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Haemodialysis Solutions

General Notices

(Solutions for Haemodialysis, Ph. Eur. monograph 0128)

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DEFINITION

Solutions of electrolytes with a concentration close to the electrolytic composition of plasma. Glucose may be included in the formulation.

Because of the large volumes used, haemodialysis solutions are usually prepared by diluting a concentrated solution with water of suitable quality (see the monograph *Haemodialysis solutions, concentrated, water for diluting (1167)*), using for example an automatic dosing device.

CONCENTRATED SOLUTIONS FOR HAEMODIALYSIS

Concentrated haemodialysis solutions are prepared and stored using materials and methods designed to produce solutions having as low a degree of microbial contamination as possible. In certain circumstances, it may be necessary to use sterile solutions.

During dilution and use, precautions are taken to avoid microbial contamination. Diluted solutions are to be used immediately after preparation.

Concentrated solutions for haemodialysis are supplied in:

— rigid, semi-rigid or flexible plastic containers;

— glass containers.

3 types of concentrated solutions are used:

1. Concentrated solutions with acetate or lactate

Several formulations of concentrated solutions are used. The concentrations of the components in the solutions are such that, after dilution to the stated volume, the concentrations of the components per litre are usually in the following ranges (see Table 0128.-1):

Table 0128.-1.

	Concentration (mmol/L)	Concentration (mEq/L)
Sodium	130 - 145	130 - 145
Potassium	0 - 3.0	0 - 3.0

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	Concentration (mmol/L)	Concentration (mEq/L)
Calcium	0 - 2.0	0 - 4.0
Magnesium	0 - 1.2	0 - 2.4
Acetate or lactate	32 - 45	32 - 45
Chloride	90 - 120	90 - 120
Glucose	0 - 12.0	

Concentrated solutions with acetate or lactate are diluted before use.

2. Concentrated acid solutions

Several formulations of concentrated solutions are used. The concentrations of the components in the solutions are such that, after dilution to the stated volume and before neutralisation with sodium hydrogen carbonate, the concentrations of the components per litre are usually in the following ranges (see Table 0128.-2):

Table 0128.-2.

	Concentration (mmol/L)	Concentration (mEq/L)
Sodium	80 - 110	80 - 110
Potassium	0 - 3.0	0 - 3.0
Calcium	0 - 2.0	0 - 4.0
Magnesium	0 - 1.2	0 - 2.4
Acetic acid	2.5 - 10	2.5 - 10
Chloride	90 - 120	90 - 120
Glucose	0 - 12.0	

Sodium hydrogen carbonate must be added immediately before use to a final concentration of not more than 45 mmol/L. The concentrated solution of sodium hydrogen carbonate is supplied in a separate container. The concentrated acid solutions and the concentrated solutions of sodium hydrogen carbonate are diluted and mixed immediately before use using a suitable device. Alternatively, sodium hydrogen carbonate in powder form may be used to prepare the solution.

3. Concentrated solutions without buffer

Several formulations of concentrated solutions without buffer are used. The concentrations of the components in the solutions are such that, after dilution to the stated volume, the concentrations of the components per litre are usually in the following ranges (see Table 0128.-3):

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Table 0128.-3.

	Concentration (mmol/L)	Concentration (mEq/L)
Sodium	130 - 145	130 - 145
Potassium	0 - 3.0	0 - 3.0
Calcium	0 - 2.0	0 - 4.0
Magnesium	0 - 1.2	0 - 2.4
Chloride	130 - 155	130 - 155
Glucose	0 - 12.0	

Concentrated solutions without buffer are used together with parenteral administration of suitable hydrogen carbonate solutions.

The following tests are carried out on the diluted, ready-to-use solutions.

IDENTIFICATION

According to the stated composition, the solution to be examined gives the following identification reactions (2.3.1):

— potassium: reaction (b);

— calcium: reaction (a);

— sodium: reaction (b);

— chlorides: reaction (a);

— lactates;

— carbonates and hydrogen carbonates;

— acetates:

— if the solution is free from glucose, use reaction (b);

— if the solution contains glucose, use the following method: to 5 mL of the solution to be examined add 1 mL of *hydrochloric acid R* in a test-tube fitted with a stopper and a bent tube, heat and collect a few millilitres of distillate; carry out reaction (b) of acetates on the distillate;

— magnesium: to 0.1 mL of *titan yellow solution R* add 10 mL of *water R*, 2 mL of the solution to be examined and 1 mL of a 4.2 g/L solution of *sodium hydroxide R*; a pink colour is produced;

— glucose: to 5 mL of the solution to be examined add 2 mL of *dilute sodium hydroxide solution R* and 0.05 mL of *copper sulfate solution R*; the solution is blue and clear; heat to boiling; an abundant red precipitate is formed.

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TESTS

Appearance of solution

The solution to be examined is clear (*2.2.1*). If it does not contain glucose, it is colourless (*2.2.2, Method I*). If it contains glucose, it is not more intensely coloured than reference solution Y_7 (*2.2.2, Method I*).

Aluminium

Maximum 10 µg/L.

Atomic absorption spectrometry (*2.2.23, Method I or II*). Use a matrix modifier (for example, *nitric acid R* and *magnesium nitrate R* in *water R*) in the same quantity for the test solution, the reference solutions and the blank solution.

Test solution If necessary, dilute the solution to be examined with *water R* to a concentration suitable for the instrument to be used.

Reference solutions. Method I – direct calibration.

Prepare the reference solutions by diluting, for example *aluminium standard solution (10 ppm Al) R* with acidified *water R*.

Reference solutions. Method II – standard additions.

Prepare at least 3 reference solutions in the test solution, in a range spanning the expected aluminium concentration of the test solution, for example by diluting *aluminium standard solution (10 ppm Al) R* with the test solution.

Blank solution *water R*.

Source Aluminium hollow-cathode lamp.

Wavelength 309.3 nm.

Atomisation device Graphite furnace.

Extractable volume (*2.9.17*)

The volume measured is not less than the nominal volume stated on the label.

Microbial contamination

TAMC: acceptance criterion 10^2 CFU/mL (*2.6.12*).

Sterility (*2.6.1*)

If the label states that the concentrated haemodialysis solution is sterile, it complies with the test for sterility.

Bacterial endotoxins (*2.6.14*)

Less than 0.25 IU/mL in the solution diluted for use.

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Pyrogens (*2.6.8*)

Solutions for which a validated test for bacterial endotoxins cannot be carried out comply with the test for pyrogens. Dilute the solution to be examined with *water for injections R* to the concentration prescribed for use. Inject 10 mL of the solution per kilogram of the rabbit's mass.

ASSAY

Determine the density (2.2.5) of the concentrated solution and calculate the content in grams per litre and in millimoles per litre.

Sodium

97.5 per cent to 102.5 per cent of the content of sodium (Na) stated on the label.

Atomic emission spectrometry (*2.2.22, Method I*).

Test solution If necessary, dilute the solution to be examined with *water R* to a concentration suitable for the instrument to be used.

Reference solutions Prepare the reference solutions using *sodium standard solution (200 ppm Na) R*.

Wavelengths 589.0 nm or 589.6 nm (sodium emits as a doublet).

Potassium

95.0 per cent to 105.0 per cent of the content of potassium (K) stated on the label.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Dilute with *water R* an accurately weighed quantity of the solution to be examined to a concentration suitable for the instrument to be used. To 100 mL of this solution add 10 mL of a 22 g/L solution of *sodium chloride R*.

Reference solutions Prepare the reference solutions using *potassium standard solution (100 ppm K) R*. To 100 mL of each reference solution add 10 mL of a 22 g/L solution of *sodium chloride R*.

Source Potassium hollow-cathode lamp.

Wavelength 766.5 nm.

Atomisation device Air-acetylene flame.

Calcium

95.0 per cent to 105.0 per cent of the content of calcium (Ca) stated on the label.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Dilute 5.0 mL of the solution to be examined to 100.0 mL with *water R*. To 3.0 mL of this solution add 5 mL of *lanthanum chloride solution R* and dilute to 50.0 mL with *water R*.

Reference solutions Into 4 identical volumetric flasks each containing 5 mL of *lanthanum chloride solution R*, introduce respectively 2.5 mL, 5.0 mL, 7.0 mL and 10.0 mL of *calcium standard solution (10 ppm Ca) R* and dilute to 50.0 mL with *water R*.

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Source Calcium hollow-cathode lamp.

Wavelength 422.7 nm.

Atomisation device Air-acetylene flame.

Magnesium

95.0 per cent to 105.0 per cent of the content of magnesium (Mg) stated on the label.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Dilute 5.0 mL of the solution to be examined to 100.0 mL with *water R*. To 2.0 mL of this solution add 5 mL of *lanthanum chloride solution R* and dilute to 50.0 mL with *water R*.

Reference solutions Into 4 identical volumetric flasks each containing 5 mL of *lanthanum chloride solution R*, introduce respectively 1.0 mL, 2.0 mL, 3.0 mL and 4.0 mL of *magnesium standard solution (10 ppm Mg) R* and dilute to 50.0 mL with *water R*.

Source Magnesium hollow-cathode lamp.

Wavelength 285.2 nm.

Atomisation device Air-acetylene flame.

Total chloride

95.0 per cent to 105.0 per cent of the content of chloride (Cl) stated on the label.

Dilute an accurately measured volume of the solution to be examined containing the equivalent of about 0.68 mEq of chloride with an appropriate volume of *water R* in order to immerse the electrode. Carry out a potentiometric titration (*2.2.20*), using *0.1 M silver nitrate*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M silver nitrate* is equivalent to 3.545 mg of Cl.

Acetate

95.0 per cent to 105.0 per cent of the content of acetate stated on the label.

To a volume of the solution to be examined, corresponding to about 0.7 mmol of acetate, add 10.0 mL of *0.1 M hydrochloric acid*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 0.1 mmol of acetate.

Lactate

95.0 per cent to 105.0 per cent of the content of lactate stated on the label.

To a volume of the solution to be examined, corresponding to about 0.7 mmol of lactate, add 10.0 mL of *0.1 M hydrochloric acid*. Then add 50 mL of *acetonitrile R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2

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points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 0.1 mmol of lactate.

Sodium hydrogen carbonate

95.0 per cent to 105.0 per cent of the content of sodium hydrogen carbonate stated on the label.

Titrate with *0.1 M hydrochloric acid* a volume of the solution to be examined corresponding to about 0.1 g of sodium hydrogen carbonate, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M hydrochloric acid* is equivalent to 8.40 mg of $NaHCO_3$.

Reducing sugars

(expressed as glucose): 95.0 per cent to 105.0 per cent of the content of glucose stated on the label.

Transfer a volume of the solution to be examined containing the equivalent of 25 mg of glucose to a 250 mL conical flask with a ground-glass neck and add 25.0 mL of *cupri-citric solution R*. Add a few grains of pumice, fit a reflux condenser, heat so that boiling occurs within 2 min and maintain boiling for exactly 10 min. Cool and add 3 g of *potassium iodide R* dissolved in 3 mL of *water R*. Carefully add, in small amounts, 25 mL of a 25 per cent *m/m* solution of *sulfuric acid R*. Titrate with *0.1 M sodium thiosulfate* using *starch solution R*, added towards the end of the titration, as indicator. Carry out a blank titration using 25.0 mL of *water R*.

Calculate the content of reducing sugars, expressed as glucose ($C_6H_{12}O_6$), using Table 0128.-4.

Table 0128.-4.

Volume of *0.1 M sodium thiosulfate* (mL)	Glucose (mg)
8	19.8
9	22.4
10	25.0
11	27.6
12	30.3
13	33.0
14	35.7
15	38.5
16	41.3

STORAGE

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At 4 °C or above.

LABELLING

The label states:

— the formula of the concentrated solution for haemodialysis expressed in grams per litre and in millimoles per litre;

— the nominal volume of the solution in the container;

— where applicable, that the concentrated solution is sterile;

— the storage conditions;

— that the concentrated solution is to be diluted immediately before use;

— the dilution to be made;

— that the volume taken for use is to be measured accurately;

— the ionic formula for the diluted solution ready for use in millimoles per litre;

— that any unused portion of solution is to be discarded;

— where applicable, that sodium hydrogen carbonate is to be added before use;

— that the solution is not to be used for intraveneous infusion.

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Haemofiltration and Haemodiafiltration Solutions

General Notices

(Solutions for Haemofiltration and Haemodiafiltration, Ph. Eur. monograph 0861)

When the Solution is intended for haemofiltration only, the title Haemofiltration Solutions may be used.

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DEFINITION

Preparations for parenteral administration containing electrolytes with a concentration close to the electrolytic composition of plasma. Glucose may be included in the formulation.

Solutions for haemofiltration and haemodiafiltration are supplied in:

— rigid or semi-rigid plastic containers;

— flexible plastic containers inside closed protective envelopes;

— glass containers.

The containers and closures comply with the requirements for containers for preparations for parenteral administration (*3.2*).

In haemofiltration and haemodiafiltration, the following formulations are used. The concentrations of the components per litre of solution are usually in the following range (see Table 0861.-1):

Table 0861.-1.

	Concentration (mmol/L)	Concentration (mEq/L)
Sodium	125 - 150	125 - 150
Potassium	0 - 4.5	0 - 4.5
Calcium	1.0 - 2.5	2.0 - 5.0
Magnesium	0.25 - 1.5	0.50 - 3.0
Acetate and/or lactate and/or hydrogen carbonate	30 - 60	30 - 60
Chloride	90 - 120	90 - 120
Glucose	0 - 25	

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When hydrogen carbonate is present, the solution of sodium hydrogen carbonate is supplied in a container or a separate compartment and is added to the electrolyte solution immediately before use.

In haemofiltration and haemodiafiltration, the following formulations may also be used (see Table 0861.-2):

Table 0861.-2.

	Concentration (mmol/L)	Concentration (mEq/L)
Sodium	130 - 167	130 - 167
Potassium	0 - 4.0	0 - 4.0
Hydrogen carbonate	20 - 167	20 - 167
Chloride	0 - 147	0 - 147

Antioxidants are not added to the solutions.

IDENTIFICATION

According to the stated composition, the solution to be examined gives the following identification reactions (*2.3.1*):

— potassium: reaction (b);

— calcium: reaction (a);

— sodium: reaction (b);

— chlorides: reaction (a);

— acetates:

  — if the solution is free from glucose, use reaction (b);

  — if the solution contains glucose, use the following method: to 5 mL of the solution to be examined add 1 mL of *hydrochloric acid R* in a test-tube fitted with a stopper and a bent tube, heat and collect a few millilitres of distillate; carry out reaction (b) of acetates on the distillate;

— lactates;

— carbonates and hydrogen carbonates;

— magnesium: to 0.1 mL of *titan yellow solution R* add 10 mL of *water R*, 2 mL of the solution to be examined and 1 mL of *1 M sodium hydroxide*; a pink colour is produced;

— glucose: to 5 mL of the solution to be examined, add 2 mL of *dilute sodium hydroxide solution R* and 0.05 mL of *copper sulfate solution R*; the solution is blue and clear; heat to boiling; an abundant red precipitate is formed.

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TESTS

Appearance of solution

The solution is clear (2.2.1). If it does not contain glucose, it is colourless (2.2.2, Method I). If it contains glucose, it is not more intensely coloured than reference solution Y_7 (2.2.2, Method I).

pH (2.2.3)

5.0 to 7.5. If the solution contains glucose, the pH is 4.5 to 6.5. If the solution contains hydrogen carbonate, the pH is 7.0 to 8.5.

Hydroxymethylfurfural

Carry out the test only if glucose is added to the preparation. To a volume of the solution to be examined containing the equivalent of 25 mg of glucose, add 5.0 mL of a 100 g/L solution of *p-toluidine R* in *2-propanol R* containing 10 per cent *V/V* of *glacial acetic acid R*, then add 1.0 mL of a 5 g/L solution of *barbituric acid R*. The absorbance (2.2.25), determined at 550 nm after allowing the mixture to stand for 2-3 min, is not greater than that of a standard prepared at the same time and in the same manner using a solution containing 10 µg of *hydroxymethylfurfural R* in the same volume as the solution to be examined (400 ppm expressed with reference to the glucose concentration). If the solution contains hydrogen carbonate, use as the standard a solution containing 20 µg of *hydroxymethylfurfural R* (800 ppm expressed with reference to the glucose concentration).

Aluminium

Maximum 10 µg/L.

Atomic absorption spectrometry (2.2.23, Method I or II). Use a matrix modifier (for example, *nitric acid R* and *magnesium nitrate R* in *water R*) in the same quantity for the test solution, the reference solutions and the blank solution.

Test solution If necessary, dilute the solution to be examined with *water R* to a concentration suitable for the instrument to be used.

Reference solutions. Method I – direct calibration.

Prepare the reference solutions by diluting, for example *aluminium standard solution (10 ppm Al) R* with acidified *water R*.

Reference solutions. Method II – standard additions.

Prepare at least 3 reference solutions in the test solution, in a range spanning the expected aluminium concentration of the test solution, for example by diluting *aluminium standard solution (10 ppm Al) R* with the test solution.

Blank solution *water R*.

Source Aluminium hollow-cathode lamp.

Wavelength 309.3 nm.

Atomisation device Graphite furnace.

Particulate contamination (2.9.19, Method I)

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Use 50 mL of the solution to be examined.

Extractable volume (2.9.17)

The solution complies with the test prescribed for parenteral infusions.

Sterility (2.6.1)

The solution complies with the test.

Bacterial endotoxins (2.6.14)

Less than 0.05 IU/mL.

Pyrogens (2.6.8)

Solutions for which a validated test for bacterial endotoxins cannot be carried out comply with the test for pyrogens. Inject per kilogram of the rabbit's mass 10 mL of the solution.

ASSAY

Sodium

97.5 per cent to 102.5 per cent of the content of sodium (Na) stated on the label.

Atomic emission spectrometry (2.2.22, Method I).

Test solution If necessary, dilute the solution to be examined with water R to a concentration suitable for the instrument to be used.

Reference solutions Prepare the reference solutions using sodium standard solution (200 ppm Na) R.

Wavelengths 589.0 nm or 589.6 nm (sodium emits as a doublet).

Potassium

95.0 per cent to 105.0 per cent of the content of potassium (K) stated on the label.

Atomic absorption spectrometry (2.2.23, Method I).

Test solution If necessary, dilute the solution to be examined with water R to a concentration suitable for the instrument to be used. To 100 mL of the solution add 10 mL of a 22 g/L solution of sodium chloride R.

Reference solutions Prepare the reference solutions using potassium standard solution (100 ppm K) R. To 100 mL of each reference solution add 10 mL of a 22 g/L solution of sodium chloride R.

Source Potassium hollow-cathode lamp.

Wavelength 766.5 nm.

Atomisation device Air-propane or air-acetylene flame.

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Calcium

95.0 per cent to 105.0 per cent of the content of calcium (Ca) stated on the label.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution If necessary, dilute the solution to be examined with *water R* to a concentration suitable for the instrument to be used.

Reference solutions Prepare the reference solutions using *calcium standard solution (400 ppm Ca) R*.

Source Calcium hollow-cathode lamp.

Wavelength 422.7 nm.

Atomisation device Air-propane or air-acetylene flame.

Magnesium

95.0 per cent to 105.0 per cent of the content of magnesium (Mg) stated on the label.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution If necessary, dilute the solution to be examined with *water R* to a concentration suitable for the instrument to be used.

Reference solutions Prepare the reference solutions using *magnesium standard solution (100 ppm Mg) R*.

Source Magnesium hollow-cathode lamp.

Wavelength 285.2 nm.

Atomisation device Air-propane or air-acetylene flame.

Total chloride

95.0 per cent to 105.0 per cent of the content of chloride (Cl) stated on the label.

Dilute an accurately measured volume of the solution to be examined containing the equivalent of about 0.68 mEq of chloride with an appropriate volume of *water R* to immerse the electrode. Carry out a potentiometric titration (*2.2.20*), using *0.1 M silver nitrate*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M silver nitrate* is equivalent to 3.545 mg of Cl.

Acetate

95.0 per cent to 105.0 per cent of the content of acetate stated on the label.

To a volume of the solution to be examined, corresponding to about 0.7 mmol of acetate, add 10.0 mL of *0.1 M hydrochloric acid*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 0.1 mmol of acetate.

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Lactate

95.0 per cent to 105.0 per cent of the content of lactate stated on the label.

To a volume of the solution to be examined, corresponding to about 0.7 mmol of lactate, add 10.0 mL of *0.1 M hydrochloric acid*. Add 50 mL of *acetonitrile R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 0.1 mmol of lactate.

Sodium hydrogen carbonate

95.0 per cent to 105.0 per cent of the content of sodium hydrogen carbonate stated on the label.

Titrate with *0.1 M hydrochloric acid*, a volume of the solution to be examined corresponding to about 0.1 g of sodium hydrogen carbonate, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M hydrochloric acid* is equivalent to 8.40 mg of $NaHCO_3$.

Lactate and hydrogen carbonate

95.0 per cent to 105.0 per cent of the content of lactates and hydrogen carbonates stated on the label.

Liquid chromatography (*2.2.29*).

Test solution The solution to be examined.

Reference solution Dissolve in 100 mL of *water for chromatography R* quantities of lactates and hydrogen carbonates, accurately weighed, in order to obtain solutions having concentrations representing about 90 per cent, 100 per cent and 110 per cent of the concentrations stated on the label.

Column:

— *size*: *l* = 0.30 m, Ø = 7.8 mm;

— *stationary phase*: *cation-exchange resin R* (9 µm);

— *temperature*: 60 °C.

Mobile phase *0.005 M sulfuric acid* previously degassed with *helium for chromatography R*.

Flow rate 0.6 mL/min.

Detection Differential refractometer.

Injection 20 µL, twice.

Order of elution Lactates, hydrogen carbonates.

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Determine the concentration of lactates and hydrogen carbonates in the test solution by interpolating the peak area for lactate and the peak height for hydrogen carbonate from the linear regression curve obtained with the reference solutions.

Reducing sugars

(expressed as glucose): 95.0 per cent to 105.0 per cent of the content of glucose stated on the label.

Transfer a volume of the solution to be examined containing the equivalent of 25 mg of glucose to a 250 mL conical flask with a ground-glass neck and add 25.0 mL of *cupri-citric solution R*. Add a few grains of pumice, fit a reflux condenser, heat so that boiling occurs within 2 min and boil for exactly 10 min. Cool and add 3 g of *potassium iodide R* dissolved in 3 mL of *water R*. Carefully add, in small amounts, 25 mL of a 25 per cent *m/m* solution of *sulfuric acid R*. Titrate with *0.1 M sodium thiosulfate* using *starch solution R*, added towards the end of the titration, as indicator. Carry out a blank titration using 25.0 mL of *water R*.

Calculate the content of reducing sugars expressed as glucose ($C_6H_{12}O_6$), using Table 0861.-3.

Table 0861.-3.

Volume of *0.1 M sodium thiosulfate* (mL)	Glucose (mg)
8	19.8
9	22.4
10	25.0
11	27.6
12	30.3
13	33.0
14	35.7
15	38.5
16	41.3

STORAGE

At 4 °C or above.

LABELLING

The label states:

— the formula of the solution for haemofiltration or haemodiafiltration, expressed in grams per litre and in millimoles per litre;

— the calculated osmolarity, expressed in milliosmoles per litre;

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— the nominal volume of the solution for haemofiltration or haemodiafiltration in the container;

— that the solution is free from bacterial endotoxins, or where applicable, that it is apyrogenic;

— the storage conditions;

— that any unused portion of solution is to be discarded.

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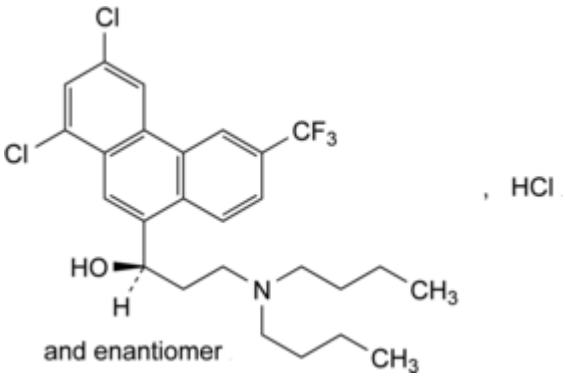
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This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Halofantrine Hydrochloride

General Notices

(Ph. Eur. monograph 1979)



$C_{26}H_{31}Cl_3F_3NO$ 536.9 *36167-63-2*

Action and use

Antiprotozoal (malaria).

Ph Eur

DEFINITION

(1*RS*)-3-(Dibutylamino)-1-[1,3-dichloro-6-(trifluoromethyl)phenanthren-9-yl]propan-1-ol hydrochloride.

Content

97.5 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, freely soluble in methanol, sparingly soluble in ethanol (96 per cent).

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It shows polymorphism (*5.9*).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *halofantrine hydrochloride CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methyl ethyl ketone R*, evaporate to dryness and record new spectra using the residues.

B. It gives reaction (b) of chlorides (*2.3.1*).

TESTS

Optical rotation (*2.2.7*)

-0.10° to + 0.10°.

Dissolve 1.00 g in *alcohol R* and dilute to 100.0 mL with the same solvent.

Absorbance (*2.2.25*)

Maximum 0.085 at 450 nm.

Dissolve 0.200 g in *methanol R* and dilute to 10.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution (a) Dissolve 40.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Test solution (b) Dilute 5.0 mL of test solution (a) to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 40.0 mg of *halofantrine hydrochloride CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (b) Dilute 5.0 mL of reference solution (a) to 50.0 mL with the mobile phase.

Reference solution (c) Dilute 1.0 mL of test solution (a) to 100.0 mL with the mobile phase. Dilute 5.0 mL of the solution to 50.0 mL with the mobile phase.

Reference solution (d) Dissolve 10.0 mg of *halofantrine impurity C CRS* in the mobile phase and dilute to 25 mL with the mobile phase. To 5.0 mL of the solution, add 5.0 mL of reference solution (a) and dilute to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.30 m, Ø = 3.9 mm,

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— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (10 µm) of irregular type, with a specific surface of 330 m^2/g, a pore size of 12.5 nm and a carbon loading of 9.8 per cent .

Mobile phase Mix 250 mL of a 2.0 g/L solution of *sodium hydroxide R*, previously adjusted to pH 2.5 with *perchloric acid R* and 750 mL of *acetonitrile R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 260 nm.

Injection 20 µL; inject the test solution (a) and reference solutions (c) and (d).

Run time 5 times the retention time of halofantrine which is about 6 min.

System suitability:

— *resolution*: minimum 3.3 between the peaks due to halofantrine and impurity C in the chromatogram obtained with reference solution (d).

Limits:

— *any impurity*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent),

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent),

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances.

Injection Test solution (b) and reference solution (b).

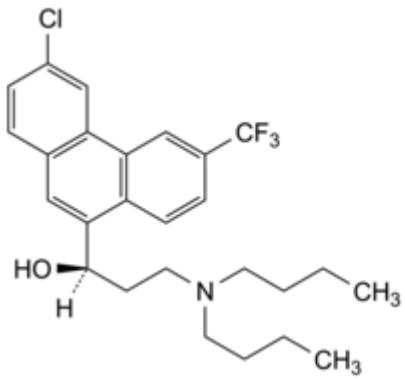
Calculate the percentage content of halofantrine hydrochloride.

STORAGE

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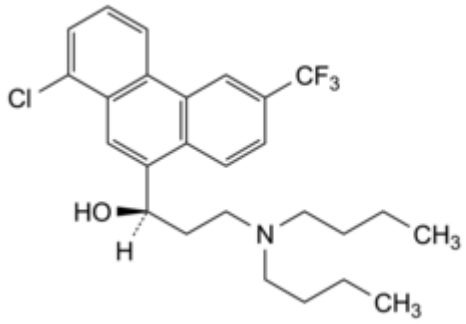
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IMPURITIES



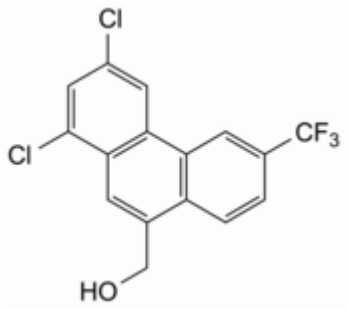
and enantiomer

A. (1*RS*)-1-[3-chloro-6-(trifluoromethyl)phenanthren-9-yl]-3-(dibutylamino)propan-1-ol (1-dechlorohalofantrine),



and enantiomer

B. (1*RS*)-1-[1-chloro-6-(trifluoromethyl)phenanthren-9-yl]-3-(dibutylamino)propan-1-ol (3-dechlorohalofantrine),



C. [1,3-dichloro-6-(trifluoromethyl)phenanthren-9-yl]methanol.

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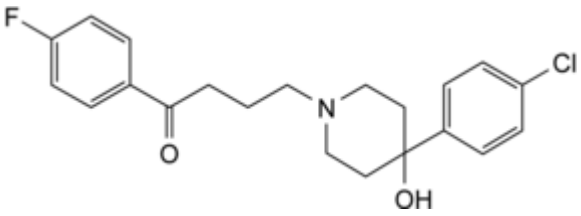
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Haloperidol

General Notices

(Ph. Eur. monograph 0616)



$C_{21}H_{23}ClFNO_2$ 375.9 *52-86-8*

Action and use

Dopamine receptor antagonist; neuroleptic.

Preparations

Haloperidol Capsules

Haloperidol Injection

Haloperidol Oral Solution

Haloperidol Tablets

Ph Eur

DEFINITION

4-[4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl]-1-(4-fluorophenyl)butan-1-one.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

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Practically insoluble in water, slightly soluble in ethanol (96 per cent), in methanol and in methylene chloride.

IDENTIFICATION

First identification: B, E.

Second identification: A, C, D, E.

A. Melting point (2.2.14): 150 °C to 153 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison haloperidol CRS.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in methanol R and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 10 mg of haloperidol CRS in methanol R and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of haloperidol CRS and 10 mg of bromperidol CRS in methanol R and dilute to 10 mL with the same solvent.

Plate TLC octadecylsilyl silica gel plate R.

Mobile phase tetrahydrofuran R, methanol R, 58 g/L solution of sodium chloride R (10:45:45 *V/V/V*).

Application 1 µL.

Development In an unsaturated tank, over 2/3 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (b):

— the chromatogram shows 2 spots which may, however, not be completely separated.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

D. Dissolve about 10 mg in 5 mL of anhydrous ethanol R. Add 0.5 mL of dinitrobenzene solution R and 0.5 mL of 2 M alcoholic potassium hydroxide R. A violet colour is produced and becomes brownish-red after 20 min.

E. To 0.1 g in a platinum crucible add 0.5 g of anhydrous sodium carbonate R. Heat over an open flame for 10 min. Allow to cool. Take up the residue with 5 mL of dilute nitric acid R and filter. To 1 mL of the filtrate add 1 mL of water R. The solution gives reaction (a) of chlorides (2.3.1).

TESTS

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Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_7 (2.2.2, Method II).

Dissolve 0.2 g in 20 mL of a 1 per cent *V/V* solution of *lactic acid R*.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use and protect from light.*

Test solution Dissolve 0.100 g of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 10 mg of *haloperidol for system suitability CRS* (containing impurities B and D) in 1.0 mL of *methanol R*.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Reference solution (c) Dissolve 10 mg of *haloperidol for peak identification CRS* (containing impurities G and H) in 1.0 mL of *methanol R*.

Column:

— *size*: *l* = 0.1 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase:

— *mobile phase A*: 17 g/L solution of *tetrabutylammonium hydrogen sulfate R1*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	90	10
2 - 17	90 → 50	10 → 50
17 - 22	50	50

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *haloperidol for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities B and D; use the chromatogram supplied with *haloperidol for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities G and H.

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Relative retention With reference to haloperidol (retention time = about 8 min): impurity B = about 0.9; impurity D = about 1.6; impurity G = about 1.8; impurity H = about 2.0.

System suitability Reference solution (a):

— *resolution*: minimum 3.0 between the peaks due to impurity B and haloperidol.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity B by 0.7;

— *impurity D*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *impurity B*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *impurities G, H*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Dissolve 0.300 g in 50 mL of a mixture of 1 volume of *anhydrous acetic acid R* and 7 volumes of *methyl ethyl ketone R*. Titrate with *0.1 M perchloric acid*, using 0.2 mL of *naphtholbenzein solution R* as indicator.

1 mL of *0.1 M perchloric acid* is equivalent to 37.59 mg of $C_{21}H_{23}ClFNO_2$.

STORAGE

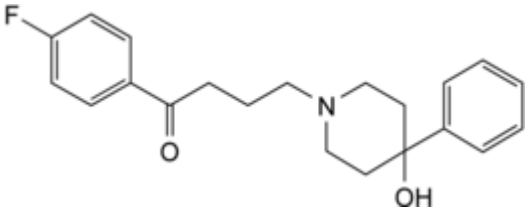
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IMPURITIES

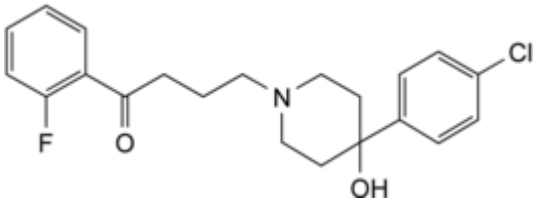
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Specified impurities B, D, G, H.

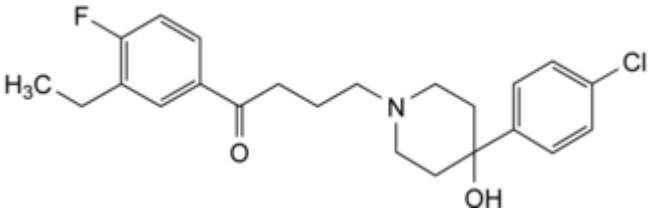
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, C, E, F.



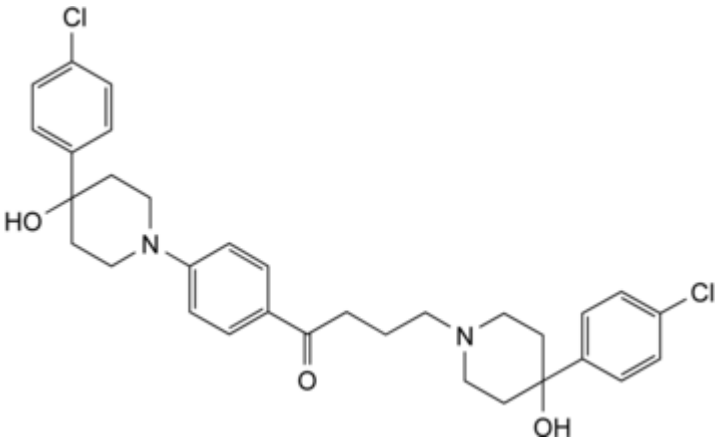
A. 1-(4-fluorophenyl)-4-(4-hydroxy-4-phenylpiperidin-1-yl)butan-1-one,



B. 4-[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]-1-(2-fluorophenyl)butan-1-one,

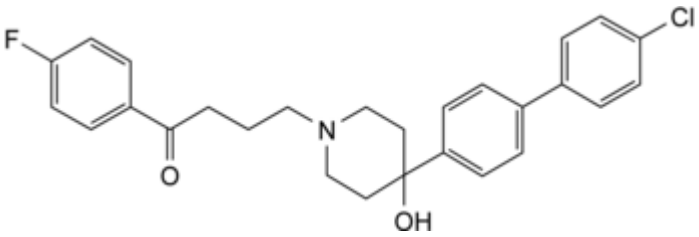


C. 4-[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]-1-(3-ethyl-4-fluorophenyl)butan-1-one,

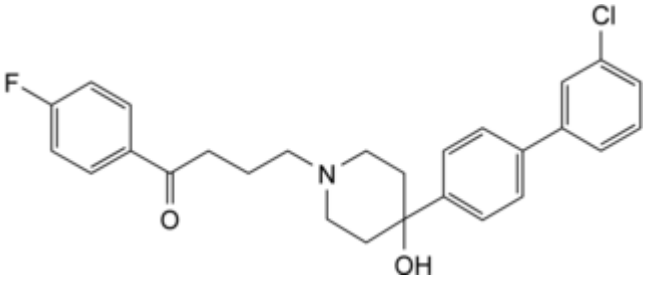


D. 4-[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]-1-[4-[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]phenyl]butan-1-one,

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E. 4-[4-(4′-chlorobiphenyl-4-yl)-4-hydroxypiperidin-1-yl]-1-(4-fluorophenyl)butan-1-one,



F. 4-[4-(3′-chlorobiphenyl-4-yl)-4-hydroxypiperidin-1-yl]-1-(4-fluorophenyl)butan-1-one,

G. unknown structure,

H. unknown structure.

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Haloperidol Capsules

General Notices

Action and use

Dopamine receptor antagonist; neuroleptic.

DEFINITION

Haloperidol Capsules contain Haloperidol.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of haloperidol, $C_{21}H_{23}ClFNO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

To a quantity of the contents of the capsules containing 10 mg of Haloperidol add 10 mL of *water* and 1 mL of 1M *sodium hydroxide* and extract with 10 mL of *ether*. Filter the ether extract through absorbent cotton, evaporate the filtrate to dryness and dry the residue at 60° at a pressure not exceeding 0.7 kPa. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of haloperidol *(RS 173)*.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.

(b) Use 900 mL of a solution containing of 0.2% w/v of *sodium chloride* and 8% v/v of 1M *hydrochloric acid* in *water*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a sample of the medium, filter and dilute with the dissolution medium if necessary, to produce a solution expected to contain 0.00006% w/v of Haloperidol.

(2) 0.00006% w/v of *haloperidol BPCRS* in dissolution medium.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (15 cm × 5 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 247 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

45 volumes of *acetonitrile* and 55 volumes of a 1% w/v solution of *ammonium acetate*.

DETERMINATION OF CONTENT

Calculate the total content of haloperidol, $C_{21}H_{23}ClFNO_2$, in the medium from the chromatograms obtained and using the declared content of $C_{21}H_{23}ClFNO_2$ in *haloperidol BPCRS*.

LIMITS

The amount of haloperidol released is not less than 70% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 1 volume of mobile phase A and 9 volumes of mobile phase B (solution A). Prepare the solutions immediately before use and protect from light.

(1) Shake a quantity of the contents of the capsules containing 10 mg of Haloperidol with 15 mL of solution A and mix with the aid of ultrasound. Dilute to 20 mL and filter.

(2) Dilute 1 volume of solution (1) to 200 volumes.

(3) 0.05% w/v of *haloperidol for system suitability EPCRS*.

(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *base-deactivated end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Hypersil BDS is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 230 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 1.7% w/v of *tetrabutylammonium hydrogen sulfate*.

Mobile phase B *acetonitrile*.

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Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	90	10	isocratic
2-17	90→50	10→50	linear gradient
17-22	50	50	isocratic
22-23	50→90	50→10	linear gradient
23-28	90	10	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to haloperidol (retention time about 8 minutes) are: impurity B, about 0.9 and impurity D, about 1.6.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity B and haloperidol is at least 3.0.

LIMITS

Identify any peak corresponding to impurity B in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (3), and multiply the area of this peak by a correction factor of 0.7.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity D is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity B is not greater than 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

Uniformity of content

Capsules containing less than 2 mg and/or less than 2% w/w of Haloperidol comply with the requirements stated under Capsules using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add sufficient of the mobile phase to the contents of one capsule to produce a solution containing 0.005% w/v of Haloperidol, disperse with the aid of ultrasound for 2 minutes, centrifuge and use the supernatant liquid.
(2) 0.005% w/v of *haloperidol BPCRS* in the mobile phase.

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CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Dissolution may be used with an injection volume of 20 µL.

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{23}ClFNO_2$ in each capsule using the declared content of $C_{21}H_{23}ClFNO_2$ in *haloperidol BPCRS*.

ASSAY

Use the average of the individual results determined in the test for Uniformity of content.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Haloperidol.

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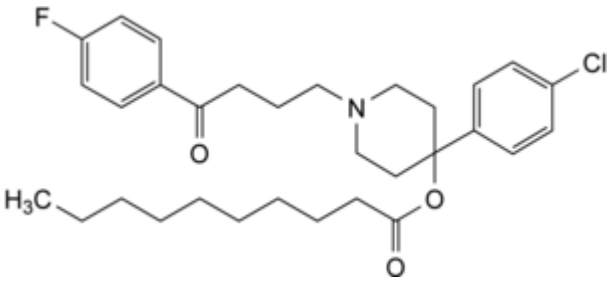
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Haloperidol Decanoate

General Notices

(Ph. Eur. monograph 1431)



$C_{31}H_{41}ClFNO_3$ 530.1 *74050-97-8*

Action and use

Dopamine receptor antagonist; neuroleptic.

Ph Eur

DEFINITION

4-(4-Chlorophenyl)-1-[4-(4-fluorophenyl)-4-oxobutyl]piperidin-4-yl decanoate.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, very soluble in ethanol (96 per cent), in methanol and in methylene chloride.

mp

About 42 °C.

IDENTIFICATION

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A. Infrared absorption spectrophotometry (2.2.24).

Comparison *haloperidol decanoate CRS*.

B. To 0.1 g in a porcelain crucible add 0.5 g of *anhydrous sodium carbonate R*. Heat over an open flame for 10 min. Allow to cool. Take up the residue with 5 mL of *dilute nitric acid R* and filter. To 1 mL of the filtrate add 1 mL of *water R*. The solution gives reaction (a) of chlorides (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution B_5 (2.2.2, *Method II*).

Dissolve 2.0 g in *methylene chloride R* and dilute to 20 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use and protect from light.*

Test solution Dissolve 0.100 g of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 2.5 mg of *bromperidol decanoate CRS* and 2.5 mg of *haloperidol decanoate CRS* in *methanol R* and dilute to 50.0 mL with the same solvent.

Reference solution (b) Dilute 5.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Column:

— *size*: *l* = 0.1 m, Ø = 4.0 mm;

— *stationary phase*: *base-deactivated octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase:

— *mobile phase A*: 27 g/L solution of *tetrabutylammonium hydrogen sulfate R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 30	80 → 40	20 → 60
30 - 35	40	60
35 - 40	40 → 80	60 → 20

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Flow rate 1.5 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 10 µL.

Relative retention With reference to haloperidol decanoate (retention time = about 24 min): impurity G = about 0.1; impurity L = about 0.2; impurity H = about 0.8; impurity I = about 0.88; impurity A = about 0.9; impurity B = about 0.98; bromperidol decanoate = about 1.02; impurity J = about 1.1; impurity C = about 1.15; impurity D = about 1.2; impurity K = about 1.22; impurity F = about 1.26; impurity E = about 1.28.

System suitability Reference solution (a):

— *resolution*: minimum 1.5 between the peaks due to haloperidol decanoate and bromperidol decanoate.

Limits:

— *impurities A, B, C, D, E, F, G, H, I, J, K*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.5 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 30 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Dissolve 0.425 g in 50 mL of a mixture of 1 volume of *anhydrous acetic acid R* and 7 volumes of *methyl ethyl ketone R*. Titrate with *0.1 M perchloric acid*, using 0.2 mL of *naphtholbenzein solution R* as indicator.

1 mL of *0.1 M perchloric acid* is equivalent to 53.01 mg of $C_{31}H_{41}ClFNO_3$.

STORAGE

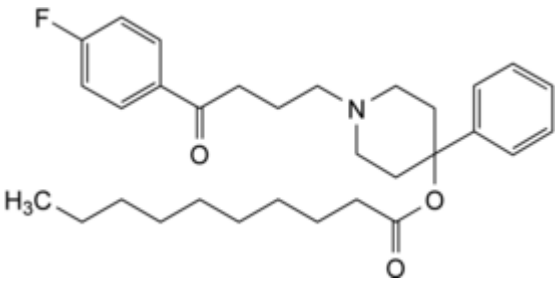
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IMPURITIES

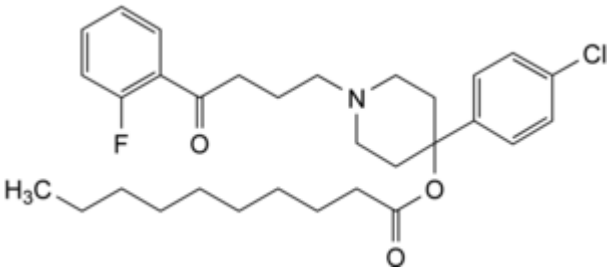
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Specified impurities A, B, C, D, E, F, G, H, I, J, K.

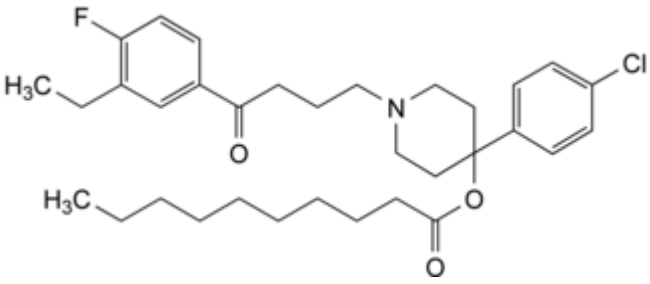
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) L.



