients with asthma because of fears that they may cause airway obstruction. However, antihistamine-induced airway obstruction has rarely been noted clinically and many patients with asthma tolerate concurrent treatment with antihistamines without obvious adverse effects. Therefore the American Academy of Allergy and Immunology has recommended that antihistamines are not contra-indicated in patients with asthma, unless an adverse reaction has previously occurred, and the FDA no longer warns against the use of over-the-counter antihistamines by people with asthma.[2]

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Children. In 2004, the FDA[1] reviewed all reports that it had received, between 1969 and 2003, of serious adverse events in children (aged from birth to 16 years) given promethazine. Of 125 reports there were 38 cases of respiratory depression, apnoea, or cardiac arrest; 29 cases of extrapyramidal dystonic reactions; 24 cases of other CNS reactions; 15 cases of seizures or seizure-like activity; 12 cases of dermatological reactions; and 5 cases of neuroleptic malignant syndrome. These reports included 22 cases of respiratory depression in patients aged 1.5 months to 2 years, 7 of which were fatal. Doses received in these 22 cases ranged from 0.45 to 6.4 mg/kg. Serious outcomes occurred with all routes of use (oral, rectal, and parenteral). US licensed product information for promethazine hydrochloride now contra-indicates its use in children under 2 years of age because of the potential for fatal respiratory depression; a strengthened warning regarding use in children aged 2 years and older advises use of the lowest effective dose and to avoid concomitant use of other drugs with respiratory depressant effects. UK licensed product information for phenothiazine antihistamines, such as promethazine and alimemazine, also warns that these should not be given to children under 2 years of age, and the *BNFC* advises that sedating antihistamines such as these should not be given to children under 2 years of age, except on specialist advice, because safety has not been established.

Concern has also been expressed about the safety in children of cough and cold preparations that contain antihistamines, cough suppressants, expectorants, and sympathomimetic decongestants, either alone or in combination. A systematic review[2] has also found no good evidence for or against the efficacy of over-the-counter (OTC) preparations in acute cough. In early 2008, the FDA[3] and MHRA[4] both advised that over-the-counter cough and cold preparations should not be given to children under 2 years of age. They warned of the potential for serious and potentially life-threatening adverse effects and that such preparations provided only symptomatic relief, at best. They also advised that if these products were to be used in children older than 2 years of age, the recommended dose should be followed carefully and measured accurately, and that only one preparation should be used to avoid overdosage of the same drug or similar drugs. A review by the FDA of the use of such preparations in older children (2 to 11 years of age) is ongoing. However, in October 2008, most US manufacturers voluntarily revised the labelling of OTC cough and cold preparations to state not for use in children aged under 4 years.[5] In early 2009, after further review, the MHRA[6] advised that OTC cough and cold preparations should not be given to children under 6 years of age as there was no robust evidence of their efficacy and because they can cause adverse effects such as allergic reactions, sleep disturbances, and hallucinations. In those aged from 6 to 12 years, such preparations should only be used as second-line therapy and for no more than 5 days; the MHRA also considers that further research is warranted in this age group. For the MHRA's suggested management of the symptoms of coughs and colds, see Cough, p. 1651.2.

An association between phenothiazine antihistamines and sudden infant death syndrome has also been investigated—see p. 639.1.

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Pregnancy. Antihistamines have been used for antiemetic therapy during pregnancy, but considerable anxiety has surrounded such use and its potential for risk to the fetus. The most widely studied preparation was *Debendox* which contained doxylamine, dicycloverine, and pyridoxine, and was known as *Bendectin* in some countries. Dicycloverine was removed from the preparation in 1976 in the USA and subsequently in other countries, and the product was withdrawn from the market in 1983 because of threatened litigation.[1] By that time *Debendox* had been used for over 27 years and in over 33 million pregnancies worldwide.[1]

Initial concern came from anecdotal reports of malformations in infants whose mothers had taken *Debendox* during pregnancy.[2,3] Evidence was found[4] of an association between prenatal exposure to the 3-component formulation of *Bendectin* and an increased risk of pyloric stenosis and possibly also defective heart valves in a study of 1369 malformed infants and 2968 healthy control cases. Other studies have suggested an increased incidence of oral clefts,[5] gastrointestinal atresia,[6] and genital tract disorders,[7] but generally such increases have been small. No overall pattern of malformations appears to have emerged, and many large studies have failed to confirm an association between doxylamine use and congenital malformations.[8-13]

A prospective study of 11 481 pregnancies found no increased incidence of either severe congenital abnormalities or perinatal mortality rates in women who had been prescribed prochlorperazine, meclozine, cyclizine, or *Bendectin* during pregnancy, although there was some evidence of an excess number of congenital abnormalities in patients taking trimethobenzamide.[14]

The Collaborative Perinatal Project[15] monitored the mothers of 50 282 children between 1958 and 1965. Of these, 5401 used antihistamines and 1309 phenothiazines during the first 4 months of pregnancy. There was no evidence to suggest that exposure to these drugs was related to malformations, although there were slight suggestions of associations between respiratory malformations and phenirамine, inguinal hernia and meclozine, inguinal hernia or genito-urinary malformations and diphenhydramine, and cardiovascular deformities and phenothiazines. A report[16] on the same study found no effects of phenothiazines on perinatal mortality, birth-weight, or IQ scores at the age of 4 years. The Collaborative Perinatal Project also noted a relationship between cardiovascular defects and inguinal hernia and dimenhydrinate exposure.[15]

Both the UK CSM[17] and the FDA in the USA[18] reviewed the literature in 1981 and concluded that while the scientific evidence did not show an increase in birth defects with *Debendox*, the risk of teratogenicity could not be completely excluded. A further review[19] by the FDA in 1999 into the reasons for withdrawal stated that the evidence supported the conclusion that the combination had not been withdrawn from the market for reasons of safety or efficacy. In some countries, such as Canada, a combination preparation of doxylamine and pyridoxine remained available for the treatment of nausea and vomiting in pregnancy; subsequently, in April 2013, the FDA approved the return of such a combination preparation onto the market. There has been a study indicating that vomiting itself is not teratogenic.[20]

Several other studies have been carried out on meclozine prompted by reports of fetal abnormalities in 10 patients associated with a preparation of meclozine and pyridoxine;[21] these studies have not supported the original reports.[22-24]

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16. Slone D, *et al.* Antenatal exposure to the phenothiazines in relation to congenital malformations, perinatal mortality rate, birth weight, and intelligence quotient score. *Am J Obstet Gynecol* 1977; 128: 486–8.
17. CSM. Data sheet change—Debendox. *Current Problems 6* 1981. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024436&RevisionSelectionMethod=LatestReleased (accessed 05/08/08)
18. FDA. Indications for Bendectin narrowed. *FDA Drug Bull* 1981; 11(1).
19. FDA. Determination that Bendectin was not withdrawn from sale for reasons of safety or effectiveness. Available at: http://www.fda.gov/OHRMS/DOCKETS/98fr/080999e.pdf (accessed 08/04/04)
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21. Watson GI. Meclozine ("Ancoloxin") and foetal abnormalities: preliminary report by the epidemic observation unit of the College of General Practitioners. *BMJ* 1962; ii: 1446.
22. Lenz W. How can the teratogenic action of a factor be established in man? *South Med J* 1971; 64 (suppl 1): 41–7.
23. Greenberg G, *et al.* Maternal drug histories and congenital abnormalities. *BMJ* 1977; 2: 853–6.
24. Shapiro S, *et al.* Meclizine in pregnancy in relation to congenital malformations. *BMJ* 1978; i: 483.

Interactions of Antihistamines

Sedating antihistamines may enhance the sedative effects of CNS depressants including alcohol, barbiturates, hypnotics, opioid analgesics, anxiolytic sedatives, and antipsychotics. Sedative interactions apply to a lesser extent with the *non-sedating antihistamines*; they do not appear to potentiate the effects of alcohol, but it should be avoided in excess.

Sedating antihistamines have an additive antimuscarinic action with other antimuscarinic drugs, such as atropine and some antidepressants (both tricyclics and MAOIs).

Potentially hazardous ventricular arrhythmias have occurred when the *non-sedating antihistamines* astemizole and terfenadine have been given with drugs liable to interfere with their hepatic metabolism, with other potentially arrhythmogenic drugs including those that prolong the QT interval, or with those likely to cause electrolyte imbalance. For full details see under Astemizole, p. 616.2, and Terfenadine, p. 641.1.

It has been suggested that some *sedating antihistamines* could mask the warning signs of damage caused by ototoxic drugs such as aminoglycoside antibacterials.

Antihistamines may suppress the cutaneous histamine response to allergen extracts (p. 2434.3) and should be stopped several days before skin testing. For the effect of antihistamines on histamine given exogenously, see p. 2525.3.

Acrivastine *(BAN, USAN, rINN)*

Acrivastin; Acrivastina; Acrivastinum; Akrivastiini; Akrivastin; BW-825C; Акривастин.

(*E*)-3-{6-[(*E*)-3-Pyrrolidin-1-yl-1-*p*-tolylprop-1-enyl]-2-pyridyl} acrylic acid.

$C_{22}H_{24}N_2O_2$=348.4

CAS — 87848-99-5.

ATC — R06AX18.

ATC Vet — QR06AX18.

UNII — A20F9XAI7W.

Uses and Administration

Acrivastine is a non-sedating antihistamine structurally related to triprolidine. It does not have any significant sedative or antimuscarinic actions. It is used for the symptomatic relief of allergic conditions such as rhinitis (p. 612.1) and various types of urticaria (p. 612.3) when it is given in oral doses of 8 mg up to three times daily. It is also used with a decongestant such as pseudoephedrine hydrochloride.

Adverse Effects and Precautions

As for the non-sedating antihistamines in general, p. 613.1 and p. 613.3, respectively. Acrivastine should be given with care in renal impairment; UK licensed product information recommends that it should not be given to patients with significant renal impairment, while product information in other countries, such as Switzerland for example, contra-indicates its use in those with a creatinine clearance of less than 50 mL/minute. Acrivastine should not be used in patients hypersensitive to triprolidine.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies acrivastine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Sedation. For a discussion of the sedative effects of antihistamines see p. 613.2.

Interactions

As for the non-sedating antihistamines in general, p. 614.3.

Pharmacokinetics

Acrivastine is well absorbed from the gastrointestinal tract and peak plasma concentrations occur in about 1.5 hours after oral use. The plasma half-life of acrivastine is about 1.5 hours and the drug does not appear to cross the blood-brain barrier to a significant extent. Acrivastine along with an active metabolite is excreted principally in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Semprex (欣民立); *Denm.*: Benadryl; *Fin.*: Benadryl; *Hong Kong*: Semprex†; *Ital.*: Semprex†; *Malaysia*: Semprex†; *Neth.*: Semprex; *Philipp.*: Semprex; *Rus.*: Semprex (Семпрекс); *S.Afr.*: Semprex; *Singapore*: Semprex; *Swed.*: Semprex†; *Switz.*: Semprex†; *Turk.*: Semprex; *UK*: Benadryl Allergy Relief.

Multi-ingredient Preparations. *Denm.*: Duact; *Fin.*: Duact; *Turk.*: Duact; *UK*: Benadryl Plus; *USA*: Semprex-D.

Alcaftadine *(USAN, rINN)*

Alcaftadina; Alcaftadinum; R-89674; Алкафтадин.

11-(1-Methylpiperidin-4-ylidene)-6,11-dihydro-5*H*-imidazo[2,1-*b*][3]benzazepine-3-carbaldehyde.

$C_{19}H_{21}N_3O$=307.4

CAS — 147084-10-4.

ATC — S01GX11.

ATC Vet — QS01GX11.

UNII — 7Z8O94ECSX.

Profile

Alcaftadine is an antihistamine (p. 610.1) that also inhibits the release of histamine from mast cells. It is used once daily, as an eye drop containing 0.25% of alcaftadine to prevent itching associated with allergic conjunctivitis in adults and children aged 2 years and over.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Lastacaft.

Alimemazine Tartrate *(BANM, rINNM)*

Alimemazina, tartrato de; Alimémazine, Tartrate d'; Alimemazini Tartras; Tartrato de alimemazina; Trimeprazine Tartrate; Алимемазина Тартрат.

NN-Dimethyl-2-methyl-3-(phenothiazin-10-yl)propylamine tartrate.

$(C_{18}H_{22}N_2S)_2C_4H_6O_6$=747.0

CAS — 84-96-8 (alimemazine); 4330-99-8 (alimemazine tartrate).

ATC — R06AD01.

ATC Vet — QR06AD01.

UNII — 362NW1LD6Z.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Alimemazine Hemitartrate). A white or very slightly yellowish powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in toluene. It deteriorates when exposed to air and light. A 2% solution in water has a pH of 5.0 to 6.5. Store in airtight containers. Protect from light.

USP 36: (Trimeprazine Tartrate). A white to off-white, odourless, crystalline powder. Soluble 1 in 2 of water, 1 in 20 of alcohol, 1 in 5 of chloroform, and 1 in 1800 of ether; very slightly soluble in benzene. Store in airtight containers. Protect from light.

Uses and Administration

Alimemazine, a phenothiazine derivative, is a sedating antihistamine with antiemetic activity and pronounced sedative effects. It also has some antimuscarinic actions. It is used mainly for the relief of urticaria (p. 612.3) and pruritus (p. 612.1); in the UK it is also licensed for pre-operative medication in children. Alimemazine may also be used in compound preparations for the symptomatic treatment of coughs (p. 611.2).

Alimemazine tartrate is given orally; doses in the UK are given as the amount of alimemazine tartrate, while those in some other countries are expressed in terms of the equivalent amount of alimemazine. Alimemazine tartrate 25 mg is equivalent to about 20 mg of alimemazine.

- The dose of alimemazine tartrate used for the relief of urticaria and pruritus in the *UK* is 10 mg two or three times daily; up to 100 mg daily has been given in refractory cases. Elderly patients are given 10 mg once or twice daily.
- Doses used in the *USA* have been lower, even allowing for them being expressed in terms of alimemazine. The usual dose was the equivalent of alimemazine 2.5 mg four times daily. However, it appears that proprietary preparations are no longer available in the USA.

For dosage in children, see below.

Administration in children. Alimemazine tartrate may be given to children to relieve urticaria and pruritus. In the UK, those over 2 years of age may be given 2.5 to 5 mg, orally, three or four times daily. Despite the view that alimemazine should not be given to younger children (see below), and although not licensed in the UK in this age group, the *BNFC* suggests that 250 micrograms/kg (maximum of 2.5 mg) three or four times daily may be given to children aged 6 months to 2 years, but only under specialist care.

The usual recommended dose in the UK for premedication in children aged 2 to 7 years is up to 2 mg/kg given orally about one to two hours before the procedure.

Anaesthesia. Alimemazine tartrate may be used for anaesthetic premedication (see p. 610.3) in children if the oral route is preferred to the more usual parenteral route of other phenothiazine antihistamines. Adverse effects have, however, been reported in children (see under Adverse Effects and Precautions, below), and in the UK alimemazine tartrate is not licensed for use in infants less than 2 years of age.

Insomnia. Antihistamines such as alimemazine tartrate have been used as alternatives to benzodiazepines for the short-term treatment of insomnia (p. 611.2), particularly for children. However, their antimuscarinic adverse effects may prove troublesome.

Regimens involving a short course of alimemazine tartrate in high dosage were tried in order to alter the sleep pattern of children with sleeping difficulties.[1,2] Adverse effects have, however, been reported in children (see under Adverse Effects and Precautions, below). The UK product is no longer indicated for short-term sedation in children and should not be used in infants less than 2 years of age.

1. Valman HB. ABC of 1 to 7 (revised): sleep problems. *BMJ* 1987; 294: 828–30.
2. Anonymous. What can be done for night waking in children? *Lancet* 1987; ii: 948–9.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively.

Children. There have been reports of adverse effects in children given alimemazine tartrate orally. Fatal malignant hyperthermia[1] and severe cardiovascular depression[2] have occurred after its use for premedication, and severe respiratory and CNS depression[3] after use as a postoperative sedative. Doses in these 3 reports ranged from 2.4 to 4.4 mg/kg. Although unconfirmed, a possible association between phenothiazine sedatives and sudden infant death syndrome has also been suggested (see Promethazine Hydrochloride, p. 639.1). Alimemazine tartrate is no longer licensed in the UK for short-term sedation in children and it is recommended that it should not be used in infants less than 2 years of age (but see Administration in children, above). The maximum recommended oral dose for premedication of children aged 2 to 7 years is 2 mg/kg. There has been a warning[4] that the use of alimemazine for deep sedation in diagnostic and therapeutic procedures in children is associated with prolonged drowsiness and that standards of monitoring, starvation, and postprocedural care should be similar to those with general anaesthesia.

1. Moyes DG. Malignant hyperpyrexia caused by trimeprazine. *Br J Anaesth* 1973; 45: 1163–4.
2. Loan WB, Cuthbert D. Adverse cardiovascular response to oral trimeprazine in children. *BMJ* 1985; 290: 1548–9.
3. Mann NP. Trimeprazine and respiratory depression. *Arch Dis Child* 1981; 56: 481–2.
4. Cray SH, Hinton W. Sedation for investigations: prolonged effect of chloral and trimeprazine. *Arch Dis Child* 1994; 71: 179.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies alimemazine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Pregnancy. For a discussion of the use of antihistamines in pregnancy, including studies involving phenothiazines, see p. 614.2.

Interactions

As for the sedating antihistamines in general, p. 614.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Vallergan; *Belg.*: Theralene; *Canad.*: Panectyl; *Fr.*: Theralene; *Irl.*: Vallergan; *Neth.*: Nedeltran; *Norw.*: Vallergan; *NZ*: Vallergan; *Rus.*: Teralligen (Тералиджен); *S.Afr.*: Vallergan; *Spain*: Variargil; *Swed.*: Theralen; *UK*: Vallergan.

Multi-ingredient Preparations. *Fr.*: Sirop Teyssedre†.

Pharmacopoeial Preparations

BP 2014: Alimemazine Tablets; Paediatric Alimemazine Oral Solution; Strong Paediatric Alimemazine Oral Solution;

USP 36: Trimeprazine Tartrate Syrup; Trimeprazine Tartrate Tablets.

Antazoline *(BAN, rINN)*

Antatsoliini; Antazolin; Antazolina; Antazolinum; Антазолин.

N-Benzyl-*N*-(2-imidazolin-2-ylmethyl)aniline.

$C_{17}H_{19}N_3$=265.4

CAS — 91-75-8.

ATC — R01AC04; R06AX05.

ATC Vet — QR01AC04; QR06AX05.

UNII — DHA8014SS1.

Antazoline Hydrochloride *(BANM, rINNM)*

Antatsoliinihydrokloridi; Antazolin hydrochlorid; Antazolina, hidrocloruro de; Antazoline, Chlorhydrate d'; Antazolin-hidroklorid; Antazolinhydrochlorid; Antazolinhydroklorid; Antazolini Hydrochloricum; Antazolini Hydrochloridum; Antazolinium Chloride; Antazolino hidrochloridas; Antazolinų chlorowodorek; Hidrocloruro de antazolina; Imidamine Hydrochloride; Phenazolinum; Антазолина Гидрохлорид.

$C_{17}H_{19}N_3$,HCl=301.8

CAS — 2508-72-7.

ATC — R01AC04; R06AX05.

ATC Vet — QR01AC04; QR06AX05.

UNII — FP8Q8F72JH.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Ph. Eur. 8: (Antazoline Hydrochloride). A white or almost white crystalline powder. Sparingly soluble in water; soluble in alcohol; slightly soluble in dichloromethane.

Antazoline Mesilate *(BANM, rINNM)*

Antazolina, mesilato de; Antazoline, Mésilate d'; Antazoline Mesylate; Antazoline Methanesulphonate; Antazolini Mesilas; Antazolinų mezylan; Imidamine Mesylate; Mesilato de antazolina; Антазолина Мезилат.

$C_{17}H_{19}N_3CH_3SO_3H$=361.5

CAS — 3131-32-6.

ATC — R01AC04; R06AX05.

ATC Vet — QR01AC04; QR06AX05.

UNII — KU470J7TY6.

Pharmacopoeias. In *Pol.*

Antazoline Phosphate *(BANM, rINNM)*

Antazolin Fosfat; Antazolina, fosfato de; Antazoline, Phosphate d'; Antazolini Phosphas; Fosfato de antazolina; Imidamine Phosphate; Антазолина Фосфат.

$C_{17}H_{19}N_3H_3PO_4$=363.4

CAS — 154-68-7.

ATC — R01AC04; R06AX05.

ATC Vet — QR01AC04; QR06AX05.

UNII — VP85FPH326.

Pharmacopoeias. In *US*.

USP 36: (Antazoline Phosphate). A white to off-white crystalline powder. Soluble in water; practically insoluble in ether and in benzene; sparingly soluble in methyl alcohol. pH of a 2% solution in water is between 4.0 and 5.0. Store in airtight containers.

Antazoline Sulfate *(BANM, rINNM)*

Antazolina, sulfato de; Antazoline, Sulfate d'; Antazoline Sulphate; Antazolini Sulfas; Imidamine Sulphate; Sulfato de antazolina; Антазолина Сульфат.

$(C_{17}H_{19}N_3)_2H_2SO_4.2H_2O$=664.8

CAS — 24359-81-7 (anhydrous antazoline sulfate).

ATC — R01AC04; R06AX05.

ATC Vet — QR01AC04; QR06AX05.

UNII — 6T74I07212.

NOTE. The above molecular formula is that provided in the *It. P.* Other sources give a molecular formula of $C_{17}H_{19}N_3.H_2SO_4$.

Pharmacopoeias. In *It.*

Uses and Administration

Antazoline, an ethylenediamine derivative, is an antihistamine used topically for the treatment of allergic conjunctivitis (p. 611.1). It is used as the hydrochloride, phosphate, or sulfate in eye drops, most commonly in a concentration of 0.5%; the mesilate has also been used. Antazoline salts are often used with a vasoconstrictor such as naphazoline hydrochloride or nitrate or xylometazoline hydrochloride.

The hydrochloride and sulfate salts of antazoline have been used topically for the treatment of minor skin irritations, but as with other antihistamines there is a risk of sensitisation. The hydrochloride has also been given orally.

Adverse Effects and Precautions

As for the antihistamines in general, p. 613.1 and p. 613.3, respectively.

Hypersensitivity. Reports of acute interstitial pneumonitis (with fever, rash, and dyspnoea)[1] and of immune thrombocytopenic purpura[2] were attributed to hypersensitivity reactions after the oral use of antazoline.

1. Pahissa A, *et al.* Antazoline-induced allergic pneumonitis. *BMJ* 1979; 2: 1328.
2. Nielsen JL, *et al.* Immune thrombocytopenia due to antazoline (Antistina). *Allergy* 1981; 36: 517–19.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Albalon-A; Antistine-Privine; Murine Allergy; ***Canad.***: Albalon-A; Refresh Eye Allergy Relief; Zincfrin-A†; ***Chile***: Bactopic Compuesto†; Nasomin; Oftalirio; Red Off Plus; Rinobanedif; Spersallerg; ***Cz.***: Sanorin-Analergin; Spersallerg; ***Denm.***: Ansal†; Antistina-Privin; Sesal; ***Ger.***: Allergopos N†; Antistin-Privin†; Spersallerg†; ***Gr.***: Spersallerg; Zincfrin-A; ***Hong Kong***: Spersallerg; Vista-Tone†; ***Hung.***: Spersallerg; ***Indon.***: Indofrin-A†; ***Irl.***: Otrivine-Antistin; RBC†; ***Ital.***: Antistin-Privina; ***Malaysia***: Alergoftal†; Napha A; Spersallerg; ***Mex.***: Midazol Oftено; Zincfrin-A; ***Norw.***: Spersallerg; ***NZ***: Otrivine-Antistin†; ***Philipp.***: Spersallerg; ***Pol.***: Dermophenazol; Oftophenazol; Rhinophenazol; Spersallerg; ***Port.***: Alergiftalmina; ***Rus.***: Sanorin-Analergin (Санорин-аналергин); Spersallerg (Сперсаллерг); ***S.Afr.***: Antistin-Privin; Covosan†; Gemini; Oculerge; Spersallerg; Zincfrin-A†; ***Singapore***: Antistin-Privin; Spersallerg; ***Spain***: Alergoftal; ***Swed.***: Antasten-Privin†; ***Switz.***: Antistin-Privin†; Spersallerg; ***Thai.***: Allergis; Antazallerge; Histaoph; Opsil-A; Spersallerg; ***Turk.***: Alergoftal; Sulfarhin; ***UK***: Otrivine-Antistin; ***Ukr.***: Sanorin-Analergin (Санорин-Аналергин); ***USA***: Antazoline-V; Genceye AC Allergy†; Vasocon-A.

Astemizole *(BAN, USAN, rINN)*

Astemitsoli; Astemizol; Astemizolas; Astémizole; Astemizolum; Asztemizol; MUD-30; Астемизол.

1-(4-Fluorobenzyl)-2-{[1-(4-methoxyphenethyl)-4-piperidyl]amino}benzimidazole.

$C_{28}H_{31}FN_4O$=458.6

CAS — 68844-77-9.

ATC — R06AX11.

ATC Vet — QR06AX11.

UNII — 7HU6337315.

NOTE. The code R-43512 has been used to describe both astemizole and its metabolite tecastemizole (norastemizole).

Pharmacopoeias. In *US.*

USP 36: (Astemizole). Store in airtight containers.

Uses and Administration

Astemizole, a piperidine derivative, is a non-sedating antihistamine with a very long duration of action. It does not have significant sedative or antimuscarinic actions. Astemizole has been used for the symptomatic relief of allergic conditions including rhinitis (p. 612.1) and conjunctivitis (p. 611.1), and skin disorders such as urticaria (p. 612.3). Preparations of astemizole have now been withdrawn from the market in most countries because of the risk of adverse effects.

Astemizole has been given in an oral dose of 10 mg once daily. This dose must not be exceeded because of the risk of cardiac arrhythmias with higher doses.

The active metabolite of astemizole, tecastemizole (norastemizole) has been investigated for the treatment of allergic rhinitis.

Adverse Effects and Precautions

As for the non-sedating antihistamines in general, p. 613.1 and p. 613.3, respectively. Increased appetite and weight gain have been reported with astemizole.

Ventricular arrhythmias, including torsade de pointes, have occurred rarely with astemizole, particularly with raised blood concentrations (see Arrhythmias below) and as a result the drug has been withdrawn from the market in most countries. To reduce the risk of developing such arrhythmias recommendations were that licensed doses should not be exceeded, and that it should be avoided in patients with cardiac or significant hepatic disease, with hypokalaemia or other electrolyte imbalance, or with known or suspected prolonged QT interval. Use with drugs liable to interfere with the hepatic metabolism of astemizole, other potentially arrhythmogenic drugs including those that prolong the QT interval, and drugs likely to cause electrolyte imbalance, is contra-indicated (see Interactions below).

Arrhythmias. Although severe life-threatening cardiovascular effects including torsade de pointes and other ventricular arrhythmias were initially reported mainly after substantial overdoses of astemizole, such reactions have also occurred rarely with doses as low as 20 to 30 mg daily and even as low as 10 mg daily in those with possible predisposing factors. There has been a report[1] of astemizole-induced torsade de pointes in a 15-year-old girl who claimed to have taken 10 mg daily for 10 weeks but pharmacokinetic data were more consistent with acute ingestion of higher doses. There have also been several reports of cardiotoxicity after accidental overdosage with astemizole in children.[2-4]

Recommendations were made by the UK CSM to reduce the risk of developing serious arrhythmias[5-7] (see Adverse Effects above for details); however, the drug has since been withdrawn in the UK and many other countries. It was considered that astemizole should be stopped immediately in patients who have syncope, and appropriate clinical evaluation including ECG monitoring instituted, because syncope has preceded or accompanied severe arrhythmias in some cases. Convulsions in patients taking astemizole may also be related to cardiovascular effects.[8]

Studies have suggested that astemizole induces ventricular arrhythmias by inhibiting cardiac potassium channels which results in prolongation of the QT interval, a risk factor for developing arrhythmias.[9] For further discussion, see p. 613.2.

1. Simons FER, *et al.* Astemizole-induced torsade de pointes. *Lancet* 1988; ii: 624.
2. Hoppu K, *et al.* Accidental astemizole overdose in young children. *Lancet* 1991; 338: 538–40.
3. Tobin JR, *et al.* Astemizole-induced cardiac conduction disturbances in a child. *JAMA* 1991; 266: 2737–40.
4. Wiley JF, *et al.* Cardiotoxic effects of astemizole overdose in children. *J Pediatr* 1992; 120: 799–802.
5. CSM. Ventricular arrhythmias due to terfenadine and astemizole. *Current Problems 35* 1992. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024453&RevisionSelectionMethod=LatestReleased (accessed 14/07/08)
6. CSM/MCA. Drug-induced prolongation of the QT interval. *Current Problems* 1996; 22: 2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024458&RevisionSelectionMethod=LatestReleased (accessed 14/07/08)
7. CSM/MCA. Astemizole (Hismanal): only available on prescription. *Current Problems* 1999; 25: 2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023233&RevisionSelectionMethod=LatestReleased (accessed 19/05/06)
8. Clark A, Love H. Astemizole-induced ventricular arrhythmias: an unexpected cause of convulsions. *Int J Cardiol* 1991; 33: 165–7.
9. Rankin AC. Non-sedating antihistamines and cardiac arrhythmia. *Lancet* 1997; 350: 1115–16.

Overdosage. Severe cardiac events have been associated with astemizole overdosage (see Arrhythmias, above); management is mainly supportive. The absorption of astemizole from the gastrointestinal tract can be prevented by giving activated charcoal[1] but because astemizole is rapidly absorbed it would need to be given as soon as possible after poisoning. Haemodialysis does not appear to increase the clearance of astemizole.

1. Laine K, *et al.* The effect of activated charcoal on the absorption and elimination of astemizole. *Hum Exp Toxicol* 1994; 13: 502–5.

Sedation. For discussion of the sedative effects of antihistamines see p. 613.2.

Interactions

As for the non-sedating antihistamines in general, p. 614.3.

Astemizole should not be given with drugs that inhibit its hepatic metabolism because of the increased risk of serious ventricular arrhythmias. These drugs include the imidazole and triazole antifungals such as ketoconazole and itraconazole, and the macrolide antibacterials clarithromycin, erythromycin, troleandomycin, and possibly other macrolides. Others, similarly to terfenadine (p. 641.1), may include serotonin reuptake inhibitors, HIV-protease inhibitors, NNRTIs, and zileuton. The metabolism of astemizole may also be inhibited by grapefruit juice and use together should be avoided.

Use with other potentially arrhythmogenic drugs (including those that prolong the QT interval) such as antiarrhythmics, tricyclic antidepressants, the antimalarials halofantrine and quinine, antipsychotics, cisapride, and the beta blocker sotalol should be avoided, as should diuretics that cause electrolyte imbalances such as hypokalaemia. The use of terfenadine and astemizole together is not recommended.

Pharmacokinetics

Absorption of astemizole from the gastrointestinal tract is rapid and is reduced by food. First-pass metabolism is extensive, therefore plasma concentrations of unchanged drug are very low. The plasma concentration of astemizole plus metabolites takes about 4 to 8 weeks to reach steady state. The metabolism of astemizole is mediated through the cytochrome P450 enzyme system by the isoenzymes CYP3A4, CYP2D6, and CYP2A6. The elimination half-life of astemizole and its metabolites at steady state is about 19 days. Unchanged astemizole is highly bound to plasma proteins and does not appear to cross the blood-brain barrier to a significant extent. Desmethylastemizole, the major metabolite of astemizole, has histamine H_1-receptor-blocking activity; tecastemizole (norastemizole) is another active metabolite. The metabolites of astemizole are excreted slowly in the urine and faeces, and undergo enterohepatic recycling. Virtually none of an oral dose is excreted as unchanged drug.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Leanimol; Maxirgot; Mibiron; Tulipe-R; Tyrenol; Varivenot; Waruzol; ***India***: Acemiz; Acipax; Alerzole; Astelong; Astizole†; Stemiz; ***Mex.***: Alerfur†; Alerken; Alermi; Aleztem†; Anerzol†; Antagon 1†; Astemina†; Astesen; Aztemin†; Aztil†; Aztrolen; Biostan; Dexodin†; Emdar†; Emizol†; Farmidal S; Fustermizol†; Histalino; Histaser; Novasten; Practizol†; Urtigen†.

Pharmacopoeial Preparations

USP 36: Astemizole Tablets.

Azatadine Maleate *(BANM, USAN, rINNM)*

Atsatadiinimaleaatti; Azatadina, maleato de; Azatadine, Maléate d'; Azatadini Maleas; Azatadinmaleat; Maleato de azatadina; Sch-10649; Азатадина Малеат.

6,11-Dihydro-11-(1-methyl-4-piperidylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine dimaleate.

$C_{30}H_{22}N_2.2C_4H_4O_4$=522.6

CAS — 3964-81-6 (azatadine); 3978-86-7 (azatadine maleate).

ATC — R06AX09.

ATC Vet — QR06AX09.

UNII — F3Q391WTX7.

Pharmacopoeias. In *US.*

USP 36: (Azatadine Maleate). A white to light cream-coloured, odourless powder. Freely soluble in water, in alcohol, in chloroform, and in methyl alcohol; practically insoluble in ether and in benzene.

Profile

Azatadine maleate is a piperidine derivative closely related to cyproheptadine. It is a sedating antihistamine (p. 610.1) with a long duration of action; it also has antimuscarinic and antiserotonin properties.

Azatadine maleate has been used for the symptomatic relief of allergic conditions including rhinitis (p. 612.1) and urticaria (p. 612.3); it was also used for other pruritic skin disorders as well as reactions to insect bites and stings. It has been given in usual oral doses of 1 mg twice daily; if necessary 2 mg twice daily has been used. For children's doses, see below. Azatadine has also been used with a decongestant such as pseudoephedrine sulfate.

Administration in children. Children aged 6 to 12 years have been given 0.5 to 1 mg azatadine maleate, orally, twice daily for the symptomatic relief of allergic conditions including rhinitis and urticaria.

Extrapyramidal effects. An acute dystonic reaction was reported in a patient who had taken azatadine maleate

20 to 30 mg orally over a 24-hour period.[1] The condition was reversed by intravenous injection of benzatropine 2 mg.

1. Joske DJL. Dystonic reaction to azatadine. *Med J Aust* 1984; **141**: 449.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Zadine†; ***Canad.***: Optimine†; ***Gr.***: Nalomet.

Multi-ingredient Preparations. ***Braz.***: Cedrin; ***Gr.***: Nalomet-D.

Pharmacopoeial Preparations
USP 36: Azatadine Maleate Tablets.

Azelastine Hydrochloride

(BANM, USAN, rINNM)

A-5610 (azelastine or azelastine hydrochloride); Atselastiini-hydrokloridi; Azelastin Hidroklorür; Azelastina, hidrocloruro de; Azélastine, chlorhydrate d'; Azelastinhydrochlorid; Azelastin-hydrochlorid; Azelastinhydrokloríd; Azelastini hydrochloridum; Azelastino hidrochloridas; E-0659 (azelastine or azelastine hydrochloride); Hidrocloruro de azelastina; W-2979M (azelastine or azelastine hydrochloride); Азеластина Гидрохлорид.

4-(*p*-Chlorobenzyl)-2-(hexahydro-1-methyl-1*H*-azepin-4-yl)-1(2*H*)-phthalazinone monohydrochloride.

$C_{22}H_{24}ClN_3O,HCl$=418.4

CAS — 58581-89-8 (azelastine); 79307-93-0 (azelastine hydrochloride).

ATC — R01AC03; R06AX19; S01GX07.

ATC Vet — QR01AC03; QR06AX19; QS01GX07.

UNII — 0L591QR10I.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.*

Ph. Eur. 8: (Azelastine Hydrochloride). A white or almost white, crystalline powder. Sparingly soluble in water; soluble in dehydrated alcohol and in dichloromethane.

Uses and Administration

Azelastine hydrochloride is an antihistamine that, in addition to its histamine H_1-receptor-blocking activity, appears to inhibit the release of inflammatory mediators from mast cells. It is used topically in the symptomatic relief of allergic conditions including rhinitis (p. 612.1) and conjunctivitis (p. 611.1). It is also used in the treatment of non-allergic rhinitis.

In the treatment of allergic **rhinitis** in adults and children aged 5 years and over, the usual dose in the UK is 140 micrograms of azelastine hydrochloride by nasal spray into each nostril twice daily. In the USA, however, 1 or 2 sprays of a similar preparation (supplying 137 micrograms per spray) may be given into each nostril twice daily in adults; children aged 5 to 12 years may be given 1 spray into each nostril twice daily. In the USA, azelastine is also licensed for the treatment of non-allergic rhinitis in adults and children aged 12 years and over. The dose is 2 sprays (274 micrograms) into each nostril twice daily. Also available in the USA is a nasal preparation supplying 205.5 micrograms of azelastine hydrochloride per spray. It may be given in a dose of 1 or 2 sprays per nostril twice daily or 2 sprays once daily for the treatment of allergic rhinitis in adults and children aged 12 years and over.

In the management of **conjunctivitis**, azelastine is licensed in the UK for the treatment and prophylaxis of seasonal allergic conjunctivitis in adults and children aged 4 years and over and for the treatment of perennial allergic conjunctivitis in adults and children aged 12 years and over. In the USA, it is licensed for the treatment of allergic conjunctivitis in adults and children aged 3 years and over. Regardless of the age and indication, a 0.05% solution is instilled into each eye twice daily; this may be increased to four times daily in severe conditions.

Azelastine hydrochloride has also been given orally.

References.

1. Lenhard G, *et al.* Double-blind, randomised, placebo-controlled study of two concentrations of azelastine eye drops in seasonal allergic conjunctivitis or rhinoconjunctivitis. *Curr Med Res Opin* 1997; **14**: 21–8.
2. Sabbah A, Marzetto M. Azelastine eye drops in the treatment of seasonal allergic conjunctivitis or rhinoconjunctivitis in young children. *Curr Med Res Opin* 1998; **14**: 161–70.
3. Duarte C, *et al.* Treatment of severe seasonal rhinoconjunctivitis by a combination of azelastine nasal spray and eye drops: a double-blind, double-placebo study. *J Investig Allergol Clin Immunol* 2001; **11**: 34–40.
4. Canonica GW, *et al.* Topical azelastine in perennial allergic conjunctivitis. *Curr Med Res Opin* 2003; **19**: 321–9.
5. Lee TA, Pickard AS. Meta-analysis of azelastine nasal spray for the treatment of allergic rhinitis. *Pharmacotherapy* 2007; **27**: 852–9.
6. Bernstein JA. Azelastine hydrochloride: a review of pharmacology, pharmacokinetics, clinical efficacy and tolerability. *Curr Med Res Opin* 2007; **23**: 2441–52.
7. Lee C, Corren J. Review of azelastine nasal spray in the treatment of allergic and non-allergic rhinitis. *Expert Opin Pharmacother* 2007; **8**: 701–9.
8. Anonymous. Azelastine (Astepro) nasal spray for allergic rhinitis. *Med Lett Drugs Ther* 2009; **51**: 29–30.

Administration in children. Doses of azelastine hydrochloride in children are similar to those used in adults (see above).

Adverse Effects and Precautions

As for the antihistamines in general, p. 613.1 and p. 613.3, respectively.

When given intranasally, irritation of the nasal mucosa and taste disturbances have been reported; somnolence, headache, and dry mouth have also been noted in some patients. Taste disturbance can occur after use in the eye.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies azelastine as possibly porphyrinogenic when given intranasally; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients. It is considered non-porphyrinogenic when used in eye preparations.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Pharmacokinetics

About 40% of an intranasal dose of azelastine reaches the systemic circulation. Elimination is via hepatic metabolism with excretion mainly in the faeces.

Azelastine is rapidly and almost completely absorbed when given *orally* and peak plasma concentrations occur in 4 to 5 hours. Azelastine undergoes hepatic metabolism; the major metabolite, demethylazelastine, has antihistamine activity. The elimination half-life of azelastine is about 25 hours, increasing to 35.5 hours after multiple oral doses, possibly as a result of accumulation of the demethyl metabolite. Azelastine and its metabolites are excreted mainly in the faeces and also in urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Alager; Allergodil; Brixia; Xanaes; ***Austral.***: Azep; Eyezep; ***Austria***: Allergodil; Allergospray; ***Belg.***: Allergodil; Otrivine Anti-Allergie; ***Braz.***: Rino-Lastin; ***Chile***: AZ Ofteno; Brixia; ***China***: Azep (爱赛平); Fu Di (芙迪); Min Qi (敏奇); Xin Bai Ke (新百克); ***Cz.***: Allergodil; ***Denm.***: Allergodil; ***Fin.***: Lastin; Oculastin; ***Fr.***: Allergodil; Proallergodil; Prorhinite†; ***Ger.***: Allergodil; Vividrin akut Azelastin; ***Gr.***: Afluon; ***Hong Kong***: Azep; ***Hung.***: Allergodil; ***India***: Arzep; Azelast; Azep; Oculast; ***Irl.***: Optilast; Rhinolast; ***Israel***: Optilast; Rhinolast; ***Ital.***: Allergodil; Lasticom; ***Jpn***: Azeptin; ***Mex.***: Amsler; Astelin; AZ Ofteno; ***Neth.***: Allergodil; Oculastin; Otrivin neusallergie azelastine; ***Norw.***: Azelvin†; Lastin; ***NZ***: Eyezep; ***Philipp.***: Azela; Azelone; Azep; ***Pol.***: Allergodil; ***Port.***: Allergodil; Azep; Oculastin; ***Rus.***: Allergodil (Аллерголил); ***S.Afr.***: Optilast; Rhinolast; ***Singapore***: Azep; ***Spain***: Afluon; Corifina; ***Swed.***: Azelvin†; Lastin; ***Switz.***: Allergodil; Otrivin rhume des foins; ***Turk.***: Allergodil; ***UK***: Aller-Eze; Optilast; Rhinolast; ***Ukr.***: Allergodil (Аллерголил); ***USA***: Astelin; Astepro; Optivar; ***Venez.***: Alergot; Allergodil; AZ; Brixia.

Multi-ingredient Preparations. ***Fin.***: Dymista; ***India***: Azeflo; Duonase; Nezalast; ***UK***: Dymista; ***USA***: Dymista.

Bamipine *(BAN, rINN)*

Bamipilini; Bamipin; Bamipina; Bamipinum; Бамипин.

N-Benzyl-*N*-(1-methyl-4-piperidyl)aniline.

$C_{19}H_{24}N_2$=280.4

CAS — 4945-47-5.

ATC — D04AA15; R06AX01.

ATC Vet — QD04AA15; QR06AX01.

UNII — Y6BHZ28O92.

Profile

Bamipine is a sedating antihistamine (p. 610.1) with pronounced sedative effects.

Bamipine and its salts have been used mainly for the symptomatic relief of allergic conditions such as urticaria (p. 612.3) and in pruritic skin disorders. Bamipine hydrochloride has been given orally; bamipine, bamipine lactate, and bamipine salicylate have all been applied topically.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Soventol; ***Ger.***: Soventol; ***Gr.***: Soventol; ***Neth.***: Soventol; ***Pol.***: Soventol.

Multi-ingredient Preparations. ***India***: Multifungin H.

Bepotastine *(USAN, rINN)*

Bepotastina; Bépotastine; Bepotastinum; Betotastine; Беротастин.

(+)-4-[[(*S*)-*p*-Chloro-α-2-pyridylbenzyl]oxy]-1-piperidinebutyric acid.

$C_{21}H_{25}ClN_2O_3$=388.9

CAS — 125602-71-3; 190786-43-7.

UNII — HYD2U48IAS.

Bepotastine Besilate *(rINNM)*

BB; Bépotastine, Bésilate de; Bepotastine Besylate (USAN); Bepotastini Besilas; Besilato de bepotastina; Betotastine Besilate; TAU-284; Беротастина Безилат.

$C_{21}H_{25}ClN_2O_3$, $C_6H_6O_3S$=547.1

CAS — 190786-44-8.

UNII — 6W18MO1QR3.

Profile

Bepotastine is an antihistamine (p. 610.1) used as the besilate in the treatment of allergic rhinitis and for the symptomatic relief of urticaria and pruritic skin disorders. The usual oral dose is 10 mg of bepotastine besilate twice daily.

Bepotastine besilate is also used in the treatment of allergic conjunctivitis in adults and children aged 2 years and over; a 1.5% solution is instilled into each affected eye twice daily.

Reviews.

1. Lyseng-Williamson KA. Oral bepotastine: in allergic disorders. *Drugs* 2010; **70**: 1579–91.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Talion (坦亮); ***Jpn***: Talion; ***USA***: Bepreve.

Bilastine *(rINN)*

Bilastina; Bilastinum; Биластин.

p-(2-[4-[1-(2-Ethoxyethyl)-2-benzimidazolyl]piperidino)ethyl)-α-methylhydratropic acid.

$C_{28}H_{37}N_3O_3$=463.6

CAS — 202189-78-4.

ATC — R06AX29.

ATC Vet — QR06AX29.

UNII — PA1123N395.

Profile

Bilastine is a long-acting non-sedating antihistamine (p. 610.1). It is used in the symptomatic treatment of allergic rhinitis, conjunctivitis, and urticaria. An oral dose of 20 mg is given once daily, at least 1 hour before or 2 hours after food.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Bellozal; ***Cz.***: Xados; ***Fin.***: Revitelle; ***Fr.***: Bilaska; Inorial; ***Irl.***: Drynol; ***Ital.***: Olisir; Robilas; ***Port.***: Bilaxten; ***Spain***: Bilaxten; Ibis; Obalix; ***Switz.***: Bilaxten; ***UK***: Ilaxten.

Bisulepin

Бисулепин.

4-[3-(Dimethylamino)propylidene]-4,9-dihydrothieno[2,3-*b*]benzo[*e*]thiepin.

$C_{17}H_{19}NS_2$=301.5

CAS — 5802-61-9 (bisulepin); 1154-12-7 (bisulepin hydrochloride).

UNII — 595726R32U.

Profile

Bisulepin is given orally as an antihistamine; the hydrochloride salt is used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Dithiaden.

Bromazine Hydrochloride *(BANM, rINNM)*

Bromazina, hidrocloruro de; Bromazine, Chlorhydrate de; Bromazini Hydrochloridum; Bromodiphenhydramine Hydro-

chloride; Hidrocloruro de bromazina; Бромазина Гидрохлорид.
2-(4-Bromobenzhydryloxy)-*NN*-dimethylethylamine hydrochloride.
$C_{17}H_{20}BrNO,HCl$=370.7
CAS — 118-23-0 (bromazine); 1808-12-4 (bromazine hydrochloride).
ATC — R06AA01.
ATC Vet — QR06AA01.
UNII — 2021683U97.

Pharmacopoeias. In *US.*

USP 36: (Bromodiphenhydramine Hydrochloride). A white to pale buff-coloured, crystalline powder having no more than a faint odour. Soluble 1 in less than 1 of water, 1 in 2 of alcohol and of chloroform, 1 in 3500 of ether, and 1 in 31 of isopropyl alcohol; insoluble in petroleum spirit. Store in airtight containers.

Profile

Bromazine hydrochloride, a monoethanolamine derivative, is a sedating antihistamine (p. 610.1) with antimuscarinic and marked sedative actions. It has been used in combination preparations for the symptomatic treatment of coughs and the common cold.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *USA:* Ambenyl Cough Syrup†; Amgenal Cough†; Bromotuss with Codeine†.

Pharmacopoeial Preparations
USP 36: Bromodiphenhydramine Hydrochloride and Codeine Phosphate Oral Solution; Bromodiphenhydramine Hydrochloride Elixir.

Brompheniramine Maleate

(BANM, rINNM)

Bromfeniramin Maleat; Bromfeniramina, maleato de; Brómfeniramin-maleát; Bromfeniraminmaleat; Bromfeniramin-maleinát; Bromfeniramino maleatas; Bromifeniramiini-maleaatti; Bromphéniramine, Maléate de; Brompheniramini Maleas; Brompheniraminmaleat; Maleato de bromfeniramina; Parabromdylamine Maleate; Бромфенирамина Малеат.
(±)-3-(4-Bromophenyl)-*NN*-dimethyl-3-(2-pyridyl)propylamine hydrogen maleate.
$C_{16}H_{19}BrN_2,C_4H_4O_4$=435.3
CAS — 86-22-6 (brompheniramine); 980-71-2 (brompheniramine maleate).
ATC — R06AB01.
ATC Vet — QR06AB01.
UNII — IXA7C9ZN03.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Brompheniramine Maleate). A white or almost white, crystalline powder. Soluble in water; freely soluble in alcohol, in dichloromethane, and in methyl alcohol. A 1% solution in water has a pH of 4.0 to 5.0. Protect from light.

USP 36: (Brompheniramine Maleate). A white, odourless, crystalline powder. Soluble 1 in 5 of water, 1 in 15 of alcohol and of chloroform; slightly soluble in ether and in benzene. pH of a 1% solution in water is between 4.0 and 5.0. Store in airtight containers. Protect from light.

Incompatibility. Brompheniramine maleate has been reported to be incompatible with some amidotrizoate, adipiodone, and iotalamate salts.

Dexbrompheniramine Maleate

(BANM, rINNM)

Dexbromfeniramina, maleato de; Dexbromphéniramine, Maléate de; Dexbrompheniramini Maleas; Maleato de dexbromfeniramina; Дексбромфенирамина Малеат.
CAS — 2391-03-9.
ATC — R06AB06.
ATC Vet — QR06AB06.
UNII — BPA9UT29BS.

Pharmacopoeias. In *US.*

USP 36: (Dexbrompheniramine Maleate). A white, odourless, crystalline powder. It exists in two polymorphic forms, one melting between 106 degrees and 107 degrees, and the other between 112 degrees and 113 degrees; a mixture of the two forms may melt between 105 degrees and 113 degrees. Soluble 1 in 1.2 of water, 1 in 2.5 of alcohol, 1 in 2 of chloroform, and 1 in 3000 of ether. pH of a 1% solution in water is about 5. Store in airtight containers. Protect from light.

Uses and Administration

Brompheniramine maleate, an alkylamine derivative, is a sedating antihistamine with antimuscarinic and moderate sedative actions.

Brompheniramine is a racemic mixture; dexbrompheniramine, the dextrorotatory isomer, has about twice the activity of brompheniramine by weight. Brompheniramine maleate and dexbrompheniramine maleate are used for the symptomatic relief of allergic conditions, mainly rhinitis (p. 612.1) and conjunctivitis (p. 611.1). They are common ingredients of compound preparations for the symptomatic treatment of coughs and the common cold (p. 611.2). Brompheniramine tannate has been used similarly.

Brompheniramine maleate is given in usual oral doses of 4 mg every four to six hours. It has also been given by subcutaneous, intramuscular, or slow intravenous injection.

Dexbrompheniramine maleate is normally given as an ingredient of decongestant preparations containing pseudoephedrine. The dose of dexbrompheniramine maleate in these oral combinations is 6 mg no more than twice daily.

Modified-release oral preparations of brompheniramine maleate or dexbrompheniramine maleate are available in some countries; dosage is specific to a particular formulation.

For dosage in children, see below.

Administration in children. Brompheniramine maleate may be given orally to children, for the symptomatic relief of allergic conditions such as rhinitis and conjunctivitis; doses are as follows:

- children aged 2 to 6 years: 1 mg every four to six hours
- those aged 6 to 12 years: 2 mg every four to six hours
- those aged over 12 years: 4 mg every four to six hours

Brompheniramine maleate is a common ingredient of compound preparations for the symptomatic treatment of coughs and the common cold. However, such preparations should be used with caution in children, and generally avoided in young children, for details see p. 614.1.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively.

Breast feeding. The American Academy of Pediatrics[1] states that, although usually compatible with breast feeding, preparations used by breast-feeding mothers which contain dexbrompheniramine maleate with pseudoephedrine have resulted in crying, irritability, and poor sleep patterns in the infant.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/04/04)

Effects on the blood. Agranulocytosis in a 34-year-old alcoholic man was possibly associated with brompheniramine therapy.[1]

1. Hardin AS, Padilla F. Agranulocytosis during therapy with a brompheniramine-medication. *J Arkansas Med Soc* 1978; 75: 206–8.

Extrapyramidal disorders. Facial dyskinesias have been reported[1,2] after use of antihistamines including brompheniramine or dexbrompheniramine maleate.

1. Thach BT, *et al.* Oral facial dyskinesia associated with prolonged use of antihistaminic decongestants. *N Engl J Med* 1975; 293: 486–7 (brompheniramine maleate, chlorpheniramine maleate, and phenindamine tartrate).
2. Barone DA, Raniolo J. Facial dyskinesia from overdose of an antihistamine. *N Engl J Med* 1980; 303: 107 (dexbrompheniramine maleate).

Withdrawal. Withdrawal symptoms have been reported[1] after stopping long-term therapy with brompheniramine maleate. A patient had been taking 48 mg almost every day for 20 years and developed tremor, nausea, depression, and apyrexial sweating within 48 hours of stopping treatment; symptoms resolved over the following weeks.

1. Kavanagh GM, *et al.* Withdrawal symptoms after discontinuation of long-acting brompheniramine maleate. *Br J Dermatol* 1994; 131: 913–14.

Interactions

As for the sedating antihistamines in general, p. 614.3.

Pharmacokinetics

Brompheniramine maleate appears to be well absorbed from the gastrointestinal tract after oral doses and peak plasma concentrations occur within about 5 hours. An elimination half-life of about 25 hours has been reported. Unchanged drug and metabolites are excreted mainly in the urine.

References.

1. Simons FER, *et al.* The pharmacokinetics and antihistaminic effects of brompheniramine. *J Allergy Clin Immunol* 1982; 70: 458–64.
2. Paton DM, Webster DR. Clinical pharmacokinetics of H_1-receptor antagonists (the antihistamines). *Clin Pharmacokinet* 1985; 10: 477–97.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.:* Dimegan; *Gr.:* Dimetane; *Hong Kong:* Bromiton†; *Malaysia:* Bomex; *Singapore:* Bomex; *Thai.:* Babycold†; Bomine; Bromma; Brompheh; Bromsir; Dimetane†; Probrom; *USA:* Alahist IR; Bidhist†; J-Tan; Lodran 12†; Lodrane 24†; Oraminic II; P-Tex†.

Multi-ingredient Preparations. *Arg.:* Factus; *Austral.:* Dimetapp DM; Dimetapp; *Braz.:* Bialerge; Decongex Plus; Dimetapp; Winter AP; *Canad.:* Cold And Allergy Liquid†; Cold Syrup; Dimetane Expectorant C; Dimetane Expectorant DC; Dimetapp Chewables for Kids; Dimetapp Cold†; Dimetapp DM Cough Cold; Dimetapp-C; Dimetapp; DM Cough and Cold; Drixoral Day/Night†; Drixoral; Drixtab†; Extra Strength Cold Syrup; Extra Strength DM Cough and Cold; Oral Infant Cold Drops; *China:* Cofetol (奥孚); Neosed (尔可适); Rhinobol (尔可安); *Cz.:* Disophrol; *Gr.:* Dimetapp New; Dimetapp; Disofrin; *Hong Kong:* America†; B.P.P.†; BPP Cough Syrup†; Brom-PP; Brom-Ramine Compound; Bromphenex†; DF Multi-Symptom; Dimeta-2; Dimetapp; Drixoral†; Eascold; Eurotapp; Fastolin; Fludane†; Futalin†; Futara†; Mecostop†; Unihist; Vidatapp Forte†; Vidatapp†; *Indon.:* Alco Plus DMP; Alco Plus; Drixora; *Irl.:* Dimotane Co†; Ilvico; *Malaysia:* Rinafort; Unihist; *Mex.:* Afrinex†; Cripofen; Dimetapp; Sedalmerck Flu; *NZ:* Dimetapp DM Cold & Cough; Dimetapp; *Philipp.:* Bromitapp; Dimerrin; *Dimetapp;* DMT; Hisdec; *Nasatapp;* Nosterol†; Pediatapp; Perbrosol; PPB; Remedril; Rhinodec; Rhinotapp; Snizeec; Solvamin; Zeditapp; *Pol.:* Disophrol†; NeoAfrin; *Port.:* Constipal†; Ilvico N; *S.Afr.:* Dimetapp†; Ilvico†; *Singapore:* Dimetapp; Rinafor; *Spain:* Disofrol; Ilvico; *Swed.:* Disofrol†; *Switz.:* Disofrol; *Thai.:* Aorinyl; Asiatapp; Bepeno-G; Bepeno; Bluco; Bromavon†; Bromceryl; Bromesep Elixir; Bromesep Expectorant; Bromesep Syrup; Bromiphed; Bromlamine; Bromped; Bromsunol; Bromtussia DC†; Bromtussia; Brontus; Centapp; Chintacold; Cold-tab; Coldate; Cotapp Expectorant; Cotapp; Daminate; Decon; Dimetapp; Ditap; Leffrin; Meditapp Expectorant†; Medtapp; MEXY; Minra; Nartap; Nased; Nasorest Expectoran; Nasorest; Nasotane; Nasotapp; Pharcold; Pharfed; Phemin; Polamine; Polydine; Polydrop; Postap Expectorant†; Postap; Rhinadine†; Sinufen; St Luke's Cold; Topamine; Unihist; *Turk.:* Disophrol; *UK:* Dimotane Co; Dimotane Expectorant; *USA:* 12 Hour Antihistamine Nasal Decongestant; 12 Hour Cold; Accuhist DM Pediatric; Accuhist PDX†; Alacol DM†; Alahist DM; Allent; Anaplex DM; Anaplex HD†; B-Vex PD; Balacall DM; BP New Allergy DM†; BPM PE DM; Brofed; Brohist D; Brom/PE/DM; Bromadine-DM; Bromaline DM†; Bromaline†; Bromarest DX; Bromatan-DM†; Bromatane DX; Bromdex D; Bromfed-DM; Bromfed-PD; Bromfed; Bromhist PDX†; Bromhist PDX; Bromhist-DM†; Bromhist-NR†; Bromhist†; Bromphen DX Cough; Brompheniramine Cough; Brompheniramine/Pseudoephedrine DM; Brotapp DM; Brotapp; Brovex ADT†; BroveX CB†; BroveX CBX†; BroveX PB C†; BroveX PB CX†; BroveX PB DM†; Brovex PB†; Brovex PD†; Brovex PEB DM; BroveX PEB; BroveX PSB DM; BroveX PSB; BroveX PSE DM; BroveX PSE; C-Tan D†; Carbodex DM; Cenhist; Childrens Dimaphen DM Cold & Cough; Coldec DM; Comtrex Acute Head Cold; Conex Cold & Allergy†; CPB WC; Cytuss-HC NR†; Dallergy DM†; DEKA; Dexaphen-SA; Dicel CD; Dimetane DX†; Dimetapp Childrens Cough & Cold; Dimetapp Cold & Fever; Dimetapp DM; Dimetapp Nighttime Flu; Dimetapp; Disobrom; Disophrol; DM/PSE/BPM; Dristan Allergy; Dristan Cold Maximum Strength Multi-symptom Formula; Drixoral Cold & Allergy; Drixoral Cold & Flu; Drixoral Plus; *Drixoral;* Drocon-CS; Endal-Cof-AC; EndaCof-DH†; Endafed; Histacol DM†; Histussin HC; Iofed; J-COF DHC; J-Tan D HC†; J-Tan D†; Lodrane 12D; Lodrane D; Lodrane†; LoHist PEB DM; LoHist PEB; LoHist PS 3; LoHist-DM; M-End Max D; M-End PE; M-END WC; Mar-Cof BP; Maximum Strength Dristan Cold; Mesehist WC; Myphetane DX†; Nalex AC; Neo DM; P-Hist DM; Panatuss DXP; PB M Allergy†; Pediahist DM†; Pediahist DM; Phenylephrine Complex; Poly-Tussin AC; Poly-Tussin DHC; Q-Tapp DM; Relhist; Respahist-II†; Respahist†; Resperal-DM†; Rondamine-DM; Rondec†; Rynex PE; Seradex-LA†; Sildec-DM; Sinadrin PE; Sinadrin Plus; Sinuhist†; SymPak II; Tanabid†; TG PSE/BRM/DM; TGQ PEH/BRM/DM; TGQ PSE/BRM/DM; TL-Hist DM; Touro A & H; Touro Allergy†; Trexbrom; Tusdec-DM†; Tusnel-HC†; Tussall; ULTRAbrom†; V-Cof; Vazobid PD; VaZol-D†; Vazotab†; Vazotan; Vazotuss HC†; Zotex-PE†; *Venez.:* Dimetapp; Ilvico; Ilvico; Metorfedrin.

Pharmacopoeial Preparations
BP 2014: Brompheniramine Tablets;
USP 36: Brompheniramine Maleate Elixir; Brompheniramine Maleate Injection; Brompheniramine Maleate Tablets; Dexbrompheniramine Maleate and Pseudoephedrine Sulfate Oral Solution.

Buclizine Hydrochloride *(BANM, USAN, rINNM)*

Buclizina, hidrocloruro de; Buclizine, Chlorhydrate de; Buclizini Hydrochloridum; Buklizin Hidroklorür; Hidrocloruro de buclizina; NSC-25141; UCB-4445; Буклизина Гидрохлорид.
(*RS*)-1-(4-*tert*-Butylbenzyl)-4-(4-chlorobenzhydryl)piperazine dihydrochloride.

$C_{28}H_{33}ClN_2.2HCl$=506.0
CAS — 82-95-1 (buclizine); 129-74-8 (buclizine hydrochloride).
ATC — R06AE01.
ATC Vet — QR06AE01.
UNII — 58FQD093NU.

Pharmacopoeias. In *Br.*

BP 2014: (Buclizine Hydrochloride). A white or slightly yellowish, crystalline powder. Practically insoluble in water; very slightly soluble in alcohol; sparingly soluble in chloroform and in propylene glycol.

Uses and Administration

Buclizine hydrochloride, a piperazine derivative, is a sedating antihistamine with antimuscarinic and moderate sedative actions. It is used mainly for its antiemetic action, particularly in the prevention of motion sickness (p. 611.3) and with analgesics in the treatment of migraine (p. 670.3). In some countries it is given in the management of allergic conditions and in pruritic skin disorders (p. 612.1). Buclizine has also been used in the treatment of vertigo (p. 612.3) associated with disorders of the vestibular system, although its value in these conditions is unproven.

For most indications, the usual dose is 25 or 50 mg daily; in severe cases up to 100 mg daily has been given.

In the treatment of migraine, buclizine hydrochloride is given in usual doses of 12.5 mg at the start of an attack or when one is known to be imminent.

For children's doses, see below.

Administration in children. An oral dose of 12.5 to 30 mg daily of buclizine hydrochloride has been given to children aged 5 to 10 years in the management of allergic conditions and as an antiemetic in, for example, the treatment of motion sickness.

Buclizine hydrochloride is also used with analgesics in the management of migraine; children aged 10 to 14 years may be given 6.25 mg at the start of an attack, or when one is known to be imminent.

Older children can be given the usual adult dose (see above).

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively.

Interactions

As for the sedating antihistamines in general, p. 614.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Longifene; ***Braz.***: Buclina; *Postafen*; ***India***: Longifene; ***S.Afr.***: Longifene†; ***Turk.***: Longifene.

Multi-ingredient Preparations. ***Braz.***: Apetil; Buclimax†; Camabol; Complevit†; Klizin; Nutrimaiz SM; Pondusvitam; Profol; Propan; ***Irl.***: Migraleve; ***Israel***: Migraleve; ***Philipp.***: Appebon with Iron; Appebon with Iron; Appebon; Appebon; *Appetason*; Appetite Plus; Appetite with Iron; Biotermin AS; Ferlette; Medifortan-AS; Pediafortan-AS; Propan with Iron; Propan; Regeron-E Plus; ***Port.***: Migraleve; ***S.Afr.***: Vomifene; ***Spain***: Migraleve; ***Switz.***: Migraleve†; ***UK***: Migraleve; ***Venez.***: Dexapostafen.

Carbinoxamine Maleate *(BANM, rINNM)*

Carbinoxamina, maleato de; Carbinoxamine, Maléate de; Carbinoxamini Maleas; Karbinoksamin Maleat; Maleato de carbinoxamina; Карбиноксамина Малеат.

2-[4-Chloro-α-(2-pyridyl)benzyloxy]-*NN*-dimethylethylamine hydrogen maleate.

$C_{16}H_{19}ClN_2O.C_4H_4O_4$=406.9
CAS — 486-16-8 (carbinoxamine); 3505-38-2 (carbinoxamine maleate).
ATC — R06AA08.
ATC Vet — QR06AA08.
UNII — 02O55696WH.

Pharmacopoeias. In *US.*

USP 36: (Carbinoxamine Maleate). A white, odourless, crystalline powder. Soluble 1 in less than 1 of water, 1 in 1.5 of alcohol and of chloroform, and 1 in 8300 of ether. pH of a 1% solution in water is between 4.6 and 5.1. Store in airtight containers. Protect from light.

Uses and Administration

Carbinoxamine maleate, a monoethanolamine derivative, is a sedating antihistamine with antimuscarinic, significant sedative, and serotonin antagonist effects. Carbinoxamine maleate is used for the relief of allergic conditions such as rhinitis (p. 612.1), and is a common ingredient of compound preparations for symptomatic treatment of coughs and the common cold (p. 611.2).

Dose recommendations for carbinoxamine maleate may vary between preparations. Licensed US product information suggests a usual oral dose of carbinoxamine maleate of 4 to 8 mg given 3 or 4 times daily. Lower doses, sometimes less than half these licensed in the US, may be used in other countries.

For children's doses, see below. Carbinoxamine polistirex has also been given orally.

Administration in children. In children, carbinoxamine maleate may be used for the symptomatic treatment of allergic conditions including rhinitis and urticaria. The oral doses below are suggested by licensed US product information; lower doses, sometimes less than half, may be used in other countries.

- children aged 2 to 3 years: 2 mg three or four times daily
- those aged 3 to 6 years: 2 to 4 mg three or four times daily
- those aged over 6 years: 4 to 6 mg three or four times daily

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively.

Interactions

As for the sedating antihistamines in general, p. 614.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Omega 100; ***Mon.***: Allergefon†; ***Rus.***: Rhinopront (Ринопронт); ***Thai.***: Histin; ***USA***: Arbinoxa; Histex CT; Histex I/E; Histex PD; Karbinal; Palgic; Pediatex.

Multi-ingredient Preparations. ***Arg.***: Aseptobron C; Omega 100 Expectorante; ***Austria***: Rhinopront†; ***Braz.***: Naldecon Bebe†; Naldecon Noite; Naldecon; Naldecon; Nasaliv; Nasaliv; Neolefrin Baby; Neolefrin; Neolefrin; Resprin; ***Chile***: Matinor; ***Gr.***: Rhinopront-S; Rhinopront; Rondec; ***Hong Kong***: Became; Coritussal†; Metoplex; Rhinopront†; ***India***: Clistin; ***Indon.***: Kenantist†; ***Malaysia***: Became; ***Mex.***: Lentostamin†; Prindex†; ***Singapore***: Became; ***Spain***: Rinomax†; ***Thai.***: Rhinar; Rhinohist; ***Turk.***: Rhinopront; Rhinopront; Rhinotussal; Rhinotussal; ***USA***: Aridex; Carbiset; Carbodec DM; Carbodec; Carbodex DM; Carboxine-PSE; Coldec D; Cordron-D†; Cordron-DM; Dacex-A; DMax; Histex HC†; Nacon; Norel LA†; Palgic DS; Palgic-D; Pediatex-D; Pediatex-DM; Pseudo-Car DM; Rondec†; Sildec-DM; Trituss-A; XiraHist DM; ***Venez.***: Resprin.

Pharmacopoeial Preparations
USP 36: Carbinoxamine Maleate Tablets; Pseudoephedrine Hydrochloride, Carbinoxamine Maleate, and Dextromethorphan Hydrobromide Oral Solution.

Cetirizine Hydrochloride

(BANM, USAN, rINNM)

Cetirizina, hidrocloruro de; Cetirizin-dihidroklorid; Cetirizindihydrochlorid; Cetirizindihydroklorid; Cétirizine, Chlorhydrate de; Cétirizine, dichlorhydrate de; Cetirizini dihydrochloridum; Cetirizini Hydrochloridum; Cetirizino dihidroclorida; Cetyryzyny dichlorowodorek; Hidrocloruro de cetirizina; P-071; Setiritsiinidihydrokloridi; Setirizin Hidroklorür; UCB-P071; Цетиризина Гидрохлорид.

The dihydrochloride of 2-[4-(4-chlorobenzhydryl)piperazin-1-yl]ethoxyacetic acid.

$C_{21}H_{25}ClN_2O_3.2HCl$=461.8
CAS — 83881-51-0 (cetirizine); 83881-52-1 (cetirizine hydrochloride).
ATC — R06AE07.
ATC Vet — QR06AE07.
UNII — 64O047KTOA.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Cetirizine Dihydrochloride; Cetirizine Hydrochloride BP 2014). A white or almost white powder. Freely soluble in water; practically insoluble in acetone and in dichloromethane. A 5% solution in water has a pH of 1.2 to 1.8. Protect from light.

USP 36: (Cetirizine Hydrochloride). White to almost white powder. Freely soluble in water; practically insoluble in acetone and in dichloromethane. pH of a 5% solution in water is between 1.2 to 1.8. Store in airtight containers. Protect from light and moisture.

Uses and Administration

Cetirizine hydrochloride, a piperazine derivative and metabolite of hydroxyzine (p. 630.3), is described as a long-acting non-sedating antihistamine with some mast-cell stabilising activity. It appears to have a low potential for drowsiness in usual doses and to be virtually free of antimuscarinic activity.

Cetirizine hydrochloride is used for the symptomatic relief of allergic conditions including rhinitis (p. 612.1) and chronic urticaria (p. 612.3). It is given in a usual oral dose of 10 mg once daily or 5 mg twice daily although, in the USA, initial doses of 5 mg daily have also been used.

It is also used with a decongestant such as pseudoephedrine hydrochloride.

For doses in children, see below. Dosage of cetirizine should be reduced in patients with hepatic or renal impairment, see below.

References.
1. Curran MP, *et al.* Cetirizine: a review of its use in allergic disorders. *Drugs* 2004; **64**: 523–61.

Administration in children. In the UK, cetirizine is licensed for use in children aged 2 years and over in the treatment of allergic rhinitis and urticaria; in the USA, it may be given to those aged 6 months and over for perennial allergic rhinitis and urticaria and to those aged 2 years and over for seasonal allergic rhinitis.

Regardless of indication, licensed oral doses of cetirizine hydrochloride are as follows:

- children aged 6 to 23 months: 2.5 mg once daily increased to a maximum of 2.5 mg twice daily in those aged 12 months and over
- children aged 2 to 5 years: 5 mg daily as a single dose or in 2 divided doses
- those aged 6 years and above: 10 mg daily as a single dose or in 2 divided doses

US licensed product information also suggests an initial dose of half the above doses, given once daily, in children aged 2 years and over and increasing as necessary.

Cetirizine is not licensed in the UK for children under 2 years of age; however, the *BNFC* suggests a dose of 250 micrograms/kg twice daily may be given to children aged 1 to 2 years.

For dose adjustment in hepatic or renal impairment, see below.

Administration in hepatic or renal impairment. In adults with hepatic or renal impairment, US licensed product information recommends that the oral dose of cetirizine hydrochloride should be 5 mg once daily. In children aged between 6 to 11 years, US product information advises the lower recommended dose of cetirizine be used. In the UK, half the normal recommended dose is advised in adults and children with renal impairment.

Adverse Effects and Precautions

As for the non-sedating antihistamines in general, p. 613.1 and p. 613.3, respectively. Cetirizine should be used with caution in patients with hepatic or renal impairment.

Arrhythmias. The ECG effects of cetirizine were studied[1] in normal subjects; doses of up to 6 times the usual recommended dose did not prolong the QT interval. Additionally, the FDA[2] in the USA and representatives of the manufacturers[3] in Belgium did not find any association between cetirizine and the development of ventricular arrhythmias. However, there has been a subsequent report[4] of torsade de pointes after overdosage with cetirizine in a hypokalaemic patient undergoing haemodialysis for chronic renal failure. See also p. 613.2.

1. Sale ME, *et al.* The electrocardiographic effects of cetirizine in normal subjects. *Clin Pharmacol Ther* 1994; **56**: 295–301.
2. Himmel MH, *et al.* Dangers of non-sedating antihistamines. *Lancet* 1997; **350**: 69.
3. Coulie P, *et al.* Non-sedating antihistamines and cardiac arrhythmias. *Lancet* 1998; **351**: 451.
4. Renard S, *et al.* Torsades de pointes induites par surdosage en cétirizine. *Arch Mal Coeur Vaiss* 2005; **98**: 157–61.

