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Excipients in the label and package leaflet of medicinal products for human use

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EXCIPIENTS IN THE LABEL AND PACKAGE LEAFLET OF MEDICINAL PRODUCTS FOR HUMAN USE

INTRODUCTION

This is a Commission guideline pursuant to Article 65 of Directive 2001/83/EC. It contains warning statements relating to the presence of certain excipients in medicinal products. Homeopathic medicinal products authorised through a special simplified registration procedure are not addressed in this guideline since for these homeopathic products there are specific labelling requirements according to Article 69.

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Article 54(c) requires that all excipients need to be declared on the labelling if the medicinal product is an injectable or a topical, or an eye preparation. Furthermore, Article 54 (1)(c) provides that: excipients known to have a recognised action or effect, and included in the guidelines published by the Commission pursuant to Article 65, need to be declared on the labelling of all other medicinal products.

Article 59 (1)(a) 2nd indent requires a full statement of the active substance and excipients in the package leaflet. Article 59 (1)(c) states that the package leaflet must include a list of information which is necessary before taking the medicinal product. Article 59(1)(c), 7th indent provides that the aforementioned information should include information on those excipients, knowledge of which is important for the safe and effective use of the medicinal product and included in the guidelines published by the Commission pursuant to Article 65.

Article 59(1) requires that the package leaflet must be in accordance with the SPC and shall be drawn up in accordance with the SPC. Therefore, consistent information should be stated in both documents.

PURPOSE

This guideline is for use by competent authorities, applicants for a Marketing Authorisation and Marketing Authorisation Holders. The Annex provides a list of the excipients which should be stated on the labelling and outlines the information which should appear in the package leaflet, for these excipients. This guideline does not apply to these substances when they are used as active substances.

DEFINITIONS AND EXAMPLES

In general, excipients may be defined as the constituents of the pharmaceutical form that is taken by or administered to the patient, other than the active substance.

According to the Annex of Directive 2001/83/EC, such constituents may include:

- colouring matter, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, flavouring and aromatic substances, etc.,
- the constituents intended to be ingested or otherwise administered to the patient, of the outer covering of the medicinal products – capsules, gelatine capsules, rectal capsules etc.

Further examples may include:

- excipient mixtures, e.g. those used for example in direct compression or in a film coat or polish for an ingested dose form.

- pH adjusters
- the constituents of printing inks used to mark the ingested dose form
- diluents present, for example in herbal extracts or vitamin concentrates
- the constituents present in a mixture of chemically related components (e.g. preservatives)

However, in the context of this guideline, residues of substances arising from the manufacturing process, impurities, residual solvents, degradation products etc. are not included in this definition.

In general, excipients are considered to be 'inert'. Whilst it is desirable that excipients should have little or no pharmacological action of their own, some do indeed have a recognised action or effect in certain circumstances. Therefore Marketing Authorisation applicants and holders should ensure that excipients are used appropriately in the formulation of their medicinal products, with regard to the information contained in the Annex.

NOMENCLATURE

The following applies to the names of all excipients on the labelling, package leaflet and in the SPC.

1. Proprietary names should not be used for individual excipients. Excipients should be referred to by their recommended international nonproprietary name (INN), the European Pharmacopoeia name, or failing this, their usual common name.

2. The name of an excipient appearing in the Annex must be accompanied by the E number if it exists. The E number alone may be used for an excipient on the labelling, provided that the full name and the E number are stated in the user package leaflet, in the section where the full qualitative composition is given.

3. Proprietary flavours or fragrances may be declared in general terms (e.g. 'orange flavour', 'citrus fragrance/perfume'); any known major components or those with a recognised action or effect should be declared specifically.

4. Chemically modified excipients should be declared in such a way as to avoid confusion with the unmodified excipient (e.g. pre-gelatinised starch).

5. pH adjusters should be mentioned by name and their function may also be stated, e.g. hydrochloric acid for pH adjustment.

6. All components of compound excipients or mixtures should be declared, listed under a general descriptive term e.g. printing ink containing x, y, z. A general descriptive term may be used on the labelling provided more information is given in the package leaflet. Any component with a recognised action or effect should be mentioned on the labelling.