A. 1-[4-(4-fluorophenyl)-4-oxobutyl]-4-phenylpiperidin-4-yl decanoate,

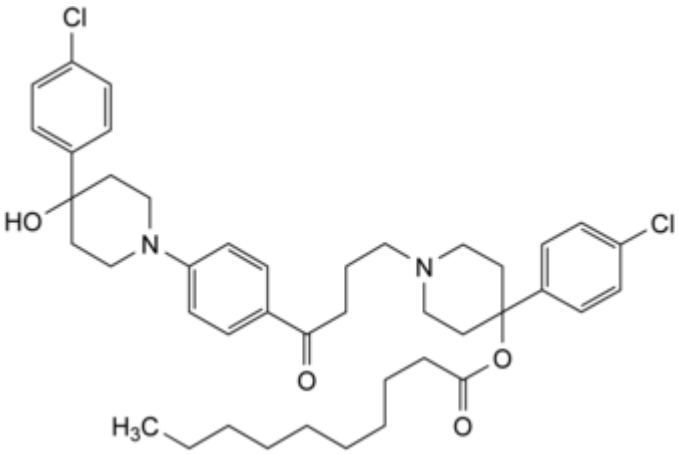


B. 4-(4-chlorophenyl)-1-[4-(2-fluorophenyl)-4-oxobutyl]piperidin-4-yl decanoate,

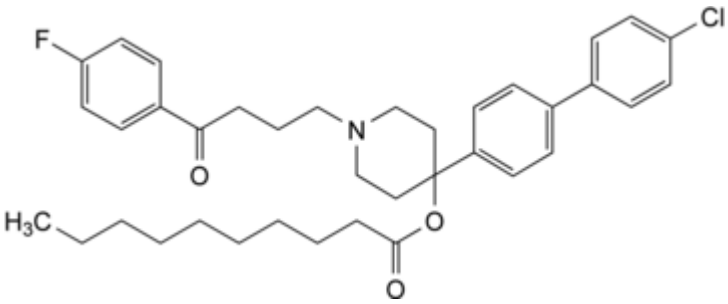


C. 4-(4-chlorophenyl)-1-[4-(3-ethyl-4-fluorophenyl)-4-oxobutyl]piperidin-4-yl decanoate,

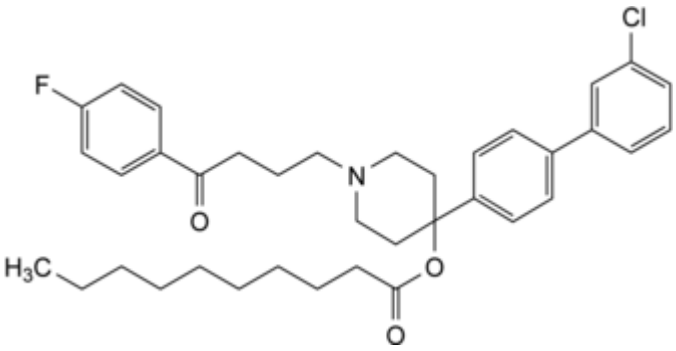
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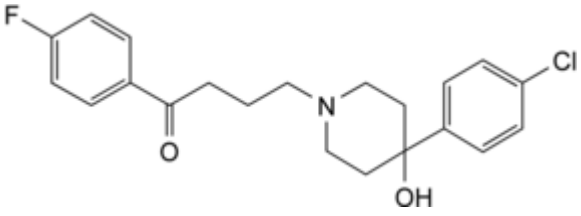
D. 4-(4-chlorophenyl)-1-[4-[4-[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]phenyl]-4-oxobutyl]piperidin-4-yl decanoate,



E. 4-(4′-chlorobiphenyl-4-yl)-1-[4-(4-fluorophenyl)-4-oxobutyl]piperidin-4-yl decanoate,

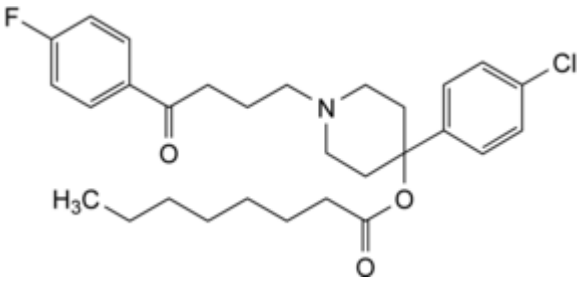


F. 4-(3′-chlorobiphenyl-4-yl)-1-[4-(4-fluorophenyl)-4-oxobutyl]piperidin-4-yl decanoate,

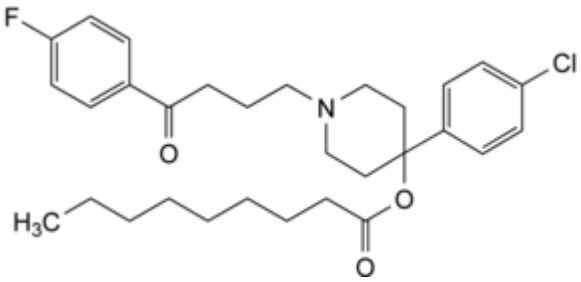


G. 4-[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]-1-(4-fluorophenyl)butan-1-one (haloperidol),

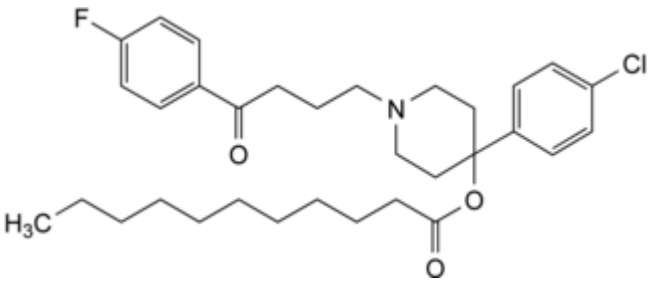
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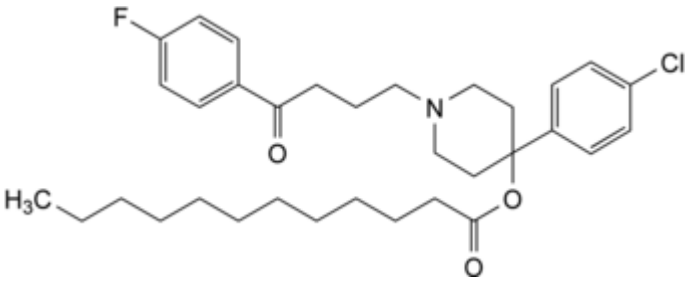
H. 4-(4-chlorophenyl)-1-[4-(4-fluorophenyl)-4-oxobutyl]piperidin-4-yl octanoate,



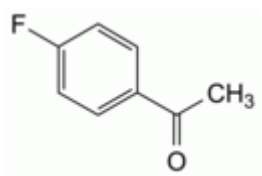
I. 4-(4-chlorophenyl)-1-[4-(4-fluorophenyl)-4-oxobutyl]piperidin-4-yl nonanoate,



J. 4-(4-chlorophenyl)-1-[4-(4-fluorophenyl)-4-oxobutyl]piperidin-4-yl undecanoate,



K. 4-(4-chlorophenyl)-1-[4-(4-fluorophenyl)-4-oxobutyl]piperidin-4-yl dodecanoate,



L. 1-(4-fluorophenyl)ethanone.

Ph Eur

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Haloperidol Injection

General Notices

Action and use

Dopamine receptor antagonist; neuroleptic.

DEFINITION

Haloperidol Injection is a sterile solution of Haloperidol in Lactic Acid diluted with Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of haloperidol, $C_{21}H_{23}ClFNO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

To a volume containing 20 mg of Haloperidol add 5 mL of *water* and 1 mL of 1M *sodium hydroxide* and extract with 10 mL of *dichloromethane*. Filter and evaporate the filtrate to dryness. Dry the residue at 60° at a pressure not exceeding 0.7 kPa. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of haloperidol *(RS 173)*.

TESTS

Acidity

pH, 2.8 to 3.6, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 1 volume of mobile phase A and 9 volumes of mobile phase B (solution A). Prepare the solutions immediately before use and protect from light.

(1) Dilute a volume of the injection with sufficient solution A to produce a solution containing 0.05% w/v of Haloperidol.

(2) Dilute 1 volume of solution (1) to 200 volumes.

(3) 0.05% w/v of *haloperidol for system suitability EPCRS*.

(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *base-deactivated end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Hypersil BDS is suitable).

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(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 230 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 1.7% w/v of *tetrabutylammonium hydrogen sulfate*.

Mobile phase B *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	90	10	isocratic
2-17	90→50	10→50	linear gradient
17-22	50	50	isocratic
22-23	50→90	50→10	linear gradient
23-28	90	10	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to haloperidol (retention time about 8 minutes) are: impurity B, about 0.9 and impurity D, about 1.6.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity B and haloperidol is at least 3.0.

LIMITS

Identify any peak corresponding to impurity B in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (3), and multiply the area of this peak by a correction factor of 0.7.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity D or impurity B is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5% of each);

the area of any other *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

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ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a volume of the injection with sufficient mobile phase to produce a solution containing 0.005% w/v of Haloperidol.

(2) 0.005% w/v of *haloperidol BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 5 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 247 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

45 volumes of *acetonitrile* and 55 volumes of a 1% w/v solution of *ammonium acetate*.

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{23}ClFNO_2$ in the injection using the declared content of $C_{21}H_{23}ClFNO_2$ in *haloperidol BPCRS*.

STORAGE

Haloperidol Injection should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Haloperidol.

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Haloperidol Oral Solution

General Notices

Haloperidol Oral Drops

Action and use

Dopamine receptor antagonist; neuroleptic.

DEFINITION

Haloperidol Oral Solution is a solution of Haloperidol in a suitable vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of haloperidol, $C_{21}H_{23}ClFNO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

To a volume containing 20 mg of Haloperidol add 1 mL of 1M *sodium hydroxide* and extract with 10 mL of *dichloromethane*. Filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of haloperidol *(RS 173)*.

TESTS

Acidity

pH, 2.5 to 3.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 1 volume of mobile phase A and 9 volumes of mobile phase B (solution A). Prepare the solutions immediately before use and protect from light.

(1) Dilute a volume of the oral solution with sufficient solution A to produce a solution containing 0.01% w/v of Haloperidol.

(2) Dilute 1 volume of solution (1) to 200 volumes.

(3) 0.01% w/v of *haloperidol for system suitability EPCRS*.

(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *base-deactivated end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Hypersil BDS is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 230 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 1.7% w/v of *tetrabutylammonium hydrogen sulfate*.

Mobile phase B *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	90	10	isocratic
2-17	90→50	10→50	linear gradient
17-22	50	50	isocratic
22-23	50→90	50→10	linear gradient
23-28	90	10	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to haloperidol (retention time about 8 minutes) are: impurity B, about 0.9 and impurity D, about 1.6.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity B and haloperidol is at least 3.0.

LIMITS

Identify any peak corresponding to impurity B in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (3), and multiply the area of this peak by a correction factor of 0.7.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity D is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity B is not greater than 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

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the sum of the areas of all *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Carry out the method for liquid chromatography, Appendix III D, using the following solutions in a mixture of 1 volume of mobile phase A and 9 volumes of mobile phase B (solution A).

(1) Dilute a volume of the oral solution with sufficient solution A to produce a solution containing 0.005% w/v of Haloperidol.

(2) 0.005% w/v of *haloperidol BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 5 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 247 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

45 volumes of *acetonitrile* and 55 volumes of a 1% w/v solution of *ammonium acetate*.

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{23}ClFNO_2$ in the oral solution using the declared content of $C_{21}H_{23}ClFNO_2$ in *haloperidol BPCRS*.

When Haloperidol Oral Solution or Haloperidol Oral Drops is prescribed or demanded and no strength is stated, an Oral Solution containing 0.2% w/v (2 mg/mL) of Haloperidol shall be dispensed or supplied.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Haloperidol.

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Haloperidol Tablets

General Notices

Action and use

Dopamine receptor antagonist; neuroleptic.

DEFINITION

Haloperidol Tablets contain Haloperidol.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of haloperidol, $C_{21}H_{23}ClFNO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

To a quantity of the powdered tablets containing 10 mg of Haloperidol add 10 mL of *water* and 1 mL of 1M *sodium hydroxide* and extract with 10 mL of *ether*. Filter the ether extract through absorbent cotton, evaporate the filtrate to dryness and dry the residue at 60° at a pressure not exceeding 0.7 kPa. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of haloperidol *(RS 173)*.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.

(b) Use 900 mL of a solution containing of 0.2% w/v of *sodium chloride* and 8% v/v of 1M *hydrochloric acid* in *water*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a sample of the medium, filter and dilute with the dissolution medium if necessary, to produce a solution expected to contain 0.00017% w/v of Haloperidol.

(2) 0.00017% w/v of *haloperidol BPCRS* in dissolution medium.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (15 cm × 5 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 247 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

45 volumes of *acetonitrile* and 55 volumes of a 1% w/v solution of *ammonium acetate*.

DETERMINATION OF CONTENT

Calculate the total content of haloperidol, $C_{21}H_{23}ClFNO_2$, in the medium from the chromatograms obtained and using the declared content of $C_{21}H_{23}ClFNO_2$, in *haloperidol BPCRS*.

LIMITS

The amount of haloperidol released is not less than 70% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 1 volume of mobile phase A and 9 volumes of mobile phase B (solution A). Prepare the solutions immediately before use and protect from light.

(1) Shake a quantity of powdered tablets containing 10 mg of Haloperidol with 15 mL of solution A and mix with the aid of ultrasound. Dilute to 20 mL and filter.

(2) Dilute 1 volume of solution (1) to 200 volumes.

(3) 0.05% w/v of *haloperidol for system suitability EPCRS*.

(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *base-deactivated end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Hypersil BDS is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 230 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 1.7% w/v of *tetrabutylammonium hydrogen sulfate*.

Mobile phase B *acetonitrile*.

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Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	90	10	isocratic
2-17	90→50	10→50	linear gradient
17-22	50	50	isocratic
22-23	50→90	50→10	linear gradient
23-28	90	10	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to haloperidol (retention time about 8 minutes) are: impurity B, about 0.9 and impurity D, about 1.6.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity B and haloperidol is at least 3.0.

LIMITS

Identify any peak corresponding to impurity B in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (3), and multiply the area of this peak by a correction factor of 0.7.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity D is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity B is not greater than 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Haloperidol comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Place one tablet in 10 mL of the mobile phase, disperse with the aid of ultrasound for 2 minutes and centrifuge. If necessary, dilute the supernatant liquid with the mobile phase to produce a solution containing 0.005% w/v of Haloperidol.
(2) 0.005% w/v of *haloperidol BPCRS* in the mobile phase.

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CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Dissolution may be used with an injection volume of 20 µL.

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{23}ClFNO_2$ in each tablet using the declared content of $C_{21}H_{23}ClFNO_2$ in *haloperidol BPCRS*.

ASSAY

For tablets containing less than 2 mg and/or less than 2% w/w of Haloperidol

Use the average of the individual results determined in the test for Uniformity of content.

For tablets containing 2 mg or more and 2% w/w or more of Haloperidol

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 60 mL of the mobile phase to a quantity of the powdered tablets containing 20 mg of Haloperidol, disperse with the aid of ultrasound for 2 minutes, add sufficient mobile phase to produce 100 mL, mix and filter.

(2) 0.020% w/v of *haloperidol BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Dissolution may be used with an injection volume of 20 µL.

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{23}ClFNO_2$ in the tablets using the declared content of $C_{21}H_{23}ClFNO_2$ in *haloperidol BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Haloperidol.

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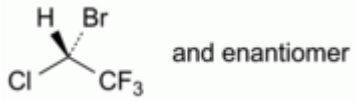
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Halothane

General Notices

(Ph. Eur. monograph 0393)



$C_2HBrClF_3$ 197.4 *151-67-7*

Action and use

General anaesthetic.

Ph Eur

DEFINITION

(*RS*)-2-Bromo-2-chloro-1,1,1-trifluoroethane to which 0.01 per cent *m/m* of thymol has been added.

CHARACTERS

Appearance

Clear, colourless, mobile, heavy, non-flammable liquid.

Solubility

Slightly soluble in water, miscible with anhydrous ethanol.

IDENTIFICATION

First identification: B.

Second identification: A, C.

A. Distillation range (see Tests).

B. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Examine the substance in a 0.1 mm cell.

Comparison *Ph. Eur. reference spectrum of halothane*.

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C. Add 0.1 mL to 2 mL of *2-methyl-2-propanol R* in a test-tube. Add 1 mL of *copper edetate solution R*, 0.5 mL of *concentrated ammonia R* and a mixture of 0.4 mL of *strong hydrogen peroxide solution R* and 1.6 mL of *water R* (solution A). Prepare a blank at the same time (solution B). Place both tubes in a water-bath at 50 °C for 15 min, cool and add 0.3 mL of *glacial acetic acid R*. To 1 mL of each of solutions A and B add 0.5 mL of a mixture of equal volumes of freshly prepared *alizarin S solution R* and *zirconyl nitrate solution R*. Solution A is yellow and solution B is red.
To 1 mL of each of solutions A and B add 1 mL of *buffer solution pH 5.2 R*, 1 mL of *phenol red solution R* diluted 1 to 10 with *water R* and 0.1 mL of *chloramine solution R*. Solution A is bluish-violet and solution B is yellow.

To 2 mL of each of solutions A and B add 0.5 mL of a mixture of 25 volumes of *sulfuric acid R* and 75 volumes of *water R*, 0.5 mL of *acetone R* and 0.2 mL of a 50 g/L solution of *potassium bromate R* and shake. Warm the tubes in a water-bath at 50 °C for 2 min, cool and add 0.5 mL of a mixture of equal volumes of *nitric acid R* and *water R* and 0.5 mL of *silver nitrate solution R2*. Solution A is opalescent and a white precipitate is formed after a few minutes; solution B remains clear.

TESTS

Acidity or alkalinity

To 20 mL add 20 mL of *carbon dioxide-free water R*, shake for 3 min and allow to stand. Separate the aqueous layer and add 0.2 mL of *bromocresol purple solution R*. Not more than 0.1 mL of *0.01 M sodium hydroxide* or 0.6 mL of *0.01 M hydrochloric acid* is required to change the colour of the indicator.

Relative density (*2.2.5*)

1.872 to 1.877.

Distillation range (*2.2.11*)

It distils completely between 49.0 °C and 51.0 °C and 95 per cent distills within a range of 1.0 °C.

Volatile related substances

Gas chromatography (*2.2.28*).

Internal standard *trichlorotrifluoroethane CRS*.

Test solution (a) The substance to be examined.

Test solution (b) Dilute 1.0 mL of *trichlorotrifluoroethane CRS* to 20.0 mL with the substance to be examined. Dilute 1.0 mL of the solution to 100.0 mL with the substance to be examined. Dilute 1.0 mL of this solution to 10.0 mL with the substance to be examined.

Column:

— *size*: *l* = 2.75 m, Ø = 5 mm;

— *stationary phase*: *silanised diatomaceous earth for gas chromatography R* (180-250 µm), the first 1.8 m being impregnated with 30 per cent *m/m* of *macrogol 400 R* and the remainder with 30 per cent *m/m* of *dinonyl phthalate R*;

— *temperature*: 50 °C.

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Carrier gas *nitrogen for chromatography R*.

Flow rate 30 mL/min.

Detection Flame ionisation.

Injection 5 µL.

Limit Test solution (b):

— *total*: not more than the area of the peak due to the internal standard, corrected if necessary for any impurity with the same retention time as the internal standard (0.005 per cent).

Thymol

Gas chromatography (*2.2.28*).

Internal standard solution Dissolve 0.10 g of *menthol R* in *methylene chloride R* and dilute to 100.0 mL with the same solvent.

Test solution To 20.0 mL of the substance to be examined add 5.0 mL of the internal standard solution.

Reference solution Dissolve 20.0 mg of *thymol R* in *methylene chloride R* and dilute to 100.0 mL with the same solvent. To 20.0 mL of this solution, add 5.0 mL of the internal standard solution.

Column:

— *material*: fused silica;

— *size*: *l* = 15 m, Ø = 0.53 mm;

— *stationary phase*: *methylpolysiloxane R* (film thickness 1.5 µm).

Carrier gas *nitrogen for chromatography R*.

Flow rate 15 mL/min.

Temperature:

— *column*: 150 °C;

— *injection port*: 170 °C;

— *detector*: 200 °C.

Detection Flame ionisation.

Injection 1.0 µL.

Limit:

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— *thymol*: 0.75 times to 1.15 times the area of the corresponding peak in the chromatogram obtained with the reference solution (0.008 per cent *m/m* to 0.012 per cent *m/m*).

Bromides and chlorides

To 10 mL add 20 mL of *water R* and shake for 3 min. To 5 mL of the aqueous layer add 5 mL of *water R*, 0.05 mL of *nitric acid R* and 0.2 mL of *silver nitrate solution R1*. The solution is not more opalescent than a mixture of 5 mL of the aqueous layer and 5 mL of *water R*.

Bromine and chlorine

To 10 mL of the aqueous layer obtained in the test for bromides and chlorides add 1 mL of *potassium iodide and starch solution R*. No blue colour is produced.

Non-volatile matter

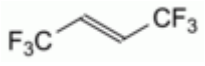
Maximum 20 mg/L.

Evaporate 50 mL to dryness on a water-bath and dry the residue in an oven at 100-105 °C for 2 h. The residue weighs a maximum of 1 mg.

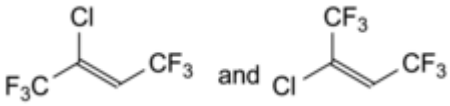
STORAGE

In an airtight container, protected from light, at a temperature not exceeding 25 °C. The choice of material for the container is made taking into account the particular reactivity of halothane with certain metals.

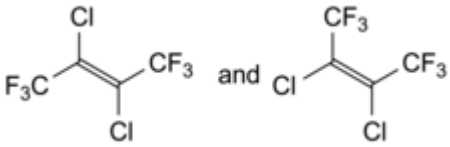
IMPURITIES



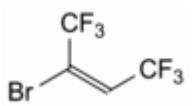
A. (*E*)-1,1,1,4,4,4-hexafluorobut-2-ene,



B. (*EZ*)-2-chloro-1,1,1,4,4,4-hexafluorobut-2-ene (*cis* and *trans*),

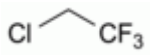


C. (*EZ*)-2,3-dichloro-1,1,1,4,4,4-hexafluorobut-2-ene (*cis* and *trans*),

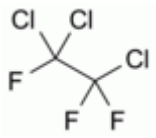


D. (*E*)-2-bromo-1,1,1,4,4,4-hexafluorobut-2-ene,

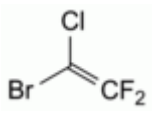
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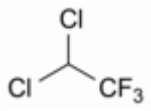
E. 2-chloro-1,1,1-trifluoroethane,



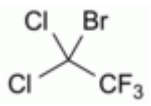
F. 1,1,2-trichloro-1,2,2-trifluoroethane,



G. 1-bromo-1-chloro-2,2-difluoroethene,



H. 2,2-dichloro-1,1,1-trifluoroethane,



I. 1-bromo-1,1-dichloro-2,2,2-trifluoroethane,



J. 1,2-dichloro-1,1-difluoroethane.

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Hard Fat

General Notices

(Ph. Eur. monograph 0462)

Ph Eur

DEFINITION

Mixture of triglycerides, diglycerides and monoglycerides, which may be obtained either by esterification of hydrogenated fatty acids of vegetable origin with glycerol or by interesterification of hydrogenated vegetable oils.

Each type of hard fat is characterised by its melting point, its hydroxyl value and its saponification value.

It does not contain additives.

CHARACTERS

Appearance

White or almost white, waxy, brittle mass.

Solubility

Practically insoluble in water, slightly soluble in anhydrous ethanol and in methylene chloride.

When heated to 50 °C it melts, giving a colourless or slightly yellowish liquid.

IDENTIFICATION

A. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 1.0 g of the substance to be examined in *methylene chloride R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel G plate R*.

Mobile phase *ether R*, *methylene chloride R* (10:90 *V/V*).

Application 2 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Expose to iodine vapour until the spots appear and examine in daylight.

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Results The chromatogram shows a spot due to triglycerides with an R_F value of about 0.7 (R_{st} 1) and may show spots due to 1,3-diglycerides (R_{st} 0.6), to 1,2-diglycerides (R_{st} 0.4) and to 1-monoglycerides (R_{st} 0.07). For substances with a low hydroxyl value, the spots due to monoglycerides and diglycerides may be faint or absent. In this case, the test for hydroxyl value (see Tests) is also carried out to confirm identification.

B. Soya bean lecithin, macrogol cetostearyl ether and polysorbate 65. Thin-layer chromatography (2.2.27).

Test solution Dissolve 1.0 g of the substance to be examined in *methylene chloride R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 0.100 g of *soya bean lecithin R* in *methylene chloride R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 0.100 g of *macrogol cetostearyl ether R* in *methylene chloride R* and dilute to 10 mL with the same solvent.

Reference solution (c) Dissolve 0.100 g of *polysorbate 65 R* in *methylene chloride R* and dilute to 10 mL with the same solvent.

Plates *TLC silica gel G plate R* (2 plates).

Mobile phase *water R*, *methanol R*, *methylene chloride R* (4:25:65 *V/V/V*).

Plate 1

Application 4 µL of the test solution and reference solution (a).
Development Over 3/4 of the plate.
Drying In air.
Detection Expose to iodine vapour until the spots appear and examine in daylight.

Results:

— the chromatogram obtained with the test solution shows no spots corresponding to those of soya bean lecithin (R_F = about 0.3 and 0.5) in the chromatogram obtained with reference solution (a);

— the chromatogram obtained with the test solution shows a spot due to triglycerides with an R_F value of about 1.0.

Plate 2

Application 4 µL of the test solution and reference solutions (b) and (c).
Development Over 3/4 of the plate.
Drying In air.
Detection Spray with *potassium iodobismuthate solution R4* and examine in daylight.

Results:

— the chromatogram obtained with the test solution shows no orange spot corresponding to that of macrogol cetostearyl ether (R_F = about 0.85) in the chromatogram obtained with reference solution (b);

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— the chromatogram obtained with the test solution shows no orange spot corresponding to that of polysorbate 65 (R_F = about 1.0) in the chromatogram obtained with reference solution (c).

C. Beeswax. Thin-layer chromatography (2.2.27).

Test solution Dissolve 1.0 g of the substance to be examined in *methylene chloride R* and dilute to 8 mL with the same solvent.

Reference solution Dissolve 0.100 g of *white beeswax R* in *methylene chloride R* and dilute to 8 mL with the same solvent.

Plate *TLC silica gel G plate R*.

Mobile phase *ethyl acetate R*, *cyclohexane R* (10:90 *V/V*).

Application 10 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Spray with a freshly prepared 100 g/L solution of *phosphomolybdic acid R* in *ethanol (96 per cent) R* and heat at 120 °C for 3 min; examine in daylight.

Results The chromatogram obtained with the test solution shows no black spot corresponding to that of white beeswax (R_F = about 0.9) in the chromatogram obtained with the reference solution.

TESTS

Alkaline impurities

Melt 10.00 g and while maintaining the temperature at about 50 °C, dissolve the melted mass in 40.0 mL of *ethanol (96 per cent) R*, mix and add 0.05 mL of *bromophenol blue solution R*. Not more than 0.75 mL of *0.01 M hydrochloric acid* is required to change the colour of the indicator to yellow.

Melting point (2.2.15)

30 °C to 45 °C, and within 2 °C of the nominal value.

Introduce the melted substance into a capillary tube and allow to stand at a temperature below 10 °C for 24 h.

Acid value (2.5.1)

Maximum 0.5.

Melt 5.0 g and dissolve in 20 mL of the prescribed mixture of solvents.

Hydroxyl value (2.5.3, Method A)

Maximum 50, and within 5 units of the nominal value; maximum 5 if the nominal value is less than 5.

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Iodine value (*2.5.4, Method A*)

Maximum 3.0.

Peroxide value (*2.5.5, Method A*)

Maximum 3.0.

Saponification value (*2.5.6*)

210 to 260, and within 5 per cent of the nominal value, determined on 2.0 g.

Sulfated ash (*2.4.14*)

Maximum 0.2 per cent.

Heat a silica crucible to redness for 30 min, allow to cool in a desiccator and weigh. Evenly distribute 1.0 g in the crucible and weigh. Dry at 100-105 °C for 1 h and ignite in a muffle furnace at 600 ± 25 °C until the substance is thoroughly charred. Carry out the test for sulfated ash (*2.4.14*) on the residue obtained, starting from “Moisten the substance to be examined...”.

STORAGE

Protected from light, at a temperature at least 5 °C below the nominal melting point.

LABELLING

The label states:

— the nominal melting point;

— the nominal hydroxyl value;

— the nominal saponification value.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for hard fat used as basis for solid dosage forms.

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Melting point

(see Tests).

Hydroxyl value

(see Tests).

Saponification value

(see Tests).

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Hard Fat with Additives

General Notices

(Ph. Eur. monograph 2731)

Ph Eur

DEFINITION

Mixture of triglycerides, diglycerides and monoglycerides, which may be obtained either by esterification of hydrogenated fatty acids of vegetable origin with glycerol or by interesterification of hydrogenated vegetable oils.

Each type of hard fat with additives is characterised by its melting point, its hydroxyl value and its saponification value.

It contains additives such as lecithin, surfactants, beeswax or a mixture thereof.

CHARACTERS

Appearance

White or pale yellow, waxy, brittle mass.

Solubility

Practically insoluble in water, slightly soluble in anhydrous ethanol and in methylene chloride.

When heated to 50 °C it melts, giving a colourless or slightly yellowish liquid.

IDENTIFICATION

A. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 1.0 g of the substance to be examined in *methylene chloride R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel G plate R*.

Mobile phase *ether R*, *methylene chloride R* (10:90 *V/V*).

Application 2 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Expose to iodine vapour until the spots appear and examine in daylight.

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Results The chromatogram shows a spot due to triglycerides with an R_F value of about 0.7 (R_{st} 1) and may show spots due to 1,3-diglycerides (R_{st} 0.6), to 1,2-diglycerides (R_{st} 0.4) and to 1-monoglycerides (R_{st} 0.07). For substances with a low hydroxyl value, the spots due to monoglycerides and diglycerides may be faint or absent. In this case, the test for hydroxyl value (see Tests) is also carried out to confirm identification.

B. Soya bean lecithin, macrogol cetostearyl ether and polysorbate 65. Thin-layer chromatography (2.2.27).

Test solution Dissolve 1.0 g of the substance to be examined in *methylene chloride R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 0.100 g of *soya bean lecithin R* in *methylene chloride R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 0.100 g of *macrogol cetostearyl ether R* in *methylene chloride R* and dilute to 10 mL with the same solvent.

Reference solution (c) Dissolve 0.100 g of *polysorbate 65 R* in *methylene chloride R* and dilute to 10 mL with the same solvent.

Plates *TLC silica gel G plate R* (2 plates).

Mobile phase *water R*, *methanol R*, *methylene chloride R* (4:25:65 *V/V/V*).

Plate 1

Application 4 µL of the test solution and reference solution (a).
Development Over 3/4 of the plate.
Drying In air.
Detection Expose to iodine vapour until the spots appear and examine in daylight.

Results:

— in the presence of soya bean lecithin, the chromatogram obtained with the test solution shows 2 spots (R_F = about 0.3 and 0.5) similar in position to the spots in the chromatogram obtained with reference solution (a);

— the chromatogram obtained with the test solution shows a spot due to triglycerides with an R_F value of about 1.0.

Plate 2

Application 4 µL of the test solution and reference solutions (b) and (c).
Development Over 3/4 of the plate.
Drying In air.
Detection Spray with *potassium iodobismuthate solution R4* and examine in daylight.

Results:

— in the presence of macrogol cetostearyl ether, the chromatogram obtained with the test solution shows an orange spot (R_F = about 0.85) similar in position to the spot in the chromatogram obtained with reference solution (b);

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— in the presence of polysorbate 65, the chromatogram obtained with the test solution shows an orange spot (R_F = about 1.0) similar in position to the spot in the chromatogram obtained with reference solution (c).

C. Beeswax. Thin-layer chromatography (2.2.27).

Test solution Dissolve 1.0 g of the substance to be examined in *methylene chloride R* and dilute to 8 mL with the same solvent.

Reference solution Dissolve 0.100 g of *white beeswax R* in *methylene chloride R* and dilute to 8 mL with the same solvent.

Plate *TLC silica gel G plate R*.

Mobile phase *ethyl acetate R*, *cyclohexane R* (10:90 *V/V*).

Application 10 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Spray with a freshly prepared 100 g/L solution of *phosphomolybdic acid R* in *ethanol (96 per cent) R* and heat at 120 °C for 3 min; examine in daylight.

Results In the presence of beeswax, the chromatogram obtained with the test solution shows a black spot (R_F = about 0.9) similar in position to the spot in the chromatogram obtained with the reference solution.

TESTS

Alkaline impurities

Melt 10.00 g and while maintaining the temperature at about 50 °C, dissolve the melted mass in 40.0 mL of *ethanol (96 per cent) R*, mix and add 0.05 mL of *bromophenol blue solution R*. Not more than 0.75 mL of *0.01 M hydrochloric acid* is required to change the colour of the indicator to yellow.

If the substance to be examined contains lecithins, not more than 3.75 mL of *0.01 M hydrochloric acid* is required to change the colour of the indicator to yellow.

Melting point (2.2.15)

30 °C to 45 °C, and within 2 °C of the nominal value.

Introduce the melted substance into a capillary tube and allow to stand at a temperature below 10 °C for 24 h.

Acid value (2.5.1)

Maximum 1.0.

Melt 5.0 g and dissolve in 20 mL of the prescribed mixture of solvents.

Hydroxyl value (2.5.3, Method A)

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Maximum 70, and within 5 units of the nominal value.

Iodine value (*2.5.4, Method A*)

Maximum 3.0.

Peroxide value (*2.5.5, Method A*)

Maximum 3.0.

Saponification value (*2.5.6*)

210 to 260, and within 5 per cent of the nominal value, determined on 2.0 g.

Sulfated ash (*2.4.14*)

Maximum 0.4 per cent.

Heat a silica crucible to redness for 30 min, allow to cool in a desiccator and weigh. Evenly distribute 1.0 g in the crucible and weigh. Dry at 100-105 °C for 1 h and ignite in a muffle furnace at 600 ± 25 °C until the substance is thoroughly charred. Carry out the test for sulfated ash (*2.4.14*) on the residue obtained, starting from “Moisten the substance to be examined...”.

STORAGE

Protected from light, at a temperature at least 5 °C below the nominal melting point.

LABELLING

The label states:

— the nominal melting point;

— the nominal hydroxyl value;

— the nominal saponification value.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

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The following characteristics may be relevant for hard fat with additives used as basis for solid dosage forms.

Melting point

(see Tests).

Hydroxyl value

(see Tests).

Saponification value

(see Tests).

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Hard Paraffin

General Notices

(Ph. Eur. monograph 1034)

Ph Eur

DEFINITION

A purified mixture of solid saturated hydrocarbons generally obtained from petroleum. It may contain a suitable antioxidant.

CHARACTERS

Appearance

Colourless or white or almost white mass; the melted substance is free from fluorescence in daylight.

Solubility

Practically insoluble in water, freely soluble in methylene chloride, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, C.

Second identification: B, C.

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *hard paraffin CRS*.

Preparation Place about 2 mg on a sodium chloride plate, heat in an oven at 100 °C for 10 min, spread the melted substance with another sodium chloride plate and remove one of the plates.

B. Acidity or alkalinity (see Tests).

C. Melting point (*2.2.16*): 50 °C to 61 °C.

TESTS

Acidity or alkalinity

To 15 g add 30 mL of boiling *water R* and shake vigorously for 1 min. Allow to cool and to separate. To 10 mL of the aqueous layer add 0.1 mL of *phenolphthalein solution R*. The solution is colourless. Not more than 1.0 mL of *0.01 M sodium hydroxide* is required to change

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the colour of the indicator to red. To a further 10 mL of the aqueous layer add 0.1 mL of *methyl red solution R*. The solution is yellow. Not more than 0.5 mL of *0.01 M hydrochloric acid* is required to change the colour of the indicator to red.

Polycyclic aromatic hydrocarbons

Use reagents for ultraviolet absorption spectrophotometry Dissolve 0.50 g in 25 mL of *heptane R* and place in a 125 mL separating funnel with unlubricated ground-glass parts (stopper, stopcock). Add 5.0 mL of *dimethyl sulfoxide R*. Shake vigorously for 1 min and allow to stand until 2 clear layers are formed. Transfer the lower layer to a 2nd separating funnel, add 2 mL of *heptane R* and shake the mixture vigorously. Allow to stand until 2 clear layers are formed. Separate the lower layer and measure its absorbance (*2.2.25*) between 265 nm and 420 nm using as the compensation liquid the clear lower layer obtained by vigorously shaking 5.0 mL of *dimethyl sulfoxide R* with 25 mL of *heptane R* for 1 min. Prepare a 7.0 mg/L reference solution of *naphthalene R* in *dimethyl sulfoxide R* and measure the absorbance of this solution at the absorption maximum at 278 nm using *dimethyl sulfoxide R* as the compensation liquid. At wavelengths from 265 nm to 420 nm, the absorbance of the test solution is not greater than one-third that of the reference solution at 278 nm.

Sulfates (*2.4.13*)

Maximum 150 ppm.

Introduce 2.0 g of the melted substance to be examined into a 50 mL ground-glass-stoppered separating funnel. Add 30 mL of boiling *distilled water R*, shake vigorously for 1 min and filter.

STORAGE

Protected from light.

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This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Heavy Bismuth Subnitrate

General Notices

(Ph. Eur. monograph 1494)

$4[BiNO_3(OH)_2],BiO(OH)$ 1462 *1304-85-4*

Ph Eur

DEFINITION

Content

71.0 per cent to 74.0 per cent of Bi (A_r 209.0) (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water and in ethanol (96 per cent). It dissolves in mineral acids with decomposition.

IDENTIFICATION

A. Dilute 1 mL of solution S1 (see Tests) to 5 mL with *water R* and add 0.3 mL of *potassium iodide solution R*. A black precipitate is formed which dissolves into an orange solution with the addition of 2 mL of *potassium iodide solution R*.

B. It gives reaction (b) of bismuth (*2.3.1*).

C. It gives the reaction of nitrates (*2.3.1*).

D. pH (*2.2.3*): maximum 2.0 for solution S2 (see Tests).

TESTS

Solution S1

Shake 5.0 g by gently heating in 10 mL of *water R* and add 20 mL of *nitric acid R*. Heat until dissolution, cool and dilute to 100 mL with *water R*.

Solution S2

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Solution S2

Place 1.00 g in a 20 mL volumetric flask and add 2.0 mL of *lead-free nitric acid R*. Allow acid attack to take place without heating and if necessary warm slightly at the end to completely dissolve the test sample. Add 10 mL of *water R*, shake and add, in small fractions, 4.5 mL of *lead-free ammonia R*; shake and allow to cool. Dilute to 20.0 mL with *water R*, shake again and allow the solids to settle. The supernatant is solution S2.

Acidity

Suspend 1.0 g in 15 mL of *water R* and shake several times. Allow to stand for 5 min and filter. To 10 mL of the filtrate, add 0.5 mL of *phenolphthalein solution R1*. Not more than 0.5 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator to pink.

Chlorides (*2.4.4*)

Maximum 200 ppm.

To 5.0 mL of solution S1, add 3 mL of *nitric acid R* and dilute to 15 mL with *water R*.

Copper

Maximum 50 ppm.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Solution S2.

Reference solutions Prepare the reference solutions using *copper standard solution (10 ppm Cu) R* and diluting with a 37 per cent *V/V* solution of *lead-free nitric acid R*.

Source Copper hollow-cathode lamp.

Wavelength 324.7 nm.

Atomisation device Air-acetylene flame.

Lead

Maximum 20 ppm.

Atomic absorption spectrometry (*2.2.23, Method II*).

Test solution Solution S2.

Reference solutions Prepare the reference solutions using *lead standard solution (10 ppm Pb) R* and diluting with a 37 per cent *V/V* solution of *lead-free nitric acid R*.

Source Lead hollow-cathode lamp.

Wavelength 283.3 nm (depending on the apparatus, the line at 217.0 nm may be used).

Atomisation device Air-acetylene flame.

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Silver

Maximum 25 ppm.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Solution S2.

Reference solutions Prepare the reference solutions using *silver standard solution (5 ppm Ag) R* and diluting with a 37 per cent *V/V* solution of *lead-free nitric acid R*.

Source Silver hollow-cathode lamp.

Wavelength 328.1 nm.

Atomisation device Air-acetylene flame.

Substances not precipitated by ammonia

Maximum 1.0 per cent.

To 20 mL of solution S1, add *concentrated ammonia R* until an alkaline reaction is produced and filter. Wash the residue with *water R*, and evaporate the combined filtrate and washings to dryness on a water-bath. To the residue, add 0.3 mL of *dilute sulfuric acid R* and ignite. The residue weighs a maximum of 10 mg.

Loss on drying (*2.2.32*)

Maximum 3.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

Dissolve with heating 0.250 g in 10 mL of a mixture of 2 volumes of *perchloric acid R* and 5 volumes of *water R*. To the hot solution, add 200 mL of *water R* and 50 mg of *xylenol orange triturate R*. Titrate with *0.1 M sodium edetate* until a yellow colour is obtained.

1 mL of *0.1 M sodium edetate* is equivalent to 20.90 mg of Bi.

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Heavy Kaolin

General Notices

(Ph. Eur. monograph 0503)

Preparation

Kaolin Poultice

When kaolin is prescribed or demanded, Light Kaolin shall be dispensed or supplied, unless it is ascertained that Light Kaolin (Natural) is required.

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DEFINITION

Purified, natural, hydrated aluminium silicate of variable composition.

CHARACTERS

Appearance

Fine, white or greyish-white, unctuous powder.

Solubility

Practically insoluble in water and in organic solvents.

IDENTIFICATION

A. To 0.5 g in a metal crucible add 1 g of *potassium nitrate R* and 3 g of *sodium carbonate R* and heat until the mixture melts. Allow to cool. To the residue add 20 mL of boiling *water R*, mix and filter. Wash the residue with 50 mL of *water R*. To the residue add 1 mL of *hydrochloric acid R* and 5 mL of *water R*. Filter. To the filtrate add 1 mL of *strong sodium hydroxide solution R* and filter. To the filtrate add 3 mL of *ammonium chloride solution R*. A gelatinous white precipitate is formed.

B. Add 2.0 g in 20 portions to 100 mL of a 10 g/L solution of *sodium laurilsulfate R* in a 100 mL graduated cylinder about 30 mm in diameter. Allow 2 min between additions for each portion to settle. Allow to stand for 2 h. The apparent volume of the sediment is not greater than 5 mL.

C. 0.25 g gives the reaction of silicates (*2.3.1*).

TESTS

Solution S

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To 4 g add a mixture of 6 mL of *acetic acid R* and 34 mL of *distilled water R*, shake for 1 min and filter.

Acidity or alkalinity

To 1.0 g add 20 mL of *carbon dioxide-free water R*, shake for 2 min and filter. To 10 mL of the filtrate add 0.1 mL of *phenolphthalein solution R*. The solution is colourless. Not more than 0.25 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to pink.

Organic impurities

Heat 0.3 g to redness in a calcination tube. The residue is only slightly more coloured than the original substance.

Adsorption power

To 1.0 g in a ground-glass-stoppered test-tube add 10.0 mL of a 3.7 g/L solution of *methylene blue R* and shake for 2 min. Allow to settle. Centrifuge and dilute the solution 1 to 100 with *water R*. The solution is not more intensely coloured than a 0.03 g/L solution of *methylene blue R*.

Swelling power

Triturate 2 g with 2 mL of *water R*. The mixture does not flow.

Substances soluble in dilute hydrochloric acid

Maximum 1 per cent.

To 5.0 g add 7.5 mL of *dilute hydrochloric acid R* and 27.5 mL of *water R* and boil for 5 min. Filter, wash the residue on the filter with *water R* and dilute the combined filtrate and washings to 50.0 mL with *water R*. To 10.0 mL of the solution add 1.5 mL of *dilute sulfuric acid R*, evaporate to dryness on a water-bath and ignite. The residue weighs a maximum of 10 mg.

Chlorides (*2.4.4*)

Maximum 250 ppm.

Dilute 2 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 0.1 per cent.

Dilute 1.5 mL of solution S to 15 mL with *distilled water R*.

Calcium (*2.4.3*)

Maximum 250 ppm.

Dilute 4 mL of solution S to 15 mL with *distilled water R*.

Microbial contamination

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TAMC: acceptance criterion 10^3 CFU/g (2.6.12).

TYMC: acceptance criterion 10^2 CFU/g (2.6.12).

LABELLING

The label states, where applicable, that the substance is suitable for internal use.

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Heavy Magnesium Carbonate

General Notices

(Ph. Eur. monograph 0043)

Action and use

Antacid; osmotic laxative.

Preparations

Calcium Carbonate and Heavy Magnesium Carbonate Chewable Tablets

Compound Magnesium Trisilicate Oral Powder

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DEFINITION

Hydrated basic magnesium carbonate.

Content

40.0 per cent to 45.0 per cent, calculated as MgO (M_r 40.30).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water. It dissolves in dilute acids with effervescence.

IDENTIFICATION

A. Bulk density (*2.9.34*): minimum 0.25 g/mL.

B. It gives the reaction of carbonates (*2.3.1*).

C. Dissolve about 15 mg in 2 mL of *dilute nitric acid R* and neutralise with *dilute sodium hydroxide solution R*. The solution gives the reaction of magnesium (*2.3.1*).

TESTS

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Solution S

Dissolve 5.0 g in 100 mL of *dilute acetic acid R*. When the effervescence has ceased, boil for 2 min, allow to cool and dilute to 100 mL with *dilute acetic acid R*. Filter, if necessary, through a previously ignited and tared porcelain or silica filter crucible of suitable porosity to give a clear filtrate.

Appearance of solution

Solution S is not more intensely coloured than reference solution B_4 (*2.2.2, Method II*).

Soluble substances

Maximum 1.0 per cent.