Effects on the liver. Life-threatening hepatitis developed in a 23-year-old man who had been taking cetirizine long-term for atopic dermatitis.[1] He recovered after treatment with prednisolone.

Recurrent acute hepatitis associated with the short-term use of cetirizine for seasonal allergic rhinitis has also been reported in a 26-year-old man.[2]

1. Watanabe M, *et al.* Severe hepatitis in a patient taking cetirizine. *Ann Intern Med* 2001; **135**: 142–3.
2. Pompili M, *et al.* Recurrent acute hepatitis associated with use of cetirizine. *Ann Pharmacother* 2004; **38**: 1844–7.

Hypersensitivity. Hypersensitivity reactions manifesting as urticaria[1,2] and fixed drug eruptions[3] have been reported with cetirizine.

1. Karamfilov T, *et al.* Cetirizine-induced urticarial reaction. *Br J Dermatol* 1999; **140**: 979–80.
2. Calista D, *et al.* Urticaria induced by cetirizine. *Br J Dermatol* 2001; **144**: 196.
3. Inamadar AC, *et al.* Multiple fixed drug eruptions due to cetirizine. *Br J Dermatol* 2002; **147**: 1025–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cetirizine as not porphyrinogenic: it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Sedation. For discussion of the sedative effects of antihistamines see p. 613.2.

Interactions

As for the non-sedating antihistamines in general, p. 614.3. However, some interactions are less likely with cetirizine than with non-sedating antihistamines such as astemizole and terfenadine, since cetirizine appears to have low hepatic metabolism and little arrhythmogenic potential (see Arrhythmias, p. 619.3).

Anticoagulants. For a report of an interaction between cetirizine and *acenocoumarol*, see under Interactions in Warfarin, p. 1532.2.

Pharmacokinetics

Cetirizine is rapidly absorbed from the gastrointestinal tract after oral doses and peak plasma concentrations occur within about an hour. Food delays the time to peak plasma concentrations but does not decrease the amount of drug absorbed. Cetirizine is highly bound to plasma proteins and has an elimination half-life of about 10 hours. It has been detected in breast milk. Cetirizine is excreted primarily in the urine mainly as unchanged drug. It does not appear to cross the blood-brain barrier to a significant extent.

References.

1. Awni WM, *et al.* Effect of haemodialysis on the pharmacokinetics of cetirizine. *Eur J Clin Pharmacol* 1990; 38: 67–9.
2. Desager JP, *et al.* A pharmacokinetic evaluation of the second-generation H_1-receptor antagonist cetirizine in very young children. *Clin Pharmacol Ther* 1993; 53: 431–5.
3. Pitsiu M, *et al.* Retrospective population pharmacokinetic analysis of cetirizine in children aged 6 months to 12 years. *Br J Clin Pharmacol* 2004; 57: 402–11.
4. Hussein Z, *et al.* Retrospective population pharmacokinetics of levocetirizine in atopic children receiving cetirizine: the ETAC study. *Br J Clin Pharmacol* 2005; 59: 28–37.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Alernix; Atopix; Cabal; Cetidac; Cetizine; Cetriler; Salvalerg; Stopaler; Zyrtec; *Austral.*: Alzene; Zilarex; Zodac; Zyrtec; *Austria*: Cetirhexal; Cetiristad; ratioAllerg; Tirizin; Zyrtec; *Belg.*: Histimed; Hyperpoll; Reactine; Zyrtec; *Braz.*: Aletir; Cetihexal; Cetirtec; Cetrizin; Zetalerg; Zetir; Zinetrin†; Zyrtec; *Canad.*: Allergy Relief; Reactine; *Chile*: Alertop; Coolips; Findaler; Histalen; Histax; Nonaler; Remitex; Rigotax; Sanaler; Sixacina; Zyrtec; *China*: An Di Pian (安迪片); An Di Xi Si (安迪西司); BeiFen (贝分); Bi Te Li (比特力); Cetrine (斯特林); Cetrizet (赛特赞); Da Nei (达内); Li Min (立派); Lian Shuang (联双); Lucheng (路成); Min Da (敏达); Shengminqing (圣敏清); Shi Di (适迪); Shuang Te (双特); Wei Di Min (威狄敏); Xi Li (昔利); Xi Ning (喜宁); Xi Te Rui (希特瑞); Xi Wa Ding (希瓦丁); Xian Da An (仙达安); Xikewei (西可韦); Xue Ting (雪町); Yi Meng (怡蒙); Yi Wei Tuo (伊维妥); Yingxin MeiShu (盈信美舒); Zinit (仙利特); Zyrtec (仙特明); *Cz.*: Alerid; Analergin; Cerex; Cetixin; Letizen; Parlazin; Reactine; Zodac; Zyrtec; *Denm.*: Alnok; Benaday; Histapharm; Tiracetin; Vialerg; Zyrtec; *Fin.*: Alzyr; Cetimax; Gardex; Heinix; Histanova†; Histec; Lomfast; Senirex†; Zanlan; Zyrtec; *Fr.*: Actifed Allergie; Alairgix; Aldirek; Humex Allergie Cetirizine; Reactine†; Virlix; Zyrtec; ZyrtecSet; *Ger.*: Ceterifug†; Ceti-Puren†; Cetiderm; CetiLich†; Cetirigamma†; Reactine; Zyrtec; *Gr.*: Agelmin; Alenstran; Alergoxal; Arzedyn; Auroxizine; Bebexin; Blezamont; Cetialfa; Cetiram; Cetirgen; Cetril; Ceziren; Cirizine; Dermizin; Enahimine; Gentiran; Habitek; Hamiltosin; Histafren; Kilsol; Lambeta; Ralizon; Remezine; Rezerc; Spatanil; Tasker; Telarix; Vitinelin; Zeda; Zepholin; Ziptek†; Znupril; *Hong Kong*: Adezio; Cerotec†; Cetihis; Cetirin; Histacet; Histasin; Histazine†; Marizine†; Parlazin; Rhinil; Ricam; Ryvel†; Sancotec†; Simtec; Sunizine; Tirizine; Vick-Tec†; Vick-Zyrt†; Zertine; Zicet†; Zyrtec; *Hung.*: Alerid†; Cetigen; Cetrin; Cetripharm†; Parlazin; Revicet; Zyrtec; *India*: A-Cet; Acit; Aglocet; Airtis; Alcare; Alcet; Alerbloc; Alerid; Alervin; Allercet; Allerzine; Alquit; Asicet; Atcet-MD; Avcet; Avizin; Bio Act; Biozin; C-Triz; Cefid; Cerizine-FT; Cetariv; Cetcip; Cetgel; Ceticad; Cetin; Cetiriz; Cetjust; Cetlong; Cetmac; Cetmet; Cetnaz; Cetos; Cetract; Cetrezol; Cetricare; Cetrid; Cetriken; Cetrilin; Cetrina-MD; Cetrine; Cetrisan; Cetritop; Cetriwal; Cetrizet; Cetrizine; Cettop; Cetven-DT; Cetzine; Cetzy; Cez; Cistin; Claritec; Cope; Coszin; CTZ; Cucet-DT; CZ-3; CZN; E-Cet-MD; Ekon-DT; Elgnil; Etric-DT; Eze; Flamoset; Floramin; Fomicet; Forzin; Hicet; Hisnofil; Hispokyn; Ifycet-DT; Incez; Incid-L; Intazin; Kidcet; Lancizin; Lezine; LGNil; M-Cet; M-Cit; Morazin; Noalzy; Odacet; Okacet; Oncet; Pancet; Rinitrin; Zyrtec; *Indon.*: Betarhin; Cerini; Cetinal; Cetrixal; Cetryn†; Cetymin†; Estin; Falergi; Histrine; Incidal-OD; Intrizin; Lerzin; Nichorizin; Ozen; Risina; Rydian; Ryvel; Ryzen; Ryzicor; Ryzo; Tiriz; Zenriz; *Irl.*: Cetirelief Allergy; Cetricure; Cetrine; Cetriz; Histek; Reactine; Tiritek Allergy; Zirpine; Zirtek Plus; Zirtek; Zirtene; Zynor†; *Israel*: Allergone; Allergy-Care; Histazine; Zyllergy; *Ital.*: Cerchio; Ceteris; Formistin; Generit; Kruzin; Reactidiem; Rinalgit; Sotrizol†; Stamidix; Suspiria; Tezastin; Zirtec; *Jpn*: Zyrtec; *Malaysia*: Adezio; Alatrol; Ceritec; Cetihis; Hismazine; Ricam; Simtec; Zicet†; Zyrtec; *Mex.*: Apoliz; Cethexal; Ceitev; Dercetina; Kenicet; Miseda; Namitace; Raamcinet; Reactine; Trizinet; Virlix; Visertral; Zyrtec; *Neth.*: Prevalin Allerstop; Reactine; Revalintabs†; Zyrtec; *Norw.*: Alzyr; Reactine†; Zyrtec; *NZ*: Razene; Zetop; Zyrtec; *Philipp.*: Aforvir; Aletor; Allerkid; Allermed; Alnix; Antrazine; Askey; Azurex; Brellercet†; Cerotec; Cet-10; Ceti-Med; Cetimin; Cetriz; Cetyrol; Ezaller; H-One; Histamed; Medan; Prixlae; Recozin; Rhinitrin; Ricam; Sigrel; Texzine; Unizef; Virlix; Virtec; Virtex; Zerlex; Zetir; Zetrix; Zinex; Zyrrigin; Zyrtec; *Pol.*: Acer†; Alermed; Alero; Alerton; Alerzina; Allertec; Amertil; Ceratio; CetAlergin; Cetigran; Cetiozone†; Cetrivax†; Cetrizen†; Cetyryzyna†; Letizen; Virlix; Zyrtec; *Port.*: Cetix; Cinaz; Rinalr†; Rinoliber; Virlix†; Zyrtec; *Rus.*: Alerza (Алерза); Allertec (Аллертек); Analergin (Аналергин)†; Cetirinax (Цетириакс); Cetrine (Цетрин); Letizen (Летизен); Parlazin (Парлазин); Zetrinal (Зетринал): Zodac (Зодак); Zyncet (Зинцет); Zyrtec (Зиртек); *S.Afr.*: Acuzyrt; Allecet; Allermine; Betek; Sinutab Sinus Allergy; Texa; Zetop; Zyncet; Zyrtec; *Singapore*: Adezio; Agelmin; Allercet; Alzytec; Ceritec; Cetihis; Cetrine; Cetrizin; Rhinil; Sancotec; Simtec; Sunizine; Terizin; Zyrtec; *Spain*: Alercina; Alerlisin; Cetimerck†; Coulergin; Rationalerg†; Reactine Plus†; Reactine†; Virlix; Zyrtec; *Swed.*: Acura; Cetimax; Cidron†; Zyrlex; *Switz.*: Cerzine; Cet-Mepha Allergie; Cetallerg; Ceteco; Cetrine; Helvecin; Hista-X; Histatec†; Triofan Allergie; Zyrtec; *Thai.*: Alerest; Aller-Go; Allercet†; Cetihis; Cetinac; Cetizin; Cetrimed; Cetrine†; Cetrizet; Cetrizin; Cettec; Ceza; Cintar; Cistamine; Cyzine; Fatec; Histec; Histica; Incidal-OD; Mantab; One-Trex; Ormist; Rentex; Rhitecin; Rizetec; Setin; Sutac; Sytrex; Terzine†; Tizine; Triz; Unicet†; Zensil; Zermed; Zertine; Zetecine; Zetrix; Zittec; Zymed; Zyrac; Zyral; Zyrazine; Zyrcon; Zyrex; Zyril; Zyrlergic; Zyrtec; Zytizine; *Turk.*: Allerset; Cetieva; Cetityrol; Cetryn; Hitrizin; Ressital; Rynset; Setiral; Virlix†; Yenizin; Zyrtec; *UAE*: Cetralon; *UK*: AllerTek; Benadryl Allergy; Benadryl One A Day; Hayfever & Allergy Relief; Hayfever Relief; Piriteze; Pollenshield; Zirtek; *Ukr.*: Allertek (Аллертек); Analergin (Аналергин); Cetrine (Цетрин)†; Cetrynal (Цетринал); Zodac (Зодак); Zyrtec (Зиртек); *USA*: All Day Allergy; Zyrtec; *Venez.*: Celay; Cetirex; Cetirivax; Cetral; Talzic; Zyrtec.

Multi-ingredient Preparations. *Arg.*: Cabal-D; Cetriler D; Zyrtec-D; *Belg.*: Cirrus; Reactine Pseudoephedrine; Rhinosinutab; *Braz.*: Zyrtec-D; *Canad.*: Reactine Allergy & Sinus; *Chile*: Alertop-D†; Findaler-D; Histalen D†; Remitex D; Rigotax-D; Sanaler-D; *China*: Si Te Meng (斯特灵); Xin Gan Ning; *Fin.*: Cirrus; *Fr.*: Actifed Rhinite Allergique; Humex Rhinite Allergique; *Ger.*: Reactine duo; *Hong Kong*: Cirrus†; Zyrtec-D; *Hung.*: Zyrtec-D; *India*: A'Cold; Aceper; Agrus-NS; Airtis Plus; Alcold; Alerid Cold; Alerid D; Allercet-DC; Allset; Ambcet; Ambrol-C; Ambrolite-D; Amcold; Amven-C; Arid Plus; Arid-D; Arid; Asicold; Belrin-D; Belrin-D; Bio-Cold; Brick; Broncodil; Calscot; Car-OD; Carcet; CCFS; Cetcip Cold; Cetcip-D; Cetin Cold; Cetin Kid; Cetin Plus; Cetiriz-D; Cetmet TCF; Cetra; Cetrifed-D; Cetrizet-D; Cetzine-A; Cez-A; Cez-D; Cezcold; Chescare; Cheston Cold; Cheston Cold; Codylex-CC; Cofstop-Z; Cofsym; Coftex-DMR; Cold-Relief; Coldec; Coldfree; Coldrest; Coldrest; Coldwar; Coldwar; Combit; Cope-D; Cor-4; Cozine; Cozymin-AF; Cozymin; CPP; CTZ Plus; CZ-Cold; Decet-BD; Decet-OD; Dextur; Elcold; Elgnil Cold; Esnopil; Etric Plus; Evercold; Fincof; Flu-4-XN; Fricold; Hicet-AX; Hicet-DC; Ifycet; Ika; Incold; Incold; Indikof-A; Kazicold; Kidcet-Cold; Kofrid Plus; Kofrid-D; Kofrid; Kol-DC; Kold Time; Koldy; Kolq; Kolq; Kozifed; Kuffdac-C; Lemohist-C; Lezine-P; Mastifen-C; Moncet; Mucorespcz; Nam Cold-Z; Nam Cold; Nam Cold; Natcold Plus; Nimucold; Noalzy Plus; Nozee; Nozik-P; Nozik; Pamagin C; Pamagin C; *Indon.*: Cirrus; *Ital.*: Naristar; Reactine; *Malaysia*: Cirrus†; Zyrtec-D; *Mex.*: Virlix-D; Zyrtec-D†; *NZ*: Zyrtec Decongestant†; *Pol.*: Cirrus; Zyrtec D; *Port.*: Cirrus†; *Singapore*: Zyrtec-D; *Spain*: Stopcold; Virlix Plus; *Thai.*: Zyrtec-D†; *Turk.*: Cirrus; *Ukr.*: Helpex Hot Cap (Хелпекс Хот Кап); Militsian Multisymptomic (Міліція Мультисимптомний); *USA*: All Day Allergy-D; Zyrtec-D; *Venez.*: Cetirivax D; Zyrtec-D.

Pharmacopoeial Preparations
BP 2014: Cetirizine Oral Solution; Cetirizine Tablets;
USP 36: Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-release Capsules; Cetirizine Hydrochloride Oral Solution; Cetirizine Hydrochloride Tablets.

Chlorcyclizine Hydrochloride *(BANM, rINNM)*

Chlorciklizino hidrochloridas; Chlorcyclizine, Chlorhydrate de; Chlorcyclizinhydrochlorid; Chlorcyclizini Hydrochloridum; Chlorcyclizinium Chloride; Chlorcyklizin-hydrochlorid; Clorciclizina, hidrocloruro de; Hidrocloruro de clorciclizina; Kloorisyklitsiinihydrokloridi; Klórciklizin-hidroklorid; Klorcyklizinhydroklorid; Хлорциклизина Гидрохлорид.

1-(4-Chlorobenzhydryl)-4-methylpiperazine hydrochloride.

$C_{18}H_{21}ClN_2.HCl$=337.3

CAS — 82-93-9 (chlorcyclizine); 1620-21-9 (chlorcyclizine hydrochloride); 14362-31-3 (chlorcyclizine hydrochloride).

ATC — R06AE04.

ATC Vet — QR06AE04.

UNII — NP87A7874U.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Chlorcyclizine Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water and in dichloromethane; soluble in alcohol. A 1% solution in water has a pH of 5.0 to 6.0. Protect from light.

Profile

Chlorcyclizine hydrochloride, a piperazine derivative, is a sedating antihistamine (p. 610.1). It has been given orally for the symptomatic relief of hypersensitivity reactions; it has also been used as an antiemetic. It has been used in topical preparations, although as with other antihistamines, there is a risk of sensitisation.

Chlorcyclizine dibunate (naftoclizine) has been used as a cough suppressant similarly to sodium dibunate (p. 1677.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Ahist.

Multi-ingredient Preparations. *Fin.*: Anervan†; *Israel*: Tendigran†; *Neth.*: Primatour; *Norw.*: Anervan†; *Spain*: Diminox Antitusigeno; *Swed.*: Anervan; Exolyt†; *USA*: Biclora-D; Biclora; Dallergy; Dallergy; NasOpen; Nasotuss; Notuss-NX†; Notuss-NXD†; Poly-Tussin D; Poly-Tussin; Stahist AD.

Chloropyramine Hydrochloride

(BANM, rINNM)

Chloropyramine, Chlorhydrate de; Chloropyramini Hydrochloridum; Cloropiramina, hidrocloruro de; Halopyramine Hydrochloride; Hidrocloruro de cloropiramina; Хлоропирамина Гидрохлорид.

N-(4-Chlorobenzyl)-*N*′*N*′-dimethyl-*N*-(2-pyridyl)ethylenediamine hydrochloride.

$C_{16}H_{20}ClN_3.HCl$=326.3

CAS — 59-32-5 (chloropyramine); 6170-42-9 (chloropyramine hydrochloride).

ATC — D04AA09; R06AC03.

ATC Vet — QD04AA09; QR06AC03.

UNII — FWA92Z14NN.

Profile

Chloropyramine hydrochloride, an ethylenediamine derivative, is an antihistamine (p. 610.1). It has been given orally in a dose of 25 mg three or four times daily or as an intramuscular injection of 20 to 40 mg.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Hung.*: Suprastin; *Mex.*: Avapena; *Rus.*: Subrestine (Субрестин); Suprastin (Супрастин); *Ukr.*: Suprastin (Супрастин).

Chlorphenamine Maleate

(BANM, rINNM)

Chlorfenamin-maleinát; Chlorfenamino maleatas; Chlorofenaminy maleinian; Chlorphénamine, Maléate de; Chlorphenamini maleas; Chlorphenaminmaleat; Chlorpheniramine Maleate; Chlorprophenpyridamine Maleate; Clorfenamina maleato de; Kloorifenamiinimaleaatti; Klorfenaminmaleat Klórfenamin-maleát; Maleato de clorfenamina Хлорфенамина Малеат.

(±)-3-(4-Chlorophenyl)-*NN*-dimethyl-3-(2-pyridyl)propylamine hydrogen maleate.

$C_{16}H_{19}ClN_2.C_4H_4O_4$=390.9

CAS — 132-22-9 (chlorphenamine); 113-92-8 (chlorphenamine maleate).

ATC — R06AB04.

ATC Vet — QR06AB04.

UNII — V1Q0O9OJ9Z.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Chlorphenamine Maleate). A white or almost white, crystalline powder. Freely soluble in water; soluble in alcohol. Protect from light.

USP 36: (Chlorpheniramine Maleate). A white, odourless, crystalline powder. Soluble 1 in 4 of water and 1 in 10 of alcohol and of chloroform; slightly soluble in ether and in benzene. Its solutions in water have a pH between 4 and 5. Store in airtight containers. Protect from light.

Incompatibility. Chlorphenamine maleate has been reported to be incompatible with calcium chloride, kanamycin sulfate, noradrenaline acid tartrate, pentobarbital sodium, and meglumine adipiodone.

Dexchlorpheniramine Maleate *(BANM, rINNM)*

Dekschlorfeniramino maleatas; Dekskloorifeniramiinimaleaatti; Dexchlorfeniramin-maleinát; Dexchlorphenamine Maleate; Dexchlorphéniramine, Maléate de; Dexchlorpheniramini Maleas; Dexchlorpheniraminmaleat; Dexclorfeniramina, maleato de; Dexklorfeniraminmaleat; Dexklórfeniramin-maleát; Maleato de dexclorfeniramina; Дексхлорфенирамина Малеат.

CAS — 25523-97-1 (dexchlorpheniramine); 2438-32-6 (dexchlorpheniramine maleate).

ATC — R06AB02.

ATC Vet — QR06AB02.

UNII — B10YD955QW.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Dexchlorpheniramine Maleate). A white or almost white, crystalline powder. Very soluble in water; freely soluble in alcohol, in dichloromethane, and in methyl alcohol. A 1% solution in water has a pH of 4.5 to 5.5. Protect from light.

USP 36: (Dexchlorpheniramine Maleate). A white, odourless, crystalline powder. Soluble 1 in 1.1 of water, 1 in 2 of alcohol, 1 in 1.7 of chloroform, and 1 in 2500 of ether; slightly soluble in benzene. pH of a 1% solution in water is between 4.0 and 5.0. Store in airtight containers. Protect from light.

Uses and Administration

Chlorphenamine maleate, an alkylamine derivative, is a sedating antihistamine that causes a moderate degree of sedation; it also has antimuscarinic activity.

Chlorphenamine is a racemic mixture; the dextrorotatory isomer, dexchlorpheniramine, has about twice the activity of chlorphenamine by weight.

Chlorphenamine maleate and dexchlorpheniramine maleate are used for the symptomatic relief of allergic conditions including urticaria and angioedema (p. 612.3), rhinitis (p. 612.1), and conjunctivitis (p. 611.1), and in pruritic skin disorders (p. 612.1). They are common ingredients of compound preparations for symptomatic treatment of coughs and the common cold (p. 611.2). Chlorphenamine may be given intravenously as an adjunct in the emergency treatment of anaphylactic shock (p. 611.1).

Chlorphenamine maleate is given in oral doses of 4 mg every 4 to 6 hours up to a maximum of 24 mg daily. It may also be given by intramuscular, by subcutaneous, or by slow intravenous injection over a period of 1 minute. The usual dose is 10 to 20 mg and the total dose given by these routes in 24 hours should not normally exceed 40 mg.

Dexchlorpheniramine maleate is given in oral doses of 2 mg every 4 to 6 hours up to a maximum of 12 mg daily.

For dosage in children, see below.

Modified-release oral preparations of chlorphenamine maleate or dexchlorpheniramine maleate are available in some countries; dosage is specific to a particular formulation.

Dexchlorpheniramine maleate has been applied topically in some countries, although as with other antihistamines there is a risk of sensitisation. Chlorphenamine polistirex (a sulfonated diethenylbenzene-ethenylbenzene copolymer complex), chlorphenamine tannate, and dexchlorpheniramine tannate are given orally and are used similarly to the maleate.

Administration in children. In children, *chlorphenamine maleate* may be given orally for the symptomatic relief of allergic conditions such as rhinitis and urticaria; doses are as follows:

- children aged 1 to 2 years: 1 mg twice daily
- those aged 2 to 6 years: 1 mg every 4 to 6 hours
- those aged 6 to 12 years: 2 mg every 4 to 6 hours

In the UK, chlorphenamine maleate is not licensed in children younger than 1 year. However, the *BNFC* suggests that children aged 1 month to 2 years of age may be given 1 mg twice daily.

Chlorphenamine maleate may be given by slow intravenous injection over a period of 1 minute, as an adjunct in the emergency treatment of anaphylactic shock. It may also be given by intramuscular, by subcutaneous, or by slow intravenous injection, for the symptomatic management of allergy. The following parenteral doses may be used:

- children aged 1 month to 1 year: 250 micrograms/kg
- those aged 1 to 5 years: 2.5 to 5 mg
- those aged 6 to 12 years: 5 to 10 mg

Alternatively, children and adolescents aged 1 to 18 years may be given a dose of 200 micrograms/kg. If necessary, intramuscular or intravenous injections may be repeated up to a total of 4 doses in 24 hours.

Dexchlorpheniramine maleate is usually used to manage allergic rhinitis in the following oral doses:

- children aged 2 to 6 years: 500 micrograms every 4 to 6 hours
- those aged 6 to 12 years: 1 mg every 4 to 6 hours

Chlorphenamine maleate and dexchlorpheniramine maleate are common ingredients of compound preparations for the symptomatic treatment of coughs and the common cold. However, such preparations should be used with caution in children, and generally avoided in young children, for details see p. 614.1.

Malaria. Chlorphenamine may be tried in patients with malaria who have chloroquine-induced pruritus (see Effects on the Skin, p. 652.2), but additionally it has been shown to have some promise as an adjunct in the treatment of chloroquine-resistant malaria itself. Early studies indicated that chlorphenamine was only one of several drugs that reversed chloroquine resistance *in vitro* in isolates of *Plasmodium falciparum*. Later clinical studies in children in Nigeria showed enhanced efficacy when chlorphenamine was given with chloroquine[1-6] or with amodiaquine.[7] The overall management of malaria is discussed on p. 644.1.

1. Sowunmi A, *et al.* Enhanced efficacy of chloroquine-chlorpheniramine combination in acute uncomplicated falciparum malaria in children. *Trans R Soc Trop Med Hyg* 1997; 91: 63–7.
2. Sowunmi A, Oduola AMJ. Comparative efficacy of chloroquine/chlorpheniramine combination and mefloquine for the treatment of chloroquine-resistant Plasmodium falciparum malaria in Nigerian children. *Trans R Soc Trop Med Hyg* 1997; 91: 689–93.
3. Sowunmi A, *et al.* Comparative efficacy of chloroquine plus chlorpheniramine and pyrimethamine/sulfadoxine in acute uncomplicated falciparum malaria in Nigerian children. *Trans R Soc Trop Med Hyg* 1998; 92: 77–81.
4. Sowunmi A, *et al.* Comparative efficacy of chloroquine plus chlorpheniramine and halofantrine in acute uncomplicated falciparum malaria in Nigerian children. *Trans R Soc Trop Med Hyg* 1998; 92: 441–5.
5. Okonkwo CA, *et al.* Effect of chlorpheniramine on the pharmacokinetics of and response to chloroquine of Nigerian children with falciparum malaria. *Trans R Soc Trop Med Hyg* 1999; 93: 306–11.
6. Ogungbamigbe TO, *et al.* Chloroquine resistant Plasmodium falciparum malaria in Osogbo Nigeria: efficacy of amodiaquine + sulfadoxine-pyrimethamine and chloroquine + chlorpheniramine for treatment. *Mem Inst Oswaldo Cruz* 2008; 103: 79–84.
7. Falade CO, *et al.* Enhanced efficacy of amodiaquine and chlorpheniramine combination over amodiaquine alone in the treatment of acute uncomplicated Plasmodium falciparum malaria in children. *Med Princ Pract* 2008; 17: 197–201.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively. Exfoliative dermatitis may develop. Injections may be irritant and cause transient hypotension or stimulation of the CNS.

Effects on the blood. There are several old and isolated reports of blood dyscrasias after use of chlorphenamine maleate; these include agranulocytosis,[1,2] thrombocytopenia,[3] pancytopenia,[4] and aplastic anaemia.[5] Haemolytic anaemia has occurred after use of dexchlorpheniramine maleate.[6] The association with antihistamine use has been questioned in some of these cases.[7]

1. Shenfield G, Spry CJF. Unusual cause of agranulocytosis. *BMJ* 1968; ii: 52–3.
2. Hardin AS. Chlorpheniramine and agranulocytosis. *Ann Intern Med* 1988; 108: 770.
3. Eisner EV, *et al.* Chlorpheniramine-dependent thrombocytopenia. *JAMA* 1975; 231: 735–6.
4. Deringer PM, Maniatis A. Chlorpheniramine-induced bone-marrow suppression. *Lancet* 1976; i: 432.
5. Kanoh T, *et al.* Aplastic anaemia after prolonged treatment with chlorpheniramine. *Lancet* 1977; i: 546–7.
6. Duran-Suarez JR, *et al.* The I antigen as an immune complex receptor in a case of haemolytic anaemia induced by an antihistaminic agent. *Br J Haematol* 1981; 49: 153–4.
7. Spry CJF. Chlorpheniramine-induced bone-marrow suppression. *Lancet* 1976; i: 545.

Effects on the senses. Chlorphenamine has been reported to affect the senses of smell and taste.[1]

1. Schiffman SS. Taste and smell in disease. *N Engl J Med* 1983; 308: 1275–9.

Extrapyramidal disorders. Facial dyskinesias have been reported[1,2] after oral doses of chlorphenamine maleate.

1. Thach BT, *et al.* Oral facial dyskinesia associated with prolonged use of antihistaminic decongestants. *N Engl J Med* 1975; 293: 486–7.
2. Davis WA. Dyskinesia associated with chronic antihistamine use. *N Engl J Med* 1976; 294: 113.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dexchlorpheniramine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Interactions

As for the sedating antihistamines in general, p. 614.3.

Antiepileptics. For a report of the effect of chlorphenamine on *phenytoin*, see p. 543.3.

Pharmacokinetics

Chlorphenamine maleate is absorbed relatively slowly from the gastrointestinal tract and peak plasma concentrations occur about 2.5 to 6 hours after oral doses. Bioavailability is low, values of 25 to 50% having been reported. Chlorphenamine appears to undergo considerable first-pass metabolism. About 70% of chlorphenamine in the circulation is bound to plasma proteins. There is wide interindividual variation in the pharmacokinetics of chlorphenamine; values ranging from 2 to 43 hours have been reported for the half-life. Chlorphenamine is widely distributed in the body, and enters the CNS.

Chlorphenamine maleate is extensively metabolised. Metabolites include desmethyl- and didesmethylchlorphenamine. Unchanged drug and metabolites are excreted mainly in the urine; excretion is dependent on urinary pH and flow rate. Only trace amounts have been found in the faeces.

A duration of action of 4 to 6 hours has been reported; this is shorter than may be predicted from pharmacokinetic parameters.

More rapid and extensive absorption, faster clearance, and a shorter half-life have been reported in children.

References.

1. Rumore MM. Clinical pharmacokinetics of chlorpheniramine. *Drug Intell Clin Pharm* 1984; 18: 701–7.
2. Paton DM, Webster DR. Clinical pharmacokinetics of H_1-receptor antagonists (the antihistamines). *Clin Pharmacokinet* 1985; 10: 477–97.
3. Yasuda SU, *et al.* The roles of CYP2D6 and stereoselectivity in the clinical pharmacokinetics of chlorpheniramine. *Br J Clin Pharmacol* 2002; 53: 519–25.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Afeme; Alergidryl; Alergitrat; Qura Plus; ***Austral.***: Polaramine; ***Austria***: Polaramin†; ***Belg.***: Kelargine; Polaramine; ***Braz.***: Alergonil; Alergyo; Alermine; Dexlerg; Expectamin F; Fenirax; Histamin; Hystin; Polaramine; Polaratin; Polaren; Polaryn; ***Canad.***: Chlor-Tripolon; Novo-Pheniram; ***Chile***: Clorprimeton; Nipolen; Prodel; Scadan; ***China***: Hui Ji (惠济); Kang Yu Deng Tong (康裕登通); Runjie (润洁); ***Denm.***: Polaramin†; ***Fr.***: Polaramine; ***Ger.***: Polaronil†; ***Gr.***: Istamex; Istaminol; Losmanin; Polaramine; ***Hong Kong***: Antamin†; Antihist†; Chloramine†; Chlorminol†; Chlorpyrimine; Coriton†; Dapriton†; Dex Antihist; Flentist†; Horamine†; Kenyamine†; Marpeniramine†; Pirimat†; Polaramine; Rhiniramine; Synchloramin†; Tromine; Uni-Dexmine†; Uni-Ramine; ***India***: Cadistin; Cepiam TR; Cesiran; Chloram; Cocorex; Cofton; Dexcpm; Dexodil; DPM-2; ***Indon.***: Chlorphenon†; Cohistan; CTM; Dehista; Orphen; Pehachlor; Polamec†; Polaramine; Polarist†; Polofar†; ***Irl.***: Piriton; ***Israel***: Ahiston; ***Ital.***: Polaramin; Trimeton; ***Malaysia***: Chloramine; Chlormine; Chlorpyrimine; Dexatamin; Dexchloramine; Kotamin; Pirimat; Polaramine; Somin; Zoramine; ***Mex.***: Alerdil; Antadex-H; Blendox†; Cloro-Trimeton; Cronal; Docsi; Hierbal; Histadryl; ***Neth.***: Polaramine; ***Norw.***: Phenamin†; Polaramin; ***NZ***: Histafen; Polaramine; ***Philipp.***: Antamin; Baromin; Chlor-Trimeton; Chlormin; Clomamin; Metromine; Valemine; Virgomine†; ***Port.***: Trenelone; ***S.Afr.***: Allergex; Allerhist†; Rhineton; ***Singapore***: Allermin; Allersin; Alleryl; Antamin; Chloramine; Chlormine; Chlorpyrimine; Dexatamin; Dexchloramine; Dextramine; Horamine; Pirimat; Piriton; Polaramine; Polarax; Rhiniramine; Somin; SP-Arnamin; Synchloramin; ***Spain***: Antihistaminico; Polaramine; ***Swed.***: Polaramin†; ***Switz.***: Arbid N; Polaramine†; ***Thai.***: Allergen; Allergin; Aly; Arc-Chlor; Chlophe; Chlophen; Chlorahist; Chloramine-S; Chloramine; Chlordon; Chlorleate; Chlorphencap; Chlorpheno; Chlorpyrimine; Cohistan†; Hisdaron; Histatab; Histatapp; Icolid Plus; Ilcid; KB Ramine; Kloramin; Patarphen; Pophen; Sinchlormine; Suramine; ***UAE***: Chlorohistol; ***UK***: Allercalm; Allergy Relief; Allerief; Calimal; Hayleve; Piriton; Pollenase Antihistamine; ***Ukr.***: Glycodin (Гликодин)†; ***USA***: Aller-Chlor; Allergy Relief; Allergy-Time; Allergy; Chlo-Amine†; Chlor-Pro; Chlor-Trimeton Allergy 4 Hour; Chlor-Trimeton; ChlorTan; ED Chlorped Jr; Ed-Chlor-Tan; Ed-Chlortan; Efidac 24 Chlorpheniramine; PediaCare Allergy Formula; Pediatan†; Pediox-S†; Pharbechlor; QDALL AR†; TanaHist PD†; Teldrin; ***Venez.***: Clorotrimeton; Liramin.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

BP 2014: Chlorphenamine Injection; Chlorphenamine Oral Solution; Chlorphenamine Tablets;

USP 36: Acetaminophen, Chlorpheniramine Maleate, and Dextromethorphan Hydrobromide Tablets; Chlorpheniramine Maleate and Phenylpropanolamine Hydrochloride Extended-release Capsules; Chlorpheniramine Maleate and Phenylpropanolamine Hydrochloride Extended-release Tablets; Chlorpheniramine Maleate and Pseudoephedrine Hydrochloride Extended-release Capsules; Chlorpheniramine Maleate and Pseudoephedrine Hydrochloride Oral Solution; Chlorpheniramine Maleate Extended-release Capsules; Chlorpheniramine Maleate Injection; Chlorpheniramine Maleate Syrup; Chlor-

pheniramine Maleate Tablets; Dexchlorpheniramine Maleate Syrup; Dexchlorpheniramine Maleate Tablets.

Chlorphenoxamine Hydrochloride

(BANM, rINNM)

Chlorphénoxamine, Chlorhydrate de; Chlorphenoxamini Hydrochloridum; Clorfenoxamina, Hidrocloruro de; Hidrocloruro de clorfenoxamina; Klorfenoksamin Hidroklorür; Хлорфеноксамина Гидрохлорид.

2-(4-Chloro-α-methylbenzhydryloxy)-*NN*-dimethylethylamine hydrochloride.

$C_{18}H_{22}ClNO,HCl$=340.3

CAS — 77-38-3 (chlorphenoxamine); 562-09-4 (chlorphenoxamine hydrochloride).

ATC — D04AA34; R06AA06.

ATC Vet — QD04AA34; QR06AA06.

UNII — 5I159322PY.

Profile

Chlorphenoxamine, a congener of diphenhydramine (p. 626.1), has antimuscarinic and antihistaminic properties. It has been used in nausea, vomiting, and vertigo, and was formerly used in the symptomatic treatment of parkinsonism. Chlorphenoxamine has also been used in hypersensitivity reactions.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Systral†; *Gr.*: Systral; *Indon.*: Systral†; *Philipp.*: Systral; *Port.*: Systral; *Thai.*: Systral; *Turk.*: Sistral†; Systral.

Multi-ingredient Preparations. *Austria*: Spirbon†.

Cinnarizine *(BAN, USAN, rINN)*

Cinarizin; Cinarizina; Cinarizinas; Cinnarizin; Cinnarizinum; Cynaryzyna; S16-MD; R-516; R-1575; Sinarizin; Sinnaritsiini; Циннаризин.

1-Benzhydryl-4-cinnamylpiperazine; (*E*)-1-(Diphenylmethyl)-4-(3-phenylprop-2-enyl)piperazine.

$C_{26}H_{28}N_2$=368.5

CAS — 298-57-7.

ATC — N07CA02.

ATC Vet — QN07CA02.

UNII — 3DJ2E1X18L.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Ph. Eur. 8: (Cinnarizine). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol and in methyl alcohol; soluble in acetone; freely soluble in dichloromethane. Protect from light.

Uses and Administration

Cinnarizine is a piperazine derivative with antihistamine, sedative, and calcium-channel blocking activity. It is used for the symptomatic treatment of nausea and vertigo caused by Ménière's disease and other vestibular disorders (see Vertigo, p. 612.3) and for the prevention and treatment of motion sickness (p. 611.3). It is also used in the management of various peripheral and cerebral vascular disorders.

In the UK, the usual oral dose for vertigo and vestibular disorders is 30 mg three times daily. For motion sickness a dose of 30 mg is taken 2 hours before the start of the journey and 15 mg every 8 hours during the journey if necessary. In other European countries, a dose of 75 mg once or twice daily may be given for vertigo and vestibular disorders. Doses of 75 mg may also be given once daily for cerebrovascular disorders and 2 or 3 times daily for peripheral vascular disorders

For doses in children, see below.

References.

1. Shupak A, *et al.* Cinnarizine in the prophylaxis of seasickness: laboratory vestibular evaluation and sea study. *Clin Pharmacol Ther* 1994; 55: 670–80.

Administration in children. Cinnarizine may be used orally in children aged 5 to 12 years. A dose of 15 mg is given three times a day for the control of vestibular disorders. For motion sickness, 15 mg is taken 2 hours before the start of the journey followed by 7.5 mg every 8 hours during the journey if necessary.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively.

There have been rare reports of extrapyramidal symptoms after taking cinnarizine, sometimes associated with depressive feelings.

High doses of cinnarizine should be used with caution in patients with hypotension because of the possibility of decreasing blood pressure further.

Extrapyramidal disorders. For reference to extrapyramidal disorders associated with the use of cinnarizine, see Flunarizine, p. 630.1.

Hypersensitivity. Immunologically-defined lichen planus pemphigoides has been reported[1] in a 72-year-old woman taking cinnarizine. Lesions began to clear when treatment was stopped but challenge with cinnarizine provoked severe itching and reactivation of pigmented lesions. Another case[2] has also been described.

1. Miyagawa S, *et al.* Lichen planus pemphigoides-like lesions induced by cinnarizine. *Br J Dermatol* 1985; 112: 607–13.
2. Ramallal M, *et al.* Lichenoid eruption associated with cinnarizine use. *Pharm World Sci* 2002; 24: 215–16.

Tinnitus. The Spanish System of Pharmacovigilance had received reports[1] of tinnitus associated with calcium-channel blockers; some of the reports, including the one relating to cinnarizine, were in patients also receiving other ototoxic drugs. WHO was said to have additional reports of tinnitus associated with calcium-channel blockers including cinnarizine.

1. Narváez M, *et al.* Tinnitus with calcium-channel blockers. *Lancet* 1994; 343: 1229–30.

Weight gain. There has been a report[1] of weight gain in 4 patients who had taken cinnarizine for 1 to 2 years; in all cases the weight gain was associated with increased appetite.

1. Navarro-Badenes J, *et al.* Weight-gain associated with cinnarizine. *Ann Pharmacother* 1992; 26: 928–30.

Interactions

As for the sedating antihistamines in general, p. 614.3.

Pharmacokinetics

Cinnarizine is absorbed from the gastrointestinal tract and peak plasma concentrations occur 2 to 4 hours after oral doses. It undergoes metabolism and has a half-life of 3 to 6 hours. Cinnarizine is excreted in the faeces mainly as unchanged drug, and in the urine predominantly as metabolites.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Dismaren; Fabracin; Folcodal; Natropas; Stugeron; *Austria*: Cinnabene†; Pericephal; Stutgeron†; *Belg.*: Stugeron; *Braz.*: Antigeron; Cinaran; Cinarite; Cinarix; Cinazon; Civertim; Cronogeron; Ductogeron; Fluxon; Labigeron; Stugerina; Stugeron; Vertigeron; Verzum; *Chile*: Cinergil; Siridone; Stugeron; *China*: Bo Rui Te (博瑞特); *Cz.*: Cinnabene†; Stugeron; *Denm.*: Sepan; *Gr.*: Derozin; Geronik; Libotasin; Stugeron; *Hong Kong*: Medozine†; Mosion-6†; Stugeron; Urizine; *Hung.*: Stugeron; *India*: Avidazine†; Cinact; Cinadil; Cinaz; Cingeron; Cini; Cinnasia; Cintac; Cintigo; Cinvert; Cinzan; Diziron; Dizril; Dizzigo; Emzine; Stugeron; Vertiron; *Indon.*: Merron; Nariz; Perifas; Stugeron; Vertizine; *Irl.*: Stugeron; *Israel*: Stunarone; *Ital.*: Cinazyn; Stugeron; Toliman; *Malaysia*: Celenid; Cinna; Cinnaron; Nazin; Stugeron; Uphageron; *Mex.*: Bulasan; Ceretec†; Cisaken; Cyslev; Dilateron-F; Dilper-INA; Karilex; Oblant; Reynaven; Stugeron; Venoxil; Winpar; *Philipp.*: Cinamin; Cinarin; Cinnabloc; Dizzinon; Nizirian; Stugeron; Vertisin; *Port.*: Cinon; Stugeron; *Rus.*: Phezam (Фезам); Stugeron (Стругерон); Stugesin (Стугезин); *S.Afr.*: Purazine†; Stugeron; *Singapore*: Celenid; Cinna; Cinnar; Cinnaron; Nazin; Stugeron; Vertigon; *Spain*: Stugeron; *Switz.*: Cerepar†; Cinnageron; Stugeron; *Thai.*: Bugeron; C-Pela; C-Ricin; Celenid†; Cenai; Cerebroad; Ceremin; Cinerine; Cinna; Cinnar; Cinnarin; Cinnarine; Cinnatab; Cinnaza; Cinrizine; Fageron†; KB Gyding; Linazine; Manoron; Medozine; Naricin; Narizine; Nazine; Siarizine; Silicin; Sorebral; Stugeron; Stugin; Stuno†; Sturon; Urizine†; Vernarin; *Turk.*: Sefal; *UK*: Stugeron; *Ukr.*: Stugeron (Стугерон); *Venez.*: Cinaren; Cinarin; Sinver; Stugeron; Vericin.

Multi-ingredient Preparations. *Arg.*: Cadencial Plus; Cinacris; Difusil; Ribex; *Belg.*: Arlevertan; Touristil; *Braz.*: Coldrin; Exit; Sureptil; *China*: Limai (利脉); Xin Naolilong (新瑞力隆); *Cz.*: Arlevert; *Fin.*: Arlevert; Rinomar; *Ger.*: Arlevert; *Hong Kong*: Cinnasin†; SE-25†; *Hung.*: Arlevert; *India*: Aridom-C; Azinorm C; Cimdom; Cinact-D; Cinadil-D; Cingeron-D; Cinnasia-D; Cintac-D; Dompon CZ; Dompro-C; Domstal-CZ; Donriz; Kandor CZ; Mosic; Neurozine; Pacidom-C; Vertigil; *Irl.*: Arlevert; *Ital.*: Arlevertan; *Neth.*: Arlevert; Primatour; *Philipp.*: Stugil; *Rus.*: Combitropil (Комбитропил); NooCam (НооКам); Omaron (Омарон); Piracezine (Пирацезин); *Spain*: Clinadil; Diclamina†; *Swed.*: Arlevert; Rinomar; *Switz.*: Arlevert; *Thai.*: Cinnapac; *UK*: Arlevert; *Ukr.*: Cinatropil (Цинатропил)†; Evrisam (Эвризам); Memosam (Мемозам); Neuro-Norm (Нейро-Норм) Omaron (Омарон); Phezam (Фезам).

Clemastine Fumarate

(BANM, USAN, rINNM)

Clemastina, fumarato de; Clémastine, Fumarate de; Clemastine Hydrogen Fumarate; Clemastini Fumaras; Fumarato de clemastina; HS-592 (clemastine); Klemastiinifumaraatti; Klemastin fumarát; Klemastin Hidrojen Fumarat; Klemastinfumarat; Klemastino fumaratas; Klemastyny fumaran; Klemasztin-fumarát; Meclastine Fumarate; Mecloprodine Fumarate; Клемастина Фумарат.

(+)-(2*R*)-2-[2-[(*R*)-4-Chloro-α-methylbenzhydryloxy]ethyl]-1-methylpyrrolidine hydrogen fumarate.

$C_{21}H_{26}ClNO,C_4H_4O_4$=460.0

CAS — 15686-51-8 (clemastine); 14976-57-9 (clemastine fumarate).

ATC — D04AA14; R06AA04.

ATC Vet — QD04AA14; QR06AA04.

UNII — 19259EGQ3D.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Clemastine Fumarate). A white or almost white, crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol (70%); slightly soluble in alcohol (50%) and in methyl alcohol. A 10% suspension in water has a pH of 3.2 to 4.2.

USP 36: (Clemastine Fumarate). A colourless to faintly yellow, odourless, crystalline powder. Very slightly soluble in water; very slightly soluble in chloroform; slightly soluble in methyl alcohol. pH of a 10% suspension in water is between 3.2 to 4.2. Store in airtight containers at a temperature not exceeding 25 degrees. Protect from light.

Uses and Administration

Clemastine fumarate, a monoethanolamine derivative, is a sedating antihistamine with antimuscarinic and moderate sedative properties. It has been reported to have a duration of action of about 10 to 12 hours. It is used for the symptomatic relief of allergic conditions including urticaria and angioedema (p. 612.3), rhinitis (p. 612.1) and conjunctivitis (p. 611.1), and in pruritic skin disorders (p. 612.1).

Clemastine is given as the fumarate although doses are expressed in terms of the base. Clemastine fumarate 1.34 mg is equivalent to about 1 mg of clemastine base. The usual oral dose is 1 mg twice daily. Up to 6 mg daily has been given, particularly for urticaria and angioedema.

Clemastine fumarate may be given by intramuscular or slow intravenous injection in a total daily dose equivalent to 4 mg of clemastine for acute allergic reactions; for prophylaxis 2 mg is given by intravenous injection.

For doses in children, see below.

Clemastine fumarate has also been used topically although as with other antihistamines, there is a risk of sensitisation.

Administration in children. Clemastine fumarate may be given to children for the symptomatic relief of allergic conditions including rhinitis, angioedema, and pruritic skin disorders. Oral doses, expressed in terms of clemastine, are as follows:

- children aged 1 to 3 years, 250 to 500 micrograms twice daily
- those aged 3 to 6 years, 500 micrograms twice daily
- those aged 6 to 12 years, 0.5 to 1 mg twice daily

Children aged 1 year and over, can be given an intramuscular dose equivalent to 25 micrograms/kg of clemastine daily, in two divided doses.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively.

Breast feeding. The American Academy of Pediatrics[1] considers that clemastine should be given with caution to breast-feeding mothers, since it has been associated with adverse effects in the infant. Drowsiness, irritability, a high-pitched cry, neck stiffness, and refusal to feed in a 10-week-old breast-fed baby occurred 12 hours after her mother started treatment with clemastine.[2] Clemastine was detected in the mother's breast milk. The baby recovered and was feeding normally on the day after the drug was stopped.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/04/04)
2. Kok THHG, *et al.* Drowsiness due to clemastine transmitted in breast milk. *Lancet* 1982; i: 914–15.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies clemastine as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Interactions

As for the sedating antihistamines in general, p. 614.3.

Pharmacokinetics

Clemastine fumarate is rapidly and almost completely absorbed from the gastrointestinal tract and peak plasma concentrations occur 2 to 4 hours after oral use. Unchanged drug and metabolites are excreted principally in the urine. An elimination half-life of about 21 hours has been reported. Clemastine is distributed into breast milk.

References.

1. Schran HF, *et al.* The pharmacokinetics and bioavailability of clemastine and phenylpropanolamine in single-component and combination formulations. *J Clin Pharmacol* 1996; 36: 911–22.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Agasten; *Canad.*: Tavist; *China*: Langjing (浪静); Si Nuo Ping (斯诺平); Tai Wei (泰威); *Cz.*: Tavegyl†; *Denm.*: Tavegil; Tavegyl; *Ger.*: Tavegil; *India*: Clamist; *Indon.*: Tavegyl; *Malaysia*: Tavetine; *Mex.*: Tavist; *Neth.*: Tavegil; Tavegyl; *Philipp.*: Marsthine; Tavegyl; Tavist; *Port.*: Tavegyl; Tavist; *Rus.*: Tavegyl (Тавегил); *S.Afr.*: Tavegyl†; *Spain*: Tavegil; *Swed.*: Tavegyl; *Switz.*: Tavegyl; *Turk.*: Tavegyl; *UK*: Tavegil; *USA*: Contac 12 Hour Allergy; Dayhist-1; Tavist Allergy.

Multi-ingredient Preparations. *Braz.*: Emistin; *China*: Feng Lai (丰莱); *Spain*: Dexa Tavegil.

Pharmacopoeial Preparations
BP 2014: Clemastine Oral Solution; Clemastine Tablets;
USP 36: Clemastine Fumarate Tablets.

Clemizole Hydrochloride *(BANM, rINNM)*

AL-20; Clemizol, hidrocloruro de; Clémizole, Chlorhydrate de; Clemizoli Hydrochloridum; Hidrocloruro de clemizol; Клемизола Гидрохлорид.

1-(4-Chlorobenzyl)-2-(pyrrolidin-1-ylmethyl)benzimidazole hydrochloride.

$C_{19}H_{20}ClN_3,HCl$=362.3

CAS — 442-52-4 (clemizole); 1163-36-6 (clemizole hydrochloride).

UNII — 85W6I13D8M.

Profile

Clemizole hydrochloride is a sedating antihistamine (p. 610.1). It has been used for the symptomatic relief of allergic conditions, in pruritic skin disorders, and in combination preparations for the treatment of symptoms of the common cold. Clemizole has also been applied topically as the hexachlorophene, the sodium sulfate, and the undecylate derivatives in topical and rectal preparations combined with corticosteroids and local anaesthetics, although as with other antihistamines, there is a risk of sensitisation.

See p. 269.2 for the use of clemizole penicillin.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Apracur; *Braz.*: Ultraproct; *Indon.*: Ultraproct†; *Thai.*: Apracur.

Clocinizine Hydrochloride *(rINNM)*

Chlorcinnazine Dihydrochloride; Clocinizina, hidrocloruro de; Clocinizine, Chlorhydrate de; Clocinizini Hydrochloridum; Hidrocloruro de clonizina; Клоцинизина Гидрохлорид.

1-[4-Chlorobenzhydryl]-4-cinnamylpiperazine dihydrochloride.

$C_{26}H_{27}ClN_2,2HCl$=475.9

CAS — 298-55-5 (clocinizine).

UNII — AE8KM1QU3Q.

Profile

Clocinizine hydrochloride, a piperazine derivative, is an antihistamine (p. 610.1) given orally in combination preparations for the symptomatic treatment of upper respiratory-tract disorders, often with a decongestant.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Spain*: Senioral.

Cyclizine *(BAN, rINN)*

Ciclizina; Cyclizinum; Cyklizin; Siklizin; Syklitsiini; Циклизин.

1-Benzhydryl-4-methylpiperazine.

$C_{18}H_{22}N_2$=266.4.

CAS — 82-92-8.

ATC — R06AE03.

ATC Vet — QR06AE03.

UNII — QRW9FCR9P2.

Pharmacopoeias. In *Br.*

BP 2014: (Cyclizine). A white or creamy white, crystalline powder. Practically insoluble in water. It dissolves in most organic solvents and in dilute acids. M.p. about 107 degrees. A saturated solution in water has a pH of 7.6 to 8.6.

Cyclizine Hydrochloride *(BANM, rINNM)*

Ciclizina, hidrocloruro de; Ciklizin-hidroklorid; Ciklizino hidrochloridas; Cyclizine, Chlorhydrate de; Cyclizinhydrochlorid; Cyclizini Hydrochloridum; Cyklizin hydrochlorid; Cyklizinhydroklorid; Hidrocloruro de ciclizina; Syklitsiinihydrokloridi; Циклизина Гидрохлорид.

$C_{18}H_{22}N_2,HCl$=302.8

CAS — 303-25-3.

ATC — R06AE03.

ATC Vet — QR06AE03.

UNII — WOO1NHP4WE.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Cyclizine Hydrochloride). A white or almost white, crystalline powder. Slightly soluble in water and in alcohol. A 2% solution in alcohol 2 vol. and water 3 vol. has a pH of 4.5 to 5.5. Protect from light.

USP 36: (Cyclizine Hydrochloride). A white, odourless, crystalline powder or small colourless crystals. Soluble 1 in 115 of water and of alcohol and 1 in 75 of chloroform; insoluble in ether. pH of a 2% solution in alcohol 2 vol. and water 3 vol. is between 4.5 and 5.5. Store in airtight containers. Protect from light.

Cyclizine Lactate *(BANM, rINNM)*

Ciclizina, lactato de; Cyclizine, Lactate de; Cyclizini Lactas; Lactato de ciclizina; Циклизина Лактат.

$C_{18}H_{22}N_2,C_3H_6O_3$=356.5

CAS — 5897-19-8.

ATC — R06AE03.

ATC Vet — QR06AE03.

UNII — 861R00J986.

Pharmacopoeias. *Br.* includes an injection of cyclizine lactate.

Incompatibility. Cyclizine lactate is reported to be incompatible with oxytetracycline hydrochloride, chlortetracycline hydrochloride, benzylpenicillin, and solutions with a pH of 6.8 or more.

Cyclizine Tartrate *(BANM, rINNM)*

Ciclizina, tartrato de; Cyclizine, Tartrate de; Cyclizini Tartras; Tartrato de ciclizina; Циклизина Тартрат.

$C_{18}H_{22}N_2,C_4H_6O_6$=416.5

ATC — R06AE03.

ATC Vet — QR06AE03.

Uses and Administration

Cyclizine, a piperazine derivative, is a sedating antihistamine with antimuscarinic activity, although the sedative effects are not marked.

It is used as an antiemetic in the management of nausea and vomiting (p. 611.3) including motion sickness, postoperative nausea and vomiting, after radiotherapy, and in drug-induced nausea and vomiting. It is included as an antiemetic with some opioids, and in combination preparations for the treatment of migraine attacks (p. 670.3). Cyclizine is also used for the symptomatic treatment of vertigo (p. 612.3) caused by Ménière's disease and other vestibular disturbances.

In the management of nausea and vomiting, cyclizine hydrochloride is given in a usual oral dose of 50 mg up to three times daily, although up to 200 mg may be given in 24 hours if necessary. For the prevention of motion sickness, the first dose should be given about 30 minutes before travelling.

Cyclizine is given intramuscularly or intravenously as the lactate. Doses of cyclizine lactate are similar to those of cyclizine hydrochloride given orally. For the prevention of postoperative nausea and vomiting the first dose of cyclizine lactate should be given about 20 minutes before the anticipated end of surgery.

Although not licensed in the UK, cyclizine is also available as suppositories on a named-patient basis.

For dosage in children, see below.

Cyclizine salts are used as antiemetics in combination with morphine or dipipanone; the use of such fixed-combination opioid preparations is considered to be unsuitable for the prolonged treatment that may be required in palliative care. See also under Interactions, p. 624.1.

Administration in children. In the management of nausea and vomiting children aged 6 to 12 years can be given 25 mg of cyclizine hydrochloride, orally, up to three times daily; older children may be given the usual adult dose (see above). Although not licensed in the UK, the *BNFC* suggests that those aged 1 month to 6 years may be given 0.5 to 1 mg/kg (maximum of 25 mg) up to three times daily.

Cyclizine lactate injection is not licensed for use in children in the UK. However, the *BNFC* suggests the following doses may be given by continuous intravenous or subcutaneous infusion over 24 hours:

- children aged 1 month to 2 years: 3 mg/kg
- those aged 2 to 5 years: 50 mg
- those aged 6 to 12 years: 75 mg
- those aged 12 to 18 years: 150 mg

Cyclizine is also available as suppositories from specialist manufacturers, but again, is not licensed for this route in the UK. The *BNFC* suggests the following rectal doses may be given, up to three times daily:

- children aged 2 to 6 years: 12.5 mg
- those aged 6 to 12 years: 25 mg
- those aged 12 to 18 years, 50 mg

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively. Cyclizine may aggravate severe heart failure. Hypotension may occur on injection.

Abuse. Cyclizine tablets have been abused either alone or with opioids for their euphoric effects.[1-7] They have been taken orally or used to make injections. It has been suggested that cyclizine dependence may occur when it is used with opioids in the treatment of chronic pain.[8] Abuse of cyclizine has been reported in cancer patients receiving it by injection to control chemotherapy- or disease-related nausea.[9]

1. Gott PH. Cyclizine toxicity—intentional drug abuse of a proprietary antihistamine. *N Engl J Med* 1968; 279: 596.
2. Kahn A, Harvey GJ. Increasing misuse of cyclizine. *Pharm J* 1985; 235: 706.
3. Atkinson MK. Misuse of cyclizine. *Pharm J* 1985; 235: 773.
4. Halpin D. Misuse of cyclizine. *Pharm J* 1985; 235: 773.
5. Council of the Pharmaceutical Society of Great Britain. Sales of preparations containing cyclizine. *Pharm J* 1985; 235: 797.
6. Ruben SM, *et al.* Cyclizine abuse among a group of opiate dependents receiving methadone. *Br J Addict* 1989; 84: 929–34.
7. Bassett KE, *et al.* Cyclizine abuse by teenagers in Utah. *Am J Emerg Med* 1996; 14: 472–4.
8. Hughes AM, Coote J. Cyclizine dependence. *Pharm J* 1986; 236: 130.
9. Bailey F, Davies A. The misuse/abuse of antihistamine antiemetic medication (cyclizine) by cancer patients. *Palliat Med* 2008; 22: 869–71.

Effects on the blood. Agranulocytosis occurred in a patient after 6 weeks of treatment with cyclizine 50 mg three times daily.[1] The blood count returned to normal once cyclizine was withdrawn.

1. Collier PM. Agranulocytosis associated with oral cyclizine. *BMJ* 1986; 292: 174.

Effects on the heart. In a study[1] of 11 patients with severe heart failure, cyclizine produced detrimental haemodynamic effects including increased systemic and pulmonary artery pressures and ventricular filling pressures, and negated the vasodilator effects of diamorphine. It was suggested that the use of cyclizine should be avoided in patients with acute myocardial infarction or severe heart failure.

1. Tan LB, *et al.* Detrimental haemodynamic effects of cyclizine in heart failure. *Lancet* 1988; i: 560–1.

Effects on the liver. An 8-year-old girl developed jaundice on 2 occasions after taking oral cyclizine hydrochloride 25 mg daily. 'Hypersensitivity hepatitis' was considered responsible.[1]

1. Kew MC, *et al.* "Hypersensitivity hepatitis" associated with administration of cyclizine. *BMJ* 1973; 2: 307.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cyclizine as probably porphyrinogenic; it should be prescribed only for

compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Pregnancy. For discussion of the use of antihistamines in pregnancy, including studies involving cyclizine, see p. 614.2.

Interactions

As for the sedating antihistamines in general, p. 614.3. Cyclizine may counteract the haemodynamic benefits of opioids (see Effects on the Heart, p. 623.3) and this should be considered before using preparations that contain a combination of cyclizine and an opioid analgesic.

General anaesthetics. For a possible interaction between cyclizine premedication and *barbiturate anaesthetics* see under Thiopental, p. 1919.3.

Pharmacokinetics

Cyclizine is absorbed from the gastrointestinal tract and has an onset of action within 2 hours. The duration of action is reported to be about 4 hours. Cyclizine is metabolised in the liver to the relatively inactive metabolite, norcyclizine. Both cyclizine and norcyclizine have plasma elimination half-lives of 20 hours. Less than 1% of the total oral dose is eliminated in the urine in 24 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Echnatol; ***Denm.***: Marzine; ***Fin.***: Marzine; ***India***: Medazine; ***Irl.***: Valoid; ***Neth.***: Kruidvat Reistablet†; ***Norw.***: Marzine; ***NZ***: Marzine†; Nausicalm; Valoid; ***S.Afr.***: Aculoid; Covamet; Emitex; Medazine; Nauzine; Pinaloid; Triazine; Valoid; ***Singapore***: Marzine; ***Switz.***: Marzine†; ***UK***: Valoid; ***USA***: Bonine for Kids; Cyclivert; Marezine.

Multi-ingredient Preparations. ***Austria***: Echnatol B_6; ***Fin.***: Vertipam†; ***India***: Migril; ***Irl.***: Cyclimorph; ***S.Afr.***: Cyclimorph; Migril; Wellconal; ***UK***: Cyclimorph; Diconal†; Migril.

Pharmacopoeial Preparations
BP 2014: Cyclizine Injection; Cyclizine Tablets; Dipipanone and Cyclizine Tablets;
USP 36: Cyclizine Hydrochloride Tablets.

Cyproheptadine Hydrochloride

(BANM, rINNM)

Ciproheptadina, hidrocloruro de; Ciproheptadin-hidroklorid; Ciproheptadino hidrocloridas; Cyproheptadine, chlorhydrate de; Cyproheptadinhydrochlorid; Cyproheptadin-hydrochlorid seskvihydrát; Cyproheptadinhydroklorid; Cyproheptadini hydrochloridum; Cyproheptadini Hydrochloridum Sesquihydricum; Hidrocloruro de ciproheptadina; Siproheptadin Hidroklorür; Syproheptadiinihydrokloridi; Ципрогептадина гидрохлорид.

4-(5*H*-Dibenzo[*a,d*]cyclohepten-5-ylidene)-1-methylpiperidine hydrochloride sesquihydrate.

$C_{21}H_{21}N,HCl,1½H_2O$=350.9

CAS — 129-03-3 (cyproheptadine); 969-33-5 (anhydrous cyproheptadine hydrochloride); 41354-29-4 (cyproheptadine hydrochloride sesquihydrate).

ATC — R06AX02.

ATC Vet — QR06AX02.

UNII — NJ82J0F8QC.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Cyproheptadine Hydrochloride). A white or slightly yellow, crystalline powder. Slightly soluble in water; sparingly soluble in alcohol; freely soluble in methyl alcohol. Protect from light.

USP 36: (Cyproheptadine Hydrochloride). A white to slightly yellow, odourless or practically odourless, crystalline powder. Soluble 1 in 275 of water, 1 in 35 of alcohol, 1 in 26 of chloroform, and 1 in 1.5 of methyl alcohol; practically insoluble in ether.

Uses and Administration

Cyproheptadine, a piperidine derivative, is a sedating antihistamine with antimuscarinic, serotonin-antagonist, and calcium-channel blocking actions. It is used as the hydrochloride for the symptomatic relief of allergic conditions including urticaria and angioedema (p. 612.3), rhinitis (p. 612.1) and conjunctivitis (p. 611.1), and in pruritic skin disorders (p. 612.1). Other uses include the management of migraine (p. 611.3). Cyproheptadine hydrochloride is given as the sesquihydrate although doses are expressed in terms of the anhydrous substance. Anhydrous cyproheptadine hydrochloride 10 mg is equivalent to about 11 mg of cyproheptadine hydrochloride sesquihydrate.

For allergic conditions and pruritus the oral dose is initially 4 mg three times daily, adjusted as necessary. The average dose requirement is 12 to 16 mg daily in three or four divided doses, but up to 32 mg daily may occasionally be necessary. Cyproheptadine is not recommended in debilitated elderly patients. For dosage in children, see below.

A dose of 4 mg is used for both prophylaxis and treatment of migraine and other vascular headaches and may be repeated after 30 minutes; patients who respond usually obtain relief with 8 mg, and this dose should not be exceeded within a 4- to 6-hour period. A maintenance dose of 4 mg may be given every 4 to 6 hours.

Other cyproheptadine salts that have been given orally include the acetylaspartate, aspartate, cyclamate, orotate, acefyllinate (7-theophyllineacetate), and the pyridoxal phosphate salt (dihexazine).

Administration in children. For allergic conditions and pruritus, the oral dose of cyproheptadine hydrochloride for children aged 2 to 6 years is 2 mg two or three times daily. This may be increased to a maximum of 12 mg daily if necessary. For children aged 7 to 14 years, 4 mg two or three times daily may be given, increased up to a maximum of 16 mg daily.

Abdominal migraine. Cyproheptadine has been tried in the prophylactic treatment of children with abdominal migraine (see Pizotifen, p. 678.2).

Angina pectoris. Cyproheptadine was used successfully to treat 2 patients with Prinzmetal's angina (p. 1254.3) refractory to standard treatment with calcium-channel blockers and nitrates.[1] Serotonin is an important endocrine mediator of coronary vasospasm and the beneficial effects of cyproheptadine were attributed to its activity as a serotonin antagonist.

1. Schecter AD, *et al.* Refractory Prinzmetal angina treated with cyproheptadine. *Ann Intern Med* 1994; 121: 113–14.

Appetite disorders. Cyproheptadine has been widely used as an appetite stimulant, including for anorexia nervosa and cachexia (see under Megestrol, p. 2289.3), but in the long-term appears to have little value in producing weight gain and such use is no longer generally recommended. There has been concern that cyproheptadine was being promoted and used inappropriately as an appetite stimulant in some developing countries.[1]

1. Anonymous. Cyproheptadine: no longer promoted as an appetite stimulant. *WHO Drug Inf* 1994; 8: 66.

Carcinoid syndrome. The management of neuroendocrine tumours (p. 716.3) is largely symptomatic. Cyproheptadine hydrochloride, a serotonin antagonist, has had limited success in relieving symptoms such as diarrhoea but somatostatin analogues may now be preferred.[1] It has been used successfully with fenclonine, aprotinin, methylprednisolone, and antibacterials to prevent complications arising from release of tumour metabolites during hepatic embolisation, a procedure sometimes used to relieve the symptoms of carcinoid syndrome.[2] There have been a few reports of tumour regression, in addition to symptomatic control, after treatment of carcinoid tumours with cyproheptadine.[3,4]

1. Caplin ME, *et al.* Carcinoid tumour. *Lancet* 1998; 352: 799–805.
2. Maton PN, *et al.* Role of hepatic arterial embolisation in the carcinoid syndrome. *BMJ* 1983; 287: 932–5. Correction to dosage. ibid.; 1664.
3. Harris AL, Smith IE. Regression of carcinoid tumour with cyproheptadine. *BMJ* 1982; 285: 475.
4. Leitner SP, *et al.* Partial remission of carcinoid tumor in response to cyproheptadine. *Ann Intern Med* 1989; 111: 760–1.

Serotonin syndrome. Cyproheptadine has been successfully used to treat the serotonin syndrome (p. 443.2) in patients who have developed the syndrome after overdoses involving serotonergic drugs or who have had their antidepressant therapy changed without an adequate wash-out period.[1,2]

1. Lappin RI, Auchincloss EL. Treatment of the serotonin syndrome with cyproheptadine. *N Engl J Med* 1994; 331: 1021–2.
2. McDaniel WW. Serotonin syndrome: early management with cyproheptadine. *Ann Pharmacother* 2001; 35: 870–3.

Sexual dysfunction. Cyproheptadine has been tried in the management of sexual dysfunction induced by SSRIs (see Effects on Sexual Function under Fluoxetine, p. 421.1) but may possibly reduce the efficacy of the SSRI.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively. Increased appetite and weight gain may occur with cyproheptadine.

Abuse. Dependence developed in a patient who took about 180 mg of oral cyproheptadine daily for 5 years.[1]

1. Craven JL, Rodin GM. Cyproheptadine dependence associated with an atypical somatoform disorder. *Can J Psychiatry* 1987; 32: 143–5.

Effects on the nervous system. Antimuscarinic toxicity manifest by hallucinations and agitation developed in a 2-year-old child taking cyproheptadine 4 mg twice daily for migraine prophylaxis.[1]

1. Watemberg NM, *et al.* Central anticholinergic syndrome on therapeutic doses of cyproheptadine. *Pediatrics* 1999; 103: 158–60.

Interference with diagnostic tests. Cyproheptadine reduced hypoglycaemia-induced growth hormone secretion by between 5 and 97% in 8 healthy subjects.[1] It was suggested that cyproheptadine therapy should be stopped before giving a pituitary function test that used growth hormone response to insulin-induced hypoglycaemia.

UK licensed product information states that cyproheptadine may cause a false-positive test result for tricyclic antidepressants in urine or serum.

1. Bivens CH, *et al.* Inhibition of hypoglycaemia-induced growth hormone secretion by the serotonin antagonists cyproheptadine and methysergide. *N Engl J Med* 1973; 289: 236–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cyproheptadine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Interactions

As for the sedating antihistamines in general, p. 614.3.

Antidepressants. For reports suggesting that cyproheptadine can reduce the efficacy of *SSRIs*, see under Fluoxetine, p. 424.2. Cyproheptadine may interfere with diagnostic tests for tricyclic antidepressants, see above.

Pharmacokinetics

After absorption from the gastrointestinal tract, cyproheptadine hydrochloride undergoes almost complete metabolism. Metabolites are excreted principally in the urine as conjugates, and also in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Periactin; ***Austria***: Periactin; ***Belg.***: Periactin; ***Braz.***: Periatin; ***Chile***: Viternum; ***Cz.***: Peritol; ***Fr.***: Periactine; ***Ger.***: Peritol; ***Gr.***: Adekin; Istam-Far; Kulinet; Periactin†; ***Hong Kong***: Appetin†; CH Syrup†; Cyprodine†; Cyprogin; Uni-Heptadine†; ***Hung.***: Peritol; ***India***: Addl App; Anabol; Apedin; Apel; Apenorm; Apeplus; Apetamin; App-Up; Appetidin; Aptaur; Bal-Riactin; Gedel; Ciplactin; Cyp-L; Cypgo; Cyphoden; Cyproden; Hito-EN; Hungree; Indocyp; Peritol; Practin; ***Indon.***: Alphahist†; Apeton; Cydifar†; Cylat†; Ennamax; Esprocy; Glocyp; Heptasan; Lexahist; Poncohist; Procuf†; Prohessen; Pronicy; Sinapdin†; ***Irl.***: Periactin†; ***Ital.***: Periactin; ***Mex.***: Viternum; ***Neth.***: Periactin; ***NZ***: Periactin; ***Pol.***: Peritol; ***Port.***: Viternum; ***Rus.***: Peritol (Перитол); ***S.Afr.***: Cipla-Actin; Periactin; ***Singapore***: Cyprotin; Periactin†; Pilian; ***Spain***: Periactin; Viternum; ***Swed.***: Periactin†; ***Thai.***: Anpro; Cycodine; Cyheptine; Cyprocap; Cyprodine; Cyprogin; Cypronam; Cyprono; Cypropicco; Cyprosian; Cyprotec; Hepdine†; Periactin Polytab; ***Turk.***: Prakten; Sipraktin; ***UK***: Periactin; ***Ukr.***: Peritol (Перитол); ***Venez.***: Cyprodin.