EXCIPIENTS IN THE LABELLING

According to Directive 2001/83/EC, all excipients in parenteral, ophthalmic and topical medicinal products must appear on the labelling. Topical medicinal products can be taken to include those medicinal products applied externally to the skin, respiratory products delivered to the lung by inhalation and any medicinal product delivered to the oral, nasal, rectal or vaginal mucosae, i.e. where the delivery may be local or transdermal.

For all other medicinal products, only those excipients known to have a recognised action or effect, included in the Commission's guideline, should be declared on the labelling. Such excipients are listed in Annex.

When a medicinal product contains any of these, the name of the excipient must be stated on the

labelling, together with a statement such as 'see leaflet for further information'.

EXCIPIENTS IN THE PACKAGE LEAFLET

According to Article 59(1)(a) 2nd indent, of Directive 2001/83/EC, all of the excipients must be stated on the package leaflet by name. Thus, all excipients, as indicated in the section on Definitions and Examples above, should be declared according to the nomenclature defined in this guideline.

In line with the provisions of Article 59(1)(c) 4th and 7th indents of Directive 2001/83/EC, the fourth column in the Annex provides information corresponding to each excipient. The text of this information is in clear and understandable terms for the patient. However, taking into account that applicants may have different house styles for their package leaflets, it is not required that the information in the Annex should be applied verbatim to the package leaflet, so applicants may choose their own style to present this information to the patient, e.g. in a 'direct' or 'indirect' style. The content or meaning of the text must not be changed.

When a warning or information statement is required according to the Annex, it must be clear in the package leaflet and SPC that the statement is linked to the presence of a particular excipient. The patient should not be left in any doubt as to whether the warning relates to the excipient or the active substance.

For some of the excipients in the Annex, the information to be included in the package leaflet may relate to more than one section of the leaflet, e.g. effects on ability to drive and operate machinery, pregnancy and lactation, undesirable effects. To simplify the presentation of the package leaflet, this information should appear only once. However, in order that the patient does not miss important and relevant information, it may be necessary to refer back to the excipient warnings section from other sections in the package leaflet. For example in the case of ethanol, it will be necessary to refer back to the excipient warnings section from those sections relating to effects on ability to drive, pregnancy and lactation, information for children, etc.

ANNEX: Excipients and Information for the Package Leaflet

Explanatory Notes

The Annex is structured as follows:

Name

This is the name of the excipient using INN or PhEur nomenclature where possible, including a reference to E-numbers where relevant

Route of administration

This is necessary because the information may depend upon the route of administration, e.g. for benzalkonium chloride the information relating to bronchospasm is relevant only for the respiratory route.

Threshold

It is accepted that excipients may only show an effect above a certain 'dose'.
Except where otherwise stated, thresholds are expressed as Maximum Daily Doses of the excipient in question, taken as part of a medicinal product.
The threshold is a value, equal to or above which it is necessary to provide the information stated.
A threshold of 'zero' means that it is necessary to state the information in all cases where the excipient is present in the medicinal product.

Information for the Package Leaflet

The information is presented here in a simple form, in clear and understandable terms for the patient.
The text often refers to the term 'per dose' meaning dose of the medicinal product.
Since doses may be extremely variable, applicants must take into account
the maximum single dose of the medicinal product, as defined in the SPC, Section 4.2.
For this reason the information sometimes contains the expression
'up to x mg per dose', for example.

If the pharmaceutical form is a solid form, e.g. tablet, capsule, suppository, powder in a sachet, it may be better to refer to the amount per tablet, capsule etc.

Comments

Text in this column is not for the patient.
It is intended to give further information on the text in the preceding column, for the benefit of applicants and the competent authorities.
In some cases these comments may appear as a contraindication in the SPC, worded in an appropriate style.