Mix 2.00 g with 100 mL of *water R* and boil for 5 min. Filter whilst hot through a sintered-glass filter (40) (*2.1.2*), allow to cool and dilute to 100 mL with *water R*. Evaporate 50 mL of the filtrate to dryness and dry at 100-105 °C. The residue weighs not more than 10 mg.

Substances insoluble in acetic acid

Maximum 0.05 per cent.

Any residue obtained during the preparation of solution S, washed, dried, and ignited at 600 ± 50 °C, weighs not more than 2.5 mg.

Chlorides (*2.4.4*)

Maximum 700 ppm.

Dilute 1.5 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 0.6 per cent.

Dilute 0.5 mL of solution S to 15 mL with *distilled water R*.

Calcium (*2.4.3*)

Maximum 0.75 per cent.

Dilute 2.6 mL of solution S to 150 mL with *distilled water R*. 15 mL of the solution complies with the test.

Iron (*2.4.9*)

Maximum 400 ppm.

Dissolve 0.1 g in 3 mL of *dilute hydrochloric acid R* and dilute to 10 mL with *water R*. Dilute 2.5 mL of the solution to 10 mL with *water R*.

ASSAY

Dissolve 0.150 g in a mixture of 2 mL of *dilute hydrochloric acid R* and 20 mL of *water R*. Carry out the complexometric titration of magnesium (*2.5.11*).

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1 mL of *0.1 M sodium edetate* is equivalent to 4.030 mg of MgO.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for heavy magnesium carbonate used as filler in tablets.

Particle-size distribution (*2.9.31* or *2.9.38*)

Bulk and tapped density (*2.9.34*)

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Heavy Magnesium Oxide

General Notices

(Ph. Eur. monograph 0041)

MgO 40.30 *1309-48-4*

Action and use

Antacid; osmotic laxative.

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DEFINITION

Content

98.0 per cent to 100.5 per cent of MgO (ignited substance).

CHARACTERS

Appearance

Fine, white or almost white powder.

Solubility

Practically insoluble in water. It dissolves in dilute acids with at most slight effervescence.

IDENTIFICATION

A. Bulk density (*2.9.34*): minimum 0.25 g/mL.

B. Dissolve about 15 mg in 2 mL of *dilute nitric acid R* and neutralise with *dilute sodium hydroxide solution R*. The solution gives the reaction of magnesium (*2.3.1*).

C. Loss on ignition (see Tests).

TESTS

Solution S

Dissolve 5.0 g in a mixture of 30 mL of *distilled water R* and 70 mL of *acetic acid R*, boil for 2 min, allow to cool and dilute to 100 mL with *dilute acetic acid R*. Filter, if necessary, through a previously ignited and tared porcelain or silica filter crucible of suitable porosity to give a clear filtrate. Keep the residue for the test for substances insoluble in acetic acid.

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Appearance of solution

Solution S is not more intensely coloured than reference solution B_3 (*2.2.2, Method II*).

Soluble substances

Maximum 2.0 per cent.

To 2.00 g add 100 mL of *water R* and boil for 5 min. Filter whilst hot through a sintered-glass filter (40) (*2.1.2*), allow to cool and dilute to 100 mL with *water R*. Evaporate 50 mL of the filtrate to dryness and dry at 100-105 °C. The residue weighs a maximum of 20 mg.

Substances insoluble in acetic acid

Maximum 0.1 per cent.

Any residue obtained during the preparation of solution S, washed, dried and ignited at 600 ± 50 °C, weighs a maximum of 5 mg.

Chlorides (*2.4.4*)

Maximum 0.1 per cent.

Dilute 1 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 1.0 per cent.

Dilute 0.3 mL of solution S to 15 mL with *distilled water R*.

Calcium (*2.4.3*)

Maximum 1.5 per cent.

Dilute 1.3 mL of solution S to 150 mL with *distilled water R*. 15 mL of the solution complies with the test.

Iron (*2.4.9*)

Maximum 0.07 per cent.

Dissolve 0.15 g in 5 mL of *dilute hydrochloric acid R* and dilute to 10 mL with *water R*. Dilute 1 mL of the solution to 10 mL with *water R*.

Loss on ignition

Maximum 8.0 per cent, determined on 1.00 g at 900 ± 25 °C.

ASSAY

Dissolve 0.320 g in 20 mL of *dilute hydrochloric acid R* and dilute to 100.0 mL with *water R*. Using 20.0 mL of the solution, carry out the complexometric titration of magnesium (*2.5.11*).

1 mL of *0.1 M sodium edetate* is equivalent to 4.030 mg of MgO.

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FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for heavy magnesium oxide used as filler in oral solid dosage forms.

Particle-size distribution (*2.9.31* or *2.9.38*)

Bulk and tapped density (*2.9.34*)

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Helium

General Notices

(Ph. Eur. monograph 2155)

He 4.00

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DEFINITION

Content

Minimum 99.5 per cent *V/V* of He.

This monograph applies to helium obtained by separation from natural gas and intended for medicinal use.

CHARACTERS

Appearance

Colourless, inert gas.

IDENTIFICATION

Examine the chromatograms obtained in the assay. The retention time of the principal peak in the chromatogram obtained with the substance to be examined is approximately the same as that of the principal peak in the chromatogram obtained with the reference gas.

TESTS

Methane

Maximum 50.0 ppm *V/V*.

Infrared analyser.

Gas to be examined The substance to be examined. It must be filtered to avoid stray light phenomena (3 µm filter).

Reference gas (a) *helium for chromatography R*.

Reference gas (b) Mixture containing 50.0 ppm *V/V* of *methane R* in *helium for chromatography R*.

The infrared analyser generally comprises an infrared source emitting broadband infrared radiation, an optical device, a sample cell, a detector and in some analysers a reference cell. The optical device may be positioned either before or after the sample cell. It consists of

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one or more optical filters, through which the broadband radiation is passed. The optical device is selected for methane determination. The measurement light beam passes through the sample cell and may also pass through a reference cell if the analyser integrates such a feature. When methane is present in the sample cell, absorption of energy in the measurement light beam will occur according to the Beer-Lambert law, and this produces a change in the detector signal. This measurement signal is compared to a reference signal to generate an output related to the concentration of methane. The generated signal is linearised in order to determine the methane content.

Calibrate the apparatus and set the sensitivity using reference gases (a) and (b). Measure the methane content in the gas to be examined.

Oxygen

Maximum 50.0 ppm *V/V*, determined using an oxygen analyser equipped with an electrochemical cell and a detector scale ranging from 0-100 ppm *V/V*.

The gas to be examined passes through a detection cell containing an aqueous solution of an electrolyte, generally potassium hydroxide. The presence of oxygen in the gas to be examined produces a variation in the electric signal recorded at the outlet of the cell that is proportional to the oxygen content.

Calibrate the analyser according to the instructions of the manufacturer. Pass the gas to be examined through the analyser using a suitable pressure regulator and airtight metal tubes and operating at the prescribed flow rates until constant readings are obtained.

Water (*2.5.28*)

Maximum 67 ppm *V/V*.

ASSAY

Gas chromatography (*2.2.28*).

Gas to be examined The substance to be examined.

Reference gas *helium for chromatography R*.

Column:

— *size*: *l* = 2 m, Ø = 4.5 mm;

— *stationary phase*: *molecular sieve for chromatography R* (0.5 nm).

Carrier gas *argon for chromatography R*.

Flow rate 60 mL/min.

Temperature:

— *column*: 50 °C;

— *detector*: 150 °C.

Detection Thermal conductivity.

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Injection 0.5 mL.

Inject the reference gas. Adjust the injected volumes and operating conditions so that the height of the peak due to helium in the chromatogram obtained is at least 35 per cent of the full scale of the recorder.

System suitability Reference gas:

— *symmetry factor*: minimum 0.6.

Calculate the content of He in the gas to be examined.

STORAGE

As compressed gas or liquid at cryogenic temperature, in appropriate containers, complying with the legal regulations.

IMPURITIES

Specified impurities *A, B, C.*

A. CH_4: methane,

B. O_2: oxygen,

C. H_2O: water.

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Heparin Calcium

General Notices

(Ph. Eur. monograph 0332)

Action and use

Anticoagulant.

Preparation

Heparin Injection

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DEFINITION

Preparation containing the calcium salt of a sulfated glycosaminoglycan present in mammalian tissues. It is prepared from the intestinal mucosae of pigs. On complete hydrolysis, it liberates D-glucosamine, D-glucuronic acid, L-iduronic acid, acetic acid and sulfuric acid. It has the property of delaying the clotting of blood by catalysing the inhibition of thrombin and factor Xa by antithrombin.

Potency

Minimum 180 IU/mg (dried substance), determined by the assay of anti-factor IIa activity as described under Assay.

PRODUCTION

The animals from which heparin calcium is derived must fulfil the requirements for the health of animals suitable for human consumption. All stages of production and sourcing are subjected to a suitable quality management system. The identity of the source species and the absence of material from possible contaminant species such as cattle, sheep and goats, is verified by appropriate testing during production. The method used to confirm the identity of the source species, and the point of application in the process, have been validated and shown to be capable of identifying the presence of material of other species at the level of 0.1 per cent (*m/m*). Species verification by methods based on polymerase chain reaction (PCR) amplification of species-specific DNA sequences has been widely shown to be an appropriate surrogate. If such a method has been chosen, it is also used to test for porcine DNA and to determine that it is present at a consistent level, in line with the manufacturing process used.

It is produced by methods of manufacturing designed to minimise or eliminate substances lowering blood pressure.

CHARACTERS

Appearance

White or almost white, hygroscopic powder.

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Solubility

Freely soluble in water.

IDENTIFICATION

A. It complies with the requirements described under Assay.

B. Carry out the assay of anti-factor Xa activity of heparin (2.7.5). The ratio of anti-factor Xa activity to anti-factor IIa activity determined as described under Assay, ranges between 0.9 and 1.1.

C. Nuclear magnetic resonance spectrometry (2.2.33).

Preparation Dissolve 20 mg of the substance to be examined in 0.7 mL of a 20 µg/mL solution of *deuterated sodium trimethylsilylpropionate R* in *deuterium oxide R*.

Comparison Dissolve 20 mg of *heparin calcium for NMR identification CRS* in 0.7 mL of a 20 µg/mL solution of *deuterated sodium trimethylsilylpropionate R* in *deuterium oxide R*.

Apparatus Spectrometer operating at minimum 300 MHz.

Acquisition of ^{1}H-NMR spectra:

— *number of transients*: minimum 16; it is adjusted until the signal-to-noise ratio is at least 1000:1 for the heparin methyl signal at 2.04 ppm;

— *temperature*: about 25 °C; test sample and reference spectra have to be obtained at the same temperature;

— *acquisition time*: minimum 2 s;

— *repetition time* (acquisition time plus delay): minimum 4 s;

— *spectral width*: 10-12 ppm, centred at around 4.5 ppm;

— *pulse width*: to give a flip angle between 30° and 90°.

Processing:

— *exponential line-broadening window function*: 0.3 Hz;

— Fourier transformation;

— trimethylsilylpropionate reference signal set at 0.00 ppm.

Results:

— the large heparin calcium signals must be present: 2.05 ppm, 3.29 ppm (doublet), 4.37 ppm, 5.35 ppm and 5.43 ppm, all within ± 0.03 ppm;

— the ^{1}H-NMR spectrum obtained with the test sample and that obtained with *heparin calcium for NMR identification CRS* are compared qualitatively after the 2 spectra have been normalised so as to have a similar intensity; dermatan sulfate with a methyl

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signal at 2.08 ± 0.02 ppm may be observed; no unidentified signals larger than 4 per cent compared to the height of the heparin signal at 5.43 ppm are present in the ranges 0.10-2.00 ppm, 2.10-3.10 ppm and 5.70-8.00 ppm; signals from the solvent or process-related substances may be present and have to be identified to be accepted.

D. Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Injection Test solution (a) and reference solution (c).

Relative retention With reference to heparin (retention time = about 26 min): dermatan sulfate and chondroitin sulfate = about 0.9; over-sulfated chondroitin sulfate = about 1.3.

System suitability Reference solution (c):

— *peak-to-valley ratio*: minimum 1.3, where H_p = height above the baseline of the peak due to dermatan sulfate and chondroitin sulfate and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to heparin.

Results The principal peak in the chromatogram obtained with test solution (a) is similar in retention time and shape to the principal peak in the chromatogram obtained with reference solution (c).

E. It complies with the test for calcium (see Tests).

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than intensity 5 of the range of reference solutions of the most appropriate colour (2.2.2, Method II).

Dissolve a quantity equivalent to 50 000 IU in *water R* and dilute to 10 mL with the same solvent.

pH (2.2.3)

5.5 to 8.0.

Dissolve 0.1 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Nucleotidic impurities

Dissolve 40 mg in 10 mL of *water R*. The absorbance (2.2.25) measured at 260 nm is not greater than 0.15.

Protein

Maximum 0.5 per cent (dried substance).

Solution A Mix 2 volumes of a 10 g/L solution of *sodium hydroxide R* and 2 volumes of a 50 g/L solution of *sodium carbonate R* and dilute to 5 volumes with *water R*.

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Solution B Mix 2 volumes of a 12.5 g/L solution of *copper sulfate pentahydrate R* and 2 volumes of a 29.8 g/L solution of *sodium tartrate R* and dilute to 5 volumes with *water R*.

Solution C Mix 1 volume of solution B and 50 volumes of solution A.

Solution D Dilute a phosphomolybdotungstic reagent in *water R*. Suitable dilutions produce solutions of pH 10.25 ± 0.25 after addition of solutions C and D to the test and reference solutions.

Test solution Dissolve the substance to be examined in *water R* to obtain a concentration of 5 mg/mL.

Reference solutions Dissolve *bovine albumin R1* in *water R* to obtain a concentration of 100 mg/mL. Prepare dilutions of the solution in *water R* as prescribed in general chapter *2.5.33, method 2*.

Blank *water R*.

Procedure To 1 mL of each reference solution, of the test solution and of the blank, add 5 mL of solution C. Allow to stand for 10 min. Add 0.5 mL of solution D, mix and allow to stand at room temperature for 30 min. Filter through a membrane filter (nominal pore size 0.45 µm). Determine the absorbances (*2.2.25*) of the solutions at 750 nm, using the solution prepared from the blank as compensation liquid.

Calculations As prescribed in general chapter *2.5.33, method 2*.

Related substances

Liquid chromatography (*2.2.29*). *Reference solutions are stable at room temperature for 24 h.*

Test solution (a) Dissolve an accurately weighed quantity of about 50 mg of the substance to be examined in 5.0 mL of *water for chromatography R*. Mix using a vortex mixer until dissolution is complete.

Test solution (b) Dissolve an accurately weighed quantity of about 0.1 g of the substance to be examined in 1.0 mL of *water for chromatography R*. Mix using a vortex mixer until dissolution is complete. Mix 500 µL of the solution and 250 µL of *1 M hydrochloric acid*, then add 50 µL of a 250 mg/mL solution of *sodium nitrite R*. Mix gently and allow to stand at room temperature for 40 min before adding 200 µL of *1 M sodium hydroxide* to stop the reaction.

Reference solution (a) Dissolve 250 mg of *heparin for physico-chemical analysis CRS* in *water for chromatography R* and dilute to 2.0 mL with the same solvent. Mix using a vortex mixer until dissolution is complete.

Reference solution (b) Add 1200 µL of reference solution (a) to 300 µL of *dermatan sulfate and over-sulfated chondroitin sulfate CRS*. Mix using a vortex mixer to homogenise.

Reference solution (c) Add 100 µL of reference solution (b) to 900 µL of *water for chromatography R*. Mix using a vortex mixer to homogenise.

Reference solution (d) Add 400 µL of reference solution (a) to 100 µL of *water for chromatography R* and mix using a vortex mixer. Add 250 µL of *1 M hydrochloric acid*, then add 50 µL of a 250 mg/mL solution of *sodium nitrite R*. Mix gently and allow to stand at room temperature for 40 min before adding 200 µL of *1 M sodium hydroxide* to stop the reaction.

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Reference solution (e) To 500 µL of reference solution (b), add 250 µL of *1 M hydrochloric acid*, then add 50 µL of a 250 mg/mL solution of *sodium nitrite R*. Mix gently and allow to stand at room temperature for 40 min before adding 200 µL of *1 M sodium hydroxide* to stop the reaction.

Precolumn:

— *size*: *l* = 0.05 m, Ø = 2 mm;

— *stationary phase*: *anion-exchange resin R* (13 µm).

Column:

— *size*: *l* = 0.25 m, Ø = 2 mm;

— *stationary phase*: *anion-exchange resin R* (9 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: dissolve 0.40 g of *sodium dihydrogen phosphate R* in 1000 mL of *water for chromatography R* and adjust to pH 3.0 with *dilute phosphoric acid R*;

— *mobile phase B*: dissolve 0.40 g of *sodium dihydrogen phosphate R* in 1000 mL of *water for chromatography R*, add 140 g of *sodium perchlorate R* and adjust to pH 3.0 with *dilute phosphoric acid R*; filter and degas;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	75	25
10 - 35	75 → 0	25 → 100
35 - 40	0	100

Flow rate 0.22 mL/min.

Detection Spectrophotometer at 202 nm.

Equilibration At least 15 min.

Injection 20 µL of test solution (b) and reference solutions (d) and (e).

Relative retention With reference to heparin (retention time = about 26 min): dermatan sulfate and chondroitin sulfate = about 0.9; over-sulfated chondroitin sulfate = about 1.3.

System suitability:

— the chromatogram obtained with reference solution (d) shows no peak at the retention time of heparin;

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— *resolution*: minimum 3.0 between the peak due to dermatan sulfate and chondroitin sulfate and the peak due to over-sulfated chondroitin sulfate in the chromatogram obtained with reference solution (e).

Limits:

— *sum of dermatan sulfate and chondroitin sulfate*: not more than the area of the peak due to dermatan sulfate and chondroitin sulfate in the chromatogram obtained with reference solution (e) (2.0 per cent);

— *any other impurity*: no peak with an area greater than 0.01 times the area of the peak due to dermatan sulfate and chondroitin sulfate in the chromatogram obtained with reference solution (e) is detected (corresponding to a disregard limit of 0.02 per cent). Disregard any peaks that appear during the initial isocratic step.

Nitrogen (2.5.9)

1.5 per cent to 2.5 per cent (dried substance), determined on 0.100 g.

Calcium

9.5 per cent to 11.5 per cent (dried substance), determined on 0.200 g by complexometric titration (2.5.11).

Loss on drying (2.2.32)

Maximum 8.0 per cent, determined on 1.000 g by drying at 60 °C over *diphosphorus pentoxide R* at a pressure not exceeding 670 Pa for 3 h.

Bacterial endotoxins (2.6.14)

Less than 0.01 IU per International Unit of heparin, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins. The addition of divalent cations may be necessary in order to fulfil the validation criteria.

ASSAY

Carry out the assay of anti-factor IIa activity of heparin (2.7.5). The estimated potency is not less than 90 per cent and not more than 111 per cent of the stated potency. The confidence limits of the estimated potency (P = 0.95) are not less than 80 per cent and not more than 125 per cent of the stated potency.

STORAGE

In an airtight container. If the substance is sterile, the container is also sterile and tamper-evident.

LABELLING

The label states the number of International Units per milligram.

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Heparin Flush Solution

General Notices

Action and use

Maintenance of patency of intravenous devices.

DEFINITION

Heparin Flush is a sterile solution of Heparin Injection, containing the sodium salt only, with sufficient Sodium Chloride to make it isotonic with blood.

PRODUCTION

The final product is produced from the drug substance where the methods of manufacturing are designed to ensure freedom from contamination by over-sulfated glycosaminoglycans.

The solution complies with the requirements stated under Parenteral Preparations and with the following requirements.

Potency

The estimated potency is not less than 90% and not more than 111% of the stated potency.

CHARACTERISTICS

A colourless or straw-coloured liquid, free from turbidity and from matter that deposits on standing.

IDENTIFICATION

A. It complies with the requirements described under Assay.

B. Carry out the assay of anti-factor Xa activity of heparin, Appendix XIV J B2. The ratio of anti-factor Xa activity to anti-factor IIa activity determined as described under Assay ranges between 0.9 and 1.1.

TESTS

Acidity or alkalinity

pH, 5.5 to 8.0, Appendix V L.

Sodium Chloride

Titrate a volume containing 6.7 % v/v of the solution with *0.1M silver nitrate VS* using *potassium chromate solution* as indicator. Each mL of *0.1M silver nitrate VS* is equivalent to 5.844 mg of NaCl. The amount of NaCl is not less than 0.85% and not more than 0.95%.

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ASSAY

Carry out the assay of anti-factor IIa activity of heparin, Appendix XIV J B2. The fiducial limits of error are not less than 80% and not more than 125% of the stated potency.

STORAGE

Heparin Flush Solution should be kept in a sealed ampoule or a stoppered vial.

LABELLING

The strength is stated as the number of IU (Units) in a suitable dose-volume except that for multi-dose containers the strength is stated as the number of IU (Units) per mL.

The label states (1) when no antimicrobial preservative is present that the preparation contains no antimicrobial preservative and that any portion of the contents not used at once should be discarded; (2) that the preparation is intended for the maintenance of patency of intravenous injection devices only and is not to be used for anticoagulant therapy.

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Heparin Injection

General Notices

Action and use

Anticoagulant.

DEFINITION

Heparin Injection is a sterile solution of Heparin Calcium or Heparin Sodium in Water for Injections.

PRODUCTION

The final product is produced from the drug substance where the methods of manufacturing are designed to ensure that substances lowering blood pressure are not introduced and to ensure freedom from contamination by over-sulfated glycosaminoglycans. The production method is validated to demonstrate that the product if tested, would comply with the test for Related substances given below.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Potency

The estimated potency is not less than 90% and not more than 111% of the stated potency.

CHARACTERISTICS

A colourless or straw-coloured liquid, free from turbidity and from matter that deposits on standing.

IDENTIFICATION

A. It complies with the requirements described under Assay.

B. Carry out the assay of anti-factor Xa activity of heparin, Appendix XIV J B2. The ratio of anti-factor Xa activity to anti-factor IIa activity, determined as described under Assay, ranges between 0.9 and 1.1.

C. Carry out the method for *nuclear magnetic resonance spectrometry*, *Appendix II C* using the following solutions.

(1) For injections containing 25 000 IU per mL, dilute 100 µL with 450 µL of *water*. For injections containing 5000 IU, 1000 IU per mL, or lower use 550 µL of each. Add 50 µL of an 0.83% w/v solution of *deuterated sodium trimethylsilylpropionate* in *deuterium oxide*.

For injections containing Heparin Calcium

(2) Dissolve 3.4 mg of *heparin calcium for NMR identification EPCRS* in 700 µL of a solution containing 650 µL of water, 40 µL of *deuterium oxide*, and 10 µL of an 0.83% w/v solution of *deuterated sodium trimethylsilylpropionate* in *deuterium oxide*.

For injections containing Heparin Sodium

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(3) Dissolve 3.4 mg of *heparin sodium for NMR identification EPCRS* in 700 µL of a solution containing 650 µL of water, 40 µL of *deuterium oxide*, and 10 µL of an 0.83% w/v solution of *deuterated sodium trimethylsilylpropionate* in *deuterium oxide*.

^{1}H-NMR spectrometer parameters

(a) Operate the spectrometer at a minimum of 400 MHz.

(b) Use a minimum of 256 transients; adjusted until the signal-to-noise ratio is at least 1000:1 for the heparin methyl signal at 2.04 ppm.

(c) Use an ambient temperature; the test sample and reference spectra must be obtained at the same temperature.

(d) Use a minimum of 2 seconds for acquisition time.

(e) Use a minimum of 4 seconds for repetition time.

(f) Use a spectral width of 10 to 16 ppm, centred at around 4.5 ppm.

(g) Use a pulse width to give a flip angle between 30° and 90°.

Processing parameters

(h) Use an exponential line-broadening window function of 0.3 Hz.

(i) Apply Fourier transformation to the collected data.

(j) Use trimethylsilylpropionate as the reference signal, set at 0.00 ppm.

Results for injections containing Heparin Calcium

In the ^{1}H-NMR spectrum obtained with solution (1):

the large heparin calcium signals must be present: 2.05 ppm, 3.29 ppm (broad singlet), 4.37 ppm, 5.35 ppm and 5.43 ppm, all within ± 0.03 ppm.

Compare the ^{1}H-NMR spectrum obtained with solution (2) qualitatively after the 2 spectra have been normalised so as to have a similar intensity; dermatan sulfate with a methyl signal at 2.08 ± 0.02 ppm may be observed; no unidentified signals larger than 4 per cent compared to the height of the heparin signal at 5.43 ppm are present in the ranges 0.10 to 2.00 ppm, 2.10 to 3.10 ppm and 5.70 to 8.00 ppm; signals from the solvent, excipients or process-related substances may be present and have to be identified to be accepted.

Results for injections containing Heparin Sodium

In the ^{1}H-NMR spectrum obtained with solution (1):

the large heparin sodium signals must be present: 2.04 ppm, 3.27 ppm (doublet), 4.34 ppm, 5.22 ppm and 5.42 ppm, all within ± 0.03 ppm.

Compare the ^{1}H-NMR spectrum obtained with solution (3) qualitatively after the 2 spectra have been normalised so as to have a similar intensity; dermatan sulfate with a methyl signal at 2.08 ± 0.02 ppm may be observed; no unidentified signals larger than 4 per cent compared to the height of the heparin signal at 5.42 ppm are present in the ranges 0.10 to 2.00 ppm, 2.10 to 3.10 ppm and 5.70 to 8.00 ppm; signals from the solvent, excipients or process-related substances may be present and have to be identified to be accepted; variations in the intensity of some signal regions of the spectrum of heparin may occur: the intensity-variable regions are between 3.35 ppm and 4.55 ppm, where the signal pattern is approximately kept but intensity varies.

D. When the injection contains Heparin Calcium, it yields reactions A and B characteristic of *calcium salts*, Appendix VI. When the injection contains Heparin Sodium, it yields reaction A characteristic of *sodium salts*, Appendix VI.

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TESTS

Acidity or alkalinity

pH, 5.5 to 8.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D using the following solutions. Solutions (3) to (6) are stable at room temperature for 24 hours.

(1) For injections containing 25 000 IU per mL, dilute 100 µL with 400 µL of *water for chromatography*. For injections containing 5000 IU, 1000 IU per mL, or lower use 500 µL of each. Mix using a vortex mixer until dissolution is complete.
(2) Mix 500 µL of solution (1) and 250 µL of 1M *hydrochloric acid*, then add 50 µL of a 25% w/v solution of *sodium nitrite*. Mix gently and allow to stand at room temperature for 40 minutes before adding 200 µL of 1M *sodium hydroxide* to stop the reaction.
(3) Dissolve 0.25 g of *heparin for physico-chemical analysis EPCRS* in *water for chromatography* and dilute to 2.0 mL with the same solvent. Mix using a vortex mixer until dissolution is complete.
(4) Add 1200 µL of solution (3) to 300 µL of *dermatan sulfate and over-sulfated chondroitin sulfate EPCRS*. Mix using a vortex mixer to homogenise.
(5) Add 400 µL of solution (3) to 100 µL of *water for chromatography* and mix using a vortex mixer. Add 250 µL of 1M *hydrochloric acid*, then add 50 µL of a 25% w/v solution of *sodium nitrite*. Mix gently and allow to stand at room temperature for 40 minutes before adding 200 µL of 1M *sodium hydroxide* to stop the reaction.
(6) To 500 µL of solution (4), add 250 µL of 1M *hydrochloric acid*, then add 50 µL of a 25% w/v solution of *sodium nitrite*. Mix gently and allow to stand at room temperature for 40 minutes before adding 200 µL of 1M *sodium hydroxide* to stop the reaction.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 2 mm) packed with *anion-exchange resin* (9 µm) (Dionex Ionpac AS11-HC is suitable) and a stainless steel pre-column (5 cm × 2 mm) packed with *anion-exchange resin* (13 µm) (Dionex Ionpac AG11-HC is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 0.22 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 202 nm.
(f) For injections containing 25000 IU per mL or 5000 IU per mL, inject 20 µL of solutions (2), (5) and (6). For injections containing 1000 IU per mL, inject 100 µL of solution (2), and 20 µL of solution (5) and (6).

MOBILE PHASE

Mobile phase A 0.040% w/v of *sodium dihydrogen orthophosphate* in *water for chromatography* adjusted to pH 3.0 with *dilute orthophosphoric acid*.

Mobile phase B 0.040% w/v of *sodium dihydrogen orthophosphate* and 14% w/v of *sodium perchlorate* in *water for chromatography*, adjusted to pH 3.0 with *dilute orthophosphoric acid*, filtered and degassed.

Equilibrate the column with the mobile phase in the initial gradient ratio for at least 15 minutes.

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Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-10	75	25	isocratic
10-35	75→0	25→100	linear gradient
35-40	0	100	isocratic
40-45	0→75	100→25	linear gradient
45-60	75	25	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to heparin (about 26 minutes) are: dermatan sulfate and chondroitin sulfate, about 0.9; over-sulfated chondroitin sulfate, 1.3.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (5), no peak is present at the retention time of heparin;

in the chromatogram obtained with solution (6), the *resolution* between the peaks due to dermatan sulfate / chondroitin sulfate and over-sulfated chondroitin sulfate is at least 3.0.

LIMITS

In the chromatogram obtained with solution (2):

the area of any peak due to dermatan sulfate and chondroitin sulfate is not greater than 0.25 times the area of the corresponding peak in the chromatogram obtained with solution (6) (2.0%);

The area of any other peak is not greater than 0.01 times the area of the peak due to dermatan sulfate and chondroitin sulfate in the chromatogram obtained with solution (6) (corresponding to a disregard limit of 0.08%). Disregard any peaks that appear during the initial isocratic step.

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C.

For a preparation supplied in a container with a nominal content of less than 100 mL, dilute the injection if necessary with *water BET* to give a solution containing 1000 IU of heparin activity per mL (solution A). The endotoxin limit concentration of solution A is 10 IU of endotoxin per mL. Carry out the test using a lysate with a declared sensitivity not less sensitive than 0.0625 IU of endotoxin per mL.

For a preparation supplied in a container with a nominal content of 100 mL or more, the endotoxin limit concentration is 0.25 IU of endotoxin per mL.

For Heparin Injection prepared from Heparin Calcium it may be necessary to add divalent cations in order to achieve the validation criteria.

ASSAY

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Carry out the assay of *anti-factor IIa activity of heparin*, Appendix XIV J B2. The fiducial limits of error are not less than 80% and not more than 125% of the stated potency.

STORAGE

Heparin Injection should be kept in a container sealed by fusion of the glass.

LABELLING

The strength is stated as the number of IU (Units) in a suitable dose-volume except that for multi-dose containers the strength is stated as the number of IU (Units) per mL.

The label states (1) whether the material is the calcium or sodium salt; (2) when no antimicrobial preservative is present that the preparation does not contain an antimicrobial preservative and that any portion of the contents not used immediately should be discarded.

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Heparin Sodium

General Notices

(Ph. Eur. monograph 0333)

Action and use

Anticoagulant.

Preparations

Heparin Flush Solution

Heparin Injection

Ph Eur

DEFINITION

Preparation containing the sodium salt of a sulfated glycosaminoglycan present in mammalian tissues. It is prepared from the intestinal mucosae of pigs. On complete hydrolysis, it liberates D-glucosamine, D-glucuronic acid, L-iduronic acid, acetic acid and sulfuric acid. It has the property of delaying the clotting of blood by catalysing the inhibition of thrombin and factor Xa by antithrombin.

Potency

Minimum 180 IU/mg (dried substance), determined by the assay of anti-factor IIa activity as described under Assay.

PRODUCTION

The animals from which heparin sodium is derived must fulfil the requirements for the health of animals suitable for human consumption. All stages of production and sourcing are subjected to a suitable quality management system. The identity of the source species and the absence of material from possible contaminant species such as cattle, sheep and goats, is verified by appropriate testing during production. The method used to confirm identity of the source species, and the point of application in the process, have been validated and shown to be capable of identifying the presence of material of other species at the level of 0.1 per cent (*m/m*). Species verification by methods based on polymerase chain reaction (PCR) amplification of species-specific DNA sequences has been widely shown to be an appropriate surrogate. If such a method has been chosen, it is also used to test for porcine DNA and to determine that it is present at a consistent level, in line with the manufacturing process used.

It is produced by methods of manufacturing designed to minimise or eliminate substances lowering blood pressure.

CHARACTERS

Appearance

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White or almost white, hygroscopic powder.

Solubility

Freely soluble in water.

IDENTIFICATION

A. It complies with the requirements described under Assay.

B. Carry out the assay of anti-factor Xa activity of heparin (2.7.5). The ratio of anti-factor Xa activity to anti-factor IIa activity determined as described under Assay, ranges between 0.9 and 1.1.

C. Nuclear magnetic resonance spectrometry (2.2.33).

Solution A A solution in *deuterium oxide R* containing 20 µg/mL of *deuterated sodium trimethylsilylpropionate R* and if the signal at 5.22 ppm is smaller than 80 per cent of the signal at 5.44 ppm, 12 µg/mL of *sodium edetate R*.

Preparation Dissolve 20 mg of the substance to be examined in 0.7 mL of solution A.

Comparison Dissolve 20 mg of *heparin sodium for NMR identification CRS* in 0.7 mL of solution A.

If stored, the sodium edetate and deuterated sodium trimethylsilylpropionate solutions must be kept in high-density, natural polyethylene bottles.

Apparatus Spectrometer operating at minimum 300 MHz.

Acquisition of ^{1}H-NMR spectra:

— *number of transients*: minimum 16; it is adjusted until the signal-to-noise ratio is at least 1000:1 for the heparin methyl signal at 2.04 ppm;

— *temperature*: about 25 °C; test sample and reference spectra have to be obtained at the same temperature;

— *acquisition time*: minimum 2 s;

— *repetition time* (acquisition time plus delay): minimum 4 s;

— *spectral width*: 10-12 ppm, centred at around 4.5 ppm;

— *pulse width*: to give a flip angle between 30° and 90°.

Processing:

— *exponential line-broadening window function*: 0.3 Hz;

— Fourier transformation;

— trimethylsilylpropionate reference signal set at 0.00 ppm.

Results:

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— the large heparin sodium signals must be present: 2.04 ppm, 3.27 ppm (doublet), 4.34 ppm, 5.22 ppm and 5.42 ppm, all within ± 0.03 ppm;

— the ^{1}H-NMR spectrum obtained with the test sample and that obtained with *heparin sodium for NMR identification CRS* are compared qualitatively after the 2 spectra have been normalised so as to have a similar intensity; dermatan sulfate with a methyl signal at 2.08 ± 0.02 ppm may be observed; no unidentified signals larger than 4 per cent compared to the height of the heparin signal at 5.42 ppm are present in the ranges 0.10-2.00 ppm, 2.10-3.10 ppm and 5.70-8.00 ppm; signals from the solvent or process-related substances may be present and have to be identified to be accepted; variations in the intensity of some signal regions of the spectrum of heparin may occur: the intensity-variable regions are between 3.35 ppm and 4.55 ppm, where the signal pattern is approximately kept but intensity varies.

D. Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Injection Test solution (a) and reference solution (c).

Relative retention With reference to heparin (retention time = about 26 min): dermatan sulfate and chondroitin sulfate = about 0.9; over-sulfated chondroitin sulfate = about 1.3.

System suitability Reference solution (c):

— *peak-to-valley ratio*: minimum 1.3, where H_p = height above the baseline of the peak due to dermatan sulfate and chondroitin sulfate and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to heparin.

Results The principal peak in the chromatogram obtained with test solution (a) is similar in retention time and shape to the principal peak in the chromatogram obtained with reference solution (c).

E. It complies with the test for sodium (see Tests).

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than intensity 5 of the range of reference solutions of the most appropriate colour (2.2.2, Method II).

Dissolve a quantity equivalent to 50 000 IU in *water R* and dilute to 10 mL with the same solvent.

pH (2.2.3)

5.5 to 8.0.

Dissolve 0.1 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Nucleotidic impurities

Dissolve 40 mg in 10 mL of *water R*. The absorbance (2.2.25) measured at 260 nm is not greater than 0.15.

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Protein

Maximum 0.5 per cent (dried substance).

Solution A Mix 2 volumes of a 10 g/L solution of *sodium hydroxide R* and 2 volumes of a 50 g/L solution of *sodium carbonate R* and dilute to 5 volumes with *water R*.

Solution B Mix 2 volumes of a 12.5 g/L solution of *copper sulfate pentahydrate R* and 2 volumes of a 29.8 g/L solution of *sodium tartrate R* and dilute to 5 volumes with *water R*.

Solution C Mix 1 volume of solution B and 50 volumes of solution A.

Solution D Dilute a phosphomolybdotungstic reagent in *water R*. Suitable dilutions produce solutions of pH 10.25 ± 0.25 after addition of solutions C and D to the test and reference solutions.

Test solution Dissolve the substance to be examined in *water R* to obtain a concentration of 5 mg/mL.

Reference solutions Dissolve *bovine albumin R1* in *water R* to obtain a concentration of 100 mg/mL. Prepare dilutions of the solution in *water R* as prescribed in general chapter *2.5.33, method 2*.

Blank *water R*.

Procedure To 1 mL of each reference solution, of the test solution and of the blank, add 5 mL of solution C. Allow to stand for 10 min. Add 0.5 mL of solution D, mix and allow to stand at room temperature for 30 min. Determine the absorbances (*2.2.25*) of the solutions at 750 nm, using the solution prepared from the blank as compensation liquid.

Calculations As prescribed in general chapter *2.5.33, method 2*.

Related substances

Liquid chromatography (*2.2.29*). *Reference solutions are stable at room temperature for 24 h.*

Test solution (a) Dissolve an accurately weighed quantity of about 50 mg of the substance to be examined in 5.0 mL of *water for chromatography R*. Mix using a vortex mixer until dissolution is complete.

Test solution (b) Dissolve an accurately weighed quantity of about 0.1 g of the substance to be examined in 1.0 mL of *water for chromatography R*. Mix using a vortex mixer until dissolution is complete. Mix 500 µL of the solution and 250 µL of *1 M hydrochloric acid*, then add 50 µL of a 250 mg/mL solution of *sodium nitrite R*. Mix gently and allow to stand at room temperature for 40 min before adding 200 µL of *1 M sodium hydroxide* to stop the reaction.

Reference solution (a) Dissolve 250 mg of *heparin for physico-chemical analysis CRS* in *water for chromatography R* and dilute to 2.0 mL with the same solvent. Mix using a vortex mixer until dissolution is complete.

Reference solution (b) Add 1200 µL of reference solution (a) to 300 µL of *dermatan sulfate and over-sulfated chondroitin sulfate CRS*. Mix using a vortex mixer to homogenise.

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Reference solution (c) Add 100 µL of reference solution (b) to 900 µL of *water for chromatography R*. Mix using a vortex mixer to homogenise.

Reference solution (d) Add 400 µL of reference solution (a) to 100 µL of *water for chromatography R* and mix using a vortex mixer. Add 250 µL of *1 M hydrochloric acid*, then add 50 µL of a 250 mg/mL solution of *sodium nitrite R*. Mix gently and allow to stand at room temperature for 40 min before adding 200 µL of *1 M sodium hydroxide* to stop the reaction.

Reference solution (e) To 500 µL of reference solution (b), add 250 µL of *1 M hydrochloric acid*, then add 50 µL of a 250 mg/mL solution of *sodium nitrite R*. Mix gently and allow to stand at room temperature for 40 min before adding 200 µL of *1 M sodium hydroxide* to stop the reaction.

Precolumn:

— *size*: *l* = 0.05 m, Ø = 2 mm;

— *stationary phase*: *anion-exchange resin R* (13 µm).

Column:

— *size*: *l* = 0.25 m, Ø = 2 mm;

— *stationary phase*: *anion-exchange resin R* (9 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: dissolve 0.40 g of *sodium dihydrogen phosphate R* in 1000 mL of *water for chromatography R* and adjust to pH 3.0 with *dilute phosphoric acid R*;

— *mobile phase B*: dissolve 0.40 g of *sodium dihydrogen phosphate R* in 1000 mL of *water for chromatography R*, add 140 g of *sodium perchlorate R* and adjust to pH 3.0 with *dilute phosphoric acid R*; filter and degas;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	75	25
10 - 35	75 → 0	25 → 100
35 - 40	0	100

Flow rate 0.22 mL/min.

Detection Spectrophotometer at 202 nm.

Equilibration At least 15 min.

Injection 20 µL of test solution (b) and reference solutions (d) and (e).

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Relative retention With reference to heparin (retention time = about 26 min): dermatan sulfate and chondroitin sulfate = about 0.9; over-sulfated chondroitin sulfate = about 1.3.

System suitability:

— the chromatogram obtained with reference solution (d) shows no peak at the retention time of heparin;

— *resolution*: minimum 3.0 between the peak due to dermatan sulfate and chondroitin sulfate and the peak due to over-sulfated chondroitin sulfate in the chromatogram obtained with reference solution (e).

Limits:

— *sum of dermatan sulfate and chondroitin sulfate*: not more than the area of the peak due to dermatan sulfate and chondroitin sulfate in the chromatogram obtained with reference solution (e) (2.0 per cent);

— *any other impurity*: no peak with an area greater than 0.01 times the area of the peak due to dermatan sulfate and chondroitin sulfate in the chromatogram obtained with reference solution (e) is detected (corresponding to a disregard limit of 0.02 per cent). Disregard any peaks that appear during the initial isocratic step.

Nitrogen (2.5.9)

1.5 per cent to 2.5 per cent (dried substance), determined on 0.100 g.

Sodium

10.5 per cent to 13.5 per cent (dried substance).

Atomic absorption spectrometry (2.2.23, Method I).

Test solution Dissolve 50 mg of the substance to be examined in a 1.27 mg/mL solution of *caesium chloride R* in *0.1 M hydrochloric acid* and dilute to 100.0 mL with the same solvent.

Reference solutions Prepare reference solutions containing 25 ppm, 50 ppm and 75 ppm of Na, using *sodium standard solution (200 ppm Na) R* diluted with a 1.27 mg/mL solution of *caesium chloride R* in *0.1 M hydrochloric acid*.

Source Sodium hollow-cathode lamp.

Wavelength 330.3 nm.

Atomisation device Flame of suitable composition (for example 11 L of air and 2 L of acetylene per minute).

Loss on drying (2.2.32)

Maximum 8.0 per cent, determined on 1.000 g by drying at 60 °C over *diphosphorus pentoxide R* at a pressure not exceeding 670 Pa for 3 h.

Bacterial endotoxins (2.6.14)

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Less than 0.01 IU per International Unit of heparin, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Carry out the assay of anti-factor IIa activity of heparin (2.7.5). The estimated potency is not less than 90 per cent and not more than 111 per cent of the stated potency. The confidence limits of the estimated potency (P = 0.95) are not less than 80 per cent and not more than 125 per cent of the stated potency.

STORAGE

In an airtight container. If the substance is sterile, the container is also sterile and tamper-evident.

LABELLING

The label states the number of International Units per milligram.

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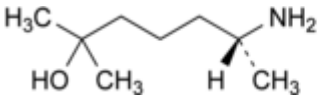
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Heptaminol Hydrochloride

General Notices

(Ph. Eur. monograph 1980)



and enantiomer , HCl

$C_8H_{20}ClNO$ 181.7 *543-15-7*

Action and use

Non-selective phosphodiesterase inhibitor; treatment of reversible airways obstruction.

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DEFINITION

(6*RS*)-6-Amino-2-methylheptan-2-ol hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

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A. To 1 mL of solution S (see Tests) add 4 mL of *water R* and 2 mL of a 200 g/L solution of *ammonium and cerium nitrate R* in *dilute nitric acid R1*. An orange-brown colour develops.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *heptaminol hydrochloride CRS*.

C. Examine the chromatograms obtained in the test for related substances.

Detection Examine in daylight.

Results The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (b).

D. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S

Dissolve 5.0 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

Acidity or alkalinity

To 10 mL of solution S add 0.1 mL of *methyl red solution R* and 0.3 mL of *0.01 M hydrochloric acid*. The solution is red. Add 0.6 mL of *0.01 M sodium hydroxide*. The solution is yellow.

Related substances

Thin-layer chromatography (*2.2.27*).

Test solution (a) Dissolve 0.50 g of the substance to be examined in *methanol R* and dilute to 5.0 mL with the same solvent.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10 mL with *methanol R*.

Reference solution (a) Dilute 3.0 mL of test solution (a) to 10.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 50.0 mL with *methanol R*.

Reference solution (b) Dissolve 0.10 g of *heptaminol hydrochloride CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (c) Dissolve 10.0 mg of *heptaminol impurity A CRS* in *methanol R* and dilute to 5.0 mL with the same solvent.

Reference solution (d) Dilute 1.0 mL of reference solution (c) to 10.0 mL with *methanol R*.

Reference solution (e) To 2.5 mL of reference solution (c) add 0.5 mL of test solution (b) and dilute to 5 mL with *methanol R*.

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Plate *TLC silica gel G plate R*.

Mobile phase *concentrated ammonia R*, *dioxan R*, *2-propanol R* (10:50:50 *V/V/V*).

Application 10 µL; apply test solutions (a) and (b) and reference solutions (a), (b), (d) and (e).

Development Over 2/3 of the plate.

Drying In air.

Detection Expose the plate to iodine vapour for at least 15 h.

System suitability The chromatogram obtained with reference solution (e) shows 2 clearly separated principal spots and the chromatogram obtained with reference solution (a) shows a single principal spot.