Multi-ingredient Preparations. ***Arg.***: Apeplus; Apetitol Forte; Ciprocort; Ciprovit Calcio; Ciprovit Energizante; Ciprovit Magnesico; Mikesan; Potencil; Sudevil Vita; ***Braz.***: Apetivit BC Apetiviton BC; Apevinat BC; Apevitin BC; Apmed; Cobactin Cobaglobal; Cobavit; Cobavital; Petivit BC; Trimetabol†; ***Chile***: Apetrol; Orodina; Peracon; Revil; Rodepan; Viternum Vitaminado; ***Hong Kong***: Calbolex†; Calibo Chewable†; Lysinevita†; Petina Compound; Tres Orix Forte†; Tricavita†; Vigueur†; ***India***: Anorexin Plus; Apel-G; Apenic; Apirich; Apitus-TC App-Up; Appe-Care; Appet; Appetidin; Asi-Liv; Atric Plus; Auz Bio Cyp; Chocy; Cipliv; Clydin; Cyaptin With Calcium; Cyaptin-SP; Cyaptin; Cydine; Cyp-L; Cypee; Cypine-TS; Cypolin Cypon DPS; Cypon-L; Cypon; Cyprea-T; Cypro-L; Cypro Cyprobit; Cyprowal; Cyproz; Decyp-P; Devlup; Forliv; Fortil Growise; Hapeast; Hapeast; Hepsandinn; Hyperin; In-OZ; Karnatakaiv; Lecyp; Livpron; LSky; Lycyp; M-Cyp; NBTone; O-AP Oraxin; Orliv; ***Mex.***: Ciprolisina; Pangavit Pediatrico; Rocavit; ***Spain***: Anti-Anorex Triple; Covitasa B12; Desarrol; Medenorex†; Novogumil; Pantobamin; Pranzo; Stolina; Tonico Juventus; Trimetabol; Troforex Pepsico†; Vita Menal; ***Ukr.***: Trimetabol (Триметабол); ***Venez.***: Cyprodex.

Pharmacopoeial Preparations
BP 2014: Cyproheptadine Tablets;
USP 36: Cyproheptadine Hydrochloride Syrup; Cyproheptadine Hydrochloride Tablets.

Deptropine Citrate *(BANM, rINNM)*

Citrato de deptropina; Deptropiinisitraatti; Deptropina, citrato de; Deptropincitrat; Deptropin-citrát; Deptropine, Citrate de; Deptropini Citras; Deptropino citratas; Dibenzheptropine Citrate; Дептропина Цитрат.

(1*R*,3*r*,5*S*)-3-(10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yloxy)tropane dihydrogen citrate.

$C_{23}H_{27}NO,C_6H_8O_7$=525.6

CAS — 604-51-3 (deptropine); 2169-75-7 (deptropine citrate).

ATC — R06AX16.

ATC Vet — QR06AX16.

UNII — 05LW13XKKR.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Deptropine Citrate). A white or almost white, microcrystalline powder. Very slightly soluble in water and in dehydrated alcohol; practically insoluble in dichloromethane. A saturated solution in water has a pH of 3.7 to 4.5. Protect from light.

Profile

Deptropine citrate is a sedating antihistamine (p. 610.1) with a marked antimuscarinic action. It was given by mouth mainly in the treatment of respiratory-tract disorders.

Desloratadine *(BAN, USAN, rINN)*

Descarboethoxyloratadine; Descarboetoxiloratadina; Desloratadin; Desloratadina; Desloratadinum; Sch-34117; Дезлоратадин.

8-Chloro-6,11-dihydro-11-(4-piperidylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine.

$C_{19}H_{19}ClN_2$=310.8

CAS — 100643-71-8.

ATC — R06AX27.

ATC Vet — QR06AX27.

UNII — FVF865388R.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Desloratadine). A white or almost white powder. Very slightly soluble or practically insoluble in water; freely soluble in alcohol; slightly soluble or very slightly soluble in heptane. It shows polymorphism.

Profile

Desloratadine, the major, active metabolite of loratadine (p. 633.2), is a non-sedating antihistamine. Desloratadine is used in the symptomatic relief of allergic conditions including rhinitis (p. 612.1) and urticaria (p. 612.3).

Desloratadine is given in an oral dose of 5 mg once daily.

It is also used with a decongestant such as pseudoephedrine sulfate.

For dosage in children, and in hepatic or renal impairment, see below.

References.

1. McClellan K, Jarvis B. Desloratadine. *Drugs* 2001; 61: 789–96.
2. Simons FER, ed. Desloratadine: clinical pharmacokinetics of a novel H_1 receptor antagonist. *Clin Pharmacokinet* 2002; 41 (suppl 1): 1–44.
3. Limon L, Kockler DR. Desloratadine: a nonsedating antihistamine. *Ann Pharmacother* 2003; 37: 237–46. Correction. *ibid.*: 454.
4. Murdoch D, *et al.* Desloratadine: an update of its efficacy in the management of allergic disorders. *Drugs* 2003; 63: 2051–77.
5. Berger WE. The safety and efficacy of desloratadine for the management of allergic disease. *Drug Safety* 2005; 28: 1101–18.
6. Canonica GW, *et al.* Efficacy of desloratadine in the treatment of allergic rhinitis: a meta-analysis of randomized, double-blind, controlled trials. *Allergy* 2007; 62: 359–66.
7. Layton D, *et al.* Examining the tolerability of the non-sedating antihistamine desloratadine: a prescription-event monitoring study in England. *Drug Safety* 2009; 32: 169–79.

Administration in children. In the UK, desloratadine is licensed for use in children aged 1 year and over in the treatment of allergic rhinitis and urticaria; in the USA, it may be given to those aged 6 months and over for perennial allergic rhinitis and urticaria and to those aged 2 years and over for seasonal allergic rhinitis.

Regardless of indication, oral doses of desloratadine are as follows:

- children aged 6 to 11 months: 1 mg once daily
- those aged 1 to 5 years: 1.25 mg once daily
- those aged 6 to 11 years: 2.5 mg once daily.

References.

1. Gupta S, *et al.* Pharmacokinetics of desloratadine in children between 2 and 11 years of age. *Br J Clin Pharmacol* 2007; 63: 534–40.
2. Gupta SK, *et al.* Desloratadine dose selection in children aged 6 months to 2 years: comparison of population pharmacokinetics between children and adults. *Br J Clin Pharmacol* 2007; 64: 174–84.

Administration in hepatic or renal impairment. US licensed product information recommends that patients with hepatic or renal impairment should be given desloratadine 5 mg orally on alternate days initially.

Breast feeding. Desloratadine is distributed into breast milk and consequently UK and US licensed product information does not recommend its use during breast feeding. For a discussion of the use of *loratadine* in breast feeding, see under Adverse Effects and Precautions, p. 633.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies desloratadine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Pregnancy. Desloratadine was not teratogenic in *animal* studies; however, product information recommends it should be used with caution, if at all, in pregnant women.

For a discussion of the use of loratadine in pregnancy, see under Adverse Effects and Precautions, p. 633.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aerius; Delorat; Desaler; Deslo; Frenaler; Hexaler; Novo Alerpriv; Predualergin; ***Austral.***: Aerius; Claramax†; ***Austria***: Aerius; ***Belg.***: Aerius; ***Braz.***: Aleradina; Desalex; Deslorana; Destadin; ***Canad.***: Aerius; ***Chile***: Aerius; D-Histaplus; Deslocross; Despeval; Despex; Mailen; Neo Larmax; Neo-Alledryl; Neoclaritine; Neohystidar; Rinaid; Rinofilax; ***China***: Aerius (恩理思); Dihengsai (地恒赛); Fu Bi Ding (芙必叮); Xin Ming Ting (信敏汀); ***Cz.***: Aerius; Azomyr; Neoclarityn; ***Denm.***: Aerius; Dasselta; ***Fin.***: Aerius; ***Fr.***: Aerius; ***Ger.***: Aerius; ***Gr.***: Aerius; Azomyr; Neoclarityn; ***Hong Kong***: Aerius; ***Hung.***: Aerius; ***India***: Alerdain; Allerede; Allergesic; D-Loratin; D-Lordex; Dazit; Delorta; Delotid; Des-OD; Desent; Deslor; Desloriv; Desnova; Dexly; Dilora; DYL; Lorday; Loreta; Neoloridin; Nucope; Otrivin-Alert; ***Indon.***: Aerius; ***Irl.***: Aerius; Azomyr; Dasselta; Neoclarityn; ***Israel***: Aerius; ***Ital.***: Aerius; Azomyr; Efestad; Neokatall; ***Malaysia***: Aerius; ***Mex.***: Aviant; Azomyr; Lirudine; ***Neth.***: Aerius; Azomyr; Dasselta; Desloratsam; Lodesdineta; Neoclarityn; ***Norw.***: Aerius; NZ: Aerius; Claramax; ***Philipp.***: Aerius; ***Pol.***: Aerius; Azomyr; Neoclarityn; ***Port.***: Aerius; Azomyr; Neoclarityn; ***Rus.***: Aerius (Эриус); Lordestin (Лордестин); ***S.Afr.***: Dazit; Desaway; Deselex; Desodene; ***Singapore***: Aerius; ***Spain***: Aerius; Azomyr; Dasselta; ***Swed.***: Aerius; Dasselta; ***Switz.***: Aerius; ***Thai.***: Aerius; ***Turk.***: Aerius; Doxafin; Lordes; ***UK***: Neoclarityn; ***Ukr.***: Aerius (Эриус); Allergostop (Аллергостоп); Desorus (Дезорус)†; Edem (Эдем); Eridez (Эридез); Loratek (Лоратек); ***USA***: Clarinex; ***Venez.***: Aerius; Desalex; Deslorat; Esparflin; Mailen.

Multi-ingredient Preparations. ***Arg.***: Desaler Cort; Frenaler Cort; Hexaler Cort; Hexaler Plus; ***Belg.***: Aerinaze; ***Canad.***: Aerius Dual Action 12 Hour; ***Cz.***: Aerinaze; ***Gr.***: Aerinaze; ***India***: DM; DYL-AX; DYL-D; Mondeslor; Neoloridin-D; Nucope-AD; ***Irl.***: Aerinaze; ***Israel***: Aerinaze; ***Neth.***: Aerinaze; ***Pol.***: Aerinaze; ***Port.***: Aerinaze; ***Singapore***: Aerius D-12; ***USA***: Clarinex-D.

Dimenhydrinate *(BAN, rINN)*

Chloranautine; Dimenhidrinat; Dimenhidrinát; Dimenhidrinatas; Dimenhidrinato; Dimenhydramina; Dimenhydrinaatti; Dimenhydrinat; Dimenhydrinát; Diménhydrinate; Dimenhydrinatum; Diphenhydramine Teoclate; Diphenhydramine Theoclate; Дименгидринат.

The diphenhydramine salt of 8-chlorotheophylline.

$C_{17}H_{21}NO,C_7H_7ClN_4O_2$=470.0

CAS — 523-87-5.

ATC — R06AA02.

ATC Vet — QR06AA02.

UNII — JB937PER5C.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Dimenhydrinate). A white or almost white, crystalline powder or colourless crystals. M.p. 102 degrees to 106 degrees. Slightly soluble in water; freely soluble in alcohol. A saturated solution in water has a pH of 7.1 to 7.6.

USP 36: (Dimenhydrinate). A white, odourless, crystalline powder. Slightly soluble in water; freely soluble in alcohol and in chloroform; sparingly soluble in ether.

Incompatibility. Dimenhydrinate has been reported to be incompatible in solution with many compounds; those most likely to be encountered include: aminophylline, glycopyrronium bromide, hydrocortisone sodium succinate, hydroxyzine hydrochloride, meglumine adipiodone, some phenothiazines, and some soluble barbiturates.

Uses and Administration

Dimenhydrinate, a monoethanolamine derivative, is a sedating antihistamine with antimuscarinic and significant sedative effects. It is used mainly as an antiemetic in the prevention and treatment of motion sickness (p. 611.3). It is also used for the symptomatic treatment of nausea and vertigo caused by Ménière's disease and other vestibular disturbances (see Vertigo, p. 612.3).

The usual oral dose of dimenhydrinate is 50 to 100 mg, given 3 or 4 times daily. For the prevention of motion sickness, the first dose should be given at least 30 minutes before travelling.

Dimenhydrinate may be given parenterally in usual doses of 50 mg, a concentration of 5% being used for intramuscular injection and 0.5% for slow intravenous injection (usually over 2 minutes).

For doses in children, see below.

Dimenhydrinate has also been given by the rectal route.

Administration in children. Dimenhydrinate can be given to children for the symptomatic treatment of nausea and vomiting associated with various conditions. The following doses may be given orally, depending on age:

- children aged 2 to 6 years: 12.5 to 25 mg every 6 to 8 hours to a maximum of 75 mg daily
- those aged 6 to 12 years: 25 to 50 mg every 6 to 8 hours to a maximum of 150 mg daily

For the prevention of motion sickness, the first dose should be given at least 30 minutes before travelling.

Alternatively, children have been given dimenhydrinate intramuscularly, in a dose of 1.25 mg/kg four times daily to a maximum of 300 mg daily.

Children and adolescents aged 12 years and over may be given usual adult doses, see above.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively.

Effects on the eyes. Dimenhydrinate 100 mg, given at 4-hourly intervals for 3 doses, was found to affect colour discrimination, night vision, reaction time, and stereopsis.[1]

1. Luria SM, *et al.* Effects of aspirin and dimenhydrinate (Dramamine) on visual processes. *Br J Clin Pharmacol* 1979; 7: 585–93.

Pregnancy. For discussion of the use of antihistamines in pregnancy, including a suggestion of a relationship between cardiovascular defects or inguinal hernia and dimenhydrinate exposure, see p. 614.2.

Interactions

As for the sedating antihistamines in general, p. 614.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Agirax; Dr Amin; Dramamine; Vertigmine; ***Austral.***: Dramamine†; ***Austria***: Emedyl; Travel-Gum; Vertirosan; ***Belg.***: Paranausine†; ***Braz.***: Dramamine†; Dramin; Neodrin; ***Canad.***: Anti-Nauseant; Anti-Nausee†; Childrens Motion Sickness Liquid; Dinate; Gravol; Motion Sickness†; Nauseatol; Novo-Dimenate; Travel Tabs; ***Chile***: Mareamin; ***China***: Yi Han Ning (贴晗柠); ***Cz.***: Travel-Gum; ***Fr.***: Nausicalm; ***Ger.***: Reisefit; Reisetablette†; Superpep; Vertigo-Vomex; Vomacur†; Vomex A; ***Gr.***: Baderol; Dravom; Drimen; Retager; Travelgum; Vertirosan; Vomex A; ***Hong Kong***: Dimate†; Dimenate; Garcol; Gravol; Gravolvick†; Neo-Diphenamine†; Novomin; Setmenate; Synavol†; Uni-Hydrin†; ***Hung.***: Daedalon; Daedalonetta; ***India***: Dramamine; Draminate; Gravol; ***Indon.***: Dramamine; Stopmun†; ***Israel***: Travamin; ***Ital.***: Lomarin; Motozina†; Travelgum; Valontan; Xamamina; ***Malaysia***: Dimenate; Dramamine†; Driminate; Hydrinate; Novomin; Votmine; Zoranate; ***Mex.***: Apo-Mina; Dimicaps; Dramamine; Dramit-GB; Vomisin; ***NZ***: Dramamine†; ***Philipp.***: Emes; Gravol; ***Pol.***: Aviomarin; ***Port.***: Draminal; Enjomin; Viabom; Vomidrine; ***Rus.***: Dramina (Драмина); Siel (Сиэль); ***Singapore***: Dimenate; Dramamine†; Medrinate; Novomin; Votmine; ***Spain***: Biodramina; Cinfamar; Travel Well; ***Swed.***: Amosyt; Calma; ***Switz.***: Antemine†; Trawell; ***Thai.***: Denim; Dimenine; Dimeno; Dimesian; Dimin; Dimonate; Divomit; Dramamine†; Dramine; Gravol†; KB Dramine; Motivan; Nausamine†; Navamin; Phrachedi†; Vomen; ***Turk.***: Anti-Em; Dramamine; Xamamina; ***UAE***: Dizinil; ***Ukr.***: Dramina (Драмина); ***USA***: Dimetabs; Dinate†; Dramamine†; Dramanate; Dymenate; Triptone; ***Venez.***: Viajesan.

Multi-ingredient Preparations. ***Austral.***: Travacalm; ***Austria***: Neo-Emedyl; Synkapton; Vertirosan Vitamin B_6; ***Belg.***: Arlevertan; ***Braz.***: Dramin B6 DL; Dramin B6; Nausicalm; Nausilon B6; ***Canad.***: Gravergol†; ***Cz.***: Arlevert; Migraeflux†; ***Fin.***: Arlevert; ***Fr.***: Mercalm; ***Ger.***: Arlevert; ***Gr.***: Vertigo-Vomex; ***Hong Kong***: Rhinocap†; ***Hung.***: Arlevert; ***Indon.***: Dramasine; ***Irl.***: Arlevert; ***Ital.***: Arlevertan; ***Mex.***: Bomine; ***Neth.***: Arlevert; ***Rus.***: Synkapton (Синкаптон); ***Spain***: Acetuber; Biodramina Cafeína; Cinfamar Cafeína; Saldeva; Salvarina; ***Swed.***: Arlevert; ***Switz.***: Antemin compositum; Arlevert; Coop Vitality†; Dragees contre les maux de voyage†; Gem Voyage Dragees contre les maux de voyage; Rhin-X; Rhinocap; Rotpunkt Apotheke dragees contre les maux de voyage; Tesero Voyage; ***Thai.***: Roxine; ***UK***: Arlevert.

Pharmacopoeial Preparations

BP 2014: Dimenhydrinate Tablets;

USP 36: Dimenhydrinate Injection; Dimenhydrinate Syrup; Dimenhydrinate Tablets.

Dimetindene Maleate *(BANM, rINNM)*

Dimethindene Maleate (USAN); Dimethindene Maleate; Dimethpyrindene Maleate; Dimethylpyrindene Maleate; Dimetindeenimaleaatti; Dimetinden Maleat; Dimétindène, Maléate de; Dimetindenil Maleas; Dimetindenmaleat; Dimetindén-maleát; Dimetinden-maleinát; Dimetindeno maleatas; Dimetindeno, maleato de; Maleato de dimetindeno; NSC-107677; Su-6518; Диметиндена Малеат.

NN-Dimethyl-2-[3-[1-(2-pyridyl)ethyl]-1*H*-inden-2-yl]ethylamine hydrogen maleate.

$C_{20}H_{24}N_2.C_4H_4O_4$=408.5

CAS — 5636-83-9 (dimetindene); 3614-69-5 (dimetindene maleate).

ATC — D04AA13; R06AB03.

ATC Vet — QD04AA13; QR06AB03.

UNII — 6LL60J9E0O.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Dimetindene Maleate). A white to almost white, crystalline powder. Slightly soluble in water; soluble in methyl alcohol. Protect from light.

Profile

Dimetindene maleate, an alkylamine derivative, is a sedating antihistamine (p. 610.1); it is mildly sedative and is reported to have mast-cell stabilising properties. It is used for the symptomatic relief of allergic conditions including urticaria and angioedema (p. 612.3) and rhinitis (p. 612.1), and in pruritic skin disorders (p. 612.1). It is also used in compound preparations for the symptomatic treatment of coughs and the common cold (p. 611.2).

Dimetindene maleate is given in an oral dose of 1 to 2 mg three times daily; modified-release preparations are also available. It may also be given by the intravenous route. Dimetindene maleate is applied topically as a 0.1% gel or lotion although, as with other antihistamines, there is a risk of sensitisation. It is used in a strength of 0.025% in compound nasal preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria:*** Fenistil; ***Belg.:*** Fenistil; ***Cz.:*** Fenistil; ***Ger.:*** Fenistil; ***Gr.:*** Fenistil; Specisun; ***Hung.:*** Fenistil; ***India:*** Foristal; ***Indon.:*** Fenistil; ***Israel:*** Fenistil; ***Ital.:*** Fenistil; ***Neth.:*** Fenistil; ***Philipp.:*** Fenistil; ***Pol.:*** Fenistil; ***Port.:*** Fenistil; Neostil†; ***Rus.:*** Fenistil (Фенистил); ***Spain:*** Fenistil; ***Switz.:*** Feniallerg; Fenistil; ***Thai.:*** Fenistil; ***Turk.:*** Fenistil; ***Ukr.:*** Fenistil (Фенистил).

Multi-ingredient Preparations. ***Arg.:*** Vibragel; ***Austria:*** Trimedil compositum†; Vibrocil; ***Belg.:*** Vibrocil; ***Braz.:*** Gripen; Trimedal; ***Cz.:*** Vibrocil; ***Gr.:*** Vibrocil-S; ***Hung.:*** Otrivin Allergia; Vibrocil; ***Israel:*** Vibrocil; ***Pol.:*** Otrivin Allergy; ***Port.:*** Vibrocil; ***Rus.:*** Vibrocil (Виброцил); ***S.Afr.:*** Vibrocil-S; Vibrocil; ***Switz.:*** Otriduo Rhume; Vibrocil; ***Ukr.:*** Vibrocil (Виброцил).

Dimetotiazine Mesilate *(BANM, rINNM)*

Dimethothiazine Mesylate; Dimetotiazina, mesilato de; Dimétotiazine, Mésilate de; Dimetotiazini Mesilas; Fonazine Mesylate (USAN); IL-6302 (dimetotiazine); Mesilato de dimetotiazina; 8599-RP (dimetotiazine); Диметотиазина Мезилат.

10-(2-Dimethylaminopropyl)-*NN*-dimethylphenothiazine-2-sulphonamide methanesulphonate.

$C_{19}H_{25}N_3O_2S_2.CH_3SO_3H$=487.6

CAS — 7456-24-8 (dimetotiazine); 7455-39-2 (dimetotiazine mesilate).

ATC — N02CX05.

ATC Vet — QN02CX05.

UNII — B28V86NGNK.

Profile

Dimetotiazine mesilate, a phenothiazine derivative, is a sedating antihistamine (p. 610.1). It has been used for the symptomatic relief of hypersensitivity reactions, in pruritic skin disorders, and in the management of headaches including migraine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Indon.:*** Migristene†; ***Mex.:*** Migristene†.

Diphenhydramine *(BAN, rINN)*

Benzhydramine; Difenhidramina; Difenhydramiini; Difenhydramin; Diphénhydramine; Diphenhydraminum; Дифенгидрамин.

2-Benzhydryloxy-*NN*-dimethylethylamine.

$C_{17}H_{21}NO$=255.4

CAS — 58-73-1.

ATC — D04AA32; R06AA02.

ATC Vet — QD04AA32; QR06AA02.

UNII — 8GTS82S83M.

Pharmacopoeias. In *Jpn.*

Jpn also includes Diphenhydramine Tannate.

Diphenhydramine Citrate *(BANM, rINNM)*

Benzhydramine Citrate; Citrato de difenhidramina; Difenhidramina, citrato de; Diphénhydramine, Citrate de; Diphenhydramini Citras; Дифенгидрамина Цитрат.

$C_{17}H_{21}NO.C_6H_8O_7$=447.5

CAS — 88637-37-0.

ATC — D04AA32; R06AA02.

ATC Vet — QD04AA32; QR06AA02.

UNII — 4OD4335209.

Pharmacopoeias. In *US.*

USP 36: (Diphenhydramine Citrate). Store in airtight containers. Protect from light.

Diphenhydramine Di(acefyllinate) *(rINNM)*

Benzhydramine Di(acefyllinate); Bietanautine; Di(acefilinato) de difenhidramina; Difenhidramina, di(acefilinato) de; Diphénhydramine Diacéfylline; Diphenhydramine Di(acephyllinate); Diphenhydramini Diacefyllinas; Дифенгидрамина Диацефиллинат.

Diphenhydramine bis(theophyllin-7-ylacetate).

$C_{17}H_{21}NO.2C_9H_{10}N_4O_4$=731.8

CAS — 6888-11-5.

ATC — D04AA32; R06AA02.

ATC Vet — QD04AA32; QR06AA02.

UNII — F3D8G86A29.

NOTE. The name Etanautine has been applied both to diphenhydramine monoacefyllinate and to ethylbenzhydramine, an antimuscarinic formerly used in the symptomatic treatment of parkinsonism.

Diphenhydramine Hydrochloride *(BANM, rINNM)*

Benzhydramine Hydrochloride; Difenhidramin Hidroklorür; Difenhidramina, hidrocloruro de; Difenhidramin-hidroklorid; Difenhidramino hidrochloridas; Difenhydramiinihydrokloridi; Difenhydramin-hydrochlorid; Difenhydraminhydroklorid; Difenhydraminy chlorowodorek; Dimedrolum; Diphénhydramine, Chlorhydrate de; Diphenhydraminhydrochlorid; Diphenhydramini Hydrochloridum; Diphenhydraminium Chloride; Hidrocloruro de difenhidramina; Дифенгидрамина Гидрохлорид.

$C_{17}H_{21}NO.HCl$=291.8

CAS — 147-24-0.

ATC — D04AA32; R06AA02.

ATC Vet — QD04AA32; QR06AA02.

UNII — TC2D6JAD40.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US.*

Jpn also includes Diphenhydramine Tannate.

Ph. Eur. 8: (Diphenhydramine Hydrochloride). A white or almost white, crystalline powder. Very soluble in water; freely soluble in alcohol. A 5% solution in water has a pH of 4.0 to 6.0. Protect from light.

USP 36: (Diphenhydramine Hydrochloride). A white, odourless, crystalline powder. It slowly darkens on exposure to light. Soluble 1 in 1 of water, 1 in 2 of alcohol and of chloroform, and 1 in 50 of acetone; very slightly soluble in ether and in benzene. Its solutions are neutral to litmus. Store in airtight containers. Protect from light.

Incompatibility. Diphenhydramine hydrochloride has been reported to be incompatible with amphotericin B, cefmetazole sodium, cefalotin sodium, hydrocortisone sodium succinate, some soluble barbiturates, some contrast media, and solutions of alkalis or strong acids.

Uses and Administration

Diphenhydramine, a monoethanolamine derivative, is a sedating antihistamine with antimuscarinic and pronounced sedative properties. It is used for the symptomatic relief of allergic conditions including urticaria and angioedema (p. 612.3), rhinitis (p. 612.1) and conjunctivitis (p. 611.1), and in pruritic skin disorders (p. 612.1). It is also used for its antiemetic properties in the treatment of nausea and vomiting (p. 611.3), particularly in the prevention and treatment of motion sickness (when it should be given at least 30 minutes before travelling), and in the treatment of vertigo of various causes (p. 612.3). Diphenhydramine is used for its antimuscarinic properties in the control of parkinsonism (p. 889.1) and drug-induced extrapyramidal disorders (p. 1049.2) (although the possibility that diphenhydramine itself may cause extrapyramidal symptoms should be remembered). Diphenhydramine has pronounced central sedative properties and may be used as a hypnotic in the short-term management of insomnia (p. 611.2). It is a common ingredient of compound preparations for symptomatic treatment of coughs and the common cold (p. 611.2), or preparations containing analgesics, particularly paracetamol. Diphenhydramine may be used parenterally as an adjunct in the emergency treatment of anaphylactic shock (p. 611.1) or when oral therapy is not feasible.

For most indications, *diphenhydramine hydrochloride* is given in usual oral doses of 25 to 50 mg three or four times daily; the maximum dose is about 300 mg daily. A dose of 50 mg may be used as a hypnotic.

When oral therapy is not feasible, diphenhydramine hydrochloride may be given by deep intramuscular injection or by intravenous injection using concentrations of 1% or 5%. Usual doses are 10 to 50 mg, although doses of 100 mg have been given. No more than 400 mg should be given in 24 hours.

For dosage in children, see below.

Diphenhydramine hydrochloride is applied topically, usually in preparations containing 1 to 2% although, as with other antihistamines, there is a risk of sensitisation.

Diphenhydramine citrate is given orally in a dose of 76 mg at night in combination preparations for its hypnotic action. *Diphenhydramine di(acefyllinate)* is given as an antiemetic for the prevention and treatment of motion sickness. The usual oral dose is 90 to 135 mg, which may be repeated if necessary at intervals of at least 6 hours, to a maximum of 540 mg daily.

Other diphenhydramine salts that have been used include the polistirex, the salicylate, and the tannate orally, the methylbromide rectally, and the laurilsulfate and the metilsulfate applied topically.

Dimenhydrinate (p. 625.2) is diphenhydramine teoclate and mefenidramium metilsulfate is diphenhydramine methylsulfomethylate.

Administration in children. Diphenhydramine hydrochloride may be used in children for the symptomatic relief of allergic conditions such as rhinitis. It is also used in the prevention and treatment of motion sickness (when it should be given at least 30 minutes before travelling). Diphenhydramine may also be given in combination preparations containing analgesics, particularly paracetamol. It may be used parenterally as an adjunct in the emergency treatment of anaphylactic shock or when oral therapy is not feasible.

The oral dose of diphenhydramine hydrochloride for most indications is as follows:

- children aged 2 to 6 years: 6.25 mg every four to six hours
- those aged 6 to 12 years: 12.5 to 25 mg every four to six hours

When oral therapy is not feasible, diphenhydramine hydrochloride may be given by deep intramuscular injection or by intravenous injection. Children may be given 5 mg/kg daily in four divided doses, to a maximum of 300 mg in 24 hours.

Diphenhydramine is a common ingredient of compound preparations for the symptomatic treatment of coughs and the common cold. However, such preparations should be used with caution in children, and generally avoided in young children, for details see p. 614.1.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively.

Abuse. Reports of the abuse of diphenhydramine hydrochloride.

1. Anonymous. Is there any evidence that Benylin syrup is addictive? *Br J* 1979; 1: 459.
2. Smith SG, Davis WM. Nonmedical use of butorphanol and diphenhydramine. *JAMA* 1984; 252: 1010.
3. Feldman MD, Behar M. A case of massive diphenhydramine abuse and withdrawal from use of the drug. *JAMA* 1986; 255: 3119–20.
4. de Nesnera AP. Diphenhydramine dependence: a need for awareness. *J Clin Psychiatry* 1996; 57: 136–7.
5. Dinndorf PA, *et al.* Risk of abuse of diphenhydramine in children and adolescents with chronic illnesses. *J Pediatr* 1998; 133: 293–5.

Extrapyramidal disorders. Reports of dystonic extrapyramidal reactions to diphenhydramine.

1. Lavenstein BL, Cantor FK. Acute dystonia: an unusual reaction to diphenhydramine. *JAMA* 1976; 236: 291.
2. Santora J, Rozek S. Diphenhydramine-induced dystonia. *Clin Pharm* 1989; 8: 471.
3. Roila F, *et al.* Diphenhydramine and acute dystonia. *Ann Intern Med* 1989; 111: 92–3.

Overdosage. In an evaluation of 136 cases, one fatal, of intoxication with diphenhydramine, the plasma concen-

tration was correlated with frequency or extent of symptoms.[1] The most common symptom was impaired consciousness; psychosis, seizures, antimuscarinic symptoms such as mydriasis, tachycardia, and tachyarrhythmias, and respiratory failure were also seen. The positive association between dose and frequency and severity of symptoms was confirmed in a more recent study;[2] it was also found that severe symptoms were more likely to occur when 1 g or more of diphenhydramine had been taken.

There have been reports[3,4] of rhabdomyolysis as an effect of oral diphenhydramine overdosage. The liberal application of a lotion containing diphenhydramine produced acute delirium with visual and auditory hallucinations in a 9-year-old boy[5] and similar effects were seen in 3 children with varicella-zoster infection after the topical application of diphenhydramine (2 of these children also received oral diphenhydramine).[6]

1. Köppel C, Tenczer J. Clinical symptomatology of diphenhydramine overdose: an evaluation of 136 cases in 1982 to 1985. *Clin Toxicol* 1987; 25: 53–70.
2. Radovanovic D, *et al.* Dose-dependent toxicity of diphenhydramine overdose. *Hum Exp Toxicol* 2000; 19: 489–95.
3. Hampel G, *et al.* Myoglobinuric renal failure due to drug-induced rhabdomyolysis. *Hum Toxicol* 1983; 2: 197–203.
4. Haas CE, *et al.* Rhabdomyolysis and acute renal failure following an ethanol and diphenhydramine overdose. *Ann Pharmacother* 2003; 37: 538–42.
5. Filloux F. Toxic encephalopathy caused by topically applied diphenhydramine. *J Pediatr* 1986; 108: 1018–20.
6. Chan CYJ, Wallander KA. Diphenhydramine toxicity in three children with varicella-zoster infection. *DICP Ann Pharmacother* 1991; 25: 130–2.

Pregnancy. A pregnant woman who was receiving diphenhydramine hydrochloride 150 mg daily for a pruritic rash gave birth to an infant who developed diarrhoea and generalised tremulousness 5 days later.[1] The delay in appearance of withdrawal symptoms was considered to be due to reduced activity of glucuronyl conjugating enzymes in the first few days of life.

For discussion of the use of antihistamines in pregnancy, including a suggestion of a relationship between inguinal hernia or genito-urinary malformations and diphenhydramine exposure, see p. 614.2. See also under Interactions, below, for a report of perinatal death possibly associated with temazepam and diphenhydramine.

1. Parkin DE. Probable Benadryl withdrawal manifestations in a new-born infant. *J Pediatr* 1974; 85: 580.

Interactions

As for the sedating antihistamines in general, p. 614.3. Diphenhydramine inhibits the cytochrome P450 isoenzyme CYP2D6 that is partly responsible for the metabolism of some beta blockers including metoprolol and the antidepressant venlafaxine.

Benzodiazepines. There has been a report[1] suggesting that a reduction in *temazepam* metabolism caused by diphenhydramine may have contributed to perinatal death after ingestion of these drugs by the mother.

1. Kargas GA, *et al.* Perinatal mortality due to interaction of diphenhydramine and temazepam. *N Engl J Med* 1985; 313: 1417–18.

Pharmacokinetics

Diphenhydramine hydrochloride is well absorbed from the gastrointestinal tract, although high first-pass metabolism appears to affect systemic availability. Peak plasma concentrations occur about 1 to 4 hours after oral doses. Diphenhydramine is widely distributed throughout the body including the CNS. It crosses the placenta and has been detected in breast milk. Diphenhydramine is highly bound to plasma proteins. Metabolism is extensive. Diphenhydramine is excreted mainly in the urine as metabolites; little is excreted as unchanged drug. The elimination half-life has been reported to range from 2.4 to 9.3 hours.

References.

1. Glazko AJ, *et al.* Metabolic disposition of diphenhydramine. *Clin Pharmacol Ther* 1974; 16: 1066–76.
2. Paton DM, Webster DR. Clinical pharmacokinetics of H_1-receptor antagonists (the antihistamines). *Clin Pharmacokinet* 1985; 10: 477–97. (includes studies indicating a correlation between plasma concentrations and both antihistaminic and sedative effects).
3. Simons KJ, *et al.* Diphenhydramine: pharmacokinetics and pharmacodynamics in elderly adults, young adults, and children. *J Clin Pharmacol* 1990; 30: 665–71.
4. Scavone JM, *et al.* Pharmacokinetics and pharmacodynamics of diphenhydramine 25 mg in young and elderly volunteers. *J Clin Pharmacol* 1998; 38: 603–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Alermina†; Amodormin; Benadryl; Caladryl D†; Fabolergic; Fadalex; Histaler; Klonadryl Antiallergico; Nelfigen†; TheraFlu Alergia†; *Austral.*: Snuzaid; Unisom; *Austria*: Calmaben; Dermodrin; Dibondrin; Histaxin; Noctor; *Belg.*: Azaron; Diphamine; Nustasium; R Calm; *Braz.*: Difenidrin; *Canad.*: Aller-Aide; Allerdryl; Allergy Elixir; Allergy Formula; Allergy Tablets; Allergy; Allernix; Anti-Itch; Benadryl; Benylin Night Cough†; Calmex; Children's Allergy Formula; Childrens Cough, Cold & Allergy†; Childrens Liquid Allergy; Diphenist; Dormax; Dormex; Dormiphen; Extra Stength Sleep Aid; Insomnal; Jack & Jill Bedtime; Jack & Jill Thin Strips Cough & Cold†; Nadryl; Neocitran Nighttime Cough; Night Cough; Nytol; Simply Sleep; Sleep Aid; Sleep-Eze D; Sominex†; Triaminic Thin Strips Nighttime Cough & Runny Nose; Unisom; *Chile*: Jaquedryl; Somol; *Cz.*: Psilo-Balsam; *Denm.*: Benylan; *Fr.*: Butix; Nautamine; *Ger.*: Betadorm D; Dolestan; Hevert-Dorm; Moradorm; nervo OPT N; Sediat; Sedopretten; Vivinox Sleep; *Gr.*: Benadryl; *Hong Kong*: Bendol; Bendrol†; Calmitch†; Diphenamine†; Histergan†; Unisom†; *Hung.*: Psilo-Balsam; *India*: Benacof; Benadryl; Cofryl; Kuffdryl; Novadryl; *Indon.*: Arcodryl; Benadryl†; Otede; Paradryl; Recodryl; Sidiadryl†; Valdres; *Israel*: Nytol; *Ital.*: Allserin; Allergan; *Jpn*: Venapasta; *Mex.*: Benadryl; Bionaryl; Bonanoti; Drafen; Glicodril; Histadryl; Indumir; Lurispan; Nytol; Ulcoid; *NZ*: Unisom; *Philipp.*: Alerace; Allerin AH; Benadryl Antihistamine; Benaxil; Dramelin; Tussicon; *Port.*: Benaderma; Benergina; Codilergi†; *Rus.*: Psilo-Balsam (Псило-Бальзам); *S.Afr.*: Betasleep; Sleepeze-PM; *Singapore*: Benadryl; Bendrol; Paxidorm; *Spain*: Benadryl†; Neosayomol; Sonodor; *Swed.*: Desentol; *Switz.*: Benocten; Bonox; Nardyl Sommeil; *Thai.*: Benadryl; Cabana; Codiphen; Dibendryl; Sedatab; Sedi; Tussodryl; *Turk.*: Allenik; Allerjin†; Benadryl; Benison; Difedrin; Fenotral; *UAE*: Amydramine II; *UK*: Adult Chesty Cough; Boots Skin Allergy Relief; Child Chesty Cough; Dreemon; Histergan; Mandalyn Paediatric Nightcalm; Nytol; Paxidorm; Sleep Aid; Sleepeaze; *Ukr.*: Dermodrin (Дермадрин); Psilo-Balsam (Псило-Бальзам); *USA*: 40 Winks; Aler-Dryl; AllerMax; Altaryl Childrens Allergy; Banophen Allergy; Ben-Tann†; Benadryl Allergy; Benadryl Childrens Allergy; Benadryl Itch; Benadryl; Childrens PediaCare Nighttime Cough; Compoz Night-time Sleep Aid; Derma-Pax; Dermamycin; Diphen AF; Diphenhist; Dormin; Dytan†; Dytuss; Genahist; Maximum Strength Sleepinal; Maximum Strength Unisom SleepGels; Miles Nervine; Nytol; Q-dryl; Scot-Tussin Allergy; Siladryl; Silphen; Simply Sleep; Sleep-Ettes D; Sleepettes Nighttime Sleep Aid; Sleepwell 2-nite; Snooze Fast; Sominex; Triaminic Children's Allergy†; Triaminic Cough & Runny Nose†; Tusstat; Twilite; Unisom SleepMelts; ZzzQuil; *Venez.*: Benadryl.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

BP 2014: Diphenhydramine Oral Solution; Diphenhydramine Tablets;

USP 36: Acetaminophen and Diphenhydramine Citrate Tablets; Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets; Diphenhydramine and Pseudoephedrine Capsules; Diphenhydramine Citrate and Ibuprofen Tablets; Diphenhydramine Hydrochloride Capsules; Diphenhydramine Hydrochloride Elixir; Diphenhydramine Hydrochloride Injection.

Diphenylpyraline Hydrochloride

(BANM, rINNM)

Difenilpiralina, hidrocloruro de; Diphénylpyraline, Chlorhydrate de; Diphenylpyralini Hydrochloridum; Hidrocloruro de difenilpiralina; Дифенилпиралина Гидрохлорид.

4-Benzhydryloxy-1-methylpiperidine hydrochloride.

$C_{19}H_{23}NO,HCl$=317.9

CAS — 147-20-6 (diphenylpyraline); 132-18-3 (diphenylpyraline hydrochloride).

ATC — R06AA07.

ATC Vet — QR06AA07.

UNII — G9FU7F1E87.

Pharmacopoeias. In *Br.*

BP 2014: (Diphenylpyraline Hydrochloride). A white or almost white, odourless or almost odourless powder. Freely soluble in water, in alcohol, and in chloroform; practically insoluble in ether.

Profile

Diphenylpyraline hydrochloride, a piperidine derivative, is a sedating antihistamine (p. 610.1) with antimuscarinic and significant sedative properties.

It has been given for the symptomatic relief of allergic conditions including rhinitis (p. 612.1), and in pruritic skin disorders (p. 612.1). It has also been used in compound preparations for the symptomatic treatment of coughs and the common cold (p. 611.2). Diphenylpyraline and diphenylpyraline hydrochloride have been applied topically although, as with other antihistamines, there is a risk of sensitisation.

Diphenylpyraline teoclate is piprinhydrinate (p. 638.1).

References.

1. Graham G, Bolt AG. Half-life of diphenylpyralline in man. *J Pharmacokinet Biopharm* 1974; 2: 191–5 (ranged from 24 to 40 hours).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Arbid-S†.

Multi-ingredient Preparations. *Austria*: Eucillin; Prurimix; *Belg.*: Rhini-San; *Canad.*: Creo-Rectal; *Ger.*: Tempil N†; *Hong Kong*: Phenahist; *India*: Cinaryl; Eskold Expectorant; Eskold; *Mex.*: Flumil; *S.Afr.*: Actophlem; Eskomade†; Solphyllex; Theophen Comp; *Switz.*: Arbid†.

Doxylamine Succinate *(BANM, rINNM)*

Doksilamin Süksinat; Doksilamino-vandenilio sukcinatas; Doksylaminivetysuksinaatti; Doxilamina, succinato de; Doxilamin-hidrogén-szukcinát; Doxylamine Hydrogen Succinate; Doxylamine, hydrogénosuccinate de; Doxylamine, Succinate de; Doxylaminhydrogensuccinat; Doxylamin-hydrogen-sukcinát; Doxylamini Hydrogenosuccinas; Doxylamini Succinas; Doxylaminium Succinate; Doxylaminvätesuccinat; Histadoxylamine Succinate; Succinato de doxilamina; Доксиламина Сукцинат.

NN-Dimethyl-2-[α-methyl-α-(2-pyridyl)benzyloxy]ethylamine hydrogen succinate.

$C_{17}H_{22}N_2O,C_4H_6O_4$=388.5

CAS — 469-21-6 (doxylamine); 562-10-7 (doxylamine succinate).

ATC — R06AA09.

ATC Vet — QR06AA09.

UNII — V98I985Y12.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Doxylamine Hydrogen Succinate; Doxylamine Succinate BP 2014). A white or almost white powder. Very soluble in water; freely soluble in alcohol. It shows polymorphism.

USP 36: (Doxylamine Succinate). A white or creamy-white powder having a characteristic odour. Soluble 1 in 1 of water, 1 in 2 of alcohol and of chloroform, and 1 in 370 of ether; very slightly soluble in benzene. Protect from light.

Uses and Administration

Doxylamine succinate, a monoethanolamine derivative, is a sedating antihistamine with antimuscarinic and pronounced sedative effects.

Doxylamine succinate is given for the symptomatic relief of hypersensitivity reactions, in pruritic skin disorders (p. 612.1), as a hypnotic in the short-term treatment of insomnia (p. 611.2), and as an ingredient of compound preparations for symptomatic treatment of coughs and the common cold (p. 611.2). Oral doses of up to 25 mg of doxylamine succinate have been given every 4 to 6 hours to a maximum of 150 mg daily. The usual hypnotic dose is 25 mg orally, up to half an hour before bedtime, although this may be increased to 50 mg if necessary.

It is also used in the management of nausea and vomiting of early pregnancy (p. 1814.3) in women who have not responded to conservative management such as dietary and lifestyle modifications. (See p. 614.2 for the controversy that has surrounded the use in pregnancy of combination products of doxylamine.) It is given orally as a modified-release combination preparation with pyridoxine hydrochloride (see Vitamin B_6 Substances, p. 2105.3); each tablet contains doxylamine succinate 10 mg and pyridoxine hydrochloride 10 mg. The recommended initial dose is 2 tablets at bedtime, taken on an empty stomach; if symptoms are not adequately controlled, the dose may be gradually increased, according to response, to a maximum of 4 tablets daily (1 in the morning and at mid-afternoon, and 2 at bedtime). This preparation should be taken regularly and not on an as-required basis; the need for continued treatment should be reassessed as the pregnancy progresses and the dose gradually tapered when stopping treatment.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively. The controversy surrounding the use in pregnancy of combination products of doxylamine is discussed on p. 614.2.

Overdosage. In an evaluation of 109 cases of intoxication with doxylamine,[1] no correlation was found between the amount ingested or plasma concentration and the frequency or extent of symptoms. The most common symptom was impaired consciousness. Psychotic behaviour, seizures, and antimuscarinic symptoms such as tachycardia and mydriasis were also seen. Rhabdomyolysis occurred in one patient and was accompanied by transient impairment of renal function. The same group commented[2] that rhabdomyolysis had been noted in 7 of 442 cases of doxylamine overdosage, with an associated rise in plasma creatine kinase and myoglobinuria, and suggested that doxylamine has a direct toxic effect on striated muscle.

1. Köppel C, *et al.* Poisoning with over-the-counter doxylamine preparations: an evaluation of 109 cases. *Hum Toxicol* 1987; 6: 355–9.
2. Köppel C, *et al.* Rhabdomyolysis in doxylamine overdose. *Lancet* 1987; i: 442–3.

The symbol † denotes a preparation no longer actively marketed

Interactions

As for the sedating antihistamines in general, p. 614.3.

Pharmacokinetics

Peak plasma concentrations of doxylamine succinate occur 2 to 3 hours after oral doses. An elimination half-life of about 10 hours has been reported.

References.
1. Friedman H, *et al.* Clearance of the antihistamine doxylamine: reduced in elderly men but not in elderly women. *Clin Pharmacokinet* 1989; 16: 312–16.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Dozile; Restavit; ***Canad.***: Unisom-2; ***Chile***: Calmex; Dorminoctil; Nocpaz†; Zarcop; ***Fr.***: Donormyl; Lidene; Noctyl; ***Ger.***: Gittalun; Hoggar Night; Mereprine†; SchlafTabs; Sedaplus; Valocordin-Doxylamin; ***Hong Kong***: Sominar†; ***Israel***: Sleep Aid; Tonight; ***NZ***: Dozile; ***Philipp.***: Unisom; ***Port.***: Dormidina; ***Rus.***: Donormyl (Донормил); ***S.Afr.***: Restwel; Somnil; ***Spain***: Dormidina; Dormiret; ***Switz.***: Sanalepsi N; ***Thai.***: Hoggar N; Sominar; ***Turk.***: Unisom; ***Ukr.***: Donormyl (Донормил); Somnil (Сомнил); ***USA***: Aldex AN; Doxytex; Unisom SleepTabs.

Multi-ingredient Preparations. ***Arg.***: Epidac; ***Austral.***: Analgesic/Calmative†; Chemists Own Dolased Day/Night Pain Relief†; Codagesic; Codalgin Plus; Dimetapp Cold & Flu Night Relief†; Dimetapp Cough, Cold & Flu; Dolased Analgesic-Calmative; Fiorinal; Maxydol; Mersyndol; Panadeine Plus†; Panalgesic; Tensodeine; ***Austria***: Wick Erkaltungs-Saft fur die Nacht†; Wick Erkaltungssirup fur die Nacht; Wick Hustensaft†; ***Belg.***: Pholco-Mereprine; ***Braz.***: EMS Expectorante; Hytos Plus; Revenil Dospan; Revenil Expectorante; Revenil; Silencium; Xpe Expectorante; ***Canad.***: Buckley's Nighttime Cold and Sinus; Cold & Flu Nighttime; Cold Flu Relief; Cold/Flu Medicine; Dalmacol; Diclectin; Medicament Sinus pour La Nuit†; Mersyndol with Codeine; Night Relief Cold & Flu†; Nighttime Cold & Flu Relief; Nighttime Cold & Flu; Nighttime; Nitetime Cold Medicine; ratio-Calmydone; Regular Strength Sinus Medication†; Sinus Medication Night; Sinus Medication; Tylenol Cold and Flu Nighttime†; Tylenol Sinus (Nighttime Relief)†; Vicks Nyquil Cold & Flu; Vicks NyQuil Cough; Vicks Nyquil Sinus; Zicam Multi-Symptom Cold & Flu Nighttime†; ***Chile***: Pluriamin; ***Fr.***: DolirhumePro; ***Ger.***: Wick Medinait fur die Nacht; Wick Medinait mit Honig und Kamillenaroma; ***India***: Bedoxin; Bookey Plus; Bookey; DBSix; Dixip; Dolibird; Domi-6; Dopyx; Doria-F; Doris-P; Dosix-F; Doxilan; Doximon; Doxinate Plus; Doxinate; Doxyfem-B6; Doxyfol; Doxyla B6 Plus; Doxyla B6; Doxylic; DPF-OD; DPF; Dymin-P; E-Preg; Emestat; Env; Erywell; Evadox; Feel Good-HR; Feel Good; Floridox; Folifact; Foxydol; Freshta Plus; Freshta-DS; Fullday; Genis; Good Day; Gooday; Goodmorn Plus; Goodmorn; Ibeln; Indaxin-B6; Kan-Fresh; Kindvom; Lupinate; MFresh; Morsi; Morsik-R; Nausik; Nomit; Noms; Nona; Norvomin; Nosic; Novotet; NVDP; Onat; Optidox; Oxidox; Rest-Aid; Vominate; ***Indon.***: Dexmolex; Siladex†; ***Irl.***: Syndol; ***Ital.***: Vicks Medinait; ***NZ***: Mersyndol; Pharmacist's Own Pain Relief Plus; ***Pol.***: Tabcin Impakt; ***Port.***: Nausefe; ***S. Afr.***: Abflex; Acurate; Adco-Dol; Asic; B-Dol; Betapyn; Cepacol Cough; Codoxol; Doxsyn†; Lenapain; Nethaprin Dospan†; Nethaprin Expectorant†; Nomopain†; Paxidal†; Pynstop; Sedapain†; Sedinol†; Syndol; Tensopyn; Vicks Medinite†; ***Spain***: Cariban; Medinait; ***Switz.***: Vicks Medinait; ***Turk.***: Vicks Medinait; ***UK***: Painex; Propain Plus; Syndol; Vicks Medinite; ***USA***: Alka-Seltzer Plus Day & Night Cold; Alka-Seltzer Plus Day & Night Cold; Alka-Seltzer Plus Night Cold; Alka-Seltzer Plus Night-Time Cold; Alka-Seltzer Plus Severe Sinus Congestion Allergy & Cough; All-Nite Cold Formula; Diclegis; Genite; Lortuss DM; Lortuss DM; Lortuss LQ; Night Time Cold/Flu Relief; Nite Time Cold Formula; NyQuil Hot Therapy; NyQuil Nighttime Cold/Flu; Nytcold Medicine; Vicks NyQuil LiquiCaps; Vicks NyQuil Multi-Symptom Cold Flu Relief; Vicks NyQuil Sinex; ***Venez.***: Mercindol.

Pharmacopoeial Preparations
USP 36: Acetaminophen, Dextromethorphan Hydrobromide, Doxylamine Succinate, and Pseudoephedrine Hydrochloride Oral Solution; Doxylamine Succinate Syrup; Doxylamine Succinate Tablets.

Ebastine *(BAN, USAN, rINN)*

Ebastiini; Ebastin; Ebastina; Ebastinas; Ébastine; Ebastinum; LAS-W-090; W-090; Эбастин.

4′-*tert*-Butyl-4-[4-(diphenylmethoxy)piperidino]butyrophenone.

$C_{32}H_{39}NO_2$=469.7

CAS — 90729-43-4.
ATC — R06AX22.
ATC Vet — QR06AX22.
UNII — TQD7Q784P1.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Ebastine). A white or almost white crystalline powder. M.p. about 86 degrees. Practically insoluble in water; very soluble in dichloromethane; sparingly soluble in methyl alcohol. Protect from light.

Profile

Ebastine, a piperidine derivative, is a non-sedating antihistamine (p. 610.1) with a long duration of action. It does not have significant sedative or antimuscarinic actions.

Ebastine is given for the symptomatic relief of allergic conditions including rhinitis (p. 612.1) and in pruritic skin disorders (p. 612.1). The usual oral dose is 10 to 20 mg daily. It is also used with a decongestant such as pseudoephedrine hydrochloride.

References.
1. Luria X. Comparative clinical studies with ebastine: efficacy and tolerability. *Drug Safety* 1999; 21 (suppl 1): 63–7.
2. Hurst M, Spencer CM. Ebastine: an update of its use in allergic disorders. *Drugs* 2000; 59: 981–1006.
3. Lasseter KC, *et al.* Pharmacokinetics and safety of ebastine in patients with impaired hepatic function compared with healthy volunteers: a phase I open-label study. *Clin Pharmacokinet* 2004; 43: 121–9.
4. Noveck RJ, *et al.* Pharmacokinetics and safety of ebastine in healthy subjects and patients with renal impairment. *Clin Pharmacokinet* 2007; 46: 525–34.
5. Sastre J. Ebastine in allergic rhinitis and chronic idiopathic urticaria. *Allergy* 2008; 63 (suppl 89): 1–20.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ebastine as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Ebastel; ***Belg.***: Estivan; ***Braz.***: Ebastel; ***China***: Kestine (开思亭); Si Jin (思金); Su Di (苏迪); ***Denm.***: Durfin†; Kestine; ***Fin.***: Kestine; Kestox; ***Fr.***: Kestin; Kestinlyo; ***Ger.***: Ebastel; ***Gr.***: Kestine; ***Hong Kong***: Kestine†; ***India***: Ebast; Erostin; ***Irl.***: Kestine†; ***Ital.***: Clever; Kestine; ***Jpn***: Ebastel; ***Mex.***: Evastel; Pinaval-T; ***Neth.***: Kestine; Netan; ***Norw.***: Kestine; ***Philipp.***: Aleva; ***Port.***: Ebastion; Estivan†; Kestine; Ribastex†; ***Rus.***: Kestine (Кестин); ***S.Afr.***: Kestine; ***Singapore***: Kestine; ***Spain***: Alastina; Bactil; Ebastel; ***Swed.***: Kestine; ***Turk.***: Kestine; ***Venez.***: Ebastel.

Multi-ingredient Preparations. ***Braz.***: Ebastel D; ***India***: EBA-P; Ebast-DC; Erostin-DC; ***Mex.***: Evastel-D; ***Philipp.***: Co-Aleva; ***Spain***: Rino Ebastel; Rinobactil.

Embramine Hydrochloride *(BANM, rINNM)*

Embramina, hidrocloruro de; Embramine, Chlorhydrate d'; Embramini Hydrochloridum; Embraminium Chloratum; Hidrocloruro de embramina; Mebrophenhydramine Hydrochloride; Mebrophenhydraminium Chloratum; Эмбрамина Гидрохлорид.

2-(4-Bromo-α-methylbenzhydryloxy)-*NN*-dimethylethylamine hydrochloride.

$C_{18}H_{22}BrNO,HCl$=384.7

CAS — 3565-72-8 (embramine); 13977-28-1 (embramine hydrochloride); 21661-63-2 (embramine teoclate).
UNII — 7BJ3V657VC.

Profile

Embramine hydrochloride, a monoethanolamine derivative, is a sedating antihistamine (p. 610.1). Embramine hydrochloride and embramine teoclate have been given orally for their antihistamine and antiemetic properties.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Medrin†; ***India***: Mebryl.

Emedastine Fumarate *(BANM, rINNM)*

AL-3432A; Emedastiinidifumaraatti; Emedastin difumarát; Emedastin Fumarat; Emedastina, fumarato de; Emedastindifumarat; Emedastine Difumarate (USAN); Émédastine, difumarate d'; Émédastine, Fumarate d'; Emedastini Difumaras; Emedastini Fumaras; Emedastyny difumaran; Fumarato de emedastina; KB-2413; KG-2413; LY-188695; Эмедастина Фумарат.

1-(2-Ethoxyethyl)-2-(hexahydro-4-methyl-1*H*-1,4-diazepin-1-yl)benzimidazole fumarate (1:2).

$C_{17}H_{26}N_4O,2C_4H_4O_4$=534.6

CAS — 87233-61-2 (emedastine); 87233-62-3 (emedastine fumarate).
ATC — S01GX06.
ATC Vet — QS01GX06.
UNII — 42MB94QOSM.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Emedastine Difumarate). A white or yellowish powder. It exhibits polymorphism. Soluble in water; sparingly soluble in dehydrated alcohol; very slightly soluble in acetone. A 0.2% solution in water has a pH of 3.0 to 4.5. Protect from light.

USP 36: (Emedastine Difumarate). A white to faintly yellow crystalline powder. Soluble in water. pH of a 0.2% solution in water is between 3.0 and 4.5. Store in airtight containers. Protect from light.

Uses and Administration

Emedastine is an antihistamine. It is instilled twice daily as the fumarate as eye drops containing the equivalent of 0.05% of emedastine for the symptomatic relief of allergic conjunctivitis (p. 611.1). It is also given orally in usual doses of 2 to 4 mg of the fumarate daily in two divided doses for allergic rhinitis (p. 612.1), urticaria (p. 612.3), and pruritic skin disorders (p. 612.1).

Adverse Effects and Precautions

As for the antihistamines in general, p. 613.1 and p. 613.3, respectively.

Ocular corneal infiltrates, local irritation, photophobia, rhinitis, and headaches have been reported after use of emedastine eye drops. Treatment should be stopped if corneal infiltrates develop.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies emedastine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Pharmacokinetics

Emedastine is absorbed from the gastrointestinal tract and peak plasma concentrations occur about 3 hours after an oral dose. Small amounts of emedastine are absorbed after application to the eye. It is mainly metabolised in the liver to two primary metabolites 5- and 6-hydroxyemedastine which are excreted in the urine along with a small amount of unchanged drug. The elimination half-life is reported to be 7 hours after an oral dose and 10 hours after topical use.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Emadine; ***Belg.***: Emadine; ***Braz.***: Emadine; ***Canad.***: Emadine; ***China***: Emadine (埃美丁); ***Cz.***: Emadine; ***Denm.***: Emadine; ***Fin.***: Emadine; ***Fr.***: Emadine†; ***Ger.***: Emadine; ***Gr.***: Emadine; ***Hong Kong***: Emadine; ***Hung.***: Emadine; ***Irl.***: Emadine; ***Israel***: Emadine; ***Ital.***: Emadine; ***Jpn***: Daren; Remicut; ***Malaysia***: Emadine; ***Neth.***: Emadine; ***Norw.***: Emadine; ***Pol.***: Emadine; ***Port.***: Emadine; ***S.Afr.***: Emadine; ***Spain***: Emadine; ***Swed.***: Emadine; ***Switz.***: Emadine; ***Thai.***: Emadine†; ***Turk.***: Emadine; ***UK***: Emadine; ***USA***: Emadine.

Pharmacopoeial Preparations
USP 36: Emedastine Ophthalmic Solution.

Epinastine Hydrochloride *(BANM, rINNM)*

Epinastina, hidrocloruro de; Epinastine, chlorhydrate d'; Epinastine, Chlorhydrate d'; Epinastinhydrochlorid; Epinastini hydrochloridum; Hidrocloruro de epinastina; WAL-801-CL; Эпинастина Гидрохлорид.

3-Amino-9,13b-dihydro-1*H*-dibenz[*c*,*f*]imidazo[1,5-*a*]azepine hydrochloride.

$C_{16}H_{15}N_3$,HCl=285.8

CAS — 80012-43-7 (epinastine).
ATC — R06AX24; S01GX10.
ATC Vet — QR06AX24; QS01GX10.
UNII — GFM41555XL.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Epinastine Hydrochloride). A white or almost white, hygroscopic, crystalline powder. Freely soluble in water and in methyl alcohol; slightly soluble in acetonitrile; sparingly soluble in dichloromethane. Store in airtight containers.

Profile

Epinastine hydrochloride is an antihistamine (p. 610.1) reported to have no significant sedative activity. It has been given orally in the management of allergic rhinitis and pruritic skin disorders. It is also used twice daily as eye

drops, usually in a concentration of 0.05%, in the symptomatic relief of allergic conjunctivitis.

References.
1. Sarashina A, *et al.* Population pharmacokinetics of epinastine, a histamine H_1 receptor antagonist, in adults and children. *Br J Clin Pharmacol* 2005; 59: 43–53.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Alket; Epioftal; Flurinol; Relestat; *Austria*: Relestat; *Belg.*: Relestat; *Braz.*: Relestat; Talerc; *Chile*: Flurinol; Relestat; *China*: Alesion (爱理胜); Kai Lai Zhi (凯莱止); *Cz.*: Purivist; *Denm.*: Relestat; *Fin.*: Relestat†; *Fr.*: Purivist; *Ger.*: Relestat; *Gr.*: Relestat; *Hong Kong*: Relestat; *Hung.*: Relestat; *Irl.*: Relestat; *Israel*: Relestat; *Ital.*: Relestat; *Jpn*: Alesion; *Mex.*: Elestat; Flurinol; *Neth.*: Relestat; *Pol.*: Relestat; *Port.*: Relestat; *S.Afr.*: Relestat; *Singapore*: Relestat; *Spain*: Relestat; *Swed.*: Relestat†; *Switz.*: Relestat; *Thai.*: Relestat; *Turk.*: Relestat; *UK*: Relestat; *USA*: Elestat; *Venez.*: Flurinol.

Multi-ingredient Preparations. *Arg.*: Flurinol D; *Braz.*: Talerc D; *Mex.*: Flurinol D.

Fexofenadine Hydrochloride

(BANM, USAN, rINNM)

Feksofenadiinihydrokloridi; Feksofenadin Hidroklorür; Fexofenadina, hidrocloruro de; Fexofénadine, Chlorhydrate de; Fexofenadinhydrochlorid; Fexofenadinhydroklorid; Fexofenadini Hydrochloridum; Hidrocloruro de fexofenadina; MDL-16455A; Terfenadine Carboxylate Hydrochloride; Фексофенадина Гидрохлорид.

(±)-*p*-[1-Hydroxy-4-[4-(hydroxydiphenylmethyl)-piperidino] butyl]-α-methylhydratropic acid hydrochloride.

$C_{32}H_{39}NO_4HCl=538.1$

CAS — 138452-21-8.

ATC — R06AX26.

ATC Vet — QR06AX26.

UNII — 25068B75ZU.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Fexofenadine Hydrochloride). A white or almost white powder. Slightly soluble in water; freely soluble in methyl alcohol; very slightly soluble in acetone. It exhibits polymorphism.

USP 36: (Fexofenadine Hydrochloride). A white to off-white powder. Slightly soluble in water; freely soluble in methyl alcohol; very slightly soluble in acetone. Store at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Fexofenadine, an active metabolite of terfenadine (p. 640.3), is a non-sedating antihistamine. It does not possess significant sedative or antimuscarinic actions. Fexofenadine is used as the hydrochloride in the symptomatic relief of allergic conditions including seasonal allergic rhinitis (p. 612.1) and chronic urticaria (p. 612.3).

In the UK a dose of fexofenadine hydrochloride 120 mg once daily is given orally in the treatment of seasonal allergic rhinitis; the recommended dose in chronic idiopathic urticaria is 180 mg once daily. US licensed product information suggests a dose of 60 mg twice daily or 180 mg once daily for both indications.

Fexofenadine is also used with a decongestant such as pseudoephedrine hydrochloride.

For doses in children or in patients with renal impairment, see below.

References.
1. Markham A, Wagstaff AJ. Fexofenadine. *Drugs* 1998; 55: 269–74.
2. Simpson K, Jarvis B. Fexofenadine: a review of its use in the management of seasonal allergic rhinitis and chronic idiopathic urticaria. *Drugs* 2000; 59: 301–21.
3. Kawashima M, *et al.* Review of fexofenadine in the treatment of chronic idiopathic urticaria. *Int J Dermatol* 2002; 41: 701–6.
4. Meeves SG, Appajosyula S. Aventis, USA]. Efficacy and safety profile of fexofenadine HCl: a unique therapeutic option in H1-receptor antagonist treatment. *J Allergy Clin Immunol* 2003; 112 (suppl): S69–S77.
5. Mansfield LE. Once-daily immediate-release fexofenadine and sustained-release pseudoephedrine combination: a new treatment option for allergic rhinitis. *Expert Opin Pharmacother* 2006; 7: 941–51.

Administration in children. Fexofenadine hydrochloride is used in children for the treatment of seasonal allergic rhinitis in an oral dose of 30 mg twice daily; in the UK it is licensed for use in children aged 6 to 11 years whereas in the USA it may be used in children as young as 2 years.

In the USA, fexofenadine is also licensed for use in paediatric chronic idiopathic urticaria. The dose in children aged 6 months to less than 2 years is 15 mg twice daily; older children may be given 30 mg twice daily.

For suggested doses in children with renal impairment see below.

Administration in renal impairment. US licensed product information recommends that initial oral doses of fexofenadine hydrochloride in adults with renal impairment should be reduced to 60 mg once daily. In children with renal impairment, the initial dose should be reduced to 30 mg once daily in patients aged 2 to 11 years, and to 15 mg once daily in children aged 6 months to less than 2 years.

UK product information advises that fexofenadine should be given with caution to patients with renal impairment; however, it also states that dose adjustment is not considered to be necessary in such patients.

Adverse Effects and Precautions

As for the non-sedating antihistamines in general, p. 613.1 and p. 613.3, respectively.

Arrhythmias. A 67-year-old man suffered syncope after taking fexofenadine 180 mg daily for 2 months.[1] His ECG showed an abnormally prolonged QT interval which shortened once fexofenadine was stopped, although the interval tended to be long even without drug therapy. Nonetheless rechallenge was positive. The manufacturers of fexofenadine have commented[2] that the patient was at risk of developing arrhythmias before taking the drug.

The ECG effects of fexofenadine have been studied[3] in normal subjects and doses of up to 480 mg daily [4 times the recommended dose for seasonal allergic rhinitis] did not prolong the QT interval. See also p. 613.2.

1. Pinto YM, *et al.* QT lengthening and life-threatening arrhythmias associated with fexofenadine. *Lancet* 1999; 353: 980.
2. Giraud T. QT lengthening and arrhythmias associated with fexofenadine. *Lancet* 1999; 353: 2072.
3. Pratt CM, *et al.* Cardiovascular safety of fexofenadine HCl. *Am J Cardiol* 1999; 83: 1451–4.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving fexofenadine, and the American Academy of Pediatrics[1] considers that it is therefore usually compatible with breast feeding.

See also under Adverse Effects and Precautions, in Terfenadine, p. 641.1.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/04/04)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fexofenadine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Psoriasis. Exacerbation of psoriasis has been reported[1] with fexofenadine use.

1. Saraswat A, Saraswat M. Pustular exacerbation of psoriasis due to fexofenadine. *Clin Exp Dermatol* 2006; 31: 477–8.

Interactions

As for the non-sedating antihistamines in general, p. 614.3.

Plasma concentrations of fexofenadine have been increased when given with erythromycin or ketoconazole, but, unlike terfenadine, licensed product information states that this was not associated with adverse effects on the QT interval.

Antacids containing aluminium and magnesium hydroxide have reduced the absorption of fexofenadine. Fruit juices including grapefruit may reduce the bioavailability of fexofenadine and use together should be avoided.

Grapefruit juice. References.

1. Dresser GK, *et al.* Effect of grapefruit juice volume on the reduction of fexofenadine bioavailability: possible role of organic anion transporting polypeptides. *Clin Pharmacol Ther* 2005; 77: 170–7.

Pharmacokinetics

Fexofenadine is rapidly absorbed after oral doses and peak plasma concentrations occur in 2 to 3 hours. It is about 60 to 70% bound to plasma proteins. Fexofenadine undergoes negligible metabolism: about 5% of the total dose is metabolised, mostly by the intestinal mucosa, with 0.5 to 1.5% of the dose undergoing hepatic biotransformation by the cytochrome P450 system. Elimination half-life of about 14 hours has been reported although this may be prolonged in patients with renal impairment. Excretion is mainly in the faeces with only 10% being present in the urine. Fexofenadine does not appear to cross the blood-brain barrier.

Fexofenadine is a metabolite of terfenadine and as such has been detected in breast milk after the use of terfenadine.

References.
1. Russell T, *et al.* Pharmacokinetics, pharmacodynamics, and tolerance of single- and multiple-dose fexofenadine hydrochloride in healthy male volunteers. *Clin Pharmacol Ther* 1998; 64: 612–21.
2. Devillier P, *et al.* Clinical pharmacokinetics and pharmacodynamics of desloratadine, fexofenadine and levocetirizine: a comparative review. *Clin Pharmacokinet* 2008; 47: 217–30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Alercas; Alerfedine; Allegra; *Austral.*: Allerfexo; Fexal; Fexotabs; Telfast; Xergic; *Austria*: Telfast; *Belg.*: Allergo Rhinathiol; Telfast; *Braz.*: Allegra; Allexofedrin; Altiva; Fexodane; Rafex; *Canad.*: Allegra; *Chile*: Aerodant†; Alexia; Allegra; Penax; *China*: BiXin (毕馨); Lai Duo Fei (莱多菲); Min Jie (敏杰); Raltiva (阿特拉); Rui Pei (瑞菲); Sailexi (赛乐西); *Cz.*: Afexil†; Ewofex; Fexigra; Telfast†; *Denm.*: Alterfast; Altifex; Histafast; Nefoxef; Telfast; *Fin.*: Alterfast†; Nefoxef; Telfast; *Fr.*: Telfast; *Ger.*: Fexofenaderm; Telfast; *Hong Kong*: Bosnum; Fexodine; Telfast; Zafil†; *Hung.*: Allegra; Altiva; Fexgen; Fexofep; Telfast; *India*: Afexdine; Alernex; Alert; Alfexo; Allefast; Allegix; Allegra; Allofex; Altiva; Fegra; Fenadin; Fexamed; Fexidine; Fexigra; Fexo; Fexodex; Fexodin; Fexofast; Fexofen; Fexona; Fexoquit; Fexot; Fexotrol; Fexova; Histagra; Histaloc; Infexo; Odifex; Oregra; *Indon.*: Telfast; *Irl.*: Telfast; *Israel*: Telfast; *Ital.*: Telfast; *Malaysia*: Fexofin; Telfast; *Mex.*: Aldifex; Allegra; Apertum-Ox; Fexoff-R; Gebenir†; Ranfast; *Neth.*: Allegra; STP-free†; Telfast; *Norw.*: Altifex; Telfast; *NZ*: Fexofast; Telfast; Xergic; *Philipp.*: Fenafex; Fexet; Fexoral; Histofen†; Neofex; Rhinogan; Sensitin; Telfast; *Pol.*: Fexofast; FexoGen; Telfast; Telfexo; *Port.*: Fexocare; Telfast; *Rus.*: Allerfex (Аллерфекс); Dinox (Динокс); Fexadin (Фексадин); Fexofast (Фексофаст); Rapido (Рапидо); Telfast (Телфаст); *S.Afr.*: Fastway; Fenofex; Fexaway; Fexo; Fexofast†; Telfast; Tellerge; *Singapore*: Telfast; *Spain*: Telfast; *Swed.*: Allegra; Nefoxef; Telfast; *Switz.*: Telfast; Telfastin Allergo; *Thai.*: Bosnum; Fenafex; Fexofast; Fexotine; Telfast; Tofexo; Vifas; *Turk.*: Feksine; Fexadyne; Fexavil; Fexizin; Fexofen; Mayfex; Telfast; Vivafeks; *UK*: Telfast; *Ukr.*: Altiva (Алтива); Fexofast (Фексофаст); Telfast (Телфаст); *USA*: Allegra; *Venez.*: Allegra; Fexidine; Fexoril; Rinolast.

Multi-ingredient Preparations. *Arg.*: Alercas D; Alerfedine D; Allegra-D; *Austral.*: Telfast Decongestant; *Braz.*: Allegra-D; Fexo-D†; *Canad.*: Allegra-D; *Chile*: Alexia D; Allegra-D; *Hong Kong*: Telfast-D; *India*: Altiva-D; *Indon.*: Fexofed; Telfast Plus; *Jpn*: Dellegra; *Malaysia*: Altiva-D; Telfast-D; *Mex.*: Allegra-D; *Singapore*: Telfast-D; *Thai.*: Telfast D†; *USA*: Allegra-D; *Venez.*: Allegra-D; Rinolast D.

Pharmacopoeial Preparations

BP 2014: Fexofenadine Tablets;

USP 36: Fexofenadine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets; Fexofenadine Hydrochloride Capsules; Fexofenadine Hydrochloride Tablets.