ANNEX: Excipients and Information for the Package Leaflet

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Aprotinin	Topical	Zero	May cause hypersensitivity or severe allergic reactions	The topical route in this case refers to sites that may have access to the circulation (e.g. wounds, body cavities etc.)
Arachis oil (peanut oil)	All	Zero	(Medicinal product) contains arachis oil (peanut oil). If you are allergic to peanut or soya, do not use this medicinal product.	Purified arachis oil may contain peanut protein. The PhEur monograph does not contain a test for residual protein. SPC: contraindication
Aspartame (E951)	Oral	Zero	Contains a source of phenylalanine. May be harmful for people with phenylketonuria	
Azo colouring agents: **For example,** **E102, tartrazine** **E110, susnset yellow FCF** **E122, azorubine, carmoisine** **E123, amaranth** **E124, ponceau 4R red, cochineal red A** **E151 brilliant black BN, black PN**	Oral	Zero	May cause allergic reactions	
Balsam of Peru	Topical	Zero	May cause skin reactions	

Benzalkonium chloride	Ocular	Zero	May cause eye irritation. Avoid contact with soft contact lenses. Remove contact lenses prior to application and wait at least 15 minutes before reinsertion. Known to discolour soft contact lenses.	
	Topical		Irritant, may cause skin reactions.	
	Respiratory	10 micrograms / delivered dose	May cause bronchospasm.	
Benzoic acid and benzoates: **for example:** **E210 benzoic acid** **E211 sodium benzoate** **E212 potassium benzoate**	Topical	Zero	Mildly irritant to the skin, eyes and mucous membranes.	
	Parenteral	Zero	May increase the risk of jaundice in newborn babies	
Benzyl alcohol	Parenteral	Exposures less than 90 mg/kg/day	Must not be given to premature babies or neonates. May cause toxic reactions and allergic reactions in infants and children up to 3 years old..	SPC: 'allergic' should be expressed as 'anaphylactoid' The amount of benzyl alcohol in mg per <volume> should be stated in the package leaflet and SPC.

		90mg/kg/day	Must not be given to premature babies or neonates. Due to the risk of fatal toxic reactions arising from exposure to benzyl alcohol in excess of 90 mg/kg/day, this product should not be used in infants and children up to 3 years old.	The amount of benzyl alcohol per <volume> should be stated in the package leaflet and SPC.
Bergamot oil Bergapten	Topical	Zero	May increase sensitivity to UV light (natural and artificial sunlight).	Does not apply when bergapten is shown to be absent from the oil
Bronopol	Topical	Zero	May cause local skin reactions (e.g. contact dermatitis).	
Butylated hydroxyanisole (E320)	Topical	Zero	May cause local skin reactions (e.g.contact dermatitis), or irritation to the eyes and mucous membranes.	
Butylated hydroxytoluene (E321)	Topical	Zero	May cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.	
Castor oil polyoxyl and castor oil polyoxyl hydrogenated	Parenteral	Zero	May cause severe allergic reactions	
	Oral	Zero	May cause stomach upset and diarrhoea	
	Topical	Zero	May cause skin reactions	
Cetostearyl alcohol including Cetyl alcohol	Topical	Zero	May cause local skin reactions (e.g. contact dermatitis).	
Chlorocresol	Topical Parenteral	Zero	May cause allergic reactions	
Dimethyl sulphoxide	Topical	Zero	May be irritant to the skin.	

Ethanol	Oral and Parenteral	Less than 100 mg per dose	This medicinal product contains small amounts of ethanol (alcohol), less than 100mg per <dose>.	This statement is to provide reassurance to parents and children concerning the low levels of alcohol in the product.
		100 mg – 3g per dose	This medicinal product contains ... vol % ethanol (alcohol), i.e. up to ... mg per dose, equivalent to ... ml beer, ... ml wine per dose. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease, or epilepsy.	The package leaflet should give the equivalent volume of beer and wine, nominally calculated assuming 5 % vol and 12% vol ethanol respectively. Separate warning statements may be needed in different parts of the PL.
	Oral and Parenteral	3 g per dose	This medicinal product contains ... vol % ethanol (alcohol), i.e. up to ... mg per dose, equivalent to ... ml beer, ... ml wine per dose. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease or epilepsy. The amount of alcohol in this medicinal product may alter the effects of other medicines. The amount of alcohol in this medicinal product may impair your ability to drive or use machines.	
Formaldehyde	Topical	Zero	May cause local skin reactions (e.g. contact dermatitis).	