Limits In the chromatogram obtained with test solution (a):

— *impurity A*: any spot corresponding to impurity A is not more intense than the spot in the chromatogram obtained with reference solution (d) (0.2 per cent),

— *any other impurity*: any spot, apart from the principal spot and any spot corresponding to impurity A is not more intense than the spot in the chromatogram obtained with reference solution (a) (0.6 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (*2.4.14*)

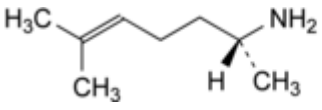
Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.140 g in 50 mL of *alcohol R* and add 5.0 mL of *0.01 M hydrochloric acid*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 18.17 mg of $C_8H_{20}ClNO$.

IMPURITIES



and enantiomer

A. (2*RS*)-6-methylhept-5-en-2-amine.

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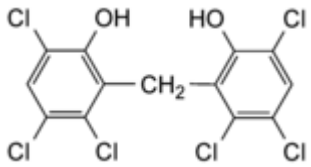
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Hexachlorophene

General Notices



$C_{13}H_6Cl_6O_2$ 406.9 *70-30-4*

Action and use

Antiseptic.

Preparation

Hexachlorophene Dusting Powder

DEFINITION

Hexachlorophene is 2,2-methylenebis(3,4,6-trichlorophenol). It contains not less than 98.0% and not more than 100.5% of $C_{13}H_6Cl_6O_2$, calculated with reference to the dried substance.

PRODUCTION

A suitable test is carried out to demonstrate that the level of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin present does not exceed 2 ppb.

CHARACTERISTICS

A white or pale buff, crystalline powder.

Practically insoluble in *water*; very soluble in *acetone*; freely soluble in *ethanol (96%)*. It dissolves in dilute solutions of the alkali hydroxides.

IDENTIFICATION

The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of hexachlorophene *(RS 174)*.

TESTS

Chloride

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Dissolve 0.50 g in 2 mL of *ethanol (96%)*, dilute to 25 mL with *water* and filter. 5 mL of the clear filtrate diluted to 15 mL with *water* complies with the *limit test for chlorides*, Appendix VII (500 ppm).

Non-phenolic substances

Dissolve 5 g in 38 mL of *methanol*, add 125 mL of 0.25M *sodium hydroxide* and extract with three 15 mL quantities of *n-pentane*, retaining any foamy interphase with the aqueous layer. Dry the combined extracts over *anhydrous sodium sulfate* and evaporate to dryness at a pressure not exceeding 2 kPa. The residue weighs not more than 37.5 mg when dried to constant weight (0.75%).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *methanol*.

(1) 1.0% w/v of the substance being examined.
(2) 0.020% w/v of the substance being examined.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography,* (10 µm) (Spherisorb ODS 1 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 300 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

1 volume of *glacial acetic acid*, 20 volumes of *water* and 100 volumes of *methanol*.

LIMITS

In the chromatogram obtained with solution (1):

the sum of the areas of any *secondary peaks* with a retention time not more than 3 times that of the principal peak is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (4.0%) and not more than one such peak has an area greater than half of the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Loss on drying

When dried to constant weight at 105°, loses not more than 1.0% of its weight. Use 1 g.

Sulfated ash

Not more than 0.1%, Appendix IX A.

ASSAY

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Dissolve 1.000 g in 25 mL of *ethanol (96%)* previously adjusted to pH 9.0 and titrate with *0.1M sodium hydroxide VS* determining the end point potentiometrically. Each mL of *0.1M sodium hydroxide VS* is equivalent to 40.69 mg of $C_{13}H_6Cl_6O_2$.

STORAGE

Hexachlorophene should be protected from light.

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Hexachlorophene Dusting Powder

General Notices

Hexachlorophene Cutaneous Powder

Zinc and Hexachlorophene Dusting Powder

Action and use

Antiseptic.

DEFINITION

Hexachlorophene Dusting Powder is a *cutaneous powder*. It is a mixture of Hexachlorophene and Zinc Oxide with a suitable inert diluent.

The dusting powder complies with the requirements stated under Topical Powders and with the following requirements.

Content of hexachlorophene, $C_{13}H_6Cl_6O_2$

90.0 to 110.0% of the stated amount.

Content of zinc oxide, ZnO

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powder containing 30 mg of Hexachlorophene with 25 mL of *ether* for 15 minutes, filter, wash the filtrate with 10 mL of *water*, dry the ether layer over *anhydrous sodium sulfate*, filter and evaporate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of hexachlorophene *(RS 174)*.

B. Shake a quantity of the powder containing 30 mg of Zinc Oxide with 10 mL of 2M *hydrochloric acid* for 15 minutes and filter. 5 mL of the filtrate yields the reaction characteristic *zinc salts*, Appendix VI.

ASSAY

For hexachlorophene

Shake a quantity of the powder containing 15 mg of Hexachlorophene with 50 mL of *methanolic tris(hydroxymethyl)methylamine solution* for 10 minutes, filter through a sintered-glass crucible (ISO 4793, porosity grade 3, is suitable), wash the filter with two 10 mL quantities of the tris(hydroxymethyl)methylamine solution and dilute the combined filtrate and washings to 100 mL with the same solution. Dilute 10 mL of the resulting solution to 50 mL with *methanolic tris(hydroxymethyl)methylamine solution* and measure the *absorbance* at the maximum at 312 nm, Appendix II B, using in the reference cell a solution prepared by diluting a further 10 mL of the solution to 50 mL with *acidified methanol*. An absorbance of 0.432 is equivalent to 15 mg of $C_{13}H_6Cl_6O_2$ in the weight of powder taken.

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For zinc oxide

To a quantity of the powder containing 90 mg of Zinc Oxide add 10 mL of 2M *nitric acid* and 20 mL of *water*, boil for 2 minutes, cool, filter and wash the filter with two 25 mL quantities of *water*. To the combined filtrate and washings add 3 g of *hexamine* and titrate with 0.05M *disodium edetate VS* using 2 mL of *xylenol orange solution* as indicator. Each mL of 0.05M *disodium edetate VS* is equivalent to 4.068 mg of ZnO.

LABELLING

The label states that the preparation should not be applied to infants or to large areas of skin except in accordance with medical advice.

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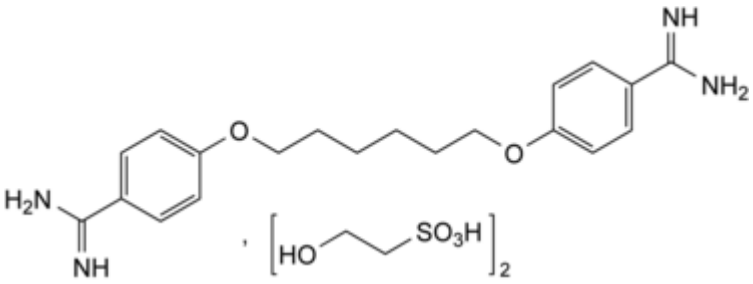
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Hexamidine Isetionate

General Notices

(Hexamidine Diisetionate, Ph. Eur. monograph 1436)



$C_{24}H_{38}N_4O_{10}S_2$ 607 *659-40-5*

Action and use

Antiprotozoal.

Ph Eur

DEFINITION

4,4′-[Hexane-1,6-diylbis(oxy)]dibenzimidamide bis(2-hydroxyethanesulfonate).

Content

98.5 per cent to 101.5 per cent (dried substance).

PRODUCTION

It is considered that alkyl 2-hydroxyethanesulfonate esters are potential impurities in hexamidine diisetionate. The manufacturing process should be developed taking into consideration the principles of quality risk management, together with considerations of the quality of starting materials, process capability and validation including, where necessary, demonstration that alkyl 2-hydroxyethanesulfonate esters are not detectable in the final product.

CHARACTERS

Appearance

White or slightly yellow powder, hygroscopic.

Solubility

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Sparingly soluble in water, slightly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *hexamidine diisetionate CRS*.

B. Dissolve about 40 mg in 5 mL of *water R* and add dropwise with shaking 1 mL of a 100 g/L solution of *sodium chloride R*. Allow to stand for 5 min. An abundant, shimmering white precipitate is slowly formed.

TESTS

Appearance of solution

Dissolve 0.50 g in *carbon dioxide-free water R*, heating at about 70 °C and dilute to 10 mL with the same solvent. Allow to cool to room temperature for 10-15 min. The solution is not more opalescent than reference suspension II (2.2.1) and not more intensely coloured than intensity 6 of the range of reference solutions of the most appropriate colour (2.2.2, *Method II*).

Acidity or alkalinity

Dissolve 2.0 g in *water R* heating at about 50 °C and dilute to 20 mL with *water R* heating at about 50 °C. Allow to cool to about 35 °C, add 0.1 mL of *methyl red solution R*. Not more than 0.25 mL of *0.05 M hydrochloric acid* or *0.05 M sodium hydroxide* is required to change the colour of the indicator.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 20.0 mg of the substance to be examined in mobile phase A and dilute to 100.0 mL with mobile phase A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 10.0 mL with mobile phase A.

Reference solution (c) Dissolve 5 mg of the substance to be examined and 5 mg of *pentamidine diisetionate CRS* in mobile phase A and dilute to 100 mL with mobile phase A. Dilute 2 mL of the solution to 5 mL with mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *styrene-divinylbenzene copolymer R* (8 µm).

Mobile phase:

— *mobile phase A*: mix 20 volumes of *acetonitrile R* and 80 volumes of a 6.8 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 3.0 with *phosphoric acid R*,

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— *mobile phase B*: mix equal volumes of *acetonitrile R* and of a 6.8 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 3.0 with *phosphoric acid R*,

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 30	100 → 0	0 → 100
30 - 35	0	100
35 - 40	0 → 100	100 → 0

Flow rate 1 mL/min.

Detection Spectrophotometer at 263 nm.

Injection 20 µL.

Relative retention With reference to hexamidine (retention time = about 6 min): impurity B = about 1.7; impurity A = about 2.0; impurity C = about 3.7; impurity D = about 4.7.

System suitability Reference solution (c):

— *resolution*: minimum 5.0 between the peaks due to hexamidine and pentamidine.

Limits:

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *impurity B*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *impurities C, D*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent);

— *any other impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent);

— *total*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

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ASSAY

Dissolve 0.250 g in 50 mL of *dimethylformamide R*. Titrate with 0.1 M tetrabutylammonium hydroxide under a current of *nitrogen R*, determining the end-point potentiometrically (2.2.20).

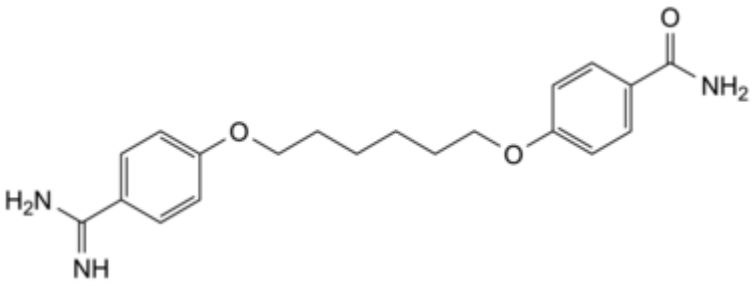
1 mL of 0.1 M tetrabutylammonium hydroxide is equivalent to 30.35 mg of $C_{24}H_{38}N_4O_{10}S_2$.

STORAGE

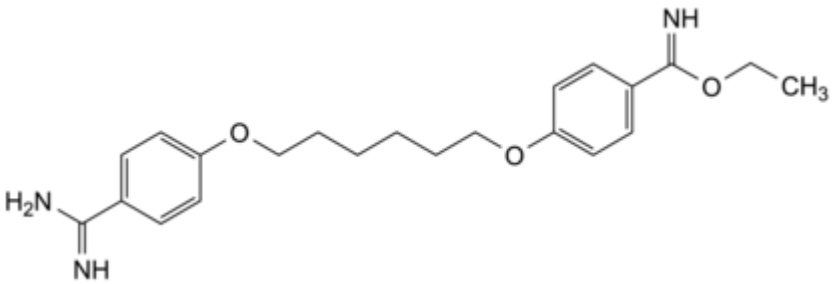
In an airtight container.

IMPURITIES

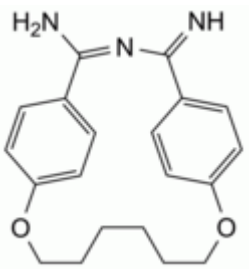
Specified impurities *A, B, C, D.*



A. 4-[[6-(4-carbamimidoylphenoxy)hexyl]oxy]benzamide,

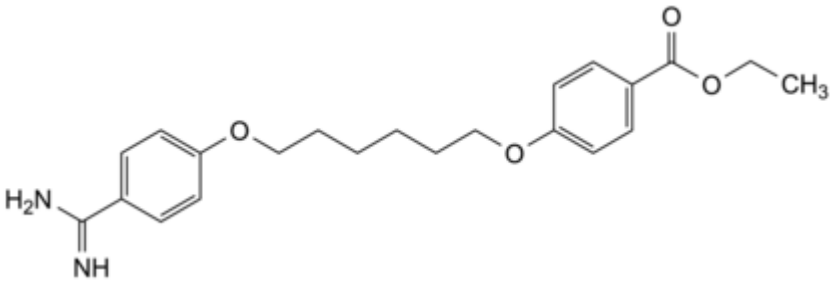


B. ethyl 4-[[6-(4-carbamimidoylphenoxy)hexyl]oxy]benzimidoate,



C. 4-imino-9,16-dioxa-3-azatricyclo[15.2.2.2^{5,8}]tricosa-1(19),2,5,7,17,20,22-heptaen-2-amine,

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D. ethyl 4-[[6-(4-carbamimidoylphenoxy)hexyl]oxy]benzoate.

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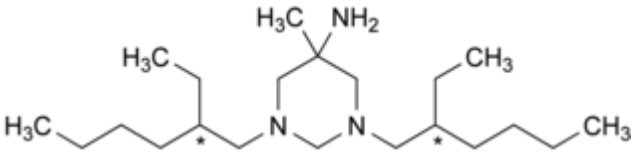
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This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Hexetidine

General Notices

(Ph. Eur. monograph 1221)



$C_{21}H_{45}N_3$ 339.6 *141-94-6*

Action and use

Antiseptic.

Ph Eur

DEFINITION

Hexetidine contains not less than 98.0 per cent and not more than the equivalent of 102.0 per cent of 1,3-bis(2-ethylhexyl)]-5-methylhexahydropyrimidin-5-amine.

CHARACTERS

An oily liquid, colourless or slightly yellow, very slightly soluble in water, very soluble in acetone, in ethanol (96 per cent) and in methylene chloride. It dissolves in dilute mineral acids.

IDENTIFICATION

First identification: A.

Second identification: B, C, D.

A. Examine by infrared absorption spectrophotometry (2.2.24), comparing with the spectrum obtained with *hexetidine CRS*.

B. Examine the chromatograms obtained in the test for related substances. The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. To 0.2 mL add 2 mL of *sulfuric acid R* and 2 mg of *chromotropic acid, sodium salt R*. Heat in a water-bath at 60 °C. A violet colour develops.

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D. Dissolve 0.2 mL in 1 mL of *methylene chloride R*. Add 0.5 mL of *copper sulfate solution R*, 0.05 mL of *0.25 M alcoholic sulfuric acid R* and 5 mL of *water R*. Shake, then allow to stand. The lower layer becomes deep blue.

TESTS

Appearance

The substance to be examined is clear (*2.2.1*)and not more intensely coloured than reference solution Y_5 or reference solution GY_5 (*2.2.2, Method II*).

Relative density (*2.2.5*)

0.864 to 0.870.

Refractive index (*2.2.6*)

1.461 to 1.467.

Optical rotation (*2.2.7*)

Dissolve 1.0 g in *ethanol R* and dilute to 10.0 mL with the same solvent. The angle of optical rotation is -0.10° to + 0.10°.

Absorbance (*2.2.25*)

Dissolve 0.50 g in *heptane R* and dilute to 50.0 mL with the same solvent. At wavelengths from 270 nm to 350 nm, the absorbance of the solution is not greater than 0.1.

Related substances

Examine by thin-layer chromatography (*2.2.27*), using *silica gel H R* as the coating substance. *Prepare the solutions immediately before use.*

Test solution (a) Dissolve 2.0 g of the substance to be examined in *heptane R* and dilute to 20 mL with the same solvent.

Test solution (b) Dilute 1 mL of test solution (a) to 10 mL with *heptane R*.

Reference solution (a) Dissolve 20 mg of *hexetidine CRS* in *heptane R* and dilute to 2 mL with the same solvent.

Reference solution (b) Dilute 1 mL of test solution (a) to 100 mL with *heptane R*.

Reference solution (c) Dilute 5 mL of reference solution (b) to 10 mL with *heptane R*.

Reference solution (d) Dissolve 10 mg of *dehydrohexetidine CRS* in test solution (a) and dilute to 10 mL with the same solution.

Apply separately to the plate 1 µL of each solution. At the bottom of a chromatographic tank, place an evaporating dish containing *concentrated ammonia R1*. Place the dried plate in the tank and close the tank. Leave the plate in contact with the ammonia vapour for 15 min. Withdraw the plate and place it in a current of air to remove the ammonia vapour. Develop over a path of 15 cm using a mixture of 20 volumes of *methanol R* and 80 volumes of *toluene R*. Allow the plate to dry in air. Expose the plate to iodine vapour for 30 min. Any spot

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in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (1 per cent) and at most two such spots are more intense than the spot in the chromatogram obtained with reference solution (c) (0.5 per cent). The test is not valid unless the chromatogram obtained with reference solution (d) shows two clearly separated spots.

Sulfated ash (*2.4.14*)

Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

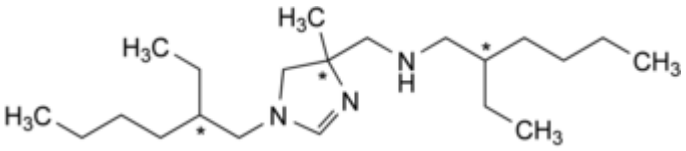
Dissolve 0.150 g in 80 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 16.98 mg of $C_{21}H_{45}N_3$.

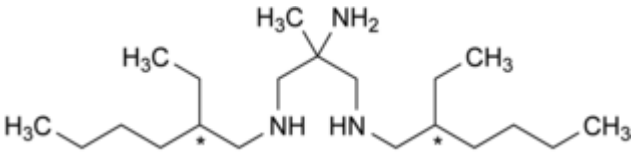
STORAGE

Store protected from light.

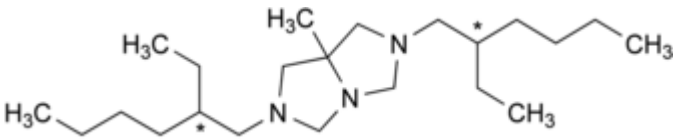
IMPURITIES



A. 2-ethyl-*N*-[[1-(2-ethylhexyl)-4-methyl-4,5-dihydro-1*H*-imidazol-4-yl]methyl]hexan-1-amine (dehydrohexetidine),

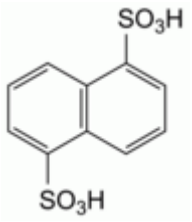


B. N^1,N^3-bis(2-ethylhexyl)-2-methylpropane-1,2,3-triamine (triamine),



C. 2,6-bis(2-ethylhexyl)-7a-methylhexahydro-1*H*-imidazo[1,5-*c*]imidazole (hexedine),

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D. naphthalene-1,5-disulfonic acid.

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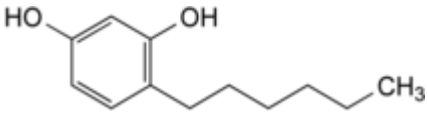
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Hexylresorcinol

General Notices

(Ph. Eur. monograph 1437)



$C_{12}H_{18}O_2$ 194.3 *136-77-6*

Action and use

Antihelminthic.

Ph Eur

DEFINITION

4-Hexylbenzene-1,3-diol.

Content

98.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Colourless, yellowish or reddish, crystalline powder or needles, turning brownish-pink on exposure to light or air.

Solubility

Very slightly soluble in water, freely soluble in ethanol (96 per cent) and in methylene chloride.

It shows polymorphism (5.9).

IDENTIFICATION

First identification: B.

Second identification: A, C, D.

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A. Melting point (2.2.14): 66 °C to 68 °C, melting may occur at about 60 °C, followed by solidification and a second melting between 66 °C and 68 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *hexylresorcinol CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

C. Thin-layer chromatography (2.2.27).

Test solution Dilute 0.1 mL of solution S (see Tests) to 10 mL with *ethanol (96 per cent) R*.

Reference solution (a) Dissolve 10 mg of *hexylresorcinol CRS* in *ethanol (96 per cent) R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of *hexylresorcinol CRS* and 10 mg of *resorcinol R* in *ethanol (96 per cent) R*, then dilute to 10 mL with the same solvent.

Plate *TLC silica gel G plate R*.

Mobile phase *methyl ethyl ketone R*, *pentane R* (50:50 *V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In air for 5 min.

Detection Spray with 3 mL of *anisaldehyde solution R* and heat at 100-105 °C for 5 min.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated principal spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

D. Dissolve 0.1 g in 1 mL of *ethanol (96 per cent) R*. Add one drop of *ferric chloride solution R1*. A green colour is produced. Add *dilute ammonia R1*. The solution changes to brown.

TESTS

Solution S

Dissolve 1.0 g in *ethanol (96 per cent) R* and dilute to 10.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1).

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Acidity

Dissolve 0.5 g in a mixture of 25 mL of *carbon dioxide-free water R* and 25 mL of *ether R* previously neutralised to *phenolphthalein solution R1* and titrate with *0.1 M sodium hydroxide*, shaking vigorously after each addition. Not more than 0.4 mL is required to change the colour of the solution.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 25 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve the contents of a vial of *hexylresorcinol for system suitability CRS* (containing impurities C and D) in 1.0 mL of the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 30 °C.

Mobile phase Mix 30 volumes of a 3.0 g/L solution of *glacial acetic acid R* previously adjusted to pH 5.9 with *dilute ammonia R1*, and 70 volumes of *methanol R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 281 nm.

Injection 20 µL.

Run time 2.5 times the retention time of hexylresorcinol.

Identification of impurities Use the chromatogram supplied with *hexylresorcinol for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities C and D.

Relative retention With reference to hexylresorcinol (retention time = about 10 min): impurity C = about 0.7; impurity D = about 1.1.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 3.0, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to hexylresorcinol.

Calculation of percentage contents:

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— *correction factor*: multiply the peak area of impurity D by 0.3;

— for each impurity, use the concentration of hexylresorcinol in reference solution (a).

Limits:

— *impurities C, D*: for each impurity, maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Water (2.5.12)

Maximum 0.5 per cent, determined on 1.00 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.100 g in 10 mL of *methanol R* in a ground-glass-stoppered flask, add 30.0 mL of *0.0167 M potassium bromate* and 2 g of *potassium bromide R*. Shake to dissolve the substance and add 15 mL of *dilute sulfuric acid R*. Stopper the flask, shake and allow to stand in the dark for 15 min, stirring continuously. Add 5 mL of *methylene chloride R* and a solution of 1 g of *potassium iodide R* in 10 mL of *water R*, allow to stand in the dark for 15 min, stirring continuously. Titrate with *0.1 M sodium thiosulfate*, using 1 mL of *starch solution R*, shaking thoroughly. Carry out a blank titration under the same conditions.

1 mL of *0.0167 M potassium bromate* is equivalent to 4.857 mg of $C_{12}H_{18}O_2$.

STORAGE

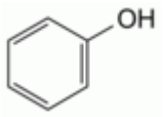
In an airtight container, protected from light.

IMPURITIES

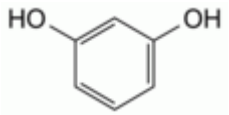
Specified impurities C, D.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B.

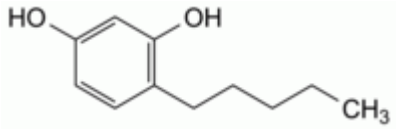
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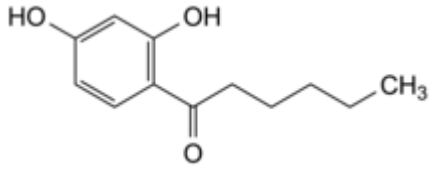
A. phenol,



B. benzene-1,3-diol (resorcinol),



C. 4-pentylbenzene-1,3-diol,



D. 1-(2,4-dihydroxyphenyl)hexan-1-one.

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High-molecular-mass Macrogols

General Notices

(Ph. Eur. monograph 2444)

Ph Eur

DEFINITION

Mixtures of high-molecular-mass macrogols (also known as polyethylene oxides). The type of high-molecular-mass macrogol is defined by a number that indicates the nominal average molecular mass in the range of 100 000 to 7 000 000. A suitable stabiliser (e.g. butylhydroxytoluene) and a suitable flowability agent (e.g. silicon dioxide) may be added.

CHARACTERS

Appearance

White or almost white, free-flowing powder.

Solubility

Freely soluble in water.

mp

Minimum 65 °C.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *high-molecular-mass macrogol CRS*.

B. Viscosity (see Tests).

TESTS

Solution S

Prepare a solution of the substance to be examined in a mixture of *carbon dioxide-free water R* and *2-propanol R* according to Table 2444.-1.

pH (*2.2.3*)

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6.0 to 10.0 for solution S.

Viscosity (2.2.10)

Determine the dynamic viscosity of solution S at 25 °C using a rotating viscometer and a suitable spindle.

Table 2444.-1. – *Solution S and viscosity*

Nominal average molecular mass	Composition of solution S (g of substance / mL of *carbon dioxide-free water R* + mL of *2-propanol R*)	Dynamic viscosity (mPa·s)	Rotation speed (r/min)
100 000	30 g / 570 + 125	12 - 50	50
200 000	30 g / 570 + 125	65 - 115	50
300 000	30 g / 570 + 125	600 - 1200	10
400 000	30 g / 570 + 125	2250 - 4500	2
600 000	30 g / 570 + 125	4500 - 8800	2
900 000	30 g / 570 + 125	8800 - 17 600	2
1 000 000	12 g / 588 + 125	400 - 800	10
2 000 000	12 g / 588 + 125	2000 - 4000	10
4 000 000	6 g / 594 + 125	1650 - 5500	2
5 000 000	6 g / 594 + 125	5500 - 7500	2
7 000 000	6 g / 594 + 125	7500 - 10 000	2

Ethylene oxide (2.4.25, Method A)

Maximum 1 ppm.

Carry out the test with the following modifications.

Stock solution Dilute 0.5 mL of *ethylene oxide stock solution R2* to 10.0 mL with *propanol R*. Dilute 1.0 mL of this solution to 50.0 mL with *propanol R*.

Test solution Weigh 0.50 g (M_T) of the substance to be examined into a 10 mL vial (other sizes may be used depending on the operating conditions). Close and allow to stand at 70 °C for 30 min.

Reference solution (a) Weigh 0.50 g (M_R) of the substance to be examined into an identical 10 mL vial and add 10 µL of the stock solution. Close and homogenise, and allow to stand at 70 °C for 30 min.

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Reference solution (b) To 0.50 mL of *ethylene oxide solution R3* in a 10 mL vial add 0.1 mL of a freshly prepared 10 mg/L solution of *acetaldehyde R*. Close and homogenise, and allow to stand at 70 °C for 30 min.

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 45 min.

Sulfated ash

Maximum 5.0 per cent, determined on 1.00 g.

Heat a silica crucible to redness for 30 min, allow to cool in a desiccator and weigh. Evenly distribute 1.00 g of the substance to be examined in the crucible and weigh. Dry at 100-105 °C for 1 h and ignite in a muffle furnace at 600 ± 25 °C, until the substance is thoroughly charred. Carry out the test for sulfated ash (*2.4.14*) on the residue obtained, starting from “Moisten the substance to be examined…”.

STORAGE

In an airtight container.

LABELLING

The label states the type of high-molecular-mass macrogol.

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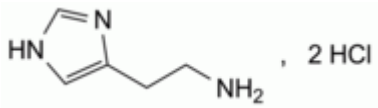
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This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Histamine Dihydrochloride

General Notices

(Ph. Eur. monograph 0143)



$C_5H_{11}Cl_2N_3$ 184.1 *56-92-8*

Ph Eur

DEFINITION

Histamine dihydrochloride contains not less than 98.5 per cent and not more than the equivalent of 101.0 per cent of 2-(1*H*-imidazol-4-yl)ethan-1-amine dihydrochloride, calculated with reference to the dried substance.

CHARACTERS

A white or almost white, crystalline powder or colourless crystals, hygroscopic, very soluble in water, soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

A. Examine by infrared absorption spectrophotometry (2.2.24), comparing with the spectrum obtained with *histamine dihydrochloride CRS*. Examine as discs prepared using 1 mg of substance.

B. Examine the chromatograms obtained in the test for histidine. The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Dissolve 0.1 g in 7 mL of *water R* and add 3 mL of a 200 g/L solution of *sodium hydroxide R*. Dissolve 50 mg of *sulfanilic acid R* in a mixture of 0.1 mL of *hydrochloric acid R* and 10 mL of *water R* and add 0.1 mL of *sodium nitrite solution R*. Add the second solution to the first and mix. A red colour is produced.

D. It gives reaction (a) of chlorides (2.3.1).

TESTS

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Solution S

Dissolve 0.5 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 10 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution Y_7 (*2.2.2, Method II*).

pH (*2.2.3*)

The pH of solution S is 2.85 to 3.60.

Histidine

Examine by thin-layer chromatography (*2.2.27*), using a *TLC silica gel G plate R*.

Test solution (a) Dissolve 0.5 g of the substance to be examined in *water R* and dilute to 10 mL with the same solvent.

Test solution (b) Dilute 2 mL of test solution (a) to 10 mL with *water R*.

Reference solution (a) Dissolve 0.1 g of *histamine dihydrochloride CRS* in *water R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 50 mg of *histidine monohydrochloride R* in *water R* and dilute to 100 mL with the same solvent.

Reference solution (c) Mix 1 mL of test solution (a) and 1 mL of reference solution (b).

Apply to the plate 1 µL of test solution (a), 1 µL of test solution (b), 1 µL of reference solution (a), 1 µL of reference solution (b) and 2 µL of reference solution (c). Develop over a path of 15 cm using a mixture of 5 volumes of *concentrated ammonia R*, 20 volumes of *water R* and 75 volumes of *acetonitrile R*. Dry the plate in a current of air. Repeat the development in the same direction, dry the plate in a current of air and spray with *ninhydrin solution R1*. Heat the plate at 110 °C for 10 min. Any spot corresponding to histidine in the chromatogram obtained with test solution (a) is not more intense than the spot in the chromatogram obtained with reference solution (b) (1 per cent). The test is not valid unless the chromatogram obtained with reference solution (c) shows 2 clearly separated spots.

Sulfates (*2.4.13*)

3 mL of solution S diluted to 15 mL with *distilled water R* complies with the limit test for sulfates (0.1 per cent).

Loss on drying (*2.2.32*)

Not more than 0.5 per cent, determined on 0.20 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Not more than 0.1 per cent, determined on 0.5 g.

ASSAY

Dissolve 0.080 g in a mixture of 5.0 mL of *0.01 M hydrochloric acid* and 50 mL of *alcohol R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the first and third points of inflexion.

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1 mL of *0.1 M sodium hydroxide* is equivalent to 9.203 mg of $C_5H_{11}Cl_2N_3$.

STORAGE

Store in an airtight container, protected from light.

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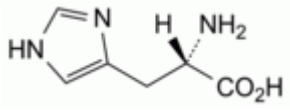
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Histidine

General Notices

(Ph. Eur. monograph 0911)



$C_6H_9N_3O_2$ 155.2 *71-00-1*

Action and use

Amino acid.

Ph Eur

DEFINITION

(2*S*)-2-Amino-3-(1*H*-imidazol-4-yl)propanoic acid.

Product of fermentation or of protein hydrolysis.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Soluble in water, very slightly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, B.

Second identification: A, C, D.

A. Specific optical rotation (see Tests).

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B. Infrared absorption spectrophotometry (2.2.24).

Comparison *histidine CRS*.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *water R*, evaporate to dryness at 60 °C and record new spectra using the residues.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *water R* and dilute to 50 mL with the same solvent.

Reference solution Dissolve 10 mg of *histidine CRS* in *water R* and dilute to 50 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase *glacial acetic acid R*, *water R*, *butanol R* (20:20:60 *V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with *ninhydrin solution R* and heat at 105 °C for 15 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

D. Dissolve 0.1 g in 7 mL of *water R* and add 3 mL of a 200 g/L solution of *sodium hydroxide R*. Dissolve 50 mg of *sulfanilic acid R* in a mixture of 0.1 mL of *hydrochloric acid R* and 10 mL of *water R* and add 0.1 mL of *sodium nitrite solution R*. Add the second solution to the first and mix. An orange-red colour develops.

TESTS

Solution S

Dissolve 2.5 g in *distilled water R*, heating in a water-bath, and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution BY_7 (2.2.2, *Method II*).

Specific optical rotation (2.2.7)

+ 11.4 to + 12.4 (dried substance).

Dissolve 2.75 g in 12.0 mL of *hydrochloric acid R1* and dilute to 25.0 mL with *water R*.

Ninhydrin-positive substances

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Amino acid analysis (2.2.56). For analysis, use Method 1.

The concentrations of the test solution and the reference solutions may be adapted according to the sensitivity of the equipment used. The concentrations of all solutions are adjusted so that the system suitability requirements described in general chapter 2.2.46 are fulfilled, keeping the ratios of concentrations between all solutions as described.

Solution A water R or a sample preparation buffer suitable for the apparatus used.

Test solution Dissolve 30.0 mg of the substance to be examined in solution A and dilute to 50.0 mL with solution A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with solution A. Dilute 2.0 mL of this solution to 10.0 mL with solution A.

Reference solution (b) Dissolve 30.0 mg of proline R in solution A and dilute to 100.0 mL with solution A. Dilute 1.0 mL of the solution to 250.0 mL with solution A.

Reference solution (c) Dilute 6.0 mL of ammonium standard solution (100 ppm NH_4) R to 50.0 mL with solution A. Dilute 1.0 mL of this solution to 100.0 mL with solution A.

Reference solution (d) Dissolve 30 mg of isoleucine R and 30 mg of leucine R in solution A and dilute to 50.0 mL with solution A. Dilute 1.0 mL of the solution to 200.0 mL with solution A.

Blank solution Solution A.

Inject suitable, equal amounts of the test, blank and reference solutions into the amino acid analyser. Run a program suitable for the determination of physiological amino acids.

System suitability Reference solution (d):

— *resolution*: minimum 1.5 between the peaks due to isoleucine and leucine.

Calculation of percentage contents:

— for any ninhydrin-positive substance detected at 570 nm, use the concentration of histidine in reference solution (a);

— for any ninhydrin-positive substance detected at 440 nm, use the concentration of proline in reference solution (b); if a peak is above the reporting threshold at both wavelengths, use the result obtained at 570 nm for quantification.

Limits:

— *any ninhydrin-positive substance*: for each impurity, maximum 0.2 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph Substances for pharmaceutical use (2034) do not apply.

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Chlorides (2.4.4)

Maximum 200 ppm.

Dilute 5 mL of solution S to 15 mL with *water R*.

Sulfates (2.4.13)

Maximum 300 ppm.

Dilute 10 mL of solution S to 15 mL with *distilled water R*.

Ammonium

Amino acid analysis (2.2.56) as described in the test for ninhydrin-positive substances with the following modifications.

Injection Test solution, reference solution (c) and blank solution.

Limit:

— *ammonium at 570 nm*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.02 per cent), taking into account the peak due to ammonium in the chromatogram obtained with the blank solution.

Iron (2.4.9)

Maximum 10 ppm.

In a separating funnel, dissolve 1.0 g in 10 mL of *dilute hydrochloric acid R*. Shake with 3 quantities, each of 10 mL, of *methyl isobutyl ketone R1*, shaking for 3 min each time. To the combined organic layers add 10 mL of *water R* and shake for 3 min. Use the aqueous layer.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.130 g in 50 mL of *water R*. Titrate with *0.1 M hydrochloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M hydrochloric acid* is equivalent to 15.52 mg of $C_6H_9N_3O_2$.

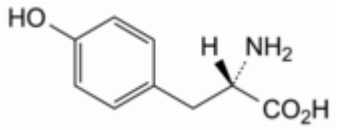
STORAGE

Protected from light.

IMPURITIES

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Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A.*



A. (2*S*)-2-amino-3-(4-hydroxyphenyl)propanoic acid (tyrosine).

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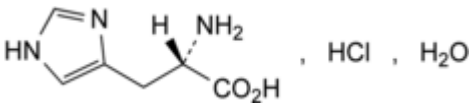
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Histidine Hydrochloride Monohydrate

General Notices

(Ph. Eur. monograph 0910)



$C_6H_{10}ClN_3O_2,H_2O$ 209.6 *5934-29-2*

Action and use

Amino acid.

Ph Eur

DEFINITION

(2*S*)-2-Amino-3-(1*H*-imidazol-4-yl)propanoic acid hydrochloride monohydrate.

Product of fermentation or of protein hydrolysis.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Freely soluble in water, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, B, C, F.

Second identification: A, B, D, E, F.

A. Specific optical rotation (see Tests).

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B. pH (see Tests).

C. Infrared absorption spectrophotometry (2.2.24).

Comparison *histidine hydrochloride monohydrate CRS*.

D. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *water R* and dilute to 50 mL with the same solvent.

Reference solution Dissolve 10 mg of *histidine hydrochloride monohydrate CRS* in *water R* and dilute to 50 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase *glacial acetic acid R*, *water R*, *butanol R* (20:20:60 *V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with *ninhydrin solution R* and heat at 105 °C for 15 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

E. Dissolve 0.1 g in 7 mL of *water R* and add 3 mL of a 200 g/L solution of *sodium hydroxide R*. Dissolve 50 mg of *sulfanilic acid R* in a mixture of 0.1 mL of *hydrochloric acid R* and 10 mL of *water R* and add 0.1 mL of *sodium nitrite solution R*. Add the second solution to the first and mix. An orange-red colour develops.

F. About 20 mg gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 2.5 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution BY_6 (2.2.2, *Method II*).

pH (2.2.3)

3.0 to 5.0 for solution S.

Specific optical rotation (2.2.7)

+ 9.2 to + 10.6 (dried substance).

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Dissolve 2.75 g in 12.0 mL of *hydrochloric acid R1* and dilute to 25.0 mL with *water R*.

Ninhydrin-positive substances

Amino acid analysis (*2.2.56*). For analysis, use Method 1.

The concentrations of the test solution and the reference solutions may be adapted according to the sensitivity of the equipment used. The concentrations of all solutions are adjusted so that the system suitability requirements described in general chapter *2.2.46* are fulfilled, keeping the ratios of concentrations between all solutions as described.

Solution A *water R* or a sample preparation buffer suitable for the apparatus used.

Test solution Dissolve 30.0 mg of the substance to be examined in solution A and dilute to 50.0 mL with solution A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with solution A. Dilute 2.0 mL of this solution to 10.0 mL with solution A.

Reference solution (b) Dissolve 30.0 mg of *proline R* in solution A and dilute to 100.0 mL with solution A. Dilute 1.0 mL of the solution to 250.0 mL with solution A.

Reference solution (c) Dilute 6.0 mL of *ammonium standard solution (100 ppm NH_4) R* to 50.0 mL with solution A. Dilute 1.0 mL of this solution to 100.0 mL with solution A.

Reference solution (d) Dissolve 30 mg of *isoleucine R* and 30 mg of *leucine R* in solution A and dilute to 50 mL with solution A. Dilute 1 mL of the solution to 200 mL with solution A.

Blank solution Solution A.

Inject suitable, equal amounts of the test, blank and reference solutions into the amino acid analyser. Run a program suitable for the determination of physiological amino acids.

System suitability Reference solution (d):

— *resolution*: minimum 1.5 between the peaks due to isoleucine and leucine.

Calculation of percentage contents:

— for any ninhydrin-positive substance detected at 570 nm, use the concentration of histidine hydrochloride monohydrate in reference solution (a);

— for any ninhydrin-positive substance detected at 440 nm, use the concentration of proline in reference solution (b); if a peak is above the reporting threshold at both wavelengths, use the result obtained at 570 nm for quantification.

Limits:

— *any ninhydrin-positive substance*: for each impurity, maximum 0.2 per cent;

— *total*: maximum 0.5 per cent;

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— *reporting threshold*: 0.05 per cent.

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

Sulfates (*2.4.13*)

Maximum 300 ppm.

Dilute 10 mL of solution S to 15 mL with *distilled water R*.

Ammonium

Amino acid analysis (*2.2.56*) as described in the test for ninhydrin-positive substances with the following modifications.

Injection Test solution, reference solution (c) and blank solution.

Limit:

— *ammonium at 570 nm*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.02 per cent), taking into account the peak due to ammonium in the chromatogram obtained with the blank solution.

Iron (*2.4.9*)

Maximum 10 ppm.

In a separating funnel, dissolve 1.0 g in 10 mL of *dilute hydrochloric acid R*. Shake with 3 quantities, each of 10 mL, of *methyl isobutyl ketone R1*, shaking for 3 min each time. To the combined organic layers add 10 mL of *water R* and shake for 3 min. Use the aqueous layer.

Loss on drying (*2.2.32*)

7.0 per cent to 10.0 per cent, determined on 1.000 g by drying in an oven at 145-150 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.160 g in 50 mL of *carbon dioxide-free water R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M sodium hydroxide* is equivalent to 19.16 mg of $C_6H_{10}ClN_3O_2$.

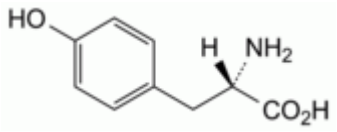
STORAGE

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IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A*.



A. (2*S*)-2-amino-3-(4-hydroxyphenyl)propanoic acid (tyrosine).

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Homatropine Eye Drops

General Notices

Action and use

Anticholinergic.

DEFINITION

Homatropine Eye Drops are a sterile solution of Homatropine Hydrobromide in Purified Water.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

Content of homatropine hydrobromide, $C_{16}H_{21}NO_3$,HBr

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. To a volume containing 60 mg of Homatropine Hydrobromide add 3 mL of 5M *ammonia*, extract with 15 mL of *chloroform*, dry the chloroform over *anhydrous sodium sulfate*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of homatropine *(RS 175)*.

B. In the Assay, the chromatogram obtained with solution (2) shows a peak with the same retention time as the peak derived from homatropine hydrobromide in the chromatogram obtained with solution (3).

C. To 1 mL of the eye drops, diluted with *water* if necessary to give a solution containing 1% w/v of Homatropine Hydrobromide, add 1 mL of 5M *ammonia*, shake with *chloroform* and evaporate the chloroform solution to dryness on a water bath. To the residue add 1.5 mL of a 2% w/v solution of *mercury(II) chloride* in *ethanol (60%)*. A yellow colour is produced which becomes red on gentle warming (distinction from most other alkaloids except atropine and hyoscyamine).

TESTS

Tropine

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Use the eye drops diluted, if necessary, with *water* to contain 1% w/v of Homatropine Hydrobromide.

(2) 0.0050% w/v of *tropine*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below.

(c) Apply 40 µL of each solution.

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(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it at 100° to 105° until the solvent has evaporated, allow to cool and spray with *dilute potassium iodobismuthate solution* until spots appear.

MOBILE PHASE

33 volumes of *anhydrous formic acid*, 33 volumes of *water* and 134 volumes of *ethyl acetate*.

LIMITS

Any spot corresponding to tropine in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%).

ASSAY

Carry out the method for *gas chromatography*, Appendix III B. Prepare a 2% w/v solution of *atropine sulfate BPCRS* (internal standard) in *methanol* (solution A).

(1) Add 1 mL of solution A and 1 mL of 5M *ammonia* to a volume of the eye drops containing 20 mg of Homatropine Hydrobromide, diluted if necessary to 5 mL with *water*. Extract with two 5-mL quantities of *chloroform*, shake the combined extracts with 1 g of *anhydrous sodium sulfate*, filter and evaporate the filtrate to dryness. Dissolve the residue in 10 mL of *dichloromethane*. To 1 mL of this solution add 0.2 mL of a mixture of 4 volumes of N,O-*bis(trimethylsilyl)acetamide* and 1 volume of *trimethylchlorosilane*, mix and allow to stand for 30 minutes.

(2) Prepare in the same manner as solution (1) but omitting the addition of solution A.

(3) Add 1 mL of solution A and 1 mL of 5M *ammonia* to 5 mL of a 0.4% w/v solution of *homatropine hydrobromide BPCRS*. Complete the procedure described under solution (1), beginning at the words 'Extract with two 5-mL quantities of *chloroform*…'.

CHROMATOGRAPHIC CONDITIONS

(a) Use a glass column (1.5 m × 4 mm) packed with *acid-washed, silanised diatomaceous support* (80 to 100 mesh) coated with 3% w/w of phenyl methyl silicone fluid (50% phenyl) (OV-17 is suitable).

(b) Use *helium* as the carrier gas at 1.7 mL per minute.

(c) Use isothermal conditions maintained at 220°.

(d) Use an inlet temperature of 220°.

(e) Use a flame ionisation detector at a temperature of 220°.

(f) Inject 1 µL of each solution.

DETERMINATION OF CONTENT

Calculate the content of $C_{16}H_{21}NO_3$,HBr using the ratios of the peaks and the declared content of $C_{16}H_{21}NO_3$,HBr in *homatropine hydrobromide BPCRS*.

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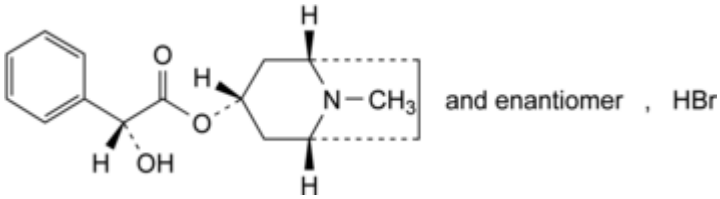
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This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Homatropine Hydrobromide

General Notices

(Ph. Eur. monograph 0500)



and enantiomer , HBr

$C_{16}H_{22}BrNO_3$ 356.3 *51-56-9*

Action and use

Anticholinergic.