Flunarizine Hydrochloride *(BANM, USAN, rINNM)*

Flunaritsiinidihydrokloridi; Flunarizina, hidrocloruro de; Flunarizin-dihydrochlorid; Flunarizindihydroklorid; Flunarizine, Chlorhydrate de; Flunarizine, dichlorhydrate de; Flunarizini dihydrochloridum; Flunarizini Hydrochloridum; Flunarizino dihidrochloridas; Hidrocloruro de flunarizina; R-14950; Флунаризина Гидрохлорид.

trans-1-Cinnamyl-4-(4,4'-difluorobenzhydryl)piperazine dihydrochloride.

$C_{26}H_{26}F_2N_2,2HCl=477.4$

CAS — 52468-60-7 (flunarizine); 30484-77-6 (flunarizine hydrochloride).

ATC — N07CA03.

ATC Vet — QN07CA03.

UNII — C11102TO53.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Ph. Eur. 8: (Flunarizine Dihydrochloride). A white or almost white hygroscopic powder. Slightly soluble in water, in alcohol, and in dichloromethane; sparingly soluble in methyl alcohol. Store in airtight containers. Protect from light.

Uses and Administration

Flunarizine is the difluorinated derivative of cinnarizine. It has antihistamine, sedative, and calcium-channel blocking activity. Flunarizine hydrochloride is used for migraine prophylaxis, for vertigo and vestibular disorders, and for peripheral and cerebral vascular disorders. It has also been used as adjunctive antiepileptic therapy in patients refractory to standard regimens.

Flunarizine is given orally as the hydrochloride although doses are expressed in terms of the base. Flunarizine hydrochloride 11.8 mg is equivalent to about 10 mg of flunarizine. The usual dose is 5 to 10 mg daily, usually given at night to minimise the effects of drowsiness.

Flunarizine betadex (flunarizine betacyclodextrin) has been used similarly.

Epilepsy. Several drugs with calcium-channel blocking activity have been investigated as adjuncts in epilepsy (p. 506.1), including flunarizine. Some individual studies have reported benefit, but a systematic review[1] concluded that although flunarizine might have a weak effect on seizure frequency the evidence was not convincing, and the withdrawal rate was significant, probably because of poor tolerability; it should therefore not be recommended as adjunctive antiepileptic therapy. The pharmacokinetic profile of flunarizine may in any case be too complex for clinical use as an antiepileptic.[2]

1. Chaisewikul R, *et al.* Calcium antagonists as an add-on therapy for drug-resistant epilepsy. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 13/06/05).
2. Hoppu K, *et al.* Flunarizine of limited value in children with intractable epilepsy. *Pediatr Neurol* 1995; 13: 143–7.

Migraine. Flunarizine reduces the frequency of migraine attacks in both adult and paediatric patients and is used for the prophylaxis of migraine (p. 670.3) in some countries. Its effects are comparable with several other prophylactic antimigraine drugs, including the generally preferred propranolol,[1-4] but it is more likely to be reserved for use when first-line drugs have proved to be ineffective or unsuitable. Its mode of action in migraine is unclear; possible mechanisms are inhibition of vasospasm induced by mediators such as serotonin and prostaglandins, inhibition of cellular hypoxia, and improved blood viscosity and erythrocyte deformability. Calcium-channel blocking activity might have a role, but evidence for the efficacy of other calcium-channel blockers in migraine prophylaxis (see Nifedipine, p. 1449.1) is less convincing than for flunarizine.

Case reports have indicated benefit with flunarizine in the prophylaxis of the rare disorder of alternating hemiplegia in childhood[5,6] but a subsequent study[7] in 12 children did not produce conclusive findings. A later long-term study[8] reported that 7 of 9 children given flunarizine for up to 5 years for hemiplegia showed a reduction in the duration of attacks, and 3 had a reduction in frequency, but only 1 of these obtained a complete cessation of episodes.

The role of antihistamines in general in the management of migraine is discussed briefly on p. 611.3.

1. Todd PA, Benfield P. Flunarizine: a reappraisal of its pharmacological properties and therapeutic use in neurological disorders. *Drugs* 1989; 38: 481–99.
2. Andersson K-E, Vinge E. β-Adrenoceptor blockers and calcium antagonists in the prophylaxis and treatment of migraine. *Drugs* 1990; 3: 355–73.
3. Soelberg Sørensen P, *et al.* Flunarizine versus metoprolol in migraine prophylaxis: a double-blind, randomized parallel group study of efficacy and tolerability. *Headache* 1991; 31: 650–7.
4. Gawel MJ, *et al.* Comparison of the efficacy and safety of flunarizine to propranolol in the prophylaxis of migraine. *Can J Neurol Sci* 1992; 19: 340–5.
5. Casaer P, Azou M. Flunarizine in alternating hemiplegia in childhood. *Lancet* 1984; ii: 579.
6. Curatolo P, Cusmai R. Drugs for alternating hemiplegic migraine. *Lancet* 1984; ii: 980.
7. Casaer P. Flunarizine in alternating hemiplegia in childhood. An international study in 12 children. *Neuropediatrics* 1987; 18: 191–5.
8. Silver K, Andermann F. Alternating hemiplegia of childhood: a study of 10 patients and results of flunarizine treatment. *Neurology* 1993; 43: 36–41.

Tourette's syndrome. A small unblinded study[1] involving 7 patients has suggested that flunarizine is more effective than placebo in the treatment of Tourette's syndrome (see Tics, p. 1030.1).

1. Micheli F, *et al.* Treatment of Tourette's syndrome with calcium antagonists. *Clin Neuropharmacol* 1990; 13: 77–83.

Vertigo. Antihistamines are the mainstay of the treatment of vertigo (p. 612.3). However, their antimuscarinic adverse effects may prove troublesome, particularly in the elderly, and they produce central sedation. Flunarizine is devoid of antimuscarinic properties, although it may produce central sedation.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively. Adverse effects also seen with flunarizine include weight gain, extrapyramidal symptoms (sometimes associated with depression), and, rarely, galactorrhoea.

Extrapyramidal disorders. Extrapyramidal motor signs (including parkinsonism, orofacial tardive dyskinesia, and akathisia) have been reported in 12 patients given flunarizine 10 to 40 mg daily for between 3 weeks and 15 months; 11 also had depression.[1] Partial or complete improvement of symptoms occurred after withdrawal of flunarizine. There have been other reports of similar effects,[2-5] but the association with flunarizine has not always been certain. Some workers have commented that flunarizine is often used in patients at increased risk of depression (migraine and geriatric patients) or extrapyramidal symptoms (geriatric patients)[2,6] or that flunarizine may unmask subclinical idiopathic Parkinson's disease.[6,7]

Extrapyramidal signs, including parkinsonism, have also been associated with the related drug, cinnarizine.[3-5] It has been suggested that such effects may be less likely to occur with cinnarizine than with flunarizine because of its shorter half-life and lower lipophilicity.[3]

1. Chouza C, *et al.* Parkinsonism, tardive dyskinesia, akathisia, and depression induced by flunarizine. *Lancet* 1986; i: 1303–4.
2. Meyboom RHB, *et al.* Parkinsonism, tardive dyskinesia, akathisia, and depression induced by flunarizine. *Lancet* 1986; ii: 292.
3. Laporte J-R, Capella D. Useless drugs are not placebos: lessons from flunarizine and cinnarizine. *Lancet* 1986; ii: 853–4.
4. Laporte J-R, Capella D. Useless drugs are not placebos. *Lancet* 1987; i: 1324.
5. Teive HAG, *et al.* Flunarizine and cinnarizine-induced parkinsonism: a historical and clinical analysis. *Parkinsonism Relat Disord* 2004; 10: 243–5.
6. Amery W. Side-effects of flunarizine. *Lancet* 1986; i: 1497.
7. Benvenuti P, *et al.* Side-effects of flunarizine. *Lancet* 1986; ii: 464.

Interactions

As for the sedating antihistamines in general, p. 614.3.

Hepatic enzyme inducers such as carbamazepine, phenytoin, and valproate may interact with flunarizine by increasing its metabolism; an increase in dosage of flunarizine may be required.

Pharmacokinetics

Flunarizine hydrochloride is well absorbed from the gastrointestinal tract, peak plasma concentrations occurring 2 to 4 hours after oral doses. Flunarizine hydrochloride is very lipophilic and is more than 90% bound to plasma proteins. It appears to undergo extensive metabolism; metabolites are excreted principally in the bile. Flunarizine hydrochloride has an elimination half-life of about 18 days.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Bercetina; Coromert; Flufenal; Mondus; Niflucan; Sibelium; ***Austria***: Sibelium; ***Belg.***: Flunarimed†; Flunatop; Sibelium; ***Braz.***: Flunarin; Fluvert; Fluzix; Sibelium; Vertigium; Vertix; ***Canad.***: Sibelium†; ***Chile***: Fleroxt; Fluxus; Irrigor; Sibelium; Zentralin; ***China***: Ao Li Bao Ke (奥力保克); Fu Rui Er (孚瑞尔); Fu Rui Lin (弗瑞林); Hua Xin (花欣); Sibelium (西比灵); ***Cz.***: Sibelium; ***Denm.***: Sibelium; ***Fr.***: Sibelium; ***Ger.***: Flunavert; Natil-N; ***Gr.***: Sibelium; ***Hong Kong***: Fludan; ***Hung.***: Sibelium; ***India***: Cinzin; Efigraine; Fine; Flubery; Flugraine; Flunarin; Flunaris; Flunatrac; Fluriz; Flury; Flutom; Fluvert; Fluz; Fzin; Graton; Grenate; Grenil-F; MGR; Migarid; Migazin; Migon; Migrecure; Migrid; Nariz; Narizine; Narzine; Nomigrain; Nubelium; ***Indon.***: Bartolium; Cevadil; Degrium; Dizilium†; Dizine; Frego; Seremig; Sibelium; Siberid; Silum; Sinral; Unalium; Xepalium; ***Irl.***: Sibelium; ***Ital.***: Flugeral; Flunagen; Fluxarten; Gradient; Issium; Sibelium; ***Malaysia***: Fludan; Forknow; Migarid; Sibelium; ***Mex.***: Axilin†; Fasolan; Naflufyl; Sibelium; ***Neth.***: Sibelium; ***Philipp.***: Flumig; Flunariz; Migralin; Sibelium; ***Port.***: Sibelium; Vasilium; Zinasen; ***S.Afr.***: Sibelium; ***Singapore***: Forknow; Narizine; Sibelium; ***Spain***: Flerudin; Flurpax; Sibelium; ***Switz.***: Sibelium; ***Thai.***: Cebrium; Cedelate; Fabelium; Finelium; Floxin; Flubelin; Fluclium; Fludan; Flulium†; Flunamed; Flunaric; Flunarium; Fluricin; Flurin; Furin; Hexilium; Liberal; Medilium†; Poli-Flunarin; Sibelium; Simoyiam; Sobelin; Sovelium; Vanid; Vertilium; Zelium; ***Turk.***: Sibelium; ***Venez.***: Fludil; Sibelium.

Multi-ingredient Preparations. ***Arg.***: Sibelium Plus; ***Braz.***: Vertizine D; ***India***: Egrin; Fluner; Mygran; Oxokool Plus.

Homochlorcyclizine Hydrochloride

(BANM, rINNM)

Hidrocloruro de homoclorciclizina; Homochlorcyclizine, Chlorhydrate d'; Homochlorcyclizini Hydrochloridum; Homoclorciclizina, hidrocloruro de; Гомохлорциклизина Гидрохлорид.

1-(4-Chlorobenzhydryl)perhydro-4-methyl-1,4-diazepine dihydrochloride.

$C_{19}H_{23}ClN_2,2HCl$=387.8

CAS — 848-53-3 (homochlorcyclizine); 1982-36-1 (homochlorcyclizine hydrochloride).

Pharmacopoeias. In *Jpn*.

Profile

Homochlorcyclizine hydrochloride, a piperazine derivative, is a sedating antihistamine (p. 610.1) with antimuscarinic and moderate sedative properties. It is used for the symptomatic relief of allergic conditions including urticaria (p. 612.3) and rhinitis (p. 612.1), and in pruritic skin disorders (p. 612.1). It is given in oral doses of 10 to 20 mg three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Hong Kong***: Homoclomin; ***Indon.***: Homoclomin; ***Jpn***: Homoclomin; ***Thai.***: Homoclomin†.

Hydroxyzine *(BAN, rINN)*

Hidroxizina; Hydroksitsiini; Hydroxizin; Hydroxyzinum; Гидроксизин.

(*RS*)-2-[2-[4-(*p*-Chloro-α-phenylbenzyl)piperazin-1-yl]ethoxy ethanol.

$C_{21}H_{27}ClN_2O_2$=374.9

CAS — 68-88-2.

ATC — N05BB01.

ATC Vet — QN05BB01.

UNII — 30550YM8OG.

Hydroxyzine Embonate *(BANM, rINNM)*

Embonato de hidroxizina; Hidroxizina, embonato de Hydroxyzine, Embonate d'; Hydroxyzine Pamoate; Hydroxyzini Embonas; Pamoato de hidroxizina; Гидроксизина Эмбонат.

2-[2-[4-(4-Chlorobenzhydryl)piperazin-1-yl]ethoxy]ethano 4,4′-methylenebis(3-hydroxy-2-naphthoate).

$C_{21}H_{27}ClN_2O_2,C_{23}H_{16}O_6$=763.3

CAS — 10246-75-0.

ATC — N05BB01.

ATC Vet — QN05BB01.

UNII — M20215MUFR.

Pharmacopoeias. In *Jpn* and *US*.

USP 36: (Hydroxyzine Pamoate). A light yellow, practically odourless powder. Soluble 1 in more than 1000 of water, of chloroform, and of ether, 1 in 700 of alcohol, 1 in 10 of dimethylformamide, and 1 in 3.5 of 10M sodium hydroxide solution; practically insoluble in methyl alcohol. Store in airtight containers.

Hydroxyzine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de hidroxizina; Hidroksizin Hidroklorür, Hidroksizino hidrochloridas; Hidroxizina, hidrocloruro de; Hidroxizin-hidroklorid; Hydroksitsiinihydrokloridi; Hydroxizinhydroklorid; Hydroxyzin dihydrochlorid; Hydroxyzindihydrochlorid; Hydroxyzine, chlorhydrate d'; Hydroxyzini Dihydrochloridum; Hydroxyzini Hydrochloridum; Гидроксизина Гидрохлорид.

$C_{21}H_{27}ClN_2O_2,2HCl$=447.8

CAS — 2192-20-3.

ATC — N05BB01.

ATC Vet — QN05BB01.

UNII — 76755771U3.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Hydroxyzine Hydrochloride). A white or almost white, crystalline, hygroscopic powder. Freely soluble in water and in alcohol; very slightly soluble in acetone. Store in airtight containers. Protect from light.

USP 36: (Hydroxyzine Hydrochloride). A white, odourless powder. Soluble 1 in 1 of water, 1 in 4.5 of alcohol, and 1 in 13 of chloroform; slightly soluble in acetone; practically insoluble in ether. Store in airtight containers.

Incompatibility. Hydroxyzine hydrochloride has been reported to be incompatible with aminophylline, benzylpenicillin salts, chloramphenicol sodium succinate, dimenhydrinate, doxorubicin hydrochloride (in a liposomal formulation), thioridazine, and some soluble barbiturates.

Stability. A mixture of hydroxyzine hydrochloride, chlorpromazine hydrochloride, and pethidine hydrochloride stored in glass or plastic syringes was found[1] to be stable for 366 days at 4 degrees and 25 degrees.

1. Conklin CA, *et al.* Stability of an analgesic-sedative combination in glass and plastic single-dose syringes. *Am J Hosp Pharm* 1985; 42: 339–42.

Uses and Administration

Hydroxyzine, a piperazine derivative, is a sedating antihistamine with antimuscarinic and significant sedative properties; it is also an antiemetic. Its main use is as an anxiolytic (p. 1028.1) but see Anxiety Disorders p. 631.1. It is also used as an adjunct to pre- and postoperative medication (see Anaesthesia, p. 610.3) and in the management of pruritus (p. 612.1) and urticaria (p. 612.3) and has been used as an adjunct to opioid analgesia in the management of cancer pain (p. 7.1).

Hydroxyzine may be given orally as the hydrochloride or the embonate; doses are expressed in terms of the hydrochloride. Hydroxyzine embonate 170 mg is equivalent to about 100 mg of hydroxyzine hydrochloride.

Usual oral doses are: 50 to 100 mg four times daily for the short-term management of anxiety; for pruritus an initial dose of 25 mg given at night, increased if necessary to 25 mg three or four times daily; and 50 to 100 mg for pre- or postoperative sedation.

Hydroxyzine hydrochloride may also be given by deep intramuscular injection. For prompt control of anxiety or

agitation 50 to 100 mg is injected intramuscularly initially, and the dose may be repeated every four to six hours as required. For other indications when oral dosage is not practical, the intramuscular dose is 25 to 100 mg. Hydroxyzine should not be given by intravenous injection since haemolysis may result.

For doses in children, see below. Dosage should be reduced in patients with hepatic or renal impairment, see below.

Administration in children. Hydroxyzine may be given to children to treat pruritus in the following oral doses expressed as the hydrochloride:

- children aged 6 months to 6 years: initially 5 to 15 mg daily increased if necessary to 50 mg daily in divided doses
- those 6 to 12 years of age: initially 15 to 25 mg daily increased if necessary to 50 to 100 mg daily in divided doses

Alternatively, 1 mg/kg daily may be given in divided doses, to a maximum of 2.5 mg/kg daily in children aged 1 to 6 years or to a maximum of 2 mg/kg daily in those aged over 6 years.

The pre- or postoperative sedative dose in children is 600 micrograms/kg orally; alternatively, a dose of 1.1 mg/kg has been given by intramuscular injection.

Children and adolescents aged 12 years and over may be given usual adult doses, see p. 630.3.

Administration in hepatic or renal impairment. In patients with hepatic impairment, UK licensed product information recommends a 33% reduction in the total oral daily dose of hydroxyzine. In patients with moderate or severe renal impairment, a dose reduction of 50% is recommended.

Anxiety disorders. Although hydroxyzine is used in the management of anxiety, there is little evidence to support its efficacy in anxious patients,[1] and the *BNF* considers that use of antihistamines solely for their sedative effect in anxiety is not appropriate.

1. Ballenger JC, *et al.* Consensus statement on generalized anxiety disorder from the International Consensus Group on Depression and Anxiety. *J Clin Psychiatry* 2001; **62** (suppl 11): 53–8. Available at: http://www.psychiatrist.com/private/supplenet/v62s11/v62s1108.pdf (accessed 15/08/08)

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively.

Intramuscular injection of hydroxyzine has been reported to cause marked local discomfort. Intravenous use has been associated with haemolysis.

Arrhythmias. ECG abnormalities, particularly alterations in T-waves, were associated with anxiolytic doses of hydroxyzine hydrochloride and were similar to those produced by thioridazine and tricyclic antidepressants.[1]

1. Hollister LE. Hydroxyzine hydrochloride: possible adverse cardiac interactions. *Psychopharmacol Comm* 1975; 1: 61–5.

Effects on sexual function. A 32-year-old man had prolonged penile erections (priapism) after taking two separate doses of hydroxyzine for a skin rash.[1] It was suggested that the effect might be due to a hydroxyzine metabolite that was found to be structurally similar to a metabolite of trazodone, a drug known to induce penile erections.

1. Thavundayil JX, *et al.* Prolonged penile erections induced by hydroxyzine: possible mechanism of action. *Neuropsychobiology* 1994; 30: 4–6.

Effects on the skin. Four children given hydroxyzine hydrochloride for restlessness developed a fixed drug eruption of the penis.[1] All recovered on drug withdrawal and subsequently had positive rechallenges.

1. Cohen HA, *et al.* Fixed drug eruption of the penis due to hydroxyzine hydrochloride. *Ann Pharmacother* 1997; 31: 327–9.

Intra-arterial injection. Accidental intra-arterial injection of hydroxyzine has led to necrosis of the extremity requiring amputation of the digits of the affected limb.[1]

1. Hardesty WH. Inadvertent intra-arterial injection. *JAMA* 1970; 213: 872.

Liver disorders. It has been suggested[1] that hydroxyzine should only be given once daily for the relief of pruritus in patients with primary biliary cirrhosis. The mean serum elimination half-lives of hydroxyzine and its metabolite cetirizine in 8 patients with primary biliary cirrhosis were prolonged at 36.6 and 25.0 hours, respectively.

1. Simons FER, *et al.* The pharmacokinetics and pharmacodynamics of hydroxyzine in patients with primary biliary cirrhosis. *J Clin Pharmacol* 1989; 29: 809–15.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies hydroxyzine as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Interactions

As for the sedating antihistamines in general, p. 614.3.

Cimetidine. A pharmacokinetic study in 16 patients noted that *cimetidine* increased the serum concentration of hydroxyzine.[1] The combination generally produced a greater suppression of the cutaneous response to histamine than hydroxyzine alone, but the difference was not significant.

1. Simons FER, *et al.* Effect of the H_2-antagonist cimetidine on the pharmacokinetics and pharmacodynamics of the H_1-antagonists hydroxyzine and cetirizine in patients with chronic urticaria. *J Allergy Clin Immunol* 1995; 95: 685–93.

Pharmacokinetics

Hydroxyzine is rapidly absorbed from the gastrointestinal tract and is metabolised. Metabolites include cetirizine (p. 619.2), which has antihistaminic activity. An elimination half-life of about 20 hours has been reported.

References.

1. Paton DM, Webster DR. Clinical pharmacokinetics of H_1-receptor antagonists (the antihistamines). *Clin Pharmacokinet* 1985; 10: 477–97.

Liver disorders. For reference to a prolonged half-life of hydroxyzine in patients with primary biliary cirrhosis, see under Adverse Effects and Precautions, above.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Ataraxone; Hyderax; ***Austria***: Atarax; ***Belg.***: Atarax; ***Braz.***: Drotizin; Hidroxine; Hixilerg; Hixizine; Pruri-Gran; Prurizin; ***Canad.***: Atarax; ***Chile***: Dalun; Fasarax; ***Cz.***: Atarax; ***Denm.***: Atarax; ***Fin.***: Atarax; ***Fr.***: Atarax; ***Ger.***: AH 3 N; Atarax; ***Gr.***: Atarax; Ictinal; Iremofar; ***Hong Kong***: Atarax; Qualidrozine; Vatarax†; ***Hung.***: Atarax; ***India***: Atarax; H-Rax; Hozen; Hydil; Hydroze; Krust; Nizod; ***Indon.***: Bestalin; Iterax; ***Irl.***: Ucerax; ***Israel***: Otarex; ***Ital.***: Atarax; ***Malaysia***: Atarax; ***Mex.***: Atarax; ***Neth.***: Atarax†; ***Norw.***: Atarax; ***NZ***: Serecid; ***Philipp.***: Iterax; ***Pol.***: Atarax; ***Port.***: Atarax; Coraphene†; ***Rus.***: Atarax (Атаракс); ***S.Afr.***: Aterax; Neurax†; ***Singapore***: Atarax; Hizin; Phymorax; ***Spain***: Atarax; ***Swed.***: Atarax; ***Switz.***: Atarax; ***Thai.***: Abacus; Actadon; Allerax; Antipru; Antizine; Atalog; Atano; Atarax; Cerax; Dormirax; Drazine; Hadarax; Histan; Hiszine; Hizin; Honsa; Hydrox; Hyzine; Katrax; Polizine; R-Rax; Taraxin; Trandrozine; Unamine†; Xyzine; ***Turk.***: Atarax; Validol; Vistaril; ***UK***: Atarax; Ucerax; ***Ukr.***: Atarax (Атаракс); ***USA***: Vistaril.

Multi-ingredient Preparations. *Braz.*: Marax; ***India***: Marax; ***S. Afr.***: Geratart†; ***Spain***: Calmoplex†; Dolodens†; ***Ukr.***: Distonin (Дистонин)†; ***USA***: Hydrophed; Marax; Theomax DF.

Pharmacopoeial Preparations

BP 2014: Hydroxyzine Oral Solution; Hydroxyzine Tablets;
USP 36: Hydroxyzine Hydrochloride Injection; Hydroxyzine Hydrochloride Syrup; Hydroxyzine Hydrochloride Tablets; Hydroxyzine Pamoate Capsules; Hydroxyzine Pamoate Oral Suspension.

Isothipendyl Hydrochloride *(BANM, rINNM)*

Hidrocloruro de isotipendil; Isothipendyl, Chlorhydrate d'; Isothipendyli Hydrochloridum; Isotipendil, hidrocloruro de; Изотипендила Гидрохлорид.

NN-Dimethyl-1-(pyrido[3,2-*b*][1,4]benzothiazin-10-ylmethyl) ethylamine hydrochloride.

$C_{16}H_{19}N_3S,HCl=321.9$

CAS — 482-15-5 (isothipendyl); 1225-60-1 (isothipendyl hydrochloride).

ATC — D04AA22; R06AD09.

ATC Vet — QD04AA22; QR06AD09.

UNII — 953AP1LBV8.

Profile

Isothipendyl hydrochloride, an azaphenothiazine derivative, is an antihistamine (p. 610.1) that has been applied topically for hypersensitivity and pruritic skin disorders although as with any antihistamine there is a risk of sensitisation. It has also been given orally and by the rectal route.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Actapront; *Braz.*: Andantol; *Fr.*: Apaisyl†; Apaisylgel; Histapaisyl; Sedermyl; ***Indon.***: Andantol; ***Israel***: Thiodantol; ***Ital.***: Calmogel; ***Mex.***: Andantol.

Multi-ingredient Preparations. ***Indon.***: Nipe; Transpulmin.

Ketotifen Fumarate *(BANM, USAN, rINNM)*

Fumarato de ketotifeno; HC-20511; (ketotifen); Ketotifeenivetyfumaraatti; Ketotifen Hydrogen Fumarate; Kétotifène, Fumarate de; Kétotifène, hydrogénofumarate de; Ketotifenfumarát; Ketotifén-hidrogén-fumarát; Ketotifenhydrogenfumarat; Ketotifeni Fumaras; Ketotifeni hydrogenofumaras; Ketotifeno, fumarato de; Ketotifeno-vanderillio fumaratas; Ketotifenvätefumarat; Кетотифена Фумарат.

4-(1-Methylpiperidin-4-ylidene)-4*H*-benzo[4,5]cyclohepta-[1,2-*b*]thiophen-10(9*H*)-one hydrogen fumarate.

$C_{19}H_{19}NOS,C_4H_4O_4=425.5$

CAS — 34580-13-7 (ketotifen); 34580-14-8 (ketotifen fumarate).

ATC — R06AX17; S01GX08.

ATC Vet — QR06AX17; QS01GX08.

UNII — H8D503WORO.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn.*

Ph. Eur. 8: (Ketotifen Hydrogen Fumarate; Ketotifen Fumarate BP 2014). A white to brownish-yellow, fine crystalline powder. Sparingly soluble in water; very slightly soluble in acetonitrile; slightly soluble in methyl alcohol.

Uses and Administration

Ketotifen is a sedating antihistamine (p. 610.2) that also has a stabilising action on mast cells analogous to that of sodium cromoglicate (p. 1226.1). It is used in the treatment of allergic conditions such as rhinitis (p. 612.1) and conjunctivitis (p. 611.1). Ketotifen has also been used in the prophylactic management of asthma, when it may take several weeks to exert its full effect; it should not be used to treat acute asthma attacks.

Ketotifen is given as the fumarate, but doses are expressed in terms of the base; ketotifen fumarate 1.38 mg is equivalent to about 1 mg of ketotifen.

Ketotifen fumarate is taken in oral doses equivalent to 1 mg of ketotifen twice daily with food, increased if necessary to 2 mg twice daily; 0.5 to 1 mg at night may be preferable for the first few days of treatment if drowsiness is likely to be a problem.

Ketotifen fumarate has also been applied topically, as eye drops equivalent to 0.025% ketotifen, used twice daily.

For children's doses, see below.

Action. It has been suggested that the anti-allergic action of ketotifen was independent of its antihistaminic properties.[1] This might be due to its effect on responses to platelet-activating factor (PAF).[2] However, the significance of PAF in the pathogenesis of asthma has been questioned.

1. Greenwood C. The pharmacology of ketotifen. *Chest* 1982; 82 (suppl): 45S–8S.
2. Morley J, *et al.* Effects of ketotifen upon responses to platelet activating factor: a basis for asthma prophylaxis. *Ann Allergy* 1986; 56: 335–40.

Administration in children. Ketotifen fumarate can be given to children for the treatment of allergic conditions such as rhinitis (p. 612.1) or conjunctivitis (p. 611.1), and has been used in the prophylactic management of asthma. Oral doses equivalent to 1 mg of ketotifen twice daily with food may be used from 3 years of age. A dose equivalent to 500 micrograms ketotifen twice daily has been given to children aged between 6 months and 3 years.

Ketotifen fumarate has also been applied topically twice daily, as eye drops equivalent to 0.025% ketotifen, in children from 3 years of age.

Asthma. Results of studies on the efficacy of ketotifen in the treatment of asthma (p. 1195.2) have been conflicting; although some have found it effective in reducing symptoms[1–4] and in enabling a reduction in use of other anti-asthmatic drugs,[2,4] others have reported no significant benefits,[5,6] and UK guidelines on the management of asthma consider ketotifen to be ineffective.[7] A systematic review[8] found that it was of benefit in improving control of asthma and wheezing in children with mild to moderate disease, but noted that the high prevalence of atopy in several of the studies reviewed meant that the results might not be generalisable to children with asthma in general. A study in children described as 'preasthmatic' (that is, being at high risk of developing asthma) suggested that long-term therapy with ketotifen decreased the risk of asthma onset.[9]

1. Paterson JW, *et al.* Evaluation of ketotifen (HC20-511) in bronchial asthma. *Eur J Clin Pharmacol* 1983; 25: 187–93.
2. Tinkelman DG, *et al.* A multicenter trial of the prophylactic effect of ketotifen, theophylline, and placebo in atopic asthma. *J Allergy Clin Immunol* 1985; 76: 487–97.
3. Miraglia Del Giudice M, *et al.* Study of the efficacy of ketotifen treatment in asthmatic children under 3 years of age. *Curr Ther Res* 1986; 40: 685–93.
4. Rackham A, *et al.* A Canadian multicenter study with Zaditen (ketotifen) in the treatment of bronchial asthma in children aged 5 to 17 years. *J Allergy Clin Immunol* 1989; 84: 286–96.
5. White MP, *et al.* Ketotifen in the young asthmatic—a double-blind placebo-controlled trial. *J Int Med Res* 1988; 16: 107–13.
6. Volovitz B, *et al.* Efficacy and safety of ketotifen in young children with asthma. *J Allergy Clin Immunol* 1988; 81: 526–30.

7. Scottish Intercollegiate Guidelines Network/British Thoracic Society. British guideline on the management of asthma: a national clinical guideline (issued May 2008, revised June 2009). Available at: http://www.sign.ac.uk/pdf/sign101.pdf (accessed 06/08/09)
8. Bassler D, *et al.* Ketotifen alone or as additional medication for long-term control of asthma and wheeze in children. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 14/04/08).
9. Bustos GJ, *et al.* Prevention of asthma with ketotifen in preasthmatic children: a three-year follow-up study. *Clin Exp Allergy* 1995; **25**: 568–73.

Conjunctivitis. References.

1. Martín AP, *et al.* The effect of ketotifen on inflammatory markers in allergic conjunctivitis: an open, uncontrolled study. *BMC Ophthalmol* 2003; **3**: 2. Available at: http://www.biomedcentral.com/content/pdf/1471-2415-3-2.pdf (accessed 17/08/10)
2. Kidd M, *et al.* Efficacy and safety of ketotifen eye drops in the treatment of seasonal allergic conjunctivitis. *Br J Ophthalmol* 2003; **87**: 1206–11.
3. Ganz M, *et al.* Ketotifen fumarate and olopatadine hydrochloride in the treatment of allergic conjunctivitis: a real-world comparison of efficacy and ocular comfort. *Adv Therapy* 2003; **20**: 79–91.
4. Abelson MB, *et al.* Efficacy and safety of single-and multiple-dose ketotifen fumarate 0.025% ophthalmic solution in a pediatric population. *Pediatr Allergy Immunol* 2004; **15**: 551–7.

Adverse Effects and Precautions

As for the antihistamines in general, p. 613.1 and p. 613.3, respectively; drowsiness may be a problem, and dry mouth and dizziness may occur at the beginning of treatment but usually resolve with continued use. Weight gain and CNS stimulation have been reported. Isolated cases of severe skin reactions, cystitis, and hepatitis have been reported. Irritation, pain, and punctate keratitis are commonly reported after topical application to the eye.

Similar precautions to those for sodium cromoglicate (p. 1227.2) should be observed in asthmatic patients. Ketotifen may take several weeks to exert its full effect; existing anti-asthma treatment should not be abruptly withdrawn after starting ketotifen therapy. It should not be used for the treatment of acute asthma attacks.

Overdosage. Overdoses of ketotifen ranging from 10 to 120 mg were reported in 8 patients.[1] Symptoms included drowsiness, confusion, dyspnoea, bradycardia or tachycardia, disorientation, and convulsions. Gastric lavage was performed in 6 patients, and all 8 recovered within 12 hours after supportive treatment.

In an overview of 21 cases of overdosage (including those reported above) the manufacturers stated that no serious signs or symptoms had been reported with doses below 20 mg, and there had been no fatalities.[2] The most serious effects reported had included unconsciousness, convulsions, bradycardia and tachycardia, and a severe hypotensive reaction. Management is essentially supportive and symptomatic.

1. Jefferys DB, Volans GN. Ketotifen overdose: surveillance of the toxicity of a new drug. *BMJ* 1981; **282**: 1755–6.
2. Le Blaye I, *et al.* Acute ketotifen overdosage: a review of present clinical experience. *Drug Safety* 1992; **7**: 387–92.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ketotifen as not porphyrinogenic when given by the ophthalmic route; it may be used as a drug of first choice and no precautions are needed. The safety of systemic formulations has not yet been classified.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Interactions

As for the sedating antihistamines in general, p. 614.3.

A reversible fall in the platelet count has been seen in a few patients receiving ketotifen with oral antidiabetics and it has been suggested that this combination should therefore be avoided.

Pharmacokinetics

Ketotifen fumarate is almost completely absorbed from the gastrointestinal tract after oral doses, but bioavailability is reported to be only about 50% due to hepatic first-pass metabolism. Peak plasma concentrations occur 2 to 4 hours after an oral dose. It is mainly excreted in the urine as inactive metabolites with a small amount of unchanged drug; the terminal elimination half-life is about 21 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Antilerg; Bilozen; Biomira†; Farmoftal; Ketocev; Respimex; Zaditen; *Austral.*: Zaditen; *Austria*: Ketotisan; Zaditen; *Belg.*: Altriabak; Zaditen; *Braz.*: Asdron; Asmalergin; Asmanon; Asmax; Asmen; Asmifen; Asmofen; Biatos; Octifen; Prurifen; Zaditen; Zetitec; *Canad.*: Zaditen; Zaditor; *Chile*: Farmoftal; Ketotisin; Oftaler; Zaditen; *China*: Bei Ka Ming (贝卡明); Rui Na Ti (瑞那替); Tong Fen (同芬); Cz.: Ketof; Zabak; Zaditen; *Denm.*: Zaditen; Zalerg; *Fin.*: Zaditen; *Fr.*: Zaditen; Zalerg; *Ger.*: Ketof†; Padiatifen†; Zaditen; *Gr.*: Cleroptic; Demetofrin; Dovidin; Ecradin; Eucycline; Fental; Firmapol; Frenasma; Isocaren; K-Drops; Kathricol; Klevistamin; Labelphen; Lavoptik; Meni-drops; Nostimex; Noxtor; Orpidix; Pellexeme; Sudaved; Urpem; Zaditen; Zeoklamin; Zethrinal; Zidofen; *Hong Kong*: Amitone; Asmafen; Astifen; Dhatifen; Ketifen†; Vidatifen†; Zaditen; *Hung.*: Zaditen; *India*: Airyfen; Albalon; Asthafen; Azofen; Ketasma; Ketorid; Ketotif; Mastifen; *Indon.*: Astifen†; Intifen; Nortifen; Prevas†; Profilas; Scanditen; Zaditen; *Irl.*: Zaditen; *Israel*: Profiten; Zaditen; *Ital.*: Alleal†; Allerket; Bentifen; Chetofen; Chetotifene; Ketoftil; Sosefen; Stamifen†; Zaditen; *Jpn*: Zaditen; *Malaysia*: Asmafen; Asmaten; Asumalife; Denerel; Dhatifen; Ketifen; Licoften; Zaditen; *Mex.*: Asmaral-K; Biotifen; Cantel†; Kasmal; Kedrop; Keraffler; Nemodine; Nomotec; Osaten; Pretifen; Saluket-H1; Ventisol; Zaditen; *Neth.*: Altriabak; Bentifen†; Zaditen; *Norw.*: Zaditen; *NZ*: Asmafen†; Zaditen; *Philipp.*: Azimef; Zadec; Zaditen; *Pol.*: Zaditen; *Port.*: Bentifen; Cipanfeno; Zabak; Zaditen; *Rus.*: Zaditen (Задитен); Zetifen (Зетифен)†; *S.Afr.*: Adco-Zetofen; Ketohexal†; Zaditen; *Singapore*: Amitone; Asmafen; Asmaten; Asumalife; Beatifen; Denerel; Dhatifen; Erliten; Licoften; SP-Totifen; Suntotifen; Tofen; Zaditen; *Spain*: Bentifen; Okeye; Zaditen; Zasten; *Swed.*: Zaditen; *Switz.*: Zabak; Zaditen; *Thai.*: Ibis; Katifen; Kenefen; Keten; Ketifen†; Keto; Ketofen; Medkofen†; Politifen; Sukafen; Sykofen; TM Fen; Zadino; Zaditen; Zetofen; Zytofen; *Turk.*: Astafen; Fumast; Mitofen; Zaditen; *UAE*: Asmafort; *UK*: Zaditen; *Ukr.*: Zaditen (Задитен); *USA*: Alaway; Claritin Eye; Itchy Eye Drops†; Visine All Day Eye Itch Relief; Zaditor; Zyrtec Itchy Eye Drops; *Venez.*: Cusolve; Ketoptic; Ketotisin; Zaditen.

Multi-ingredient Preparations. *Arg.*: Hyalcrom NF; *China*: Xu Hong (旭宏); *India*: Azofen-T; Mastifen-C; Mastifen-S; *Mex.*: Hyalcrom NF.

Latrepirdine *(USAN, rINN)*

BRN-0622478; Dimebol; Dimebolin; Dimeboline; Dimebon; Dimebone; Latrepirdina; Latrépirdine; Latrepirdinum; PF-1913539; Латрепирдин; Димеболин.

2,3,4,5-Tetrahydro-2,8-dimethyl-5-[2-(6-methyl-3-pyridinyl) ethyl]-1*H*-pyrido[4,3-*b*]indole.

$C_{21}H_{25}N_3$=319.5

CAS — 3613-73-8 (latrepirdine); 97657-92-6 (latrepirdine dihydrochloride); 14292-23-0 (latrepirdine x-hydrochloride).

UNII — OD9237K1Z6.

Profile

Latrepirdine is an antihistamine that is reported to also have neuroprotective effects. It is under investigation as the dihydrochloride in the treatment of Alzheimer's disease (see Dementia, p. 388.1) and Huntington's disease.

References.

1. Doody RS, *et al.* Effect of dimebon on cognition, activities of daily living, behaviour, and global function in patients with mild-to-moderate Alzheimer's disease: a randomised, double-blind, placebo-controlled study. *Lancet* 2008; **372**: 207–15.
2. Kieburtz K, *et al.* A randomized, placebo-controlled trial of latrepirdine in Huntington disease. *Arch Neurol* 2010; **67**: 154–60.

Levocabastine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de levocabastina; Levocabastina, hidrocloruro de; Lévocabastine, chlorhydrate de; Levocabastinhydrochlorid; Levocabastini Hydrochloridum; Levokabastiinihydrokloridi; Levokabastin-hydrochlorid; Levokabastinhydroklorid; Levokabastino hidrochloridas; Levokabasztinhidroklorid; R-50547; Левокабастина Гидрохлорид.

(-)-*trans*-1-[*cis*-4-Cyano-4-(*p*-fluorophenyl)cyclohexyl]-3-methyl-4-phenylisonipecotic acid hydrochloride.

$C_{26}H_{29}FN_2O_2$,HCl=457.0

CAS — 79516-68-0 (levocabastine); 79547-78-7 (levocabastine hydrochloride); 79449-98-2 (cabastine).

ATC — R01AC02; S01GX02.

ATC Vet — QR01AC02; QS01GX02.

UNII — 124XMA6YEI.

NOTE. Cabastine *(rINN)* is the racemate of levocabastine.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Levocabastine Hydrochloride). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol and in a 0.2% solution of sodium hydroxide; sparingly soluble in methyl alcohol. Protect from light.

USP 36: (Levocabastine Hydrochloride). Protect from light.

Uses and Administration

Levocabastine, a piperidine derivative, is a long-acting and potent antihistamine with a rapid onset of action. Levocabastine hydrochloride equivalent to 0.05% levocabastine is used topically twice daily as eye drops or as a nasal spray in the treatment of allergic conjunctivitis (p. 611.1) and rhinitis (p. 612.1), respectively, in adults and children aged 9 years and over. The frequency of the dose in both conditions may be increased to 3 or 4 times daily if necessary. It is recommended that treatment should be stopped if there is no improvement within 3 days.

References.

1. Noble S, McTavish D. Levocabastine: an update of its pharmacology, clinical efficacy and tolerability in the topical treatment of allergic rhinitis and conjunctivitis. *Drugs* 1995; **50**: 1032–49.
2. Doughty MJ. Levocabastine, a topical ocular antihistamine available as a pharmacy medicine – a literature review. *Pharm J* 2002; **268**: 367–70.

Administration in children. For dosage in children, see above.

Adverse Effects and Precautions

As for the antihistamines in general, p. 613.1 and p. 613.3, respectively. The most common adverse effects reported with levocabastine eye drops are transient stinging and burning of the eyes, urticaria, dyspnoea, drowsiness, and headache. With nasal use headache, nasal irritation, somnolence, and fatigue have been noted. The use of levocabastine nasal spray is not recommended in those with significant renal impairment.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies levocabastine as probably not porphyrinogenic when given intra-nasally; it may be used as a drug of first choice and no precautions are needed. When given ophthalmically it has been classified as not porphyrinogenic.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Pharmacokinetics

Levocabastine is absorbed after both nasal and ocular use. Systemic availability has been estimated at 60 to 80% after nasal doses and 30 to 60% after ocular use. However absolute peak plasma concentrations are low. Plasma protein binding is about 55%. An elimination half-life of 35 to 40 hours has been reported for all routes of delivery. Elimination of levocabastine is mainly renal with 70% excreted as unchanged drug and 10% as an inactive acetylglucuronide metabolite; the remaining 20% is excreted unchanged in the faeces.

Trace amounts of levocabastine have been found in breast milk after ocular and nasal use.

References.

1. Heykants J, *et al.* The pharmacokinetic properties of topical levocabastine: a review. *Clin Pharmacokinet* 1995; **29**: 221–30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Histimet; *Austral.*: Livostin; *Austria*: Livostin; *Belg.*: Livostin; *Braz.*: Livostin; *Canad.*: Livostin; *Chile*: Livostin†; *China*: Livostin (立复汀); *Cz.*: Livostin; *Denm.*: Benaliv; Livostin†; *Fin.*: Livostin; *Fr.*: Allergiflash; Levofree; Levophta; *Ger.*: Livocab; *Gr.*: Livostin; *Israel*: Livostin; *Ital.*: Levoreact; Levostab; Livocab†; Livostin; *Jpn*: Livostin; *Mex.*: Livostin; *Neth.*: Livocab; *Norw.*: Livostin; *NZ*: Livostin; *Port.*: Livostin; *S.Afr.*: Livostin; Sinumax Allergy; *Spain*: Biliana; Livocab†; Reactine Levocabastina; *Swed.*: Livostin; *Switz.*: Livostin; *Turk.*: Livostin†; *Venez.*: Livostin.

Levocetirizine *(BAN, USAN, rINN)*

Levocetirizina; Lévocétirizine; Levocetirizinum; Левоцетиризин.

(2-{4-[(*R*)-*p*-Chloro-α-phenylbenzyl]-1-piperazinyl}ethoxy) acetic acid.

$C_{21}H_{25}ClN_2O_3$=388.9

CAS — 130018-77-8.

ATC — R06AE09.

ATC Vet — QR06AE09.

UNII — 6U5EA9RT2O.

Levocetirizine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de levocetirizina; Lévocétirizine, Chlorhydrate de; Levocetirizine Dihydrochloride (USAN); Levocetirizini Hydrochloridum; UCB-28556; Левоцетиризина Гидрохлорид.

$C_{21}H_{25}ClN_2O_3$,2HCl=461.8

CAS — 130018-87-0 (levocetirizine dihydrochloride); 823178-28-5 (levocetirizine hydrochloride).

ATC — R06AE09.

ATC Vet — QR06AE09.

UNII — SOD6A38AGA (levocetirizine dihydrochloride), W69HSF2416 (levocetirizine hydrochloride).

Profile

Levocetirizine is the *R*-enantiomer of cetirizine (p. 619.2 and is used similarly, as the hydrochloride, for the symptomatic relief of allergic conditions including rhiniti

(p. 612.1) and chronic urticaria (p. 612.3). The usual oral dose of levocetirizine hydrochloride is 5 mg once daily. US licensed product information suggests that the dose should be given in the evening, and that a dose of 2.5 mg may be adequate in some patients.

For doses in children or in patients with renal impairment, see below.

References.
1. Scheinfeld N. The new antihistamines—desloratadine and levocetirizine: a review. *J Drugs Dermatol* 2002; **1**: 311–16.
2. Tillement JP, *et al.* Compared pharmacological characteristics in humans of racemic cetirizine and levocetirizine, two histamine H1-receptor antagonists. *Biochem Pharmacol* 2003; **66**: 1123–6.
3. Horak F, *et al.* Levocetirizine has a longer duration of action on improving total nasal symptoms score than fexofenadine after single administration. *Br J Clin Pharmacol* 2005; **60**: 24–31.
4. Netis E, *et al.* Levocetirizine in the treatment of chronic idiopathic urticaria: a randomized, double-blind, placebo-controlled study. *Br J Dermatol* 2006; **154**: 533–8.
5. Hair PI, Scott LJ. Levocetirizine: a review of its use in the management of allergic rhinitis and skin allergies. *Drugs* 2006; **66**: 973–96.
6. Devillier P, *et al.* Clinical pharmacokinetics and pharmacodynamics of desloratadine, fexofenadine and levocetirizine: a comparative review. *Clin Pharmacokinet* 2008; **47**: 217–30.

Administration in children. Levocetirizine hydrochloride may be given orally to children for the symptomatic relief of allergic rhinitis and chronic idiopathic urticaria, although licensed doses may vary between countries.

In the UK, children aged 2 to 6 years may be given a dose of 2.5 mg daily in 2 divided doses, and those older than 6 years may be given the adult dose of 5 mg once daily.

In the USA, levocetirizine hydrochloride is licensed for the symptomatic treatment of seasonal allergic rhinitis in children aged 2 years and older, and for perennial allergic rhinitis and chronic idiopathic urticaria in children aged 6 months and older. Doses are lower than those used in the UK, at 1.25 mg given once daily in the evening to children aged from 6 months to 5 years, 2.5 mg in the evening for those aged 6 to 11 years, and the adult dose of 5 mg daily only given to children aged 12 years and older.

For doses in children with renal impairment, see below.

Administration in renal impairment. The dose of levocetirizine hydrochloride should be reduced in patients with renal impairment according to creatinine clearance (CC), although recommendations can vary between countries. The following oral doses have been suggested for adults in the UK and for adults and adolescents aged 12 years and over in the USA:

- CC 50 to 79 mL/minute: 5 mg once daily in the UK; 2.5 mg once daily in the USA
- CC 30 to 49 mL/minute: 5 mg every other day in the UK; 2.5 mg every other day in the USA
- CC 10 to 29 mL/minute: 5 mg once every 3 days in the UK; 2.5 mg once every 3 or 4 days in the USA
- CC less than 10 mL/minute and patients undergoing dialysis: contra-indicated in both the UK and USA

Data are lacking for the use of levocetirizine in children with renal impairment. UK licensed product information suggests that the dose should be adjusted on an individual basis, taking into account the patient's renal clearance and body-weight.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Analerg; Cetimer L; Levomine; Supraler; *Austral.*: Xyzal; *Austria*: Xyzall; *Belg.*: Xyzall; *Braz.*: Zyxem; *Chile*: Alerfix; Degraler; Dofitex; Levorigotax; Neo Alertop; Xuzal; *China*: Chang Ran (畅然); Di Min (迪皿); Nuo Si Da (诺思达); Qi Ping (齐平); Qiang Yi (强溢); Xikexin (西可新); Xyzal (优泽); *Cz.*: Cezera; Lavaz; Lecivriens; Levozine; Silardex; Sintir; Volnostin; Xyzal; Zenaro; *Denm.*: Levazyr; Xyzal; *Fin.*: Levazyr; Nocedan; Xyzal; *Fr.*: Xyzall; *Ger.*: Xusal; *Gr.*: Xozal; *Hong Kong*: Xyzal; *Hung.*: Histisynt; Lertazin; Levocep; Novocetrin; Sefaller; Xyzal; *India*: Adicure; Airitis; Alcare-L; Alcetra; Alci; Aldine; Alertriz; Alervo; Aleva; Alexfix; Alidil; Allcet-DC; Allrite; Alnacet; Alquit-L; Altase; Altin-LE; Alvicet; Alzero; Arcet; Arizin-L; Atcet-LV; Belrin-LZ; Bencet-L; Bincet-L; Biolev; Biozine; Borox; Cefid-L; Cetjust L; Cetliv; Cetlong-L; Cetom-L; Cetril; Cetrina-LV; Cetrite; Cetsafe; Ciz-L; Ciz-LE; Covil; CTLevo; Deall; Dilevocet; Eelax; Ekon-XL; Elcet; Elcy; Elnacin; Eliz; Enocet-LV; Fitin; Fitzine-MD; Flamoset; Folcet; Genuhist; Glencet; Hatric; Hicet-L; His; Histachek; Idalez; Incet-L; Incet; Kind; Kurecet; L-5; L-Asicet; L-CBit; L-Cet; L-Cetridoc; L-Cetrizet; L-Cetron; L-Cit; L-CZN; L-Siacet; L-Triz; Labocet; Largy; Laveta; Lavoriz; Lazine; LCN; LCRal; LCZ; LDZin; Le Zyncet; Lecetzy; Lecope; Lecy; Leczine-MD; Leday; Leeviz; Leez; Lehist; Lentocit; Leoriv; Lepit; Lerid; Lerzin; Leset; Lesie; Lest; Lestal; Let; Leverest; Levoace; Levoc; Levocet; Levocetriwal; Levocets; Levodil; Levogo; Levohext; Levokair; Levonitrin; Levorid; Levoril; Levoriz; Levosiz; Levosoz; Levostar; Levotin; Levotra; Levotrin; Levoz; Levozin; Levzed; Lexzin; Lezer; Lezo; LFast; LG; Livit; Livot-MD; Lizine; Loviroc; Luzel; Luzer; Lycet; Lycit; Macliz; Medicet-L; NBLcet; Nislevo; Nizla; Noal-LC; Notril; Novolev; Nucet; Nucez; Okacet-L; Oriel; Ostril; Oxycet; Teczine; *Indon.*: Xyzal; *Irl.*: Muntel; Rinozal; Xyzal; *Ital.*: Xyzal; *Jpn*: Xyzal; *Malaysia*: Xyzal; *Mex.*: Xuzal; Zyxem; *Neth.*: Cetirmar; Levocetira; Virdos†; Xyzal; *Norw.*: Xyzal; *Philipp.*: L-zet; Lisinex; Xyzal; Zocet; *Pol.*: Cezera; Lirra; Xyzal; Zenaro; Zyx; *Port.*: Levrix; Xyzal; *Rus.*: Suprastinex (Супрастинекс); Xyzal (Ксизал); *S.Afr.*: Xyzal; *Singapore*: Xyzal; *Spain*: Aralevo; Muntel; Xazal; *Switz.*: Xyzal; *Thai.*: Xyzal; *Turk.*: Crebros; Xyzal; *UK*: Xyzal; *Ukr.*: Aleron (Алерон); Alerzin (Алерзин); Cetrilev (Цетрилев); Xyzal (Ксизал); Zenaro (Зенаро); Zilola (Зилола); *USA*: Xyzal.

Multi-ingredient Preparations. *India*: Abcet; Acolate Plus; Acolate; Airitis Plus; Airway-L; Alcare-CC; Alcetra Plus; Aldine-D; Allrite-D; Alnacet-AL; Alnacet-M; Ambicet; Amlee-P; Arokast; Borox-L; Breathery-L; Carlev; Cetliv A; Cetry Plus; Ciz Cold; Ciz-LE-D; Cold Calm; Cold-CZ; Coldastat-LX; Covil-A; CZ-L; Dilevocet-M; Dilevocet-Plus; Elcet-P; Elcy-A; Festa; Fitin-CF; Folcet-MT; Hatric-2; Hatric-3; His-P; Hiskast; Idalez Plus; Kurecet-M; L-Cit Plus; L-Montus; L-Triz Plus; L-Triz-A; Largy-M; Laveta-A; Laveta-D; Lazine Plus; Lazine-D; Lazine-M; LCBit-P; LCN-Plus; LCRal Plus; LCZ-Plus; LCZ-XP; Le Zyncet-A; Le Zyncet-D; Le-Zyncet-M; Lecope-AD; Lecope-DX; Leczine-A; Leday-CC; Lemont-LC; Lenex; Lenomol; Lepit-A; Lepit-AM; Lepit-MK; Leverest Plus; Leverest-AM; Leverest-MK; Levocet Plus; Levocet-D; Levocet-M; Levoclic-M; Levogo Plus; Levorid D; Levoriz Plus; Levoriz-AM; Levoriz-MK; Levostar Plus Exp; Levostar Plus; Levostar-AM; Levostar-D; Levotan; Levotin Plus; Levotra-A; Levotra-M; Levotrin-M; Levotrin-P; Levoz-M; Levzed-A; Levzed-MK; Lexzin-P; Lezo-AM; LFast-AM; LG Plus; LG-Plus; Luka; Luzei-M; Luzer-A; Luzer-M; Lycit-M; M-Kast-L; Molly-Plus; Mondeo-LC; Montair-LC; Montasma Plus; Montbre; Montegen-L; Montek-LC; Montilife; Montlu-L; Montral; Monty; Mosha-L; Mucopen; Mucoresp-CT; Nam Cold-L; NBLcet Plus; Nislevo-MK; Nizla Plus; Noal-LM; Nucez Plus; Nukast; Okasma; Ontelio-L; Oox-LC; *Philipp.*: Co-Altria; Zykast.

Loratadine *(BAN, USAN, rINN)*

Loratadiini; Loratadin; Loratadina; Loratadinum; Loratadyna; Sch-29851; Лоратадин.

Ethyl 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine-1-carboxylate.

$C_{22}H_{23}ClN_2O_2$=382.9

CAS — 79794-75-5.

ATC — R06AX13.

ATC Vet — QR06AX13.

UNII — 7AJO3BO7QN.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Loratadine). A white or almost white, crystalline powder. It exhibits polymorphism. Practically insoluble in water; freely soluble in acetone and in methyl alcohol.

USP 36: (Loratadine). A white to off-white powder. Insoluble in water; freely soluble in acetone, in chloroform, in methyl alcohol, and in toluene.

Uses and Administration

Loratadine, a piperidine derivative related to azatadine, is a long-acting, non-sedating antihistamine with no significant antimuscarinic activity. It is used for the symptomatic relief of allergic conditions including rhinitis (p. 612.1) and chronic urticaria (p. 612.3). It is also used with a decongestant such as pseudoephedrine sulfate.

Loratadine is given in an oral dose of 10 mg once daily; alternatively, 5 mg every 12 hours may be given. For dosage in children or in patients with hepatic or renal impairment, see below.

References.
1. Haria M, *et al.* Loratadine: a reappraisal of its pharmacological properties and therapeutic use in allergic disorders. *Drugs* 1994; **48**: 617–37.

Administration in children. Loratadine is used orally for the symptomatic relief of seasonal allergic rhinitis and chronic idiopathic urticaria in children. Doses, according to age, are:

- 2 to 5 years, 5 mg once daily
- 6 years and over, usual adult doses, see above

For doses in children with hepatic or renal impairment, see below.

Administration in hepatic or renal impairment. US product information recommends that adults and children aged 6 years and over with hepatic failure or renal impairment (glomerular filtration rate less than 30 mL/minute) should be given an initial oral dose of loratadine 10 mg on alternate days; in younger children aged 2 years and over, the dose is 5 mg on alternate days.

Adverse Effects and Precautions

As for the non-sedating antihistamines in general, p. 613.1 and p. 613.3, respectively.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving loratadine, and the American Academy of Pediatrics[1] considers that it is therefore usually compatible with breast feeding. However, UK licensed product information recommends that loratadine should not be used in breast-feeding mothers.

A study[2] in 6 women reported that about 0.03% of a single 40-mg oral dose of loratadine was distributed into breast milk over 48 hours as loratadine and its active metabolite, desloratadine.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/04/04)
2. Hilbert J, *et al.* Excretion of loratadine in human breast milk. *J Clin Pharmacol* 1988; **28**: 234–9.

Effects on the liver. Two patients[1] developed severe necroinflammatory liver injury after receiving loratadine 10 mg daily for allergic rhinitis. Although both recovered after drug withdrawal, one patient required a liver transplantation and recovery was prolonged.

The product information notes that abnormal hepatic function including jaundice, hepatitis, and hepatic necrosis has been reported rarely.

1. Schiano TD, *et al.* Subfulminant liver failure and severe hepatotoxicity caused by loratadine use. *Ann Intern Med* 1996; **125**: 738–40.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies loratadine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Pregnancy. UK product information does not recommend the use of loratadine in pregnancy.

Analysis of data collected by the Swedish Medical Birth Registry between 1994 and 2001 revealed 15 cases of hypospadias among a cohort of 2780 newborns exposed to loratadine during the first trimester of pregnancy.[1] The authors noted that the individual risk for having an infant with hypospadias after loratadine use is small (less than 1%) and the attributive risk of extra cases in the population is low. The US CDC has also analysed data from the National Birth Defects Prevention study;[2] they found no increase in the risk of second- or third-degree hypospadias in the infants of women who used loratadine in early pregnancy. In addition, an earlier prospective multicentre study[3] in 161 women taking a median dose of loratadine 10 mg daily in the first trimester of pregnancy suggested that its use was not associated with a significant risk of major congenital malformations.

1. Källén B, Olausson PO. Monitoring of maternal drug use and infant congenital malformations: does loratadine cause hypospadias? *Int J Risk Safety Med* 2001; **14**: 115–19.
2. CDC. Evaluation of an association between loratadine and hypospadias — United States, 1997-2001. *MMWR* 2004; **53**: 219–21. Also available at: http://www.cdc.gov/mmwr/PDF/wk/mm5310.pdf (accessed 11/05/04)
3. Moretti ME, *et al.* Fetal safety of loratadine use in the first trimester of pregnancy: a multicenter study. *J Allergy Clin Immunol* 2003; **111**: 479–83.

Sedation. For discussion of the sedative effects of antihistamines see p. 613.2.

Interactions

As for the non-sedating antihistamines in general, p. 614.3.

Loratadine is metabolised by cytochrome P450 isoenzymes CYP3A4 and CYP2D6. Therefore use with other drugs that inhibit or are metabolised by these hepatic enzymes may result in changes in plasma concentrations of either drug and, possibly, adverse effects. Drugs known to inhibit one or other of these enzymes include cimetidine, erythromycin, ketoconazole, quinidine, fluconazole, and fluoxetine.

Antibacterials. Data held on file by the manufacturer show that *erythromycin* can inhibit the metabolism of loratadine. However, even when given in large doses loratadine does not appear to cause the cardiac conduction disorders associated with the non-sedating antihistamines astemizole (see p. 616.2) and terfenadine (see p. 640.3).[1] Similarly, *clarithromycin* seemed to inhibit the metabolism of loratadine and its active metabolite desloratadine.[2]

1. Affrime MB, *et al.* Three month evaluation of electrocardiographic effects of loratadine in humans. *J Allergy Clin Immunol* 1993; **91**: 259.
2. Carr RA, *et al.* Steady-state pharmacokinetics and electrocardiographic pharmacodynamics of clarithromycin and loratadine after individual or concomitant administration. *Antimicrob Agents Chemother* 1998; **42**: 1176–80.

Antifungals. *Ketoconazole* appears to be able to inhibit the metabolism of loratadine and at therapeutic doses, is about 3 times more inhibitory than erythromycin (Antibacterials, above).[1] However, the concentrations of ketoconazole required are reported to be much higher than those required to inhibit the metabolism of astemi-

zole or terfenadine. Clearance of the active metabolite desloratadine is also reduced.

1. Brannan MD, *et al.* Effects of various cytochrome P450 inhibitors on the metabolism of loratadine. *Clin Pharmacol Ther* 1995; 57: 193.

Gastrointestinal drugs. *Cimetidine* appears to have an inhibitory effect on the metabolism of loratadine and also attenuates the clearance of its active metabolite desloratadine although no clinically significant consequences have been seen.[1]

1. Brannan MD, *et al.* Effects of various cytochrome P450 inhibitors on the metabolism of loratadine. *Clin Pharmacol Ther* 1995; 57: 193.

Pharmacokinetics

Loratadine is rapidly absorbed from the gastrointestinal tract after oral doses and peak plasma concentrations occur in about 1 hour. Bioavailability is increased and time to peak plasma concentrations is delayed when taken with food. Loratadine undergoes extensive metabolism. The major metabolite, desloratadine (p. 625.1), has potent antihistaminic activity. Reported mean elimination half-lives for loratadine and desloratadine are 8.4 and 28 hours, respectively. Loratadine is about 98% bound to plasma proteins; desloratadine is less extensively bound. Loratadine and its metabolites have been detected in breast milk, but do not appear to cross the blood-brain barrier to a significant extent. Most of a dose is excreted equally in the urine and faeces, mainly in the form of metabolites.

Renal impairment. The disposition of loratadine does not appear to be significantly altered in patients with severe renal impairment and haemodialysis does not appear to be an effective means of removing loratadine or its metabolite desloratadine from the body.[1]

1. Matzke GR, *et al.* Pharmacokinetics of loratadine in patients with renal insufficiency. *J Clin Pharmacol* 1990; 30: 364–71.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Aerotina; Alergiano; Alergipan; Alergitrat L; Alermuc; Alerpriv; Algistop†; Aseptobron Descongestivo; Bedix; Benadryl 24; Biloina; Clarityne; Devedryl; Dexitis; Excelentia Antialergico; Hisplex; Lisaler; Loisan; Loralivio; Loratine†; Loremex Antialergico; Megalorat; Mudantil L; Nilitro; Nularef; Omega 100 L; Pulmosan Aller; Sinaler; Tabcin Alergia; Vagran; Vixidone L; *Austral.*: Alledine; Allerese; Claratyne; Lorano; Lorastyne; *Austria*: Allermon; Clarityn; Lictyn†; Lorano; *Belg.*: Claritine; Rupton; Sanelor; *Braz.*: Alergaliv; Clarileg; Claritin; Clistin; Cloratadd; Histadin; Loradine; Loradrina D; Loralerg; Loranil; Lorasliv; Loratamed; Loremix; Loritil; Neo Loratadin; *Canad.*: Claritin; *Chile*: Alergan; Alledryl; Clarityne; Frenaler; Hysticlar; Lontadex†; Loptame; Primorix; *China*: Ao Hui Feng (奥惠丰); Ao Mi Xin (奥米新); Ao Shu (奥纾); Bai Wei Le (百为乐); Bang Nuo (邦诺); Bi Sai Ning (彼赛宁); Bi Yan Tong (毕研通); Chang Ke (常克); Clarityne (开瑞坦); Da Sheng Rui Li (大生瑞丽); Fei Ge Man (菲格曼); Fu Lai Xi (福莱西); Hua Chang (华畅); Jin Su Rui (金苏瑞); Jing Wei (精威); Ke Mi (可米); Kui Yin (奎因); Lei Ning (雷宁); Min Li Ke (敏立可); Profadine (百为坦); Rui Fu (瑞孚); Run Lai (润来); She Tai (舍泰); Shi Nuo Min (施诺敏); Shi Tai Shu (史泰舒); Shu Rui (抒瑞); Shun Ta Xin (顺他欣); Tai Ming Ke (泰明可); Xian Ning (先宁); Xin Da Yue (信达悦); Xing Yuan Jia (星元佳); Xue Fei (雪菲); Yi Fei (亿菲); Yi Li Xin (伊利欣); Yi Shu Chang (逸舒长); Yibang (怡邦); ZhengShu (天晴正舒); Zhi Min (正敏); *Cz.*: Claritine; Erolin; Flonidan; Loranol†; Roletra†; *Denm.*: Clarityn; Loradis; Lorapharm; Mildin; *Fin.*: Clarityn; Histadin; Loraxin; Tuulix; *Fr.*: Clarityne; Doliallergie; Humex Allergie Loratadine; Zaprilis; *Ger.*: Lisino†; Lobeta†; Lora-Lich; Lora-Puren†; Loraderm; Lorano†; *Gr.*: Allerdrug; Allergofact; Biliranin; Bollinol; Claritynе; Difmedol; Helporigin; Hobatadine; Horestyl; Igir; Latoren; Lora; Loratab; Novacloxab; Ralinet; Ristotadin; Tirlor; Utel; Zelmar; *Hong Kong*: Allertyn; Carin; Clarinet†; Claritynе; CP-Loradine; Erolin; Ezede; Loradin; Loranox†; Loraton; Loratyn†; Lorita†; Lotadine; Lotin; Marlora†; Rinityn; Rotifar†; Sunadine; Voratadine†; *Hung.*: Claritine; Erolin; Flonidan; Lorano; Roletra; *India*: Alaspan; Algyfree; Allerban; Aura; Claridin; Cozy; Eldin-MD; Intralor; Japlor; Latar; Lonlor; Lor; Lora; Lorange; Lorariv; Loratia; Loratin; Lorfast; Lorid; Loridin; Lorin; Lorinol; Lorispa; Lorkind; Lorly; Lormeg; Loronet; LR; LTD; Nexx; *Indon.*: Alernitis; Allohex; Alloris; Anhissen†; Anlos; Clarihis; Claritin; Clatatin; Cronitin; Dayhist; Folerin; Hislorex†; Histaritin†; Imunex†; Inclarin; Klinset; Lergia†; Lesidas; Logista; Lolergi; Loran; Lorapharm†; Lorihis; Nosedin; Nufalora; Prohistin; Pylor; Rahistin; Rihest; Safetin†; Sohotin; Tinnic; Urtilar; Winatin; Xepalodin; *Irl.*: Clareeze Allergy; Claritynе; Histaclar; Lorat; *Israel*: Allergyx; Lorastine; Loratrim; *Ital.*: Claritynе; Fristamin; *Jpn*: Claritin; *Malaysia*: Carin; Claritynе; Ezede; Loradine; Ridamin; Roletra; Rotifar; Tirlor; *Mex.*: Alerfin; Aludix; Antilergal; Biodin; Biolorat; Claritynе; Curyken; Dimegan; Dissen; Ditana; Doralan; Dotagil; Dymaten; Efectine; Fartadin; Grimeral; Histina†; Histox; HL-ysta; Inigrin; Laritol; Lertamine; Lictyn; Liferamin; Lotan; Lotinex; Lotos; Lovarin†; Neoalexil; Nidatar; Quimtadine; Rodakin†; Roletra†; Sensibit; Serralsina; Sitinir; Urtisin; Vincidal; *Neth.*: Allerfre; Claritine; Kruidvat Hooikoortstabletten; Lorastad; Otrivin neusallergie loratadine†; *Norw.*: Claritynе; *NZ*: Claratyne; Lora-Tabs; Loraclear; *Philipp.*: Allerta; Clarihist; Claritin; Flamitin; Folerin; Immunix; Lergicyl†; Loradex†; Loradine; Lorahist; Lorange; Lorano; Loratyne; Lordam; Lordane; Loren; Lorfast; Lorid; Onemin; Prevahist; Rinityn; Toral; Zylohist; *Pol.*: Alerfan†; Aleric; Claritine; Flonidan; Lorafast†; Lorahexal†; Loram; Loratan; Loratine; Nalergine; Rotadin†; *Port.*: Alerdaune; Alertrin; Claritine; Crizin; Evertine; Histadin; Loraxine†; Profenox; Zolargene; *Rus.*: Alerpriv (Алерприв); Clargotil (Кларготил); Clarisens (Кларисенс); Claritine (Кларитин); Clarotadine (Кларотадин); Erolin (Эролин); Klallergine (Клаллергин); Klarfast (Кларфаст); Klaridol (Кларидол); Klarifer (Кларифер); Lomilan (Ломилан); Lorahexal (Лорагексал); Lorid (Лорид); Loridin (Лоридин); Lotaren (Лотарен); *S.Afr.*: Clarinese; Claritynе; Laura; Lorahist; Lorano; Lorfast; Lormeg; Pollentyme; Rhinigine; Rohist; *Singapore*: Allertyn; Alloris; Ardin; Carin; Claritynе; Ezede; Halodin; Histalor; Loracin; Lorfast; Loridin; Lotadine; Ridamin†; Rinityn; Roletra; Tirlor†; *Spain*: Civeran; Claritynе; Velodan†; *Swed.*: Claritynе; Versal†; *Switz.*: Claritine; Lora Allergie; Lorado; Loratine; *Thai.*: Alertyne; Aller-Tab; Allerdine; Allersil; Aridine; Botidine; Caradine†; Carinose; Clalodine; Clarid; Claridine; Clarigy; Claritex; Claritino; Claritynе; Fatyne†; Halodin; Hisracon; Histadine; Kalidin; Klaryne; Lindine; Logadine; Lolergy; Loracine; Loradine; Loragis; Loranox; Lorapac; Lordin; Loridin; Lorin†; Lorita; Lorsedin; Lortadine; Lotidyne; Ridamin†; Rityne; Roletra; Sanotyne; Tiradine; Tirlor; *Turk.*: Alarin; Claritine; Histadin; Klodin; Loradif; Lorantis; Lorateva; Loritine; Ritin; *UAE*: Loratin; *UK*: Claritynе; *Ukr.*: Agistam (Агистам)†; Aleric (Алерик); Claritin (Кларитин); Lorano (Лорано); Lorizan (Лоризан); *USA*: Alavert; Claritin; Non-Drowsy Allergy; *Venez.*: Alerdina; Biolorat; Claritynе; Lorat; Loraval; Lorex; Loriden; Lotal; Polaramine Reformulado; Tirlor.

Multi-ingredient Preparations. *Arg.*: Alerpriv D; Aliviatos; Antitusivo L; Bedix-D; Benadryl 24 D; Celestamine-L; Ciprocort D; Ciprocort L; Clarifriol; Claritynе Cort; Claritynе D; Corticas L; Cortistamin L; Decidex Plus; Dexaprof D; Hisiamino Corteroid L; Ideobron; Ideogrip; Labsalerg-B; Lisaler Beta; Loisan-D; Lorabrox; Loremex Antigripal†; Loremex Descongestivo; Nastizol-L; Nularef Cort; Nularef-D; Paracetamol Grip NF; Pulmonix Grip; Pulmonix Plus; Sinaler B; Sinaler D; Toraxan; Vagran D; Vixidone LB; *Austral.*: Clarinase†; *Austria*: Clarinase; *Belg.*: Clarinase; *Braz.*: Alergaliv D; Claritin-D; Cloratadd D; Histadin D; Histamix D; Loralerg-D; Loranil D; Loremix D; Loritil D; Neofedrin; *Canad.*: Chlor-Tripolon ND†; Claritin Allergy & Sinus; Liberator†; *Chile*: Alledryl D; Clarinase; Frenaler-D; Larmax D†; Lertamine Extra†; Lertamine; Rinomex; *China*: Bai Wei Qing (百为晴); Clarinase (开瑞能); Hui Fei Shun (惠菲顺); Jin De Fei (金得菲); Ke Shuai (可帅); QiKe (琦克); Wei Kuai (维快); Zhuang Qi (壮奇); *Cz.*: Clarinase; *Denm.*: Clarinase; *Fin.*: Clarinase†; *Gr.*: Claritynе D; *Hong Kong*: Clariflu; Clarinase; Rhinos; *Hung.*: Clarinase; *India*: Amy; Claridin-D; Colbid; Cozy-AM; Cozy-AM; Loran-D; Loratin D; Lorfast-AM; Lorfast-AM; Lorfast-D; Loridin-D; Lormeg-D; Nam Cold-SR; *Indon.*: Aldisa; Clarinase; Cronase; Glanos†; Rhinos; *Israel*: Clarinase; *Malaysia*: Allerpid; Carinox; Clarinase; *Mex.*: Alerfin Ex; Bisincof; Bramint; Bronar; Broquixol; Celestamine NS; Clariflu; Clarifriol; Claritynе D; Coricidin Expec; Dimegan D; Doralan-Ax; Efectine D; Farmalor; Fluxibit; Graldep†; Laritol D; Laritol Ex; Laritol G; Lertamine D; Linfarden; Lyrsedin†; Quimtadine DSQ†; Quimtafriol†; Sensibit D-NF; Sensibit D; Sensibit XP; Sibilex; Tadinar-C; Tamex; Tavexyl; TheraFlu 24; TheraFlu N 12; TheraFlu TD; *Philipp.*: Claricort; Clarinase; Loraped; Rhinase†; Rhinos†; *Pol.*: Clarinase†; Claritine Active; *Port.*: Claridon; *Rus.*: Antigrippin-Maximum (Антигриппин-Максимум); Antigrippin-Maximum (Антигриппин-Максимум); *S.Afr.*: Claritynе D†; Demazin NS; *Singapore*: Clarinase; De-cold; *Spain*: Claritynе Plus; Narine; *Thai.*: Clarinase; *Turk.*: Clarinase; *Ukr.*: Pulmolor (Пульмолор); *USA*: Alavert Allergy & Sinus D; Allergy Relief & Nasal Decongestant; Claritin-D; Loratadine D; *Venez.*: Ambroclar; Celestamincort; Claricort; Claridex; Claridexultra; Clariflu; Clarigrip; Fedyclar; Lokarin; Loracert.