	Oral	Zero	May cause stomach upset and diarrhoea	
Fructose	Oral Parenteral	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product	SPC proposal: Patients with rare hereditary problems of fructose intolerance should not take this medicine**.**
		5 g	Contains x g fructose per dose. This should be taken into account in patients with diabetes mellitus.	
	Oral liquids, lozenges and chewable tablets	Zero	May be harmful to the teeth	Information to be included only when the medicinal product may be intended for chronic use, e.g. for two weeks or more
Galactose	Parenteral	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product	SPC proposal: Patients with rare hereditary problems of galactose intolerance e.g. galactosaemia should not take this medicine.
	Oral	Zero	If you have been told by your doctor that you have an intolerance to some sugars contact your doctor before taking this medicinal product	SPC proposal: Patients with rare hereditary problems of galactose intolerance e.g. galacotosaemia, or glucose-galactose malabsorption should not take this medicine.
	Oral Parenteral	5 g	Contains x g galactose per dose. This should be taken into account in patients with diabetes mellitus	
Glucose	Oral	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product	SPC proposal: Patients with rare glucose-galactose malabsorption should not take this medicine

	Oral Parenteral	5 g	Contains x g glucose per dose. This should be taken into account in patients with diabetes mellitus	
	Oral liquids, lozenges and chewable tablets	Zero	May be harmful to the teeth	Information to be included only when the medicinal product may be intended for chronic use, e.g. for two weeks or more
Glycerol	Oral	10g/dose	May cause headache, stomach upset and diarrhoea	
	Rectal	1 g	May have a mild laxative effect	
Heparin **(as an excipient)**	Parenteral	Zero	May cause allergic reactions and reduced blood cell counts which may affect the blood clotting system. Patients with a history of heparin-induced allergic reactions should avoid the use of heparin-containing medicines.	
Hydrogenated Glucose syrup **(or Maltitol Liquid)**	Oral	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product	SPC proposal: Patients with rare hereditary problems of fructose intolerance should not take this medicine.

		10 g	May have a mild laxative effect Calorific value 2.3 kcal/g of hydrogenated glucose syrup.	
Invert sugar	Oral	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product	SPC proposal: Patients with rare hereditary problems of fructose intolerance or glucose-galactose malabsorption should not take this medicine
		5 g	Contains x g of a mixture of fructose and glucose per dose. This should be taken into account in patients with diabetes mellitus	
	Oral liquids, lozenges and chewable tablets	Zero	May be harmful to the teeth	Information to be included only when the medicinal product may be intended for chronic use, e.g. for two weeks or more
Lactitol, E966	Oral	Zero	If you have been told by your doctor that you have an intolerance to some sugars contact your doctor before taking this medicinal product	SPC proposal: Patients with rare hereditary problems of fructose intolerance, galactose intolerance, galactosaemia or glucose-galactose malabsorption should not take this medicine**.**
		10 g	May have a mild laxative effect Calorific value 2.1 kcal/g lactitol	

Lactose	Oral	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product	SPC proposal: Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
		5 g	Contains x g lactose (x/2 g glucose and x/2 g galactose) per dose. This should be taken into account in patients with diabetes mellitus	
Lanolin (see Wool Fat)	Topical	Zero	May cause local skin reactions (e.g. contact dermatitis)	
Latex **Natural Rubber (latex)**	All	Zero	The container of this medicinal product contains latex rubber. May cause severe allergic reactions.	Not a typical excipient, but a warning is considered necessary
Maltitol E965 and Isomaltitol E953, Maltitol Liquid **(see Hydrogenated Glucose Syrup)**	Oral	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product	SPC proposal: Patients with rare hereditary problems of fructose intolerance should not take this medicine.
		10 g	May have a mild laxative effect Calorific value 2.3 kcal/g maltitol (or isomaltitol)	
Mannitol, E421	Oral	10 g	May have a mild laxative effect	