Preparation

Homatropine Eye Drops

Ph Eur

DEFINITION

(1*R*,3*r*,5*S*)-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl (2*RS*)-2-hydroxy-2-phenylacetate hydrobromide.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Freely soluble in water, sparingly soluble in ethanol (96 per cent).

mp

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About 215 °C, with decomposition.

IDENTIFICATION

First identification: A, C.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *homatropine hydrobromide CRS*.

B. Dissolve 50 mg in 1 mL of *water R* and add 2 mL of *dilute acetic acid R*. Heat and add 4 mL of *picric acid solution R*. Allow to cool, shaking occasionally. Collect the crystals, wash with 2 quantities, each of 3 mL, of iced *water R* and dry at 100-105 °C. The crystals melt (2.2.14) at 182 °C to 186 °C.

C. It gives reaction (a) of bromides (2.3.1).

TESTS

Solution S

Dissolve 1.25 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, *Method II*).

pH (2.2.3)

5.0 to 6.5 for solution S.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (a) Dilute 5.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (b) Dilute 5.0 mL of reference solution (a) to 25.0 mL with the mobile phase.

Reference solution (c) Dissolve 5.0 mg of *hyoscine hydrobromide CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. To 10.0 mL of this solution add 0.5 mL of the test solution and dilute to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.1 m, Ø = 4.6 mm,

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— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (3 µm),

— *temperature*: 40 °C.

Mobile phase Mix 33 volumes of *methanol R2* and 67 volumes of a solution prepared as follows: dissolve 6.8 g of *potassium dihydrogen phosphate R* and 7.0 g of *sodium heptanesulfonate monohydrate R* in 1000 mL of *water R* and adjust to pH 2.7 with a 330 g/L solution of *phosphoric acid R*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 10 µL.

Run time 3 times the retention time of homatropine.

Relative retention With reference to homatropine (retention time = about 6.8 min): impurity C = about 0.2; impurity A = about 0.9; impurity B = about 1.1; impurity D = about 1.9.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to homatropine and impurity B,

— *symmetry factor*: maximum 2.5 for the peak due to homatropine.

Limits:

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent),

— *impurities B, C, D*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent),

— *any other impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent),

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent); disregard the peak due to the bromide ion which appears close to the peak due to the solvent,

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

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Dissolve 0.300 g in a mixture of 5.0 mL of *0.01 M hydrochloric acid* and 50 mL of *alcohol R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

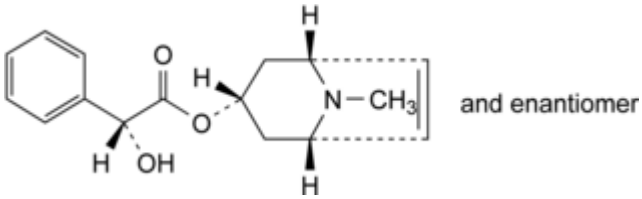
1 mL of *0.1 M sodium hydroxide* is equivalent to 35.63 mg of $C_{16}H_{22}BrNO_3$.

STORAGE

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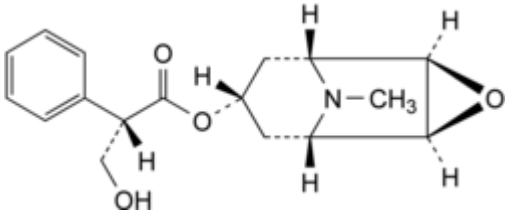
IMPURITIES

Specified impurities *A, B, C, D.*

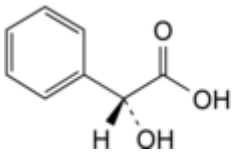


and enantiomer

A. (1*R*,3*s*,5*S*)-8-methyl-8-azabicyclo[3.2.1]oct-6-en-3-yl (2*RS*)-2-hydroxy-2-phenylacetate (dehydrohomatropine),

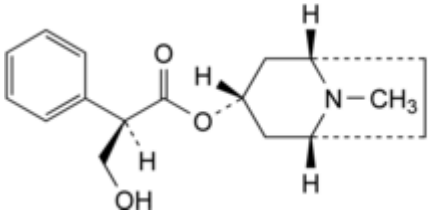


B. (1*R*,2*R*,4*S*,5*S*,7*s*)-9-methyl-3-oxa-9-azatricyclo[3.3.1.$0^{2,4}$]non-7-yl (2*S*)-3-hydroxy-2-phenylpropanoate (hyoscine),



and enantiomer

C. (2*RS*)-2-hydroxy-2-phenylacetic acid (mandelic acid),



and enantiomer

D. (1*R*,3*r*,5*S*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (2*RS*)-3-hydroxy-2-phenylpropanoate (atropine).

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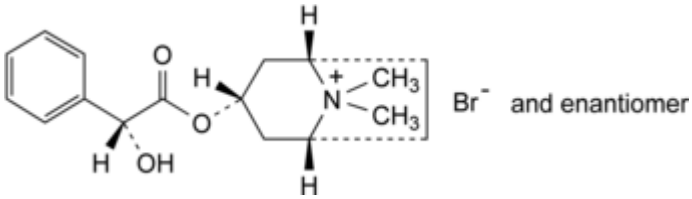
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Homatropine Methylbromide

General Notices

(Ph. Eur. monograph 0720)



$C_{17}H_{24}BrNO_3$ 370.3 *80-49-9*

Action and use

Anticholinergic.

Ph Eur

DEFINITION

(1*R*,3*r*,5*S*)-3-[[(2*RS*)-2-Hydroxy-2-phenylacetyl]oxy]-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Freely soluble in water, soluble in ethanol 96 per cent.

mp

About 190 °C.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *homatropine methylbromide CRS*.

B. It gives reaction (a) of bromides (*2.3.1*).

TESTS

Solution S

Dissolve 1.25 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

4.5 to 6.5 for solution S.

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture *acetonitrile R1*, mobile phase A (9:41 *V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Reference solution (a) Dilute 5.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 5.0 mL of this solution to 50.0 mL with the solvent mixture.

Reference solution (b) Dilute 5.0 mL of reference solution (a) to 25.0 mL with the solvent mixture.

Reference solution (c) Dissolve 5.0 mg of *homatropine hydrobromide CRS* (impurity B) in the solvent mixture and dilute to 50.0 mL with the solvent mixture. To 10.0 mL of the solution add 0.5 mL of the test solution and dilute to 100.0 mL with the solvent mixture.

Reference solution (d) Dissolve 2.0 mg of *homatropine methylbromide for system suitability CRS* (containing impurity A) in 1.0 mL of the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 25 °C.

Mobile phase:

— *mobile phase A*: dissolve 3.4 g of *potassium dihydrogen phosphate R* and 5.0 g of *sodium pentanesulfonate monohydrate R* in 980 mL of *water for chromatography R*, adjust to pH 3.0 with a 330 g/L solution of *phosphoric acid R* and dilute to 1000 mL with *water*

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for chromatography R;

— *mobile phase B*: mix 400 mL of mobile phase A and 600 mL of *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	70	30
2 - 15	70 → 30	30 → 70

Flow rate 1.4 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 10 µL.

Relative retention With reference to homatropine methylbromide (retention time = about 5 min): impurity A = about 0.9; impurity B = about 1.2.

Identification of impurities Use the chromatogram supplied with *homatropine methylbromide for system suitability CRS* and the chromatogram obtained with reference solution (d) to identify the peak due to impurity A; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity B.

System suitability:

— *resolution*: minimum 2.5 between the peaks due to homatropine methylbromide and impurity B in the chromatogram obtained with reference solution (c);

— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity A and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to homatropine methylbromide in the chromatogram obtained with reference solution (d).

Limits:

— *impurities A, B*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent); disregard the peak due to the bromide ion which appears close to the peak due to the solvent;

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

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Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in 10 mL of *water R*. Titrate with *0.1 M silver nitrate*. Determine the end-point potentiometrically (2.2.20), using a silver indicator electrode and a silver-silver chloride reference electrode.

1 mL of *0.1 M silver nitrate* is equivalent to 37.03 mg of $C_{17}H_{24}BrNO_3$.

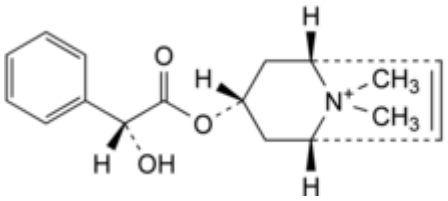
STORAGE

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IMPURITIES

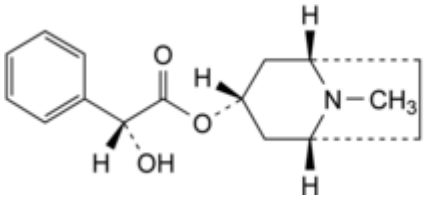
Specified impurities A, B.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) C, D, E, F.



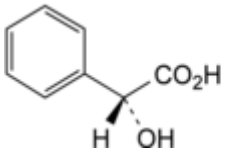
and enantiomer

A. (1*R*,3*s*,5*S*)-3-[[(2*RS*)-2-hydroxy-2-phenylacetyl]oxy]-8,8-dimethyl-8-azoniabicyclo[3.2.1]oct-6-ene (methyldehydrohomatropine),



and enantiomer

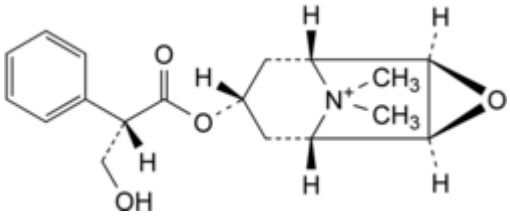
B. (1*R*,3*r*,5*S*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (2*RS*)-2-hydroxy-2-phenylacetate (homatropine),



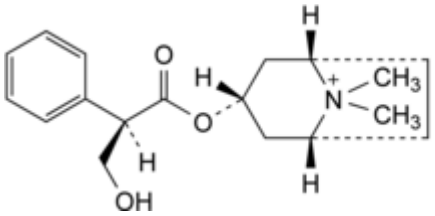
and enantiomer

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C. (2*RS*)-2-hydroxy-2-phenylacetic acid (mandelic acid),

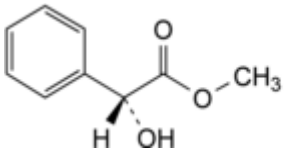


D. (1*R*,2*R*,4*S*,5*S*,7*s*)-7-[[(2*S*)-3-hydroxy-2-phenylpropanoyl]oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane (methylhyoscine),



and enantiomer

E. (1*R*,3*r*,5*S*)-3-[[(2*RS*)-3-hydroxy-2-phenylpropanoyl]oxy]-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane (methylatropine),



and enantiomer

F. methyl (2*RS*)-2-hydroxy-2-phenylacetate (methyl mandelate).

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Honey

General Notices

(Ph. Eur. monograph 2051)

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DEFINITION

Honey is produced by bees (*Apis mellifera* L.) from the nectar of plants or from secretions of living parts of plants which the bees collect, transform by combining with specific substances of their own, deposit, dehydrate, store and leave in the honey comb to ripen and mature.

PRODUCTION

If the bee has been exposed to treatment to prevent or cure diseases or to any substance intended for preventing, destroying or controlling any pest, unwanted species of plants or animals, appropriate measures are taken to ensure that the levels of residues are as low as possible.

CHARACTERS

Appearance

Viscous liquid which may be partly crystalline, almost white to dark brown.

IDENTIFICATION

Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.6 g of the substance to be examined in 50 mL of *ethanol (30 per cent V/V) R*.

Reference solution Dissolve 0.5 g of *fructose R*, 0.5 g of *glucose R* and 0.1 g of *sucrose R* in 100 mL of *ethanol (30 per cent V/V) R*.

Plate *TLC silica gel plate R*.

Mobile phase *water R*, *acetonitrile R* (13:87 *V/V*).

Application 5 µL as bands.

Development 3 times over a path of 15 cm.

Drying In warm air.

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Detection Spray with a solution prepared as follows: dissolve 2 g of *diphenylamine R* and 2 mL of *aniline R* in 100 mL of *acetone R*. Add a 850 g/L solution of *phosphoric acid R* until the precipitate formed dissolves again (about 15-20 mL). Examine in daylight after heating at 100-105 °C for 5-10 min.

Results See below the sequence of the zones present in the chromatograms obtained with the reference solution and the test solution. Furthermore, the weak brown zone due to sucrose in the chromatogram obtained with the reference solution may be present in the chromatogram obtained with the test solution. One or more other weak zones may be present in the chromatogram obtained with the test solution.

Top of the plate	
_____	_____
Fructose: an intense brown zone	An intense brown zone (fructose)
Glucose: an intense greyish-blue zone	An intense greyish-blue zone (glucose)
_____	_____
Sucrose: a brown zone	2 to 3 brownish-grey zones
Reference solution	**Test solution**

TESTS

Refractive index (*2.2.6*)

Minimum 1.487 (equivalent to a maximum water content of 20 per cent).

Homogenise 100 g and transfer into a flask. Close tightly and place in a water-bath at 50 ± 0.2 °C until all sugar crystals have dissolved. Cool the solution to 20 °C and rehomogenise. Immediately after rehomogenisation, cover the surface of the refractometer prism evenly with the sample. Determine the refractive index after 2 min if using an Abbe refractometer and after 4 min if using a digital refractometer. Use the average value of 2 determinations.

Conductivity (*2.2.38*)

Maximum 800 $\mu S \cdot cm^{-1}$.

Using the value obtained for the refractive index, determine the water content of the substance to be examined from Table 2051.-1. Using this information, dissolve an amount of the substance to be examined equivalent to 20.0 g of honey dry solids, in *water R* to produce 100.0 mL.

Optical rotation (*2.2.7*)

Maximum + 0.6°.

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Using the value obtained for the refractive index, determine the water content of the substance to be examined from Table 2051.-1. Using this information, dissolve an amount of the substance to be examined, equivalent to 20.0 g of honey dry solids, in 50 mL of *water R*. Add 0.2 mL of *concentrated ammonia R* and dilute to 100.0 mL with *water R*. If necessary decolourise the solution with *activated charcoal R*.

Table 2051.-1. – *Relationship of water content of honey to refractive index*

Water content (per cent *m/m*)	**Refractive index at 20 °C**
15.0	1.4992
15.2	1.4987
15.4	1.4982
15.6	1.4976
15.8	1.4971
16.0	1.4966
16.2	1.4961
16.4	1.4956
16.6	1.4951
16.8	1.4946
17.0	1.4940
17.2	1.4935
17.4	1.4930
17.6	1.4925
17.8	1.4920
18.0	1.4915
18.2	1.4910
18.4	1.4905
18.6	1.4900
18.8	1.4895
19.0	1.4890
19.2	1.4885
19.4	1.4880

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Water content (per cent *m/m*)	Refractive index at 20 °C
19.6	1.4875
19.8	1.4870
20.0	1.4865

5-Hydroxymethylfurfural

Maximum 80 ppm, calculated on dry solids.

Using the value obtained for the refractive index, determine the water content of the substance to be examined from Table 2051.-1. Using this information, dissolve an amount of the substance to be examined, equivalent to 5.0 g of honey dry solids, in 25 mL of *water R* and transfer to a 50.0 mL volumetric flask with the same solvent. Add 0.5 mL of a 150 g/L solution of *potassium ferrocyanide R* and mix. Add 0.5 mL of a 300 g/L solution of *zinc acetate R*, mix and dilute to 50.0 mL with *water R* (a drop of *anhydrous ethanol R* may be added to avoid foaming). Filter. Transfer 5.0 mL of the filtered solution into each of 2 tubes. To one tube add 5.0 mL of *water R* (test solution). To the other tube add 5.0 mL of a 2.0 g/L solution of *sodium hydrogensulfite R* (reference solution). Determine the absorbance (*2.2.25*) of the test solution against the reference solution at 284 nm and 336 nm within 60 min. If the absorbance at 284 nm is greater than 0.8, dilute to the same extent the test solution with *water R* and the reference solution with a 2.0 g/L solution of *sodium hydrogensulfite R* so as to obtain an absorbance of less than 0.8.

Calculate the content of 5-hydroxymethylfurfural from the expression:

$$\left(A_1 - A_2\right) \times D \times 149.7$$

A_1 = absorbance at 284 nm,

A_2 = absorbance at 336 nm,

D = dilution factor, where applicable.

Chlorides (*2.4.4*)

Maximum 350 ppm, determined on 15 mL of a 10 g/L solution.

Sulfates (*2.4.13*)

Maximum 250 ppm, determined on 15 mL of a 40 g/L solution.

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This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Human Coagulation Factor IX (rDNA) Powder for Solution for Injection

General Notices

(Ph. Eur. monograph 2994)

Ph Eur

DEFINITION

Sterile, freeze-dried preparation of closely related glycoproteins, which have the same amino acid sequence (415 amino acids) as the naturally occurring Ala 148 allelic form analogue (plasma-derived coagulation factor IX). The preparation is intended for intravenous injection.

Potency

80 per cent to 125 per cent of the potency stated on the label when determined using the conditions described under Assay.

Human coagulation factor IX (rDNA) powder for solution for injection complies with the monograph on Parenteral preparations (0520) and with the following additional requirements.

PRODUCTION

Human coagulation factor IX (rDNA) powder for solution for injection is prepared from *Human coagulation factor IX (rDNA) concentrated solution (2522)*. The concentrated solution is diluted with a formulation buffer containing excipients such as histidine, sucrose, glycine and polysorbate 80. This preparation is passed through a bacteria-retentive filter, distributed aseptically into the final containers and freeze-dried. The containers are closed under vacuum or under an inert gas. Where excipients other than those mentioned above are used, their compatibility with the tests described hereafter must be confirmed.

CHARACTERS

Appearance (before reconstitution)

White, hygroscopic powder or friable mass, free from visible foreign matter.

IDENTIFICATION

A. It complies with the limits of the assay.

B. Polyacrylamide gel electrophoresis (*2.2.31*).

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Examine the electropherograms obtained in the test for impurities with molecular masses differing from that of human coagulation factor IX (rDNA).

Calculate the relative mobility (in per cent) of the main band in the electropherogram obtained with the test solution with reference to the mobility of the main band in the electropherogram obtained with reference solution (a), using the following expression:

$$\frac{M_1 - M_2}{M_2} \times 100$$

M_1 = molecular mass of the main band in the electropherogram obtained with the test solution;

M_2 = molecular mass of the main band in the electropherogram obtained with reference solution (a).

Results:

— the electropherogram obtained with the test solution is similar to the electropherogram obtained with reference solution (a);

— the mobility of the main band in the electropherogram obtained with the test solution is within 10 per cent of that of the main band in the electropherogram obtained with reference solution (a).

TESTS

Reconstitute the preparation to be examined as stated on the label immediately before carrying out the identification, test (except those for solubility and water) and assay.

Formulation buffer

Dissolve 19.53 g of *glycine R*, 1.55 g of *histidine R* and 10.00 g of *sucrose R* in 1000 mL of *water R*. Add 50 µL of *polysorbate 80 R* and adjust to pH 6.8 with *hydrochloric acid R*.

Appearance of solution

After reconstitution, the solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*), without visible particles.

Solubility

To a vial of the preparation to be examined add the volume of the diluent stated on the label at the recommended temperature. The preparation dissolves completely with gentle swirling within 5 min.

pH (*2.2.3*)

The limit is approved by the competent authority.

Related proteins

Liquid chromatography (*2.2.29*).

Test solution Dilute the reconstituted preparation to be examined with the formulation buffer to obtain a concentration of 0.5 mg/mL.

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Reference solution Dissolve the contents of a vial of *human coagulation factor IX (rDNA) CRS* in the formulation buffer to obtain a concentration of about 0.5 mg/mL.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *styrene-divinylbenzene copolymer R* (10 µm) with a pore size of 400 nm;

— *temperature*: 37 °C.

Mobile phase:

— *mobile phase A*: add 1 mL of *trifluoroacetic acid R* to 1000 mL of *water for chromatography R*;

— *mobile phase B*: mix 1 mL of *trifluoroacetic acid R*, 200 mL of *water for chromatography R* and 800 mL of *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 0.5	75	25
0.5 - 30	75 → 20	25 → 80
30 - 31	20 → 0	80 → 100
31 - 33	0	100

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 214 nm.

Injection 100 µL; perform at least 3 injections using an automatic injector.

Relative retention With reference to the 2nd peak of the double peak due to human coagulation factor IX (rDNA) (retention time = about 12-14 min): related protein A = about 0.75; related protein B = about 0.78; related protein C = about 0.80; related protein D = about 0.85; related protein E = about 0.93.

System suitability Reference solution:

— the chromatogram obtained is qualitatively similar to the chromatogram supplied with *human coagulation factor IX (rDNA) CRS*;

— *repeatability*: maximum relative standard deviation of 3 per cent for the total area of the peak due to human coagulation factor IX (rDNA), determined on 3 injections performed immediately before the run;

— *peak-to-valley ratio*: minimum 1.2, where H_p = height above the baseline of the peak due to related protein E and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to human coagulation factor IX (rDNA).

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Report individual relative peak areas considering the peak area of the entire chromatogram. Individual relative per cent peak areas are calculated as the average of the 3 injections of the test solution.

Peaks due to related proteins A and D are not always present.

Results:

— the profile of the chromatogram obtained with the test solution corresponds to that of the chromatogram obtained with the reference solution, except for minor peaks due to impurities, that may be absent in the chromatogram obtained with the test solution.

Limits:

— *related protein C*: maximum 0.6 per cent.

Impurities with molecular masses differing from that of human coagulation factor IX (rDNA)

Polyacrylamide gel electrophoresis (2.2.31) using a gradient gel with the following modifications.

Gel dimensions 1.0 mm thick.

Resolving gel 3-15 per cent acrylamide gradient gel.

Acrylamide solution *30 per cent acrylamide/bisacrylamide (36.5:1) solution R*.

To prepare a 15 per cent acrylamide solution, add *sucrose R* to obtain a concentration of 142 g/L.

The following elements are provided as examples for loading the gel-forming apparatus to prepare the stacking gel.

Stacking gel The stacking gel solution is prepared by mixing:

— 100 volumes of *30 per cent acrylamide/bisacrylamide (36.5:1) solution R*;

— 125 volumes of *1 M tris-hydrochloride buffer solution pH 6.8 R*;

— 740.5 volumes of *water R*;

— 1.5 volumes of *tetramethylethylenediamine R*;

— 33 volumes of a 150 mg/mL solution of *ammonium persulfate R*.

Load the compartments of the gradient-forming apparatus with the acrylamide solutions and proceed as per the instructions of the equipment supplier to obtain the polymerised gradient gel.

After polymerisation is completed, rinse the gradient gel with *water R*. Remove any excess liquid. Pour the stacking gel solution into the equipment, insert a clean comb and allow for polymerisation.

Alternatively, commercially available gradient gels may be used.

Test solution Dilute the reconstituted preparation to be examined with the formulation buffer to obtain a concentration of about 1 mg/mL.

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Reference solution (a) Dissolve the contents of a vial of *human coagulation factor IX (rDNA) CRS* in the formulation buffer to obtain a concentration of about 1 mg/mL.

Reference solution (b) A 0.01 mg/mL solution of *bovine albumin R* in the formulation buffer.

Reference solution (c) A solution of molecular mass markers suitable for calibrating SDS-polyacrylamide gels in the range of 5-200 kDa.

Sample buffer *Concentrated SDS-PAGE sample buffer for reducing conditions R* containing dithiothreitol as the reducing agent.

Sample treatment Incubate in a water-bath for 5 min.

Application 35 µL.

Use *SDS-PAGE running buffer R* for running the gel.

For each gel, run 1 lane with reference solution (b), 2 lanes with reference solution (c), 2 lanes with the incubated reducing buffer (as blank) and at least 1 lane with reduced reference solution (a); use the remaining lanes for reduced test solutions.

Detection By Coomassie staining.

Identification of bands Human coagulation factor IX (rDNA) has an approximate molecular mass of 55 kDa, and related protein bands with molecular masses of approximately 54 kDa, 44 kDa, 29-32 kDa, 27 kDa and 14 kDa are present.

System suitability:

— a clear background is obtained after destaining;

— the band in the electropherogram obtained with reference solution (b) is clearly visible;

— all expected bands in the electropherogram obtained with reference solution (c) are visible;

— the bands in the electropherogram obtained with reference solution (c) are clearly separated;

— no band is visible in the blank lanes.

Results:

— the electropherogram obtained with the test solution is similar to the electropherogram obtained with reference solution (a);

— no new band in the electropherogram obtained with the test solution has an intensity greater than that of the band in the electropherogram obtained with reference solution (b).

Impurities with molecular masses greater than that of human coagulation factor IX (rDNA)

Size-exclusion chromatography (*2.2.30*): use the normalisation procedure.

Test solution Dilute the reconstituted preparation to be examined with the formulation buffer to obtain a concentration of 400 µg/mL.

Reference solution Dissolve the contents of a vial of *human coagulation factor IX (rDNA) CRS* in the formulation buffer to obtain a concentration of about 400 µg/mL.

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Resolution solution Dissolve the contents of a vial of *human coagulation factor IX (rDNA) CRS* in the formulation buffer to obtain a concentration of about 400 µg/mL. Desalt and concentrate the preparation to be examined using a suitably validated procedure. Reconstitute the recovered material in *0.1 M phosphate buffer solution pH 8.0 R* to obtain a concentration of 400 µg/mL. To 500 µL of this solution add 1.4 µL of a 250 mg/L solution of *glutaraldehyde R*. Mix and incubate at 37 °C for 120 min.

Blank solution The formulation buffer.

Precolumn:

— *size*: *l* = 0.04 m, Ø = 6 mm;

— *stationary phase*: *hydrophilic silica gel for chromatography R* (5 µm) of a grade suitable for the fractionation of globular proteins in the relative molecular mass range of 10 000 to 500 000.

Column:

— *size*: *l* = 0.30 m, Ø = 7.8 mm;

— *stationary phase*: *hydrophilic silica gel for chromatography R* (5 µm) of a grade suitable for the fractionation of globular proteins in the relative molecular mass range of 10 000 to 500 000.

Mobile phase Dissolve 7.10 g of *anhydrous disodium hydrogen phosphate R* and 8.77 g of *sodium chloride R* in 1000 mL of *water for chromatography R*. Adjust to pH 7.00 ± 0.05 with *phosphoric acid R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 214 nm.

Injection 50 µL; perform 3 injections using an automatic injector maintained at 2-8 °C.

Retention time Human coagulation factor IX (rDNA) = about 9 min.

System suitability:

— the chromatogram obtained with the reference solution is qualitatively similar to the chromatogram supplied with *human coagulation factor IX (rDNA) CRS*;

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to the high molecular mass species and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to human coagulation factor IX (rDNA) in the chromatogram obtained with the resolution solution.

Calculate the relative area (in per cent) of the sum of the peaks with retention times less than that of human coagulation factor IX (rDNA), with reference to the area of the peak due to human coagulation factor IX (rDNA). Any shoulder appearing on the descending part of the peak due to human coagulation factor IX (rDNA) is included in its area.

Result:

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— the profile of the chromatogram obtained with the test solution corresponds to that of the chromatogram obtained with the reference solution.

Limit:

— *sum of the peaks eluted before the principal peak*: maximum 1.8 per cent.

Activated human coagulation factor IX (rDNA) (2.6.22)

Dilute the reconstituted preparation to be examined with *tris(hydroxymethyl)aminomethane buffer solution pH 7.5 R* to obtain a concentration of human coagulation factor IX (rDNA) of 20 IU/mL. For each of the dilutions, the coagulation time is not less than 150 s.

Osmolality (2.2.35)

The limit is approved by the competent authority.

Water (2.5.32)

Maximum 2.0 per cent.

Sterility (2.6.1)

It complies with the test.

Bacterial endotoxins (2.6.14)

Less than 1 IU per 100 IU of factor IX activity.

ASSAY

Protein

Size-exclusion chromatography (2.2.30) as described in the test for impurities with molecular masses greater than that of human coagulation factor IX (rDNA) with the following modifications.

Prepare triplicate dilutions of the test solution.

Reference solutions Dissolve the contents of a vial of *human coagulation factor IX (rDNA) CRS* in the formulation buffer to obtain a concentration of 1 mg/mL. Further dilute the solution to prepare a standard curve with concentrations in the range of 100-800 µg/mL (5 concentrations, typically 100 µg/mL, 200 µg/mL, 400 µg/mL, 600 µg/mL and 800 µg/mL).

Plot peak areas versus injected protein content and perform linear regression to create a standard curve.

System suitability (in addition to those described in the test for impurities with molecular masses greater than that of human coagulation factor IX (rDNA)):

— the correlation coefficient (r^2) calculated for the standard curve is not less than 0.995.

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Calculate the protein concentration of each replicate of the preparation to be examined using the standard curve and the assigned content in *human coagulation factor IX (rDNA) CRS*.

Potency

Assay of human coagulation factor IX (*2.7.11*). The estimated potency is not less than 80 per cent and not more than 125 per cent of the stated potency. The confidence limits (P = 0.95) are not less than 80 per cent and not more than 120 per cent of the estimated potency.

Human coagulation factor IX concentrate BRP is suitable for use as a reference preparation.

STORAGE

In an airtight container, protected from light, at a temperature of 2 °C to 8 °C.

LABELLING

The label states:

— the factor IX content in International Units;

— the name of any excipient and added substance;

— the composition and volume of the liquid to be used for reconstitution.

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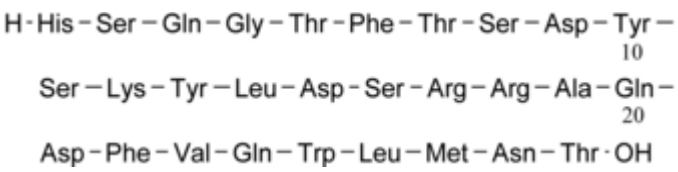
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Human Glucagon

General Notices

(Glucagon, Human, Ph. Eur. monograph 1635)



$C_{153}H_{225}N_{43}O_{49}S$ 3483

Action and use

Hormone; treatment of hypoglycaemia.

Preparation

Human Glucagon Injection

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DEFINITION

Polypeptide having the same structure (29 amino acids) as the hormone produced by the α-cells of the human pancreas, which increases the blood-glucose concentration by promoting rapid breakdown of liver glycogen.

Content

92.5 per cent to 105.0 per cent (anhydrous substance).

PRODUCTION

Human glucagon is produced by a method based on recombinant DNA (rDNA) technology. During the course of product development it must be demonstrated that the manufacturing process produces a product having a biological activity of not less than 1 IU/mg using a suitable validated bioassay.

Host-cell-derived proteins

The limit is approved by the competent authority.

Host-cell- and vector-derived DNA

The limit is approved by the competent authority.

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CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water and in most organic solvents. It is soluble in dilute mineral acids and in dilute solutions of alkali hydroxides.

IDENTIFICATION

A. Peptide mapping. Liquid chromatography (2.2.29).

Test solution Prepare a 5 mg/mL solution of the substance to be examined in *0.01 M hydrochloric acid*. Mix 200 µL of this solution with 800 µL of *0.1 M ammonium carbonate buffer solution pH 10.3 R* (diluted stock solution). Prepare a 2 mg/mL solution of *α-chymotrypsin for peptide mapping R* in *0.1 M ammonium carbonate buffer solution pH 10.3 R* and add 25 µL of this solution to the diluted stock solution. Place the solution in a closed vial at 37 °C for 2 h. Remove the vial and stop the reaction immediately by adding 120 µL of *glacial acetic acid R*.

Reference solution Prepare a 1 mg/mL solution of *human glucagon CRS* in *0.1 M ammonium carbonate buffer solution pH 10.3 R* (diluted stock solution) and continue as described for the test solution.

Column:

— *size*: *l* = 0.05 m, Ø = 4 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: mix 500 µL of *trifluoroacetic acid R* and 1000 mL of *water R*;

— *mobile phase B*: mix 500 µL of *trifluoroacetic acid R* with 600 mL of *anhydrous ethanol R* and add 400 mL of *water R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 35	100 → 53	0 → 47
35 - 45	53 → 0	47 → 100
45 - 46	0 → 100	100 → 0
46 - 75	100	0

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 215 nm.

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Equilibration With mobile phase A for at least 15 min.

Injection 20 µL.

System suitability The chromatogram obtained with the reference solution is qualitatively similar to the chromatogram supplied with *human glucagon CRS*.

Results The profile of the chromatogram obtained with the test solution corresponds to that of the chromatogram obtained with the reference solution.

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with reference solution (a).

TESTS

Related proteins and deamidated forms

Liquid chromatography (*2.2.29*): use the normalisation procedure.

Test solution Dissolve the substance to be examined in *0.01 M hydrochloric acid* to obtain a concentration of 0.5 mg/mL. *Maintain the solution at 2-8 °C.*

Reference solution (a) Dissolve the contents of a vial of *human glucagon CRS* in *0.01 M hydrochloric acid* to obtain a concentration of 0.5 mg/mL. *Maintain the solution at 2-8 °C.*

Reference solution (b) Dissolve the substance to be examined in *0.01 M hydrochloric acid* to obtain a concentration of about 0.5 mg/mL. Heat at 50 °C for 48 h (*in situ* preparation of all 4 deamidated forms of glucagon at a total concentration of not less than 7 per cent).

Column:

— *size*: *l* = 0.15 m, Ø = 3 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 45 °C.

Mobile phase:

— *mobile phase A*: dissolve 16.3 g of *potassium dihydrogen phosphate R* in 800 mL of *water R*, adjust to pH 2.7 with *phosphoric acid R* and add 200 mL of *acetonitrile for chromatography R*;

— *mobile phase B*: *acetonitrile for chromatography R*, *water R* (40:60 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 25	61	39

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
29 - 30	12	88
30 - 31	12 → 61	88 → 39

NOTE The end time of the isocratic elution may be adjusted so that the gradient begins after elution of the peak due to deamidated glucagon 4 (see relative retention below).

Flow rate 0.5 mL/min.

Detection Spectrophotometer at 214 nm.

Injection 15 µL.

Relative retention With reference to glucagon (retention time = about 21 min): deamidated glucagon 1 = about 1.1; deamidated glucagon 4 = about 1.4.

System suitability:

— *resolution*: minimum 1.5 between the peaks due to glucagon and deamidated glucagon 1 in the chromatogram obtained with reference solution (b);

— *symmetry factor*: maximum 1.8 for the peak due to glucagon in the chromatogram obtained with reference solution (a);

— *repeatability*: maximum relative standard deviation of 2.0 per cent after 5 injections of reference solution (a);

— 4 peaks eluting after the principal peak, that correspond to the deamidated forms, are clearly visible in the chromatogram obtained with reference solution (b).

Limits:

— *deamidated forms*: maximum 0.8 per cent;

— *total*: maximum 3.0 per cent.

Water (2.5.32)

Maximum 10 per cent, determined on 50 mg.

Bacterial endotoxins (2.6.14)

Less than 10 IU/mg.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related proteins and deamidated forms with the following modification.

Injection Test solution and reference solution (a).

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Calculate the percentage content of human glucagon ($C_{153}H_{225}N_{43}O_{49}S$) taking into account the assigned content of $C_{153}H_{225}N_{43}O_{49}S$ in *human glucagon CRS*.

STORAGE

In an airtight container, protected from light, at a temperature lower than -15 °C.

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Human Glucagon for Injection

General Notices

Action and use

Hormone; treatment of hyperglycaemia.

DEFINITION

Human Glucagon for Injection is a sterile material consisting of freeze-dried Human Glucagon (produced by recombinant DNA technology) with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections stated under Parenteral Preparations and with the following requirements.

Content of glucagon, $C_{153}H_{225}N_{43}O_{49}S$

75.0 to 104.0% of the stated amount.

IDENTIFICATION

In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH of a 0.1% w/v solution, 2.5 to 3.5, Appendix V L.

Related proteins and deamidated forms

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions and the normalisation procedure.

(1) Dissolve the powder being examined in 0.01M *hydrochloric acid* to obtain the equivalent of 0.05% w/v of human glucagon. *Maintain the solution at 2° to 8°.*

(2) Dissolve the contents of a vial of *human glucagon EPCRS* in 0.01M *hydrochloric acid* to obtain a concentration of 0.05 % w/v. *Maintain the solution at 2° to 8°.*

(3) Dissolve the powder being examined in 0.01M *hydrochloric acid* to obtain a concentration of about 0.05% w/v human glucagon. Heat at 50° for 48 hours (generation of all 4 deamidated forms of glucagon at a total concentration of not less than 7%).

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (15 cm × 3.0 mm) packed with *octadecylsilyl silica gel for chromatography* (3 µm) (ACE 3 C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 0.5 mL per minute.

(d) Use a column temperature of 45°.

(e) Use a detection wavelength of 214 nm.

(f) Inject 15 µL of each solution.

MOBILE PHASE

Mobile phase A 200 volumes of *acetonitrile for chromatography* and 800 volumes of the solution prepared as described below.

Dissolve 16.3 g of *potassium dihydrogen orthophosphate* in 800 mL of *water*, adjust to pH 2.7 with *orthophosphoric acid*.

Mobile phase B 400 volumes of *acetonitrile for chromatography* and 600 volumes of *water*.

Use the following gradient elution.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-25	61	39	isocratic
25-29	61→12	39→88	linear gradient
29-30	12	88	isocratic
30-31	12→61	88→39	re-equilibration

Note: The relative retention time with respect to glucagon (retention time about 21 minutes) of deamidated glucagon 1 is about 1.1. The end time of the isocratic elution may be adjusted so that the gradient begins after elution of the peak due to deamidated glucagon 4 (relative retention with reference to glucagon about 1.4).

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution factor* between the peak due to glucagon and the following peak due to deamidated glucagon 1 is at least 1.5;

the 4 peaks eluting after the principal peak, that correspond to the deamidated forms, are clearly visible;

and, in the chromatogram obtained with solution (2):

the *symmetry factor* of the peak due to glucagon is a maximum of 1.8;

the *repeatability* has a maximum relative standard deviation of 2.0% after 5 injections.

LIMITS

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In the chromatogram obtained with solution (1):

the total area of all deamidated forms is not greater than 10.0%;

the total area of all *secondary peaks* is not greater than 15.0%.

Water

Not more than 5.0%, Appendix IX C, Method III. Use the entire freeze dried contents of the sealed container (containing 1 mg of the powder).

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. Dissolve the contents of the sealed container in *water BET* to give a solution containing 1 mg of Human Glucagon per mL (solution A). The endotoxin limit concentration of solution A is 10 IU of endotoxin per mL.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the method described under Related proteins and deamidated forms, injecting solutions (1) and (2).

DETERMINATION OF CONTENT

Calculate the content of human glucagon ($C_{153}H_{225}N_{43}O_{49}S$) from the chromatograms obtained and using the declared content of $C_{153}H_{225}N_{43}O_{49}S$ in *human glucagon EPCRS*.

STORAGE

Human Glucagon for Injection should be protected from light and stored strictly in accordance with the manufacturer’s instructions.

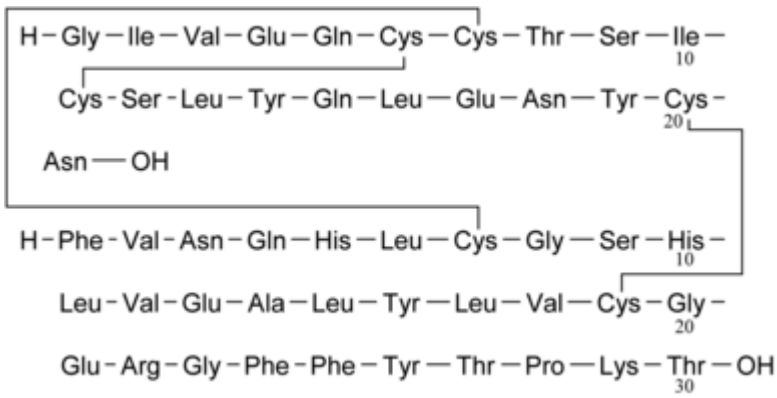
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Human Insulin

General Notices

(Ph. Eur. monograph 0838)



$C_{257}H_{383}N_{65}O_{77}S_6$ 5808

Action and use

Hormone; treatment of diabetes mellitus.

Preparation

Insulin Preparations

Ph Eur

DEFINITION

Human insulin is a 2-chain peptide having the structure of the antidiabetic hormone produced by the human pancreas.

Content

95.0 per cent to 105.0 per cent of human insulin $C_{257}H_{383}N_{65}O_{77}S_6$ plus A21 desamido human insulin (dried substance).

By convention, for the purpose of labelling insulin preparations, 0.0347 mg of human insulin is equivalent to 1 IU of insulin.

PRODUCTION

Human insulin 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.

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Where applicable, the animals from which human insulin is derived must fulfil the requirements for the health of animals suitable for human consumption.

Human insulin is produced under conditions designed to minimise the degree of microbial contamination.

For human insulin produced by enzymatic modification of insulin obtained from the pancreas of the pig, the manufacturing process is validated to demonstrate removal of any residual proteolytic activity. The competent authority may require additional tests.

For human insulin produced by a method based on rDNA technology, prior to release the following tests are carried out on each batch of human insulin, unless exemption has been granted by the competent authority.

Host-cell-derived proteins

The limit is approved by the competent authority.

Single chain precursor

The limit is approved by the competent authority. Use a suitably sensitive method.

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water and in ethanol (96 per cent). It dissolves in dilute mineral acids and with decomposition in dilute solutions of alkali hydroxides.

IDENTIFICATION

A. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with reference solution (a).

B. Peptide mapping (*2.2.55*).

SELECTIVE CLEAVAGE OF THE PEPTIDE BONDS

Test solution Prepare a 2.0 mg/mL solution of the substance to be examined in *0.01 M hydrochloric acid* and transfer 500 µL of this solution to a clean tube. Add 2.0 mL of *HEPES buffer solution pH 7.5 R* and 400 µL of a 1 mg/mL solution of *Staphylococcus aureus strain V8 protease, type XVII-B R*. Cap the tube and incubate at 25 °C for 6 h. Stop the reaction by adding 2.9 mL of *sulfate buffer solution pH 2.0 R*.

Reference solution Prepare at the same time and in the same manner as for the test solution but using *human insulin CRS* instead of the substance to be examined.

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CHROMATOGRAPHIC SEPARATION. Liquid chromatography (2.2.29).

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: octadecylsilyl silica gel for chromatography R (3 µm) with a pore size of 8 nm;

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: mix 100 mL of acetonitrile for chromatography R, 200 mL of sulfate buffer solution pH 2.0 R and 700 mL of water R; filter and degas;

— *mobile phase B*: mix 200 mL of sulfate buffer solution pH 2.0 R, 400 mL of acetonitrile for chromatography R and 400 mL of water R; filter and degas;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 60	90 → 30	10 → 70
60 - 65	30 → 0	70 → 100
65 - 70	0	100

Flow rate 1 mL/min.

Detection Spectrophotometer at 214 nm.

Equilibration At initial conditions for at least 15 min. Carry out a blank run using the above-mentioned gradient.

Injection 50 µL.

System suitability:

— the chromatogram obtained with the reference solution is qualitatively similar to the chromatogram of human insulin digest supplied with human insulin CRS;

— in the chromatogram obtained with the reference solution, identify the peaks due to digest fragments I, II and III;

symmetry factor Maximum 1.5 for the peaks due to fragments II and III;

resolution Minimum 3.4 between the peaks due to fragments II and III;

Results The profile of the chromatogram obtained with the test solution corresponds to that of the chromatogram obtained with the reference solution.

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NOTE: the retention time of fragment I is the same for porcine insulin and for human insulin. The retention times of fragments II and IV are the same for all insulins. The retention time of fragment III is the same for bovine insulin and for porcine insulin.

TESTS

Impurities with molecular masses greater than that of insulin

Size-exclusion chromatography (2.2.30): use the normalisation procedure.

Test solution Prepare a solution containing 4 mg/mL of the substance to be examined in *0.01 M hydrochloric acid*.

Resolution solution Use a solution of insulin (about 4 mg/mL), containing more than 0.4 per cent of high molecular mass proteins. An injectable insulin preparation, whether a solution or a suspension, that has been clarified with a sufficient amount of *6 M hydrochloric acid R*, containing the indicated percentage of high molecular mass proteins, or a solution prepared from insulin, dissolved in *0.01 M hydrochloric acid*, may be used. Insulin containing the indicated percentage of high molecular mass proteins may be prepared by allowing insulin powder to stand at room temperature for about 10 days.

Maintain the solutions at 2-8 °C and use within 7 days. If an automatic injector is used, maintain the temperature at 2-8 °C.

Column:

— *size*: *l* = 0.3 m, Ø = minimum 7.5 mm;

— *stationary phase*: *hydrophilic silica gel for chromatography R* (5-10 µm) with a pore size of 12-12.5 nm, of a grade suitable for the separation of insulin monomer from dimer and polymers.

Mobile phase Mix 15 volumes of *glacial acetic acid R*, 20 volumes of *acetonitrile R* and 65 volumes of a 1.0 g/L solution of *arginine R*; filter and degas.

Flow rate 0.5 mL/min.

Detection Spectrophotometer at 276 nm.

Equilibration Before using a new column for chromatographic analysis, equilibrate by repeated injections of an insulin solution containing high molecular mass proteins. This can be done by at least 3 injections of the resolution solution. The column is equilibrated when repeatable results are obtained from 2 subsequent injections.

Injection 100 µL.

Run time About 35 min.