Pharmacopoeial Preparations

BP 2014: Loratadine Tablets;

USP 36: Loratadine Oral Solution; Loratadine Orally Disintegrating Tablets; Loratadine Tablets.

Mebhydrolin *(BAN, rINN)*

Mebhidrolina; Mebhydroline; Mebhydrolinum; Мебгидролин.

5-Benzyl-1,2,3,4-tetrahydro-2-methyl-γ-carboline.

$C_{19}H_{20}N_2$=276.4

CAS — 524-81-2.

ATC — R06AX15.

ATC Vet — QR06AX15.

UNII — 9SUK987XVY.

Mebhydrolin Napadisilate *(BANM, rINNM)*

Diazolinum; Mebhidrolina, napadisilato de; Mebhydrolin Napadisylate; Mebhydrolin Naphthalenedisulphonate; Mebhydroline, Napadisilate de; Mebhydrolini Napadisilas; Napadisilato de mebhidrolina; Мебгидролина Нападизилат.

Mebhydrolin naphthalene-1,5-disulphonate.

$(C_{19}H_{20}N_2)_2C_{10}H_8O_6S_2$=841.1

CAS — 6153-33-9.

ATC — R06AX15.

ATC Vet — QR06AX15.

UNII — O5G04R825M.

Profile

Mebhydrolin, an ethylenediamine derivative, is a sedating antihistamine (p. 610.1) with antimuscarinic and sedative properties. It has been given orally as the base or as the napadisilate salt for the symptomatic relief of allergic conditions including urticaria and rhinitis, and in pruritic skin disorders. Granulocytopenia and agranulocytosis have been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Indon.*: Biolergy†; Gabiten; Histapan: Incitin†; Interhistin; Tralgi; Zoline; *Israel*: Cidalin†; *Rus.*: Diazolin (Диазолин); *S.Afr.*: Fabahistin†; *Thai.*: Dalhist†; Dayhist: Hydrolate; Manocidal; Manoeidai†; Medal; Posidol.

Multi-ingredient Preparations. *Rus.*: Diacine (Диацин).

Meclozine Hydrochloride

(BANM, pINNM)

Hidrocloruro de meclozina; Meclizine Hydrochloride Meclizinium Chloride; Meclozina, hidrocloruro de; Méclozine, Chlorhydrate de; Meclozini Dihydrochloridum Meclozini hydrochloridum; Meklotsiinihydrokloridi; Meklozin Hidroklorür; Meklozin-dihydrochlorid; Meklozin-hidroklorid Meklozinhydroklorid; Meklozino hidrochloridas; Meklozyny chlorowodorek; Parachloramine Hydrochloride; Меклозина Гидрохлорид.

1-(4-Chlorobenzhydryl)-4-(3-methylbenzyl)piperazine dihydrochloride.

$C_{25}H_{27}ClN_2.2HCl$=463.9

CAS — 569-65-3 (meclozine); 1104-22-9 (anhydrous meclozine hydrochloride); 31884-77-2 (meclozine hydrochloride monohydrate).

ATC — R06AE05.

ATC Vet — QR06AE05.

UNII — L997QXC9J1 (anhydrous meclizine hydrochloride), HDP7W44CIO (meclizine hydrochloride monohydrate).

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

US specifies the monohydrate.

Ph. Eur. 8: (Meclozine Dihydrochloride). A white or yellowish-white, slightly hygroscopic, crystalline powder Slightly soluble in water; soluble in alcohol and in dichloromethane. Store in airtight containers.

USP 36: (Meclizine Hydrochloride). The monohydrate is white or slightly yellowish crystalline powder that has a slight odour. Practically insoluble in water and in ether freely soluble in chloroform, in pyridine, and in acid alcohol-water mixtures; slightly soluble in dilute acids and in alcohol. Store in airtight containers.

Uses and Administration

Meclozine hydrochloride, a piperazine derivative, is a sedating antihistamine with antimuscarinic and moderate sedative properties. It is mainly used for its antiemetic action, which may last for up to 24 hours. Meclozine hydrochloride is used in the prevention and treatment of nausea and vomiting associated with a variety of conditions including motion sickness (p. 611.3) and for the symptomatic treatment of vertigo (p. 612.3) caused by Ménière's disease and other vestibular disorders. Meclozine hydrochloride has also been used for the symptomatic relief of hypersensitivity reactions and pruritic skin disorders (p. 612.1).

The usual oral dose of meclozine hydrochloride for motion sickness is 25 to 50 mg taken either the night before or about one hour before travelling and repeated every 24 hours if necessary; up to 100 mg daily in divided doses has been given for the treatment of vertigo and vestibular disorders. For doses in children, see below.

Both meclozine hydrochloride and meclozine base have been given by the rectal route; doses are similar to those given orally.

Administration in children. Meclozine hydrochloride may be given orally for the prevention and treatment of motion sickness in children. The following doses should be given either the night before or about one hour before travelling and repeated every 24 hours if necessary:

- children aged 2 to 6 years: 6.25 mg once daily
- those aged 6 to 12 years: 12.5 mg once daily

Older children and adolescents may be given usual adult doses, see above.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively. For reports of the use of antihistamines, including meclozine, in pregnancy, see p. 614.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies meclozine as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Interactions

As for the sedating antihistamines in general, p. 614.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Agyrax; Postafene; *Braz.*: Meclin; *Canad.*: Bonamine†; *Chile*: Bonamina†; *Denm.*: Postafen; *Fin.*: Postafen; *Fr.*: Agyrax; *Gr.*: Emetostop; Postafene; *Hong Kong*: Postafene†; Sea Far†; *Irl.*: Sea-Legs; *Mex.*: Chiclida; Marenin; *Neth.*: Suprimal; *Norw.*: Postafen; *NZ*: Sea-Legs; *Philipp.*: Bonamine; Dizitab; Nodiz; Postadoxine; *Port.*: Navicalm†; *Rus.*: Bonine (Бонин)†; *Spain*: Chiclida; Dramine†; Navicalm; *Swed.*: Postafen; *Turk.*: Postadoxine; *UK*: Sea-Legs; Traveleeze; *USA*: Antivert; Antrizine; Bonine; Dizmiss; Dramamine Less Drowsy Formula; Meni-D†.

Multi-ingredient Preparations. *Austria*: Contravert B_6†; *Hong Kong*: Navidoxine†; *India*: Diligan; Pregnidoxin; *Malaysia*: Veloxin; *Mex.*: Bonadoxina; Bonalen; Bonazin†; Emediba†; Liatriz; Mediflar; Meclison; Pidoxina; Vo-Remi; *Neth.*: Emesafene; *S.Afr.*: Geratar†; *Switz.*: Itinerol B_6; *Venez.*: Bonadoxina.

Pharmacopoeial Preparations
USP 36: Meclizine Hydrochloride Tablets.

Mepyramine *(BAN, rINN)*

Mepiramina; Mépyramiini; Mepyramin; Mépyramine; Mepyraminum; Pyranisamine; Pyrilamine; Мепирамин.
2-(*N*-*p*-Anisyl-*N*-2-pyridylamino)ethyldimethylamine.
$C_{17}H_{23}N_3O$=285.4
CAS — 91-84-9.
ATC — D04AA02; R06AC01.
ATC Vet — QD04AA02; QR06AC01.
UNII — HPE317O9TL.

Mepyramine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de mepiramina; Mepiramina, hidrocloruro de; Mépyramine, Chlorhydrate de; Mepyramini Hydrochloridum; Pyranisamine Hydrochloride; Pyrilamine Hydrochloride; Мепирамина Гидрохлорид.
$C_{17}H_{23}N_3O$,HCl=321.8
CAS — 6036-95-9.
ATC — D04AA02; R06AC01.
ATC Vet — QD04AA02; QR06AC01.
UNII — 5T3R4P0I14.

Mepyramine Maleate *(BANM, rINNM)*

Maleato de mepiramina; Mepiramin Maleat; Mepiramina, maleato de; Mepiramin-maleát; Mepiramino maleatas; Mepyramiinimaleaatti; Mepyramin maleinát; Mépyramine, Maléate de; Mepyramini maleas; Mepyraminmaleat; Pyranisamine Maleate; Pyrilamine Maleate; Мепирамина Малеат.
Mepyramine hydrogen maleate.
$C_{17}H_{23}N_3O$,$C_4H_4O_4$=401.5
CAS — 59-33-6.
ATC — D04AA02; R06AC01.
ATC Vet — QD04AA02; QR06AC01.
UNII — R35D29L3ZA.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Mepyramine Maleate). A white or slightly yellowish, crystalline powder. Very soluble in water; freely soluble in alcohol. M.p. 99 degrees to 103 degrees. A 2% solution in water has a pH of 4.9 to 5.2. Protect from light.

USP 36: (Pyrilamine Maleate). A white crystalline powder usually having a faint odour. Soluble 1 in 0.5 of water, 1 in 3 of alcohol, 1 in 15 of dehydrated alcohol, and 1 in 2 of chloroform; slightly soluble in ether and in benzene. Its solutions are acid to litmus. Store in airtight containers. Protect from light.

Uses and Administration

Mepyramine, an ethylenediamine derivative, is a sedating antihistamine with antimuscarinic and sedative properties. Mepyramine maleate is used for the symptomatic relief of hypersensitivity reactions and in pruritic skin disorders (p. 612.1). Mepyramine maleate is also a common ingredient of compound preparations for the symptomatic treatment of coughs and the common cold (p. 611.2).

A cream containing 2% mepyramine maleate is used topically for insect bites or stings, and for hypersensitivity and pruritic skin conditions but, as with any antihistamine, there is a risk of sensitisation. It has also been used in eye drops.

Mepyramine maleate has been given orally at night as a hypnotic in the short-term management of insomnia (p. 611.2).

In some countries mepyramine maleate is available for parenteral use. Mepyramine hydrochloride has also been given parenterally or by the rectal route. Mepyramine tannate and mepyramine acefyllinate have been used orally.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively.

Interactions

As for the sedating antihistamines in general, p. 614.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Relaxa-Tabs†; *Braz.*: Alergitanil†; *Hong Kong*: Anthisan; Antihist†; *Irl.*: Anthisan; Boots Bite & Sting Relief Antihistamine; *NZ*: Anthisan; *S.Afr.*: Aisan; Anthisan; Antihist†; Mepyraderm; Mepyrimal; *Spain*: Fluidasa; *UK*: Anthisan; *USA*: Pyrilex†.

Multi-ingredient Preparations. *Arg.*: Drynisan; Everfem; Fadanasal; Piracalamina; *Belg.*: Nortussine; *Braz.*: Beclase†; Conidrin; Engov; Enjoy; Gripsay; Naridrin; Nariflux; Nasogrip; Posdrink†; *Canad.*: Extra Strength Multi-Symptom PMS Relief; Hycomine†; Jack & Jill; Menstrual Midol; Midol PMS; Midol Teen; Multi-Symptom PMS Relief; Pamprin; Prefrin A†; ratio-Theo-Bronc; Relievol PMS; Tylenol Menstrual; *Chile*: Alerzona†; Dolo-Esan Periodo Menstrual; Kitadol Periodo Menstrual; Minfaden; Panagesic Periodo Menstrual; Predual; Rinolergan; Sentual Periodo; Tapsin Periodo Menstrual; *Fr.*: Nortussine†; *Gr.*: Prefrin A; *Hong Kong*: Alox†; Alphate†; Aselan†; *India*: Anthical; *Irl.*: Wasp-Eze; *Israel*: Alnase; Phenyphrine-Azol†; *Ital.*: Balsamina Kroner; Vasofen; *Mex.*: Femsedin Kutz; Lentostamin†; *Pol.*: Kato-Nasal; Pro-Miss; *Port.*: Antigrippine; *Rus.*: Femizol (Фемизол); *S.Afr.*: Adco-Metaxol; Codef†; Colcaps†; Coughcod†; Docsed†; Flucol†; Histodor†; Histodor; *Switz.*: Fenipic; Parapic; Stilex; Stilex; *Thai.*: Antergan; *Turk.*: Peditus; Stilex; *UAE*: Profinal FM†; *UK*: Anthisan Plus; Wasp-Eze; *USA*: 4-Way Fast Acting; Albatussin; C-Tanna 12D; Calamycin; Codal-DH†; Codal-DM†; Codimal DM†; Codimal PH†; Conal†; Corzall Plus; De-Chlor MR†; Deconsal CT†; Duonate; Gelhist; HC Derma-Pax; Midol Maximum Strength Multi-Symptom Menstrual; Midol Pre-Menstrual Syndrome; Myci-Spray; MyHist-DM; MyHist-PD†; Nalex-A 12†; Naltrx†; ND-Gesic; P-Hist; P-Tanna; Pamprin; Poly Hist DHC; Poly Hist DM; Premsyn PMS; Pro-Red AC; Pro-Red†; Pyrichlor PE; Pyril D; Pyril DM; Pyrlex CB; R-Tanna†; R-Tannamine; R-Tannate; Rectagene Medicated Rectal Balm; Resperal; Rhinatate; Robitussin Night Relief; Ryna-12†; Rynesa 12S†; Soothaderm; Tanoral; Tri-Tannate; Tricodene Cough & Cold; Triotann†; Triplex AD†; Tritan; Tussi-12 D; Tussi-12D S; Tussplex; Vanacof-8; Viravan-DM; Viravan-P†; Viravan-PDM; Viravan; Z-Xtra; Zotex-C; *Venez.*: Pi-Fedrin; Pinazo.

Pharmacopoeial Preparations
BP 2014: Mepyramine Tablets;
USP 36: Pyrilamine Maleate Tablets.

Mequitazine *(BAN, rINN)*

LM-209; Mekitatsiini; Mekitazin; Mequitazina; Méquitazine; Mequitazinum; Мекитазин.
10-(Quinuclidin-3-ylmethyl)phenothiazine.
$C_{20}H_{22}N_2S$=322.5
CAS — 29216-28-2.
ATC — R06AD07.
ATC Vet — QR06AD07.
UNII — Y463242LY2.

Pharmacopoeias. In *Jpn.*

Uses and Administration

Mequitazine, a phenothiazine derivative, is a sedating antihistamine with antimuscarinic and mild sedative properties.

Mequitazine is used for the symptomatic relief of allergic conditions including urticaria (p. 612.3), rhinitis (p. 612.1) and conjunctivitis (p. 611.1), and in pruritic skin disorders (p. 612.1). It has been given in usual oral doses of 5 mg twice daily.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively.

Mequitazine is used as a racemic mixture, and there is some evidence that a risk of significant prolongation of the QT interval may be associated with the *l*-mequitazine enantiomer. It should be avoided in patients with long QT syndrome, electrolyte disturbances such as hypokalaemia, or significant bradycardia. It should also be avoided in patients known to be slow cytochrome isoenzyme P450 CYP2D6 metabolisers because of the potential for accumulation of *l*-mequitazine.

Sedation. For discussion of the sedative effects of antihistamines, see p. 613.2. When mequitazine is given in the recommended dosage of 5 mg twice daily the incidence of sedation appears comparable with that of terfenadine. Sedation has, however, occurred after doses of 10 mg twice daily.

Interactions

As for the sedating antihistamines in general, p. 614.3.

Mequitazine should be avoided in patients taking inhibitors of the cytochrome P450 isoenzyme CYP2D6 and potentially arrhythmogenic drugs including those that prolong the QT interval.

Antibacterials. For a report of torsade de pointes in a patient taking *spiramycin* and mequitazine, see Cytochrome P450 Isoenzymes under Interactions of Spiramycin, p. 358.3.

Pharmacokinetics

After absorption from the gastrointestinal tract, mequitazine is metabolised. Unchanged drug and metabolites are excreted principally in the bile.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Primalan; *Chile*: Mircol; *Fr.*: Primalan; Quitadrill†; *Ger.*: Metaplexan†; *Gr.*: Istalar; *Mex.*: Primalan; *Philipp.*: Primalan; *Port.*: Primalan; *Rus.*: Primalan (Прималан); *Spain*: Mircol.

Methdilazine *(BAN, rINN)*

Metdilatsiini; Metdilazin; Metdilazina; Methdilazinum; Metodilazina; Метдилазин.
10-(1-Methylpyrrolidin-3-ylmethyl)phenothiazine.
$C_{18}H_{20}N_2S$=296.4
CAS — 1982-37-2.
ATC — R06AD04.
ATC Vet — QR06AD04.
UNII — 4Q13LY9Z8X.

Methdilazine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de metodilazina; Methdilazine, Chlorhydrate de; Methdilazini Hydrochloridum; Metodilazina, hidrocloruro de; Метдилазина Гидрохлорид.
$C_{18}H_{20}N_2S$,HCl=332.9
CAS — 1229-35-2.
ATC — R06AD04.
ATC Vet — QR06AD04.
UNII — T0GSO02UEZ.

Pharmacopoeias. In *US.*

USP 36: (Methdilazine Hydrochloride). A light tan crystalline powder having a slight characteristic odour. Soluble 1 in 2 of water and of alcohol, 1 in 6 of chloroform, and 1 in 1 of 0.1N hydrochloric acid and of 0.1N sodium hydroxide solution; practically insoluble in ether. pH of a 1% solution in water is between 4.8 and 6.0. Store in airtight containers. Protect from light.

Profile

Methdilazine, a phenothiazine derivative, is a sedating antihistamine (p. 610.1) with antimuscarinic and sedative activity. Methdilazine is also reported to have serotonin-antagonist properties. It has been used for the symptomatic relief of hypersensitivity reactions and particularly for the control of pruritic skin disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Dilosyn.

Multi-ingredient Preparations. *India*: Dilosyn Expectorant.

Pharmacopoeial Preparations
USP 36: Methdilazine Hydrochloride Syrup; Methdilazine Hydrochloride Tablets.

Mizolastine *(BAN, rINN)*

Mitsolastiini; Mizolastin; Mizolastina; Mizolastinum; SL-85.0324-00; Мизопастин.
2-[1-[1-(4-Fluorobenzyl)-1*H*-benzimidazol-2-yl]-4-piperidyl (methyl)amino]pyrimidin-4(1*H*)-one.
$C_{24}H_{25}FN_6O$=432.5
CAS — 108612-45-9.
ATC — R06AX25.
ATC Vet — QR06AX25.
UNII — 244O1F90NA.

Uses and Administration

Mizolastine is a non-sedating antihistamine with a long duration of action. It does not have significant antimuscarinic actions; it is reported to have mast-cell stabilising properties. Mizolastine is used for the symptomatic relief of allergic conditions including rhinitis (p. 612.1), conjunctivitis (p. 611.1), and skin disorders such as urticaria (p. 612.3). The oral dose is 10 mg once daily.

References.
1. Leynadier F, *et al.* Efficacy and safety of mizolastine in seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 1996; 76: 163–8.
2. Brostoff J, *et al.* Efficacy of mizolastine, a new antihistamine, compared with placebo in the treatment of chronic idiopathic urticaria. *Allergy* 1996; 51: 320–5.
3. Stern MA, *et al.* Can an antihistamine delay appearance of hayfever symptoms when given prior to pollen season? *Allergy* 1997; 52: 440–4.

Adverse Effects and Precautions

As for the non-sedating antihistamines in general, p. 613.1 and p. 613.3, respectively. Mizolastine has only a weak potential to prolong the QT interval (see also Arrhythmias, p. 613.2) and has not been associated with arrhythmias. However, the manufacturers have warned against the use of mizolastine in patients with significant cardiac or hepatic disease, with hypokalaemia or other electrolyte imbalance, or with known or suspected QT prolongation. Use with drugs liable to interfere with the hepatic metabolism of mizolastine or with other potentially arrhythmogenic drugs should also be avoided (see under Interactions, below).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mizolastine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Interactions

As for the non-sedating antihistamines in general, p. 614.3. Moderate increases in plasma concentrations of mizolastine have been reported with erythromycin and ketoconazole; use with macrolide antibacterials or systemic imidazole antifungals is contra-indicated by the manufacturer. They also advise against use of mizolastine with drugs known to prolong the QT interval, such as class I and III antiarrhythmics.

Other potent inhibitors of or substrates for the hepatic metabolism of mizolastine include cimetidine, ciclosporin, and nifedipine; caution is advised if given together.

Pharmacokinetics

Mizolastine is rapidly absorbed from the gastrointestinal tract and peak plasma concentrations occur after about 1.5 hours. Plasma protein binding is about 98%. The mean elimination half-life is about 13 hours. Mizolastine is mainly metabolised by glucuronidation although other metabolic pathways are involved, including metabolism by the cytochrome P450 isoenzyme CYP3A4, with the formation of inactive hydroxylated metabolites.

References.
1. Rosenzweig P, *et al.* Pharmacodynamics and pharmacokinetics of mizolastine (SL 85.0324), a new nonsedative H_1 antihistamine. *Ann Allergy* 1992; 69: 135–9.
2. Lebrun-Vignes B, *et al.* Clinical pharmacokinetics of mizolastine. *Clin Pharmacokinet* 2001; 40: 501–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Mizollen; *China*: Ao Ni Jie (奥尼捷); Mizollen (皿治林); Nile (尼乐); *Fr.*: Mizollen; *Ger.*: Mizollen; Zolim; *Gr.*: Mizollen; Oriens; *India*: Elina; *Israel*: Mizollen; *Ital.*: Mizollen; Zolistam; *Mex.*: Mistamine; *Neth.*: Mizollen; *Pol.*: Mizollen†; *Port.*: Mizollen; Zolistam†; *S.Afr.*: Mizollen; *Spain*: Mizolen; Zolistan; *Swed.*: Mizollen†; *Switz.*: Mizollen†; *UK*: Mizollen.

Moxastine Teoclate *(rINNM)*

Mephenhydramine Theoclate; Mephenhydrinate; Moxastine, Téoclate de; Moxastine Theoclate; Moxastini Teoclas; Teoclato de moxastina; Моксастина Теоклат.
2-(1,1-Diphenylethoxy)-*N*,*N*-dimethylethylamine 8-chlortheophyllinate.
$C_{18}H_{23}NO.C_6H_7ClN_4O_2$=472.0
CAS — 3572-74-5 (moxastine); 21661-62-1 (moxastine teoclate).
UNII — JS66J1RZ9J.

Profile

Moxastine teoclate is an antihistamine with antiemetic properties. It is used to treat nausea and vertigo associated with Ménière's disease and other vestibular disorders, and for the prevention and treatment of motion sickness.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Kinedryl.

Multi-ingredient Preparations. *Rus.*: Kinedril (Кинедрил).

Niaprazine *(rINN)*

1709-CERM; Niaprazina; Niaprazinum; Ниапразин.
N-[3-(4-*p*-Fluorophenylpiperazin-1-yl)-1-methylpropyl]nicotinamide.
$C_{20}H_{25}FN_4O$=356.4
CAS — 27367-90-4.
ATC — N05CM16.
ATC Vet — QN05CM16.
UNII — R2H3YN6E3L.

Profile

Niaprazine, a piperazine derivative, is an antihistamine (p. 610.1) used in children for its sedative and hypnotic properties. The usual oral dose is 1 mg/kg at night.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Nopron†; *Ital.*: Nopron.

Olopatadine Hydrochloride

(BANM, USAN, pINNM)

ALO-4943A; Hidrocloruro de olopatadina; KW-4679; Olopatadin Hidroklorür; Olopatadina, hidrocloruro de; Olopatadine, Chlorhydrate d'; Olopatadini Hydrochloridum; Ononатадина Гидрохлорид.
11-[(*Z*)-3-(Dimethylamino)propylidene]-6,11-dihydrodibenz[*b*,*e*]oxepin-2-acetic acid hydrochloride.
$C_{21}H_{23}NO_3$,HCl=373.9
CAS — 113806-05-6 (olopatadine); 140462-76-6 (olopatadine hydrochloride).
ATC — R01AC08; S01GX09.
ATC Vet — QS01GX09.
UNII — 2XG66W44KF.

Pharmacopoeias. In *US*.

USP 36: (Olopatadine Hydrochloride). A white, crystalline powder. Sparingly soluble in water; very slightly soluble in anhydrous alcohol; very soluble in formic acid. pH of a 1% solution in water is between 2.0 and 4.0. Store in airtight containers. Protect from light.

Uses and Administration

Olopatadine hydrochloride is an antihistamine with mast-cell stabilising properties. It is used twice daily as eye drops containing the equivalent of 0.1% of olopatadine base in the treatment of allergic conjunctivitis (p. 611.1); alternatively, 0.2% eye drops are available for once-daily use. In the treatment of seasonal allergic rhinitis (p. 612.1) the usual dose is 1.33 mg of olopatadine hydrochloride by nasal spray into each nostril twice daily. For doses used in children, see below.

References.
1. Abelson MB. A review of olopatadine for the treatment of ocular allergy. *Expert Opin Pharmacother* 2004; 5: 1979–94.
2. McGill JI. A review of the use of olopatadine in allergic conjunctivitis. *Int Ophthalmol* 2004; 25: 171–9.
3. Abelson MB, *et al.* Efficacy of olopatadine ophthalmic solution 0.2% in reducing signs and symptoms of allergic conjunctivitis. *Allergy Asthma Proc* 2007; 28: 427–33.
4. Abelson MB, *et al.* Efficacy of once-daily olopatadine 0.2% ophthalmic solution compared to twice-daily olopatadine 0.1% ophthalmic solution for the treatment of ocular itching induced by conjunctival allergen challenge. *Curr Eye Res* 2007; 32: 1017–22.
5. Shah SR, *et al.* Effects of olopatadine hydrochloride nasal spray 0.6% in the treatment of seasonal allergic rhinitis: a phase III, multicenter, randomized, double-blind, active- and placebo-controlled study in adolescents and adults. *Clin Ther* 2009; 31: 99–107.

Administration in children. Olopatadine eye drops may be used for allergic conjunctivitis in children aged 3 years and over in the same doses as those used in adults (see above). In seasonal allergic rhinitis, children aged 6 to 11 years may be given a dose of 665 micrograms of olopatadine hydrochloride by nasal spray into each nostril twice daily.

Adverse Effects and Precautions

As for the antihistamines in general, p. 613.1 and p. 613.3, respectively. Headache and stinging or burning of the eye are common after ocular use. When given intranasally, common adverse effects include bitter taste, headache and epistaxis. Somnolence has been reported with both routes.

Pharmacokinetics

Olopatadine is absorbed after nasal use; the average systemic bioavailability is 57%. Absorption after ocular use is said to be minimal. Plasma protein binding is about 55%. Based on oral pharmacokinetics studies, the elimination half-life is reported to be 8 to 12 hours. Elimination is primarily renal with 60 to 70% excreted as unchanged drug; about 17% is excreted in the faeces.

Olopatadine has been detected in breast milk after oral use in *animals*.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Olopat; Patanol; Zoloatla; *Austral.*: Patanol; *Belg.*: Opatanol; *Braz.*: Patanol; *Canad.*: Pataday; Patanol; *Chile*: Patanol; *China*: Allelock (阿洛刻); Patanol (帕坦洛); *Cz.*: Opatanol; *Denm.*: Opatanol; *Fin.*: Opatanol; *Fr.*: Opatanol; *Ger.*: Opatanol; *Gr.*: Opatanol; *Hong Kong*: Pataday; Patanol; *Hung.*: Opatanol; *India*: Alerchek; Dynolap; O-Dir; Olgeria; Olo; Oloblu; Olodin; Opat; *Indon.*: Patanol; *Irl.*: Opatanol; *Israel*: Pataday; Patanol; *Ital.*: Opatanol; *Jpn*: Allelock; Patanol; *Malaysia*: Pataday; Patanol; *Mex.*: Patanol; *Neth.*: Opatanol; *Norw.*: Opatanol; *NZ*: Patanol; *Philipp.*: Pataday; Patanol; *Pol.*: Opatanol; *Port.*: Opatanol; *Rus.*: Opatanol (Опатанол); *S.Afr.*: Patanol; *Singapore*: Patanol; *Spain*: Opatanol; *Swed.*: Opatanol; *Switz.*: Opatanol; *Thai.*: Patanol; *Turk.*: Hexos; Patanol; *UK*: Opatanol; *Ukr.*: Opatanol (Опатанол); *USA*: Pataday; Patanase; Patanol; *Venez.*: Patanol.

Pharmacopoeial Preparations
USP 36: Olopatadine Hydrochloride Ophthalmic Solution.

Oxatomide *(BAN, USAN, rINN)*

Oksatomidi; Oxatomid; Oxatomida; Oxatomidum; R-35443; Оксатомид.
1-[3-(4-Benzhydrylpiperazin-1-yl)propyl]benzimidazolin-2-one.
$C_{27}H_{30}N_4O$=426.6
CAS — 60607-34-3.
ATC — R06AE06.
ATC Vet — QR06AE06.
UNII — J31IL9Z2EE.

Profile

Oxatomide, a piperazine derivative, is a sedating antihistamine (p. 610.1) that has also been reported to have mast-cell stabilising properties. It is used for the symptomatic relief of allergic conditions including urticaria (p. 612.3), rhinitis (p. 612.1), and conjunctivitis (p. 611.1). Oxatomide is given as the anhydrous substance or as the monohydrate; doses are expressed as the anhydrous substance. Oxatomide monohydrate 1.04 mg is equivalent to about 1 mg of anhydrous oxatomide. The usual oral dose is 30 mg twice daily. The hydrate has also been applied topically but, as with other antihistamines, there is a risk of sensitisation.

Effects on the nervous system. Acute dystonic reactions and long-lasting impaired consciousness were associated with oxatomide therapy in 6 children.[1] Impaired consciousness varied from lethargy and somnolence to a clinical picture resembling encephalitis and persisted for 2 days or more in 3 patients. Plasma-oxatomide concentrations

were measured in 3 patients and found to be high, although 2 of these had been given the recommended dose.

1. Casteels-Van Daele M, *et al.* Acute dystonic reactions and long-lasting impaired consciousness associated with oxatomide in children. *Lancet* 1986; i: 1204–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Fensedyl; Tinset; ***Austria***: Tinset†; ***Chile***: Tinset†; ***Fr.***: Tinset†; ***Gr.***: Tinset; ***Indon.***: Oxtin; Tinset; ***Ital.***: Tinset; ***Jpn***: Celtect; ***Mex.***: Tinset; ***Neth.***: Tinset; ***Port.***: Tinset; ***S.Afr.***: Tinset; ***Spain***: Cobiona†; Oxatokey†; ***Thai.***: Tinset.

Multi-ingredient Preparations. ***Arg.***: Causalon Bronquial; Causalon Grip; Letondal.

Oxomemazine *(rINN)*

Oxomemazina; Oxométazine; Oxomemazinum; RP-6847; Trimeprazine *SS*-Dioxide; Оксомемазин.

10-(3-Dimethylamino-2-methylpropyl)phenothiazine 5,5-dioxide.

$C_{18}H_{22}N_2O_2S$=330.4

CAS — 3689-50-7.

ATC — R06AD08.

ATC Vet — QR06AD08.

UNII — 305MB38V1C.

Oxomemazine Hydrochloride *(rINNM)*

Hidrocloruro de oxomemazina; Oxométazine, Chlorhydrate d'; Oxomemazini Hydrochloridum; Оксомемазина Гидрохлорид.

$C_{18}H_{22}N_2O_2S$,HCl=366.9

CAS — 4784-40-1.

ATC — R06AD08.

ATC Vet — QR06AD08.

Pharmacopoeias. In ***Fr.***

Profile

Oxomemazine, a phenothiazine derivative, is a sedating antihistamine (p. 610.1) used for the symptomatic relief of hypersensitivity reactions and in pruritic skin disorders (p. 612.1). It is also an ingredient of compound preparations for the symptomatic treatment of coughs and the common cold (p. 611.2).

Oxomemazine has been given orally in doses ranging from about 5 to 13 mg daily in divided doses. It has also been given by the rectal route. Oxomemazine hydrochloride has been used similarly by mouth.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Toplexil; ***Neth.***: Toplexil; ***Switz.***: Toplexil N.

Multi-ingredient Preparations. ***Belg.***: Toplexil; ***Braz.***: Expec; Iodesin; KI-Expectorante; Toplexil; ***Gr.***: Toplexil; ***Indon.***: Comtusi; Oroxin; Oxopect; Toplexil; ***Israel***: Oxacatin.

Parathiazine Teoclate *(pINNM)*

Parathiazine, Téoclate de; Parathiazini Teoclas; Parathiazone Theoclate; Pyrathiazine Theoclate; Teoclato de paratiazina; Паратиазина Теоклат.

10-(2-Pyrrolidin-1-ylethyl)phenothiazine 8-chlorotheophyllinate.

$C_{18}H_{20}N_2S,C_7H_7ClN_4O_2$=511.0

CAS — 84-08-2 (parathiazine); 14006-99-6 (parathiazine teoclate); 522-25-8 (parathiazine monohydrochloride).

Profile

Parathiazine is a phenothiazine derivative with the properties of the antihistamines (p. 610.1). It has been given as the teoclate as an antiemetic.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Indon.***: Anvomer B6; Emegrav B6; Mediamer B6; Pregvomit; Provomer; Pyramer; Voldiamer B6.

Phenindamine Tartrate *(BANM, USAN, rINNM)*

Fenindamina, tartrato de; Phenindamine Acid Tartrate; Phénindamine, Tartrate de; Phenindamini Tartras; Phenindaminium Tartrate; Tartrato de fenindamina; Фениндамина Тартрат.

1,2,3,4-Tetrahydro-2-methyl-9-phenyl-2-azafluorene hydrogen tartrate; 2,3,4,9-Tetrahydro-2-methyl-9-phenyl-1*H*-indeno[2,1-c]pyridine hydrogen tartrate.

$C_{19}H_{19}N,C_4H_6O_6$=411.5

CAS — 82-88-2 (phenindamine); 569-59-5 (phenindamine tartrate).

ATC — R06AX04.

ATC Vet — QR06AX04.

UNII — 28725X3PV8.

Pharmacopoeias. In *Br.*

BP 2014: (Phenindamine Tartrate). A white or almost white, odourless or almost odourless, voluminous powder. Sparingly soluble in water; slightly soluble in alcohol; practically insoluble in chloroform and in ether. A 1% solution in water has a pH of 3.4 to 3.9. Protect from light.

Profile

Phenindamine, a piperidine derivative, is a sedating antihistamine (p. 610.1); however, it may be mildly stimulating in certain individuals. It has been used as the tartrate for the symptomatic relief of allergic conditions including urticaria and rhinitis, and as an ingredient of compound preparations for coughs and the common cold.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Nolahist†.

Multi-ingredient Preparations. ***USA***: P-V-Tussin†.

Pheniramine *(BAN, rINN)*

Feniramiini; Feniramin; Feniramina; Phéniramine; Pheniraminum; Prophenpyridamine; Фенирамин.

NN-Dimethyl-3-phenyl-3-(2-pyridyl)propylamine.

$C_{16}H_{20}N_2$=240.4

CAS — 86-21-5.

ATC — R06AB05.

ATC Vet — QR06AB05.

UNII — 134FM9ZZ6M.

Pheniramine Aminosalicylate *(BANM, rINNM)*

Aminosalicilato de feniramina; Feniramina, aminosalicilato de; Pheniramine 4-Aminosalicylate; Pheniramine *p*-Aminosalicylate; Phéniramine, Aminosalicylate de; Pheniramine Para-aminosalicylate; Pheniramini Aminosalicylas; Фенирамина Аминосалицилат.

Pheniramine 4-amino-2-hydroxybenzoate.

$C_{16}H_{20}N_2,C_7H_7NO_3$=393.5

CAS — 3269-83-8.

ATC — R06AB05.

ATC Vet — QR06AB05.

Pheniramine Maleate *(BANM, USAN, rINNM)*

Feniramiinimaleaatti; Feniramin Hidrojen Maleat; Feniramin Maleat; Feniramin maleinát; Feniramina, maleato de; Feniraminmaleat; Feniramin-maleát; Feniramino maleatas; Maleato de feniramina; Phéniramine, maléate de; Pheniramini Maleas; Pheniraminium Maleate; Pheniraminmaleat; Prophenpyridamine Maleate; Фенирамина Малеат.

Pheniramine hydrogen maleate.

$C_{16}H_{20}N_2,C_4H_4O_4$=356.4

CAS — 132-20-7.

ATC — R06AB05.

ATC Vet — QR06AB05.

UNII — NYW9056S5B.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Pheniramine Maleate). A white or almost white, crystalline powder. Very soluble in water; freely soluble in alcohol, in dichloromethane, and in methyl alcohol. M.p. 106 degrees to 109 degrees. A 1% solution in water has a pH of 4.5 to 5.5. Protect from light.

USP 36: (Pheniramine Maleate). A white crystalline powder having a faint amine-like odour. Soluble in water and in alcohol. pH of a 1% solution in water is between 4.5 and 5.5.

Uses and Administration

Pheniramine, an alkylamine derivative, is a sedating antihistamine with antimuscarinic and moderate sedative properties.

It is used as the maleate for the symptomatic relief of allergic conditions including urticaria and angioedema (p. 612.3), rhinitis (p. 612.1), and conjunctivitis (p. 611.1), and in pruritic skin disorders (p. 612.1). It has also been used for its antiemetic properties in the prevention and control of motion sickness (p. 611.3). Pheniramine maleate is used as an ingredient of compound preparations for the symptomatic treatment of coughs and the common cold (p. 611.2). It is also used with a decongestant in eye and nasal preparations.

Pheniramine maleate is given orally in doses up to about 45 mg three times daily. In some countries pheniramine maleate has been given parenterally.

The aminosalicylate, the hydrochloride, and the tannate have also been used.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively.

Abuse. References to the abuse of oral pheniramine.

1. Jones IH, *et al.* Pheniramine as an hallucinogen. *Med J Aust* 1973; 1: 382–6.
2. Csillag ER, Landauer AA. Alleged hallucinogenic effect of a toxic overdose of an antihistamine preparation. *Med J Aust* 1973; 1: 653–4.
3. Buckley NA, *et al.* Pheniramine—a much abused drug. *Med J Aust* 1994; 160: 188–92.

Pregnancy. For discussion of the use of antihistamines, including pheniramine, in pregnancy, see p. 614.2.

Interactions

As for the sedating antihistamines in general, p. 614.3.

Pharmacokinetics

The pharmacokinetics of pheniramine and its metabolites, *N*-desmethylpheniramine and *N*-didesmethylpheniramine, were investigated in 6 healthy subjects.[1] After oral doses of pheniramine aminosalicylate, peak-plasma pheniramine concentrations were reached in 1 to 2.5 hours. The terminal half-life ranged between 8 and 17 hours after intravenous doses (pheniramine maleate) and 16 and 19 hours after oral doses. The total recovery of pheniramine as unchanged drug and metabolites from the urine was 68 to 94% of the intravenous dose and 70 to 83% of the oral dose.

1. Witte PU, *et al.* Pharmacokinetics of pheniramine (Avil) and metabolites in healthy subjects after oral and intravenous administration. *Int J Clin Pharmacol Ther Toxicol* 1985; 23: 59–62.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Avil; ***India***: Avil; ***Indon.***: Avil; ***Turk.***: Avil; ***UAE***: Histol.

Multi-ingredient Preparations. ***Arg.***: Mira Klonal; Mirus; Refenax Colirio; Visuclar; ***Austral.***: Avil Decongestant†; Naphcon-A; Visine Allergy; ***Austria***: Neo Citran; ***Belg.***: Naphcon-A; ***Braz.***: Clanistil; Claril; Cristalin; ***Canad.***: Ak Vernacon; Calmylin Ace; Citron Chaud DM†; Cold & Flu; Diopticon A; Dirouge; Dristan; Hot Lemon Cough and Colds Relief DM; Hot Lemon Relief for Symptoms of Cold and Flu; Hot Lemon Relief for Symptoms of Cough and Cold; Hot Lemon Relief; Hot Lemon†; Naphcon-A; Neo Citran Colds & Flu; Neo Citran DM; Neocitran Extra Strength Cold and Flu†; Opcon-A; Pulmorphan Pediatrique; Pulmorphan; Rhume et de la Grippe†; Rhume et de la Toux†; Rhume et Grippe; Robitussin AC; TheraFlu Cold & Flu; Visine Advance Allergy; ***Chile***: Clarimir F; Dessolets; Miral; Naphcon-A; ***China***: Naphcon-A (那素达); Cz.: Fervex†; ***Fr.***: Fervex; ***Hong Kong***: Dristan Nasal Spray†; Fortolin Nite†; Konjunktival; Naphcon-A; Opcon-A; ***Hung.***: Fervex†; Neo Citran; ***India***: Avil Expectorant; Cof Q; Cosavil†; Dristan Nasal Drops†; ***Indon.***: Flamergi; Isotic Azora; Naphcon-A; ***Israel***: TheraFlu Colds & Flu†; TheraFlu Cough & Colds†; Tussosedan†; ***Ital.***: Stillergy; Tetramil; Triaminic Flu; ***Malaysia***: Naphcon-A; ***Mex.***: Eyrasil; Istasol; Mirus; Opcon-A; Solutina; ***NZ***: Naphcon-A; Visine Allergy; ***Philipp.***: Decocon A; Irazol; Naphcon-A; Optaphen; Vistallerg; ***Pol.***: Fervex; Theraflu ExtraGRIP; ***Rus.***: Febricet (Фебрицет); Fervex (Фервекс); Flucoldin (Флуколдин); Grippoflu Extra Cold and Flu (Гриппофлю От Простуды И Гриппа); Influnorm (Инфлюнорм); Pentalgin (Пенталгин); Rinicold Hot-Mix (Риникол ХотМикс); Rinzasip (Ринзасип); Rinzasip with Vitamin C (Ринзасип с Витамином С); Stopgripan (Стопгрипан); Theraflu (Терафлю); TheraFlu Flu and Cold (ТераФлю от Гриппа и Простуды Экстра); ***S.Afr.***: Calasthetic; Coff-Up†; Dristan Decongestant Nasal Mist†; ***Singapore***: Naphcon-A; ***Switz.***: Neo Citran Grippe/refroidissement; ***Thai.***: Naphcon-A; ***Turk.***: Antibeksin; ***UAE***: Histol Exp†; ***Ukr.***: Grippocitron (Гриппоцитрон); Milistan Hot Tea for Children Orange (Мілістан Гарячий Чай Для Дітей Зі Смаком Апельсина); Milistan Hot Tea Lemon (Мілістан Гарячий Чай Зі Смаком Лимона); Rinza Hotsip (Ринза Хотсип); Rinza Hotsip with Vitamin C (Ринза Хотсип с Витамином С); Stopgripan (Стопгрипан)†; Theraflu (Терафлю); Theraflu Extra (Терафлю Экстра); TheraFlu Flu and Cold (Терафло Від Грипу Та Застуди); ***USA***: Dristan Nasal Spray; Naphazoline Plus†; Naphcon-A; Naphoptic-A; Ocuhist; Opcon-A; Scot-Tussin Original 5-Action; TheraFlu Cold & Cough; Tussirex; Visine-A; ***Venez.***: Soluclear; Tempragrip.

Pharmacopoeial Preparations
USP 36: Naphazoline Hydrochloride and Pheniramine Maleate Ophthalmic Solution.

Phenyltoloxamine Citrate *(BANM, rINNM)*

C-5581H (phenyltoloxamine); Citrato de feniltoloxamina; Feniltoloxamina, citrato de; Phényltoloxamine, Citrate de; Phenyltoloxamini Citras; Phenyltolyloxamine Citrate; PRN (phenyltoloxamine); Фенилтолоксамина Цитрат.
2-(2-Benzylphenoxy)-*NN*-dimethylethylamine dihydrogen citrate.
$C_{17}H_{21}NO,C_6H_8O_7$=447.5
CAS — 92-12-6 (phenyltoloxamine); 1176-08-5 (phenyltoloxamine citrate).
UNII — 8UE48MJH8M.

Pharmacopoeias. In *US.*

USP 36: (Phenyltoloxamine Citrate). A white crystalline powder. Very soluble in boiling water; slightly soluble in cold water and in alcohol; practically insoluble in cold acetone, in solvent ether, and in toluene. pH of a 1% solution in water is between 3.2 and 4.2.

Profile

Phenyltoloxamine citrate, a monoethanolamine derivative, is a sedating antihistamine (p. 610.1). It is usually given orally in combination preparations with a decongestant or analgesic. Phenyltoloxamine citrate has been used in nasal preparations. Phenyltoloxamine polistirex has also been given orally.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Codipront†; ***Braz.***: Setux Expectorante; Setux; ***Canad.***: Tussionex; ***Chile***: Matinor; Sinutab; ***Fr.***: Biocidan; ***Hong Kong***: Codipront; ***Indon.***: Codipront cum Expectorant; Codipront cum Expectorant; Codipront; ***Israel***: Codivis; ***Philipp.***: Sinutab PE; ***Port.***: Codipront; ***Rus.***: Orinol Plus (Орнол Плюс); ***S.Afr.***: Adco-Sinal Co; Dequa-Flu†; Pholtex Linctus; Sinustop with Codeine†; Sinustop†; Sinutab with Codeine; Sinutab†; Suncodin; ***Switz.***: Codipront†; ***Thai.***: Codipront; ***Turk.***: Benzoleks†; ***USA***: Anabar†; Be-Flex Plus†; Biphenox; BP Poly-650; By-Ache†; Cafgesic Forte†; Chlorex-A†; Combiflex ES†; Combiflex†; Comhist LA; Digex NF; Digex†; Durabac Forte; Durabac; Duraxin†; Flextra; Hyflex†; Lagesic; Levacet; Lobac†; Major-gesic; Momentum; Nalex-A†; Norel SR; Pain-gesic; Phenylgesic; Relagesic; Staflex; Tetra-Mag†; ZFlex; Zgesic; ***Venez.***: Codipront.

Pimethixene *(rINN)*

BP-400; Pimethixène; Pimethixenum; Pimetixene; Pimetixeno; Пиметиксен.
9-(1-Methyl-4-piperidylidene)thioxanthene.
$C_{19}H_{19}NS$=293.4
CAS — 314-03-4.
ATC — R06AX23.
ATC Vet — QR06AX23.
UNII — T46J20J26F.

Profile

Pimethixene is reported to be a sedating antihistamine (p. 610.1) and an inhibitor of serotonin. It is given to children in usual oral doses of about 1.8 to 5.5 mg daily for coughs. It has been used as a sedative and for the treatment of respiratory disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Ansiotex; Muricalm; ***Fr.***: Calmixene.

Multi-ingredient Preparations. ***Braz.***: Santussal.

Piprinhydrinate *(BAN, rINN)*

Diphenylpyraline Teoclate; Diphenylpyraline Theoclate; Piprinhidrinato; Piprinhydrinatum; Пипрингидринат.
The diphenylpyraline salt of 8-chlorotheophylline; 4-Benzhydryloxy-1-methylpiperidine salt of 8-chlorotheophylline.
$C_{19}H_{23}NO,C_7H_7ClN_4O_2$=496.0
CAS — 606-90-6.
UNII — 5I78REJ7XL.

Profile

Piprinhydrinate, a piperidine derivative, is an antihistamine (p. 610.1) that has been given orally as an ingredient of compound preparations for the symptomatic relief of coughs and the common cold.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Thai.***: Plokon†.

Promethazine *(BAN, rINN)*

Prometatsiini; Prometazin; Prometazina; Prométhazine; Promethazinum; Прометазин.
Dimethyl (1-methyl-2-phenothiazin-10-ylethyl)amine.
$C_{17}H_{20}N_2S$=284.4
CAS — 60-87-7.
ATC — D04AA10; R06AD02.
ATC Vet — QD04AA10; QR06AD02.
UNII — FF28EJO494.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of promethazine:
Finegan; Finnagan.

Promethazine Hydrochloride *(BANM, rINNM)*

Diprazinum; Hidrocloruro de prometazina; Proazamine Chloride; Prometatsiinihydrokloridi; Prometazin Hidroklorür; Prometazina, hidrocloruro de; Prometazin-hidroklorid; Prometazinhydroklorid; Prometazino hidrochloridas; Prometazyny chlorowodorek; Prométhazine, chlorhydrate de; Promethazin-hydrochlorid; Promethazinhydrochlorid; Promethazini Hydrochloridum; Promethazinium Chloride; Прометазина Гидрохлорид.
$C_{17}H_{20}N_2S$,HCl=320.9
CAS — 58-33-3.
ATC — D04AA10; R06AD02.
ATC Vet — QD04AA10; QR06AD02.
UNII — R61ZEH7111.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Promethazine Hydrochloride). A white or faintly yellowish, crystalline powder. Very soluble in water; freely soluble in alcohol and in dichloromethane. A 10% solution in water has a pH of 4.0 to 5.0. Protect from light.

USP 36: (Promethazine Hydrochloride). A white to faint yellow, practically odourless, crystalline powder. Slowly oxidises and acquires a blue colour on prolonged exposure to air. Freely soluble in water, in hot dehydrated alcohol, and in chloroform; practically insoluble in acetone, in ether, and in ethyl acetate. pH of a 5% solution in water is between 4.0 to 5.0. Store in airtight containers. Protect from light.

Adsorption. The adsorption of promethazine hydrochloride onto various glass and plastic containers and infusion systems has been studied.[1-4] Factors affecting the degree of adsorption included the particular material tested and the pH of the solution.

1. Kowaluk EA, *et al.* Interactions between drugs and polyvinyl chloride infusion bags. *Am J Hosp Pharm* 1981; 38: 1308–14.
2. Kowaluk EA, *et al.* Interactions between drugs and intravenous delivery systems. *Am J Hosp Pharm* 1982; 39: 460–7.
3. Rhodes RS, *et al.* Stability of meperidine hydrochloride, promethazine hydrochloride, and atropine sulfate in plastic syringes. *Am J Hosp Pharm* 1985; 42: 112–5.
4. Martens HJ, *et al.* Sorption of various drugs in polyvinyl chloride, glass, and polyethylene-lined infusion containers. *Am J Hosp Pharm* 1990; 47: 369–73.

Incompatibility. Solutions of promethazine hydrochloride are incompatible with alkaline substances, which precipitate the insoluble promethazine base. Compounds reported to be incompatible with promethazine hydrochloride include aminophylline, barbiturates, benzylpenicillin salts, carbenicillin sodium, chloramphenicol sodium succinate, chlorothiazide sodium, cefmetazole sodium, cefoperazone sodium, cefotetan disodium, dimenhydrinate, doxorubicin hydrochloride (in a liposomal formulation), furosemide, heparin sodium, hydrocortisone sodium succinate, meticillin sodium, morphine sulfate, nalbuphine hydrochloride, and some contrast media and parenteral nutrient solutions.

Promethazine Teoclate *(BAN, rINN)*

Prometazina, teoclato de; Prométhazine, Téoclate de; Promethazine Theoclate; Promethazini Teoclas; Teoclato de prometazina; Прометазина Теоклат.
The promethazine salt of 8-chlorotheophylline.
$C_{17}H_{20}N_2S,C_7H_7ClN_4O_2$=499.0
CAS — 17693-51-5.
ATC — D04AA10; R06AD02.
ATC Vet — QD04AA10; QR06AD02.
UNII — S5PUP23U26.

Pharmacopoeias. In *Br.*

BP 2014: (Promethazine Teoclate). A white or almost white, odourless or almost odourless powder. Very slightly soluble in water; sparingly soluble in alcohol; freely soluble in chloroform; practically insoluble in ether. Protect from light.

Uses and Administration

Promethazine, a phenothiazine derivative, is a sedating antihistamine with antimuscarinic, significant sedative, and some serotonin-antagonist properties. It is usually given as the hydrochloride or teoclate. Promethazine embonate and promethazine maleate have also been given orally. Promethazine dioxide (dioxopromethazine) has been used as the hydrochloride in eye and nasal drops. The antihistamine action has been reported to last for between 4 and 12 hours.

Promethazine hydrochloride is used for the symptomatic relief of allergic conditions including urticaria and angioedema (p. 612.3), rhinitis (p. 612.1) and conjunctivitis (p. 611.1), and in pruritic skin disorders (p. 612.1). It may be given intravenously as an adjunct in the emergency treatment of anaphylactic shock (p. 611.1).

Promethazine hydrochloride and promethazine teoclate are used for their antiemetic action in the prevention and treatment of nausea and vomiting in conditions such as motion sickness, drug-induced vomiting, and postoperative vomiting (p. 611.3). They are also used for the symptomatic treatment of nausea and vertigo caused by Ménière's disease and other vestibular disorders (see Vertigo, p. 612.3). Promethazine hydrochloride is also employed pre- and postoperatively in surgery and obstetrics for its sedative effects and for the relief of apprehension (see Anaesthesia, p. 610.3); it is often given with pethidine hydrochloride. Promethazine hydrochloride may be used for night-time sedation (see Insomnia, p. 611.2).

Promethazine hydrochloride is a common ingredient of compound preparations for the symptomatic treatment of coughs and the common cold (p. 611.2).

The following doses have been given **orally.**

- For the treatment of *allergic conditions* promethazine hydrochloride is usually given in a dose of 25 mg at night increased to 25 mg twice daily if necessary; owing to its pronounced sedative effect it is preferably given at night but an alternative dose is 10 to 20 mg two or three times daily.
- Promethazine hydrochloride is given in doses of 20 to 50 mg at night for the short-term management of *insomnia* although its prolonged duration of action can lead to considerable drowsiness the following day.
- For the prevention of *motion sickness* promethazine hydrochloride can be given in a dose of 20 or 25 mg the night before travelling followed by a similar dose the following morning if necessary. The teoclate is used similarly. For the prevention of motion sickness the dose of promethazine teoclate is 25 mg given either on the night, or one to two hours, before travelling. For the treatment of motion sickness, a dose of promethazine teoclate 25 mg may be given as soon as possible and repeated in the evening, followed by a third dose the next evening.
- For nausea and vomiting arising from causes such as *labyrinthitis* a dose of promethazine teoclate 25 mg at night is usually adequate; this may be increased to 50 or 75 mg at night or to 25 mg two or three times daily if necessary to a maximum of 100 mg daily.
- For *severe vomiting in pregnancy* the *BNF* recommends a dose of promethazine teoclate 25 mg at night, increased if necessary to a maximum of 100 mg.

Promethazine hydrochloride is also given by the **rectal** route as suppositories. Doses are similar to those given orally.

Promethazine hydrochloride is given **parenterally** by deep intramuscular injection as a solution of 25 or 50 mg/mL. It may also be given by slow intravenous injection or injected into the tubing of a freely running infusion in a concentration of not more than 25 mg/mL although it is usually diluted to 2.5 mg/mL. The rate of infusion should not exceed 25 mg/minute. The usual parenteral dose for all indications apart from nausea and vomiting is 25 to 50 mg; a dose of 100 mg should not be exceeded. Doses of 12.5 to 25 mg, repeated at intervals of not less than 4 hours, may be given for the treatment of nausea and vomiting, although not more than 100 mg is usually given in 24 hours.

For doses in children, see p. 639.1.

Promethazine has been used **topically** to provide relief in hypersensitivity disorders of the skin and for burns but, as with other antihistamines, it may produce skin sensitisation.

Administration in children. Promethazine may be given to children **orally**, dosage being dependent on age, indication, and the salt used.

For *allergic conditions*, promethazine hydrochloride can be given as follows:

- children aged 2 to 5 years: 5 to 15 mg daily in one or two divided doses
- those aged 5 to 10 years: 10 to 25 mg daily in one or two divided doses

For *night sedation or premedication*, promethazine hydrochloride can be given as follows:

- children aged 2 to 5 years: 15 to 20 mg
- those aged 5 to 10 years: 20 to 25 mg

For the prevention of *motion sickness*, the following doses of promethazine hydrochloride may be given the night before the journey and repeated on the following morning (6 to 8 hours later) if necessary:

- children aged 2 to 5 years: 5 mg
- those aged 5 to 10 years: 10 mg

Promethazine teoclate may also be given orally to children aged 5 to 10 years for the prevention of motion sickness in a dose of 12.5 mg given either on the night, or one to two hours, before travelling. For the treatment of motion sickness, a dose of promethazine teoclate 12.5 mg may be given as soon as possible and repeated in the evening, followed by a third dose the next evening.

Children aged 5 to 10 years may also receive promethazine teoclate for nausea and vomiting from causes such as *labyrinthitis* in a dose of 12.5 to 37.5 mg daily.

Children aged over 10 years may be given oral promethazine in doses similar to those used in adults (see p. 638.3).

Children aged 5 to 10 years may be given 6.25 to 12.5 mg of promethazine hydrochloride by deep **intramuscular** injection, for *allergic conditions* or *sedation*. Older children may be given the usual adult dose (see above).

Although not licensed in the UK for children aged under 2 years, the *BNFC* suggests those aged 1 month to 12 years may be given promethazine hydrochloride for *sedation in intensive care*. A dose of 0.5 to 1 mg/kg (to a maximum of 25 mg), four times daily, **orally**, or by deep **intramuscular** or **slow intravenous** injection has been suggested, adjusted according to response. Adolescents aged 12 to 18 years may be given 25 to 50 mg four times daily.

Sedation. For reference to the use of lytic cocktails of chlorpromazine, promethazine, and pethidine, and the view that alternatives should be considered in children, see under Pethidine, p. 122.2.

Adverse Effects

As for the sedating antihistamines in general, p. 613.1.

Cardiovascular adverse effects are more commonly seen after injection, and bradycardia, tachycardia, transient minor increases in blood pressure, and occasional hypotension have all been reported with promethazine hydrochloride. Jaundice and blood dyscrasias have been reported, and extrapyramidal effects may occur at high doses.

Parenteral administration of promethazine may cause various problems, ranging from pain and burning, to paralysis, thrombophlebitis, severe spasm of distal vessels, necrosis, and gangrene; such adverse effects are particularly seen after inadvertent intra-articular injection.

Overdosage. A toxic neurological syndrome, which included CNS depression, acute excitomotor manifestations, ataxia and visual hallucinations, plus peripheral antimuscarinic effects developed in 2 children aged 44 months and 16 months after topical application of a 2% promethazine cream providing between 12.9 and 26 mg/kg.[1] The older child had also received hydroxyzine 10 mg orally 1 hour earlier.

1. Shawn DH, McGuigan MA. Poisoning from dermal absorption of promethazine. *Can Med Assoc J* 1984; 130: 1460–1.

Sudden infant death syndrome. Although some early reports raised the possibility of an association between the use of phenothiazine antihistamines and the sudden infant death syndrome (SIDS) this has not been confirmed. Following an initial report that 4 of 7 infants with SIDS had been given alimemazine before death and that a series of severe apnoeic crises had been seen in the twin of a SIDS victim given promethazine,[1] the same workers studied 52 SIDS victims, 36 near-miss infants (those who had had severe unexplained episodes of cyanosis or pallor during sleep), and 175 control subjects to investigate the role of nasopharyngitis and phenothiazines in this syndrome.[2] They found that there was no difference in the incidence of nasopharyngitis between the 3 groups, but the proportion of infants given phenothiazines was higher in both the SIDS group (23%) and the near-miss group (22%) than in the control group (2%). In a subsequent study,[3] they found that the incidence of central and obstructive sleep apnoeas was increased in 4 healthy infants given promethazine for 3 days, although the duration of the attacks was unaltered and generally short, with a range of 3 to 10 seconds. A report on behalf of the European Commission,[4] stated that no link between sudden deaths in infants and drug use had been confirmed by national drug monitoring centres. It was likely that the risk of apnoea was associated with all sedative drugs, especially in overdose.[4] Previously, phenothiazine-induced hyperthermia had been proposed as a contributory factor in SIDS.[5]

For general precautions regarding the use of antihistamines in children, see p. 614.1.

1. Kahn A, Blum D. Possible role of phenothiazines in sudden infant death. *Lancet* 1979; ii: 364–5.
2. Kahn A, Blum D. Phenothiazines and sudden infant death syndrome. *Pediatrics* 1982; 70: 75–8.
3. Kahn A, *et al.* Phenothiazine-induced sleep apneas in normal infants. *Pediatrics* 1985; 75: 844–7.
4. Cockfield, Phenergan, Theralene, Algotropyl—drugs responsible for the death of new-born babies. *Off J EC* 1986; 29: C130/25–6.
5. Stanton AN. Sudden infant death syndrome and phenothiazines. *Pediatrics* 1983; 71: 986–7.

Precautions

As for the sedating antihistamines in general, p. 613.3.

Intravenous injections of promethazine hydrochloride must be given slowly and extreme care must be taken to avoid extravasation or inadvertent intra-arterial injection, because of the risk of severe irritation and tissue damage. Deep intramuscular injection is preferred but may be painful; promethazine should not be given by subcutaneous injection.

False negative and positive results have been reported with some pregnancy tests.

Anaesthesia. In 8 healthy subjects promethazine 25 mg intravenously decreased lower oesophageal sphincter pressure and increased the incidence of gastro-oesophageal reflux.[1] It might, therefore, increase the risk of regurgitation and aspiration of gastric contents during induction of and recovery from anaesthesia. The effect was attributed to the antimuscarinic properties of promethazine.

1. Brock-Utne JG, *et al.* The action of commonly used antiemetics on the lower oesophageal sphincter. *Br J Anaesth* 1978; 50: 295–8.

Children. A possible association between phenothiazine sedatives and sudden infant death syndrome has been suggested, but has not been confirmed (see under Adverse Effects, above). The current view in the UK and USA is that promethazine should not be given to children under 2 years of age.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies promethazine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Pregnancy. For discussion of the use of antihistamines in pregnancy, including studies involving phenothiazines, see p. 614.2.

Renal impairment. Phenothiazine-induced toxic psychosis occurred in a patient with chronic renal failure who had been given promethazine.[1]

1. McAllister CJ, *et al.* Toxic psychosis induced by phenothiazine administration in patients with chronic renal failure. *Clin Nephrol* 1978; 10: 191–5.

Interactions

As for the sedating antihistamines in general, p. 614.3.

Pharmacokinetics

Promethazine is well absorbed after oral or intramuscular doses and peak plasma concentrations occur 2 to 3 hours after a dose by these routes, although there is low systemic bioavailability after oral doses, due to high first-pass metabolism in the liver. Promethazine crosses the blood-brain barrier and the placenta, and is distributed into breast milk. Values ranging from 76 to 93% have been reported for plasma-protein binding. Promethazine undergoes extensive metabolism, mainly to promethazine sulfoxide, and also to *N*-desmethylpromethazine. It is excreted slowly via the urine and bile, chiefly as metabolites. Elimination half-lives of 5 to 14 hours have been reported.

References.

1. Taylor G, *et al.* Pharmacokinetics of promethazine and its sulphoxide metabolite after intravenous and oral administration to man. *Br J Clin Pharmacol* 1983; 15: 287–93.
2. Paton DM, Webster DR. Clinical pharmacokinetics of H_1-receptor antagonists (the antihistamines). *Clin Pharmacokinet* 1985; 10: 477–97.
3. Stavchansky S, *et al.* Bioequivalence and pharmacokinetic profile of promethazine hydrochloride suppositories in humans. *J Pharm Sci* 1987; 76: 441–5.
4. Strenkoski-Nix LC, *et al.* Pharmacokinetics of promethazine hydrochloride after administration of rectal suppositories and oral syrup to healthy subjects. *Am J Health-Syst Pharm* 2000; 57: 1499–1505.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Fenergan; *Austral.*: Avomine; Fenezal; Phenergan; *Belg.*: Phenergan; *Braz.*: Alergiderm†; Cremefenergan; Fenergan; Pamergan; Profergan; Promergan; Prometazol; *Canad.*: Histantil; *Cz.*: Prothazin; *Denm.*: Phenergan; *Fr.*: Phenergan; *Ger.*: Atosil; Closin; Proneurin†; Prothanon†; *Gr.*: Phenergan; Titanox; *Hong Kong*: Anvomin; Fenamin†; Fenazin†; Promin†; Synvomin†; Uni-Prozine†; Xepagan; *Hung.*: Pipolphen; *India*: Avomine; Ceedokid; Emin; Emispan; Histazine; Normagan; Phenergan; *Indon.*: Nufapreg; Phenergan†; *Irl.*: Phenergan; *Israel*: Prothiazine; *Ital.*: Pargan; Farganesse; Fenazil; *Malaysia*: Votazine; Zoralix; *Norw.*: Phenergan; *NZ*: Allersoothe; Avomine; Phenergan; *Philipp.*: Metagon; Phenerzin; Promet; Promezin; Zinmet; *Pol.*: Diphergan; Polfergan; *Port.*: Fenergan; *Rus.*: Pipolphen (Пипольфен); Pipolzine (Пипользин); *S.Afr.*: Avomine; Brunazine; Daralix†; Lenazine; Phenergan; Prohist; Receptozine; *Singapore*: Fenazin; Phenergan; Promagen; Prozine; Synvomin; Votazine; Xepagan; *Spain*: Fenergan Topico; Frinova†; *Swed.*: Lergigan; *Thai.*: Meta†; Phenergan; Procodyl; *UAE*: Histaloc; *UK*: Avomine; Phenergan; Sominex; Vertigon; Zit; *Ukr.*: Pipolphen (Пипольфен); *USA*: Phenadoz; Phenergan; Promethegan.

Multi-ingredient Preparations. *Austral.*: Painstop Night-Time Pain Reliever; Panquil†; Tixylix Night†; *Braz.*: Dorilen; Doriless; Fenergan Expectorante; Lisador; Lisantil; Sedador; *China*: Fufang Dan An Pian (复方胆氯片); Fufang Lixueping (复方利血平); Ke Li An (克立安); Kefei (可非); *Cz.*: Coldrex Nite; *Fr.*: Algotropyl; Fluisedal; Rhinathiol Promethazine; Transmert†; Tussisedal; *Ger.*: Prothazin; *Hong Kong*: Against Cough†; Coughlin†; Dhasedyl; Double 'P' Syrup†; Ephedyl-DM†; Ephedyl†; Ephendyln†; Pendil†; Fendyl; Marsedyl II†; Marsedyl†; Methorsedyl; Mucoprom; Nosazine†; P.E.D.†; PEC; Pecolin†; Phensedyn; Pholix†; Promethazine Compound Linctus†; Prosedyl†; Rhinathiol Promethazine; Sedylin†; Tripe P; Wel-Coplex†; *India*: Ceedokid Plus; Childryl; Crophen; Emispan Plus; Emispan-H; Febrinil-P; Fevomax; Fevril; Fido-P; Kelvin Plus; Kelvin-P; Lincotuss-P; Nimkair-P; Paral-P; Paratel Plus; Tixylix; *Indon.*: Berlifed; Halmezin; Neo Davenol†; Phenadex; Prome; Promedex; Promethazine Ikapharmindo; *Irl.*: Night Nurse; *Israel*: Promethazine Expectorants; Prothiazine Expectorant; *Ital.*: Nuleron; Tachinotte; *Malaysia*: Axcel Dextrozine; CP Cough Syrup; Dextrodyl; Dextromethorphan Compound; Dhasedyl DM; Hosedyl DM; Mucoease Plus; Mucoprom; Phensedyl Dry Cough; Rhinathiol Promethazine; Russedyl Plus; Sedilix DM; Sinovid; *Neth.*: Promethazine comp†; *NZ*: Tixylix; *Rus.*: Coldrex Nite (Колдрекс Найт); Prothiazine Expectorant (Протиазин Экспекторант); *S.Afr.*: Acustop†; Adco-Kiddipayne; Adco-Salterpyn; Ban Pain; Brunacod†; Colcaps; Dequa-Coff; Fevapar†; Go-Pain; Goldgesic; Histodor†; Infacet†; Infapain Forte; Kid-Eeze; Lenazine Forte; Lentogesic; Medipyn; Megapyn†; Mepromol†; Painagon; Pedpain†; Phensedyl; Pynmed; Stilpane; Stopayne; Tenston; Tixylix†; Vacudol†; *Singapore*: Beacodyl; Cophadyl-E; Cophadyl; Dhasedyl DM; Dhasedyl; Ephedyl DM; Ephedyl; Phensedyl; Procodin; Promedyl; Promelix; Rhinathiol Promethazine; Sedilix DM; Sedilix SP-Codrine; SP-Cosedyl; Sunsedyl; *Spain*: Actithiol Antihist; Penergan Expectorante; Psicosoma; *Swed.*: Lergigan comp; *Switz.*: Rhinathiol Promethazine†; *Thai.*: Codyl; Cofcodyl; Comodine Cough; Decos†; Nordyl†; Nortuss†; Phencodin†; Phensedyl; Poly-Cof†; Teradyl†; Tussidyl; *Turk.*: Artu; *UAE*: Flukit; *UK*: Day & Night Nurse; Night Nurse; Pamergan P100; Tixylix Night-Time†; *USA*: Meprozine†; Peutazine VC with Codeine; Phenameth DM; Pherazine DM; Pherazine VC with Codeine; Pherazine VC; Pherazine with Codeine; Prometh VC Plain†; Prometh with Dextromethorphan; Promethazine VC with Codeine; *Venez.*: Preveral con Codeina; Preveral con Dextrometorfano.

Pharmacopoeial Preparations

BP 2014: Promethazine Hydrochloride Tablets; Promethazine Injection; Promethazine Oral Solution; Promethazine Teoclate Tablets;

USP 36: Promethazine Hydrochloride Injection; Promethazine Hydrochloride Suppositories; Promethazine Hydrochloride Syrup; Promethazine Hydrochloride Tablets.

Propiomazine *(BAN, USAN, rINN)*

CB-1678 (propiomazine or propiomazine maleate); Propiomatsiini; Propiomazin; Propiomazina; Propiomazinum; Wy-1359 (propiomazine or propiomazine maleate); Пропиомазин.

1-[10-(2-Dimethylaminopropyl)phenothiazin-2-yl]propan-1-one.

$C_{20}H_{24}N_2OS$=340.5

CAS — 362-29-8.

ATC — N05CM06.

ATC Vet — QN05CM06.

UNII — 24Z70PM79Y.

The symbol † denotes a preparation no longer actively marketed

Propiomazine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de propiomazina; Propiomazine, Chlorhydrate de; Propiomazini Hydrochloridum; Пропиомазина Гидрохлорид.

$C_{20}H_{24}N_2OS,HCl$=376.9

CAS — 1240-15-9.

ATC — N05CM06.

ATC Vet — QN05CM06.

UNII — 70BO17YR03.

Propiomazine Maleate *(BANM, rINNM)*

CB-1678 (propiomazine or propiomazine maleate); Maleato de propiomazina; Propiomazina, maleato de; Propiomazine Hydrogen Maleate; Propiomazine, Maléate de; Propiomazini Maleas; Wy-1359 (propiomazine or propiomazine maleate); Пропиомазина Малеат.

$C_{20}H_{24}N_2OS,C_4H_4O_4$=456.6

CAS — 3568-23-8.

ATC — N05CM06.

ATC Vet — QN05CM06.

Profile

Propiomazine, a phenothiazine derivative, is a sedating antihistamine (p. 610.1) that has been used for its sedative and antiemetic properties in insomnia (p. 611.2) and nausea and vomiting (p. 611.3).

Propiomazine is given as the maleate but doses are expressed in terms of the base; propiomazine maleate 1.3 mg is equivalent to about 1 mg of propiomazine. Doses equivalent to 25 to 50 mg orally at night have been given as a hypnotic.