Organic Mercury compounds **For example** **Thiomersal** **Phenylmercuric nitrate, acetate, borate)**	Ocular	Zero	May cause allergic reactions.	See EMEA Public Statement, 8 July 1999, Ref. EMEA/20962/99
	Topical	Zero	May cause local skin reactions (e.g. contact dermatitis) and discolouration	
	Parenteral	Zero	This medicinal product contains (thiomersal) as a preservative and it is possible that <you/your child> may experience an allergic reaction. Tell your doctor if <you/your child> have/has any known allergies.	See EMEA Public Statement, 8 July 1999, Ref. EMEA/20962/99
			Tell your doctor if you/your child have/has experienced any health problems after previous administration of a vaccine.	Additional statement to be mentioned for vaccines
Parahydroxybenzoates and their esters **For example** **E214 Ethyl hydroxybenzoate** **E216 Propylhydroxybenzoate** **E217 Sodium propylhydroxybenzoate** **E218 Methylhydroxybenzoate** **E219 Sodium methylhydroxybenzoate**	Oral Ocular Topical	Zero	May cause allergic reactions (possibly delayed).	
	Parenteral Respiratory	Zero	May cause allergic reactions (possibly delayed), and exceptionally, bronchospasm.	
Phenylalanine	All	Zero	This medicine contains phenylalanine. May be harmful for people with phenylketonuria	

Potassium	Parenteral	Less than 1 mmol per <dose>	This medicine contains potassium, less than 1 mmol (39 mg) per <dose>, i.e. essentially 'potassium- free'.	Information relates to a threshold based on the total amount of K^+ in the medicinal product It is especially relevant to products used in paediatric doses, to provide information to prescribers and reassurance to parents concerning the low level of K^+ in the product.
	Parenteral Oral	1 mmol per <dose>	This medicine contains x mmol (or y mg) potassium per <dose>. To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.	
	Parenteral – intravenous	30 mmol/l	May cause pain at the site of injection.	
Propylene glycol and esters	Topical	Zero	May cause skin irritation	
	Oral Parenteral	400mg/kg adults 200mg/kg children	May cause alcohol-like symptoms	
Sesame oil	All	Zero	May rarely cause severe allergic reactions.	

Sodium	Parenteral	Less than 1 mmol per <dose>	This medicinal product contains less than 1 mmol sodium (23 mg) per <dose>, i.e. essentially 'sodium- free'.	Information relates to a threshold based on the total amount of Na^+ in the medicinal product It is especially relevant to products used in paediatric doses, to provide information to prescribers and reassurance to parents concerning the low level of Na^+ in the product.
	Oral Parenteral	1 mmol per <dose>	This medicinal product contains x mmol (or y mg) sodium per dose. To be taken into consideration by patients on a controlled sodium diet	
Sorbic acid and salts	Topical	Zero	May cause local skin reactions, (e.g. contact dermatitis).	
Sorbitol E420	Oral Parenteral	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product	SPC proposal: Patients with rare hereditary problems of fructose intolerance should not take this medicine**.**
	Oral	10 g	May have a mild laxative effect Calorific value 2.6 kcal/g sorbitol	
Soya oil (and Hydrogenated Soya oil)	All	Zero	(Medicinal product) contains soya oil. If you are allergic to peanut or soya, do not use this medicinal product.	In line with Arachis oil. SPC: contraindication.
Stearyl alcohol	Topical	Zero	May cause local skin reactions (e.g. contact dermatitis)	

Sucrose	Oral	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product	SPC proposal: Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
		5g	Contains x g of sucrose per dose. This should be taken into account in patients with diabetes mellitus.	
	Oral liquids, lozenges and chewable tablets	Zero	May be harmful to the teeth.	Information to be included only when the medicinal product may be intended for chronic use, e.g. for two weeks or more
Sulphites including metabisulphites **For example:** **E220 sulphur dioxide** **E221 sodium sulphite** **E222sodium bisulphite** **E223 Sodium metabisulphite** **E224Potassium metabisulphite** **E228 Potassium bisulphite**	Oral Parenteral Respiratory	Zero	May rarely cause severe hypersensitivity reactions and bronchospasm	
Wheat starch	Oral	Zero	Suitable for people with coeliac disease. Patients with wheat allergy (different from coeliac disease) should not take this medicine.	Wheat Starch may contain gluten, but only in trace amounts, and is therefore

				considered safe for people with coeliac disease. (Gluten in wheat starch is limited by the test for total protein described in the PhEur monograph.)
Wool Fat (Lanolin)	Topical	Zero	May cause local skin reactions (e.g. contact dermatitis)	
Xylitol	Oral	10 g	May have a laxative effect Calorific value 2.4 kcal/g xylitol	