Retention time Polymeric insulin complexes = 13-17 min; covalent insulin dimer = about 17.5 min; insulin monomer = about 20 min; salts = about 22 min.

System suitability Resolution solution:

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to the dimer and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to the monomer.

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Limits The sum of the areas of any peaks with a retention time less than that of the principal peak is not greater than 1.0 per cent of the total area of the peaks. Disregard any peak with a retention time greater than that of the peak due to insulin.

Related proteins

Liquid chromatography (2.2.29) as described under Assay, following the elution conditions as described below:

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 30	42	58
30 - 44	42 → 11	58 → 89
44 - 50	11	89

Maintain the solutions at 2-8 °C and use within 24 h. Perform a system suitability test (resolution, linearity) as described in the assay. If necessary, the relative proportions of the mobile phases may be adjusted to ensure complete elution of A21 desamido porcine insulin before commencement of the gradient. The profile of the gradient may also be adjusted to ensure complete elution of all insulin related impurities.

Inject 20 µL of reference solution (a), 20 µL of reference solution (b), 20 µL of reference solution (c) and 20 µL of the test solution. If necessary, adjust the injection volume to a volume between 10 µL and 20 µL in accordance with the results obtained in the test for linearity as described in the assay. Record the chromatograms for approximately 50 min. In the chromatogram obtained with reference solution (a), A21 desamido human insulin appears as a small peak after the principal peak and has a retention time of about 1.3 relative to the principal peak. In the chromatogram obtained with the test solution, the area of the peak due to A21 desamido human insulin is not greater than 2.0 per cent of the total area of the peaks; the sum of the areas of all peaks, apart from those due to human insulin and that due to A21 desamido human insulin, is not greater than 2.0 per cent of the total area of the peaks. For semi-synthetic human insulin only: in the chromatogram obtained with the test solution, the area of any peak corresponding to the peak due to porcine insulin in the chromatogram obtained with reference solution (c) is not greater than 1.0 per cent of the total area of the peaks.

The following test applies only to human insulin produced by enzymatic modification of porcine insulin.

Proinsulin-like immunoreactivity (PLI)

Maximum 10 ppm, calculated with reference to the dried substance and determined by a suitably sensitive immunochemical method (2.7.1) such as radio-immunoassay. Use the International Reference Reagent for porcine proinsulin to calibrate the method.

Zinc

Maximum 1.0 per cent (dried substance).

Atomic absorption spectrometry (2.2.23, Method I).

Test solution Dissolve 50.0 mg of the substance to be examined in *0.01 M hydrochloric acid* and dilute to 25.0 mL with the same acid. Dilute if necessary to a suitable concentration (for example, 0.4-1.6 µg of Zn per millilitre) with *0.01 M hydrochloric acid*.

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Reference solutions Use solutions containing 0.40 µg, 0.80 µg, 1.00 µg, 1.20 µg and 1.60 µg of Zn per millilitre, freshly prepared by diluting *zinc standard solution (5 mg/mL Zn) R* with *0.01 M hydrochloric acid*.

Source Zinc hollow-cathode lamp.

Wavelength 213.9 nm.

Atomisation device Air-acetylene flame of suitable composition (for example, 11 L of air and 2 L of acetylene per minute).

Loss on drying (*2.2.32*)

Maximum 10.0 per cent, determined on 0.200 g by drying in an oven at 105 °C for 24 h.

Sulfated ash (*2.4.14*)

Maximum 2.5 per cent, determined on 0.200 g (dried substance).

Bacterial endotoxins (*2.6.14*)

Less than 10 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for removal of bacterial endotoxins.

ASSAY

Liquid chromatography (*2.2.29*).

Test solution Dissolve 40.0 mg of the substance to be examined in *0.01 M hydrochloric acid* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve the contents of a vial of *human insulin CRS* in *0.01 M hydrochloric acid* to obtain a concentration of 4.0 mg/mL.

Reference solution (b) Dissolve the contents of a vial of *insulin porcine for system suitability CRS* in *0.01 M hydrochloric acid* to obtain a concentration of 4 mg/mL.

Reference solution (c) Dilute 1.0 mL of reference solution (b) to 50.0 mL with *0.01 M hydrochloric acid*. To 1.0 mL of this solution add 1.0 mL of reference solution (a).

Reference solution (d) Dilute 1.0 mL of reference solution (a) to 10.0 mL with *0.01 M hydrochloric acid*.

Resolution solution Mix 1.0 mL of reference solution (a) and 1.0 mL of reference solution (b).

Maintain the solutions at 2-8 °C and use within 48 h. If an automatic injector is used, maintain at 2-8 °C.

Column:

— *size*: *l* = 0.25, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

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Mobile phase Mix 42 volumes of mobile phase A and 58 volumes of mobile phase B, adjusting the composition of the mixture if necessary.

Prepare and maintain the following solutions at a temperature of at least 20 °C:

— *mobile phase A*: dissolve 28.4 g of *anhydrous sodium sulfate R* in *water R* and dilute to 1000 mL with the same solvent; add 2.7 mL of *phosphoric acid R*; adjust to pH 2.3, if necessary, with *ethanolamine R*; filter and degas;

— *mobile phase B*: mix 550 mL of mobile phase A with 450 mL of *acetonitrile R*. Warm the solution to a temperature of at least 20 °C in order to avoid precipitation (mixing of mobile phase A with acetonitrile is endothermic); filter and degas.

Flow rate 1 mL/min.

Detection Spectrophotometer at 214 nm.

System suitability:

— *resolution*: inject 20 µL of the resolution solution and 20 µL of reference solution (b). Record the chromatogram of the resolution solution until the peak corresponding to the principal peak in the chromatogram obtained with reference solution (b) is clearly visible. In the chromatogram obtained with the resolution solution, identify the peaks due to porcine insulin and human insulin. The test is not valid unless the resolution between the peaks due to human insulin and porcine insulin is at least 1.2. If necessary, adjust the concentration of acetonitrile in the mobile phase until this resolution is achieved.

— *linearity*: inject 20 µL each of reference solutions (a) and (d). The test is not valid unless the area of the principal peak in the chromatogram obtained with reference solution (a) is 10 ± 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (d). If this test fails, adjust the injection volume to between 10 µL and 20 µL, in order that the responses are within the linearity range of the detector.

Injection 20 µL of the test solution and reference solution (a).

Calculate the content of human insulin $C_{257}H_{383}N_{65}O_{77}S_6$ plus A21 desamido human insulin using the areas of the corresponding peaks in the chromatograms obtained with the test solution and reference solution (a) and the declared content of human insulin plus A21 desamido human insulin in *human insulin CRS*.

STORAGE

In an airtight container, protected from light, at -18 °C or below, until released by the manufacturer. When thawed, insulin is stored at 5 ± 3 °C 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.

LABELLING

The label states whether the substance is produced by enzymatic modification of porcine insulin or by rDNA technology.

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Hyaluronidase

General Notices

(Ph. Eur. monograph 0912)

Action and use

Used to promote absorption of fluid into tissues.

Preparation

Hyaluronidase Injection

Ph Eur

DEFINITION

Enzyme extracted from mammalian testes (for example bovine testes) and capable of hydrolysing mucopolysaccharides of the hyaluronic acid type. It may contain a suitable stabiliser.

Potency

Minimum 300 IU of hyaluronidase activity per milligram (dried substance).

PRODUCTION

The animals from which hyaluronidase is derived must fulfil the requirements for the health of animals suitable for human consumption.

CHARACTERS

Appearance

White or yellowish-white, amorphous powder.

Solubility

Soluble in water, practically insoluble in acetone and in anhydrous ethanol.

IDENTIFICATION

A solution containing the equivalent of 100 IU of hyaluronidase in 1 mL of a 9 g/L solution of *sodium chloride R* depolymerises an equal volume of a 10 g/L solution of *sodium hyaluronate BRP* in 1 min at 20 °C as shown by a pronounced decrease in viscosity. This action is destroyed by heating the hyaluronidase at 100 °C for 30 min.

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TESTS

Appearance of solution

The solution is clear (*2.2.1*).

Dissolve 0.10 g in *water R* and dilute to 10 mL with the same solvent.

pH (*2.2.3*)

4.5 to 7.5.

Dissolve 30 mg in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Loss on drying (*2.2.32*)

Maximum 5.0 per cent, determined on 0.500 g by drying at 60 °C at a pressure not exceeding 670 Pa for 2 h.

Bacterial endotoxins (*2.6.14*)

Less than 0.2 IU per IU of hyaluronidase.

ASSAY

The activity of hyaluronidase is determined by comparing the rate at which it hydrolyses *sodium hyaluronate BRP* with the rate obtained with the International Standard, or a reference preparation calibrated in International Units, using a slope-ratio assay.

Substrate solution To 0.10 g of *sodium hyaluronate BRP* in a 25 mL conical flask add slowly 20.0 mL of *water R* at 4 °C. The rate of addition must be slow enough to allow the substrate particles to swell (about 5 min). Maintain at 4 °C and stir for at least 12 h. Store at 4 °C and use within 4 days.

For the test solution and the reference solution, prepare the solution and carry out the dilution at 0 °C to 4 °C.

Test solution Dissolve a suitable amount of the substance to be examined in *hyaluronidase diluent R* so as to obtain a solution containing 0.6 ± 0.3 IU of hyaluronidase per millilitre.

Reference solution Dissolve a suitable amount of *hyaluronidase BRP* in *hyaluronidase diluent R* so as to obtain a solution containing 0.6 IU of hyaluronidase per millilitre.

In a reaction vessel, mix 1.50 mL of *phosphate buffer solution pH 6.4 R* and 1.0 mL of the substrate solution and equilibrate at 37 ± 0.1 °C. At time t_1 = 0 (first chronometer) add 0.50 mL of the test solution containing E_t mg of the enzyme to be examined, mix, measure the viscosity of the solution using a suitable viscometer maintained at 37 ± 0.1 °C and record the outflow time t_2 using a second chronometer (graduated in 0.1 second intervals), several times during about 20 min (read on the first chronometer). The following viscometer has been found suitable: Ubbelohde microviscometer (DIN 51 562, Part 2), capillary type MII, viscometer constant about 0.1 mm^2/s^2.

Repeat the procedure using 0.50 mL of the reference solution containing E_r mg of *hyaluronidase BRP*.

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Calculate the viscosity ratio from the expression:

$$\eta_r = \frac{k \times t_2}{0.6915}$$

k	=	the viscometer constant in mm^2/s^2 (indicated on the viscometer);
t_2	=	the outflow time (in seconds) of the solution;
0.6915	=	the kinematic viscosity in mm^2/s of the buffer solution at 37 °C.

Since the enzymatic reaction continues during the outflow time measurements, the real reaction time equals $t_1 + t_2/2$, half of the outflow time ($t_2/2$) for which a certain measurement is valid being added to the time t_1 at which the measurement is started. Plot $(\ln \eta_r)^{-1}$ as a function of the reaction time ($t_1 + t_2/2$) in seconds. A linear relationship is obtained. Calculate the slope for the substance to be examined (b_t) and the reference preparation (b_r).

Calculate the specific activity in International Units per milligram from the expression:

$$\frac{b_t}{b_r} \times \frac{E_r}{E_t} \times A$$

A	=	the specific activity of *hyaluronidase BRP* in International Units per milligram.

Carry out the complete procedure at least three times and calculate the average activity of the substance to be examined.

STORAGE

In an airtight container, at a temperature of 2 °C to 8 °C. If the substance is sterile, the container is also sterile and tamper-evident.

LABELLING

The label states the activity in International Units per milligram.

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Hyaluronidase Injection

General Notices

Action and use

Used to promote absorption of fluid into tissues.

DEFINITION

Hyaluronidase Injection is a sterile solution of Hyaluronidase in Water for Injections. It is prepared by dissolving Hyaluronidase for Injection in the requisite amount of Water for Injections immediately before use.

The injection complies with the requirements stated under Parenteral Preparations.

STORAGE

Hyaluronidase Injection should be used immediately after preparation.

HYALURONIDASE FOR INJECTION

DEFINITION

Hyaluronidase for Injection is a sterile material consisting of Hyaluronidase with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Potency

The estimated potency is not less than 90% and not more than 115% of the stated potency.

IDENTIFICATION

A solution containing 100 IU in 1 mL of a 0.9% w/v solution of *sodium chloride* depolymerises an equal volume of a 1% w/v solution of *sodium hyaluronate EPBRP* at 20° in 1 minute, as shown by a pronounced decrease in viscosity. This action is destroyed by heating the initial solution at 100° for 30 minutes.

TESTS

Acidity or alkalinity

pH of a 0.3% w/v solution in *carbon dioxide-free water*, 4.5 to 7.5, Appendix V L.

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Clarity and colour of solution

A 1.0% w/v solution in *carbon dioxide-free water* is *clear*, Appendix IV A, and not more than faintly yellow.

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. Dissolve the contents of the sealed container in *water BET* to give a solution containing 150 IU of Hyaluronidase per mL (solution A). The endotoxin limit concentration of solution A is 30 IU per mL.

ASSAY

Carry out the Assay described under Hyaluronidase.

LABELLING

The label of the sealed container states the total number of IU (Units) contained in it.

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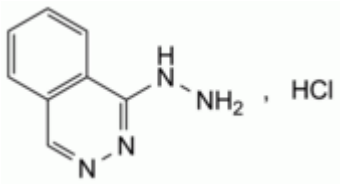
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Hydralazine Hydrochloride

General Notices

(Ph. Eur. monograph 0829)



$C_8H_9ClN_4$ 196.6 *304-20-1*

Action and use

Vasodilator; treatment of hypertension.

Preparations

Hydralazine Injection

Hydralazine Tablets

Ph Eur

DEFINITION

1-Hydrazinylphthalazine hydrochloride.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Soluble in water, slightly soluble in ethanol (96 per cent), very slightly soluble in methylene chloride.

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About 275 °C, with decomposition.

IDENTIFICATION

First identification: A, D,.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *hydralazine hydrochloride CRS*.

B. Dissolve 0.5 g in a mixture of 8 mL of *dilute hydrochloric acid R* and 100 mL of *water R*. Add 2 mL of *sodium nitrite solution R*, allow to stand for 10 min and filter. The precipitate, washed with *water R* and dried at 100-105 °C, melts (2.2.14) at 209 °C to 212 °C.

C. Dissolve about 10 mg in 2 mL of *water R*. Add 2 mL of a 20 g/L solution of *nitrobenzaldehyde R* in *ethanol (96 per cent) R*. An orange precipitate is formed.

D. Dissolve 11 mg in 2 mL of *water R*, acidify with 1 drop of *dilute sulfuric acid R* and add 1 mL of a 6.25 g/L solution of *silver sulfate R*. Shake and allow to stand. A curdled, white precipitate is formed. Centrifuge and wash the precipitate with 3 quantities, each of 1 mL, of a 0.5 per cent *V/V* solution of *sulfuric acid R*. Carry out this operation rapidly in subdued light, disregarding the fact that the supernatant may not become perfectly clear. Suspend the precipitate in 1 mL of *water R* and add 0.2 mL of *ammonia R*. Shake vigorously for at least 1 min. The precipitate dissolves easily with the possible exception of a few large particles that dissolve slowly.

TESTS

Solution S

Dissolve 0.5 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution GY_6 (2.2.2, *Method II*).

Dilute 4 mL of solution S to 20 mL with *water R*.

pH (2.2.3)

3.5 to 4.2 for solution S.

Impurity B

Liquid chromatography (2.2.29).

Solvent mixture *water R*, *acetonitrile R* (30:70 *V/V*).

Solution A Dilute 1 mL of *benzaldehyde R* to 100 mL with a mixture of 10 volumes of *water R* and 90 volumes of *methanol R*.

Test solution Dissolve 20.0 mg of the substance to be examined in 1 mL of *water R* and dilute to 5.0 mL with solution A. Shake for 20 min to allow completion of the derivatisation reaction (hydrazine (impurity B) reacts with benzaldehyde to give benzaldehyde azine). Dilute

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2.0 mL of the solution to 5.0 mL with the solvent mixture.

Reference solution Dissolve 65.0 mg of *hydrazine dihydrochloride R* (impurity B) in *water R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of the solution to 100.0 mL with *water R*. Dilute 5.0 mL of this solution to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 5.0 mL with solution A. Shake for 20 min to allow completion of the derivatisation reaction (hydrazine (impurity B) reacts with benzaldehyde to give benzaldehyde azine). Dilute 2.0 mL of this solution to 5.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase 1.0 g/L solution of *sodium edetate R*, *acetonitrile R* (30:70 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 310 nm.

Injection 20 µL.

Run time 1.5 times the retention time of benzaldehyde azine.

Retention time Benzaldehyde azine = about 12 min.

System suitability Reference solution:

— *signal-to-noise ratio*: minimum 20 for the peak due to benzaldehyde azine.

Calculation of content:

— for impurity B, use the concentration of hydrazine dihydrochloride in the reference solution and the peak areas due to benzaldehyde azine.

Limit:

— *impurity B*: maximum 10 ppm.

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Solution A 6.0 g/L solution of *glacial acetic acid R*.

Buffer solution Dissolve 0.97 g of *tetrabutylammonium bromide R* and 1.87 g of *sodium laurilsulfate R* in *water for chromatography R* and dilute to 1000 mL with the same solvent. Adjust to pH 3.0 with a 9.81 g/L solution of *sulfuric acid R*.

Test solution Dissolve 25.0 mg of the substance to be examined in solution A and dilute to 50.0 mL with solution A.

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Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with solution A. Dilute 1.0 mL of this solution to 10.0 mL with solution A.

Reference solution (b) Dissolve 7.5 mg of *1-chlorophthalazine R* (impurity A) in solution A and dilute to 100 mL with solution A. Dilute 1 mL of the solution to 10 mL with solution A. Dilute 1 mL of this solution to 10 mL with the test solution.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *diisopropylcyanosilyl silica gel for chromatography R* (5 µm).

Mobile phase *acetonitrile for chromatography R*, buffer solution (23:77 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 20 µL.

Run time Twice the retention time of hydralazine.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A.

Relative retention With reference to hydralazine (retention time = about 13 min): impurity A = about 0.8.

System suitability Reference solution (b):

— *resolution*: minimum 4.0 between the peaks due to impurity A and hydralazine.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity A by 0.6;

— for each impurity, use the concentration of hydralazine hydrochloride in reference solution (a).

Limits:

— *impurity A*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo*.

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Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 80.0 mg in 25 mL of *water R*. Add 35 mL of *hydrochloric acid R* and titrate with *0.05 M potassium iodate*, determining the end-point potentiometrically (*2.2.20*) using a platinum indicator electrode.

1 mL of *0.05 M potassium iodate* is equivalent to 9.832 mg of $C_8H_9ClN_4$.

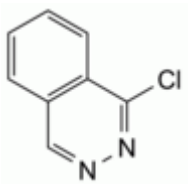
STORAGE

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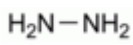
IMPURITIES

Specified impurities A, B.

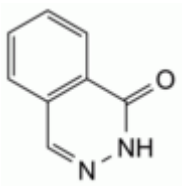
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) C, D.



A. 1-chlorophthalazine,

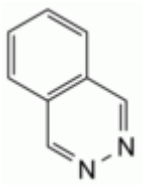


B. hydrazine,



C. phthalazin-1(2*H*)-one,

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D. phthalazine.

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Hydralazine Injection

General Notices

Action and use

Vasodilator; treatment of hypertension.

DEFINITION

Hydralazine Injection is a sterile solution of Hydralazine Hydrochloride in Water for Injections. It is prepared by dissolving Hydralazine Hydrochloride for Injection in the requisite amount of Water for Injections immediately before use. For intravenous infusion, the Hydralazine Hydrochloride for Injection should be dissolved in, and then diluted with, an appropriate volume of a suitable diluent.

The injection complies with the requirements stated under Parenteral Preparations.

STORAGE

Hydralazine Injection deteriorates on storage and should be used immediately after preparation.

HYDRALAZINE HYDROCHLORIDE FOR INJECTION

DEFINITION

Hydralazine Hydrochloride for Injection is a sterile material consisting of Hydralazine Hydrochloride with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of hydralazine hydrochloride, $C_8H_8N_4,HCl$

98.0 to 114.0% of the stated amount.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of hydralazine hydrochloride *(RS 177)*.

B. The *light absorption*, Appendix II B, in the range 230 to 350 nm of a 0.002% w/v solution exhibits four maxima, at 240, 260, 305 and 315 nm.

C. Yield the reactions characteristic of *chlorides*, Appendix VI.

TESTS

Acidity

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Acidity

pH of a 2% w/v solution, 3.5 to 4.2, Appendix V L.

Clarity of solution

A 2.0% w/v solution is not more opalescent than *reference suspension II*, Appendix IV A.

Colour of solution

A 2.0% w/v solution in 0.01M *hydrochloric acid* is not more intensely coloured than *reference solution* GY_6, Appendix IV B, Method II.

Hydrazine

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dissolve the contents of a sealed container in sufficient 0.1M *methanolic hydrochloric acid* to produce a solution containing 0.5% w/v of Hydralazine Hydrochloride. To 2 mL add 1 mL of a 2% w/v solution of *salicylaldehyde* in *methanol* and 0.1 mL of *hydrochloric acid*, centrifuge and decant the supernatant liquid.

(2) Prepare in the same manner as solution (1), but use 2 mL of a 0.00025% w/v solution of *hydrazine sulfate* in 0.1M *methanolic hydrochloric acid* in place of the solution of the material being examined.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 40 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and spray with *dimethylaminobenzaldehyde solution R1*.

MOBILE PHASE

The upper layer of the mixture obtained by shaking together 20 volumes of 13.5M *ammonia*, 20 volumes of *ethyl acetate* and 80 volumes of *hexane* and allow to stand.

LIMITS

Any spot corresponding to hydrazine in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2).

Uniformity of content

Sealed containers each containing 20 mg or less of Hydralazine Hydrochloride comply with the requirements stated under Parenteral Preparations, Powders for Injections or Infusions using the following method of analysis. Dissolve the contents of a sealed container in sufficient *water* to produce 100 mL and dilute a volume containing 1 mg of Hydralazine Hydrochloride to 100 mL with *water*. Measure the *absorbance* of the resulting solution at the maximum at 260 nm, Appendix II B. Calculate the content of $C_8H_8N_4$,HCl taking 535 as the value of A(1%, 1 cm) at the maximum at 260 nm.

ASSAY

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Determine the weight of the contents of 10 containers described in the test for *uniformity of weight*, Appendix XII C1, Powders for Parenteral Use.

Dissolve 0.1 g of the mixed contents of the 10 containers in a mixture of 25 mL of *water* and 35 mL of *hydrochloric acid* and titrate with *0.025M potassium iodate VS* determining the end point potentiometrically using a platinum indicator electrode and a calomel reference electrode. Each mL of *0.025M potassium iodate VS* is equivalent to 4.916 mg of $C_8H_8N_4$,HCl. Calculate the content of $C_8H_8N_4$,HCl in a container of average content weight.

STORAGE

The sealed container should be protected from light.

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Hydralazine Tablets

General Notices

Action and use

Vasodilator; treatment of hypertension.

DEFINITION

Hydralazine Tablets contain Hydralazine Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of hydralazine hydrochloride, $C_8H_8N_4,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Dissolve a quantity of the powdered tablets containing 0.1 g of Hydralazine Hydrochloride in 10 mL of *water*, make alkaline with 2 mL of 5M *ammonia* and extract with two 10-mL quantities of *chloroform*. Combine the chloroform extracts and evaporate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of hydralazine *(RS 176)*.

B. Shake a quantity of the powdered tablets containing 25 mg of Hydralazine Hydrochloride with 30 mL of *methanol* for 15 minutes, add sufficient *methanol* to produce 50 mL and filter. Dilute 1 volume of the filtrate to 50 volumes with *water*. The *light absorption* of the resulting solution, Appendix II B, in the range 230 to 350 nm exhibits four maxima, at 240, 260, 305 and 315 nm.

C. Extract a quantity of the powdered tablets containing 0.1 g of Hydralazine Hydrochloride with two 25-mL quantities of *methanol*, filter the combined extracts and evaporate to dryness. To 5 mL of a 1% w/v solution of the residue in *methanol* add 5 mL of a 2% w/v solution of *2-nitrobenzaldehyde* in *ethanol (96%)*. An orange precipitate is produced.

TESTS

Hydrazine

Carry out the method for *thin-layer chromatography*, Appendix III A, using a silica gel precoated plate (Merck silica gel 60 plates are suitable) and as the mobile phase the upper layer obtained by shaking together 20 volumes of 13.5M *ammonia*, 20 volumes of *ethyl acetate* and 80 volumes of *hexane* and allowing to separate. Apply separately to the plate 40 µL of each of the following solutions. For solution (1) extract a quantity of the powdered tablets containing 50 mg of Hydralazine Hydrochloride with 10 mL of 0.1M *methanolic hydrochloric acid*; to 2 mL add 1 mL of a 2% w/v solution of *salicylaldehyde* in *methanol* and 0.1 mL of *hydrochloric acid*, centrifuge and use the supernatant liquid. Prepare solution (2) in the same manner, but using 2 mL of a 0.00025% w/v solution of *hydrazine sulfate* in 0.1M *methanolic hydrochloric acid* in place of the solution of the substance being examined. After removal of the plate, allow it to dry in air and spray with

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dimethylaminobenzaldehyde solution R1. Any spot corresponding to hydrazine in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Weigh and powder 20 tablets. To a quantity of the powder containing 50 mg of Hydralazine Hydrochloride add 50 mL of *water* and shake for 20 minutes. Add 60 mL of *hydrochloric acid* and titrate with *0.025M potassium iodate VS* determining the end point potentiometrically using platinum and calomel electrodes. Each mL of *0.025M potassium iodate VS* is equivalent to 4.916 mg of $C_8H_8N_4$,HCl.

STORAGE

Hydralazine Tablets should be protected from light.

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Hydrated Aluminium Hydroxide for Adsorption

General Notices

(Ph. Eur. monograph 1664)

$[AlO(OH)],xH_2O$

Ph Eur

DEFINITION

Content

90.0 per cent to 110.0 per cent of the content of aluminium stated on the label.

NOTE: *shake the gel vigorously for at least 30 s immediately before examining*.

CHARACTERS

Appearance

White or almost white, translucent, viscous, colloidal gel. A supernatant may be formed upon standing.

Solubility

A clear or almost clear solution is obtained with alkali hydroxide solutions and mineral acids.

IDENTIFICATION

Solution S (see Tests) gives the reaction of aluminium.

To 10 mL of solution S add about 0.5 mL of *dilute hydrochloric acid R* and about 0.5 mL of *thioacetamide reagent R*. No precipitate is formed. Add dropwise 5 mL of *dilute sodium hydroxide solution R*. Allow to stand for 1 h. A gelatinous white precipitate is formed which dissolves upon addition of 5 mL of *dilute sodium hydroxide solution R*. Gradually add 5 mL of *ammonium chloride solution R* and allow to stand for 30 min. The gelatinous white precipitate is re-formed.

TESTS

Solution S

Add 1 g to 4 mL of *hydrochloric acid R*. Heat at 60 °C for 1 h, cool, dilute to 50 mL with *distilled water R* and filter if necessary.

pH (*2.2.3*)

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5.5 to 8.5.

Adsorption power

Dilute the substance to be examined with *distilled water R* to obtain an aluminium concentration of 5 mg/mL. Prepare *bovine albumin R* solutions with the following concentrations of bovine albumin: 0.5 mg/mL, 1 mg/mL, 2 mg/mL, 3 mg/mL, 5 mg/mL and 10 mg/mL. If necessary, adjust the gel and the *bovine albumin R* solutions to pH 6.0 with *dilute hydrochloric acid R* or *dilute sodium hydroxide solution R*.

For adsorption, mix 1 part of the diluted gel with 4 parts of each of the solutions of *bovine albumin R* and allow to stand at room temperature for 1 h. During this time shake the mixture vigorously at least 5 times. Centrifuge or filter through a non-protein-retaining filter. Immediately determine the protein content (*2.5.33, Method 2*) of either the supernatant or the filtrate.

It complies with the test if no bovine albumin is detectable in the supernatant or filtrate of the 2 mg/mL *bovine albumin R* solution (maximum level of adsorption) and in the supernatant or filtrate of *bovine albumin R* solutions of lower concentrations. Solutions containing 3 mg/mL, 5 mg/mL and 10 mg/mL *bovine albumin R* may show bovine albumin in the supernatant or filtrate, proportional to the amount of bovine albumin in the solutions.

Sedimentation

If necessary, adjust the substance to be examined to pH 6.0 using *dilute hydrochloric acid R* or *dilute sodium hydroxide solution R*. Dilute with *distilled water R* to obtain an aluminium concentration of approximately 5 mg/mL. If the aluminium content of the substance to be examined is lower than 5 mg/mL, adjust to pH 6.0 and dilute with a 9 g/L solution of *sodium chloride R* to obtain an aluminium concentration of about 1 mg/mL. After shaking for at least 30 s, place 25 mL of the preparation in a 25 mL graduated cylinder and allow to stand for 24 h.

It complies with the test if the volume of the clear supernatant is less than 5 mL for the gel with an aluminium content of about 5 mg/mL.

It complies with the test if the volume of the clear supernatant is less than 20 mL for the gel with an aluminium content of about 1 mg/mL.

Chlorides (*2.4.4*)

Maximum 0.33 per cent.

Dissolve 0.5 g in 10 mL of *dilute nitric acid R* and dilute to 500 mL with *water R*.

Nitrates

Maximum 100 ppm.

Place 5 g in a test-tube immersed in ice-water, add 0.4 mL of a 100 g/L solution of *potassium chloride R*, 0.1 mL of *diphenylamine solution R* and, dropwise with shaking, 5 mL of *sulfuric acid R*. Transfer the tube to a water-bath at 50 °C. After 15 min, any blue colour in the solution is not more intense than that in a standard prepared at the same time and in the same manner using 5 mL of *nitrate standard solution (100 ppm NO_3) R*.

Sulfates (*2.4.13*)

Maximum 0.5 per cent.

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Dilute 2 mL of solution S to 20 mL with *water R*.

Ammonium (*2.4.1, Method B*)

Maximum 50 ppm, determined on 1.0 g.

Prepare the standard using 0.5 mL of *ammonium standard solution (100 ppm NH_4) R*.

Arsenic (*2.4.2, Method A*)

Maximum 1 ppm, determined on 1 g.

Iron (*2.4.9*)

Maximum 15 ppm, determined on 0.67 g.

Bacterial endotoxins (*2.6.14*)

Less than 5 IU of endotoxin per milligram of aluminium, if intended for use in the manufacture of an adsorbed product without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Dissolve 2.50 g in 10 mL of *hydrochloric acid R*, heating for 30 min at 100 °C on a water-bath. Cool and dilute to 20 mL with *water R*. To 10 mL of the solution, add *concentrated ammonia R* until a precipitate is obtained. Add the smallest quantity of *hydrochloric acid R* needed to dissolve the precipitate and dilute to 20 mL with *water R*. Carry out the complexometric titration of aluminium (*2.5.11*). Carry out a blank titration.

STORAGE

At a temperature not exceeding 30 °C. Do not allow to freeze. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

LABELLING

The label states the declared content of aluminium.

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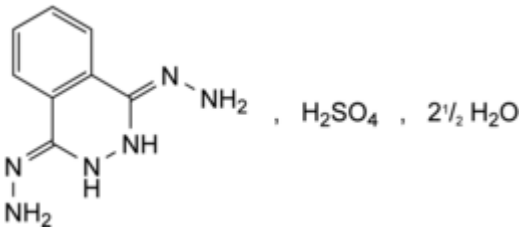
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Hydrated Dihydralazine Sulfate

General Notices

(Ph. Eur. monograph 1310)



$C_8H_{12}N_6O_4S,2½H_2O$ 333.3

Dihydralazine sulfate, anhydrous *7327-87-9*

Action and use

Vasodilator.

Ph Eur

DEFINITION

(Phthalazine-1,4(2*H*,3*H*)-diylidene)dihydrazine sulfate 2.5-hydrate.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or slightly yellow, crystalline powder.

Solubility

Slightly soluble in water, practically insoluble in anhydrous ethanol. It dissolves in dilute mineral acids.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *Ph. Eur. reference spectrum of dihydralazine sulfate hydrated*.

B. Dissolve about 50 mg in 5 mL of *dilute hydrochloric acid R*. The solution gives reaction (a) of sulfates (*2.3.1*).

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

Dissolve 0.20 g in *dilute nitric acid R* and dilute to 10 mL with the same acid.

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution Dissolve 50.0 mg of the substance to be examined in a 6 g/L solution of *glacial acetic acid R* and dilute to 50.0 mL with the same solution.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase containing 0.5 g/L of *sodium edetate R*. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase containing 0.5 g/L of *sodium edetate R*.

Reference solution (b) Dilute 1.0 mL of the test solution to 50.0 mL with the mobile phase containing 0.5 g/L of *sodium edetate R*.

Reference solution (c) Dissolve 5 mg of *dihydralazine for system suitability CRS* in a 6 g/L solution of *glacial acetic acid R* and dilute to 5 mL with the same solution.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped cyanosilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 22 volumes of *acetonitrile for chromatography R* and 78 volumes of a solution containing 1.44 g/L of *sodium laurilsulfate R* and 0.75 g/L of *tetrabutylammonium bromide R*, then adjust to pH 3.0 with *dilute sulfuric acid R1*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 20 µL.

Run time Twice the retention time of dihydralazine.

Relative retention With reference to dihydralazine: impurity A = about 0.8.

System suitability Reference solution (c):

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— the peaks due to impurity A and dihydralazine are baseline separated as in the chromatogram supplied with *dihydralazine for system suitability CRS*.

Limits:

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (2 per cent);

— *impurity C*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *sum of impurities other than A*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.01 per cent).

Impurity B

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Test solution Dissolve 40.0 mg of *hydrazine sulfate R* (impurity B) in *water R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of the solution to 25.0 mL with *water R*. To 0.50 mL of this solution, add 0.200 g of the substance to be examined and dissolve in 6 mL of *dilute hydrochloric acid R*, then dilute to 10.0 mL with *water R*. In a centrifuge tube with a ground-glass stopper, place immediately 0.50 mL of this solution and 2.0 mL of a 60 g/L solution of *benzaldehyde R* in a mixture of equal volumes of *methanol R* and *water R*. Shake for 90 s. Add 1.0 mL of *water R* and 5.0 mL of *heptane R*. Shake for 1 min and centrifuge. Use the upper layer.

Reference solution Dissolve 40.0 mg of *hydrazine sulfate R* (impurity B) in *water R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of the solution to 25.0 mL with *water R*. To 0.50 mL of this solution, add 6 mL of *dilute hydrochloric acid R* and dilute to 10.0 mL with *water R*. In a centrifuge tube with a ground-glass stopper, place 0.50 mL of this solution and 2.0 mL of a 60 g/L solution of *benzaldehyde R* in a mixture of equal volumes of *methanol R* and *water R*. Shake for 90 s. Add 1.0 mL of *water R* and 5.0 mL of *heptane R*. Shake for 1 min and centrifuge. Use the upper layer.

Blank solution Prepare in the same manner as for the reference solution but replacing the 0.50 mL of hydrazine sulfate solution by 0.50 mL of *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase 0.3 g/L solution of *sodium edetate R*, *acetonitrile R* (30:70 *V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 305 nm.

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Injection 20 µL.

Relative retention With reference to benzaldehyde: benzaldehyde azine (benzalazine) corresponding to impurity B = about 1.8.

Limit:

— *impurity B*: the area of the peak due to benzaldehyde azine is not greater than twice the area of the corresponding peak in the chromatogram obtained with the reference solution (10 ppm).

Iron (*2.4.9*)

Maximum 20 ppm.

To the residue obtained in the test for sulfated ash add 0.2 mL of *sulfuric acid R* and heat carefully until the acid is almost completely eliminated. Allow to cool and dissolve the residue with heating in 5.5 mL of *hydrochloric acid R1*. Filter the hot solution through a filter previously washed 3 times with *dilute hydrochloric acid R*. Wash the crucible and the filter with 5 mL of *water R*. Combine the filtrate and the washings and neutralise with about 3.5 mL of *strong sodium hydroxide solution R*. Adjust to pH 3-4 with *acetic acid R* and dilute to 20 mL with *water R*. Prepare the standard with 5 mL of *iron standard solution (2 ppm Fe) R* and 5 mL of *water R*.

Loss on drying (*2.2.32*)

13.0 per cent to 15.0 per cent, determined on 1.000 g by drying *in vacuo* at 50 °C at a pressure not exceeding 0.7 kPa for 5 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

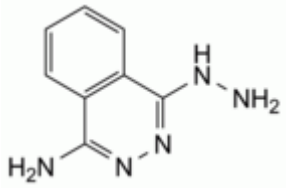
ASSAY

Dissolve 60.0 mg in 25 mL of *water R*. Add 35 mL of *hydrochloric acid R* and titrate slowly with *0.05 M potassium iodate*, determining the end-point potentiometrically (*2.2.20*), using a suitable reference electrode and a platinum indicator electrode.

1 mL of *0.05 M potassium iodate* is equivalent to 7.208 mg of $C_8H_{12}N_6O_4S$.

IMPURITIES

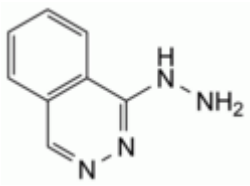
Specified impurities *A, B, C.*



A. 4-hydrazinophthalazin-1-amine,

B. H_2N-NH_2: hydrazine,

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C. (phthalazin-1-yl)hydrazine (hydralazine).

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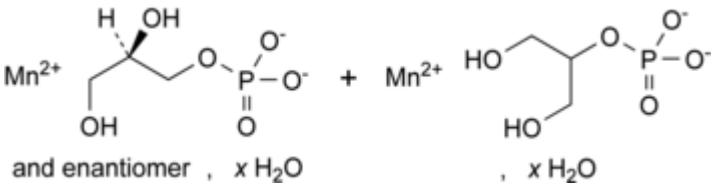
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Hydrated Manganese Glycerophosphate

General Notices

(Ph. Eur. monograph 2163)



$C_3H_7MnO_6P,xH_2O$ 225.0 (anhydrous substance)

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DEFINITION

Mixture of variable proportions of hydrated manganese(II) (2*RS*)-2,3-dihydroxypropyl phosphate and hydrated manganese(II) 2-hydroxy-1-(hydroxymethyl)ethyl phosphate.

Content

97.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or pale pink, hygroscopic powder.

Solubility

Practically insoluble in water and in ethanol (96 per cent). It is freely soluble in dilute mineral acids.

IDENTIFICATION

A. Mix 1 g with 1 g of *potassium hydrogen sulfate R* in a test tube fitted with a delivery tube. Heat strongly and direct the white vapour towards a piece of filter paper impregnated with a freshly prepared 10 g/L solution of *sodium nitroprusside R*. The filter paper develops a blue colour in contact with *piperidine R*.

B. Disperse 50 mg in 5 mL of *water R*. Add 0.5 mL of *ammonium sulfide solution R*. A pale pink precipitate is formed that dissolves on the addition of 1 mL of *acetic acid R*.

C. Ignite 0.1 g in a crucible. Take up the residue with 5 mL of *nitric acid R* and heat on a water-bath for 1 min. Filter. The filtrate gives reaction (b) of phosphates (*2.3.1*).

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TESTS

Solution S

Dissolve 5.0 g in 20 mL of *dilute hydrochloric acid R*. Filter if necessary. Add *dilute ammonia R1* until a precipitate is formed. Dissolve the precipitate by adding the minimum quantity needed of *dilute hydrochloric acid R* and dilute to 100 mL with *distilled water R*.

Glycerol and ethanol (96 per cent)-soluble substances

Maximum 1.0 per cent.

Shake 1.00 g with 25 mL of *ethanol (96 per cent) R* for 1 min. Filter. Evaporate the filtrate to dryness on a water-bath and dry the residue at 70 °C for 1 h. The residue weighs a maximum of 10 mg.

Chlorides (*2.4.4*)

Maximum 0.15 per cent.

Dissolve 0.22 g in a mixture of 1 mL of *nitric acid R* and 10 mL of *water R* and dilute to 100 mL with *water R*.

Phosphates (*2.4.11*)

Maximum 0.3 per cent.

Dilute 1.0 mL of solution S to 100.0 mL with *water R*. To 10 mL of this solution add 140 mL of *water R*.

Sulfates (*2.4.13*)

Maximum 0.2 per cent.

Dilute 5 mL of solution S to 50 mL with *distilled water R*.

Iron (*2.4.9*)

Maximum 50 ppm.

Dilute 4 mL of solution S to 10 mL with *water R*.

Loss on drying (*2.2.32*)

Maximum 12.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

ASSAY

To 0.200 g add 1.5 mL of *1 M hydrochloric acid*, 50 mL of *water R*, 10 mg of *ascorbic acid R* and 20 mL of *ammonium chloride buffer solution pH 10.0 R*. Stir until dissolution. Immediately add 0.3 mL of a 2 g/L solution of *mordant black 11 R* in *triethanolamine R* and titrate with *0.1 M sodium edetate* until the colour changes from violet to pure blue.

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1 mL of *0.1 M sodium edetate* is equivalent to 22.50 mg of $C_3H_7MnO_6P$.

STORAGE

In an airtight container.

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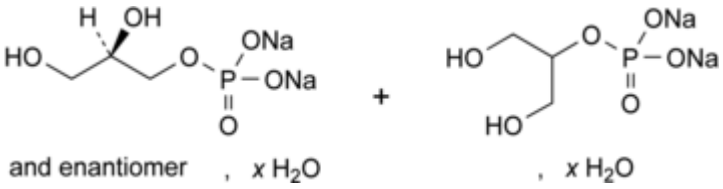
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Hydrated Sodium Glycerophosphate

General Notices

(Ph. Eur. monograph 1995)



$C_3H_7Na_2O_6P,xH_2O$ 216.0 (anhydrous substance)

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DEFINITION

Mixture of variable proportions of hydrated disodium (2*RS*)-2,3-dihydroxypropyl phosphate and hydrated disodium 2-hydroxy-1-(hydroxymethyl)ethyl phosphate. The mixture may contain various amounts of other glycerophosphate esters.

Content

98.0 per cent to 105.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or crystals.

Solubility

Freely soluble in water, practically insoluble in acetone and in ethanol (96 per cent).

IDENTIFICATION

A. Solution S (see Tests) gives reaction (a) of sodium (2.3.1).

B. To 0.1 g add 5 mL of *dilute nitric acid R*. Heat to boiling and boil for 1 min. Cool. The solution gives reaction (b) of phosphates (2.3.1).

C. In a test-tube fitted with a glass tube, mix 0.1 g with 5 g of *potassium hydrogen sulfate R*. Heat strongly and direct the white vapour into 5 mL of *decolorised fuchsin solution R*. A violet-red colour develops which becomes violet upon heating for 30 min on a water-bath.

TESTS

Solution S

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Solution S

Dissolve 10.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is not more opalescent than reference suspension II (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

Alkalinity

To 10 mL of solution S add 0.2 mL of *phenolphthalein solution R*. Not more than 1.0 mL of *0.1 M hydrochloric acid* is required to change the colour of the indicator (n_2).

Glycerol and ethanol (96 per cent)-soluble substances

Maximum 1.0 per cent.

Shake 1.000 g with 25 mL of *ethanol (96 per cent) R* for 10 min. Filter. Evaporate the filtrate on a water-bath and dry the residue at 70 °C for 1 h. The residue weighs not more than 10 mg.

Chlorides (*2.4.4*)

Maximum 200 ppm.

Dilute 2.5 mL of solution S to 15 mL with *water R*.

Phosphates (*2.4.11*)

Maximum 0.1 per cent.

Dilute 1 mL of solution S to 10 mL with *water R*. Dilute 1 mL of this solution to 100 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 500 ppm.

Dilute 3 mL of solution S to 15 mL with *water R*.

Calcium

Maximum 100 ppm, if intended for use in the manufacture of parenteral preparations.

Inductively coupled plasma-atomic emission spectrometry (*2.2.57*).

Test solution Dissolve 0.50 g in a 1 per cent *V/V* solution of *nitric acid R* and dilute to 50.0 mL with the same solution.

Reference solutions Prepare the reference solutions using *calcium standard solution (100 ppm Ca) R*, diluting with a 1 per cent *V/V* solution of *nitric acid R*.

Wavelength 396.8 nm.

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Iron (*2.4.9*)

Maximum 20 ppm.

Dilute 5 mL of solution S to 10 mL with *water R*.

Water (*2.5.12*)

25.0 per cent to 35.0 per cent, determined on 0.100 g.

ASSAY

Dissolve 0.250 g in 30 mL of *water R*. Titrate with *0.05 M sulfuric acid*, determining the end-point potentiometrically (*2.2.20*), (n_1).

Calculate the percentage content of sodium glycerophosphate (anhydrous substance) using the following expression:

$$\frac{216.0\left(n_1 - \frac{n_2}{4}\right)}{m(100 - a)}$$

a	=	percentage content of water;
n_1	=	volume of *0.05 M sulfuric acid* used in the assay, in millilitres;
n_2	=	volume of *0.1 M hydrochloric acid* used in the test for alkalinity, in millilitres;
m	=	mass of the substance to be examined, in grams.

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Hydrochloric Acid

General Notices

(Concentrated Hydrochloric Acid, Ph. Eur. monograph 0002)

HCl 36.46 *7647-01-0*

Preparation

Dilute Hydrochloric Acid

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DEFINITION

Content

35.0 per cent *m/m* to 39.0 per cent *m/m*.

CHARACTERS

Appearance

Clear, colourless, fuming liquid.

Solubility

Miscible with water.

Relative density

About 1.18.