Propiomazine hydrochloride has been given parenterally.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies propiomazine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Swed.*: Propavan.

Quifenadine Hydrochloride *(rINNM)*

Hidrocloruro de quifenadina; Quifénadine, Chlorhydrate de; Quifenadini Hydrochloridum; Хифенадина Гидрохлорид.

α,α-Diphenyl-3-quinuclidinemethanol hydrochloride.

$C_{20}H_{23}NO,HCl$=329.9

CAS — 10447-39-9 (quifenadine); 10447-38-8 (quifenadine hydrochloride).

ATC — R06AX31.

ATC Vet — QR06AX31.

Profile

Quifenadine is an antihistamine given orally as the hydrochloride.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Rus.*: Phencarol (Фенкарол); *Ukr.*: Phencarol (Фенкарол).

Rupatadine *(rINN)*

Rupatadina; Rupatadinum; Рупатадин.

8-Chloro-6,11-dihydro-11-[1-[(5-methyl-3-pyridyl)methyl]-4-piperidylidene]-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine.

$C_{26}H_{26}ClN_3$=416.0

CAS — 158876-82-5.

ATC — R06AX28.

ATC Vet — QR06AX28.

UNII — 2AE8M83G3E.

Rupatadine Fumarate *(rINNM)*

Fumarato de rupatadina; Rupatadine, Fumarate de; Rupatadini Fumaras; UR-12592 Fumarate; Рупатадина Фумарат.

8-Chloro-6,11-dihydro-11-[1-[(5-methyl-3-pyridyl)methyl]-4-piperidylidene]-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (*E*)-2-butenedioate.

$C_{26}H_{26}ClN_3,C_4H_4O_4$=532.0

CAS — 182349-12-8.

ATC — R06AX28.

ATC Vet — QR06AX28.

Profile

Rupatadine is an antihistamine with platelet-activating factor (PAF) antagonist activity that is used for the treatment of allergic rhinitis (p. 612.1) and chronic idiopathic urticaria (p. 612.3). It is given as the fumarate although doses are expressed in terms of the base; rupatadine fumarate 12.8 mg is equivalent to about 10 mg of rupatadine. The usual oral dose is the equivalent of 10 mg once daily of rupatadine.

References.

1. Izquierdo I, *et al.* Rupatadine: a new selective histamine H1 receptor and platelet-activating factor (PAF) antagonist: a review of pharmacological profile and clinical management of allergic rhinitis. *Drugs Today* 2003; 39: 451–68.
2. Keam SJ, Plosker GL. Rupatadine: a review of its use in the management of allergic disorders. *Drugs* 2007; 67: 457–74.
3. Fantin S, *et al.* International Rupatadine study group. A 12-week placebo-controlled study of rupatadine 10 mg once daily compared with cetirizine 10 mg once daily, in the treatment of persistent allergic rhinitis. *Allergy* 2008; 63: 924–31.
4. Valero A, *et al.* Safety of rupatadine administered over a period of 1 year in the treatment of persistent allergic rhinitis: a multicentre, open-label study in Spain. *Drug Safety* 2009; 32: 33–42.

Effects on the cardiovascular system. Licensed product information states that the cardiac safety of rupatadine has been assessed; no adverse ECG effects were noted when rupatadine was given in doses of up to 10 times the normal dose. Nevertheless, it is recommended that rupatadine is used with caution in patients with known prolongation of the QT interval, uncorrected hypokalaemia, or conditions such as bradycardia or acute myocardial ischaemia.

A review of Spanish and Portuguese spontaneous reporting scheme data found 5 cases of heart rhythm disturbances in patients taking rupatadine.[1] Such effects included palpitations and tachycardia and 1 case of torsade de pointes in an elderly man.

1. Carvajal A, *et al.* Heart rhythm disturbances associated with rupatadine: a case series from the Spanish and Portuguese pharmacovigilance systems. *Clin Pharmacol Ther* 2009; 85: 481–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Rupafin; *Austria*: Rupafin; *Belg.*: Rupatall; *Braz.*: Rupafin; *Cz.*: Tamalis; *Fr.*: Wystamm; *Ger.*: Rupafin†; Urtimed; *Gr.*: Rupafin; *India*: Levostar-R; *Irl.*: Rupafin; *Ital.*: Pafinur; Rupafin; *Neth.*: Rupafin; *Pol.*: Rupafin; *Port.*: Rinialer; *Spain*: Alergoliber; Rinialer; Rupafin; *Thai.*: Rupafin; *Turk.*: Rupafin; *UK*: Rupafin.

Sequifenadine *(rINN)*

Bicarphene (sequifenadine or sequifenadine hydrochloride); Bikarfen (sequifenadine or sequifenadine hydrochloride); Sequifenadina; Séquifénadine; Sequifenadinum; Сехифенадин.

α,α-Di-*o*-tolyl-3-quinuclidinemethanol.

$C_{22}H_{27}NO$=321.5

CAS — 57734-69-7.

UNII — C7Q3TBR3FP.

Profile

Sequifenadine is an antihistamine used in a wide range of allergic conditions. A usual dose is 50 to 100 mg given orally 2 or 3 times daily. Sequifenadine is reported also to have antiserotonin properties.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Rus.*: Histafen (Гистафен); *Ukr.*: Gistaphen (Гистафен).

Setastine Hydrochloride *(rINNM)*

EGIS-2062; EGYT-2062; Hidrocloruro de setastina; Setastina, hidrocloruro de; Sétastine, Chlorhydrate de; Setastini Hydrochloridum; Сетастина Гидрохлорид.

1-[2-[(*p*-Chloro-α-methyl-α-phenylbenzyl)oxy]ethyl]hexahydro-1*H*-azepine hydrochloride.

$C_{22}H_{28}ClNO,HCl$=394.4

CAS — 64294-95-7 (setastine).

Profile

Setastine hydrochloride, a derivative of clemastine, is an antihistamine that has been claimed to have no sedative activity. It is given for the symptomatic relief of hypersensitivity disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Qi Qi (齐齐); *Hung.*: Loderix†.

Terfenadine *(BAN, USAN, rINN)*

MDL-9918; RMI-9918; Terfenadiini; Terfenadin; Terfenadina; Terfenadinas; Terfénadine; Terfenadinum; Терфенадин.

1-(4-*tert*-Butylphenyl)-4-[4-(α-hydroxybenzhydryl)piperidino]butan-1-ol.

$C_{32}H_{41}NO_2$=471.7

CAS — 50679-08-8.

ATC — R06AX12.

ATC Vet — QR06AX12.

UNII — 7BA5G9Y06Q.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Terfenadine). A white or almost white, crystalline powder. It shows polymorphism. Very slightly soluble in water and in dilute hydrochloric acid; freely soluble in dichloromethane; soluble in methyl alcohol. Protect from light.

Uses and Administration

Terfenadine, a piperidine derivative, is a non-sedating antihistamine. It does not have significant antimuscarinic actions. It has been used for the symptomatic relief of allergic conditions including rhinitis (p. 612.1) and conjunctivitis (p. 611.1) and skin disorders such as urticaria (p. 612.3).

The maximum oral dose of terfenadine is 120 mg daily given either as 60 mg twice daily or 120 mg in the morning; a starting dose of 60 mg daily in a single dose or in two divided doses is recommended for rhinitis and conjunctivitis.

For dosage in renal impairment see below.

Administration in renal impairment. Half the usual oral daily dose of terfenadine (see above) has been suggested for patients with creatinine clearance less than 40 mL/minute.

Adverse Effects and Precautions

As for the non-sedating antihistamines in general, p. 613.1. Erythema multiforme and galactorrhoea have also been reported.

Ventricular arrhythmias, including torsade de pointes, have occurred rarely with terfenadine, particularly in association with raised blood concentrations (see Arrhythmias, below). To *reduce the risk* of developing such arrhythmias the recommended dose should **not** be exceeded and terfenadine should be **avoided** in patients with cardiac or significant hepatic disease, with hypokalaemia or other electrolyte imbalance, or with known or suspected prolonged QT interval. Use with drugs liable to interfere with the hepatic metabolism of terfenadine, other potentially arrhythmogenic drugs including those that prolong the QT interval, and drugs likely to cause electrolyte imbalance is **contra-indicated** (see Interactions, p. 641.1). If palpitations, dizziness, syncope, or convulsions occur terfenadine should be withdrawn and the patient investigated for potential arrhythmias.

Alopecia. Hair loss was associated with use of terfenadine in a 24-year-old patient.[1] Regrowth occurred when treatment was stopped.

1. Jones SK, Morley WN. Terfenadine causing hair loss. *BMJ* 1985; 291 940.

Arrhythmias. Ventricular arrhythmias including torsade de pointes have occurred with terfenadine at doses greater than those recommended[1] and also at normal doses in patients whose metabolism of terfenadine is impaired by drugs or by liver disease. Generalised convulsions and a quinine-like effect on the ECG have also been reported after a presumed overdose of terfenadine.[2] Consequently recommendations have been made to *reduce the risk* of developing serious arrhythmias (see Adverse Effects and Precautions, above, for details), including those from the UK CSM.[3,4] Terfenadine should be stopped immediately and the patient evaluated for potential arrhythmias, in those who have syncope, palpitations, dizziness, or convulsions after taking terfenadine.

Studies[5] have suggested that the ventricular arrhythmias are due to terfenadine itself rather than its active metabolite fexofenadine (p. 629.1). Terfenadine has been shown to inhibit cardiac potassium channels, which results in prolongation of the QT interval, a risk factor for developing arrhythmias, while the non-sedating antihistamines cetir-

izine, fexofenadine, and loratadine have had no demonstrable effect[5,6] (see also p. 613.2).

1. MacConnell TJ, Stanners AJ. Torsades de pointes complicating treatment with terfenadine. *BMJ* 1991; **302:** 1469.
2. Davies AJ, *et al.* Cardiotoxic effect with convulsions in terfenadine overdose. *BMJ* 1989; **298:** 325.
3. CSM. Ventricular arrhythmias due to terfenadine and astemizole. *Current Problems 35* 1992. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024453&RevisionSelectionMethod=LatestReleased (accessed 14/07/08)
4. CSM/MCA. Drug-induced prolongation of the QT interval. *Current Problems* 1996; **22:** 2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024458&RevisionSelectionMethod=LatestReleased (accessed 14/07/08)
5. Woolsey RL, *et al.* Mechanism of the cardiotoxic actions of terfenadine. *JAMA* 1993; **269:** 1532–6.
6. Rankin AC. Non-sedating antihistamines and cardiac arrhythmia. *Lancet* 1997; **350:** 1115–16.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving terfenadine, and the American Academy of Pediatrics[1] considers that it is therefore usually compatible with breast feeding.

In a study[2] of 4 healthy lactating women given 60 mg of terfenadine every 12 hours for 48 hours, terfenadine was undetected in breast milk; its active metabolite, fexofenadine, was excreted in limited amounts.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] *Correction. ibid.;* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/04/04)
2. Lucas BD, *et al.* Terfenadine pharmacokinetics in breast milk in lactating women. *Clin Pharmacol Ther* 1995; **57:** 398–402.

Effects on the liver. Three episodes of acute hepatitis with jaundice occurred in a patient taking terfenadine intermittently over a period of 17 months.[1] Liver function tests returned to normal after the drug was stopped. Two further cases[2] of cholestatic hepatitis associated with terfenadine have been reported. Again, liver function tests returned to normal after drug withdrawal. A study[3] by the Boston Collaborative Drug Surveillance Program of 210 683 patients who had received prescriptions for terfenadine concluded that the use of terfenadine was rarely associated with important idiopathic liver disease. The investigators found only 3 cases of acute liver disease where a causal connection to terfenadine could not be ruled out; all these patients had also received a hepatotoxic drug and had made a full recovery.

1. Larrey D, *et al.* Terfenadine and hepatitis. *Ann Intern Med* 1985; **103:** 634.
2. Sahai A, Villeneuve JP. Terfenadine-induced cholestatic hepatitis. *Lancet* 1996; **348:** 552–3.
3. Myers MW, Jick H. Terfenadine and risk of acute liver disease. *Br J Clin Pharmacol* 1998; **46:** 251–3.

Effects on the nervous system. Non-sedating effects on the CNS have been reported after a single dose of terfenadine;[1] these have included anxiety, palpitations, and insomnia. The UK manufacturers commented that clinical studies suggest that the incidence of such effects is similar to that seen after placebo.[2]

Workers who had described a generalised tonic-clonic seizure in a patient taking terfenadine[3] later reported that the patient had subsequently had a second unprovoked seizure[4] and now considered that terfenadine may not have been the cause of his original seizure. Convulsions have been reported after overdosage with terfenadine (see under Arrhythmias, p. 640.3).

The sedative effects of the older antihistamines and the lower incidence of such effects with the non-sedating antihistamines including terfenadine are discussed under Sedation on p. 613.2.

1. Napke E, Biron P. Nervous reactions after first dose of terfenadine in adults. *Lancet* 1989; **ii:** 615–16.
2. Masheter HC. Nervous reactions to terfenadine. *Lancet* 1989; **ii:** 1034.
3. Tidswell P, d'Assis-Fonseca A. Generalised seizure due to terfenadine. *BMJ* 1993; **307:** 241.
4. Tidswell P, d'Assis-Fonseca A. Generalised seizure due to terfenadine. *BMJ* 1993; **307:** 736.

Hypersensitivity. Terfenadine use was associated with 108 reports of skin reactions, including rashes, urticaria, angioedema, photosensitivity reactions and peeling of the skin of the hands or feet.[1]

1. Stricker BHCh, *et al.* Skin reactions to terfenadine. *BMJ* 1986; **293:** 536.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies terfenadine as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Interactions

As for the non-sedating antihistamines in general, p. 614.3.

Terfenadine should not be given with drugs that inhibit its hepatic metabolism because of the increased risk of serious ventricular arrhythmias. These drugs include the triazole and imidazole antifungals such as itraconazole and ketoconazole, the macrolide antibacterials including clarithromycin, erythromycin, josamycin, and troleandomycin, the streptogramin antibacterial quinupristin/dalfopristin, the serotonin reuptake inhibitors citalopram, fluoxetine, fluvoxamine, nefazodone, and paroxetine, the HIV-protease inhibitors, the NNRTIs delavirdine and efavirenz, and zileuton. The metabolism of terfenadine may also be inhibited by grapefruit juice and use together should be avoided.

Use with other potentially arrhythmogenic drugs (including those that prolong the QT interval) such as antiarrhythmics, tricyclic antidepressants, the antimalarials halofantrine and quinine, antipsychotics, cisapride, probucol, pentamidine isetionate, and the beta blocker sotalol should be avoided as should diuretics that cause electrolyte imbalances especially hypokalaemia. The use of terfenadine and astemizole together is not recommended.

General references.

1. Kivistö KT, *et al.* Inhibition of terfenadine metabolism: pharmacokinetic and pharmacodynamic consequences. *Clin Pharmacokinet* 1994; **27:** 1–5.

Antibacterials. Pharmacokinetic studies have shown that the macrolide antibacterials *erythromycin*[1] and *clarithromycin*[2] interfere with the metabolism of terfenadine leading to its accumulation. A high plasma-terfenadine concentration is associated with prolongation of the QT interval, and arrhythmias such as torsade de pointes have been reported in patients given terfenadine with erythromycin[3] or *troleandomycin*.[4]

1. Honig PK, *et al.* Changes in the pharmacokinetics and electrocardiographic pharmacodynamics of terfenadine with concomitant administration of erythromycin. *Clin Pharmacol Ther* 1992; **52:** 231–8.
2. Honig P, *et al.* Effect of erythromycin, clarithromycin and azithromycin on the pharmacokinetics of terfenadine. *Clin Pharmacol Ther* 1993; **53:** 161.
3. Biglin KE, *et al.* Drug-induced torsades de pointes: a possible interaction of terfenadine and erythromycin. *Ann Pharmacother* 1994; **28:** 282.
4. Fournier P, *et al.* Une nouvelle cause de torsades de pointes: association terfenadine et troleandomycine. *Ann Cardiol Angeiol (Paris)* 1993; **42:** 249–52.

Antidepressants. Cardiac abnormalities have been reported in 2 patients taking *fluoxetine* with terfenadine.[1,2] Similarly, the use of *nefazodone* with terfenadine has resulted in prolongation of the QT interval.[3]

1. Swinn MP. Potential terfenadine-fluoxetine interaction. *Ann Pharmacother* 1993; **27:** 1404–5.
2. Marchiando RJ, Cook MD. Probable terfenadine-fluoxetine-associated cardiac toxicity. *Ann Pharmacother* 1995; **29:** 937–8.
3. Abernethy DR, *et al.* Loratadine and terfenadine interaction with nefazodone: both antihistamines are associated with QTc prolongation. *Clin Pharmacol Ther* 2001; **69:** 96–103.

Antiepileptics. For reference to an interaction between terfenadine and *carbamazepine*, see p. 517.2.

Antifungals. Pharmacokinetic studies have shown that *itraconazole*[1] and *ketoconazole*[2] interfere with the metabolism of terfenadine leading to its accumulation. A high plasma-terfenadine concentration is associated with prolongation of the QT interval, and arrhythmias such as torsade de pointes have been reported in patients given terfenadine with ketoconazole[3] or itraconazole.[1,4] While there has been a pharmacokinetic study[5] that suggested that the interaction between terfenadine and *fluconazole* might not be clinically significant, as the mechanism of the interaction appeared to involve the metabolite of terfenadine and did not lead to accumulation of the cardiotoxic parent compound, this may not always be the case. Studies in a small group of patients who had abnormal patterns of terfenadine metabolism found increases in terfenadine concentrations associated with ECG abnormalities when terfenadine was given with high doses of fluconazole.[6]

1. Pohjola-Sintonen S, *et al.* Itraconazole prevents terfenadine metabolism and increases risk of torsades de pointes ventricular tachycardia. *Eur J Clin Pharmacol* 1993; **45:** 191–3.
2. Honig PK, *et al.* Terfenadine-ketoconazole interaction: pharmacokinetic and electrocardiographic consequences. *JAMA* 1993; **269:** 1513–18.
3. Monahan BP, *et al.* Torsades de pointes occurring in association with terfenadine use. *JAMA* 1990; **264:** 2788–90.
4. Crane JK, *et al.* Syncope and cardiac arrhythmia due to an interaction between itraconazole and terfenadine. *Am J Med* 1993; **95:** 445–6.
5. Honig PK, *et al.* The effect of fluconazole on the steady-state pharmacokinetics and electrocardiographic pharmacodynamics of terfenadine in humans. *Clin Pharmacol Ther* 1993; **53:** 630–6.
6. Cantilena LR, *et al.* Fluconazole alters terfenadine pharmacokinetics and electrocardiographic pharmacodynamics. *Clin Pharmacol Ther* 1995; **57:** 185.

Calcium-channel blockers. For reference to an interaction between terfenadine and *nifedipine*, see p. 1453.3.

Grapefruit juice. A study[1] in healthy subjects given terfenadine and grapefruit juice for 7 days found raised plasma-terfenadine concentrations and prolongation of the QT interval. These effects were less pronounced when terfenadine was given 2 hours before grapefruit juice, but were nevertheless quantifiable in some subjects. In another study QT interval changes were not found in healthy subjects given single doses of terfenadine and grapefruit juice.[2] However, the highly variable pharmacokinetics between individuals led the authors to conclude that prolongation of the QT interval was possible following single doses. The probable mechanism of the interaction is inhibition of the metabolism of terfenadine by the cytochrome P450 isoenzyme CYP3A4.

1. Benton RE, *et al.* Grapefruit juice alters terfenadine pharmacokinetics, resulting in prolongation of repolarization on the electrocardiogram. *Clin Pharmacol Ther* 1996; **59:** 383–8.
2. Rau SE, *et al.* Grapefruit juice-terfenadine single-dose interaction: magnitude, mechanism, and relevance. *Clin Pharmacol Ther* 1997; **61:** 401–9.

Pharmacokinetics

Terfenadine is rapidly absorbed from the gastrointestinal tract and peak plasma concentrations occur within about 2 hours. It is a prodrug and undergoes extensive first-pass metabolism in the liver to its active metabolite the carboxylic acid derivative fexofenadine (p. 629.1). The other main metabolite is an inactive piperidine-carbinol derivative. About 97% of terfenadine is bound to plasma proteins; fexofenadine is reported to be less extensively bound. Terfenadine does not appear to cross the blood-brain barrier to a significant extent; limited amounts of fexofenadine, but not the parent drug, have been detected in breast milk. An elimination half-life of 16 to 23 hours has been reported for terfenadine. The metabolites, and traces of unchanged drug, are excreted in the urine and the faeces.

References.

1. Eller MG, *et al.* Pharmacokinetics of terfenadine in healthy elderly subjects. *J Clin Pharmacol* 1992; **32:** 267–71.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Min An Fen (敏安芬); ***Gr.***: Sminosan; Syneptine; Terfedin; Tricosal; Voromin; ***Hong Kong***: Histafen†; Tamagon†; ***India***: Daylert; Histafen; Trexyl; ***Indon.***: Alpenaso†; Histastop†; Terfin; ***S.Afr.***: Fendin†; ***Spain***: Ternadin; ***Turk.***: Teradin†.

Multi-ingredient Preparations. ***China***: Livzon Ganle (丽珠感乐); ***India***: Tusant; ***Indon.***: Rhinofed.

Pharmacopoeial Preparations
BP 2014: Terfenadine Oral Suspension; Terfenadine Tablets.

Thenyldiamine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de tenildiamina; Tenildiamina, hidrocloruro de; Thényldiamine, Chlorhydrate de; Thenyldiamini Hydrochloridum; Thenyldiaminium Chloride; Тенилдиамина Гидрохлорид.

NN-Dimethyl-*N'*-(2-pyridyl)-*N'*-(3-thenyl)ethylenediamine hydrochloride.

$C_{14}H_{19}N_3S,HCl$=297.8

CAS — 91-79-2 (thenyldiamine); 958-93-0 (thenyldiamine hydrochloride).

UNII — 7ZQC1892H9.

Profile

Thenyldiamine hydrochloride, an ethylenediamine derivative, is an antihistamine (p. 610.1). It is given orally as an ingredient of compound preparations for the symptomatic treatment of coughs and the common cold.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ital.***: NTR.

Thiethylperazine *(BAN, USAN, rINN)*

Thiéthylpérazine; Thiethylperazinum; Tietilperazina; Tietylperazin; Tietyyliperatsiini; Тиэтилперазин.

2-Ethylthio-10-[3-(4-methylpiperazin-1-yl)-propyl]phenothiazine.

$C_{22}H_{29}N_3S_2$=399.6

CAS — 1420-55-9.

ATC — R06AD03.

ATC Vet — QR06AD03.

UNII — 8ETK1WAF6R.

Thiethylperazine Malate *(BANM, rINNM)*

Malato de tietilperazina; Thiéthylpérazine, Malate de; Thiethylperazini Malas; Tietilperazina, malato de; Тиэтилперазина Малат.

$C_{22}H_{29}N_3S_2.2C_4H_6O_5$=667.8

CAS — 52239-63-1.

ATC — R06AD03.

ATC Vet — QR06AD03.
UNII — HP46XK89XB.

Thiethylperazine Maleate *(BANM, USAN, rINNM)*

GS-95; Maleato de tietilperazina; NSC-130044; Thiethylperazine Dimaleate; Thiéthylpérazine, Maléate de; Thiethylperazini Maleas; Tietilperazina, maleato de; Тиэтилперазина Малеат.

$C_{22}H_{29}N_3S_2.2C_4H_4O_4$=631.8

CAS — 1179-69-7.
ATC — R06AD03.
ATC Vet — QR06AD03.
UNII — RUK64CF26E.

Pharmacopoeias. In *Swiss* and *US*.

USP 36: (Thiethylperazine Maleate). A yellowish granular powder, odourless or has not more than a slight odour. Soluble 1 in 1700 of water and 1 in 530 of alcohol; practically insoluble in chloroform and in ether; slightly soluble in methyl alcohol. pH of a 0.1% solution in water is between 2.8 and 3.8. Store in airtight containers. Protect from light.

Incompatibility. Incompatibility has been reported between injections of thiethylperazine maleate and nalbuphine hydrochloride.[1]

1. Jump WG, *et al.* Compatibility of nalbuphine hydrochloride with other preoperative medications. *Am J Hosp Pharm* 1982; 39: 841–3.

Profile

Thiethylperazine, a phenothiazine derivative with a piperazine side-chain, is a sedating antihistamine (p. 610.1) used as an antiemetic for the control of nausea and vomiting (p. 611.3) associated with surgical procedures and cancer therapy. It has also been used for the management of vertigo (p. 612.3) and motion sickness although there is some doubt over its efficacy for these indications.

Thiethylperazine is given as the maleate or malate and doses are expressed in terms of the appropriate salt. Thiethylperazine maleate 10 mg is equivalent to about 10.53 mg of thiethylperazine malate.

Thiethylperazine *maleate* is given in usual oral doses of 6.5 mg up to three times daily; the maleate has also been given rectally. Where oral dosage is impractical similar doses of the *malate* may be given by deep intramuscular injection.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies thiethylperazine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Torecan; ***Cz.***: Torecan; ***Hung.***: Torecan; ***Ital.***: Torecan; ***Mex.***: Torecan; ***Pol.***: Torecan; ***Rus.***: Torecan (Торекан); ***Spain***: Torecan; ***Swed.***: Torecan†; ***Switz.***: Torecan.

Pharmacopoeial Preparations
USP 36: Thiethylperazine Maleate Suppositories; Thiethylperazine Maleate Tablets.

Thonzylamine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de tonzilamina; Thonzylamine, Chlorhydrate de; Thonzylamini Hydrochloridum; Tonzilamina, hidrocloruro de; Тонзиламина Гидрохлорид.

N-p-Anisyl-*N*′*N*′-dimethyl-*N*-(pyrimidin-2-yl)ethylenediamine hydrochloride.

$C_{16}H_{22}N_4O.HCl$=322.8

CAS — 91-85-0 (thonzylamine); 63-56-9 (thonzylamine hydrochloride).
ATC — D04AA01; R01AC06; R06AC06.
ATC Vet — QD04AA01; QR01AC06; QR06AC06.
UNII — 6K9YKD48Y4.

Profile

Thonzylamine hydrochloride, an ethylenediamine derivative, is an antihistamine (p. 610.1) that has been used for the symptomatic relief of hypersensitivity disorders. It has been given orally and applied topically as an ointment, but as with other antihistamines, there is a risk of skin sensitisation with the ointment. It is also used in nasal preparations for congestion, and in eye drops with a vasoconstrictor such as naphazoline nitrate for allergic conjunctivitis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Tonamil.

Multi-ingredient Preparations. ***Ital.***: Ascotodin; Collirio Alfa Antistaminico; Imidazyl Antistaminico; Iristamina; Narlisim; Pupilla Antistaminico; ***Port.***: Narizima; ***USA***: NasOpen PE; Vanacof APE.

Trimethobenzamide Hydrochloride *(rINNM)*

Hidrocloruro de trimetobenzamida; Triméthobenzamide, Chlorhydrate de; Trimethobenzamidi Hydrochloridum; Trimetobenzamid Hidroklorür; Trimetobenzamida, hidrocloruro de; Триметобензамида Гидрохлорид.

N-[4-(2-Dimethylaminoethoxy)benzyl]-3,4,5-trimethoxybenzamide hydrochloride.

$C_{21}H_{28}N_2O_5.HCl$=424.9

CAS — 138-56-7 (trimethobenzamide); 554-92-7 (trimethobenzamide hydrochloride).
UNII — WDQSP1SX7Q.

Pharmacopoeias. In *US*.

USP 36: (Trimethobenzamide Hydrochloride). A white crystalline powder having a slight phenolic odour. Soluble 1 in 2 of water, 1 in 59 of alcohol, 1 in 67 of chloroform, and 1 in 720 of ether; insoluble in benzene.

Uses and Administration

Trimethobenzamide hydrochloride, a monoethanolamine derivative, is a sedating antihistamine used as an antiemetic in the control of nausea and vomiting (p. 611.3) including postoperative nausea and vomiting.

The usual dose is 300 mg orally or 200 mg by deep intramuscular injection three or four times daily. In 2007, the FDA ordered a stop to the marketing and distribution of rectal trimethobenzamide products, because they lack evidence of efficacy.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively. Dose adjustment should be considered for patients with any renal impairment.

Pain at the site of intramuscular injection and local irritation after rectal use have been noted.

Pregnancy. For discussion of the use of antihistamines in pregnancy, including some evidence of an excess number of congenital abnormalities in infants born to mothers exposed to trimethobenzamide, see p. 614.2.

Interactions

As for the sedating antihistamines in general, p. 614.3.

Pharmacokinetics

Maximum plasma concentrations may occur after about 30 minutes of giving trimethobenzamide intramuscularly, and about 45 minutes after oral use. Relative bioavailability between an oral dose of 300 mg and an intramuscular dose of 200 mg is believed to be similar. Between 30 to 50% of a single dose is excreted unchanged in the urine within 48 to 72 hours. The mean elimination half-life is about 7 to 9 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Turk.***: Ametik; Anti-Vomit; Emedur; Vomet; Vomitin; ***USA***: Ticon; Tigan.

Multi-ingredient Preparations. ***Turk.***: Emedur; ***USA***: Emergent-Ez.

Pharmacopoeial Preparations
USP 36: Trimethobenzamide Hydrochloride Capsules; Trimethobenzamide Hydrochloride Injection.

Tripelennamine Citrate *(BANM, rINNM)*

Citrato de tripelenamina; Tripelenamina, citrato de; Tripélennamine, Citrate de; Tripelennamini Citras; Tripelennaminium Citrate; Трипеленнамина Цитрат.

N-Benzyl-*N*′*N*′-dimethyl-*N*-(2-pyridyl)ethylenediamine dihydrogen citrate.

$C_{16}H_{21}N_3.C_6H_8O_7$=447.5

CAS — 91-81-6 (tripelennamine); 6138-56-3 (tripelennamine citrate).
ATC — D04AA04; R06AC04.
ATC Vet — QD04AA04; QR06AC04.
UNII — 30OC46A3J9.

Tripelennamine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de tripelenamina; Tripelenamina, hidrocloruro de; Tripélennamine, Chlorhydrate de; Tripelennamini Hydrochloridum; Tripelennaminium Chloride; Трипеленнамина Гидрохлорид.

$C_{16}H_{21}N_3.HCl$=291.8

CAS — 154-69-8.
ATC — D04AA04; R06AC04.
ATC Vet — QD04AA04; QR06AC04.
UNII — FWV8GJ56ZN.

Pharmacopoeias. In *US*.

USP 36: (Tripelennamine Hydrochloride). A white crystalline powder. It slowly darkens on exposure to light. Soluble 1 in 1 of water, 1 in 6 of alcohol and of chloroform, and 1 in 350 of acetone; insoluble in ether, in ethyl acetate, and in benzene. Its solutions are practically neutral to litmus. Protect from light.

Profile

Tripelennamine, an ethylenediamine derivative, is a sedating antihistamine (p. 610.1) with antimuscarinic and moderate sedative properties. It has been used for the symptomatic relief of hypersensitivity reactions. It may also be used in compound preparations for the symptomatic treatment of coughs and the common cold (p. 611.2).

Tripelennamine has been given orally as the citrate or the hydrochloride. Tripelennamine hydrochloride has also been applied topically to the skin, although, as with other antihistamines, there is a risk of sensitisation.

Abuse. References to the intravenous abuse of tripelennamine alone[1] or with pentazocine in the combination known as T's and blues.[2-4]

1. Addington J, el-Guebaly N. Intravenous tripelennamine abuse in schizophrenia. *Can J Psychiatry* 1996; 41: 63.
2. Showalter CV. T's and blues: abuse of pentazocine and tripelennamine. *JAMA* 1980; 244: 1224–5.
3. von Almen WF, Miller JM. "Ts and Blues" in pregnancy. *J Reprod Med* 1986; 31: 236–9.
4. McGwier BW, *et al.* Acute myocardial infarction associated with intravenous injection of pentazocine and tripelennamine. *Chest* 1992; 101: 1730–2.

Overdosage. A severe toxic reaction, including agitation, hallucinations, and myoclonic jerks occurred in an 8-year-old child who was sprayed over the trunk and extremities with tripelennamine hydrochloride 2.1375 g in the treatment of severe poison ivy poisoning.[1] It was likely that inhalation of the fine mist of the aerosol spray contributed to the reaction but in this patient the initial reaction began 3 hours after exposure suggesting that percutaneous absorption through the multiple skin lesions probably contributed significantly. The original reaction was inadvertently prolonged by subsequent treatment with diphenhydramine hydrochloride and promethazine hydrochloride.

1. Schipior PG. An unusual case of antihistamine intoxication. *J Pediatr* 1967; 71: 589–91.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Azaron; ***Austria***: Azaron ***Canad.***: Vagin-X; ***Fin.***: Etono; ***Ger.***: Azaron; ***Indon.***: Tripel ***Neth.***: Azaron; ***Spain***: Azaron.

Multi-ingredient Preparations. ***Arg.***: Quemicetina Nasal Compuesta; ***India***: Bradex-Vioform; ***Pol.***: Viosept†; ***Ukr.***: Viosep (Виосепт)†; ***USA***: Di-Delamine.

Pharmacopoeial Preparations
USP 36: Tripelennamine Hydrochloride Tablets.

Triprolidine Hydrochloride

(BANM, rINNM)

Hidrocloruro de triprolidina; Triprolidina, hidrocloruro de; Triprolidine, Chlorhydrate de; Triprolidini Hydrochloridum; Трипролидина Гидрохлорид.

(*E*)-2-[3-(Pyrrolidin-1-yl)-1-*p*-tolylprop-1-enyl]pyridine hydrochloride monohydrate.

$C_{19}H_{22}N_2.HCl.H_2O$=332.9

CAS — 486-12-4 (triprolidine); 550-70-9 (anhydrous triprolidine hydrochloride); 6138-79-0 (triprolidine hydrochloride monohydrate).
ATC — R06AX07.
ATC Vet — QR06AX07.
UNII — YAN7R5L890.

Pharmacopoeias. In *Br.* and *US*.

BP 2014: (Triprolidine Hydrochloride). A white, odourless or almost odourless, crystalline powder. Freely soluble in water and in alcohol; very soluble in chloroform; practically insoluble in ether.

USP 36: (Triprolidine Hydrochloride). A white crystalline powder, having no more than a slight, but unpleasant, odour. Soluble 1 in 2.1 of water, 1 in 1.8 of alcohol, 1 in 1 of chloroform, and 1 in 2000 of ether. Its solutions are alkaline to litmus. Store in airtight containers. Protect from light.

Uses and Administration

Triprolidine hydrochloride, an alkylamine derivative, is a sedating antihistamine with antimuscarinic and mild sedative effects. It is used for the symptomatic relief of allergic conditions including urticaria (p. 612.3) and rhinitis (p. 612.1), and in pruritic skin disorders (p. 612.1). It is often used in compound preparations with pseudoephedrine hydrochloride for rhinitis and in other preparations for the symptomatic treatment of coughs and the common cold (p. 611.2).

It is given orally, the usual dose being 2.5 mg up to four times daily.

Triprolidine tannate has been used similarly.

Triprolidine hydrochloride has also been applied topically to the skin although, as with other antihistamines, there is a risk of sensitisation.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p. 613.1 and p. 613.3, respectively. UK product information for acrivastine has warned that acrivastine should not be used in patients hypersensitive to triprolidine.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving triprolidine, and the American Academy of Pediatrics[1] considers that it is therefore usually compatible with breast feeding.

In a study[2] in 3 women of the excretion of triprolidine and pseudoephedrine, taken orally in a combined preparation, triprolidine was found to reach concentrations in breast milk similar to those found in plasma in one subject, and slightly lower than in plasma in the others. It was calculated that 0.06 to 0.2% of the ingested dose was distributed into breast milk over 24 hours. Concentrations of pseudoephedrine in breast milk exceeded those in plasma in all 3 women.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *Ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 30/01/04)
2. Findlay JWA, *et al.* Pseudoephedrine and triprolidine in plasma and breast milk of nursing mothers. *Br J Clin Pharmacol* 1984; 18: 901–6.

Interactions

As for the sedating antihistamines in general, p. 614.3.

Pharmacokinetics

After absorption from the gastrointestinal tract, triprolidine is metabolised; a carboxylated derivative accounts for about half the dose excreted in the urine. Reported half-lives vary from 3 to 5 hours or more. Triprolidine is distributed into breast milk.

General references.

1. Paton DM, Webster DR. Clinical pharmacokinetics of H_1-receptor antagonists (the antihistamines). *Clin Pharmacokinet* 1985; 10: 477–97.
2. Miles MV, *et al.* Pharmacokinetics of oral and transdermal triprolidine. *J Clin Pharmacol* 1990; 30: 572–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Kemian (刻免); *UAE*: Sedofan T; *USA*: Vanahist PD; Zymine†.

Multi-ingredient Preparations. *Arg.*: Actifedrin; *Austral.*: Actifed CC Junior†; Actifed†; Codral Original Day & Night Cold & Flu; Sudafed Sinus Day & Night Relief†; Sudafed Sinus Pain & Allergy Relief†; *Belg.*: Actifed†; *Braz.*: Actifedrin; Trifedrin; *Canad.*: Actifed Plus; Actifed; CoActifed; CoActifed; Covan; ratio-Cotridin Expectorant; ratio-Cotridin; *Chile*: Actifedrin Antitusivo; Actifedrin; *China*: Feidile (菲迪乐); Photifed-M (澳特斯); Xin Tai Luo Qi (新泰洛其); *Fr.*: Actifed; *Ger.*: Rhinopront Kombi; *Gr.*: Actifedon; *Hong Kong*: Actifed Compound; Antifort; Decofed†; Fedac Compound; Fedac; Prolifed; Syncofit Compound†; Syncofit†; Uni-Fedra Compound; Uni-Fedra DM†; Uni-Fedra†; Vidalidine†; *India*: Actifed DM; Actifed Plus; Actifed; Actiflu Plus; Actiflu; Ascoril-D; Brodil-D; Corex-T; Deletus D; Deletus; Isofed; Megatuss-D; Nocold Plus; Oox-DM; Teguphen; *Indon.*: Actifed Plus Cough Suppressant; Actifed Plus Expectorant; Actifed; Actigesic†; Alerfed; Crofed; Eflin; Flutrop; Gifed; Grafed; Lapifed DM; Lapifed Expectorant; Lapifed; Librofed; Nasafed Plus†; Nasafed†; Nichofed; Nostel; Protifed†; Quantidex; Stop Cold; Tremenza; Trifed; Trifedrin Plus; Trifedrin; Valved DM; Valved; Zentra; *Irl.*: Actifed; Benylin Childrens Cough and Cold; Benylin Dual Action Dry; *Israel*: Cold-Care; Histafed Comp; Histafed Expectorant; Histafed; Histamine-Care; *Ital.*: Actifed Composto; Actifed; Actigrip; *Malaysia*: Actifed DM; Actifed Expectorant; Actifed; Actihist Expectorant†; Actihist-Co†; Actihist†; Actimin; Axcel Tridine; Beatafed; Cough-EN; Deco Expectorant; Deco Syrup; Decol†; Fedac; Pabron Cold & Flu†; Pabron Cough & Sinus; Pabron Cough-D; Peace; Pseudoephedrine T; Rhynacol†; *Mex.*: Actifed DM†; Actifed†; Giparlix; *NZ*: Actifed†; Codral Daytime/Nightime†; Sudafed Day/Nightime Relief†; Sudafed Sinus Pain & Allergy Relief†; *Pol.*: Acatar Acti-Tabs; Actifed; Actitrin; *Port.*: Actifed; Dinaxil; *Rus.*: Fastoric Plus (Фасторик Плюс); *S. Afr.*: Actifed Cold & Fever†; Actifed Dry Cough Regular; Actifed Dry Cough Sugar Free†; Actifed; Acuflu P; Acugest Co†; Acugest DM†; Acugest Expect†; Acugest†; Acutussive†; Adco-Flupain; Adco-Muco Expect†; Adco-Neofed; Adco-Tussend; Betafed; Coryx†; Fludactil Co†; Flusin Sinus; Linctifed; Medifed; Merck-Cough Linctus†; Merck-Expectorant†; Merck-Fed; Sinuclear; Tixylix Flu†; Trifen; *Singapore*: Actifed Compound; Actifed DM; Actifed Expectorant; Actifed; Actihist; Afidil; Beactafed Co; Beactafed; Cough-EN; Decondine; Fedac Compound; Fedac DM; Fedac; Peacef; SP-Rhinodyl; Syncofit; Trisedyl; *Spain*: Cinfatos Descongestivo; Iniston Antitusivo y Descongestivo; Iniston Descongestivo†; Iniston Expectorante y Descongestivo; *Thai.*: A-fed; Actifed DM†; Actifed†; Actil; Actiplex†; Adulfed; Clinikold†; Cofed; Coldifed; Colidin; Colidine; Consudine; Decolfed; Fafed; Feddic; Hiscifed; KB Pophedin; Medifed; Medofed; Milafed; Nasifed; Nasolin; Nostrilet; Pabron SN; Pacifed; Policol; Policold; Polyfed†; Pondactil; Profed; Prophedin; Sidan†; Sinofed; Sinusaid; SP-Fed; Sudophrine; Sufed†; Suphedrine; Trifed; Triofed; Tripo; Triprodrine; Trisodine; Vefed; Vesprolid-HCl; *Turk.*: A-ferin; Actidem; Actifed; *UAE*: Sedofan DM; Sedofan; *UK*: Benylin Childrens Coughs & Colds; Multi-Action Actifed Chesty Coughs Expectorant; Multi-Action Actifed Dry Coughs; Multi-Action Actifed; Sudafed Plus; *Ukr.*: Actifed (Актифед)†; Actifed Expectorant (Актифед Экспекторант)†; Trifed (Трайфед)†; Trifed-Expectorant (Трайфед-Экспекторант)†; *USA*: Actagen-C Cough; Actagen; Actifed Cold & Allergy; Actifed Cold & Sinus; Actifed Plus; Actifed; Allercon; Allerfrim with Codeine†; Allerfrim†; Allerphed; Altafed; Aprodine with Codeine†; Aprodine†; Bayer Select Night Time Cold; Cenafed Plus†; Ed A-Hist PSE; Entre-Hist PSE; Genac; Hist-PSE; Poly Hist NC; Prohist CF; Silafed; Trifed-C Cough; Triofed; Tripohist D†; Triposed; Zymine HC†; Zymine-D.

Pharmacopoeial Preparations

BP 2014: Triprolidine Tablets;

USP 36: Triprolidine and Pseudoephedrine Hydrochlorides Syrup; Triprolidine and Pseudoephedrine Hydrochlorides Tablets; Triprolidine Hydrochloride Syrup; Triprolidine Hydrochloride Tablets.

Tritoqualine *(rINN)*

L-554; Tritocualina; Tritoqualinum; Тритоквалин.

7-Amino-4,5,6-triethoxy-3-(5,6,7,8-tetrahydro-4-methoxy-6-methyl-1,3-dioxolo[4,5-*g*]isoquinolin-5-yl)phthalide.

$C_{26}H_{32}N_2O_8$=500.5

CAS — 14504-73-5.

ATC — R06AX21.

ATC Vet — QR06AX21.

UNII — F4MWS166YH.

Profile

Tritoqualine is stated to inhibit histidine decarboxylase which catalyses the conversion of histidine to histamine. It has no action on histamine H_1-receptors and at therapeutic doses has no sedative or antimuscarinic effects. It has the uses of antihistamines (p. 610.2) and has been given orally in usual doses of 200 to 600 mg daily in 2 or 3 divided doses for the symptomatic relief of hypersensitivity reactions including allergic rhinitis and urticaria.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Hypostamine†.

Antimalarials

This chapter describes the main drugs used in the treatment and prophylaxis of malaria, one of the most serious protozoal infections in man. An estimated 40% of the world's population may be at risk of malaria; more than 500 million develop clinical infection, which is often very severe, and 1 to 3 million die each year. WHO produces guidelines for its strategic control and the management of malaria is under constant review. Measures to control malaria include *protection* from mosquito bites, *prophylaxis* with antimalarial drugs, and prompt *treatment* of any infection that develops. They also involve *vector control*; it is now recognised that for many countries vector eradication is an unrealistic aim.

Malaria

Malaria is a serious and potentially fatal disease, particularly in the case of falciparum malaria (see below) and especially in non-immune individuals (patients are classified as *non-immune* if they have recently or not previously been exposed to *Plasmodium* infection and as *semi-immune* or *immune* if they have a history of prolonged exposure). It is such a problem in many parts of the world that a global partnership named Roll Back Malaria[1] has been founded by WHO, United Nations Development Programme, UNICEF, and the World Bank with the aim of significantly reducing the world's malaria burden and virtually eliminating preventable deaths due to malaria by 2015. Prompt diagnosis and effective treatment of malaria are crucial.[2,3]

Malaria is traditionally caused by infection with any of 4 species of *Plasmodium* protozoa. *P. falciparum* causes falciparum (malignant tertian or subtertian) malaria, which is the most serious form and can be rapidly fatal in non-immune individuals if not treated promptly. The other 3 species cause what are often termed non-falciparum or 'benign' malarias: *P. vivax* causes vivax (benign tertian) malaria, which is widespread but rarely fatal, although symptoms during the primary attack can be severe; *P. malariae* causes quartan malaria, which is generally mild, but can cause fatal nephrosis; and *P. ovale* causes ovale (ovale tertian) malaria, which is the least common type of non-falciparum malaria and produces clinical features similar to *P. vivax*.[4] A fifth species that normally occurs in monkeys, *P. knowlesi*, has more recently emerged as a cause of malaria (termed monkey malaria) in travellers returning from forested areas in South-East Asia.[2] The organism closely resembles *P. malariae* on microscopy, but causes a wide spectrum of disease.[5] Although most cases are uncomplicated and respond promptly to treatment, about 10% of patients develop potentially fatal complications.[5]

The **life cycle** of *Plasmodium* is complex, comprising a sexual phase (sporogony) in the mosquito (vector) and an asexual phase (schizogony) in man (see Figure 1, below).

- Infection in man is usually caused by *sporozoites* from the bite of an infected female anopheline mosquito. It may rarely be acquired in other ways, congenitally via the placenta, or through blood transfusion, needlestick injuries, or organ transplantation.
- After an infected mosquito bite, sporozoites rapidly enter liver parenchymal cells, where they undergo *exoerythrocytic* or *pre-erythrocytic schizogony* forming *tissue schizonts* which mature and release thousands of *merozoites* into the blood on rupture of the cell.
- Merozoites enter erythrocytes where they transform into *trophozoites*. These produce *blood schizonts* which, as they mature, rupture and release merozoites into the circulation, which can infect other erythrocytes.
  This is termed the *erythrocytic cycle* and it is this periodic release of merozoites that is responsible for the characteristic periodicity of the fever in malaria.
- After several erythrocytic cycles, depending on the type of malaria, some erythrocytic forms develop into sexual *gametocytes*. Ingestion of infected blood containing gametocytes by a biting female mosquito allows the life cycle to be completed with the sexual phase in the mosquito.
- In *P. vivax* and *P. ovale* infections, some of the sporozoites entering the liver cells enter a latent tissue stage in the form of *hypnozoites*, which are responsible for recurrence of malaria caused by these organisms.

Recurrences resulting from the persistence of latent tissue forms are often referred to as *relapses* while renewed attacks caused by persistent residual erythrocytic forms are termed *recrudescences*. True relapses do not occur with falciparum or quartan malarias.

Clinical manifestations of malaria

The clinical symptoms of malaria are varied and non-specific; they usually include fever, fatigue, malaise, headache, myalgia, and sweating. Vomiting occurs in about 20% of patients, and mild diarrhoea in less than 5%. As the infection progresses, the spleen enlarges and the patient may develop anaemia and thrombocytopenia. The prognosis worsens with increasing parasite counts, more mature parasites, and more neutrophils containing malaria pigment.[6] Severe falciparum malaria may be complicated by acute renal failure, pulmonary oedema, and cerebral dysfunction. None of the clinical features of malaria are diagnostic and WHO recommends[3] that all patients should have a confirmed parasitological diagnosis, using either microscopy or the rapid diagnostic tests (based on parasite specific antigens or enzymes) that are now widely available, before antimalarial drug treatment is started. However, treatment should not be withheld if tests are unavailable and there is clinical suspicion of malaria. Any patient who has been in a malarial area in the previous two months should be considered to have malaria until proved otherwise.

Antimalarial drugs

Antimalarial drugs can be classified by the stage of the parasitic life cycle they affect. Thus:

Blood schizontocides act on the erythrocytic stages of the parasite that are directly responsible for the clinical symptoms of the disease. They can produce a clinical cure or suppression of infection by susceptible strains of all 4 species of malaria parasite but, since they have no effect on exoerythrocytic forms, do not produce a radical cure of ovale or vivax malarias.

Tissue schizontocides act on the exoerythrocytic stages of the parasite and are used for causal prophylaxis to prevent invasion of the blood cells, or as anti-relapse drugs to produce radical cures of vivax and ovale malarias.

Gametocytocides destroy the sexual forms of the parasite to interrupt transmission of the infection to the mosquito vector.

Sporontocides have no direct effect on the gametocytes in the human host but prevent sporogony in the mosquito.

Antimalarial drugs can also be classified by the chemical group to which they belong, which in turn determines the stage of the life cycle they affect. The principal antimalarial drugs, classified according to *drug group* and *activity*, are listed in Table 1 p. 645.

The quinolone antibacterials have been studied for their antimalarial activity. The 9-aminoacridines, such as mepacrine, are no longer used in the treatment of malaria.

The differing mechanisms of action of antimalarial drugs sometimes allow the use of combinations of antimalarials to improve efficacy. Such combinations are usually designed to potentiate each other, for instance by acting at sequential steps in the parasite's folic acid pathway (e.g. pyrimethamine with sulfadoxine or dapsone). Alternatively, a combination may be complementary, when the drugs involved act against different stages in the life cycle of the parasite (e.g. the use of chloroquine with primaquine to produce radical cure of *P. vivax* or *P. ovale* infections). The rationale behind the use of such combinations may be to enhance efficacy, particularly when drug resistance is a problem (see below), or it may be an attempt to delay the development of resistance to one or more of the drugs used.

Resistance.

Resistance to antimalarials has been documented for *P. falciparum*, *P. vivax*, and *P. malariae* and is seen with all classes of antimalarials, including artemisinin and its derivatives, for which resistance has been reported in some parts of South-East Asia (particularly the Cambodia-Thailand border).[3,7-9] Chloroquine resistance in *P. falciparum* now occurs virtually everywhere that *P. falciparum* malaria is transmitted, with the exception of certain parts of Central America and the Caribbean.[3,10] Resistance in *P. falciparum* to proguanil and pyrimethamine is apparent in many endemic areas. Cross-resistance between proguanil and pyrimethamine may also occur. Resistance in *P. falciparum* to the combination pyrimethamine-sulfadoxine (*Fansidar*) has spread rapidly in South-East Asia, but also occurs in other parts of the world including parts of South America, southern China, and Africa.[3,10] Mefloquine resistance is frequent in some areas of South-East Asia and migrant workers are thought to have spread mefloquine resistance to India and Bangladesh. Resistance has also occurred in the Amazon region of South America and, sporadically, in Africa, but generally, clinical mefloquine resistance outside South-East Asia is rare.[3,10] Resistance to quinine and halofantrine has also been noted. Cross-resistance between halofantrine and mefloquine may occur, as evidenced by reduced responses to halofantrine in some patients who have had treatment failure with mefloquine.[10] The emergence of multidrug resistance in *P. falciparum* makes the selection of effective prophylaxis and treatment difficult.

Multidrug resistance is defined as resistance to three or more antimalarial compounds from different chemical classes, of which two of the classes are the 4-aminoquinolines (e.g. chloroquine) and diaminopyrimidines (e.g. pyrimethamine-sulfadoxine (*Fansidar*)). Multidrug resistance occurs in South-East Asia (particularly along the borders of Thailand with Burma and Cambodia) and in the Amazon basin.[2,3]

P. vivax has developed resistance rapidly to pyrimethamine-sulfadoxine (*Fansidar*) in many areas and resistance to chloroquine and primaquine has also been reported in several parts of the world.[3,10] However, it remains sensitive to chloroquine in South-East Asia, the Indian subcontinent, the Korean peninsula, the Middle East, north-east Africa, and most of South and Central America.[3] Resistance of *P. malariae* to chloroquine has been seen in Indonesia.[3]

A knowledge of the geographical distribution and degree of resistance is important for the selection of appropriate control measures and for the development of policies for the rational use of antimalarial drugs. Resistance can be prevented, or slowed considerably, by selecting effective drugs and drug combinations according to local patterns of resistance, combining antimalarials with different mechan-

Figure 1. Life cycle of the malaria parasite *Plasmodium*.

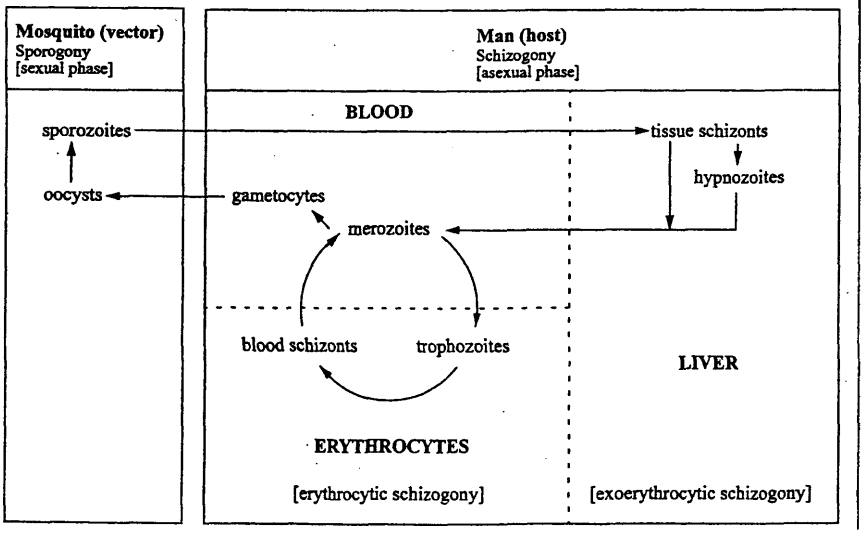

Table 1. Principal antimalarial drugs.

Antimalarial groups	Principal drugs	Activity
4-Aminoquinolines	Chloroquine Hydroxychloroquine Amodiaquine	Rapid-acting blood schizontocides. Some gametocytocidal activity.
8-Aminoquinolines	Primaquine Tafenoquine	Tissue schizontocide. Also gametocytocidal activity and some activity at other stages of the parasite's life-cycle.
Artemisinin and its derivatives (Sesquiterpene lactones)	Artemether Artenimol Artesunate	Blood schizontocide.
Biguanides	Proguanil Chlorproguanil	Tissue schizontocides and slow-acting blood schizontocides. Some sporontocidal activity. Dihydrofolate reductase inhibitors.
Diaminopyrimidines	Pyrimethamine	Tissue schizontocide and slow-acting blood schizontocide. Some sporontocidal activity. Dihydrofolate reductase inhibitor. Usually used with antimalarials that inhibit different stages of folate synthesis (sulfonamides or sulfones) to form synergistic combinations.
Dichlorobenzylidines	Lumefantrine	Blood schizontocide.
Hydroxynaphthoquinones	Atovaquone	Blood schizontocide. Usually given in combination with proguanil.
Lincosamides	Clindamycin	Blood schizontocides. Some tissue schizontocidal activity.
4-Methanolquinolines	Cinchona alkaloids Quinine Quinidine	Rapid-acting blood schizontocides. Some gametocytocidal activity.
	Mefloquine	Blood schizontocide.
Naphthyridines (Acridines)	Pyronaridine	Blood schizontocide. Usually given in combination with artesunate.
9-Phenanthrenemethanols	Halofantrine	Blood schizontocide.
4-Piperazinoquinolines	Piperaquine	Blood schizontocide. Usually given in combination with artenimol. Hydroxypiperaquine has also been studied.
Sulfonamides	Sulfadoxine Sulfametopyrazine	Blood schizontocides. Dihydropteroate and folate synthesis inhibitors. Usually given in combination with pyrimethamine.
Sulfones	Dapsone	Blood schizontocide. Folate synthesis inhibitor. Usually given in combination with pyrimethamine.
Tetracyclines	Doxycycline Tetracycline	Blood schizontocides. Some tissue schizontocidal activity.

isms of action, preventing indiscriminate and uncontrolled use, and ensuring very high cure rates through full compliance with the correct antimalarial dose regimens. Malaria control strategies also need to involve other measures such as vector control and health education.[3,11]

TREATMENT OF MALARIA

Malaria is treated with a *blood schizontocide*, selected with due regard to the prevalence of specific patterns of drug resistance in the area of infection. In the case of vivax and ovale malarias (see below) subsequent treatment with a *tissue schizontocide* is needed where it is considered appropriate to prevent relapse.

Antimalarials are generally given orally, although in order to obtain a rapid response in patients with severe or complicated falciparum malaria (see below) it may be necessary to start with parenteral therapy, the patient being transferred to oral therapy when feasible.[3] Where there are only minimal healthcare facilities and parenteral therapy is not possible or may be delayed, artemisinin or artesunate suppositories may be given.

Treatment of falciparum malaria.

In most parts of the world *P. falciparum* is now resistant to chloroquine and therefore, apart from the rare circumstance of exposure in one of the few remaining areas of chloroquine sensitivity, chloroquine is **not** suitable for treatment. Resistance to pyrimethamine-sulfadoxine (*Fansidar*) has also occurred in most countries where it was used in place of chloroquine.[4]

In **uncomplicated falciparum malaria** (symptomatic malaria without signs of severity or evidence of vital organ dysfunction) artemisinin-based combination drug therapy (ACT) is recommended by WHO[3] for treatment in all *malaria endemic areas*. Such combinations include either artemisinin or one of its derivatives paired with a long-acting partner drug; it is the level of resistance to the partner drug that determines the specific choice of ***first-line*** ACT used in a country or region. A course of at least 3 days is required for optimal efficacy. Recommended ACTs are:

- artemether-lumefantrine (*Riamet*)
- artesunate and amodiaquine (in areas where resistance to amodiaquine is low)
- artesunate and pyrimethamine-sulfadoxine (*Fansidar*) (in areas where pyrimethamine-sulfadoxine efficacy is still high)
- artesunate and mefloquine
- artenimol and piperaquine

Due to the continued spread of resistance to component drugs such as chloroquine, amodiaquine, and pyrimethamine-sulfadoxine (Fansidar), use of non-artemisinin-based combinations is no longer recommended by WHO for first-line treatment of malaria. Recommended ***second-line*** regimens used in the management of treatment failure (within 14 days of initial treatment) are:

- an alternative ACT known to be effective in the region
- artesunate with either tetracycline, doxycycline, or clindamycin (given for 7 days)
- quinine with either tetracycline, doxycycline, or clindamycin (given for 7 days)

In *non-endemic areas* the British Infection Society[12] and the Health Protection Agency Advisory Committee on Malaria Prevention in UK Travellers[13] recommend treating uncomplicated falciparum malaria or mixed infections with one of the following:

- oral quinine sulfate plus follow-on treatment with either doxycycline or clindamycin
- atovaquone-proguanil (*Malarone*)
- artemether-lumefantrine (*Riamet*)

In the USA, the CDC[14] recommends that uncomplicated falciparum malaria acquired in a chloroquine-sensitive area may be treated with oral chloroquine. Hydroxychloroquine may be used as an alternative. Malaria acquired in chloroquine-resistant areas is treated with one of the following:

- atovaquone-proguanil (*Malarone*)
- artemether-lumefantrine (*Coartem*)
- quinine sulfate plus doxycycline, tetracycline, or clindamycin (doxycycline or tetracycline are generally preferred as more data on efficacy are available)
- mefloquine (although when used in treatment doses it is associated with a higher rate of severe neuropsychiatric events and should only be given when one of the other 3 options cannot be used)

In **severe or complicated falciparum malaria** including cerebral malaria, parenteral treatment is required to produce adequate blood concentrations as quickly as possible.[3] Patients need to be closely monitored while undergoing parenteral therapy and treatment is changed to an oral antimalarial as soon as the patient's condition permits.

In *malaria endemic areas*, intravenous or intramuscular artesunate is the recommended first-line treatment, although quinine, given by slow, rate-controlled, intravenous infusion or intramuscular injection is an acceptable alternative if parenteral artesunate is not available; intravenous quinidine is considered more toxic than quinine and should only be used if no other effective parenteral drugs are available.

Where referral to an appropriate healthcare facility delays intravenous therapy, pre-referral treatment with intramuscular artesunate, artemether, or quinine, or rectal artesunate is recommended. Where referral is impossible, rectal treatment should be continued until the patient can tolerate oral medication.[3]

Parenteral therapy should continue for at least 24 hours; after this, when the patient can tolerate oral therapy, it is necessary to continue and complete treatment with an effective oral follow-on regimen, and suitable alternatives are:[3]

- artesunate with amodiaquine
- artemether with lumefantrine
- artenimol with piperaquine
- artesunate with sulfadoxine-pyrimethamine
- artesunate with either clindamycin or doxycycline
- quinine with either clindamycin or doxycycline

In *non-endemic areas* intravenous quinine plus either oral doxycycline or oral clindamycin are recommended by authorities in the UK;[12,13] intravenous artesunate may be available on a named patient basis for the most severe cases if they are not responding to quinine therapy, are possibly infected with quinine-resistant *falciparum*, or quinine is contra-indicated. In the USA,[15] intravenous quinidine gluconate is used, in place of intravenous quinine, with doxycycline, tetracycline, or clindamycin; if required, intravenous artesunate is also available on an emergency basis from the CDC.

Supportive therapy in patients with severe or complicated malaria needs to be directed at reducing hyperpyrexia, controlling convulsions, maintaining fluid balance, and correcting hypoglycaemia. Severe malaria is associated with rapid development of anaemia, and blood transfusions are recommended for children with a haemoglobin concentration of less than 5 g per 100 mL (haematocrit less than 15%) living in areas of high transmission or for those with a haemoglobin level of 7 g per 100 mL (haematocrit threshold of 20%) living in an area of low transmission.[3] Although the benefit of exchange transfusion has not been proven in comparative studies, UK and US guidelines recommend that it be considered for patients with a parasite density of more than 10% or if the patient has cerebral malaria, renal complications, or acute respiratory distress syndrome.[13,14] Prophylactic use of anticonvulsants is not recommended and the use of intravenous or intramuscular phenobarbital resulted in increased mortality due to respiratory arrest.[3] Since iron might be involved in the pathogenesis of cerebral malaria, the iron chelator desferrioxamine has been tried in addition to standard antimalarial therapy, but any benefit is yet to be established and WHO advises against its use.[3] Anecdotal reports of the value of corticosteroids in cerebral malaria have not been substantiated by controlled studies and they have no place in the management of this condition.[3,16] There is insufficient data to recommend the use of osmotic diuretics such as mannitol to reduce intracranial pressure in patients with cerebral malaria.[17] Other approaches such as the use of hyperimmune serum or monoclonal antibody to tumour necrosis factor have also been unsuccessful.

Treatment of non-falciparum or benign malarias.

Non-falciparum malarias, which are usually caused by *P. vivax* or, less commonly, by *P. ovale* or *P. malariae*, can be debilitating but are usually less severe than falciparum malaria. Treatment for *P. vivax* and *P. ovale* includes a *radical cure*: that is, cure of both the blood and liver stage infections in order to prevent relapse and recrudescence. Treatment of *P. malariae* does not include radical cure as no hypnozoites are formed during infection. Chloroquine is still generally the drug of choice (but chloroquine-resistant vivax infection has been reported from some areas—notably Papua New Guinea, Indonesia, Burma, and Vanuatu). Either chloroquine or hydroxychloroquine alone are adequate for *P. malariae* and *P. knowlesi* infections; for those caused by *P. vivax* or *P. ovale* a tissue schizontocide, usually primaquine, is added for radical cure.[3,12-14] In areas where ACTs are being used as first-line treatment for *P. falciparum* malaria, they may be given with primaquine for *P. vivax* infection as an alternative to chloroquine, with the exception of artesunate and pyrimethamine-sulfadoxine (*Fansidar*) as *P. vivax* resistance to pyrimethamine-sulfadoxine (*Fansidar*) is rapidly developing.[3] WHO[3] recommends that chloroquine-resistant *P. vivax* may be treated with an ACT (based on amodiaquine, mefloquine, or piperaquine) followed by primaquine for radical cure, while the CDC[14] recommends that patients not responding to chloroquine monotherapy or those with chloroquine-resistant infections should be given either quinine sulfate plus doxycycline (or tetracycline), or atovaquone-proguanil (*Malarone*), followed by primaquine; an alternative is mefloquine followed by primaquine. UK[13] guidelines recommend that resistant vivax malaria be treated with one of the 3 regimens used for the treatment of uncomplicated falciparum malaria (see above). Radical cure is inappropriate for patients living within an endemic area since re-infection is likely and therefore WHO[3] recommends that it should be limited to patients resident in areas where transmission is *very low* or *absent*, and it may be attempted in *epidemic situations*, but should be postponed

until the post-epidemic period when the risk of re-infection is lower. Other patients should simply be treated with a further course of chloroquine in the event of relapse or re-infection. Severe vivax malaria should be treated the same way as severe and complicated falciparum malaria (see above).[3]

Treatment of malaria during pregnancy. Malaria is especially dangerous during pregnancy and the seriousness of the disease usually outweighs any potential risk from treatment. Malaria infection during pregnancy can result in maternal anaemia, miscarriage, premature birth, congenital malaria infection, low birth-weight, and neonatal death.[2,14,18] Pregnant women living in areas where malaria transmission is low or unstable have little or no acquired immunity and are 2 to 3 times more likely to develop severe disease than non-pregnant women living in the same area;[3,14] however, those living in endemic areas where malaria transmission is high have often acquired partial immunity.

For pregnant women living in *endemic areas* quinine plus follow-on treatment with clindamycin (or quinine monotherapy where clindamycin is not available) may be given for first-line treatment of uncomplicated falciparum malaria in the first trimester. Data regarding the use of artemisinin derivatives in the first trimester are at present limited; however, artesunate with clindamycin can be given if first-line treatment fails, or is unavailable. In the second or third trimester an ACT (excluding artenimol with piperaquine) known to be effective in the region, or either artesunate or quinine may be given, plus follow-on treatment with clindamycin.[3] For the treatment of severe malaria in the first trimester quinine or artesunate may be used;[2,3] however, care should be taken that patients given quinine do not become hypoglycaemic. Artemisinin derivatives (particularly artesunate but alternatively, artemether) are the drugs of choice for treatment of severe malaria in the second and third trimesters.[2,3]

In *non-endemic areas* it is recommended that uncomplicated falciparum malaria in pregnancy be treated with quinine plus follow-on treatment with clindamycin.[12-14,19] Atovaquone-proguanil (*Malarone*), artemether-lumefantrine (Coartem), or mefloquine may be given as alternatives where first-line treatment is not tolerated or no other treatment options are available.[14,19] Although fetal abnormalities have been associated with the use of high doses of chloroquine, extensive clinical experience suggests it is safe; its value is limited, however, due to resistance. The CDC recommends oral chloroquine for pregnant women with malaria infections acquired in chloroquine-sensitive areas and with non-falciparum malaria; hydroxychloroquine may be used as an alternative. Chloroquine-resistant *P. vivax* should be treated with quinine.[14] Radical cure for patients with vivax or ovale malaria during pregnancy should be postponed until after delivery due to the risk of intravascular haemolysis in the mother and fetus;[14,18] weekly chloroquine should be given during the remaining weeks of pregnancy.[3,14] WHO recommends chloroquine or amodiaquine for pregnant women with *P. vivax* malaria.[2] For treatment of severe malaria, recommendations[19] are similar to those for women living in endemic areas (see above).

There may be difficulty if other drugs are required as opinion varies over their suitability. The tetracyclines are contra-indicated due to adverse effects on bone growth and teeth.

Treatment of splenomegaly syndrome. A few individuals infected with *Plasmodium* develop chronic hyperreactive malarial splenomegaly syndrome, an aberrant immunological response formerly known as the tropical splenomegaly syndrome. Traditionally, patients have first received a full course of antimalarial chemotherapy appropriate to the causative species followed by lengthy and probably lifelong chemoprophylaxis; however, a study in 312 patients suggested that pyrimethamine given with folinic acid for 30 days could produce a rapid reduction of splenomegaly which persisted for at least 3 months.[20]

PROPHYLAXIS OF MALARIA

Chemoprophylaxis of malaria may refer to absolute prevention of infection (*causal prophylaxis*) or to suppression of parasitaemia and its symptoms (*clinical prophylaxis*). Causal prophylaxis is provided by tissue schizontocides which destroy the exoerythrocytic forms of the parasite. Clinical prophylaxis is provided by blood schizontocides which, if continued until all exoerythrocytic forms of the parasite are destroyed, will ultimately produce a *suppressive cure*. In *P. falciparum* infections this would be achieved by about a month after the last infected bite, but relapses with *P. vivax* and *P. ovale* may still occur after standard clinical prophylactic regimens due to the presence of latent exoerythrocytic forms (hypnozoites).

The continuing increase in the prevalence of strains of *P. falciparum* resistant to chloroquine and other antimalarials, along with growing evidence of toxicity of some regimens, make recommendations for malaria prophylaxis increasingly difficult. Absolute protection cannot be guaranteed by any chemoprophylactic regimen currently in use and the importance and efficacy of methods of avoiding bites from infected mosquitoes, such as the use of *protective clothing, bed netting, insect repellents*, and *insecticides* must be stressed.[2,11] WHO recommends the following measures to protect against mosquito bites:

- application of an effective insect repellent to exposed skin, especially between dusk and dawn when mosquitoes commonly bite
- accommodation in buildings with screens over doors and windows
- use of mosquito nets at night, preferably impregnated with pyrethroid insecticides such as permethrin or deltamethrin
- and use of anti-mosquito sprays or insecticide dispensers, or mosquito coils in bedrooms at night

Studies have shown that insecticide-impregnated mosquito nets can reduce mortality substantially.[21] In addition to these measures, travellers should be advised, even if chemoprophylaxis has been taken regularly, to regard **any** fever *after the first week* and for *up to 1 year after possible exposure*, especially within the first 3 months, as being caused by malaria and to seek medical advice **immediately**. Some authorities advise that travellers should also have antimalarial drugs ready for emergency self-treatment (*standby treatment*) when prompt medical attention is not available (see below).

Chemoprophylaxis should be reserved for those at high **risk**, notably *non-immune visitors*; widespread chemoprophylaxis in *immune or semi-immune* populations is no longer recommended except for women who are *pregnant*. For the elderly, pregnant women, and children, careful consideration should be given as to whether travel to areas where falciparum malaria occurs is absolutely necessary. WHO specifically advises pregnant women not to travel to areas where transmission of malaria occurs and also advises against taking babies and young children to areas with risk of falciparum malaria.[2] Advice on chemoprophylaxis must be based on a knowledge of the occurrence and susceptibility of *Plasmodium* strains in specific geographical areas. Local variations due to altitude, seasonal variations in temperature and rainfall, the degree of urbanisation, and many other factors further complicate the issue. WHO collates information provided by national health administrations and regularly publishes this information to assist in advising international travellers on the current situation; similar information is provided at national level by local institutes specialising in tropical diseases. However, the situation is so complex that advice differs. Recommendations issued by various authorities are usually for short-term stays and expert advice should be sought if long-term cover is required.

It is generally recommended that chemoprophylaxis should start about 1 week (or longer for mefloquine) before exposure to malaria, or if this is not possible at the earliest opportunity up to 1 or 2 days before exposure; this is partly to ensure that the patient is able to tolerate the drug. Chemoprophylaxis should continue throughout exposure and for at least 4 weeks after leaving the malarious area, with the exception of atovaquone-proguanil (*Malarone*) which may be stopped one week after leaving.

Prophylactic regimens.

Depending upon the risk of infection and the availability and standard of local medical care, WHO[2] has made recommendations on chemoprophylaxis and/or standby treatment for non-immune travellers:

- in areas where there is limited risk of any malaria transmission no chemoprophylaxis is needed; measures to protect against mosquito bites should be used
- in areas where *P. falciparum* is *absent* or still *sensitive to chloroquine*, or there is a risk of *P. vivax*, travellers can take chloroquine for prophylaxis
- in areas with a risk of *P. vivax* and *P. falciparum*, as well as *emerging resistance* to chloroquine, travellers can take chloroquine plus proguanil
- in areas of high risk of *P. falciparum* and where there is *multidrug resistance*, or in areas of low to moderate risk of *P. falciparum* but high levels of multidrug resistance, mefloquine, doxycycline, or atovaquone-proguanil (*Malarone*) is recommended. These recommendations are subject to the local patterns of drug resistance

WHO[2] also recommends that for the small number of travellers who would be unable to obtain prompt medical attention when malaria is suspected (within 24 hours of the onset of symptoms), it may be necessary to provide for a course of self-treatment (**standby treatment**). Clear instructions must be given and persons taking standby medication must seek medical advice as soon as possible and resume any prophylaxis on completing the course. The basis upon which the choice of prophylaxis is made (as detailed above) in turn broadly determines the appropriate choice of standby treatment. Thus one of the following treatment regimens can be used:

- artemether-lumefantrine
- atovaquone-proguanil
- quinine plus doxycycline or clindamycin

In each instance, prophylaxis should be resumed 1 week after the *first* standby treatment dose, except for mefloquine prophylaxis which should be resumed at least 12 hours after the *last* treatment dose of quinine.

In the USA, recommendations for prophylaxis are provided by the CDC.[22] For chloroquine-sensitive malaria, recommended alternatives include chloroquine (or hydroxychloroquine) alone, atovaquone-proguanil (*Malarone*), doxycycline, or mefloquine. Primaquine may also be considered for short-term travellers to areas with mainly *P. vivax* transmission, providing they are not G6PD-deficient. For all areas with chloroquine-resistant malaria, 3 alternatives are available, mefloquine, doxycycline, or atovaquone-proguanil (*Malarone*). Atovaquone-proguanil (*Malarone*) is recommended for emergency standby treatment. Presumptive antirelapse therapy (or terminal prophylaxis) with primaquine is also advocated during the last 2 weeks of prophylaxis to prevent relapses due to *P. vivax* or *P. ovale* in persons returning from prolonged exposure in areas where relapsing malaria is endemic.

UK experts[23] have also published guidelines for the prophylaxis of malaria. In areas where *P. falciparum* is sensitive to chloroquine, travellers can either take chloroquine or proguanil for prophylaxis. In areas of little chloroquine resistance travellers can take chloroquine plus proguanil, while travellers to areas of high infection risk or where there is chloroquine resistance may take mefloquine, doxycycline, or atovaquone-proguanil (*Malarone*) as prophylaxis. Standby treatment with chloroquine is recommended for travellers to chloroquine-sensitive areas who do not take any prophylaxis or who take proguanil as prophylaxis. Atovaquone-proguanil (*Malarone*), artemether-lumefantrine (*Riamet*), or quinine plus doxycycline or clindamycin are recommended in areas with chloroquine resistance.

Malaria vaccines are under development and several are currently undergoing clinical evaluation (see p. 2398.1).

Prophylaxis during pregnancy. The choice of drugs for prophylaxis during pregnancy is limited and whenever possible, women who are pregnant or likely to become so should avoid travelling to malarious areas (see also above). In pregnant women who cannot avoid travelling to endemic areas, chloroquine may be given alone for prophylaxis in the few areas where *P. falciparum* is sensitive to chloroquine, or with proguanil in areas where resistance is emerging.[2] Folate supplements (folic acid 5 mg daily) need to be taken with proguanil. Mefloquine is normally avoided during the first trimester but may be given during the second and third trimesters and CDC[22] and UK[23,24] guidelines consider that it may be used *with caution* in the first trimester, especially in areas where there is a high risk of acquiring falciparum malaria. Doxycycline, atovaquone-proguanil (*Malarone*), or primaquine are contra-indicated in pregnant women by most experts; the *BNF* considers that atovaquone-proguanil (*Malarone*) should be avoided during pregnancy unless there is no suitable alternative. In non-pregnant women of child-bearing potential, pregnancy needs to be avoided for 3 months after completing mefloquine prophylaxis and for one week after doxycycline prophylaxis.

For pregnant women living in endemic areas, routine antimalarial drugs have been shown to reduce antenatal parasitaemia; during first and second pregnancies, severe antenatal anaemia and perinatal deaths may also be reduced and birth-weight may be improved.[25] WHO[11] recommends that, in areas of stable transmission of *P. falciparum* malaria, pregnant women should be given **intermittent preventative treatment (IPT)** with an antimalarial drug, usually pyrimethamine-sulfadoxine (*Fansidar*). The first dose should be given after quickening in the second trimester and further doses should be given at intervals of at least one month apart. For maximum benefit 2 or 3 doses of IPT should be given. For further information on the use of pyrimethamine in pregnancy, see under Precautions for Pyrimethamine, p. 664.1. Pregnant women and their newborn should also sleep under insecticide-treated nets.[3] In areas of low or unstable malaria transmission, where pregnant women have low immunity to malaria, use of insecticide-treated nets and prompt case management of pregnant women with fever and malarial illness is recommended. In addition, all pregnant women should take iron and folate supplements.

Prophylaxis during breast feeding. It is generally accepted for most antimalarials that the amounts distributed into breast milk and consumed by nursing infants are too small to be harmful, although they are also too small to provide protection.[2,22] However, doxycycline is contra-indicated during breast feeding, and advice regarding atovaquone-proguanil (*Malarone*) varies: in the UK it is contra-indicated,[23] but in the USA it may be given once the infant weighs over 5 kg;[22] both permit use if no suitable alternative is available. Mefloquine is probably safe to use in breast-feeding mothers.[23]

Prophylaxis in children. Chloroquine and proguanil may be given in scaled down doses to children of all ages but

the choice of alternative drugs may be restricted, especially in very young children, and consideration should be given to whether their travel to malarious areas is absolutely necessary (see also above). Mefloquine is an option for use in children and infants weighing 5 kg or more[2] if travelling to areas with chloroquine-resistant *P. falciparum* and atovaquone-proguanil (*Malarone*) may be given to children weighing 11 kg or more; the CDC considers that it may be used in infants weighing at least 5 kg. Doxycycline is contra-indicated in children less than 8 years of age, and higher age limits may apply in some countries such as the UK.[2,22,23] As in pregnant women (above), IPT is being explored as a means of reducing malaria in infants in areas of sustained high transmission;[26] the strategy for infants (IPTi) involves giving 2 or 3 doses of antimalarials during the first year of life, timed to coincide with routine vaccinations. A meta-analysis[27] of 6 studies involving infants in Africa reported that IPTi with sulfadoxine-pyrimethamine (*Fansidar*) led to a 30% reduction in the incidence of clinical malaria. For sub-Saharan Africa, the WHO technical expert group on preventative chemotherapy[28] has recommended that implementation of IPTi with sulfadoxine-pyrimethamine be considered in specific areas, such as those where there is moderate-to-high malaria transmission without high levels of resistance to sulfadoxine-pyrimethamine (the efficacy of sulfadoxine-pyrimethamine is decreasing in many areas,[28] and its use as IPTi has been shown to be of no benefit in areas of very high sulfadoxine-pyrimethamine resistance[29]).

Prophylaxis in epilepsy. In subjects with a history of epilepsy, the UK guidelines[23] advise that both chloroquine and mefloquine are unsuitable for prophylaxis. In areas without chloroquine resistance, proguanil alone is recommended. In areas with a high risk of chloroquine resistance, atovaquone-proguanil (*Malarone*) or doxycycline may be considered, but the metabolism of doxycycline may be influenced by antiepileptics. Dapsone with pyrimethamine (*Maloprim*) was considered to have been of particular value in travellers with epilepsy, especially children, but is no longer available in the UK.

Prophylaxis in HIV-infected travellers. HIV-infected travellers may take chloroquine routinely for antimalarial prophylaxis but its potential immunosuppressive effects should be recognised; proguanil, mefloquine, or doxycycline can also be used. Although patients with AIDS may be at increased risk of adverse effects to sulfonamides, a combination such as pyrimethamine-sulfadoxine (*Fansidar*) can be used for standby treatment if an alternative is not available.

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Amodiaquine *(BAN, rINN)*

Amodiactin; Amodiaquin; Amodiaquina; Amodiaquinum; Амодиахин.

4-(7-Chloro-4-quinolylamino)-2-(diethylaminomethyl) phenol.

$C_{20}H_{22}ClN_3O$=355.9

CAS — 86-42-0.

ATC — P01BA06.

UNII — 220236ED28.

Pharmacopoeias. In *Int.* and *US.*

USP 36: (Amodiaquine). Very pale yellow to light tan-yellow, odourless, powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in 1.0N hydrochloric acid. Store in airtight containers.

Amodiaquine Hydrochloride *(BANM, rINNM)*

Amodiaquina, hidrocloruro de; Amodiaquine, Chlorhydrate d'; Amodiaquini Hydrochloridum; Hidrocloruro de amodiaquina; Амодиахина Гидрохлорид.

4-(7-Chloro-4-quinolylamino)-2-(diethylaminomethyl) phenol dihydrochloride dihydrate.

$C_{20}H_{22}ClN_3O,2HCl,2H_2O$=464.8

CAS — 69-44-3 (anhydrous amodiaquine hydrochloride); 6398-98-7 (amodiaquine hydrochloride dihydrate).

ATC — P01BA06.

UNII — K6PW25574L.

Pharmacopoeias. In *Fr., Int.*, and *US.*

USP 36: (Amodiaquine Hydrochloride). A yellow, odourless, crystalline powder. Soluble 1 in 25 of water and 1 in 78 of alcohol; very slightly soluble in chloroform, in ether, and in benzene. Store in airtight containers.

Sorption. For reference to loss of amodiaquine hydrochloride from solutions during membrane filtration, see Chloroquine, p. 650.2.

Uses and Administration

Amodiaquine is a 4-aminoquinoline antimalarial with an action similar to that of chloroquine (p. 650.2). It is as effective as chloroquine against chloroquine-sensitive strains of *Plasmodium falciparum* and is also effective against some chloroquine-resistant strains, although resistance to amodiaquine has developed and there may be partial cross-resistance between amodiaquine and chloroquine. To prevent the emergence and spread of drug resistant parasites WHO recommends that amodiaquine be given with an artemisinin derivative, such as artesunate, for the treatment of uncomplicated falciparum malaria or chloroquine-resistant vivax malaria. Amodiaquine is not recommended for the prophylaxis of malaria because of resistance and the risk of major toxicity.

Amodiaquine is given orally as the hydrochloride, but doses are expressed in terms of amodiaquine base; amodiaquine hydrochloride 260 mg is equivalent to about 200 mg of amodiaquine base. For the treatment of falciparum malaria and uncomplicated chloroquine-resistant vivax malaria in adults and children 5 months of age and older, a total dose of 30 mg/kg is given over 3 days (10 mg/kg daily for 3 days). Treatment of vivax malaria must be followed by radical cure with primaquine.

A fixed-dose combination product of amodiaquine and artesunate (ASAQ) has been developed in order to improve patient adherence and avoid monotherapy, thereby decreasing the risk of acquired drug resistance, and is available in some countries.

References.

1. Olliaro P, Mussano P. Amodiaquine for treating malaria. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 17/05/05).
2. McIntosh HM, Jones KL. Chloroquine or amodiaquine combined with sulfadoxine-pyrimethamine for treating uncomplicated malaria. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 18/07/06).
3. Bukirwa H, Critchley J. Sulfadoxine-pyrimethamine plus artesunate versus sulfadoxine-pyrimethamine plus amodiaquine for treating uncomplicated malaria. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 18/07/06).
4. Zwang J, *et al*. Efficacy of artesunate-amodiaquine for treating uncomplicated P. falciparum malaria in Sub-Saharan Africa: a multi-centre analysis. *Malar J* 2009; 8: 203.
5. Faye B, *et al*. Efficacy and tolerability of artesunate-amodiaquine (Camoquin plus) versus artemether-lumefantrine (Coartem) against uncomplicated *Plasmodium falciparum* malaria: multisite trial in Senegal and Ivory Coast. *Trop Med Int Health* 2010; 15: 608–13.
6. Kauss T, *et al*. Fixed artesunate-amodiaquine combined pre-formulation study for the treatment of malaria. *Int J Pharm* 2010; 399: 198–204.

Administration in children. Amodiaquine may be used in children from 5 months of age for the treatment of uncomplicated falciparum malaria, or uncomplicated, chloroquine-resistant vivax malaria; doses are the same as for adults (see above).

References to the use of amodiaquine-containing therapy in children.

1. Cairns M, *et al*. Amodiaquine dosage and tolerability for intermittent preventive treatment to prevent malaria in children. *Antimicrob Agents Chemother* 2010; 54: 1265–74.
2. Mbacham WF, *et al*. Efficacy of amodiaquine, sulphadoxine-pyrimethamine and their combination for the treatment of uncomplicated *Plasmodium falciparum* malaria in children in Cameroon at the time of policy change to artemisinin-based combination therapy. *Malar J* 2010; 9: 34.

Adverse Effects and Precautions

As for Chloroquine, p. 651.2, although amodiaquine was associated with hepatitis and a much higher incidence of agranulocytosis when it was used for the prophylaxis of malaria.

Incidence of adverse effects. Early isolated reports of severe neutropenia with amodiaquine usually concerned use in anti-inflammatory doses for rheumatoid arthritis, but there was a cluster of cases in 1986 associated with its use in malaria prophylaxis.[1] In all, 23 cases of agranulocytosis, 7 of which were fatal, were reported in the UK, USA, and Switzerland during a 12-month period ending March 1986. Nearly all of these patients had used the drug at a dosage of 400 mg weekly and the periods of exposure ranged from 3 to 24 weeks.[1] Some of these patients also had evidence of liver damage[1] and there have been other reports of hepatotoxicity associated with the prophylactic use of amodiaquine.[2] Examination of data submitted to the UK CSM[3] suggested that the frequency of adverse reactions to amodiaquine was about 1 in 1700 for serious reactions, 1 in 2200 for blood disorders, 1 in 15 650 for serious hepatic disorders, and 1 in 15 650 for fatal reactions. In contrast the frequency of agranulocytosis in users in France[4] has been estimated to be 1 in 25 000. Worldwide[4] the risk of severe reactions appears to be between 1 in 1000 and 1 in 5000. The manufacturers reportedly had 42 cases of serious adverse effects during amodiaquine prophylaxis, between 1985 and 1991; there were 28 cases of agranulocytosis (9 deaths) and 14 of hepatitis (3 deaths).[5]

In contrast, the risk of adverse events when amodiaquine is used for treatment, rather than prophylaxis of malaria appears to be substantially lower, likely because the relatively shorter courses used for treatment are associated with lower cumulative drug exposure than with prophylaxis.[6] Certain populations may be at higher risk however, and in a cohort study[7] of children being treated for malaria in Uganda, treatment with amodiaquine plus artesunate led to a significantly higher risk of neutropenia in HIV-infected children compared with HIV-uninfected children (44% and 6% respectively); risk was highest among children also receiving antiretroviral therapy (particularly regimens containing zidovudine).

It has been suggested that an immunological reaction to amodiaquine quinone imine, which can be produced by autoxidation among other processes, may partially account for amodiaquine's greater tendency to induce agranulocytosis compared with chloroquine.[8,9]

The acute toxicity of amodiaquine appears to differ from that of chloroquine in that there have been no reports of cardiovascular symptoms after overdosage with amodiaquine[10] but intoxication with amodiaquine is also far less frequent than chloroquine poisoning. However, large doses of amodiaquine have been reported to produce syncope, spasticity, convulsions, and involuntary movements.[10]

1. Anonymous. Amodiaquine and agranulocytosis. *WHO Drug Inf* 1987; 1: 5–6.

2. Larrey D, *et al.* Amodiaquine-induced hepatitis. *Ann Intern Med* 1986; 104: 801–3.
3. Phillips-Howard PA, West LJ. Serious adverse drug reactions to pyrimethamine–sulphadoxine, pyrimethamine–dapsone and to amodiaquine in Britain. *J R Soc Med* 1990; 83: 82–5.
4. Anonymous. Development of recommendations for the protection of short-stay travellers to malaria endemic areas: memorandum from two WHO meetings. *Bull WHO* 1988; 66: 177–96.
5. Olliaro P, *et al.* Systematic review of amodiaquine treatment in uncomplicated malaria. *Lancet* 1996; 348: 1196–1201.
6. Olliaro P. Disease and drug interactions: treating malaria with artesunate plus amodiaquine in patients also receiving treatment for concomitant HIV infection. *Clin Infect Dis* 2008; 46: 992–3.
7. Gasasira AF, *et al.* High risk of neutropenia in HIV-infected children following treatment with artesunate plus amodiaquine for uncomplicated malaria in Uganda. *Clin Infect Dis* 2008; 46: 985–91.
8. Winstanley PA, *et al.* The toxicity of amodiaquine and its principal metabolites towards mononuclear leucocytes and granulocyte/monocyte colony forming units. *Br J Clin Pharmacol* 1990; 29: 479–85.
9. Park BK, Kitteringham NR. Drug–protein conjugation and its immunological consequences. *Drug Metab Rev* 1990; 22: 87–144.
10. Jaeger A, *et al.* Clinical features and management of poisoning due to antimalarial drugs. *Med Toxicol* 1987; 2: 242–73.

Pregnancy. A study[1] to assess the safety and efficacy of amodiaquine or amodiaquine plus sulfadoxine-pyrimethamine in 900 pregnant women (in their second or third trimester) reported that PCR-corrected parasitological failure by day 28 was 14%, 11%, 3%, and 0% in those given chloroquine, sulfadoxine-pyrimethamine, amodiaquine alone, and amodiaquine plus sulfadoxine-pyrimethamine, respectively. No serious adverse effects were reported.

WHO considers that amodiaquine may be an alternative to chloroquine for treatment of malaria due to *P. vivax* during pregnancy (see Treatment of Malaria during Pregnancy, under Malaria, p. 644.1).

1. Tagbor H, *et al.* Efficacy, safety, and tolerability of amodiaquine plus sulphadoxine-pyrimethamine used alone or in combination for malaria treatment in pregnancy: a randomised trial. *Lancet* 2006; 368: 1349–56.

Pharmacokinetics

Amodiaquine hydrochloride is readily absorbed from the gastrointestinal tract. Amodiaquine is rapidly converted in the liver, via the cytochrome P450 isoenzyme CYP2C8, to the active metabolite desethylamodiaquine, only a negligible amount of amodiaquine being excreted unchanged in the urine. The plasma elimination half-life of desethylamodiaquine has varied from 1 to 10 days or more. Amodiaquine and desethylamodiaquine have been detected in the urine several months after use.

References.
1. Winstanley P, *et al.* The disposition of amodiaquine in man after oral administration. *Br J Clin Pharmacol* 1987; 23: 1–7.
2. White NJ, *et al.* Pharmacokinetics of intravenous amodiaquine. *Br J Clin Pharmacol* 1987; 23: 127–35.
3. Winstanley PA, *et al.* The disposition of amodiaquine in Zambians and Nigerians with malaria. *Br J Clin Pharmacol* 1990; 29: 695–701.
4. Krishna S, White NJ. Pharmacokinetics of quinine, chloroquine and amodiaquine: clinical implications. *Clin Pharmacokinet* 1996; 30: 263–99.
5. Gil JP. Amodiaquine pharmacogenetics. *Pharmacogenomics* 2008; 9: 1385–90.
6. Navaratnam V, *et al.* Tolerability and pharmacokinetics of non-fixed and fixed combinations of artesunate and amodiaquine in Malaysian healthy normal volunteers. *Eur J Clin Pharmacol* 2009; 65: 809–21.
7. Stepniewska K, *et al.* Population pharmacokinetics of artesunate and amodiaquine in African children. *Malar J* 2009; 8: 200.
8. Jullien V, *et al.* Population pharmacokinetics and pharmacodynamic considerations of amodiaquine and desethylamodiaquine in Kenyan adults with uncomplicated malaria receiving artesunate-amodiaquine combination therapy. *Antimicrob Agents Chemother* 2010; 54: 2611–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Flavoquine†; *India*: Basoquin†; Camoquin†.

Multi-ingredient Preparations. *Belg.*: Amonate†; *China*: Artemodi; *Gr.*: Arsuamoon.

Pharmacopoeial Preparations
USP 36: Amodiaquine Hydrochloride Tablets.

Artemisinin Derivatives

Artemisinina, derivados.

Artemether *(BAN, USAN, rINN)*

Artemeetteri; Artemeter; Arteméter; Artemetero; Artéméther; Artemetherum; Dihydroartemisinin Methyl Ether; Dihydroqinghaosu Methyl Ether; o-Methyldihydroartemisinin; SM-224; Артеметер.
(3*R*,5a*S*,6*R*,8a*S*,9*R*,10*S*,12*R*,12a*R*)-Decahydro-10-methoxy-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin.
$C_{16}H_{26}O_5$=298.4
CAS — 71963-77-4.
ATC — P01BE02.
UNII — C7D6T3H22J.

Pharmacopoeias. In *Chin.* and *Int.*

Artemisinin *(rINN)*

Artearnuin; Artemisiini; Artemisinina; Artemisinine; Artémisinine; Artemisininum; Huanghuahaosu; Qinghaosu; Артемизинин.
(3*R*,5a*S*,6*R*,8a*S*,9*R*,12*S*,12a*R*)-Octahydro-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one.
$C_{15}H_{22}O_5$=282.3
CAS — 63968-64-9.
ATC — P01BE01.
UNII — 9RMU91N5K2.

Pharmacopoeias. In *Chin.*, *Int.*, and *Viet.*

Artemotil *(rINN)*

Artémotil; Artemotilo; Artemotilum; Beta-arteether; Dihydroartemisinin Ethyl Ether; Dihydroqinghaosu Ethyl Ether; SM-227; Артемотил.
(3*R*,5a*S*,6*R*,8a*S*,9*R*,10*S*,12*R*,12a*R*)-Decahydro-10-ethoxy-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin.
$C_{17}H_{28}O_5$=312.4
CAS — 75887-54-6.
ATC — P01BE04.
UNII — XGL7GFB9YI.

Pharmacopoeias. In *Int.*

Artenimol *(USAN, rINN)*

Arténimol; Artenimolum; Dihydroartemisinin; Dihydroqinghaosu; Артенимол.
(3*R*,5a*S*,6*R*,8a*S*,9*R*,10*S*,12*R*,12a*R*)-Decahydro-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10-ol.
$C_{15}H_{24}O_5$=284.4
CAS — 81496-81-3.
ATC — P01BE05.
UNII — 6A9OS0735X.

Pharmacopoeias. In *Chin.* and *Int.*

Artesunate *(BAN, USAN, rINN)*

Artesunat; Artésunate; Artesunato; Artesunatum; Артезунат.
(3*R*,5a*S*,6*R*,8a*S*,9*R*,10*S*,12*R*,12a*R*)-Decahydro-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano-[4,3-*j*]-1,2-benzodioxepin-10-ol hydrogen succinate.
$C_{19}H_{28}O_8$=384.4
CAS — 83507-69-1; 88495-63-0; 182824-33-5.
ATC — P01BE03.
UNII — 6OW3249T9M.

Pharmacopoeias. In *Int.* and *Viet.*

Sodium Artesunate *(BANM, rINNM)*

Artésunate de Sodium; Artesunato sódico; Dihydroartemisinin Hemisuccinate Sodium; Dihydroqinghaosu Hemisuccinate Sodium; Natrii Artesunatum; SM-804; Натрий Артезунат.
(3*R*,5a*S*,6*R*,8a*S*,9*R*,10*S*,12*R*,12a*R*)-Decahydro-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano-[4,3-*j*]-1,2-benzodioxepin-10-ol hydrogen succinate sodium.
$C_{19}H_{27}O_8Na$=406.4
CAS — 82864-68-4.
UNII — CN5E49Z611.

Uses and Administration

Artemisinin is a sesquiterpene lactone isolated from *Artemisia annua*, a herb that has traditionally been used in China for the treatment of malaria. It is a potent and rapidly acting blood schizontocide active against *Plasmodium vivax* and against both chloroquine-sensitive and chloroquine-resistant strains of *P. falciparum*.

Artemisinin has been given orally or rectally in the treatment of malaria (see p. 649.1); regimens were often empirical with typical rectal doses ranging from 10 to 40 mg/kg daily over a variable number of days. However, it has largely been replaced in practice by its derivatives such as artemether and artesunate.

The following *oral* doses are recommended by WHO for the treatment of uncomplicated falciparum malaria.

Artesunate, when used with other antimalarials such as amodiaquine, mefloquine, or pyrimethamine-sulfadoxine, is given orally to provide a target dose of 4 mg/kg once daily, for 3 days.

Artenimol is given with piperaquine orally to provide a target dose of 4 mg/kg once daily, for 3 days.

Artemether is given orally with lumefantrine to provide a target dose of 1.7 mg/kg twice daily, for 3 days.

Fixed-dose combination products containing an artemisinin derivative and another antimalarial have been developed in order to improve patient adherence and avoid monotherapy, thereby decreasing the risk of acquired drug resistance; these formulations are recommended over co-packaged or loose tablets combinations. The following fixed-dose combinations have been licensed for use in some countries:

- artemether with lumefantrine (for further dosing information, see under Lumefantrine, p. 656.3)
- artenimol with piperaquine (for further dosing information, see under Piperaquine, p. 659.3)
- artesunate with amodiaquine
- artesunate with pyronaridine phosphate (for further dosing information, see under Pyronaridine Phosphate, p. 664.3)

For *parenteral* use in severe malaria, WHO recommends **artesunate** 2.4 mg/kg intravenously or intramuscularly, repeated after 12 and 24 hours and then once daily thereafter. The patient should then be transferred to an appropriate oral regimen (see p. 644.1) after at least 24 hours of parenteral therapy and complete a full course of oral treatment. Alternatively, in the USA a 5-dose regimen of 2.4 mg/kg intravenously at 0, 12, 24, 48, and 72 hours has been recommended, with oral follow-on treatment using atovaquone-proguanil (*Malarone*), doxycycline, clindamycin, or mefloquine.

If artesunate is not available, intramuscular **artemether** may be substituted in a dose of 3.2 mg/kg on day 1, followed by 1.6 mg/kg daily thereafter. **Artemotil** may also be used intramuscularly for the treatment of severe falciparum malaria; the suggested regimen is an initial dose of 4.8 mg/kg, evenly divided over both anterior thighs, followed by doses of 1.6 mg/kg given after 6, 24, 48, and 72 hours (injected into alternating thighs).

Where *rectal* **artesunate** is required for pre-referral treatment of severe malaria, a single dose of 10 mg/kg has been recommended.

For details of doses in children, see below.

Other derivatives of artemisinin are under investigation or commercial development (see Administration of Artemisinin Derivatives, below).

Reviews.
1. McIntosh H, Olliaro P. Artemisinin derivatives for treating uncomplicated malaria. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1999 (accessed 17/05/05).
2. McIntosh H, Olliaro P. Artemisinin derivatives for treating severe malaria. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2000 (accessed 17/05/05).
3. Olliaro PL, Taylor WR. Developing artemisinin based drug combinations for the treatment of drug resistant falciparum malaria: a review. *J Postgrad Med* 2004; 50: 40–4.
4. Afolabi BB, Okoromah CAN. Intramuscular arteether for treating severe malaria. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 14/06/11).
5. Ashley EA, White NJ. Artemisinin-based combinations. *Curr Opin Infect Dis* 2005; 18: 531–6.
6. Davis TME, *et al.* Artemisinin-based combination therapies for uncomplicated malaria. *Med J Aust* 2005; 182: 181–5.
7. Bukirwa H, Critchley JA. Sulfadoxine-pyrimethamine plus artesunate versus sulfadoxine-pyrimethamine plus amodiaquine for treating uncomplicated malaria. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 18/07/06).
8. Aweeka FT, German PI. Clinical pharmacology of artemisinin-based combination therapies. *Clin Pharmacokinet* 2008; 47: 91–102.
9. Rosenthal PJ. Artesunate for the treatment of severe falciparum malaria. *N Engl J Med* 2008; 358: 1829–36.
10. Sinclair D, *et al.* Artemisinin-based combination therapy for treating uncomplicated malaria. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2009 (accessed 01/09/09).
11. Douglas NM, *et al.* Artemisinin combination therapy for vivax malaria. *Lancet Infect Dis* 2010; 10: 405–16.

Administration of artemisinin derivatives. To overcome the poor solubility of *artemisinin* in water several dosage forms and routes have been tried. More potent derivatives with more suitable pharmaceutical properties have also been developed, notably the methyl ether derivative, *artemether*, and the ethyl ether derivative, *artemotil*, which are more lipid soluble; the sodium salt of the hemisuccinate ester, *sodium artesunate*, which is soluble in water but appears to have poor stability in aqueous solutions; and *sodium artelinate*, which is both soluble and stable in water. The active metabolite of these derivatives, *artenimol*, has also been developed as a pharmaceutical preparation. Other derivatives that have been studied include *arteflene* and *alpha-beta arteether*.

Several preparations of artemisinin derivatives are available either commercially or for studies organised by bodies such as WHO. These include oral formulations of artemether, artesunate, artemisinin itself, and artenimol; intramuscular formulations of artemotil, artemether, and artesunate; intravenous formulations of *artelinic acid* and artesunate; and suppositories of artemether, artemisinin, artesunate, and artenimol.

Administration in children. The artemisinin derivatives may be used in infants and children for the treatment of both uncomplicated falciparum malaria and severe malaria; the main derivatives currently in use are artesunate and artemether. For uncomplicated falciparum malaria WHO[1] recommends that combinations based on the same artemisinin derivatives as in adults be used, in equivalent

doses per kg body-weight (see p. 648.2); the specific combination chosen will be influenced by the safety and tolerability of the partner drug.

For treatment of severe malaria, WHO[1] recommends initial parenteral therapy (preferably with artesunate) followed by a complete course of an appropriate oral regimen (see p. 644.1) once the patient has completed at least 24 hours of parenteral therapy, and can tolerate oral medication. The following parenteral doses are recommended:

- **artesunate** 2.4 mg/kg *intravenously* or *intramuscularly*, repeated after 12 and 24 hours and given once daily thereafter
- **artemether** 3.2 mg/kg *intramuscularly*, followed by 1.6 mg/kg daily thereafter

Rectal artesunate may be used for pre-referral treatment of severe malaria in children in the same doses as for adults (see p. 648.2).[1]

Alternatively, in the USA[2] a 5-dose regimen of **artesunate** 2.4 mg/kg *intravenously* at 0, 12, 24, 48, and 72 hours (followed by treatment with atovaquone-proguanil (*Malarone*), clindamycin, or mefloquine) has been recommended for treatment of severe malaria.

A systematic review[3] has shown that oral formulations (granules, oral suspensions, or dispersible tablets) of artemisinin combinations that were designed specifically for paediatric dosage resulted in improved tolerance of therapy, with no loss of efficacy.

1. WHO. *Guidelines for the treatment of malaria* 2nd ed. Geneva: WHO, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf (accessed 09/07/10) Update (issued April 2011), available at: http://www.who.int/malaria/publications/atoz/mal_treatchild_revised.pdf (accessed 20/05/11)
2. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.
3. Kurth F, *et al.* Do paediatric drug formulations of artemisinin combination therapies improve the treatment of children with malaria? A systematic review and meta-analysis. *Lancet Infect Dis* 2010; **10**: 125–32.

Malaria. A systematic review[1] has suggested that intravenous artesunate should be the treatment of choice for adults and children with severe malaria (p. 644.1) in all geographical regions of the world. WHO[2] similarly recommends artesunate, given intravenously or intramuscularly, as the preferred treatment for severe malaria in both adults and children; intramuscular artemether or parenteral quinine can be considered where parenteral artesunate is not available. Rectal artesunate has been successful and is recommended by WHO[2] if parenteral therapy is not possible. In acute uncomplicated malaria artemisinin derivatives are usually given orally. Those used have been artemisinin, artemether, artenimol, or artesunate.

Although the increasing first-line use of artemisinin derivatives has been driven by the development of resistance to conventional treatment, resistance to this class of drugs has begun to develop in its turn, and no new group of drugs is yet in a position to replace them; treatment of artemisinin-resistant malaria will require optimisation of combinations of existing drugs.[3]

1. Sinclair D, *et al.* Artesunate versus quinine for treating severe malaria. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2011 (accessed 08/07/11).
2. WHO. *Guidelines for the treatment of malaria.* 2nd ed. Geneva: WHO, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf (accessed 09/07/10) Update issued (April 2011), available at: http://www.who.int/malaria/publications/atoz/mal_treatchild_revised.pdf (accessed 20/05/11)
3. Dondorp AM, *et al.* Artemisinin resistance: current status and scenarios for containment. *Nat Rev Microbiol* 2010; **8**: 272–80.

Schistosomiasis. Findings of a reduced intensity of *Schistosoma mansoni* infection in patients treated with sodium artesunate for malaria[1] prompted further investigation into the use of artemisinin derivatives for the control of schistosomiasis (p. 148.1). A double-blind placebo-controlled study[2] in children negative for *S. mansoni* found a significantly lower incidence of infection in those given artemether orally. There was also a significant reduction in the prevalence of *Plasmodium falciparum* infection. Some studies in China have confirmed the benefits of artemether or artesunate, often with praziquantel, against *S. japonicum*.[3] Another, open-label study appeared to suggest that a combination of mefloquine with artesunate was effective against *S. haematobium* and *S. mansoni*, see p. 657.3. However, in a randomised, double-blind, placebo-controlled study,[4] combination therapy with artemether plus praziquantel was no more effective in the treatment of acute *S. japonicum* infection than praziquantel alone.

1. De Clercq D, *et al.* Efficacy of artesunate against Schistosoma mansoni infections in Richard Toll, Senegal. *Trans R Soc Trop Med Hyg* 2000; **94**: 90–1.
2. Utzinger J, *et al.* Oral artemether for prevention of Schistosoma mansoni infection: randomised controlled trial. *Lancet* 2000; **355**: 1320–5.
3. Xiao S-H. Development of antischistosomal drugs in China, with particular consideration to praziquantel and the artemisinins. *Acta Trop* 2005; **96**: 133–67.
4. Hou XY, *et al.* A randomized, double-blind, placebo-controlled trial of safety and efficacy of combined praziquantel and artemether treatment for acute schistosomiasis japonica in China. *Bull WHO* 2008; **86**: 788–95.

Adverse Effects and Precautions

Artemisinin and its derivatives appear to be generally well tolerated, although there have been reports of mild gastrointestinal disturbance (including nausea, vomiting, diarrhoea, and abdominal pain), pruritus and rash, dizziness, headache, tinnitus, neutropenia, elevated liver enzyme values, and ECG abnormalities including prolongation of the QT interval. Some parenteral artemisinin derivatives are formulated in sesame oil, which may rarely cause severe allergic reaction.

Evidence of severe neurotoxicity has been seen in *animals* given high doses.

General references to adverse effects associated with artemisinin derivatives.

1. Price R, *et al.* Adverse effects in patients with acute falciparum malaria treated with artemisinin derivatives. *Am J Trop Med Hyg* 1999; **60**: 547–55.
2. Medhi B, *et al.* Pharmacokinetic and toxicological profile of artemisinin compounds: an update. *Pharmacology* 2009; **84**: 323–32.
3. Efferth T, Kaina B. Toxicity of the antimalarial artemisinin and its dervatives [sic]. *Crit Rev Toxicol* 2010; **40**: 405–21.

Effects on the blood. For a report of severe haemolytic anaemia occurring in patient after taking artemether-lumefantrine and mention of neutropenia in HIV-infected patients treated with amodiaquine-artesunate, see p. 656.3 and p. 647.3 respectively.

Effects on the heart. Bradycardia was reported in 10 of 34 patients who received artemether orally for 4 days.[1] Other ECG abnormalities, such as QT-interval prolongation, have also been reported, although most studies have found no such effects.[2]

1. Karbwang J, *et al.* Comparison of oral artemether and mefloquine in acute uncomplicated falciparum malaria. *Lancet* 1992; **340**: 1245–8.
2. WHO. *Guidelines for the treatment of malaria.* 2nd ed. Geneva: WHO, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf (accessed 25/05/11)

Effects on the liver. Acute hepatitis was reported in a patient who took a herbal supplement supplying artemisinin 7.5 mg/kg daily for 10 days;[1] when the supplement was stopped, the patient's symptoms and liver function tests returned to normal over a 2 week period. Analysis of the supplement confirmed the presence and quantity of artemisinin and the absence of other contaminants or pharmaceutically active ingredients.

1. CDC. Hepatitis temporally associated with an herbal supplement containing artemisinin – Washington, 2008. *MMWR* 2009; **58**: 854–6.

Effects on the nervous system. Neurotoxicity has been reported in *animals* given artemotil or artemether; toxicity appears to relate to the sustained blood concentrations that occur after intramuscular administration, and is much less frequent when similar doses are given by the oral route or when similar doses of water-soluble artemisinin derivatives (such as artesunate) are used.[1] Clinical studies in humans have so far failed to show similar findings. However, there has been a report[2] of acute cerebellar dysfunction manifesting as ataxia and slurred speech in a patient who took a 5-day course of oral artesunate. Tremor, lack of coordination, restlessness, anxiety, hyperreflexia, and spasticity were also reported[3] in a patient misdiagnosed with malaria and treated with five 10-day courses of artesunate, and one 10-day course of chloroquine (p. 650.1). Symptoms improved markedly once the drugs were stopped, and neurotoxicity was felt to be a cumulative result of multiple artesunate courses, although chloroquine use may have also contributed.

1. WHO. *Guidelines for the treatment of malaria.* 2nd ed. Geneva: WHO, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf (accessed 25/05/11)
2. Miller LG, Panosian CB. Ataxia and slurred speech after artesunate treatment for falciparum malaria. *N Engl J Med* 1997; **336**: 1328.
3. Franco-Paredes C, *et al.* Neurotoxicity due to antimalarial therapy associated with misdiagnosis of malaria. *Clin Infect Dis* 2005; **40**: 1710–1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies the combination of artemether plus lumefantrine as probably porphyrinogenic: it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

For a discussion of the use of other antimalarials in patients with porphyria, see under Precautions for Chloroquine, p. 653.1.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 12/10/11)

Pregnancy. Artesunate or artemether was used to treat multidrug-resistant falciparum malaria in 83 pregnant women in Thailand; of 73 pregnancies resulting in live births none showed evidence of any congenital abnormality.[1] Sixteen of the women were given artesunate during the first trimester; of these, 12 had normal deliveries, 1 was lost to study, and 3 had spontaneous abortions.

No undue adverse effects on the neonates occurred in a study[2] involving 45 women treated for multidrug-resistant malaria during their second or third trimester of pregnancy with either artemether or artemether plus mefloquine. Intramuscular artemether was also used to treat chloroquine/quinine-resistant falciparum malaria in 28 pregnant women in eastern Sudan. Artemether was given to 1 woman during the first trimester, to 12 during the second trimester, and to 15 during the third trimester. One baby was delivered at 32 weeks but died 6 hours later; all the other babies were delivered at full term and there were no reports of congenital abnormalities.[3]

WHO[4] recommends that, where available, artesunate is the first option, and artemether is the second, for the parenteral treatment of severe falciparum malaria during the second and third trimesters. In the first trimester, until more evidence becomes available, artesunate may be considered as an option.

1. McGready R, *et al.* Artemisinin derivatives in the treatment of falciparum malaria in pregnancy. *Trans R Soc Trop Med Hyg* 1998; **92**: 430–3.
2. Sowunmi A, *et al.* Randomised trial of artemether versus artemether and mefloquine for the treatment of chloroquine/sulfadoxine[sic]-pyrimethamine-resistant falciparum malaria during pregnancy. *J Obstet Gynaecol* 1998; **18**: 322–7.
3. Adam I, *et al.* Artemether in the treatment of falciparum malaria during pregnancy in eastern Sudan. *Trans R Soc Trop Med Hyg* 2004; **98**: 509–13.
4. WHO. *International travel and health.* 2011 ed. Available at: http://www.who.int/ith/en (accessed 25/05/11)

Interactions

Use of artemisinin derivatives with drugs that prolong the QT interval should be avoided if possible; caution is advised when artemisinin derivatives are given with other antimalarials that have this propensity.

Artemisinin has been reported to be a potent inhibitor of the cytochrome P450 isoenzyme CYP1A2,[1] and might interact with drugs metabolised via this enzyme (such as theophylline). In contrast it is said to be an inducer of CYP2A6,[2] although the clinical implications of this are unclear.

1. Bapiro TE, *et al.* Artemisinin and thiabendazole are potent inhibitors of cytochrome P450 1A2 (CYP1A2) activity in humans. *Eur J Clin Pharmacol* 2005; **61**: 755–61.
2. Asimus S, *et al.* Artemisinin and CYP2A6 activity in healthy subjects. *Eur J Clin Pharmacol* 2008; **64**: 283–92.

Grapefruit juice. The oral bioavailability of artemether may be increased if taken with grapefruit juice.[1]

1. van Agtmael MA, *et al.* The effect of grapefruit juice on the time-dependent decline of artemether plasma levels in healthy subjects. *Clin Pharmacol Ther* 1999; **66**: 408–14.

Pharmacokinetics

Peak plasma concentrations of *artemisinin* occur about 3 hours after an oral dose, and 11 hours after a rectal dose. It undergoes hepatic metabolism, mainly via the cytochrome P450 isoenzyme CYP2B6, and is a potent inducer of its own metabolism; very little artemisinin is recovered in the urine, and inactive metabolites are excreted in the bile. The elimination half-life of artemisinin is about 2 to 3 hours.

Artemisinin derivatives are rapidly absorbed after an oral dose, with peak-plasma concentrations occurring after less than an hour for artesunate, and after 2 to 3 hours for artemether. Peak-plasma concentrations occur later (at 4 to 7 hours) when artesunate is given rectally. Absorption of intramuscular artemether is highly variable, with peak-serum concentrations occurring anywhere from 2 to 10 hour after a dose. For intramuscular artemotil, absorption is even slower and more erratic, with some patients having undetectable plasma concentrations until more than 24 hours after a dose.

After absorption, artemisinin derivatives (but not artemisinin itself) are rapidly biotransformed to the active metabolite artenimol (dihydroartemisinin). Biotransformation of artesunate by hydrolysis is almost immediate, such that artesunate is often regarded as a prodrug. In contrast, biotransformation of artemether and artemotil occurs more slowly, via CYP3A4-mediated demethylation. Artenimol is ultimately converted to inactive metabolites via cytochrome P450 and other enzyme systems, which are then excreted in the bile. The elimination half-life of artemether can range from 2 to 12 hours in patients with malaria. There are very few published data on the pharmacokinetics of artemotil, but its elimination half-life appears to be longer than that of artemether.

Reviews.

1. White NJ, *et al.* Clinical pharmacokinetics and pharmacodynamics of artemether-lumefantrine. *Clin Pharmacokinet* 1999; **37**: 105–25.
2. Svensson US, Ashton M. Identification of the human cytochrome P450 enzymes involved in the in vitro metabolism of artemisinin. *Br J Clin Pharmacol* 1999; **48**: 528–35.
3. Navaratnam V, *et al.* Pharmacokinetics of artemisinin-type compounds. *Clin Pharmacokinet* 2000; **39**: 255–70.
4. Gautam A, *et al.* Pharmacokinetics and pharmacodynamics of endoperoxide antimalarials. *Curr Drug Metab* 2009; **10**: 289–306.

5. Mercer AE, Sarr Sallah M. The pharmacokinetic evaluation of artemisinin drugs for the treatment of malaria in paediatric populations. *Expert Opin Drug Metab Toxicol* 2011; 7: 427–39.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Arinate†; Artesiane; *Braz.*: Paluther; Plasmotrim; *China*: Cotecxin; *Gr.*: Artemax†; *India*: Aartee; AB-AT; Ab-Ther; ABA-AT; ABA; ABC-9; Abkwik; Abter; Acter; Adthec; Alfabet; Alither; Alnather; Altinate; Amther; Arh Plus; Arh; Arh; Arial; Arither; Armer; Arnet; Artem E; Artemotial; Artesa; Artestar; Artfin; Arth; Artimal; Artisin; Artiz; Asunate; Ate; Avbet; Beta Plus; Betamotil; Bioart; Cadither; Chingasu; Crush; Cumal; DMel; Dunate; Duther; E Mal; E-Dalther; Elther; Emsunate; Endomal-AT; Endomal-O; Endomal; Eralpha; Erod-M; Falciat; Falcicare; Falcicure; Falcide; Falciddum-AB; Falciddum; Falcifast; Falcigo; Falcimax; Falcinex; Falcinil; Falciquin; Falcither; Falcized; Falcy; Falcydol; Falcyguard; Falcynate; Falno; Falpar; Falrap; Falz; Flamether; Foal-BR; Fydomal; Geether; Gether; Gleether; Gofalcy; Hosither; Karat; Keether; L-Ther; Laboether; Larinate; Larither; LB Ether; Lemal; Leother; Lether; M-Quit; Malater; Malatrit-E; Malatrit-S; Malexit; Maligon-Art; Malijet; Malisor; Malither; Malnate-R; Malnate; Malona; Malther; Martis; Match; Mate; Maver; Maxinate; MDTher; Melat; Melbet-A; Melovar; Methicap; Mononate; Mosether; Myquine; Naya-AB; Nisunate; Orinate; Oxynate-AR; Palther; Paluther; Rapither-AB; *Indon.*: Artem; *Neth.*: Artecef.

Multi-ingredient Preparations. *Austral.*: Riamet; *Austria*: Riamet; *Belg.*: Amonatet†; Co-Arinate; Co-Artesiane; Riamet; *China*: An Li Kang (安立康); Artemodi; Duo-Cotecxin; Ke Tai Fu (科泰复); *Cz.*: Riamet†; *Fr.*: Riamet; *Ger.*: Riamet; *Gr.*: Arsuamoon; Riamet; *India*: Alither; Alphabetas; Arh-L; Ariufe; Arsumet-L; Arte Plus; Coartrin; Combither; Falcigo Plus; Falcimax Plus; Falcirid; Larinate Kit; Larinate-MF; Lumeart; Lumecap-A; Lumerax; Lumether; Malatrit-EL; Masunate; *Indon.*: Coartem; *Irl.*: Eurartesim; *Kor.*: Pyramax; *Neth.*: Eurartesim; Riamet; *Philipp.*: Coartem; *Port.*: Falcitrim; Riamet; *S.Afr.*: Coartem; *Singapore*: Riamet; *Swed.*: Riamet; *Switz.*: Riamet; *Thai.*: Coartem; *UK*: Eurartesim; Riamet; *USA*: Coartem.

Chloroquine *(BAN, rINN)*

Chlorochin; Chlorochina; Chloroquin; Chloroquinum; Clorochina; Cloroquina; Klorokiini; Klorokin; Хлорохин.

4-(7-Chloro-4-quinolylamino)pentyldiethylamine; 7-Chloro-4-(4-diethylamino-1-methylbutylamino)quinoline.

$C_{18}H_{26}ClN_3$=319.9

CAS — 54-05-7.

ATC — P01BA01.

UNII — 886U3H6UFF.

Pharmacopoeias. In *US*.

USP 36: (Chloroquine). A white or slightly yellow, odourless, crystalline powder. M.p. 87 degrees to 92 degrees. Very slightly soluble in water; soluble in chloroform, in ether, and in dilute acids. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Chloroquine Hydrochloride *(BANM, rINNM)*

Chloroquine, Chlorhydrate de; Chloroquini Hydrochloridum; Cloroquina, hidrocloruro de; Hidrocloruro de cloroquina; Хлорохина Гидрохлорид.

$C_{18}H_{26}ClN_3.2HCl$=392.8

CAS — 3545-67-3.

ATC — P01BA01.

UNII — NT0J0815S5.

Pharmacopoeias. *US* includes an injection.

Chloroquine Phosphate *(BANM, rINNM)*

Chingaminum; Chlorochin-difosfát; Chlorochinium Phosphoricum; Chlorochinum Diphosphoricum; Chlorochiny fosforan; Chlorokvino fosfatas; Chloroquine, Phosphate de; Chloroquini Diphosphas; Chloroquini Phosphas; Chloroquinphosphat; Cloroquina, fosfato de; Fosfato de cloroquina; Khingamin; Klorokiinifosfaatti; Klorokinfosfat; Klorokin-foszfát; Quingamine; SN-7618; Хлорохина Фосфат.

$C_{18}H_{26}ClN_3.2H_3PO_4$=515.9

CAS — 50-63-5.

ATC — P01BA01.

UNII — 6E17K3343P.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 8: (Chloroquine Phosphate). A white or almost white, hygroscopic, crystalline powder. It exists in two forms, one melting at about 195 degrees and the other at about 218 degrees. Freely soluble in water; very slightly soluble in alcohol and in methyl alcohol. A 10% solution in water has a pH of 3.8 to 4.3. Store in airtight containers. Protect from light.

USP 36: (Chloroquine Phosphate). A white, odourless, crystalline powder, which slowly discolours on exposure to light. It exists in two polymorphic forms, one melting between 193 degrees and 195 degrees and the other between 210 degrees and 215 degrees; mixture of the two forms melts between 193 degrees and 215 degrees. Freely soluble in water; practically insoluble in alcohol, in chloroform, and in ether. Its solutions have a pH of about 4.5.

Chloroquine Sulfate *(BANM, rINNM)*

Chlorochin-sulfát monohydrát; Chlorochiny siarczan; Chlorokvino sulfatas; Chloroquine, Sulfate de; Chloroquine Sulphate; Chloroquini Sulfas; Chloroquini Sulfas Monohydricus; Chloroquini Sulphas; Chloroquinsulfat; Cloroquina, sulfato de; Klorokiinisulfaatti; Klorokinsulfat; Klorokin-szulfát; RP-3377; Sulfato de cloroquina; Хлорохина Сульфат.

$C_{18}H_{26}ClN_3.H_2SO_4.H_2O$=436.0

CAS — 132-73-0 (anhydrous chloroquine sulfate).

ATC — P01BA01.

UNII — OE48649K6N.

Pharmacopoeias. In *Eur.* (see p. vii) and *Int.*

Ph. Eur. 8: (Chloroquine Sulfate). A white or almost white crystalline powder. Freely soluble in water and in methyl alcohol; very slightly soluble in alcohol. An 8% solution in water has a pH of 4.0 to 5.0. Store in airtight containers. Protect from light.

Sorption. Studies using low concentrations of chloroquine phosphate or chloroquine sulfate indicate that chloroquine shows pH-dependent binding to several materials used in medical equipment and membrane filters, including soda glass and various plastics such as cellulose acetate, cellulose propionate, methacrylate butadiene styrene, polypropylene, PVC, ethylvinyl acetate, and polyethylene.[1-3] Although this effect may not be of relevance at doses used clinically,[4] laboratory workers undertaking assays and sensitivity testing must recognise that significant reductions in concentrations can occur when chloroquine is prepared or stored in equipment made from these materials.[2,3] As the effect of borosilicate glass or polystyrene appears to be minimal, it has been suggested that they may be suitable for use in such procedures.[2,3]

Similar sorption has also been reported during membrane filtration of solutions of amodiaquine hydrochloride, mefloquine hydrochloride, or quinine sulfate.[1]

1. Baird JK, Lambros C. Effect of membrane filtration of antimalarial drug solutions on in vitro activity against Plasmodium falciparum. *Bull WHO* 1984; 62: 439–44.
2. Yahya AM, *et al.* Binding of chloroquine to glass. *Int J Pharmaceutics* 1985; 25: 217–23.
3. Yahya AM, *et al.* Investigation of chloroquine binding to plastic materials. *Int J Pharmaceutics* 1986; 34: 137–43.
4. Martens HJ, *et al.* Sorption of various drugs in polyvinyl chloride, glass, and polyethylene-lined infusion containers. *Am J Hosp Pharm* 1990; 47: 369–73.

Uses and Administration

Chloroquine is a 4-aminoquinoline antimalarial used in the treatment and prophylaxis of malaria (p. 644.1), as well as the treatment of hepatic amoebiasis (p. 919.1). It may also be used in the management of inflammatory disorders such as rheumatoid arthritis and SLE (below), as well as in sarcoidosis (p. 651.1), various skin disorders (p. 651.2) and porphyria cutanea tarda (p. 651.1). It has also been used as an adjunct to standard treatment for malignant neoplasms of the brain (p. 651.1).

Chloroquine is used for the prophylaxis and treatment of malaria due to susceptible strains of *Plasmodium ovale*, *P. vivax*, and *P. malariae*. It has also been used for susceptible strains of *P. falciparum* but in most of the world *P. falciparum* is now resistant to chloroquine, which should *not* therefore be given for treatment. Chloroquine is a rapid-acting blood schizontocide with some gametocytocidal activity against *P. ovale*, *P. vivax*, *P. malariae*, and immature gametocytes of *P. falciparum*. Since it has no activity against exoerythrocytic forms, it does not produce a radical cure of vivax or ovale malarias. The mechanism of action of chloroquine against blood schizonts remains unclear, but it may influence haemoglobin digestion by raising intravesicular pH in malaria parasite cells. It also interferes with synthesis of nucleoproteins by the parasite.

Chloroquine may be given as the phosphate, sulfate, or hydrochloride. Doses are normally expressed in terms of chloroquine base, and as a general guide:

- chloroquine base 300 mg is equivalent to about chloroquine phosphate 500 mg or chloroquine sulfate 400 mg
- chloroquine base 40 mg is equivalent to about chloroquine hydrochloride 50 mg

Oral bioavailability is increased when chloroquine is taken with food.

For the **treatment of malaria** caused by chloroquine-sensitive strains of *P. vivax*, *P. ovale*, and *P. malariae*, the usual total oral dose is the equivalent of about 25 mg/kg of chloroquine base given over 3 days. This total dose has been given in a variety of ways. One way is to give 10 mg/kg followed after 6 to 8 hours by 5 mg/kg, then 5 mg/kg daily for the next 2 days; alternatively, 10 mg/kg may be given daily for the first 2 days and 5 mg/kg on the third day. Sometimes doses are not expressed in terms of body-weight but as 600 mg followed after 6 to 8 hours by 300 mg, then 300 mg daily for the next 2 days.

Chloroquine has been given by injection for patients who are unable to take oral medication; the intravenous route is preferred and a slow rate of infusion is essential, the required dose of 25 mg/kg being given in several infusions over 30 to 32 hours. Should the patient recover sufficiently to be able to take chloroquine orally then the intravenous regimen should be halted and oral therapy started.

For **prophylaxis of malaria** in areas where *P. falciparum* is absent or in one of the few remaining areas where it is still sensitive to chloroquine, a dose equivalent to about 300 mg of chloroquine base is given once each week, beginning about one week before exposure and continuing throughout, and for at least 4 weeks after, exposure. In areas of chloroquine-resistant malaria, but with a low risk of infection, chloroquine is given with proguanil; where there is a high risk of infection alternative antimalarial regimens are recommended.

In the treatment of **hepatic amoebiasis**, chloroquine is used with an intestinal amoebicide. The usual dose is the equivalent of 600 mg of chloroquine base daily for 2 days then 300 mg daily for 2 or 3 weeks.

When chloroquine is used for *long-term therapy* in conditions such as rheumatoid arthritis or lupus erythematosus, the dosage in obese patients should be calculated on the basis of lean body-weight in order to avoid excessive dosage.

In **rheumatoid arthritis**, response to treatment may not be apparent for up to 6 months, but if there is no improvement by then treatment should be stopped. The usual dose is the equivalent of chloroquine base 150 mg daily (maximum 2.5 mg/kg daily). For precautions and guidelines concerning use by rheumatologists see under Effects on the Eyes, p. 651.2.

In discoid and systemic **lupus erythematosus** chloroquine is used in a dose equivalent to 150 mg (maximum 2.5 mg/kg) of base daily.

In the management of **light-sensitive skin eruptions**, adults may be given the equivalent of 150 to 300 mg of chloroquine base daily during periods of intense light exposure.

For details of doses in children, see below.

Administration in children. In children, chloroquine may be used orally in the treatment and prophylaxis of malaria. It may be given as the phosphate, sulfate, or hydrochloride salt, but doses are normally expressed in terms of chloroquine base.

For the **treatment of malaria** caused by chloroquine-sensitive strains of *P. vivax*, *P. ovale*, and *P. malariae*, children may be given a total dose of 25 mg/kg chloroquine base distributed over 3 days in one of the following regimens:

- 10 mg/kg initially, 5 mg/kg 6 to 8 hours later, then 5 mg/kg once daily for the next 2 days
- 10 mg/kg once daily for 2 days, then 5 mg/kg on the third day

For **prophylaxis of malaria** in areas where *P. falciparum* is absent or still sensitive to chloroquine, children may be given a weekly dose of 5 mg/kg (to a maximum of 310 mg per dose); prophylaxis should begin about 1 week before the period of malaria exposure and continue until 4 weeks after. Alternatively, UK malaria experts[1] suggest the following weekly doses based on fractions of the adult dose (see above), noting that body-weight is a better guide to dosage than age for children over 6 months of age:

- under 6 kg (up to 12 weeks of age): one-eighth the adult dose
- 6 to 9.9 kg (3 to 11 months): one-quarter the adult dose
- 10 to 15.9 kg (1 year to 3 years 11 months): three-eighths the adult dose
- 16 to 24.9 kg (4 years to 7 years 11 months): half the adult dose
- 25 to 44.9 kg (8 year to 12 years 11 months): three-quarters the adult dose
- 45 kg and over (13 years and over): the adult dose (see above)

1. Public Health England. Guidelines for malaria prevention in travellers from the UK (issued August 2013). Available at: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1203496943523 (accessed 24/10/13)

Inflammatory disorders. Chloroquine and hydroxychloroquine possess anti-inflammatory properties and they have been tried or used with some benefit in a range of inflammatory conditions which often have an immunological basis, although they rarely constitute first-line therapy in these disorders. Such conditions include rheumatoid arthritis and SLE (see under Hydroxychloroquine,

p. 655.3 and p. 656.1 respectively), ulcerative colitis,[1] infantile interstitial pneumonitis,[2,3] asthma,[4] giant cell arteritis,[5] and various skin disorders (see below). The mode of action in these conditions is unclear. Results of studies have been conflicting but it does appear that chloroquine and hydroxychloroquine might have some immunosuppressive effects.[6,7]

1. Mayer L, Sachar DB. Efficacy of chloroquine in the treatment of inflammatory bowel disease. *Gastroenterology* 1988; 94: A293.
2. Springer C, *et al.* Chloroquine treatment in desquamative interstitial pneumonia. *Arch Dis Child* 1987; 62: 76–7.
3. Kerem E, *et al.* Sequential pulmonary function measurements during treatment of infantile chronic interstitial pneumonitis. *J Pediatr* 1990; 116: 61–7.
4. Dewey A, *et al.* Chloroquine as a steroid sparing agent for asthma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 08/10/09).
5. Le Guennec P, *et al.* Management of giant cell arteritis: value of synthetic antimalarial agents: a retrospective study of thirty six patients. *Rev Rhum* 1994; 61: 423–8.
6. Bygbjerg IC, Flachs H. Effect of chloroquine on human lymphocyte proliferation. *Trans R Soc Trop Med Hyg* 1986; 80: 231–5.
7. Prasad RN, *et al.* Immunopharmacology of chloroquine. *Trans R Soc Trop Med Hyg* 1987; 81: 168–9.

Malignant neoplasms of the brain. Chloroquine is a strong DNA-intercalating agent and inhibitor of lysosomic enzymes.[1] As a result, there has been interest in its ability to sensitise cancer cells to the cytotoxic effects of radio- and chemotherapy, particularly in patients with glioblastoma multiforme (GBM), the treatment of which is described under Malignant Neoplasms of the Brain, p. 701.2.

In a randomised, double-blind, placebo-controlled study[2] involving 30 patients with GBM, addition of long-term chloroquine therapy to the standard treatment regimen of surgery, radiotherapy, and chemotherapy (with carmustine) resulted in a median survival of 24 months, compared with only 11 months for those not treated with chloroquine. A subsequent retrospective study[3] observing 41 patients given chloroquine as an optional adjunct to conventional treatment noted similar improvement in survival compared with controls.

1. Munshi A. Chloroquine in glioblastoma–new horizons for an old drug. *Cancer* 2009; 115: 2380–3.
2. Sotelo J, *et al.* Adding chloroquine to conventional treatment for glioblastoma multiforme: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2006; 144: 337–43.
3. Briceño E, *et al.* Institutional experience with chloroquine as an adjuvant to the therapy for glioblastoma multiforme. *Surg Neurol* 2007; 67: 388–91.

Porphyria cutanea tarda. Chloroquine and hydroxychloroquine have been used with some benefit in the treatment of porphyria cutanea tarda (p. 1556.1) and low doses (such as chloroquine phosphate 125 mg or hydroxychloroquine sulfate 200 mg given twice weekly) have been considered by some to be useful in patients unsuitable for phlebotomy.[1-4] However, the acute increase in urinary porphyrins and fall in hepatic porphyrin content produced by these drugs have been associated with a variable degree of hepatotoxicity[5,6] and others prefer to use desferrioxamine.[7]

1. Grossman ME, *et al.* Porphyria cutanea tarda. *Am J Med* 1979; 67: 277–86.
2. Cainelli T, *et al.* Hydroxychloroquine versus phlebotomy in the treatment of porphyria cutanea tarda. *Br J Dermatol* 1983; 108: 593–600.
3. Ashton RE, *et al.* Low-dose oral chloroquine in the treatment of porphyria cutanea tarda. *Br J Dermatol* 1984; 111: 609–13.
4. Stölzel U, *et al.* Hemochromatosis (HFE) gene mutations and response to chloroquine in porphyria cutanea tarda. *Arch Dermatol 2003*; 139: 309–13.
5. Scholnick PL, *et al.* The molecular basis of the action of chloroquine in porphyria cutanea tarda. *J Invest Dermatol* 1973; 61: 226–32.
6. Rossmann-Ringdahl I, Olsson R. Porphyria cutanea tarda: effects and risk factors for hepatotoxicity from high-dose chloroquine treatment. *Acta Derm Venereol* 2007; 87: 401–5.
7. Rocchi E. Treatment of porphyria cutanea tarda. *Br J Dermatol* 1987; 116: 139–40.

Rheumatoid arthritis. For reference to the use of chloroquine in the treatment of rheumatoid arthritis, see under Hydroxychloroquine, p. 655.3.

Sarcoidosis. Chloroquine and hydroxychloroquine have been tried in the management of sarcoidosis (p. 1612.2) as alternatives or adjuncts to corticosteroid therapy.

References.

1. O'Leary TJ, *et al.* The effects of chloroquine on serum 1,25-dihydroxyvitamin D and calcium metabolism in sarcoidosis. *N Engl J Med* 1986; 315: 727–30.
2. Adams JS, *et al.* Effective reduction in the serum 1,25-dihydroxyvitamin D and calcium concentration in sarcoidosis-associated hypercalcemia with short-course chloroquine therapy. *Ann Intern Med* 1989; 111: 437–8.
3. DeSimone DP, *et al.* Granulomatous infiltration of the talus and abnormal vitamin D and calcium metabolism in a patient with sarcoidosis: successful treatment with hydroxychloroquine. *Am J Med* 1989; 87: 694–6.
4. Jones E, Callen JP. Hydroxychloroquine is effective therapy for control of cutaneous sarcoidal granulomas. *J Am Acad Dermatol* 1990; 23: 487–9.
5. Zic JA, *et al.* Treatment of cutaneous sarcoidosis with chloroquine: review of the literature. *Arch Dermatol* 1991; 127: 1034–40.
6. Baltzan M, *et al.* Randomized trial of prolonged chloroquine therapy in advanced pulmonary sarcoidosis. *Am J Respir Crit Care Med* 1999; 160: 192–7.

Scorpion stings. Local infiltration of 2.5 mL (161 mg) of a parenteral chloroquine formulation has been used to relieve pain from scorpion stings (p. 2418.1) in Ghana.[1]

1. Yenli EM, *et al.* Managing scorpion stings in the tropics: chloroquine as an effective drug. *Trop Doct* 2010; 40: 119–20.

Skin disorders. In addition to their use in lupus erythematosus hydroxychloroquine and chloroquine have been tried in some other skin disorders including polymorphic light eruptions[1] (see Photosensitivity Disorders, p. 1686.2), lichen planus[2,3] (p. 1685.2), cutaneous symptoms of dermatomyositis (p. 1611.1), erythema nodosum,[4,5] and recurrent erythema multiforme (p. 1684.3). It has also been tried in mild type 2 lepra reactions (erythema nodosum leprosum, see Leprosy, p. 188.3). Hydroxychloroquine, in particular, has been successfully used to treat idiopathic follicular mucinosis.[6]

1. Murphy GM, *et al.* Hydroxychloroquine in polymorphic light eruption: a controlled trial with drug and visual sensitivity monitoring. *Br J Dermatol* 1987; 116: 379–86.
2. Mostafa WZ. Lichen planus of the nail: treatment with antimalarials. *J Am Acad Dermatol* 1989; 20: 289–90.
3. De Argila D, *et al.* Isolated lichen planus of the lip successfully treated with chloroquine phosphate. *Dermatology* 1997; 195: 284–5.
4. Alloway JA, Franks LK. Hydroxychloroquine in the treatment of chronic erythema nodosum. *Br J Dermatol* 1995; 132: 661–2.
5. Jarrett P, Goodfield MJD. Hydroxychloroquine and chronic erythema nodosum. *Br J Dermatol* 1996; 134: 373.
6. Schneider SW, *et al.* Treatment of so-called idiopathic follicular mucinosis with hydroxychloroquine. *Br J Dermatol* 2010; 163: 420–3.

Systemic lupus erythematosus. For reference to the use of chloroquine in cutaneous lupus erythematosus and SLE, see Hydroxychloroquine, p. 656.1.

Adverse Effects

Adverse effects from dosage regimens of chloroquine used in the treatment and prophylaxis of malaria are generally less common and less severe than those associated with the higher doses used for prolonged periods in rheumatoid arthritis.

Frequent adverse effects of chloroquine include headache, various skin eruptions, pruritus, and gastrointestinal disturbances such as nausea, vomiting, and diarrhoea. More rarely, mental changes including psychotic episodes and hallucinations, delirium, anxiety, and agitation, insomnia, depression, and personality changes may occur. Polyneuritis and convulsions have also been reported.

Visual disturbances such as blurred vision and difficulties in focusing have occurred but these are more common with higher doses, when they may be associated with keratopathy or retinopathy, as discussed under Effects on the Eyes, below. Keratopathy usually occurs in the form of corneal opacities and is normally reversible when chloroquine is withdrawn. Retinopathy is the most serious adverse effect of chloroquine on the eyes and it can result in severe visual impairment. Changes may be irreversible and can even progress after chloroquine is stopped. Those taking high doses of chloroquine for prolonged periods appear to be at greatest risk of developing retinopathy.

Other uncommon adverse effects from prolonged use include loss of hair, bleaching of hair pigment, bluish-black pigmentation of the mucous membranes and skin, photosensitivity, tinnitus, reduced hearing, nerve deafness, neuromyopathy, and myopathy, including cardiomyopathy.

Blood disorders have been reported rarely. They include pancytopenia, aplastic anaemia, reversible agranulocytosis, thrombocytopenia, and neutropenia.

There have also been rare reports of changes in liver function, including hepatitis and abnormal liver function tests.

Parenteral therapy with chloroquine can be hazardous and rapid intravenous dosage or the use of high doses can result in cardiovascular toxicity and other symptoms of acute overdosage.

Acute overdosage with chloroquine is extremely dangerous and death can occur within a few hours. Initial effects include headache, gastrointestinal disturbances, drowsiness, and dizziness. Hypokalaemia may occur within a few hours of ingestion of chloroquine. Visual disturbances may be dramatic with a sudden loss of vision. However, the main effect of overdosage with chloroquine is cardiovascular toxicity with hypotension and cardiac arrhythmias progressing to cardiovascular collapse, convulsions, cardiac and respiratory arrest, coma, and death.

Effects on the eyes. The main adverse effects of chloroquine and hydroxychloroquine on the eye are keratopathy and retinopathy.

Keratopathy, characterised by corneal deposits, may occur within a few weeks of starting treatment. However, patients are often asymptomatic and fewer than 50% of affected patients complain of visual symptoms such as photophobia, haloes around lights, or blurred vision. Keratopathy is completely reversible on withdrawal of treatment and is not usually considered to be a contra-indication to continued treatment.[1]

Retinopathy is potentially more serious. The outcome on stopping treatment is unpredictable and changes may be irreversible or may even progress.[2,3] Delayed-onset retinopathy has also been reported in patients many years after cessation of treatment.[4] The reported incidence of retinopathy varies according to the methodology and criteria used.[1,5,6] From studies in patients on long-term antimalarial treatment, it was reported[1] that an accumulation of 100 g of chloroquine [phosphate] (250 mg daily for 1 year) might cause retinopathy; the risk was significantly increased as the total dosage exceeded 300 g. Experience in rheumatology also indicates that the incidence of retinal toxicity is dose-related. While the total cumulative dose, the duration of treatment, and the age of the patient might all affect the incidence of retinal toxicity,[7,8] the daily dose might be the most important factor.[9] It has been suggested that the risk of retinal damage is small with daily doses of up to 4 mg/kg of chloroquine phosphate (= about 2.5 mg/kg of chloroquine base daily) or up to 6.5 mg/kg of hydroxychloroquine sulfate.[9] In obese patients, excessive dosage should be avoided by calculating dosage on the basis of lean body-weight. It appears that retinopathy is rarely, if ever, associated with the weekly dosages of chloroquine recommended for the prophylaxis of malaria.[10,11]

In the UK, a review group[12] convened by the Royal College of Ophthalmologists made **recommendations** regarding use by rheumatologists and dermatologists. Chloroquine should only be used if other drugs have failed as there are inadequate data to advise on a safe daily or cumulative dose; thus the following recommendations relate only to *hydroxychloroquine* as no guidelines have been published for chloroquine.

- Baseline assessment before treatment with hydroxychloroquine is commenced (maximum daily dosage 6.5 mg/kg lean body-weight) should consist of checking renal and hepatic function, questioning the patient about visual impairment not corrected by glasses, and recording near visual acuity.
- Thereafter, patients should be monitored annually with enquiry about visual symptomatology, rechecking of acuity, and assessment for impaired vision.
- Patients should be referred to an ophthalmologist if problems are detected either before or during treatment.
- Those taking long-term hydroxychloroquine should be subject to occasional ophthalmological review after 5 years of continuous treatment.

UK licensed product information for *chloroquine* recommends ophthalmic examination at 3 to 6 monthly intervals in patients receiving continuous high doses for more than a year, or weekly treatment for more than 3 years, or for those in whom total intake exceeds 100 g or 1.6 g/kg.

Similar guidelines on screening have been issued in the USA.[13]

1. Bernstein HN. Ophthalmologic considerations and testing in patients receiving long-term antimalarial therapy. *Am J Med* 1983; 75 (suppl 1A): 25–34.
2. Ogawa S, *et al.* Progression of retinopathy long after cessation of chloroquine therapy. *Lancet* 1979; i: 1408.
3. Easterbrook M. Ocular effects and safety of antimalarial agents. *Am J Med* 1988; 85 (suppl 4A): 23–9.
4. Ehrenfeld M, *et al.* Delayed-onset chloroquine retinopathy. *Br J Ophthalmol* 1986; 70: 281–3.
5. Finbloom DS, *et al.* Comparison of hydroxychloroquine and chloroquine use and the development of retinal toxicity. *J Rheumatol* 1985; 12: 692–4.
6. Morsman CDG, *et al.* Screening for hydroxychloroquine retinal toxicity: is it necessary? *Eye* 1990; 4: 572–6.
7. Elman A, *et al.* Chloroquine retinopathy in patients with rheumatoid arthritis. *Scand J Rheumatol* 1976; 5: 161–6.
8. Marks JS, Power BJ. Is chloroquine obsolete in treatment of rheumatic disease? *Lancet* 1979; i: 371–3.
9. Mackenzie AH. Dose refinements in long-term therapy of rheumatoid arthritis with antimalarials. *Am J Med* 1983; 75 (suppl 1A): 40–5.
10. Breckenridge A. Risks and benefits of prophylactic antimalarial drugs. *BMJ* 1989; 299: 1057–8.
11. Lange WR, *et al.* No evidence for chloroquine-associated retinopathy among missionaries on long-term malaria chemoprophylaxis. *Am J Trop Med Hyg* 1994; 51: 389–92.
12. Bourke B *et al.* Royal College of Ophthalmologists, British Association of Dermatologists, and British Society for Rheumatology. Hydroxychloroquine and ocular toxicity: recommendations on screening (October 2009). Available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Hydroxychloroquine_and_Ocular_Toxicity_final%20Oct%202009.pdf (accessed 04/08/10)
13. Marmor MF, *et al.* American Academy of Ophthalmology. Revised recommendations on screening for chloroquine and hydroxychloroquine retinopathy. *Ophthalmology* 2011; 118: 415–22.