IDENTIFICATION

A. Dilute with *water R*. The solution is strongly acid (*2.2.4*).

B. It gives reaction (a) of chlorides (*2.3.1*).

C. It complies with the limits of the assay.

TESTS

Appearance of solution

To 2 mL add 8 mL of *water R*. The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

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Free chlorine

Maximum 4 ppm.

To 15 mL add 100 mL of *carbon dioxide-free water R*, 1 mL of a 100 g/L solution of *potassium iodide R* and 0.5 mL of *iodide-free starch solution R*. Allow to stand in the dark for 2 min. Any blue colour disappears on the addition of 0.2 mL of *0.01 M sodium thiosulfate*.

Sulfates (*2.4.13*)

Maximum 20 ppm.

To 6.4 mL add 10 mg of *sodium hydrogen carbonate R* and evaporate to dryness on a water-bath. Dissolve the residue in 15 mL of *distilled water R*.

Residue on evaporation

Maximum 0.01 per cent.

Evaporate 100.0 g to dryness on a water-bath or using a rotary evaporator and dry the residue at 100-105 °C. The residue weighs a maximum of 10 mg.

ASSAY

Weigh accurately a ground-glass-stoppered flask containing 30 mL of *water R*. Introduce 1.5 mL of the acid to be examined and weigh again. Titrate with *1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *1 M sodium hydroxide* is equivalent to 36.46 mg of HCl.

STORAGE

In a stoppered container made of glass or another inert material, at a temperature not exceeding 30 °C.

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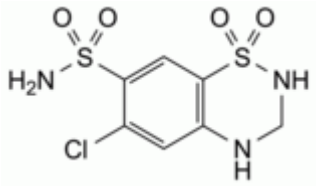
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Hydrochlorothiazide

General Notices

(Ph. Eur. monograph 0394)



$C_7H_8ClN_3O_4S_2$ 297.7 *58-93-5*

Action and use

Thiazide diuretic.

Preparations

Co-amilozide Oral Solution

Co-amilozide Tablets

Co-triamterzide Tablets

Hydrochlorothiazide Tablets

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DEFINITION

6-Chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

Content

97.5 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

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Very slightly soluble in water, soluble in acetone, sparingly soluble in ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides.

It shows polymorphism (5.9).

IDENTIFICATION

First identification: B.

Second identification: A, C, D.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 50.0 mg in 10 mL of *0.1 M sodium hydroxide* and dilute to 100.0 mL with *water R*. Dilute 2.0 mL of this solution to 100.0 mL with *0.01 M sodium hydroxide*.

Spectral range 250-350 nm.

Absorption maxima At 273 nm and 323 nm.

Absorbance ratio A_{273}/A_{323} = 5.4 to 5.7.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *hydrochlorothiazide CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *ethanol R1*, evaporate to dryness and record new spectra using the residues.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 50 mg of the substance to be examined in *acetone R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 50 mg of *hydrochlorothiazide CRS* in *acetone R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 25 mg of *chlorothiazide R* in reference solution (a) and dilute to 5 mL with reference solution (a).

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *ethyl acetate R*.

Application 2 µL.

Development Over 1/2 of the plate.

Drying In a current of air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (b):

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— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

D. Gently heat about 1 mg with 2 mL of a freshly prepared 0.5 g/L solution of *chromotropic acid, sodium salt R* in a cooled mixture of 35 volumes of *water R* and 65 volumes of *sulfuric acid R*. A violet colour develops.

TESTS

Acidity or alkalinity

Shake 0.5 g of the powdered substance to be examined with 25 mL of *water R* for 2 min and filter. To 10 mL of the filtrate, add 0.2 mL of *0.01 M sodium hydroxide* and 0.15 mL of *methyl red solution R*. The solution is yellow. Not more than 0.4 mL of *0.01 M hydrochloric acid* is required to change the colour of the indicator to red.

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture Dilute 50.0 mL of a mixture of equal volumes of *acetonitrile R1* and *methanol R2* to 200.0 mL with *phosphate buffer solution pH 3.2 R1*.

Test solution (a) Dissolve 30.0 mg of the substance to be examined in 5 mL of a mixture of equal volumes of *acetonitrile R1* and *methanol R2*, using sonication if necessary, and dilute to 20.0 mL with *phosphate buffer solution pH 3.2 R1*.

Test solution (b) Dilute 1.0 mL of test solution (a) to 20.0 mL with *phosphate buffer solution pH 3.2 R1*.

Reference solution (a) Dissolve 3 mg of *chlorothiazide CRS* (impurity A) and 3 mg of *hydrochlorothiazide CRS* in 5 mL of a mixture of equal volumes of *acetonitrile R1* and *methanol R2*, using sonication if necessary, and dilute to 20.0 mL with *phosphate buffer solution pH 3.2 R1*. Dilute 5.0 mL of this solution to 100.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 30.0 mg of *hydrochlorothiazide CRS* in 5 mL of a mixture of equal volumes of *acetonitrile R1* and *methanol R2*, using sonication if necessary, and dilute to 20.0 mL with *phosphate buffer solution pH 3.2 R1*. Dilute 1.0 mL of this solution to 20.0 mL with *phosphate buffer solution pH 3.2 R1*.

Reference solution (d) Dissolve 3 mg of *hydrochlorothiazide for peak identification CRS* (containing impurities B and C) in 0.5 mL of a mixture of equal volumes of *acetonitrile R1* and *methanol R2*, using sonication if necessary, and dilute to 2.0 mL with *phosphate buffer solution pH 3.2 R1*.

Column:

— *size*: *l* = 0.1 m, Ø = 4.6 mm;

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— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase:

— *mobile phase A*: to 940 mL of *phosphate buffer solution pH 3.2 R1* add 60.0 mL of *methanol R2* and 10.0 mL of *tetrahydrofuran R* and mix;

— *mobile phase B*: to a mixture of 500 mL of *methanol R2* and 500 mL of *phosphate buffer solution pH 3.2 R1* add 50.0 mL of *tetrahydrofuran R* and mix;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 17	100 → 55	0 → 45
17 - 30	55	45

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 224 nm.

Injection 10 µL of test solution (a) and reference solutions (a), (b) and (d).

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity A; use the chromatogram supplied with *hydrochlorothiazide for peak identification CRS* and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities B and C.

Relative retention With reference to hydrochlorothiazide (retention time = about 8 min): impurity B = about 0.7; impurity A = about 0.9; impurity C = about 2.8.

System suitability Reference solution (a):

— *resolution*: minimum 2.5 between the peaks due to impurity A and hydrochlorothiazide.

Limits:

— *impurities A, B, C*: for each impurity, not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Chlorides (*2.4.4*)

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Maximum 100 ppm.

Dissolve 1.0 g in 25 mL of *acetone R* and dilute to 30 mL with *water R*. Prepare the standard using 5 mL of *acetone R* containing 15 per cent *V/V* of *water R* and 10 mL of *chloride standard solution (5 ppm Cl) R*.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Mobile phase:

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 4	80	20
4 - 10	80 → 20	20 → 80

Flow rate 1.6 mL/min.

Injection Test solution (b) and reference solutions (a) and (c).

Relative retention With reference to hydrochlorothiazide (retention time = about 2.2 min): impurity A = about 0.9.

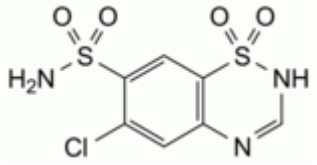
System suitability Reference solution (a):

— *resolution*: minimum 2.0 between the peaks due to impurity A and hydrochlorothiazide.

Calculate the percentage content of $C_7H_8ClN_3O_4S_2$ taking into account the assigned content of *hydrochlorothiazide CRS*.

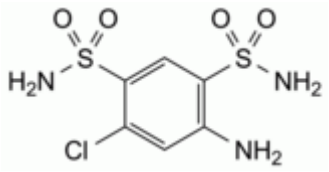
IMPURITIES

Specified impurities *A, B, C.*

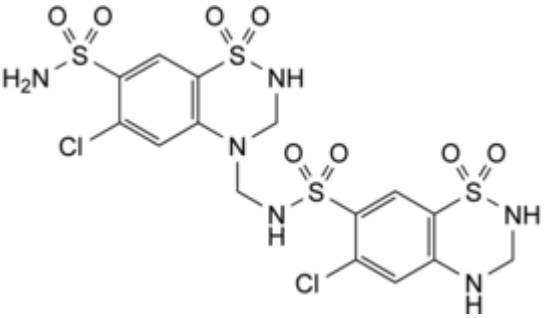


A. 6-chloro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (chlorothiazide),

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B. 4-amino-6-chlorobenzene-1,3-disulfonamide (salamide),



C. 6-chloro-*N*-[(6-chloro-7-sulfamoyl-2,3-dihydro-4*H*-1,2,4-benzothiadiazin-4-yl 1,1-dioxide)methyl]-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

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Hydrochlorothiazide Tablets

General Notices

Action and use

Thiazide diuretic.

DEFINITION

Hydrochlorothiazide Tablets contain Hydrochlorothiazide.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of hydrochlorothiazide, $C_7H_8ClN_3O_4S_2$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Triturate a quantity of the powdered tablets containing 10 mg of Hydrochlorothiazide with 10 mL of *acetone* and filter.

(2) 0.1% w/v of *hydrochlorothiazide BPCRS* in *acetone*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel GF_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in a current of air, examine under *ultraviolet light (254 nm)* and then treat the plate by *Method I* and examine again.

MOBILE PHASE

ethyl acetate.

CONFIRMATION

By each method of visualisation the principal spot in the chromatogram obtained with solution (1) corresponds in colour and intensity to that in the chromatogram obtained with solution (2).

TESTS

Related substances

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Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 50 mg of Hydrochlorothiazide with 25 mL of a mixture of equal volumes of *acetonitrile* and *methanol* and dilute to 100 mL with *phosphate buffer solution pH 3.2 R1*. Filter through a glass-fibre filter (Whatman 0.45µ GD/X is suitable).

(2) Dilute 1 volume of solution (1) to 100 volumes with a mixture containing 1 volume of *methanol*, 1 volume of *acetonitrile* and 2 volumes of *phosphate buffer solution pH 3.2 R1*.

(3) Dissolve, with the aid of ultrasound, 15 mg each of *hydrochlorothiazide BPCRS* and *chlorothiazide BPCRS* in 25 mL of a mixture of equal volumes of *acetonitrile* and *methanol* and dilute to 100 mL with *phosphate buffer solution pH 3.2 R1*. Dilute 5 volumes of this solution to 100 volumes with the same solvent mixture.

(4) Dilute 1 volume of solution (2) to 10 volumes with a mixture containing 1 volume of *methanol*, 1 volume of *acetonitrile* and 2 volumes of *phosphate buffer solution pH 3.2 R1*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (3 µm) (Phenosphere ODS 3µ or Microsorb ODS 3µ is suitable).

(b) Use gradient elution and the mobile phases described below.

(c) Use a flow rate of 0.8 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 224 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE A

10 volumes of *tetrahydrofuran*, 60 volumes of *methanol* and 940 volumes of *phosphate buffer solution pH 3.2 R1*.

MOBILE PHASE B

50 volumes of *tetrahydrofuran*, 500 volumes of *methanol* and 500 volumes of *phosphate buffer solution pH 3.2 R1*.

Equilibrate the column for at least 20 minutes with mobile phase A.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-17	100→55	0→45	linear gradient
17-30	55	45	isocratic
30-35	55→100	45→0	linear gradient
35-50	100	0	re-equilibration

SYSTEM SUITABILITY

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The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks corresponding to chlorothiazide and hydrochlorothiazide is at least 2.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the sum of the areas of any *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (2.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Weigh and powder 20 tablets. To a quantity of the powder containing 30 mg of Hydrochlorothiazide add 50 mL of 0.1M *sodium hydroxide*, shake for 20 minutes and dilute to 100 mL with 0.1M *sodium hydroxide*. Mix, filter, dilute 5 mL of the filtrate to 100 mL with *water* and measure the *absorbance* of the resulting solution at the maximum at 273 nm, Appendix II B. Calculate the content of $C_7H_8ClN_3O_4S_2$ taking 520 as the value of A(1%, 1 cm) at the maximum at 273 nm.

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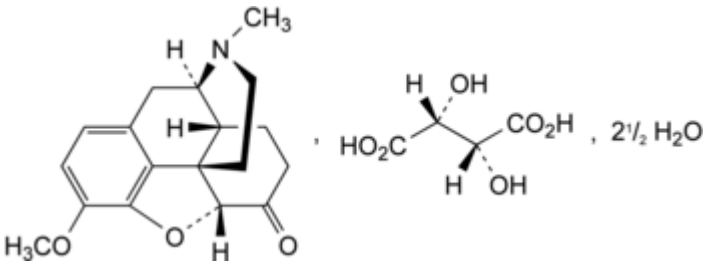
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Hydrocodone Hydrogen Tartrate Hydrate

General Notices

(Hydrocodone Hydrogen Tartrate 2.5-Hydrate, Ph. Eur. monograph 1784)



$C_{22}H_{27}NO_9,2.5H_2O$ 494.5

Action and use

Opioid receptor agonist; antitussive.

Ph Eur

DEFINITION

4,5α-Epoxy-3-methoxy-17-methylmorphinan-6-one hydrogen (2*R*,3*R*)-2,3-dihydroxybutanedioate 2.5-hydrate.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, hygroscopic, crystalline powder.

Solubility

Freely soluble or soluble in water, sparingly soluble in ethanol (96 per cent), practically insoluble in cyclohexane.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *hydrocodone hydrogen tartrate 2.5-hydrate CRS*.

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If the spectra obtained in the solid state show differences, dry the substance to be examined and the reference substance at 105 °C and record new spectra using the residues.

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_5 (*2.2.2, Method II*).

Dissolve 0.5 g in *water R* and dilute to 10 mL with the same solvent.

pH (*2.2.3*)

3.2 to 3.8.

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

Specific optical rotation (*2.2.7*)

-87 to -91 (anhydrous substance).

Dissolve 2.50 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.100 g of the substance to be examined in mobile phase A and dilute to 10.0 mL with mobile phase A.

Reference solution (a) Dissolve 5 mg of *oxycodone hydrochloride CRS* (impurity D) in mobile phase A, add 0.5 mL of the test solution and dilute to 5.0 mL with mobile phase A.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (c) Dissolve 20 mg of *benzophenone CRS* (impurity H) in 50.0 mL of *methanol R*. Dilute 1.0 mL of this solution to 20.0 mL with mobile phase A.

Reference solution (d) Dissolve the contents of a vial of *hydrocodone for peak identification CRS* (containing impurities B, C, D, E, F and I) in 1.0 mL of mobile phase A.

Reference solution (e) Dissolve 5 mg of *morphine sulfate CRS* (impurity A) in 5 mL of mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

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— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: dissolve 1.08 g of *sodium octanesulfonate R* in *water R*, adjust to pH 2.0 with *phosphoric acid R* and dilute to 1000 mL with *water R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	80	20
15 - 30	80 → 70	20 → 30
30 - 40	70 → 40	30 → 60
40 - 42	40	60

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 283 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *hydrocodone for peak identification CRS* and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities B, C, D, E, F and I; use the chromatogram obtained with reference solution (e) to identify the peak due to impurity A.

Relative retention With reference to hydrocodone (retention time = about 14 min): impurity A = about 0.3; impurity K = about 0.43; impurity B = about 0.57; impurity C = about 0.61; impurity D = about 0.9; impurity E = about 1.1; impurity F = about 1.5; impurity I = about 2.0; impurity H = about 2.9.

System suitability Reference solution (a):

— *resolution*: minimum 3.0 between the peaks due to impurity D and hydrocodone.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity I by 0.2;

— *impurity I*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent);

— *impurity H*: not more than 0.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.1 per cent);

— *impurities A, B, C, D, E, F, K*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

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— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (2.5.12)

7.0 per cent to 12.0 per cent, determined on 0.100 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.350 g in 60 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 44.95 mg of $C_{22}H_{27}NO_9$.

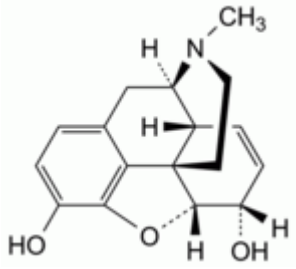
STORAGE

In an airtight container, protected from light.

IMPURITIES

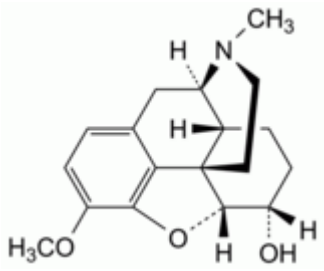
Specified impurities *A, B, C, D, E, F, H, I, K.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *G, J.*

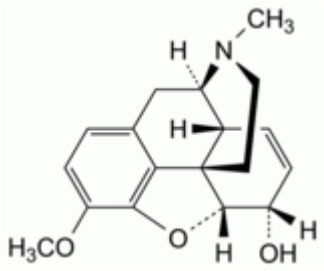


A. morphine,

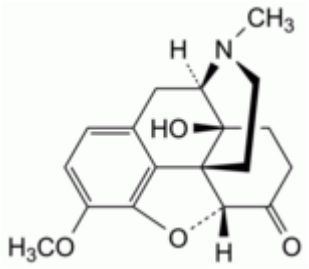
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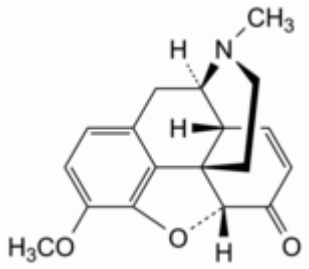
B. 4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol (dihydrocodeine),



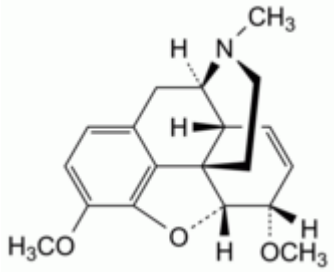
C. codeine,



D. 4,5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one (oxycodone),

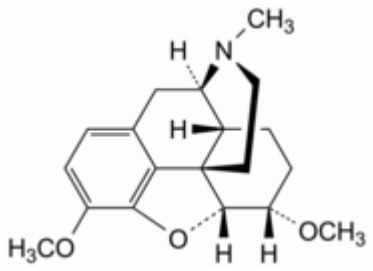


E. 7,8-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one (codeinone),

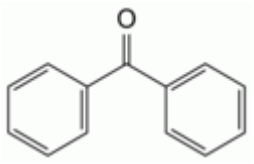


F. 7,8-didehydro-4,5α-epoxy-3,6α-dimethoxy-17-methylmorphinan (methylcodeine),

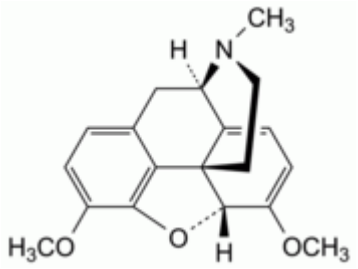
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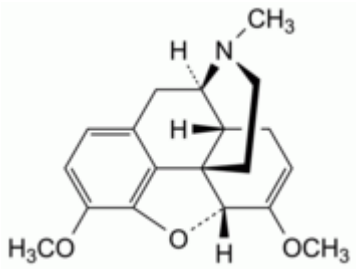
G. 4,5α-epoxy-3,6α-dimethoxy-17-methylmorphinan (tetrahydrothebaine),



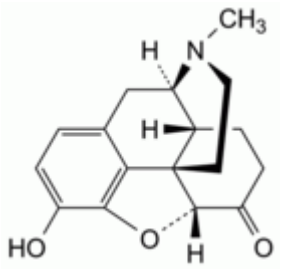
H. diphenylmethanone (benzophenone),



I. 6,7,8,14-tetradehydro-4,5α-epoxy-3,6-dimethoxy-17-methylmorphinan (thebaine),



J. 6,7-didehydro-4,5α-epoxy-3,6-dimethoxy-17-methylmorphinan,



K. 4,5α-epoxy-3-hydroxy-17-methylmorphinan-6-one.

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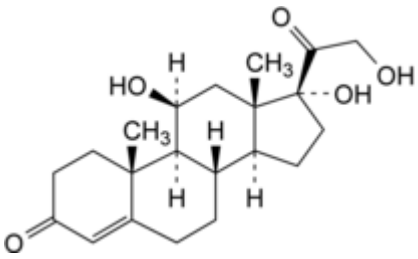
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Hydrocortisone

General Notices

(Ph. Eur. monograph 0335)



$C_{21}H_{30}O_5$ 362.5 *50-23-7*

Action and use

Corticosteroid.

Preparations

Hydrocortisone Cream

Hydrocortisone and Clioquinol Cream

Hydrocortisone and Neomycin Cream

Hydrocortisone Ointment

Hydrocortisone and Clioquinol Ointment

Miconazole and Hydrocortisone Cream

Miconazole and Hydrocortisone Ointment

Tretinoin, Hydrocortisone and Hydroquinone Cream

Ph Eur

DEFINITION

11β,17,21-Trihydroxypregn-4-ene-3,20-dione.

Content

97.0 per cent to 103.0 per cent (dried substance).

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CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, sparingly soluble in acetone and in ethanol (96 per cent), slightly soluble in methylene chloride.

It shows polymorphism (5.9).

IDENTIFICATION

First identification: A, B.

Second identification: C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *hydrocortisone CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *acetone R*, evaporate to dryness on a water-bath and record new spectra using the residues.

B. Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (c).

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (c).

C. Thin-layer chromatography (2.2.27).

Solution A Dissolve 25 mg of the substance to be examined in *methanol R* and dilute to 5 mL with the same solvent.

Solution B Dissolve 25 mg of *hydrocortisone CRS* in *methanol R* and dilute to 5 mL with the same solvent.

Test solution (a) Dilute 2 mL of solution A to 10 mL with *methylene chloride R*.

Test solution (b) Transfer 0.4 mL of solution A to a glass tube 100 mm long and 20 mm in diameter and fitted with a ground-glass stopper or a polytetrafluoroethylene cap. Evaporate the solvent with gentle heating under a stream of *nitrogen R*. Add 2 mL of a 15 per cent *V/V* solution of *glacial acetic acid R* and 50 mg of *sodium bismuthate R*. Stopper the tube and shake the suspension in a mechanical shaker, protected from light, for 1 h. Add 2 mL of a 15 per cent *V/V* solution of *glacial acetic acid R* and filter into a 50 mL separating funnel, washing the filter with 2 quantities, each of 5 mL, of *water R*. Shake the clear filtrate with 10 mL of *methylene chloride R*. Wash the organic layer with 5 mL of *1 M sodium hydroxide* and then with 2 quantities, each of 5 mL, of *water R*. Dry over *anhydrous sodium sulfate R*.

Reference solution (a) Dilute 2 mL of solution B to 10 mL with *methylene chloride R*.

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Reference solution (b) Transfer 0.4 mL of solution B to a glass tube 100 mm long and 20 mm in diameter and fitted with a ground-glass stopper or a polytetrafluoroethylene cap. Evaporate the solvent with gentle heating under a stream of *nitrogen R*. Add 2 mL of a 15 per cent *V/V* solution of *glacial acetic acid R* and 50 mg of *sodium bismuthate R*. Stopper the tube and shake the suspension in a mechanical shaker, protected from light, for 1 h. Add 2 mL of a 15 per cent *V/V* solution of *glacial acetic acid R* and filter into a 50 mL separating funnel, washing the filter with 2 quantities, each of 5 mL, of *water R*. Shake the clear filtrate with 10 mL of *methylene chloride R*. Wash the organic layer with 5 mL of *1 M sodium hydroxide* and then with 2 quantities, each of 5 mL, of *water R*. Dry over *anhydrous sodium sulfate R*.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase A Add a mixture of 1.2 volumes of *water R* and 8 volumes of *methanol R* to a mixture of 15 volumes of *ether R* and 77 volumes of *methylene chloride R*.

Mobile phase B *butanol R* saturated with *water R*, *toluene R*, *ether R* (5:15:80 *V/V/V*).

Application 5 µL of test solution (a) and reference solution (a), 25 µL of test solution (b) and reference solution (b), applying the latter 2 in small quantities to obtain small spots.

Development Over a path of 15 cm with mobile phase A, and then over a path of 15 cm with mobile phase B.

Drying In air.

Detection A Examine in ultraviolet light at 254 nm.

Results A The principal spot in each of the chromatograms obtained with test solutions (a) and (b) is similar in position and size to the principal spot in the chromatogram obtained with the corresponding reference solution.

Detection B Spray with *alcoholic solution of sulfuric acid R* and heat at 120 °C for 10 min or until the spots appear; allow to cool, and examine in daylight and in ultraviolet light at 365 nm.

Results B The principal spot in each of the chromatograms obtained with test solutions (a) and (b) is similar in position, colour in daylight, fluorescence in ultraviolet light at 365 nm and size to the principal spot in the chromatogram obtained with the corresponding reference solution; the principal spots in the chromatograms obtained with test solution (b) and reference solution (b) have an R_F value distinctly higher than that of the principal spots in the chromatograms obtained with test solution (a) and reference solution (a).

D. Add about 2 mg to 2 mL of *sulfuric acid R* and shake to dissolve. Within 5 min, an intense brownish-red colour develops with a green fluorescence that is particularly intense when examined in ultraviolet light at 365 nm. Add the solution to 10 mL of *water R* and mix. The colour fades and a clear solution remains. The fluorescence in ultraviolet light does not disappear.

TESTS

Specific optical rotation (*2.2.7*)

+ 162 to + 168 (dried substance).

Dissolve 0.200 g in *methanol R*, dilute to 25.0 mL with the same solvent and sonicate for 10 min.

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Related substances

Liquid chromatography (2.2.29).

Solvent mixture acetonitrile R, water R (40:60 *V/V*).

Test solution Dissolve 20 mg of the substance to be examined in the solvent mixture, dilute to 10.0 mL with the solvent mixture and sonicate for 10 min.

Reference solution (a) Dissolve 4 mg of prednisolone CRS (impurity A), 2 mg of cortisone R (impurity B), 8 mg of hydrocortisone acetate CRS (impurity C) and 6 mg of Reichstein's substance S R (impurity F) in 40 mL of acetonitrile R and dilute to 100.0 mL with water R. Dilute 0.5 mL of the solution to 5.0 mL with the test solution.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 2 mg of hydrocortisone CRS in 1.0 mL of the solvent mixture and sonicate for 10 min.

Reference solution (d) Dissolve 2 mg of hydrocortisone for peak identification CRS (containing impurities D, E, G, H, I and N) in 1.0 mL of the solvent mixture and sonicate for 10 min.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: base-deactivated end-capped octadecylsilyl silica gel for chromatography R (5 µm).

Mobile phase:

— *mobile phase A*: water R;

— *mobile phase B*: acetonitrile R;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 18	74	26
18 - 32	74 → 55	26 → 45
32 - 48	55 → 30	45 → 70

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL of the test solution and reference solutions (a), (b) and (d).

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Identification of impurities Use the chromatogram supplied with *hydrocortisone for peak identification CRS* and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities D, E, G, H, I and N; use the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, C and F.

Relative retention With reference to hydrocortisone (retention time = about 24 min): impurity D = about 0.2; impurity H = about 0.3; impurity I = about 0.5; impurity G = about 0.8; impurity E = about 0.86; impurity A = about 0.96; impurity B = about 1.1; impurity F = about 1.4; impurity C = about 1.5; impurity N = about 1.7.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 3.0, where H_p = height above the baseline of the peak due to impurity A and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to hydrocortisone.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity D = 1.8; impurity E = 2.7;

— *impurities C, D, E, I*: for each impurity, not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *impurity G*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.4 per cent);

— *impurity F*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *impurities A, B*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *impurities H, N*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 20 times the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

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Dissolve 0.100 g in *ethanol (96 per cent) R* and dilute to 100.0 mL with the same solvent. Dilute 2.0 mL of the solution to 100.0 mL with *ethanol (96 per cent) R*. Measure the absorbance (2.2.25) at the absorption maximum at 241.5 nm.

Calculate the content of $C_{21}H_{30}O_5$ taking the specific absorbance to be 440.

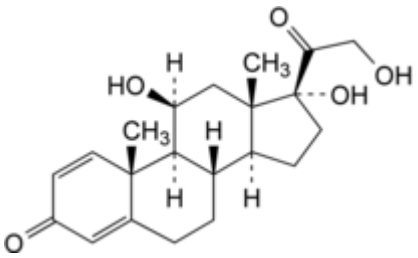
STORAGE

Protected from light.

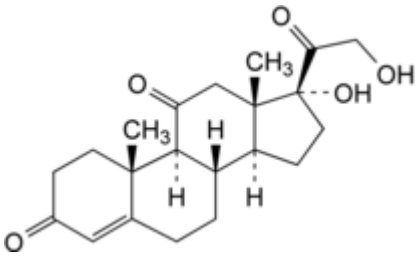
IMPURITIES

Specified impurities *A, B, C, D, E, F, G, H, I, N.*

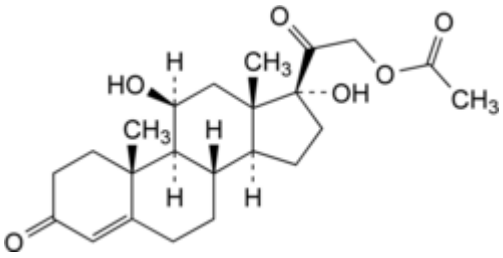
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *J, K, L, M, O.*



A. 11β,17,21-trihydroxypregna-1,4-diene-3,20-dione (prednisolone),

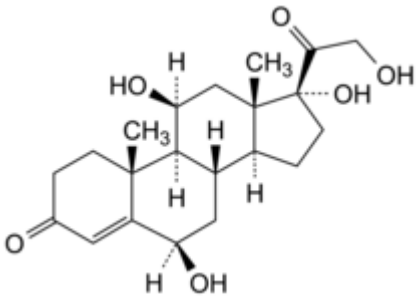


B. 17,21-dihydroxypregn-4-ene-3,11,20-trione (cortisone),

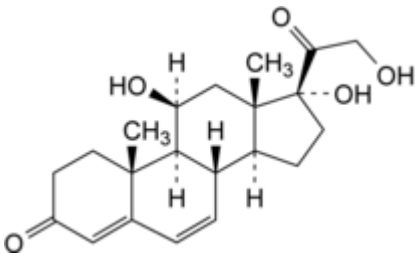


C. 11β,17-dihydroxy-3,20-dioxopregn-4-en-21-yl acetate (hydrocortisone acetate),

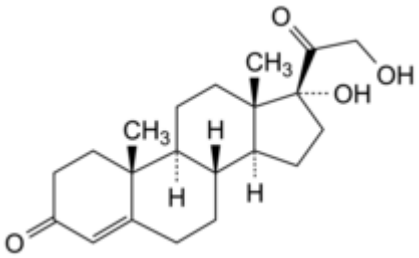
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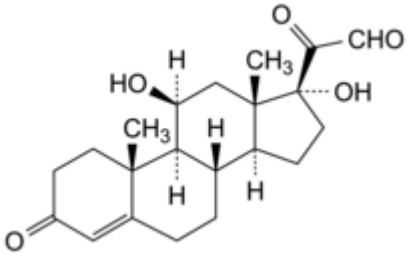
D. 6β,11β,17,21-tetrahydroxypregn-4-ene-3,20-dione (6β-hydroxyhydrocortisone),



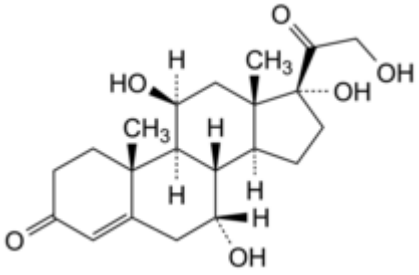
E. 11β,17,21-trihydroxypregna-4,6-diene-3,20-dione (Δ6-hydrocortisone),



F. 17,21-dihydroxypregn-4-ene-3,20-dione (Reichstein's substance S),

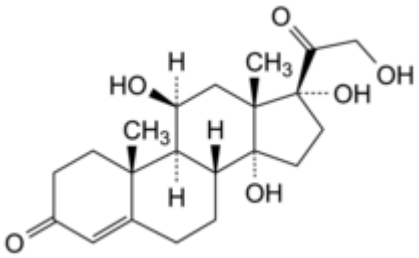


G. 11β,17-dihydroxy-3,20-dioxopregn-4-en-21-al (hydrocortisone-21-aldehyde),

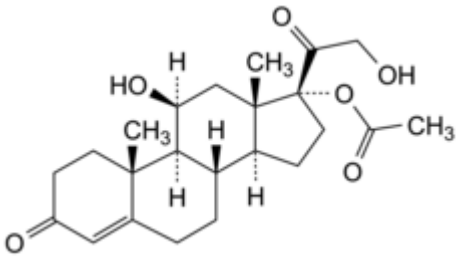


H. 7α,11β,17,21-tetrahydroxypregn-4-ene-3,20-dione (7α-hydroxyhydrocortisone),

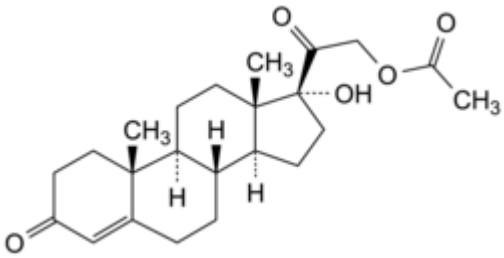
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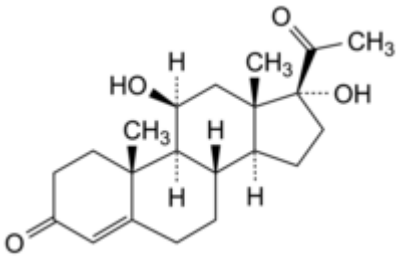
I. 11β,14,17,21-tetrahydroxypregn-4-ene-3,20-dione (14α-hydroxyhydrocortisone),



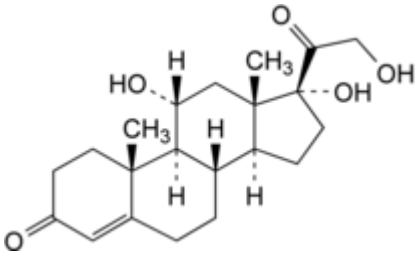
J. 11β,21-dihydroxy-3,20-dioxopregn-4-en-17-yl acetate (hydrocortisone-17-acetate),



K. 17-hydroxy-3,20-dioxopregn-4-en-21-yl acetate (Reichstein's substance S-21-acetate),

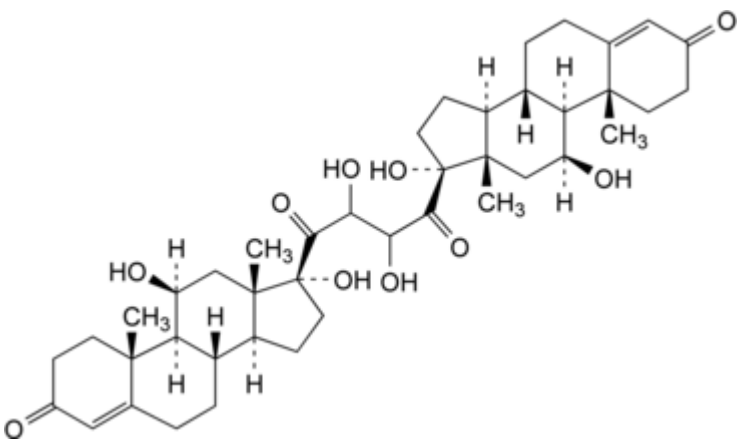


L. 11β,17-dihydroxypregn-4-ene-3,20-dione (oxenol),

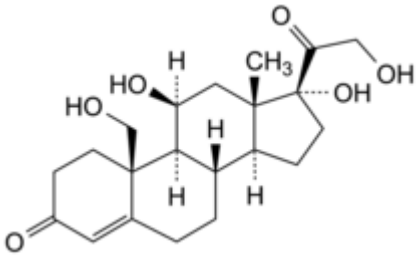


M. 11α,17,21-trihydroxypregn-4-ene-3,20-dione (*epi*-hydrocortisone),

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N. 11β,17,21-trihydroxy-21-(11β,17,21-trihydroxy-3,20-dioxopregn-4-en-21-yl)pregn-4-ene-3,20-dione (hydrocortisone dimer),



O. 11β,17,19,21-tetrahydroxypregn-4-ene-3,20-dione (19-hydroxyhydrocortisone).

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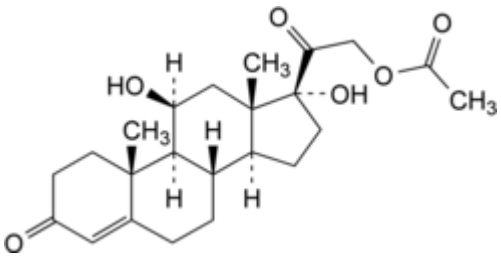
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Hydrocortisone Acetate

General Notices

(Ph. Eur. monograph 0334)



$C_{23}H_{32}O_6$ 404.5 *50-03-3*

Action and use

Corticosteroid.

Preparations

Clotrimazole and Hydrocortisone Acetate Cream

Gentamicin and Hydrocortisone Acetate Ear Drops

Hydrocortisone Acetate Cream

Hydrocortisone Acetate and Neomycin Ear Drops

Hydrocortisone Acetate and Neomycin Eye Drops

Hydrocortisone Acetate and Neomycin Eye Ointment

Hydrocortisone Acetate Injection

Hydrocortisone Acetate Ointment

Hydrocortisone Acetate Oral Suspension

Miconazole and Hydrocortisone Acetate Cream

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DEFINITION

11β,17-Dihydroxy-3,20-dioxopregn-4-en-21-yl acetate.

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Content

97.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, slightly soluble in anhydrous ethanol and in methylene chloride.

IDENTIFICATION

First identification: A, B.

Second identification: C, D, E.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *hydrocortisone acetate CRS*.

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with test solution (b) is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (d).

C. Thin-layer chromatography (2.2.27).

Test solution (a) Dissolve 25 mg of the substance to be examined in *methanol R* and dilute to 5 mL with the same solvent (solution A). Dilute 2 mL of the solution to 10 mL with *methylene chloride R*.

Test solution (b) Transfer 2 mL of solution A to a 15 mL glass tube with a ground-glass stopper or a polytetrafluoroethylene cap. Add 10 mL of *saturated methanolic potassium hydrogen carbonate solution R* and immediately pass a stream of *nitrogen R* briskly through the solution for 5 min. Stopper the tube. Heat in a water-bath at 45 °C protected from light for 2 h 30 min. Allow to cool.

Reference solution (a) Dissolve 25 mg of *hydrocortisone acetate CRS* in *methanol R* and dilute to 5 mL with the same solvent (solution B). Dilute 2 mL of the solution to 10 mL with *methylene chloride R*.

Reference solution (b) Transfer 2 mL of solution B to a 15 mL glass tube with a ground-glass stopper or a polytetrafluoroethylene cap. Add 10 mL of *saturated methanolic potassium hydrogen carbonate solution R* and immediately pass a stream of *nitrogen R* briskly through the solution for 5 min. Stopper the tube. Heat in a water-bath at 45 °C protected from light for 2 h 30 min. Allow to cool.

Plate *TLC silica gel F_{254} plate R*.

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Mobile phase Add a mixture of 1.2 volumes of *water R* and 8 volumes of *methanol R* to a mixture of 15 volumes of *ether R* and 77 volumes of *methylene chloride R*.

Application 5 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection A Examine in ultraviolet light at 254 nm.

Results A The principal spot in each of the chromatograms obtained with the test solutions is similar in position and size to the principal spot in the chromatogram obtained with the corresponding reference solution.

Detection B Spray with *alcoholic solution of sulfuric acid R* and heat at 120 °C for 10 min or until the spots appear and allow to cool; examine in daylight and in ultraviolet light at 365 nm.

Results B The principal spot in each of the chromatograms obtained with the test solutions is similar in position, colour in daylight, fluorescence in ultraviolet light at 365 nm and size to the principal spot in the chromatogram obtained with the corresponding reference solution. The principal spots in the chromatograms obtained with test solution (b) and reference solution (b) have an R_F value distinctly lower than that of the principal spots in the chromatograms obtained with test solution (a) and reference solution (a).

D. Add about 2 mg to 2 mL of *sulfuric acid R* and shake to dissolve. Within 5 min an intense brownish-red colour develops with a green fluorescence which is particularly intense when viewed in ultraviolet light at 365 nm. Add this solution to 10 mL of *water R* and mix. The colour fades and the fluorescence in ultraviolet light does not disappear.

E. About 10 mg gives the reaction of acetyl (*2.3.1*).

TESTS

Specific optical rotation (*2.2.7*)

+ 158 to + 167 (dried substance).

Dissolve 0.250 g in *dioxan R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture *acetic acid R*, *water R*, *methanol R* (1:10:90 *V/V/V*).

Test solution (a) Dissolve 25.0 mg of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with the solvent mixture.

Reference solution (a) Dissolve 2 mg of *hydrocortisone acetate CRS* and 2 mg of *prednisolone acetate CRS* (impurity C) in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

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Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 5 mg of *hydrocortisone acetate for peak identification CRS* (containing impurities A, B, D, E and G) in 5 mL of the solvent mixture.

Reference solution (d) Dissolve 25.0 mg of *hydrocortisone acetate CRS* in the solvent mixture and dilute to 25.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 400 mL of *acetonitrile R* with 550 mL of *water for chromatography R* and allow to equilibrate; dilute to 1000 mL with *water for chromatography R* and mix again.

Flow rate 1 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL of test solution (a) and reference solutions (a), (b) and (c).

Run time 4 times the retention time of hydrocortisone acetate.

Identification of impurities Use the chromatogram supplied with *hydrocortisone acetate for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B, D, E and G; use the chromatogram obtained with reference solution (a) to identify the peak due to impurity C.

Relative retention With reference to hydrocortisone acetate (retention time = about 10 min): impurity A = about 0.4; impurity B = about 0.7; impurity C = about 0.9; impurity D = about 1.2; impurity G = about 1.8; impurity E = about 2.3.

System suitability Reference solution (a):

— *resolution*: minimum 1.5 between the peaks due to impurity C and hydrocortisone acetate.

Limits:

— *impurity C*: not more than 6 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.6 per cent);

— *impurity A*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *impurities B, D, E*: for each impurity, not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

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— *impurity G*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 15 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C for 3 h.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Injection Test solution (b) and reference solution (d).

Run time 1.5 times the retention time of hydrocortisone acetate.

Retention time Hydrocortisone acetate = about 10 min.

Calculate the percentage content of $C_{23}H_{32}O_6$ taking into account the assigned content of *hydrocortisone acetate CRS*.

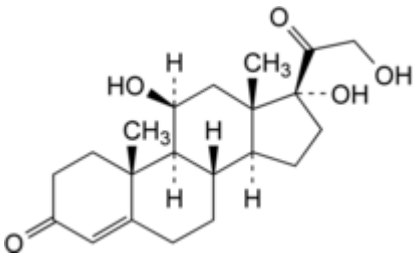
STORAGE

Protected from light.

IMPURITIES

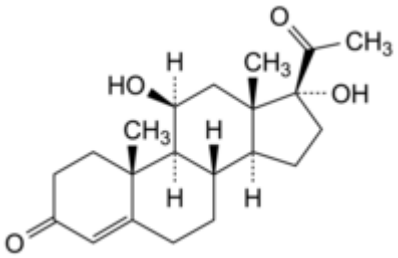
Specified impurities *A, B, C, D, E, G.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *F.*

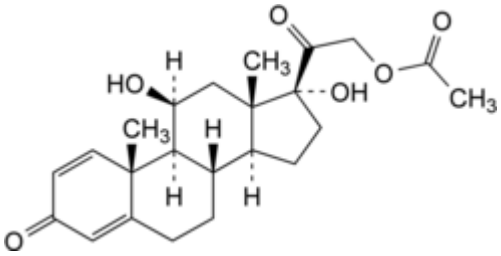


A. 11β,17,21-trihydroxypregn-4-ene-3,20-dione (hydrocortisone),

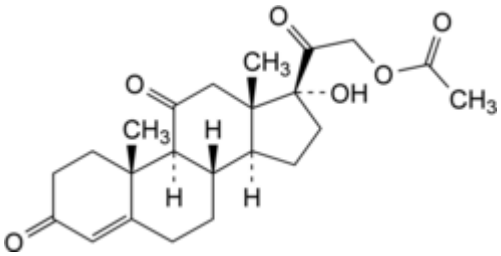
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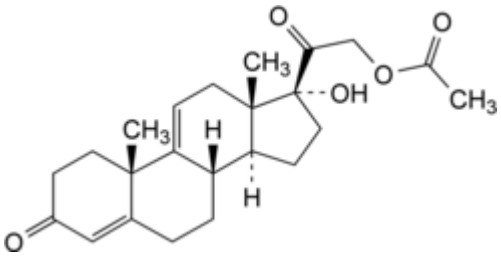
B. 11β,17-dihydroxypregn-4-ene-3,20-dione (oxenol),



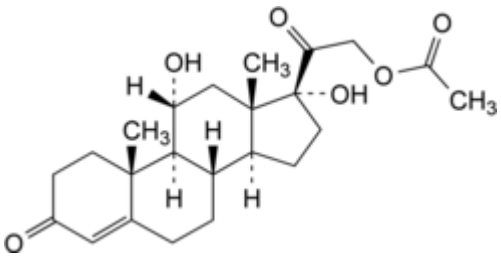
C. 11β,17-dihydroxy-3,20-dioxopregna-1,4-dien-21-yl acetate (prednisolone acetate),



D. 17-hydroxy-3,11,20-trioxopregn-4-en-21-yl acetate (cortisone acetate),

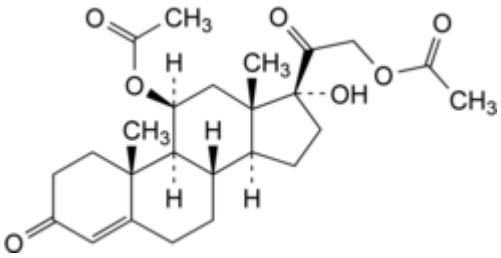


E. 17-hydroxy-3,20-dioxopregna-4,9(11)-dien-21-yl acetate,



F. 11α,17-dihydroxy-3,20-dioxopregn-4-en-21-yl acetate (*epi*-hydrocortisone acetate),

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G. 17-hydroxy-3,20-dioxopregn-4-ene-11β,21-diyl diacetate.