Effects on glucose metabolism. While hypoglycaemia has occurred with quinine (see p. 667.1), it was not generally thought to be associated with *chloroquine*; however, there has been a report of its occurrence in a patient with reactive hypoglycaemia who was using chloroquine for the management of psoriatic arthritis.[1]

Recurrent hypoglycaemia was also reported in a non-diabetic patient given *hydroxychloroquine* for the treatment of rheumatoid arthritis.[2]

1. Abu-Shakra M, Lee P. Hypoglycemia: an unusual adverse reaction to chloroquine. *Clin Exp Rheumatol* 1994; 12: 95.

2. Cansu DÜ, Korkmaz C. Hypoglycaemia induced by hydroxychloroquine in a non-diabetic patient treated for RA. *Rheumatology (Oxford)* 2008; 47: 378–9.

Effects on the hair. Hair depigmentation is a rare, but reversible adverse effect of chloroquine.[1,2] Most cases have occurred after 3 consecutive months of treatment with daily oral doses of 500 mg or more, although rapid onset is also possible;[1] hypopigmentation seldom occurs with daily doses of less than 300 mg.[2] These effects are entirely reversible, with normal pigmentation returning once the dose of chloroquine is stopped or reduced.[2] Although hydroxychloroquine has also very rarely been reported to cause hypopigmentation,[2,3] chloroquine-induced hypopigmentation has resolved after chloroquine was replaced with hydroxychloroquine.[2]

1. Donovan JC, Price VH. Images in clinical medicine. Chloroquine-induced hair hypopigmentation. *N Engl J Med* 2010; 363: 372.
2. Di Giacomo TB, *et al.* Chloroquine -induced hair depigmentation. *Lupus* 2009; 18: 264–6.
3. Meller S, *et al.* Clinical image: blonde by prescription. *Arthritis Rheum* 2008; 58: 2286.

Effects on the heart. Studies in patients with malaria[1] and in healthy subjects[2] indicate that the acute cardiovascular toxicity that may be associated with parenteral use of chloroquine is related to transiently high plasma concentrations produced during the early part of the distribution phase; these findings appear to confirm that the dosage rate is a major determinant of this toxicity. Cardiac conduction abnormalities, including heart block and sudden cardiac arrest, have also occurred in patients receiving long-term oral therapy with chloroquine,[3,4] including use in lupus erythematosus,[5,6] as well as after chloroquine overdosage or abuse.[7,8] Histological changes in endomyocardial biopsy specimens from 2 patients with cardiomyopathy associated with chloroquine or hydroxychloroquine therapy were found to be virtually identical to those seen in the skeletal muscle of patients with chloroquine-induced myopathy[9] (see also Effects on the Muscles, below).

1. White NJ, *et al.* Parenteral chloroquine for treating falciparum malaria. *J Infect Dis* 1987; 155: 192–201.
2. Looareesuwan S, *et al.* Cardiovascular toxicity and distribution kinetics of intravenous chloroquine. *Br J Clin Pharmacol* 1986; 22: 31–6.
3. Ogola ESN, *et al.* Chloroquine related complete heart block with blindness: case report. *East Afr Med J* 1992; 69: 50–2.
4. Aslanger E, Altun I. Sudden cardiac arrest in a patient taking chloroquine. *Resuscitation* 2009; 80: 285–6.
5. Piette J-C, *et al.* Chloroquine cardiotoxicity. *N Engl J Med* 1987; 317: 710–11.
6. Baguet J-P, *et al.* Chloroquine cardiomyopathy with conduction disorders. *Heart* 1999; 81: 221–3.
7. Ihenacho HNC, Magulike E. Chloroquine abuse and heart block in Africans. *Aust N Z J Med* 1989; 19: 17–21.
8. Phipps C, *et al.* Fatal chloroquine poisoning: a rare cause of sudden cardiac arrest. *Ann Acad Med Singapore* 2011; 40: 296–2.
9. Ratliff NB, *et al.* Diagnosis of chloroquine cardiomyopathy by endomyocardial biopsy. *N Engl J Med* 1987; 316: 191–3.

Effects on mental function. Serious psychotic effects (depersonalisation and anxiety) developed in a healthy subject who took a standard 3-day course of oral chloroquine for the treatment of *Plasmodium falciparum* malaria, as part of a clinical study. Three weeks after completing the course she still had serious concentration problems and her symptoms gradually resolved over the next 4 months.[1]

1. Telgt DS, *et al.* Serious psychiatric symptoms after chloroquine treatment following experimental malaria infection. *Ann Pharmacother* 2005; 39: 551–4.

Effects on the muscles. The myopathy induced by chloroquine is characterised by progressive weakness and atrophy of proximal muscles and can develop insidiously after periods of therapy ranging from a few weeks to a few years.[1] There are often mild sensory changes, depression of tendon reflexes, and abnormal nerve conduction studies suggestive of an associated peripheral neuropathy. The myopathy is reversible on withdrawal of treatment but recovery may take several months. Cardiomyopathy may also occur (see under Effects on the Heart, above). Similar effects have been reported with hydroxychloroquine.[2] In a retrospective review of 4405 patients with rheumatic disorders, 214 had received chloroquine or hydroxychloroquine and, of these, 3 developed myopathy.[3]

1. Mastaglia FL. Adverse effects of drugs on muscle. *Drugs* 1982; 24: 304–21.
2. Estes ML, *et al.* Chloroquine neuromyotoxicity. *Am J Med* 1987; 82: 447–55.
3. Avina-Zubieta JA, *et al.* Incidence of myopathy in patients treated with antimalarials: a report of three cases and a review of the literature. *Br J Rheumatol* 1995; 34: 166–70.

Effects on the nervous system. Apart from neuropathies (see Effects on the Muscles, above) other adverse effects of chloroquine on the nervous system have included isolated reports of extrapyramidal symptoms and other involuntary movements[1,2] (in patients being treated for malaria), nystagmus[3] (in a patient on prolonged treatment for rheumatoid arthritis), and convulsions[4,5] and nonconvulsive status epilepticus[6] (in patients on malaria prophylaxis).

1. Umez-Eronini EM, Eronini EA.. Chloroquine induced involuntary movements. *BMJ* 1977; 1: 945–6.
2. Singhi S, *et al.* Chloroquine-induced involuntary movements. *BMJ* 1977; 2: 520.
3. Marks JS. Motor polyneuropathy and nystagmus associated with chloroquine phosphate. *Postgrad Med J* 1979; 55: 569.
4. Fish DR, Espir MLE. Convulsions associated with prophylactic antimalarial drugs: implications for people with epilepsy. *BMJ* 1988; 297: 526–7.
5. Fish DR, Espri MLE. Malaria prophylaxis and epilepsy. *BMJ* 1988; 297: 1267.
6. Mülhauser P, *et al.* Chloroquine and nonconvulsive status epilepticus. *Ann Intern Med* 1995; 123: 76–7.

Effects on the skin. *Pruritus* is common in patients given chloroquine for the treatment of malaria and it may become so severe as to compromise treatment. Itching starts a few hours after use but usually remits spontaneously within 72 hours. Although antihistamines are generally thought ineffective,[1,2] a few patients may obtain some relief.[3] The incidence of pruritus is purported to be higher in black patients, but this may only reflect the greater number of black patients surveyed. The aetiology of this reaction is unknown, but this apparent higher incidence has prompted suggestions that it may have a genetic basis[4] or be related to the affinity of chloroquine for melanin.[2] Chloroquine's main metabolite, monodesethylchloroquine, has been implicated,[5] although there is also some evidence suggesting that patients with pruritus metabolise chloroquine more slowly.[6] A survey[1] in Nigeria found that, of 1100 patients, 74% had pruritus during antimalarial therapy; 61% of these reacted to chloroquine, 30% reacted to amodiaquine, 2.5% to Fansidar (pyrimethamine-sulfadoxine), and, 6.5% reacted to all three. In another study in Nigeria,[4] the incidence of pruritus was reported to be 14% (8 of 56 patients) for chloroquine, 27% (14 of 52) for amodiaquine, and 13% (7 of 53) for halofantrine; none of 58 patients receiving quinine or 82 patients receiving mefloquine had pruritus. In contrast, in a study in Thailand only 1.9% of 1189 chloroquine-treated patients reported pruritus.[7]

There have been rare reports of more severe cutaneous reactions associated with chloroquine, including *toxic epidermal necrolysis*,[8,9] *erythema multiforme*,[10] and *Stevens-Johnson syndrome*,[11] although the causal role of chloroquine is not always clear as some of these patients also received other antimalarials, sometimes at an inappropriate dosage. In a more recent case of toxic epidermal necrolysis,[12] chloroquine given alone for malaria prophylaxis was the probable cause. A young patient receiving radiotherapy developed a localised bullous eruption and rapid progressive moist desquamation on the third day of treatment with oral chloroquine for malaria.[13] For a discussion including the possible effect of chloroquine on the incidence of erythema multiforme in patients taking pyrimethamine with sulfadoxine, see Adverse Effects with Sulfonamides, under Pyrimethamine, p. 663.3.

1. Ajayi AA, *et al.* Epidemiology of antimalarial-induced pruritus in Africans. *Eur J Clin Pharmacol* 1989; 37: 539–40.
2. Osifo NG. Chloroquine-induced pruritus among patients with malaria. *Arch Dermatol* 1984; 120: 80–2.
3. Okor RS. Responsiveness of chloroquine-induced pruritus to antihistamine therapy—clinical survey. *J Clin Pharm Ther* 1990; 15: 147–50.
4. Sowunmi A, *et al.* Pruritus and antimalarial drugs in Africans. *Lancet* 1989; II: 213.
5. Essien EE, *et al.* Chloroquine disposition in hypersensitive and non-hypersensitive subjects and its significance in chloroquine-induced pruritus. *Eur J Drug Metab Pharmacokinet* 1989; 14: 71–7.
6. Ademowo OG, *et al.* The disposition of chloroquine and its main metabolite desethylchloroquine in volunteers with and without chloroquine-induced pruritus: evidence for decreased chloroquine metabolism in volunteers with pruritus. *Clin Pharmacol Ther* 2000; 67: 237–41.
7. Bussaratid V, *et al.* Frequency of pruritus in Plasmodium vivax malaria patients treated with chloroquine in Thailand. *Trop Doct* 2000; 30: 211–14.
8. Kanwar AJ, Singh OP. Toxic epidermal necrolysis—drug induced. *Indian J Dermatol* 1976; 21: 73–7.
9. Phillips-Howard PA, Warwick Buckler J. Idiosyncratic reaction resembling toxic epidermal necrolysis caused by chloroquine and Maloprim. *BMJ* 1988; 296: 1605.
10. Steffen R, Somaini B. Severe cutaneous adverse reactions to sulfadoxine-pyrimethamine in Switzerland. *Lancet* 1986; i: 610.
11. Bamber MG, *et al.* Fatal Stevens-Johnson syndrome associated with Fansidar and chloroquine. *J Infect* 1986; 13: 31–3.
12. Boffa MJ, Chalmers RJG. Toxic epidermal necrolysis due to chloroquine phosphate. *Br J Dermatol* 1994; 131: 444–5.
13. Rustogi A, *et al.* Unexpected skin reaction induced by radiotherapy after chloroquine use. *Lancet Oncol* 2006; 7: 608–9.

Overdosage. For adverse effects associated with chloroquine overdosage, see Treatment of Adverse Effects, below.

Treatment of Adverse Effects

Acute overdosage with chloroquine can be rapidly lethal and intensive symptomatic supportive treatment should be started immediately (see Acute Poisoning, p. 1537.1). The first steps should be to maintain adequate respiration and to correct any cardiovascular disturbances. Early use of adrenaline with diazepam (see below) may minimise the cardiotoxicity of chloroquine and control arrhythmias. The benefit of gastric decontamination is uncertain, but the UK *National Poisons Information Service* advises that the use of oral activated charcoal can be considered for adults or children who present within 1 hour of ingesting more than the equivalent of 20 mg/kg of chloroquine base; alternatively for adults, gastric lavage can be considered within 1 hour of a potentially life-threatening overdose (but see below). Intravenous sodium bicarbonate should be given to correct metabolic acidosis. Other methods to increase the elimination of chloroquine, such as dialysis, are probably of little use.

Overdosage. Chloroquine overdosage is the most severe and frequent cause of intoxication with antimalarial drugs and chloroquine is often used for suicide attempts. Severe toxic manifestations may occur within 1 to 3 hours and fatal outcomes usually occur within 2 to 3 hours of drug ingestion. The major clinical symptoms are of neurological, respiratory, and cardiovascular toxicity;[1] death is usually due to cardiac arrest related to the direct effect of chloroquine on the myocardium.[2] Chloroquine has a low safety margin: doses of 20 mg/kg are considered toxic and 30 mg/kg may be lethal. The mortality rate in some published studies has ranged from 10 to 30%.[1]

Gastric lavage is not generally recommended by the UK *National Poisons Information Service* but they suggest it may be considered in adults if seen within 1 hour of a potentially life-threatening overdose of chloroquine. However, it has been noted that if it were attempted it should be preceded by correction of severe cardiovascular disturbances and institution of artificial ventilation because insertion of the stomach tube may induce sudden cardiac arrest or convulsions; induction of emesis is contra-indicated because of the risk of lung aspiration.[1]

Activated charcoal has been recommended to limit absorption of chloroquine that may be left in the gut.[3] There is no evidence to indicate that attempts to increase chloroquine elimination such as acidification of the urine, haemodialysis, peritoneal dialysis, or exchange transfusion are effective in overdosage. Elimination in the urine is more dependent on haemodynamic status than on infusion of osmotic solutions or acidification. Any clearance achieved by haemoperfusion or haemodialysis is low in comparison with the normal total body clearance.[1]

It is not clear if correction of hypokalaemia is essential, but giving potassium should be avoided in the initial phases of intoxication when conduction disturbances still exist. The degree of hypokalaemia may be correlated with the severity of chloroquine intoxication and might be useful diagnostically.[4] However, chloroquine-induced hypokalaemia may be due to a transport-dependent mechanism rather than to true potassium depletion and overzealous correction could result in hyperkalaemia.[4]

Since there had been no effective treatment for severe chloroquine poisoning, one group of workers tried using early mechanical ventilation, with adrenaline and high doses of diazepam, both given intravenously, to counteract cardiotoxicity, with encouraging results.[2] Diazepam had earlier been shown to decrease the cardiotoxicity of chloroquine in *animal* studies and there had been several clinical reports of beneficial responses. It was considered that routine use of adrenaline before the onset of cardiac arrhythmia might be beneficial in the treatment of severe chloroquine poisoning.[2] UK licensed product information for chloroquine suggests giving adrenaline by intravenous infusion in a dose of 250 nanograms/kg per minute initially, with increments of 250 nanograms/kg per minute until adequate systolic blood pressure is restored, and diazepam by intravenous infusion in a dose of 2 mg/kg over 30 minutes as a loading dose, followed by 1 to 2 mg/kg per day for up to 2 to 4 days.

Overdosage with hydroxychloroquine has responded to measures similar to those used in the management of chloroquine overdosage.[5]

1. Jaeger A, *et al.* Clinical features and management of poisoning due to antimalarial drugs. *Med Toxicol* 1987; 2: 242–73.
2. Riou B, *et al.* Treatment of severe chloroquine poisoning. *N Engl J Med* 1988; 318: 1–6.
3. Neuvonen PJ, *et al.* Prevention of chloroquine absorption by activated charcoal. *Hum Exp Toxicol* 1992; 11: 117–20.
4. Clemessy J-L, *et al.* Hypokalaemia related to acute chloroquine ingestion. *Lancet* 1995; 346: 877–80.
5. Jordan P, *et al.* Hydroxychloroquine overdose: toxicokinetics and management. *J Toxicol Clin Toxicol* 1999; 37: 861–4.

Precautions

Excessive doses of chloroquine and hydroxychloroquine are associated with retinal or visual field changes and the precautions to be taken in order to minimise such toxicity are discussed under Effects on the Eyes in Adverse Effects, p. 651.2. There may be a temporary effect on visual accommodation.

Care is necessary when giving chloroquine to patients with hepatic or renal impairment, or to those with severe gastrointestinal disorders, a history of psoriasis, or

neurological disorders, especially a history of epilepsy (see below for advice not to use for malaria prophylaxis). Chloroquine should be used with caution in patients with myasthenia gravis as it may aggravate the condition. Patients with G6PD deficiency should be observed for haemolytic anaemia during chloroquine treatment (but see below). Full blood counts should be performed at regular intervals during extended treatment with chloroquine. Although there have been reports of fetal abnormalities associated with the use of chloroquine during pregnancy, the risks of malaria are considered to be greater and there appears to be no justification for withholding chloroquine for the treatment or prophylaxis of malaria.

It is important that if chloroquine is given intravenously it should be by slow infusion (typically around 0.8 to 1.25 mg/kg per hour) otherwise severe cardiotoxicity may develop.

Breast feeding. Chloroquine is distributed into breast milk, but not in an amount adequate to provide chemoprophylaxis against malaria for the infant (see under Pharmacokinetics, p. 654.2). Furthermore, no adverse effects have been seen in breast-feeding infants whose mothers were receiving chloroquine, and the most recent guidance from the American Academy of Pediatrics considered[1] that it was therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 16/04/04)

Epilepsy. After reports[1,2] of convulsions associated with the use of chloroquine for malaria prophylaxis in 4 previously healthy patients and in 2 patients with a history of seizures, it has been suggested that prospective travellers who have a history of epilepsy should be warned of the risk. Although it was initially considered[3] that this should not restrict the use of chloroquine, UK malaria experts have recommended that it should be avoided for malaria prophylaxis in patients with epilepsy.[4]

1. Fish DR, Espir MLE. Convulsions associated with prophylactic antimalarial drugs: implications for people with epilepsy. *BMJ* 1988; 297: 526–7.
2. Fish DR, Espir MLE. Malaria prophylaxis and epilepsy. *BMJ* 1988; 297: 1267.
3. Hellgren U, Rombo L. Malaria prophylaxis and epilepsy. *BMJ* 1988; 297: 1267.
4. Public Health England. Guidelines for malaria prevention in travellers from the UK (issued August 2013). Available at: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1203496943523 (accessed 24/10/13)

G6PD deficiency. Licensed product information for chloroquine advises that the drug be used with caution in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, as there may be a risk of haemolysis. However, a review[1] noted that reports of haemolysis in G6PD-deficient patients given chloroquine involved its use with other agents known to cause haemolysis and that there were no reports showing an association between chloroquine monotherapy and haemolysis in G6PD-deficient patients. It concluded that, while it was prudent to use caution in G6PD-deficient patients when combining chloroquine with drugs that may cause haemolysis, there was no basis upon which to contravene chloroquine monotherapy.

1. Youngster I, *et al.* Medications and glucose-6-phosphate dehydrogenase deficiency: an evidence-based review. *Drug Safety* 2010; 33: 713–26.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies *chloroquine* as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1] Other drugs used for the prophylaxis and/or treatment of malaria such as *doxycycline, hydroxychloroquine, mefloquine, proguanil* (alone or with *atovaquone*), and *quinine* are also classified as possibly porphyrinogenic.

Tetracycline and the combination of *artemether plus lumefantrine* are classified as probably porphyrinogenic, while *clindamycin* is classified as porphyrinogenic; they should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

Atovaquone is classified as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

Pyrimethamine is not classified.

Chloroquine has been tried in the treatment of porphyria cutanea tarda, but this may be associated with hepatotoxicity (see under Uses, p. 651.1).

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 10/10/11)

Pregnancy. There has been concern about the potential teratogenic effects of chloroquine because of a few case reports including defects in hearing and vision.[1] Two of 169 infants, born to women given chloroquine 300 mg weekly throughout pregnancy, had birth defects compared with 4 of 454 control infants whose mothers had not received antimalarials; the difference was not significant. Similarly, a randomised, placebo-controlled study[2] in 951 pregnant Thai women found that the use of prophylactic chloroquine (dosed as above) during pregnancy had no impact on maternal anaemia, infant birth-weight, gestational age, or development, or on their growth, neurological development, or visual acuity at 1 year of age. The data suggested that chloroquine in the recommended *prophylactic* doses is not a strong teratogen and that its proved antimalarial benefits outweigh any possible risk of low-grade teratogenicity. The UK *National Teratology Information Service*[3] notes that, despite isolated case reports suggesting an increased risk of ototoxicity, the majority of studies have similarly failed to find any increased risk to the fetus from *high* maternal doses of chloroquine during pregnancy; based on the available data, they consider that chloroquine does not lead to an increased teratogenic risk and the drug may therefore be used at any stage of pregnancy if indicated and anticipated to be effective.[3]

1. Wolfe MS, Cordero JF. Safety of chloroquine in chemosuppression of malaria during pregnancy. *BMJ* 1985; 290: 1466–7.
2. Villegas L, *et al.* Chloroquine prophylaxis against vivax malaria in pregnancy: a randomized, double-blind, placebo-controlled trial. *Trop Med Int Health* 2007; 12: 209–18.
3. National Teratology Information Service. Use of chloroquine in pregnancy (issued September 2008). Available at: http://www.toxbase.org/upload/Pregnancy%20pdfs/Chloroquine%202008.pdf (accessed 08/06/11)

Psoriatic arthritis. It is recommended that chloroquine and hydroxychloroquine should not be used in the treatment of psoriatic arthritis as exacerbations of skin lesions can occur. Some patients may go on to develop generalised erythroderma with subsequent exfoliative dermatitis.[1] However, there has been controversy over the reported incidence of this adverse effect.[2,3]

1. Slagel GA, James WD. Plaquenil-induced erythroderma. *J Am Acad Dermatol* 1985; 12: 857–62.
2. Luzar MJ. Hydroxychloroquine in psoriatic arthropathy: exacerbations of psoriatic skin lesions. *J Rheumatol* 1982; 9: 462–4.
3. Sayers ME, Mazanec DJ. Use of antimalarial drugs for the treatment of psoriatic arthritis. *Am J Med* 1992; 93: 474–5.

Renal impairment. Although the elimination of chloroquine is prolonged in renal impairment no dosage adjustment is required in the treatment of malaria. Similarly, dosage reduction is not required for chloroquine prophylaxis except in those with severe renal impairment. Doses tend to be reduced when it is given for longer periods to patients with renal impairment.

Interactions

There is an increased risk of inducing ventricular arrhythmias if chloroquine is used with halofantrine (see p. 655.1) or other arrhythmogenic drugs such as amiodarone and moxifloxacin. There is an increased risk of convulsions when chloroquine is given with mefloquine. The absorption of chloroquine can be reduced by antacids or kaolin; when any of these drugs are used with chloroquine dosing should be separated by at least 4 hours. The metabolism of chloroquine may be inhibited by cimetidine.

Agalsidase. For a warning that chloroquine should not be used with *agalsidase alfa* or *beta*, see p. 2438.1.

Antiepileptics. Chloroquine may lower the convulsive threshold and thus antagonise the actions of antiepileptics such as *carbamazepine* and *valproate*.

Antimalarials. Chloroquine should not be used with *halofantrine* since the latter prolongs the QT interval and therefore there is an increased potential to induce arrhythmias (see p. 655.1). Use of chloroquine with *mefloquine* increases the risk of convulsions. Also use of chloroquine with *proguanil* may increase the incidence of proguanil-associated mouth ulceration.[1] The activity of chloroquine may be affected when it is given with other *antimalarials*. *Quinine* and chloroquine when used together may be antagonistic.[2] Mixtures of chloroquine with *quinine, mefloquine, amodiaquine, artemisinin,* or *pyrimethamine-sulfadoxine* were antagonistic *in vitro* against *Plasmodium falciparum*.[3]

1. Drysdale SF, *et al.* Proguanil, chloroquine, and mouth ulcers. *Lancet* 1990; 335: 164.
2. Hall AP. Quinine and chloroquine antagonism in falciparum malaria. *Trans R Soc Trop Med Hyg* 1973; 67: 425.
3. Stahel E, *et al.* Antagonism of chloroquine with other antimalarials. *Trans R Soc Trop Med Hyg* 1988; 82: 221.

Antimicrobials. A woman who had previously tolerated chloroquine alone had acute dystonic reactions when also given *metronidazole*.[1] Chloroquine may also reduce the gastrointestinal absorption of *ampicillin* (see p. 219.3).

1. Achumba JI, *et al.* Chloroquine-induced acute dystonic reactions in the presence of metronidazole. *Drug Intell Clin Pharm* 1988; 22: 308–10.

Ciclosporin. Chloroquine has been reported to increase plasma concentrations of ciclosporin (see p. 1957.1).

Digoxin. Hydroxychloroquine has been reported to increase plasma concentrations of digoxin (see p. 1357.1).

Gastrointestinal drugs. Patients often wish to take chloroquine with food, antacids, or other gastrointestinal drugs to alleviate gastrointestinal irritation. Dosage with *food* may be beneficial as it appears to improve the absorption of chloroquine.[1,2] However, *antacids* or *kaolin* can reduce the absorption of chloroquine and it is therefore recommended that they should be given at least 4 hours apart.[3,4]

Cimetidine and chloroquine should be used with caution as *cimetidine* can significantly reduce the metabolism and elimination of chloroquine and increase its volume of distribution;[5] *ranitidine*, however, appears to have little effect on the pharmacokinetics of chloroquine.[6]

1. Tulpule A, Krishnaswamy K. Effect of food on bioavailability of chloroquine. *Eur J Clin Pharmacol* 1982; 23: 271–3.
2. Lagrave M, *et al.* The influence of various types of breakfast on chloroquine levels. *Trans R Soc Trop Med Hyg* 1985; 79: 559.
3. McElnay JC, *et al.* In vitro experiments on chloroquine and pyrimethamine absorption in the presence of antacid constituents or kaolin. *J Trop Med Hyg* 1982; 85: 153–8.
4. McElnay JC, *et al.* The effect of magnesium trisilicate and kaolin on the in vivo absorption of chloroquine. *J Trop Med Hyg* 1982; 85: 159–63.
5. Ette EI, *et al.* Chloroquine elimination in humans: effect of low-dose cimetidine. *J Clin Pharmacol* 1987; 27: 813–16.
6. Ette EI, *et al.* Effect of ranitidine on chloroquine disposition. *Drug Intell Clin Pharm* 1987; 21: 732–4.

Levothyroxine. For a report of a possible interaction of chloroquine with levothyroxine, see p. 2341.3.

Praziquantel. For a report of reduced bioavailability of praziquantel when given with chloroquine, see p. 165.2.

Vaccines. Although chloroquine has been reported to reduce the antibody response to *human diploid rabies vaccine* (see p. 2415.1), the immune response to other vaccines used in routine immunisation schedules (tetanus, diphtheria, measles, poliomyelitis, typhoid, and BCG) has not been found to be altered by chloroquine prophylaxis.[1,2]

1. Greenwood BM. Chloroquine prophylaxis and antibody response to immunisation. *Lancet* 1984; ii: 402–3.
2. Wolfe MS. Precautions with oral live typhoid (Ty 21a) vaccine. *Lancet* 1990; 336: 631–2.

Pharmacokinetics

Chloroquine is rapidly and almost completely absorbed from the gastrointestinal tract when given orally. Absorption is also rapid after intramuscular or subcutaneous use. It is widely distributed into body tissues and has a large apparent volume of distribution. It accumulates in high concentrations in some tissues, such as the kidneys, liver, lungs, and spleen and is strongly bound in melanin-containing cells such as those in the eyes and the skin. It also crosses the placenta. Chloroquine is eliminated very slowly from the body and it may persist in tissues for months or even years after stopping therapy.

Chloroquine is extensively metabolised in the liver, mainly to monodesethylchloroquine with smaller amounts of bisdesethylchloroquine (didesethylchloroquinine) and other metabolites being formed. Monodesethylchloroquine has been reported to have some activity against *Plasmodium falciparum*. Chloroquine and its metabolites are excreted in the urine, with about half of a dose appearing as unchanged drug and about 10% as the monodesethyl metabolite. Chloroquine and its monodesethyl metabolite are both distributed into breast milk.

General references.

1. Krishna S, White NJ. Pharmacokinetics of quinine, chloroquine and amodiaquine; clinical implications. *Clin Pharmacokinet* 1996; 30: 263–99.
2. Ducharme J, Farinotti R. Clinical pharmacokinetics and metabolism of chloroquine: focus on recent advancements. *Clin Pharmacokinet* 1996; 31: 257–74.
3. Obua C, *et al.* Population pharmacokinetics of chloroquine and sulfadoxine and treatment response in children with malaria: suggestions for an improved dose regimen. *Br J Clin Pharmacol* 2008; 65: 493–501.
4. Lee SJ, *et al.* Chloroquine pharmacokinetics in pregnant and nonpregnant women with vivax malaria. *Eur J Clin Pharmacol* 2008; 64: 987–92.
5. Karunajeewa HA, *et al.* Pharmacokinetics of chloroquine and monodesethylchloroquine in pregnancy. *Antimicrob Agents Chemother* 2010; 54: 1186–92.

Chloroquine is rapidly **absorbed** from the gastrointestinal tract but peak plasma concentrations after *oral* doses can vary considerably.[1] A mean peak plasma concentration of 76 nanograms/mL has been obtained in healthy adults a mean of 3.6 hours after giving the equivalent of 300 mg of chloroquine base orally as tablets.[2] In children with uncomplicated malaria given the equivalent of 10 mg/kg peak plasma concentrations of 250 nanograms/mL have been reached after 2 hours;[3] a mean peak of 134 nanograms/mL has been obtained after 5 hours in healthy children given a similar dose.[4] *Nasogastric* use has also

produced therapeutic concentrations in children with severe falciparum malaria.[5]

Oral bioavailability is increased if chloroquine is taken with food[6,7] and some beverages[8] and may also be affected by the state of health of the patient; mean values have ranged from about 70% in patients with malaria[9] to 78 or 89% in healthy adults.[2] Although oral bioavailability appears to be unaltered in moderately undernourished adults[10] it has been reported that it may be significantly reduced in children with kwashiorkor.[4]

Preliminary studies with chloroquine suppositories indicated that, although *rectal* bioavailability is less than half of that of oral chloroquine, sustained therapeutic concentrations may be achieved.[11]

Absorption is also rapid after *subcutaneous* or *intramuscular* injection and mean peak plasma concentrations of chloroquine have been obtained within about 30 minutes.[5,9,12]

Chloroquine has a large apparent volume of **distribution**. A multicompartmental model appears to be necessary to describe the distribution kinetics of chloroquine.[2,13] After intravenous dosage there is a multi-exponential decline in plasma concentrations as chloroquine distributes out of a central compartment that has been estimated to be several orders of magnitude smaller than the total volume of distribution.[5,14] This slow distribution out of the central compartment produces transiently high cardiotoxic concentrations of chloroquine if the overall rate of parenteral delivery is not carefully controlled.

Reported mean values for **protein binding** have ranged from about 58 to 64%.[15,16] Chloroquine is also bound to platelets and granulocytes so that the plasma concentration is only 10 to 15% of that in whole blood.[17] If these cells are not removed by gentle centrifugation during analysis, erroneously high plasma concentrations will be reported. Furthermore, as chloroquine concentrations determined in serum are higher than those in plasma, probably due to release of chloroquine from platelets during coagulation, it is crucial to state whether analysis has been done on whole blood, serum, or properly separated plasma.

About 50% of a dose of chloroquine is **metabolised** in the liver, mainly to the *N*-dealkylated metabolite monodesethylchloroquine; smaller amounts of bisdesethylchloroquine, 7-chloro-4-aminoquinoline, and *N*-oxidation products are formed. Some of these metabolites may contribute to the cardiotoxicity associated with chloroquine. In one study, peak plasma concentrations of 7-chloro-4-aminoquinoline were found to be twice those of unchanged chloroquine despite the fact that only relatively small amounts are formed; this appears to be due to its fast rate of formation and long elimination half-life.[18]

A mean of 42 to 47% of a dose has been reported to be **excreted** in the urine as unchanged chloroquine and 7 to 12% as monodesethylchloroquine.[2] Various estimates of the terminal elimination half-life of chloroquine range from several days to up to 2 months, but its slow release from tissues ensures that small amounts may still be detected after a year.[18,19]

1. Hellgren U, *et al.* On the question of interindividual variations in chloroquine concentrations. *Eur J Clin Pharmacol* 1993; 45: 383–5.
2. Gustafsson LL, *et al.* Disposition of chloroquine in man after single intravenous and oral doses. *Br J Clin Pharmacol* 1983; 15: 471–9.
3. Adelusi SA, *et al.* Kinetics of the uptake and elimination of chloroquine in children with malaria. *Br J Clin Pharmacol* 1982; 14: 483–7.
4. Walker O, *et al.* Single dose disposition of chloroquine in kwashiorkor and normal children—evidence for decreased absorption in kwashiorkor. *Br J Clin Pharmacol* 1987; 23: 467–72.
5. White NJ, *et al.* Chloroquine treatment of severe malaria in children: pharmacokinetics, toxicity, and new dosage recommendations. *N Engl J Med* 1988; 319: 1493–1500.
6. Tulpule A, Krishnaswamy K. Effect of food on bioavailability of chloroquine. *Eur J Clin Pharmacol* 1982; 23: 271–3.
7. Lagrave M, *et al.* The influence of various types of breakfast on chloroquine levels. *Trans R Soc Trop Med Hyg* 1985; 79: 539.
8. Mahmoud BM, *et al.* Significant reduction in chloroquine bioavailability following coadministration with the Sudanese beverages aradaib, karkadi and lemon. *J Antimicrob Chemother* 1994; 33: 1005–9.
9. White NJ, *et al.* Parenteral chloroquine for treating falciparum malaria. *J Infect Dis* 1987; 155: 192–201.
10. Tulpule A, Krishnaswamy K. Chloroquine kinetics in the undernourished. *Eur J Clin Pharmacol* 1983; 24: 273–6.
11. WHO. Severe and complicated malaria. 2nd ed. *Trans R Soc Trop Med Hyg* 1990; 84 (suppl 2): 1–65.
12. Phillips RE, *et al.* Divided dose intramuscular regimen and single dose subcutaneous regimen for chloroquine: plasma concentrations and toxicity in patients with malaria. *BMJ* 1986; 293: 13–16.
13. Prisk-Holmberg M, *et al.* The single dose kinetics of chloroquine and its major metabolite desethylchloroquine in healthy subjects. *Eur J Clin Pharmacol* 1984; 26: 521–30.
14. Looareesuwan S, *et al.* Cardiovascular toxicity and distribution kinetics of intravenous chloroquine. *Br J Clin Pharmacol* 1986; 22: 31–6.
15. Walker O, *et al.* Characterization of chloroquine plasma protein binding in man. *Br J Clin Pharmacol* 1983; 15: 375–7.
16. Ofori-Adjei D, *et al.* Protein binding of chloroquine enantiomers and desethylchloroquine. *Br J Clin Pharmacol* 1986; 22: 356–8.
17. Gustafsson LL, *et al.* Pitfalls in the measurement of chloroquine concentrations. *Lancet* 1983; i: 126.
18. Ette EI, *et al.* Pharmacokinetics of chloroquine and some of its metabolites in healthy volunteers: a single dose study. *J Clin Pharmacol* 1989; 29: 457–62.
19. Gustafsson LL, *et al.* Chloroquine excretion following malaria prophylaxis. *Br J Clin Pharmacol* 1987; 24: 221–4.

Distribution into breast milk. Studies[1,2] have suggested that it is safe for mothers to breast feed when they are receiving chloroquine for treatment of malaria. Although chloroquine and its monodesethyl metabolite are distributed into breast milk, it has been estimated that the amount that would be consumed by an infant is well below the therapeutic range and separate chemoprophylaxis for the infant is required.

There appear to be no data on the excretion of hydroxychloroquine in milk after doses appropriate for the prevention or treatment of malaria, but hydroxychloroquine has been detected in breast milk from 2 mothers receiving doses of 400 mg daily for SLE or rheumatoid arthritis.[3,4] One group of workers estimated that, calculated on a body-weight basis, a 9-month-old infant could receive about 2% of a maternal dose via breast feeding.[3]

1. Ogunbona FA, *et al.* Excretion of chloroquine and desethylchloroquine in human milk. *Br J Clin Pharmacol* 1987; 23: 473–6.
2. Akintonwa A, *et al.* Placental and milk transfer of chloroquine in humans. *Ther Drug Monit* 1988; 10: 147–9.
3. Nation RL, *et al.* Excretion of hydroxychloroquine in human milk. *Br J Clin Pharmacol* 1984; 17: 368–9.
4. Østensen M, *et al.* Hydroxychloroquine in human breast milk. *Eur J Clin Pharmacol* 1985; 28: 357.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Nivaquine; ***Austral.***: Chlorquin†; ***Austria***: Resochin; ***Belg.***: Nivaquine; ***Braz.***: Diclokin†; Quinacris; ***Cz.***: Delagil; ***Denm.***: Malarex; ***Fin.***: Heliopar; ***Fr.***: Nivaquine; ***Ger.***: Resochin; Weimerquin†; ***Gr.***: Demoquine; ***Hong Kong***: Chlorocin†; Syncoquin†; ***Hung.***: Delagil; ***India***: Bitaquine; C-Quin; Cadiquin; Chlorolex; Clokit; Cloquin; E-Vivax; Emquin; Idiquin; Ingaquine; Jagquin; La-Quin; Lariago; Larover; Malaquin; Maliago; Maligon; Malswift; Melubrin; Neoquine; Nivaquine-P; Paraquin; Resochin; ***Indon.***: Avloclor†; Malarex; Mexaquin†; Resochin; Riboquin; ***Irl.***: Avloclor†; ***Mex.***: Aralen; Maclorex†; ***Neth.***: Nivaquine; ***NZ***: Chlorquin†; Nivaquine†; ***Philipp.***: Aralen†; Chlorofoz; Chloromax; Clorkin; ***Pol.***: Arechin; ***Port.***: Resochina; ***Rus.***: Delagil (Делагил); ***S.Afr.***: Daramal; Mirquin; Nivaquine; Plasmoquine; ***Singapore***: Malarex; ***Spain***: Resochin; ***Switz.***: Chlorochin; Nivaquine; ***Thai.***: Chewoquine; Diroquine; Genocin; Malacin; Maliaquine†; Nitaquin; P-Roquine; Sinmoquin; ***UK***: Avloclor; Malarivon; Malaviron; Nivaquine; ***Ukr.***: Delagil (Делагил); ***USA***: Aralen.

Multi-ingredient Preparations. ***Fr.***: Nopalu; Savarine; ***Gr.***: Savarine; ***Rus.***: Insanovin (Инсановин); ***Thai.***: Chewoquine SC.

Pharmacopoeial Preparations

BP 2014: Chloroquine Phosphate Tablets; Chloroquine Sulphate Injection; Chloroquine Sulphate Tablets;
USP 36: Chloroquine Hydrochloride Injection; Chloroquine Phosphate Oral Suspension; Chloroquine Phosphate Tablets.

Chlorproguanil Hydrochloride *(BANM, rINNM)*

Chlorproguanil, Chlorhydrate de; Chlorproguanili Hydrochloridum; Clorproguanil, hidrocloruro de; Hidrocloruro de clorproguanil; M-5943; Хлорпрогуанила Гидрохлорид.

1-(3,4-Dichlorophenyl)-5-isopropylbiguanide hydrochloride.

$C_{11}H_{15}Cl_2N_5$,HCl=324.6

CAS — 537-21-3 (chlorproguanil); 15537-76-5 (chlorproguanil hydrochloride).

UNII — 6T04V14CU9.

NOTE. The names Lapdap and Dacart have been used as trade names for fixed-dose combinations of chlorproguanil with dapsone, and chlorproguanil with dapsone and artesunate, respectively.

Profile

Chlorproguanil is a biguanide antimalarial used for malaria prophylaxis similarly to proguanil (p. 661.3). It has sometimes been given as a fixed-dose combination with dapsone. Combination with both dapsone and artesunate has also been investigated for malaria treatment. However, combination products have been associated with decreases in haemoglobin concentrations in patients with G6PD deficiency.

Reviews.

1. Bukirwa H, *et al.* Chlorproguanil-dapsone for treating uncomplicated malaria. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 17/05/05).
2. Fanello CI, *et al.* A randomised trial to assess the efficacy and safety of chlorproguanil/dapsone + artesunate for the treatment of uncomplicated Plasmodium falciparum malaria. *Trans R Soc Trop Med Hyg* 2008; 102: 412–20.
3. Owusu-Agyei S, *et al.* An open label, randomised trial of artesunate +amodiaquine, artesunate+chlorproguanil-dapsone and artemether-lumefantrine for the treatment of uncomplicated malaria. *PLoS One* 2008; 3: e2530.
4. Fanello CI, *et al.* High risk of severe anaemia after chlorproguanil-dapsone+artesunate antimalarial treatment in patients with G6PD (A-) deficiency. *PLoS One* 2008; 3: e4031.
5. Premji Z, *et al.* Chlorproguanil-dapsone-artesunate versus artemether-lumefantrine: a randomized, double-blind phase III trial in African children and adolescents with uncomplicated Plasmodium falciparum malaria. *PLoS One* 2009; 4: e6682.
6. Tiono AB, *et al.* Chlorproguanil-dapsone-artesunate versus chlorproguanil-dapsone: a randomized, double-blind, phase III trial in African children, adolescents, and adults with uncomplicated *Plasmodium falciparum* malaria. *Am J Trop Med Hyg* 2009; 81: 969–78.

Halofantrine Hydrochloride

(BANM, USAN, rINNM)

Alofantrina Cloridrato; drug entry is base); Halofantriinihydrokloridi; Halofantrin hydrochlorid; Halofantrina, hidrocloruro de; Halofantrine, Chlorhydrate d'; Halofantrine chlorhydrate de; Halofantrin-hidroklorid; Halofantrinhydrochlorid; Halofantrinhydrochlorid; Halofantrini Hydrochloridum; Halofantrino hidrochloridas; Hidrocloruro de halofantrina; WR-171669; Галофантрина Гидрохлорид.

(RS)-3-Dibutylamino-1-(1,3-dichloro-6-trifluoromethyl-9-phenanthryl)propan-1-ol hydrochloride; 1,3-Dichloro-α-[2-(dibutylamino)ethyl]-6-trifluoromethyl-9-phenanthrenemethanol hydrochloride.

$C_{26}H_{30}Cl_2F_3NO$,HCl=536.9

CAS — 69756-53-2 (halofantrine); 36167-63-2 (halofantrine hydrochloride); 66051-63-6 (±-halofantrine).

ATC — P01BX01.

UNII — H77DL0Y630.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Halofantrine Hydrochloride). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in methyl alcohol. Protect from light.

Uses and Administration

Halofantrine is a 9-phenanthrenemethanol antimalarial that has been used in the *treatment* of uncomplicated chloroquine-resistant falciparum and of chloroquine resistant vivax malaria (see p. 644.1). Halofantrine is a blood schizontocide but has no activity against exoerythrocytic forms. Its value is limited by its unpredictable bioavailability and by cardiotoxicity. It should *not* be used where mefloquine has been used for prophylaxis (for cardiac hazard, see Effects on the Heart, below). Halofantrine should also *not* be used for malaria prophylaxis and is no longer recommended for standby treatment.

In the treatment of malaria, halofantrine hydrochloride has been given orally as 3 doses of 500 mg at intervals of 6 hours, on an empty stomach. A second course should be given after a week to patients with little or no previous exposure to malaria.

For details of doses in children, see below.

Administration in children. Halofantrine has been used in children from 1 year of age for the treatment of uncomplicated chloroquine-resistant falciparum or chloroquine resistant vivax malaria. A total oral dose of about 24 mg/kg, divided into 3 doses given at 6-hour intervals has been recommended; children weighing more than 40 kg may be dosed as for adults (see above).

Adverse Effects and Precautions

Adverse effects associated with halofantrine include diarrhoea, abdominal pain, nausea, vomiting, pruritus, and rash. Transient elevation of serum transaminases, intravascular haemolysis, and hypersensitivity reactions have also been reported.

Halofantrine can adversely affect the heart particularly by prolonging QT interval. Serious ventricular arrhythmias have been reported and fatalities have occurred. As a result it is contra-indicated in patients known to have a prolonged QT interval or those with cardiac disease or a family history of congenital QT prolongation, and also in those with unexplained syncopal attacks, thiamine deficiency, or electrolyte disturbances, or taking other arrhythmogenic drugs (see also Effects on the Heart, below, and Interactions, p. 655.1).

Halofantrine is not recommended during pregnancy or breast feeding. It should not be taken on a full stomach since this increases its bioavailability and thus the risk of toxicity; after taking halofantrine, fatty food should be avoided for 24 hours.

Effects on the blood. Halofantrine has been associated with acute intravascular haemolysis.[1,2]

1. Vachon P, *et al.* Halofantrine and acute intravascular haemolysis. *Lancet* 1992; 340: 909–10.
2. Mojon M, *et al.* Intravascular haemolysis following halofantrine intake. *Trans R Soc Trop Med Hyg* 1994; 88: 91.

Effects on the heart. Prolonged PR[1,2] and QT[1–5] intervals have been reported in patients given halofantrine and there are individual reports of fatal cardiac arrest[1,5] and of torsade de pointes.[4] In 1994, the UK CSM[6] noted that QT interval prolongation occurred at recommended doses of halofantrine in the majority of patients and that worldwide there had been 14 reports of cardiac arrhythmias associated with halofantrine; 8 patients were known to

have died. To reduce the risk of arrhythmias they stressed that halofantrine should *not* be taken with meals, with other drugs that may induce arrhythmias (e.g. quinine, chloroquine, and mefloquine; tricyclic antidepressants; antipsychotics; certain antiarrhythmics; and the antihistamines terfenadine and astemizole), or with drugs causing electrolyte disturbances. They also stated that it should *not* be given to patients known to have prolongation of the QT interval or with any form of cardiac disease associated with QT interval prolongation or ventricular arrhythmia (e.g. coronary heart disease, cardiomyopathy, or congenital heart disease). Some workers[2] have suggested ECG screening of all patients before starting treatment with halofantrine. Others[7] found pretreatment ECGs to be poorly predictive of QT lengthening during treatment. Children may have serious cardiac effects at standard doses.[8] A later review,[9] which included data from the manufacturer's database, analysed 35 deaths thought to be due to halofantrine-associated cardiotoxicity, including 5 children, occurring between 1988 and 2005. In the great majority of cases there were predisposing factors such as underlying heart disease, higher than recommended dosage, or use with another drug that prolonged QT intervals. The authors re-iterated the need to check for contra-indications (particularly in women) before prescribing, in those countries where halofantrine was still in use.

1. Nosten F, *et al.* Cardiac effects of antimalarial treatment with halofantrine. *Lancet* 1993; **341**: 1054–6.
2. Monlun E, *et al.* Cardiac complications of halofantrine: a prospective study of 20 patients. *Trans R Soc Trop Med Hyg* 1995; **89**: 430–3.
3. Castot A, *et al.* Prolonged QT interval with halofantrine. *Lancet* 1993; **341**: 1541.
4. Monlun E, *et al.* Prolonged QT interval with halofantrine. *Lancet* 1993; **341**: 1541–2.
5. Anonymous. Halofantrine: revised data sheet. *WHO Drug Inf* 1993; **7**: 66–7.
6. CSM/MCA. Cardiac arrhythmias with halofantrine (Halfan). *Current Problems* 1994; **20**: 6. Available at: http://www.mhra.gov.uk/home/groups/pl-p/documents/publication/con2023215.pdf (accessed 04/08/10)
7. Matson PA, *et al.* Cardiac effects of standard-dose halofantrine therapy. *Am J Trop Med Hyg* 1996; **54**: 229–31.
8. Sowunmi A, *et al.* Cardiac effects of halofantrine in children suffering from acute uncomplicated falciparum malaria. *Trans R Soc Trop Med Hyg* 1998; **92**: 446–8.
9. Bouchaud O, *et al.* Fatal cardiotoxicity related to halofantrine: a review based on a worldwide safety data base. *Malar J* 2009; **8**: 289.

Effects on the skin. For a comparison of the incidence of pruritus associated with halofantrine and other antimalarials, see Effects on the Skin under Adverse Effects of Chloroquine, p. 652.2.

Interactions

Halofantrine prolongs the QT interval and should not be used with other drugs that have the potential to induce cardiac arrhythmias, in particular the antimalarials mefloquine, chloroquine, and quinine, and also tricyclic antidepressants, phenothiazine antipsychotics, some antiarrhythmics (including amiodarone, disopyramide, flecainide, procainamide, quinidine, and the beta blocker sotalol), cisapride, and the antihistamines astemizole and terfenadine. Also, halofantrine should not be given with drugs that cause electrolyte disturbances (such as diuretics) or with HIV-protease inhibitors.

Grapefruit juice. In a study in 12 healthy patients, the bioavailability of halofantrine was reported to be increased when taken with grapefruit juice and this was found to accentuate halofantrine-associated QT prolongation.[1] It was suggested that grapefruit juice should be contra-indicated during use of halofantrine.

1. Charbit B, *et al.* Pharmacokinetic and pharmacodynamic interaction between grapefruit juice and halofantrine. *Clin Pharmacol Ther* 2002; **72**: 514–23.

Tetracycline. Plasma concentrations of halofantrine were increased in 8 healthy subjects who were also given tetracycline.[1]

1. Bassi PU, *et al.* Effects of tetracycline on the pharmacokinetics of halofantrine in healthy volunteers. *Br J Clin Pharmacol* 2004; **58**: 52–5.

Pharmacokinetics

Halofantrine is slowly and erratically absorbed after oral dosage. Although it appears in the circulation within about 1 hour, peak concentrations occur in 3 to 7 hours. Bioavailability of halofantrine is increased when given with or after food, particularly food high in fat content, and it must therefore be taken on an empty stomach because of the risk of cardiotoxicity. The elimination half-life of halofantrine varies considerably between individuals, but is generally about 1 to 2 days. Halofantrine is metabolised in the liver, its major metabolite being desbutylhalofantrine, which appears to be as active as the parent compound. Excretion of halofantrine is mainly via the faeces.

References.
1. Karbwang J, Na Bangchang K. Clinical pharmacokinetics of halofantrine. *Clin Pharmacokinet* 1994; **27**: 104–19.
2. Watkins WM, *et al.* Halofantrine pharmacokinetics in Kenyan children with non-severe and severe malaria. *Br J Clin Pharmacol* 1995; **39**: 283–7.
3. Ohrt C, *et al.* Pharmacokinetics of an extended-dose halofantrine regimen in patients with malaria and in healthy volunteers. *Clin Pharmacol Ther* 1995; **57**: 525–32.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Halfan; *Port.*: Halfan; *S.Afr.*: Halfan.

Hydroxychloroquine Sulfate

(BANM, rINNM)

Hidroxicloroquina, sulfato de; Hydroxychloroquine, Sulfate d'; Hydroxychloroquine Sulphate; Hydroxychloroquini Sulfas; Oxichlorochin Sulphate; Sulfato de Hidroxicloroquina; Win-1258-2; Гидроксихлорохина Сульфат.

2-[*N*-[4-(7-Chloro-4-quinolylamino)pentyl]-*N*-ethylamino] ethanol sulphate.

$C_{18}H_{26}ClN_3O,H_2SO_4$=433.9

CAS — 118-42-3 (hydroxychloroquine); 747-36-4 (hydroxychloroquine sulfate).

ATC — P01BA02.

UNII — 8Q2869CNVH.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Hydroxychloroquine Sulfate). A white or almost white, odourless or almost odourless, crystalline powder. Freely soluble in water; practically insoluble in alcohol, in chloroform, and in ether. A 1% solution in water has a pH of 3.5 to 5.5. Protect from light.

USP 36: (Hydroxychloroquine Sulfate). A white or practically white, odourless, crystalline powder. It exists in two forms, the usual form melting at about 240 degrees and the other form at about 198 degrees. Freely soluble in water; practically insoluble in alcohol, in chloroform, and in ether. Its solutions in water have a pH of about 4.5. Protect from light.

Uses and Administration

Hydroxychloroquine sulfate is a 4-aminoquinoline antimalarial with actions similar to those of chloroquine (p. 650.2). Although used in the treatment and prophylaxis of malaria (see p. 644.1), its main roles are in the management of systemic and discoid lupus erythematosus (p. 656.1) and rheumatoid arthritis (below). It has also been tried for prophylaxis of venous thromboembolism (p. 656.1). Additionally, hydroxychloroquine has been used similarly to chloroquine in the management of porphyria cutanea tarda (p. 651.1), sarcoidosis (p. 651.1), and various skin disorders (p. 651.2).

Hydroxychloroquine sulfate is given orally.

In **lupus erythematosus** and **rheumatoid arthritis**, response to treatment may not be apparent for up to 6 months but if there is no improvement by then, treatment should be stopped. In the UK, treatment is usually started with 400 mg daily in divided doses with meals. In the USA, recommended initial doses are 400 to 600 mg daily for rheumatoid arthritis and 400 mg once or twice daily for lupus erythematosus. Doses are reduced to the minimum effective dose for maintenance; this is usually 200 to 400 mg daily but should not exceed 6.5 mg/kg daily (or 400 mg daily whichever is the smaller). To avoid excessive dosage in obese patients, special care is needed to calculate the dosage on the basis of lean body-weight. For further details, see under Effects on the Eyes in Chloroquine, p. 651.2.

Hydroxychloroquine sulfate is also used in similar doses for the treatment of **light-sensitive skin eruptions**, but treatment should only be given during periods of maximum exposure to light.

Hydroxychloroquine sulfate may be used in **malaria** both for treatment and prophylaxis, when chloroquine is not available, with the same limitations as for chloroquine. In the USA, a licensed dose for *prophylaxis* of malaria is 400 mg every 7 days. Prophylaxis should be started 2 weeks before the period of malaria exposure and continue until 8 weeks after exposure has ended; if a two-week lead-in period is not possible, an initial loading dose of 800 mg can be used, given in 2 divided doses 6 hours apart. In *treating* an acute malarial attack, a dose of 800 mg has been used, followed after 6 to 8 hours by 400 mg and a further 400 mg on each of the 2 following days; alternatively, a single dose of 800 mg has been given.

For details of doses in children, see below.

Administration in children. Hydroxychloroquine sulfate may be used orally in infants and children for the management of certain inflammatory conditions, and also for the prophylaxis and treatment of malaria, where it is subject to the same limitations as chloroquine (see Uses and Administration of Chloroquine, p. 650.2).

For the treatment of **rheumatoid arthritis** (juvenile idiopathic arthritis), discoid or systemic **lupus erythematosus**, and **light-sensitive skin eruptions**; UK licensed product information suggests that infants and children may be given an oral dose of up to 6.5 mg/kg daily, based on ideal body-weight (or 400 mg daily, whichever is the smaller).

For **treatment of malaria**, US licensed product information recommends that infants and children may be given an initial oral dose of 13 mg/kg (to a maximum of 800 mg), followed by 6.5 mg/kg (to a maximum of 400 mg) after 6, 24, and 48 hours. For **prophylaxis**, 6.5 mg/kg (to a maximum of 400 mg) given once every 7 days is recommended. Prophylaxis should be started 2 weeks before the period of malaria exposure and continue until 8 weeks after exposure has ended; if a two-week lead-in period is not possible, an initial loading dose of 13 mg/kg (to a maximum of 800 mg) can be used, given in 2 divided doses 6 hours apart.

Diabetes. As a result of reported hypoglycaemic effects with chloroquine and hydroxychloroquine (see Effects on Glucose Metabolism, under Chloroquine, p. 651.3), there has been interest in whether such drugs might improve glucose tolerance or prevent diabetes in patients at risk.

In a prospective, multicentre, 21-year observational study[1] involving 4905 patients with rheumatoid arthritis, incident diabetes occurred at a significantly lower rate among patients who had ever taken hydroxychloroquine, versus those who had not (5.2 cases, versus 8.9 cases per 1000 patient years of observation respectively). The relative risk of developing diabetes also progressively declined with increased duration of hydroxychloroquine use. Others[2] have also reported a reduction in risk based on retrospective data.

1. Wasko MCM, *et al.* Hydroxychloroquine and risk of diabetes in patients with rheumatoid arthritis. *JAMA* 2007; **298**: 187–93.
2. Bili A, *et al.* Hydroxychloroquine use and decreased risk of diabetes in rheumatoid arthritis patients. *J Clin Rheumatol* 2011; **17**: 115–20.

Inflammatory disorders. For the use of hydroxychloroquine and chloroquine in a range of inflammatory conditions, see under Chloroquine, p. 650.3 and under Rheumatoid Arthritis, below.

Porphyria cutanea tarda. For reference to the use of hydroxychloroquine in the treatment of porphyria cutanea tarda, see under the Uses and Administration of Chloroquine, p. 651.1.

Rheumatoid arthritis. Hydroxychloroquine and chloroquine are used orally as disease-modifying antirheumatic drugs (DMARDs) in the management of **rheumatoid arthritis** (p. 13.2) in an attempt to suppress the rate of cartilage erosion or alter the course of the disease.[1] They are considered to be less effective than the other DMARDs but they are usually better tolerated and so may be preferred in patients with milder forms of the disease.[2] Additional benefit has been obtained using antimalarials with other DMARDs especially methotrexate and sulfasalazine,[3-5] although adverse effects may be more common. For reference to precautions to reduce the incidence of retinopathy, see under Effects on the Eyes in Adverse Effects of Chloroquine, p. 651.2.

Generally the lowest effective dose should be used for maintenance to minimise toxicity; for hydroxychloroquine sulfate this should not exceed 6.5 mg/kg lean body-weight daily. Daily doses of 200 or 400 mg are commonly used but one study indicates that there is little advantage in using the higher dose.[6]

Experience with antimalarials to treat **juvenile idiopathic arthritis** (p. 12.1) is limited and the results have been variable.[7,8]

Chloroquine and hydroxychloroquine have also been reported to be of use in **palindromic rheumatism**.[9-11]

1. Suarez-Almazor ME, *et al.* Antimalarials for treating rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 17/05/05).
2. HERA Study Group. A randomized trial of hydroxychloroquine in early rheumatoid arthritis: the HERA study. *Am J Med* 1995; **98**: 156–68.
3. Clegg DO, *et al.* Safety and efficacy of hydroxychloroquine as maintenance therapy for rheumatoid arthritis after combination therapy with methotrexate and hydroxychloroquine. *J Rheumatol* 1997; **24**: 1896–1902.
4. O'Dell JR. Triple therapy with methotrexate, sulfasalazine, and hydroxychloroquine in patients with rheumatoid arthritis. *Rheum Dis Clin North Am* 1998; **24**: 465–77.
5. O'Dell JR, *et al.* Treatment of rheumatoid arthritis with methotrexate and hydroxychloroquine, methotrexate and sulfasalazine, or a combination of the three medications: results of a two-year, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2002; **46**: 1164–70.
6. Pavelka K, *et al.* Hydroxychloroquine sulphate in the treatment of rheumatoid arthritis: a double blind comparison of two dose regimens. *Ann Rheum Dis* 1989; **48**: 542–6.
7. Brewer EJ, *et al.* Penicillamine and hydroxychloroquine in the treatment of severe juvenile rheumatoid arthritis. *N Engl J Med* 1986; **314**: 1269–76.

8. Grondin C. *et al.* Slow-acting antirheumatic drugs in chronic arthritis of childhood. *Semin Arthritis Rheum* 1988; 18: 38–47.
9. Richardson MR, Zalin AM. Treatment of palindromic rheumatism with chloroquine. *BMJ* 1987; 294: 741.
10. Hanonen P, *et al.* Treatment of palindromic rheumatism with chloroquine. *BMJ* 1987; 294: 1289.
11. Youssef W, *et al.* Palindromic rheumatism: a response to chloroquine. *J Rheumatol* 1991; 18: 35–7.

Sarcoidosis. Chloroquine and hydroxychloroquine have been tried in the management of sarcoidosis (p. 1612.2) as alternatives or adjuncts to corticosteroid therapy. For references to the use of hydroxychloroquine, see under Chloroquine, p. 651.1.

Skin disorders. For reference to the use of hydroxychloroquine in a variety of skin disorders, see under Chloroquine, p. 651.2.

Systemic lupus erythematosus. Antimalarials have been widely used in the treatment of lupus erythematosus (p. 1613.3), particularly its cutaneous manifestations, although much of the evidence is based on case series and reports.[1] Hydroxychloroquine is most widely used,[1,2] as it is thought to have fewer adverse effects than chloroquine, although any benefit with chloroquine generally starts to become evident within several weeks of starting treatment, whereas it may take up to 2 months for any effect of hydroxychloroquine to be seen. For extracutaneous disease, antimalarials are often combined with other drugs; treatment may be continued for many years. For reference to precautions to reduce the risk of retinopathy see Effects on the Eyes, under Adverse Effects of Chloroquine, p. 651.2. There is evidence from a case-control study[3] that long-term hydroxychloroquine treatment is associated with improved survival in patients with SLE, and some consider it to be underused.[2] It has been suggested that hydroxychloroquine may also have a role in reducing the thrombotic symptoms of SLE, including in patients with antiphospholipid syndrome.[4]

1. Wozniacka A, McCauliffe DP. Optimal use of antimalarials in treating cutaneous lupus erythematosus. *Am J Clin Dermatol* 2005; 6: 1–11.
2. Costedoat-Chalumeau N, *et al.* Hydroxychloroquine dans le traitement du lupus: le renouveau. *Rev Med Interne* 2008; 29: 735–7.
3. Alarcón GS, *et al.* Effect of hydroxychloroquine on the survival of patients with systemic lupus erythematosus: data from LUMINA, a multiethnic US cohort (LUMINA I). *Ann Rheum Dis* 2007; 66: 1168–72.
4. Petri M. Use of hydroxychloroquine to prevent thrombosis in systemic lupus erythematosus and in antiphospholipid antibody-positive patients. *Curr Rheumatol Rep* 2011; 13: 77–80.

Venous thromboembolism. Standard prophylaxis for surgical patients at high risk of venous thromboembolism (p. 1274.1) is usually with an anticoagulant. Hydroxychloroquine has been described by some as an antiplatelet agent[1] and although its mechanism of action is uncertain the incidence of fatal pulmonary embolism has been reduced in patients given hydroxychloroquine prophylactically after total hip replacement;[2] the usual daily divided oral dose was about 800 mg from the day before surgery until discharge; larger doses had been used.

See also Systemic Lupus Erythematosus, above.

1. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy—III: reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. *BMJ* 1994; 308: 235–46.
2. Loudon JR. Hydroxychloroquine and postoperative thromboembolism after total hip replacement. *Am J Med* 1988; 85: (suppl 4A): 57–61.

Adverse Effects, Treatment, and Precautions

As for Chloroquine, p. 651.2.

Breast feeding. Hydroxychloroquine has been detected in human breast milk[1,2] but no adverse effects have been seen in breast-fed infants and the American Academy of Pediatrics considers[3] that it is therefore usually compatible with breast feeding.

1. Nation RL, *et al.* Excretion of hydroxychloroquine in human milk. *Br J Clin Pharmacol* 1984; 17: 368–9.
2. Østensen M, *et al.* Hydroxychloroquine in human breast milk. *Eur J Clin Pharmacol* 1985; 28: 357.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 19/04/04)

Effects on the eyes. The main adverse effects of chloroquine and hydroxychloroquine on the eye are keratopathy and retinopathy. With respect to retinopathy, precautions should be taken in patients undergoing long-term treatment, as described under Chloroquine on p. 651.2.

Further references.

1. Jones SK. Ocular toxicity and hydroxychloroquine: guidelines for screening. *Br J Dermatol* 1999; 140: 3–7.
2. Tripp JM, Malbach HL. Hydroxychloroquine-induced retinopathy: a dermatologic perspective. *Am J Clin Dermatol* 2006; 7: 171–5.
3. Tehrani R, *et al.* Ocular toxicity of hydroxychloroquine. *Semin Ophthalmol* 2008; 23: 201–9.
4. Wolfe F, Marmor MF. Rates and predictors of hydroxychloroquine retinal toxicity in patients with rheumatoid arthritis and systemic lupus erythematosus. *Arthritis Care Res (Hoboken)* 2010; 62: 775–84.
5. Bergholz R, *et al.* Evaluation of risk factors for retinal damage due to chloroquine and hydroxychloroquine. *Br J Ophthalmol* 2010; 94: 1637–42.
6. Payne JF, *et al.* Clinical characteristics of hydroxychloroquine retinopathy. *Br J Ophthalmol* 2011; 95: 245–50.
7. Michaelides M, *et al.* Retinal toxicity associated with hydroxychloroquine and chloroquine: risk factors, screening, and progression despite cessation of therapy. *Arch Ophthalmol* 2011; 129: 30–9.

Effects on glucose metabolism. For the effects of hydroxychloroquine on glucose metabolism, see under Chloroquine, p. 651.3.

Overdosage. References[1-4] to the management of hydroxychloroquine overdose. Management has largely been based on that used for overdoses of chloroquine (p. 652.2).

1. Marquardt K, Albertson TE. Treatment of hydroxychloroquine overdose. *Am J Emerg Med* 2001; 19: 420–4.
2. Ling Ngan Wong A, *et al.* Hydroxychloroquine overdose: case report and recommendations for management. *Eur J Emerg Med* 2008; 15: 16–8.
3. Olgers TJ, *et al.* Ernstige intoxicatie met hydroxychloroquine, met hemodynamische instabiliteit: casuistische ondersteuning voor behandeling met diazepam. *Ned Tijdschr Geneeskd* 2008; 152: 509–12.
4. Gunja N, *et al.* Survival after massive hydroxychloroquine overdose. *Anaesth Intensive Care* 2009; 37: 130–3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies hydroxychloroquine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

For a discussion of the use of other antimalarials in patients with porphyria, see under Precautions for Chloroquine, p. 653.1.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 10/10/11)

Pregnancy. In a study[1] of 133 pregnancies in 90 women treated with hydroxychloroquine, no statistical difference in pregnancy outcome was found compared with a control group consisting of 70 pregnancies in 53 women. It was concluded that the findings supported preliminary evidence for the safety of hydroxychloroquine treatment in pregnancy, and that treatment should probably therefore be maintained during pregnancy in patients with SLE. A later systematic review[2] also concluded that there was no increased risk of congenital defects, spontaneous abortion, fetal death or prematurity associated with use of hydroxychloroquine for auto-immune diseases during pregnancy.

1. Costedoat-Chalumeau N, *et al.* Safety of hydroxychloroquine in pregnant patients with connective tissue diseases: a study of one hundred thirty-three cases compared with a control group. *Arthritis Rheum* 2003; 48: 3207–11.
2. Sperber K, *et al.* Systematic review of hydroxychloroquine use in pregnant patients with autoimmune diseases. *Pediatr Rheumatol Online J* 2009; 7: 9.

Interactions

As for Chloroquine, p. 653.2.

Pharmacokinetics

The pharmacokinetics of hydroxychloroquine are similar to those of chloroquine (see p. 653.3).

References.
1. Tett SE, *et al.* Bioavailability of hydroxychloroquine tablets in healthy volunteers. *Br J Clin Pharmacol* 1989; 27: 771–9.
2. Miller DR, *et al.* Steady-state pharmacokinetics of hydroxychloroquine in rheumatoid arthritis. *DICP Ann Pharmacother* 1991; 25: 1302–5.
3. Ducharme J, *et al.* Enantioselective disposition of hydroxychloroquine after a single oral dose of the racemate to healthy subjects. *Br J Clin Pharmacol* 1995; 40: 127–33.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Axokine; Evoquin; Metirel; Narbon; Plaquenil; Polirreumin; ***Austral.***: Plaquenil; ***Belg.***: Plaquenil; ***Braz.***: Plaquinol; Reuquinol; ***Canad.***: Apo-Hydroxyquine; Plaquenil; Pro-Hydroxyquine; ***Chile***: Ilinol; Plaquinol; ***China***: Fen Le (纷乐); Plaquenil (赛能); ***Cz.***: Plaquenil; ***Denm.***: Ercoquin; Plaquenil; ***Fin.***: Oxiklorin; ***Fr.***: Plaquenil; ***Ger.***: Quensyl; ***Gr.***: Plaquenil; ***Hong Kong***: Plaquenil; ***India***: HCQS; HQTor; Hydrocad; Hydroquin; Oxcq; Oxy-Q; ***Irl.***: Plaquenil; ***Israel***: Plaquenil; ***Ital.***: Plaquenil; ***Malaysia***: Plaquenil; ***Mex.***: Plaquenil; ***Neth.***: Plaquenil; ***Norw.***: Plaquenil; ***NZ***: Plaquenil; ***Philipp.***: Plaquenil; ***Port.***: Plaquinol; ***Rus.***: Immard (Иммард); Plaquenil (Плаквенил); ***Singapore***: Plaquenil; ***Spain***: Dolquine; ***Swed.***: Plaquenil; ***Switz.***: Plaquenil; ***Thai.***: HCQS; Hydroquin; Plaquenil; ***Turk.***: Plaquenil; ***UK***: Plaquenil; ***Ukr.***: Immard (Иммард); Plaquenil (Плаквенил); ***USA***: Plaquenil; ***Venez.***: Plaquinol.

Pharmacopoeial Preparations

BP 2014: Hydroxychloroquine Tablets;
USP 36: Hydroxychloroquine Sulfate Tablets.

Lumefantrine *(BAN, USAN, rINN)*

Benflumelol; Benflumetol; Lumefantrin; Lumefantrina; Luméfantrine; Lumefantrinum; Lumefantryna; Лумефантрин.

2,7-Dichloro-9-[(4-chlorophenyl)methylene]-α-[(dibutylamino)methyl]-9*H*-fluorene-4-methanol.

$C_{30}H_{32}Cl_3NO$=528.9

CAS — 82186-77-4.

UNII — F38R0JR742.

Pharmacopoeias. In *Chin.*

Uses and Administration

Lumefantrine is a dichlorobenzylidine derivative given orally with artemether (p. 648.1) for the treatment of uncomplicated falciparum malaria (p. 644.1). In some countries, the combination is also used for the treatment of chloroquine-resistant non-falciparum malaria. Lumefantrine is a blood schizontocide with a relatively slow onset of action but it has a longer duration of action than artemether. The combination is given as a six-dose regimen, with each dose containing lumefantrine 480 mg and artemether 80 mg. The first dose is given at initial diagnosis, with subsequent doses given after 8, 24, 36, 48, and 60 hours; it has been suggested that doses be given after a milky drink or fat-containing food to ensure adequate absorption.

For details of dosing in children, see below.

References.
1. Omari AAA, *et al.* Artemether-lumefantrine (six-dose regimen) for treating uncomplicated falciparum malaria. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 19/07/06).
2. Omari AAA, *et al.* Artemether-lumefantrine (four-dose regimen) for treating uncomplicated falciparum malaria. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 19/07/06).
3. Kokwaro G, *et al.* Artemether/lumefantrine in the treatment of uncomplicated falciparum malaria. *Expert Opin Pharmacother* 2007; 8: 75–94.
4. Adjei GO, *et al.* Artemether-lumefantrine: an oral antimalarial for uncomplicated malaria in children. *Expert Rev Anti Infect Ther* 2009; 7: 669–81.
5. Ngasala BE, *et al.* Efficacy and effectiveness of artemether-lumefantrine after initial and repeated treatment in children < 5 years of age with acute uncomplicated *Plasmodium falciparum* malaria in rural Tanzania: a randomized trial. *Clin Infect Dis* 2011; 52: 873–82.

Administration in children. Lumefantrine may be given orally to infants and children, with artemether, for the treatment of **uncomplicated falciparum malaria**. In some countries, the combination is also used for the treatment of **chloroquine-resistant non-falciparum malaria**. A total of 6 doses are given, starting at diagnosis and repeated after 8, 24, 36, 48, and 60 hours; recommended doses according to body-weight are as follows:

- 5 to 14 kg: lumefantrine 120 mg with artemether 20 mg
- 15 to 24 kg: lumefantrine 240 mg with artemether 40 mg
- 25 to 34 kg: lumefantrine 360 mg with artemether 60 mg
- over 35 kg: as for adults (see above)

It has been suggested that doses be given after a milky drink or fat-containing food to ensure adequate absorption.

Adverse Effects and Precautions

Adverse effects associated with the combination of lumefantrine with artemether commonly include headache, dizziness, sleep disturbance, palpitations, gastrointestinal disturbances, anorexia, pruritus, rash, cough, arthralgia, myalgia, and fatigue.

Lumefantrine-artemether may cause prolongation of the QT interval, and therefore should be avoided in patients with serum-potassium or magnesium disturbances, any clinical condition known to prolong the QT interval (such as congenital long QT syndrome, symptomatic cardiac arrhythmia, or severe heart failure), or a family history of sudden cardiac death.

Lumefantrine-artemether should be given with caution in severe hepatic or renal impairment and ECG and blood potassium monitored.

Effects on the blood. Severe haemolytic anaemia necessitating corticosteroid treatment, blood transfusion, and haemodialysis occurred in a patient after taking 8 lumefantrine-artemether tablets after a malarial attack.[1] It was considered that, given its molecular similarity to other antimalarials known to cause haemolysis, the causative drug was probably lumefantrine.

1. Mérat S, *et al.* Case report: combination artemether-lumefantrine and haemolytic anaemia following a malarial attack. *Trans R Soc Trop Med Hyg* 2003; 97: 433–4.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies the combination of lumefantrine plus artemether as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]