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Hydrocortisone Acetate and Neomycin Ear Drops

General Notices

Hydrocortisone and Neomycin Ear Drops

Action and use

Corticosteroid + Aminoglycoside antibacterial.

DEFINITION

Hydrocortisone Acetate and Neomycin Ear Drops are a suspension of Hydrocortisone Acetate in a solution of Neomycin Sulfate in Purified Water.

The ear drops comply with the requirements stated under Ear Preparations and with the following requirements.

Content of hydrocortisone acetate, $C_{23}H_{32}O_6$

90.0 to 110.0% w/v of the stated amount.

IDENTIFICATION

A. Comply with test A for Identification described under Hydrocortisone and Neomycin Cream using the following solutions. For solution (1) add 10 mL of *chloroform* to a quantity of the ear drops containing 5 mg of Hydrocortisone Acetate in a separating funnel, shake for 2 to 3 minutes and allow the layers to separate. Filter if necessary and use the chloroform layer. Solution (2) contains 0.05% w/v of *hydrocortisone acetate BPCRS* in *chloroform*.

B. In the Assay for hydrocortisone acetate the chromatogram obtained with solution (3) shows a peak with the same retention time as the peak due to hydrocortisone acetate in the chromatogram obtained with solution (1).

C. Comply with test C for Identification described under Hydrocortisone and Neomycin Cream. For solution (1) dilute a volume containing 3500 IU of Neomycin Sulfate with *water* to 2.5 mL, shake with 3 mL of *chloroform*, centrifuge and use the clear, upper layer.

TESTS

Acidity or alkalinity

pH, 6.5 to 8.0, Appendix V L.

Neamine

Comply with the test described under Hydrocortisone and Neomycin Cream. For solution (1) dilute a volume containing 3500 IU of Neomycin Sulfate with 2.5 mL of *water*, shake gently with 3 mL of *chloroform*, centrifuge and use the aqueous layer.

Neomycin C

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Comply with the test described under Hydrocortisone and Neomycin Cream but using as solution (2) a solution prepared in the following manner. Dilute the ear drops with 0.02M *sodium tetraborate* to contain 700 IU per mL. To 0.5 mL of the resulting solution add 1.5 mL of a freshly prepared 2% w/v solution of *1-fluoro-2,4-dinitrobenzene* in *methanol*, heat in a water bath at 60° for 1 hour, cool and dilute the solution to 25 mL with the mobile phase; allow to stand and use the clear, lower layer.

ASSAY

For hydrocortisone acetate

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Solution (1) contains 0.020% w/v of *hydrocortisone acetate BPCRS* and 0.016% w/v of *fluoxymesterone BPCRS* (internal standard) in *chloroform*. For solution (2) shake a quantity of the ear drops containing 10 mg of Hydrocortisone Acetate with 25 mL of a 0.032% w/v solution of *fluoxymesterone BPCRS* in *chloroform*, add 25 mL of *chloroform*, mix and filter through *anhydrous sodium sulfate*.

The chromatographic procedure may be carried out using (a) a stainless steel column (30 cm × 3.9 mm) packed with *silica gel for chromatography* (10 µm) (µPorasil is suitable), (b) a mixture of 425 volumes of *butyl chloride*, 425 volumes of *butyl chloride* saturated with *water*, 70 volumes of *tetrahydrofuran*, 35 volumes of *methanol* and 30 volumes of *glacial acetic acid* as the mobile phase with a flow rate of 1 mL per minute and (c) a detection wavelength of 254 nm.

Calculate the content of $C_{23}H_{32}O_6$ in the ear drops using the declared content of $C_{23}H_{32}O_6$ in *hydrocortisone acetate BPCRS*.

For neomycin sulfate

Dilute a volume containing 3500 IU to 50 mL with sterile *phosphate buffer pH 8.0*, dilute 10 mL of the resulting solution to 100 mL with the same solvent and carry out the *microbiological assay of antibiotics*, Appendix XIV A. The precision of the assay is such that the fiducial limits of error are not less than 95% and not more than 105% of the estimated potency. The upper fiducial limit of error is not less than 90.0% and the lower fiducial limit of error is not more than 115.0% of the stated number of IU per mL.

LABELLING

The strength with respect to Neomycin Sulfate is stated as the number of IU (Units) per mL.

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Hydrocortisone Acetate and Neomycin Eye Drops

General Notices

Hydrocortisone and Neomycin Eye Drops

Action and use

Corticosteroid + Aminoglycoside antibacterial.

DEFINITION

Hydrocortisone Acetate and Neomycin Eye Drops are a sterile suspension of Hydrocortisone Acetate in a solution of Neomycin Sulfate in Purified Water.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

Content of hydrocortisone acetate, $C_{23}H_{32}O_6$

90.0 to 110.0% w/v of the stated amount.

IDENTIFICATION

A. Comply with test A for Identification described under Hydrocortisone and Neomycin Cream using the following solutions. For solution (1) add 10 mL of *chloroform* to a quantity of the eye drops containing 5 mg of Hydrocortisone Acetate in a separating funnel, shake for 2 to 3 minutes and allow the layers to separate. Filter if necessary and use the chloroform layer. Solution (2) contains 0.05% w/v of *hydrocortisone acetate BPCRS* in *chloroform*.

B. In the Assay for hydrocortisone acetate the chromatogram obtained with solution (2) shows a peak with the same retention time as the peak due to hydrocortisone acetate in the chromatogram obtained with solution (1).

C. Comply with test C for Identification described under Hydrocortisone and Neomycin Cream. For solution (1) dilute a volume containing 3500 IU of Neomycin Sulfate with *water* to 2.5 mL, shake with 3 mL of *chloroform*, centrifuge and use the clear, upper layer.

TESTS

Acidity or alkalinity

pH, 6.5 to 8.0, Appendix V L.

Neamine

Comply with the test described under Hydrocortisone and Neomycin Cream. For solution (1) dilute a volume containing 3500 IU of Neomycin Sulfate with 2.5 mL of *water*, shake gently with 3 mL of *chloroform*, centrifuge and use the aqueous layer.

Neomycin C

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Comply with the test described under Hydrocortisone and Neomycin Cream but using as solution (2) a solution prepared in the following manner. Dilute the eye drops with 0.02M *sodium tetraborate* to contain 700 IU per mL. To 0.5 mL of the resulting solution add 1.5 mL of a freshly prepared 2% w/v solution of *1-fluoro-2,4-dinitrobenzene* in *methanol*, heat in a water bath at 60° for 1 hour, cool and dilute the solution to 25 mL with the mobile phase; allow to stand and use the clear, lower layer.

ASSAY

For hydrocortisone acetate

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Solution (1) contains 0.020% w/v of *hydrocortisone acetate BPCRS* and 0.016% w/v of *fluoxymesterone BPCRS* (internal standard) in *chloroform*. For solution (2) shake a quantity of the eye drops containing 10 mg of Hydrocortisone Acetate with 25 mL of a 0.032% w/v solution of *fluoxymesterone BPCRS* in *chloroform*, add 25 mL of *chloroform*, mix and filter through *anhydrous sodium sulfate*.

The chromatographic procedure may be carried out using (a) a stainless steel column (30 cm × 3.9 mm) packed with *silica gel for chromatography* (10 µm) (µPorasil is suitable), (b) a mixture of 425 volumes of *butyl chloride*, 425 volumes of *butyl chloride* saturated with *water*, 70 volumes of *tetrahydrofuran*, 35 volumes of *methanol* and 30 volumes of *glacial acetic acid* as the mobile phase with a flow rate of 1 mL per minute and (c) a detection wavelength of 254 nm.

Calculate the content of $C_{23}H_{32}O_6$ in the eye drops using the declared content of $C_{23}H_{32}O_6$ in *hydrocortisone acetate BPCRS*.

For neomycin sulfate

Dilute a volume containing 3500 IU to 50 mL with sterile *phosphate buffer pH 8.0*, dilute 10 mL of the resulting solution to 100 mL with the same solvent and carry out the *microbiological assay of antibiotics*, Appendix XIV A. The precision of the assay is such that the fiducial limits of error are not less than 95% and not more than 105% of the estimated potency. The upper fiducial limit of error is not less than 90.0% and the lower fiducial limit of error is not more than 115.0% of the stated number of IU per mL.

LABELLING

The strength with respect to Neomycin Sulfate is stated as the number of IU (Units) per mL.

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Hydrocortisone Acetate and Neomycin Eye Ointment

General Notices

Action and use

Corticosteroid + Aminoglycoside antibacterial.

DEFINITION

Hydrocortisone Acetate and Neomycin Eye Ointment is a sterile preparation containing Hydrocortisone Acetate and Neomycin Sulfate in a suitable basis.

The eye ointment complies with the requirements stated under Eye Preparations and with the following requirements.

Content of hydrocortisone acetate, $C_{23}H_{32}O_6$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. Complies with test A for Identification described under Hydrocortisone and Neomycin Cream using the following solutions. For solution (1) add 10 mL of *hexane* saturated with *acetonitrile* to a quantity of the ointment containing 5 mg of Hydrocortisone Acetate and shake for 2 to 3 minutes. Add 10 mL of *acetonitrile* saturated with *hexane*, shake for 10 minutes and allow the layers to separate. Centrifuge, filter the acetonitrile layer if necessary, evaporate 5 mL to dryness and dissolve the residue in 5 mL of a mixture of equal volumes of *chloroform* and *ethanol (96%)*. Solution (2) contains 0.05% w/v of *hydrocortisone acetate BPCRS* in a mixture of equal volumes of *chloroform* and *ethanol (96%)*.

B. In the Assay for hydrocortisone acetate the chromatogram obtained with solution (3) shows a peak with the same retention time as the peak due to hydrocortisone acetate in the chromatogram obtained with solution (1).

C. Complies with test C for Identification described under Hydrocortisone and Neomycin Cream. For solution (1) shake a quantity containing 7000 IU of Neomycin Sulfate with 10 mL of *chloroform*, add 5 mL of *water*, shake, centrifuge and use the clear, upper layer.

TESTS

Neamine

Complies with the test described under Hydrocortisone and Neomycin Cream. For solution (1) disperse a quantity containing 7000 IU of Neomycin Sulfate in 10 mL of *chloroform*, shake gently with 5 mL of *water*, centrifuge and use the aqueous layer.

Neomycin C

Complies with the test described under Hydrocortisone and Neomycin Cream.

ASSAY

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ASSAY

For hydrocortisone acetate

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Solution (1) contains 0.025% w/v of *hydrocortisone acetate BPCRS* and 0.050% w/v of *fluoxymesterone BPCRS* (internal standard) in *chloroform*. For solution (2) shake a quantity of the ointment containing 25 mg of Hydrocortisone Acetate with 20 mL of a 0.25% w/v solution of *fluoxymesterone BPCRS* in *chloroform* and several glass beads for 30 minutes. Centrifuge; to 10 mL of the clear, supernatant layer add sufficient *chloroform* to produce 50 mL.

The chromatographic procedure may be carried out using (a) a stainless steel column (30 cm × 3.9 mm) packed with *silica gel for chromatography* (10 µm) (µPorasil is suitable), (b) a mixture of 425 volumes of *butyl chloride*, 425 volumes of *butyl chloride* saturated with *water*, 70 volumes of *tetrahydrofuran*, 35 volumes of *methanol* and 30 volumes of *glacial acetic acid* as the mobile phase with a flow rate of 1 mL per minute and (c) a detection wavelength of 254 nm.

Calculate the content of $C_{23}H_{32}O_6$ in the ointment using the declared content of $C_{23}H_{32}O_6$ in *hydrocortisone acetate BPCRS*.

For neomycin sulfate

Dissolve a quantity containing 3500 IU in 50 mL of *ether*, extract the solution with three 30-mL quantities of sterile *phosphate buffer pH 8.0* and discard the ether phase. Pass *nitrogen* through the combined aqueous extracts to remove dissolved ether, dilute to 100 mL with sterile *phosphate buffer pH 8.0* and carry out the *microbiological assay of antibiotics*, Appendix XIV A. The precision of the assay is such that the fiducial limits of error are not less than 95% and not more than 105% of the estimated potency. The upper fiducial limit of error is not less than 90.0% and the lower fiducial limit of error is not more than 115.0% of the stated number of IU per g.

LABELLING

The strength with respect to Neomycin Sulfate is stated as the number of IU (Units) per g.

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Hydrocortisone Acetate Cream

General Notices

Action and use

Corticosteroid.

DEFINITION

Hydrocortisone Acetate Cream contains Hydrocortisone Acetate in a suitable basis.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of hydrocortisone acetate, $C_{23}H_{32}O_6$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel G* as the coating substance and a mixture of 77 volumes of *dichloromethane*, 15 volumes of *ether*, 8 volumes of *methanol* and 1.2 volumes of *water* as the mobile phase. Apply separately to the plate 5 µL of each of the following solutions.
For creams containing more than 0.5% w/w of Hydrocortisone Acetate, prepare two solutions in the following manner. For solution (1) mix a quantity of the cream containing 25 mg of Hydrocortisone Acetate with 10 mL of *methanol (90%)*, add 50 mL of hot *hexane* and shake. Discard the upper layer, add 5 g of *anhydrous sodium sulfate* to the lower layer, mix and filter through a glass microfibre filter (Whatman GF/C is suitable). Solution (2) is a mixture of equal volumes of solution (1) and a 0.25% w/v solution of *hydrocortisone acetate BPCRS* in *methanol*.

For creams containing 0.5% w/w or less of Hydrocortisone Acetate, prepare solution (1) in the same manner as solution (1) described above but using a quantity of the cream containing 5 mg of Hydrocortisone Acetate. Solution (2) is a mixture of equal volumes of solution (1) and a 0.05% w/v solution of *hydrocortisone acetate BPCRS* in *methanol*.

After removal of the plate, allow it to dry in air and spray with *alkaline tetrazolium blue solution*. The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2), which appears as a single, compact spot.

B. In the Assay, the chromatogram obtained with solution (2) shows a peak with the same retention time as the peak due to hydrocortisone acetate in the chromatogram obtained with solution (1).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

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For creams containing more than 0.5% w/w of Hydrocortisone Acetate, prepare solutions (1) and (2) in the following manner. For solution (1) dissolve 25 mg of *hydrocortisone acetate BPCRS* in 45 mL of *methanol*, add 5 mL of a 0.5% w/v solution of *betamethasone* (internal standard) in *methanol* and add sufficient *water* to produce 100 mL. For solution (2) disperse, by shaking, a quantity containing 25 mg of Hydrocortisone Acetate in 40 mL of a solution prepared by mixing 75 mL of *methanol* with 25 mL of a 15% w/v solution of *sodium chloride*. Add 50 mL of hot *hexane*, shake and separate the lower layer. Repeat the extraction using two 10 mL quantities of the methanolic sodium chloride solution. Add 5 mL of *methanol* to the combined extracts and sufficient *water* to produce 100 mL, mix and filter through a glass microfibre filter paper (Whatman GF/C is suitable).

For creams containing 0.5% w/w or less of Hydrocortisone Acetate, prepare solutions (1) and (2) in the following manner. For solution (1) dissolve 5 mg of *hydrocortisone acetate BPCRS* in 45 mL of *methanol* and add 5 mL of a 0.110% w/v solution of *betamethasone* (internal standard) in *methanol* and sufficient *water* to produce 100 mL. Prepare solution (2) in the same manner as solution (2) above but use a quantity containing 5 mg of Hydrocortisone Acetate.

For all creams prepare solution (3) in the same manner as solution (2) but adding 5 mL of the appropriate internal standard solution in place of the 5 mL of methanol before diluting to volume.

The chromatographic procedure may be carried out using (a) a stainless steel column (10 cm × 5 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable), (b) *methanol (50%)* as the mobile phase with a flow rate of 2 mL per minute and (c) a detection wavelength of 240 nm.

Calculate the content of $C_{23}H_{32}O_6$ in the preparation being examined using the declared content of $C_{23}H_{32}O_6$ in *hydrocortisone acetate BPCRS*.

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Hydrocortisone Acetate Injection

General Notices

Action and use

Corticosteroid.

DEFINITION

Hydrocortisone Acetate Injection is a sterile suspension of Hydrocortisone Acetate in Water for Injections. It is prepared using aseptic technique.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of hydrocortisone acetate, $C_{23}H_{32}O_6$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Filter a volume containing 50 mg of Hydrocortisone Acetate through a sintered-glass filter, wash the residue with four 5-mL quantities of *water*, dissolve in 20 mL of *chloroform*, wash the chloroform solution with four 10-mL quantities of *water*, discard the washings, filter the chloroform solution through absorbent cotton and evaporate the filtrate to dryness. The residue complies with the following tests.

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of hydrocortisone acetate *(RS 179)*.

B. Complies with the test for *identification of steroids*, Appendix III A, using *impregnating solvent I* and *mobile phase B*.

C. Yields the reaction characteristic of *acetyl groups*, Appendix VI.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a volume of the injection containing 50 mg of Hydrocortisone Acetate, add 70 mL of *methanol*. Shake to produce a clear solution and dilute to 100 mL with *methanol*. Dilute 10 mL of the resulting solution to 20 mL with *water*.

(2) Dissolve 25 mg of *hydrocortisone acetate BPCRS* in 50 mL of *methanol* and add sufficient *water* to produce 100 mL.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 5 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

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(d) Use an ambient column temperature.

(e) Use a detection wavelength of 240 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

50 volumes of *methanol* and 50 volumes of *water*.

DETERMINATION OF CONTENT

Calculate the content of $C_{23}H_{32}O_6$ in the injection from the chromatograms obtained using the declared content of $C_{23}H_{32}O_6$ in *hydrocortisone acetate BPCRS*.

STORAGE

Hydrocortisone Acetate Injection should be protected from light.

LABELLING

The label states (1) that it is intended for local action; (2) that the container should be gently shaken before a dose is withdrawn.

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Hydrocortisone Acetate Ointment

General Notices

Action and use

Corticosteroid.

DEFINITION

Hydrocortisone Acetate Ointment contains Hydrocortisone Acetate in a suitable basis.

The ointment complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of hydrocortisone acetate, $C_{23}H_{32}O_6$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A using the following solutions.

For ointments containing more than 0.5% w/w of Hydrocortisone Acetate

(1) Disperse a quantity containing 25 mg of Hydrocortisone Acetate in 5 mL of hot *hexane*, cool, extract with 10 mL of *methanol (90%)* and filter.

(2) Equal volumes of solution (1) and a 0.25% w/v solution of *hydrocortisone acetate BPCRS* in *methanol*.

For ointments containing 0.5% w/w or less of Hydrocortisone Acetate

(1) Disperse a quantity containing 5 mg of Hydrocortisone Acetate in 5 mL of hot *hexane*, cool, extract with 10 mL of *methanol (90%)* and filter.

(2) Equal volumes of solution (1) and a 0.05% w/v solution of *hydrocortisone acetate BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) After removal of the plate, dry in air and spray with *alkaline tetrazolium blue solution*.

MOBILE PHASE

1.2 volumes of *water*, 8 volumes of *methanol*, 15 volumes of *ether* and 77 volumes of *dichloromethane*.

CONFIRMATION

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The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2) which appears as a single, compact spot.

B. In the Assay, the chromatogram obtained with solution (2) shows a peak with the same retention time as the peak due to hydrocortisone acetate in the chromatogram obtained with solution (1).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D using the following solutions.

For ointments containing more than 0.5% w/w of Hydrocortisone Acetate

(1) Disperse a quantity of the ointment containing 25 mg of Hydrocortisone Acetate in 100 mL of hot *hexane*, cool and extract with 20 mL of a solution prepared by mixing 3 volumes of *methanol* and 1 volume of a 15% w/v solution of *sodium chloride*. Repeat the extraction using two 10-mL quantities of the methanolic sodium chloride solution. Add 5 mL of *methanol* to the combined extracts and sufficient *water* to produce 100 mL, mix and filter through a glass microfibre filter (Whatman GF/C is suitable).
(2) Dissolve 25 mg of *hydrocortisone acetate* *BPCRS* in 45 mL of *methanol*, add 5 mL of a 0.5% w/v solution of *betamethasone* (internal standard) in *methanol* and sufficient *water* to produce 100 mL.
(3) Prepare in the same manner as solution (1) but add 5 mL of the internal standard solution in place of the 5 mL of methanol before diluting to volume.

For ointments containing 0.5% w/w or less of Hydrocortisone Acetate

(1) Disperse a quantity of the ointment containing 5 mg of Hydrocortisone Acetate in 100 mL of hot *hexane*, cool and extract with 20 mL of a solution prepared by mixing 3 volumes of *methanol* and 1 volume of a 15% w/v solution of *sodium chloride*. Repeat the extraction using two 10-mL quantities of the methanolic sodium chloride solution. Add 5 mL of *methanol* to the combined extracts and sufficient *water* to produce 100 mL, mix and filter through a glass microfibre filter (Whatman GF/C is suitable).
(2) Dissolve 5 mg of *hydrocortisone acetate* *BPCRS* in 45 mL of *methanol*, add 5 mL of a 0.110% w/v solution of *betamethasone* (internal standard) in *methanol* and add sufficient *water* to produce 100 mL.
(3) Prepare in the same manner as solution (1) but add 5 mL of the internal standard solution in place of the 5 mL of methanol before diluting to volume.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column 10 cm × 5 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 240 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

50 volumes of *methanol* and 50 volumes of *water*.

DETERMINATION OF CONTENT

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Calculate the content of $C_{23}H_{32}O_6$ in the ointment using the declared content of $C_{23}H_{32}O_6$ in *hydrocortisone acetate BPCRS*.

STORAGE

Hydrocortisone Acetate Ointment should be protected from light.

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Hydrocortisone Acetate Oral Suspension

General Notices

NOTE: *This monograph has been developed to cover unlicensed formulations.*

Action and use

Corticosteroid.

DEFINITION

Hydrocortisone Acetate Oral Suspension is a suspension of Hydrocortisone Acetate in a suitable flavoured aqueous vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral suspension also complies with the requirements stated under Unlicensed Medicines.

Content of hydrocortisone, $C_{21}H_{30}O_5$

95.0 to 105.0% of the stated amount.

The oral suspension should be shaken vigorously before carrying out the following tests.

IDENTIFICATION

A. Filter a volume of the oral suspension containing the equivalent of 50 mg of hydrocortisone through a sintered-glass filter, wash the residue with four 5-mL quantities of *water*, dissolve in 20 mL of *dichloromethane*, wash the dichloromethane solution with four 10-mL quantities of *water*, discard the washings, filter the dichloromethane solution through absorbent cotton and evaporate the filtrate to dryness. The residue complies with the test for *identification of steroids*, Appendix III A, using *impregnating solvent I* and *mobile phase B*.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that of the principal peak in the chromatogram obtained with solution (2).

C. The residue obtained in test A yields the reaction characteristic of *acetyl groups*, Appendix VI.

TESTS

Dissolution

Complies with the requirements stated under Unlicensed Medicines, Oral Suspensions. Use a volume of the oral suspension containing one dose.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

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(1) To a weighed quantity of the oral suspension containing the equivalent of 10 mg of hydrocortisone add 50 mL of *methanol*, mix with the aid of ultrasound, dilute to 100 mL with *methanol* and filter (Whatman No. 1 paper is suitable).

(2) 0.01% w/v of *hydrocortisone BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 240 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

4 volumes of a 1% w/v solution of *acetic acid* in *water* and 6 volumes of *methanol*.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_{21}H_{30}O_5$, weight in volume, using the declared content of $C_{21}H_{30}O_5$ in *hydrocortisone BPCRS*.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of hydrocortisone.

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Hydrocortisone and Clioquinol Cream

General Notices

Action and use

Corticosteroid.

DEFINITION

Hydrocortisone and Clioquinol Cream contains Hydrocortisone and Clioquinol, the latter in *very fine powder*, in a suitable basis.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of hydrocortisone, $C_{21}H_{30}O_5$

92.5 to 107.5% of the stated amount.

Content of clioquinol, C_9H_5ClINO

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Disperse, by warming and shaking, a quantity of the cream containing 2.5 g of Hydrocortisone in 10 mL of *ethanol (96%)*, cool, allow to stand at 0° for 30 minutes, filter and use the filtrate.

(2) 0.25% w/v of *hydrocortisone BPCRS* in *ethanol (96%)*.

(3) Dissolve 12.5 mg of *hydrocortisone BPCRS* in 5 mL of solution (1).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air and spray with *alkaline tetrazolium blue solution*.

MOBILE PHASE

1.2 volumes of *water*, 8 volumes of *methanol*, 15 volumes of *ether* and 77 volumes of *dichloromethane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2). The principal spot in the chromatogram obtained with solution (3) appears as a single, compact spot.

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B. In the Assay for hydrocortisone, the chromatogram obtained with solution (3) shows a peak with the same retention time as the peak due to hydrocortisone in the chromatogram obtained with solution (1).

C. Fuse a quantity of the cream containing 0.1 g of Clioquinol with *anhydrous sodium carbonate*, dissolve the fused mass in *water* and acidify with 2M *nitric acid*. Add *silver nitrate solution*; a pale yellow precipitate is produced which is insoluble in 5M *ammonia*. Add 5M *ammonia* until the solution becomes alkaline, boil gently, filter and acidify the filtrate with 2M *nitric acid*; a white precipitate is produced which darkens on exposure to light.

ASSAY

For hydrocortisone

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 30 mL of *2,2,4-trimethylpentane* to a quantity of the cream containing 10 mg of Hydrocortisone and warm on a water bath until the preparation has melted. Extract the warm mixture with successive quantities of 30, 20 and 20 mL of *methanol (80%)*, combine the aqueous methanolic layers, cool to about 20° and dilute to 100 mL with the same solvent.

(2) Dissolve 5 mg of *hydrocortisone BPCRS* in 5 mL of a 4% v/v solution of *bromobenzene* (internal standard) in *methanol* and dilute to 50 mL with *methanol (80%)*.

(3) Prepare in the same manner as solution (1) but adding 10 mL of a 4% v/v solution of *bromobenzene* in *methanol* to the cooled methanolic extract.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 5 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 242 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

methanol (65%).

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{30}O_5$ in the cream using the declared content of $C_{21}H_{30}O_5$ in *hydrocortisone BPCRS*.

For clioquinol

To a quantity of the cream containing 25 mg of Clioquinol add 80 mL of a hot mixture of 6 volumes of *water* and 24 volumes of *2-methoxyethanol* and heat on a water bath for 5 minutes. Cool in ice for 10 minutes, allow to warm to room temperature, dilute to 100 mL with the aqueous methoxyethanol, mix and filter. To 10 mL of the filtrate add 10 mL of *2-methoxyethanol* and 2 mL of a solution prepared by dissolving 0.5 g of *iron(III) chloride hexahydrate* in 80 mL of *2-methoxyethanol* and adding 0.1 mL of *hydrochloric acid* and sufficient *2-methoxyethanol* to produce 100 mL. Dilute the solution to 25 mL with *2-methoxyethanol* and measure the *absorbance* of the resulting

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solution at the maximum at 650 nm, Appendix II B, using in the reference cell a solution prepared by treating 10 mL of the aqueous methoxyethanol in the same manner beginning at the words 'add 10 mL of *2-methoxyethanol*…'.

Repeat the operation beginning at the words 'add 10 mL of *2-methoxyethanol*…' using 10 mL of a solution prepared in the following manner. Dissolve 0.125 g of *clioquinol BPCRS* in sufficient *2-methoxyethanol* to produce 50 mL, warming to effect solution; add 1 mL of *water* to 5 mL of the solution and add sufficient of a mixture of 6 volumes of *water* and 24 volumes of *2-methoxyethanol* to produce 50 mL. Calculate the content of C_9H_5ClINO from the *absorbances* obtained and using the declared content of C_9H_5ClINO in *clioquinol BPCRS*.

STORAGE

Hydrocortisone and Clioquinol Cream should be protected from light.

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Hydrocortisone and Clioquinol Ointment

General Notices

Action and use

Corticosteroid.

DEFINITION

Hydrocortisone and Clioquinol Ointment contains Hydrocortisone and Clioquinol, the latter in *very fine powder*, in a suitable basis.

The ointment complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of hydrocortisone, $C_{21}H_{30}O_5$

92.5 to 107.5% of the stated amount.

Content of clioquinol, C_9H_5ClINO

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel G* as the coating substance and a mixture of 77 volumes of *dichloromethane*, 15 volumes of *ether*, 8 volumes of *methanol* and 1.2 volumes of *water* as the mobile phase. Apply separately to the plate 5 µl of each of the following solutions. For solution (1) disperse, by warming and shaking, a quantity of the ointment containing 2.5 g of Hydrocortisone in 10 ml of *ethanol (96%)*, cool, allow to stand at 0° for 30 minutes, filter and use the filtrate. Solution (2) contains 0.25% w/v of *hydrocortisone BPCRS* in *ethanol (96%)*. For solution (3) dissolve 12.5 mg of *hydrocortisone BPCRS* in 5 ml of solution (1). After removal of the plate, allow it to dry in air and spray with *alkaline tetrazolium blue solution*. The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2). The principal spot in the chromatogram obtained with solution (3) appears as a single, compact spot.

B. In the Assay for hydrocortisone the chromatogram obtained with solution (3) shows a peak with the same retention time as the peak due to hydrocortisone in the chromatogram obtained with solution (1).

C. Fuse a quantity of the ointment containing 0.1 g of Clioquinol with *anhydrous sodium carbonate*, dissolve the fused mass in *water* and acidify with 2M *nitric acid*. Add *silver nitrate solution*; a pale yellow precipitate is produced which is insoluble in 5M *ammonia*. Add 5M *ammonia* until the solution becomes alkaline, boil gently, filter and acidify the filtrate with 2M *nitric acid*; a white precipitate is produced which darkens on exposure to light.

ASSAY

For hydrocortisone

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Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) dissolve 5 mg of *hydrocortisone BPCRS* in 5 ml of a 4% v/v solution of *bromobenzene* (internal standard) in *methanol* and dilute to 50 ml with *methanol (80%)*. For solution (2) add 30 ml of *2,2,4-trimethylpentane* to a quantity of the ointment containing 10 mg of Hydrocortisone and warm on a water bath until the preparation has melted. Extract the warm mixture with successive quantities of 30, 20 and 20 ml of *methanol (80%)*, combine the aqueous methanolic layers, cool to about 20° and dilute to 100 ml with the same solvent. Prepare solution (3) in the same manner as solution (2) but adding 10 ml of a 4% v/v solution of *bromobenzene* in *methanol* to the cooled methanolic extract.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 5 mm) packed with *octadecylsilyl silica gel for chromatography* (Spherisorb ODS 1 is suitable), (b) *methanol (65%)* as the mobile phase with a flow rate of 1 ml per minute and (c) a detection wavelength of 242 nm.

Calculate the content of $C_{21}H_{30}O_5$ in the ointment using the declared content of $C_{21}H_{30}O_5$ in *hydrocortisone BPCRS*.

For clioquinol

To a quantity containing 25 mg of Clioquinol add 80 ml of a hot mixture of 24 volumes of *2-methoxy-ethanol* and 6 volumes of *water* and heat on a water bath for 5 minutes. Cool in ice for 10 minutes, allow to warm to room temperature, dilute to 100 ml with the aqueous methoxyethanol, mix and filter. To 10 ml of the filtrate add 10 ml of *2-methoxyethanol* and 2 ml of a solution prepared by dissolving 0.5 g of *iron(III) chloride hexahydrate* in 80 ml of *2-methoxyethanol* and adding 0.1 ml of *hydrochloric acid* and sufficient *2-methoxyethanol* to produce 100 ml. Dilute the solution to 25 ml with *2-methoxyethanol* and measure the *absorbance* of the resulting solution at the maximum at 650 nm, Appendix II B, using in the reference cell a solution prepared by treating 10 ml of the aqueous methoxyethanol in the same manner beginning at the words ‘add 10 ml of *2-methoxyethanol*…’.

Repeat the operation beginning at the words ‘add 10 ml of *2-methoxyethanol*…’ using 10 ml of a solution prepared in the following manner. Dissolve 0.125 g of *clioquinol BPCRS* in sufficient *2-methoxyethanol* to produce 50 ml, warming to effect solution; add 1 ml of *water* to 5 ml of the solution and add sufficient of a mixture of 6 volumes of *water* and 24 volumes of *2-methoxyethanol* to produce 50 ml. Calculate the content of C_9H_5ClINO from the *absorbances* obtained using the declared content of C_9H_5ClINO in *clioquinol BPCRS*.

STORAGE

Hydrocortisone and Clioquinol Ointment should be protected from light.

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Hydrocortisone and Neomycin Cream

General Notices

Action and use

Corticosteroid + Aminoglycoside antibacterial.

DEFINITION

Hydrocortisone and Neomycin Cream contains Hydrocortisone and Neomycin Sulfate in a suitable basis.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of hydrocortisone, $C_{21}H_{30}O_5$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Add 10 mL of *hexane* saturated with *acetonitrile* to a quantity of the preparation being examined containing 5 mg of Hydrocortisone and shake for 2 to 3 minutes. Add 10 mL of *acetonitrile* saturated with *hexane*, shake for 10 minutes and allow the layers to separate. Centrifuge, filter the acetonitrile layer if necessary, evaporate 5 mL to dryness and dissolve the residue in 5 mL of a mixture of equal volumes of *chloroform* and *ethanol (96%)*.

(2) 0.05% w/v of *hydrocortisone BPCRS* in a mixture of equal volumes of *chloroform* and *ethanol (96%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel GF_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and spray with *alkaline tetrazolium blue solution*.

MOBILE PHASE

8 volumes of *methanol* and 90 volumes of *dichloromethane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

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B. In the Assay for hydrocortisone the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to hydrocortisone in the chromatogram obtained with solution (2).

C. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Disperse a quantity containing 7000 IU of Neomycin Sulfate with 10 mL of *chloroform*, add 5 mL of *water*, shake, centrifuge and use the clear, upper layer.

(2) 0.2% w/v of *neomycin sulfate EPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a silica gel precoated plate (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, spray with a 1% w/v solution of *ninhydrin* in *butan-1-ol* and heat at 105° for 2 minutes.

MOBILE PHASE

20 volumes of *chloroform*, 40 volumes of 13.5M *ammonia* and 60 volumes of *methanol*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

TESTS

Neamine

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dissolve a quantity containing 7000 IU of Neomycin Sulfate in 10 mL of *chloroform*, shake gently with 5 mL of *water*, centrifuge and use the aqueous layer.

(2) 0.004% w/v of *neamine EPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel H*.

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate dry it in a current of warm air, heat at 110° for 10 minutes and spray the hot plate with a solution prepared immediately before use by diluting *sodium hypochlorite solution* with *water* to contain 0.5% of available chlorine. Dry in a current of cold air until a sprayed area of the plate below the line of application gives at most a very faint blue colour with a drop of a 0.5% w/v solution of *potassium iodide* in *starch mucilage*; avoid prolonged exposure to the cold air. Spray the plate with a 0.5% w/v solution of *potassium iodide* in *starch mucilage*.

MOBILE PHASE

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Freshly prepared 3.85% w/v solution of *ammonium acetate*.

CONFIRMATION

Any spot corresponding to neamine in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2).

Neomycin C

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity containing 3500 IU of Neomycin Sulfate with 10 mL of *chloroform*, add 5 mL of 0.02M *sodium tetraborate*, mix, allow to separate and centrifuge the upper layer. Proceed as for solution (2) but using 0.5 mL of the clear supernatant liquid in place of 0.5 mL of the neomycin sulfate solution.

(2) Add 1.5 mL of a freshly prepared 2% w/v solution of *1-fluoro-2,4-dinitrobenzene* in *methanol* to 0.5 mL of a 0.10% w/v solution of *neomycin sulfate EPCRS* in 0.02M *sodium tetraborate*, heat in a water bath at 60° for 1 hour and cool; dilute the solution to 25 mL with the mobile phase, allow to stand and use the clear lower layer.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *silica gel for chromatography* (5 µm) (Nucleosil 100-5 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.6 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 350 nm.

(f) Inject 10 µL of each solution.

(g) Pass the mobile phase through the column for several hours before starting the analysis. Record the chromatogram for 1.4 times the retention time of the peak due to neomycin B.

MOBILE PHASE

0.5 mL of *glacial acetic acid*, 1.0 mL of *water* and 97 mL of *tetrahydrofuran*, with sufficient of a 2.0% v/v solution of *absolute ethanol* in *ethanol-free chloroform* to produce 250 mL.

SYSTEM SUITABILITY

The chromatogram obtained with solution (2) shows a principal peak due to neomycin B and a major *secondary peak* due to neomycin C with a retention time relative to neomycin B of about 0.6.

The *column efficiency*, determined using the peak due to neomycin B in the chromatogram obtained with solution (2), should be at least 13,000 *theoretical plates* per metre.

LIMITS

In the chromatogram obtained with solution (1):

the area of the peak corresponding to neomycin C is 3 to 15% of the sum of the areas of the peaks corresponding to neomycin B and neomycin C.

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ASSAY

For hydrocortisone

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *chloroform*.

(1) Shake together a quantity of the preparation being examined containing 25 mg of Hydrocortisone, several small glass beads and 25 mL of a 0.036% w/v solution of *fluoxymesterone BPCRS in chloroform* for 15 minutes, add sufficient *chloroform* to produce 50 mL, mix and centrifuge. Remove any excipient material present at the interface and use the clear supernatant liquid.

(2) 0.010% w/v of *hydrocortisone BPCRS* and 0.018% w/v of *fluoxymesterone BPCRS* (internal standard).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (30 cm × 3.9 mm) packed with *silica gel for chromatography* (10 µm) (µPorasil is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

30 volumes of *glacial acetic acid*, 35 volumes of *methanol*, 70 volumes of *tetrahydrofuran*, 425 volumes of *butyl chloride* and 425 volumes of *butyl chloride* saturated with *water*.

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{30}O_5$ in the cream using the declared content of $C_{21}H_{30}O_5$ in *hydrocortisone BPCRS*.

For neomycin sulfate

Stir a quantity containing 4200 IU with 15 mL of *chloroform* until the emulsion is completely broken. Transfer to a separating funnel with 25 mL of *phosphate buffer pH 8.0* and 5 mL of *chloroform*, shake vigorously, allow to separate and reserve the aqueous phase. Extract the chloroform layer with two 25-mL quantities of *phosphate buffer pH 8.0* and discard the chloroform layer. Pass *nitrogen* through the combined aqueous solutions to remove dissolved chloroform and dilute to 100 mL with sterile *phosphate buffer pH 8.0*. Dilute 10 mL of the resulting solution to 50 mL with the same solvent and carry out the *microbiological assay of antibiotics*, Appendix XIV A. The precision of the assay is such that the fiducial limits of error are not less than 95% and not more than 105% of the estimated potency. The upper fiducial limit of error is not less than 90.0% and the lower fiducial limit of error is not more than 115.0% of the stated amount.

LABELLING

The strength with respect to Neomycin Sulfate is stated as the number of IU (Units) per g.

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Hydrocortisone Cream

General Notices

Action and use

Corticosteroid.

DEFINITION

Hydrocortisone Cream contains Hydrocortisone in a suitable basis.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of hydrocortisone, $C_{21}H_{30}O_5$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

For creams containing more than 0.5% w/w of Hydrocortisone:

(1) Mix a quantity containing 25 mg of Hydrocortisone with 10 mL of *methanol (90%)*, add 50 mL of hot *hexane* and shake. Separate the lower layer, add 5 g of *anhydrous sodium sulfate*, mix and filter through a glass microfibre filter (Whatman GF/C is suitable).

(2) 0.25% w/v of *hydrocortisone BPCRS* in *methanol*.

(3) A mixture of equal volumes of solutions (1) and (2).

For creams containing 0.5% w/w or less of Hydrocortisone:

(1) Prepare in the same manner as solution (1) above but use a quantity containing 5 mg of Hydrocortisone.

(2) 0.05% w/v of *hydrocortisone BPCRS* in *methanol*.

(3) A mixture of equal volumes of solutions (1) and (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, spray with *alkaline tetrazolium blue solution* and examine in white light.

MOBILE PHASE

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1.2 volumes of *water*, 8 volumes of *methanol*, 15 volumes of *ether* and 77 volumes of *dichloromethane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2); if it does not, the principal spot in the chromatogram obtained with solution (3) appears as a single, compact spot.

B. In the Assay, the chromatogram obtained with solution (2) shows a peak with the same retention time as the peak due to hydrocortisone in the chromatogram obtained with solution (3).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

For creams containing more than 0.5% w/w of Hydrocortisone:

Prepare a 0.5% w/v solution of *betamethasone* (internal standard) in *methanol* (solution A).

(1) Disperse, by shaking, a quantity of the cream containing 25 mg of Hydrocortisone in 40 mL of a mixture of 3 volumes of *methanol* and 1 volume of a 15% w/v solution of *sodium chloride*. Add 50 mL of hot *hexane*, shake and separate the lower layer. Repeat the extraction using a further two 10-mL quantities of the methanolic sodium chloride solution. To the combined extracts add 5 mL of solution A and sufficient *water* to produce 100 mL, mix and filter through a glass microfibre paper (Whatman GF/C is suitable).
(2) Prepare in the same manner as solution (1), but add 5 mL of *methanol* in place of the 5 mL of solution A.
(3) Dissolve 25 mg of *hydrocortisone BPCRS* in 45 mL of *methanol*, add 5 mL of solution A and add sufficient *water* to produce 100 mL.

For creams containing 0.5% w/w or less of Hydrocortisone:

Prepare a 0.110% w/v solution of *betamethasone* (internal standard) in *methanol* (solution B).

(1) Disperse, by shaking, a quantity of the cream containing 5 mg of Hydrocortisone in 40 mL of a mixture of 3 volumes of *methanol* and 1 volume of a 15% w/v solution of *sodium chloride*. Add 50 mL of hot *hexane*, shake and separate the lower layer. Repeat the extraction using a further two 10-mL quantities of the methanolic sodium chloride solution. To the combined extracts add 5 mL of solution B and sufficient *water* to produce 100 mL, mix and filter through a glass microfibre paper (Whatman GF/C is suitable).
(2) Prepare in the same manner as solution (1), but add 5 mL of *methanol* in place of the 5 mL of solution B.
(3) Dissolve 5 mg of *hydrocortisone BPCRS* in 45 mL of *methanol* and add 5 mL of solution B and sufficient *water* to produce 100 mL.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 5 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 240 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

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methanol (50%).

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{30}O_5$ in the cream using the ratios of the peaks and the declared content of $C_{21}H_{30}O_5$ in *hydrocortisone BPCRS*.

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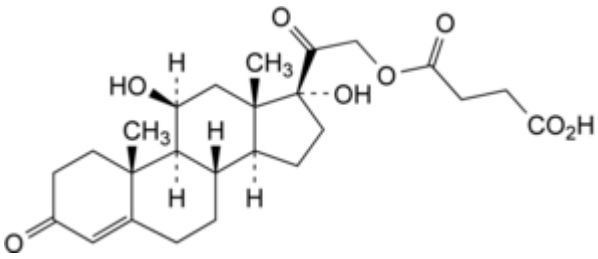
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Hydrocortisone Hydrogen Succinate

General Notices

(Ph. Eur. monograph 0768)



$C_{25}H_{34}O_8$ 462.5 *2203-97-6*

Action and use

Corticosteroid.

Preparations

Hydrocortisone Sodium Succinate Injection

Hydrocortisone Oromucosal Tablets

Ph Eur

DEFINITION

11β,17-Dihydroxy-3,20-dioxopregn-4-en-21-yl hydrogen butanedioate.

Content

97.0 per cent to 103.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, hygroscopic powder.

Solubility

Practically insoluble in water, freely soluble in acetone and in anhydrous ethanol. It dissolves in dilute solutions of alkali carbonates and alkali hydroxides.

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IDENTIFICATION

First identification: A, B.

Second identification: C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Preparation Dry the substances before use at 100-105 °C for 3 h.

Comparison *hydrocortisone hydrogen succinate CRS*.

B. Thin-layer chromatography (2.2.27).

Solvent mixture *methanol R*, *methylene chloride R* (1:9 *V/V*).

Test solution Dissolve 10 mg of the substance to be examined in the solvent mixture and dilute to 10 mL with the solvent mixture.

Reference solution (a) Dissolve 20 mg of *hydrocortisone hydrogen succinate CRS* in the solvent mixture and dilute to 20 mL with the solvent mixture.

Reference solution (b) Dissolve 10 mg of *methylprednisolone hydrogen succinate CRS* in reference solution (a) and dilute to 10 mL with reference solution (a).

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *anhydrous formic acid R*, *anhydrous ethanol R*, *methylene chloride R* (0.1:1:15 *V/V/V*).

Application 5 µL.

Development Over a path of 15 cm.

Drying In air.

Detection A Examine in ultraviolet light at 254 nm.

Results A The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

Detection B Spray with *alcoholic solution of sulfuric acid R*. Heat at 120 °C for 10 min or until the spots appear. Allow to cool. Examine in daylight and in ultraviolet light at 365 nm.

Results B The principal spot in the chromatogram obtained with the test solution is similar in position, colour in daylight, fluorescence in ultraviolet light at 365 nm and size to the principal spot in the chromatogram obtained with reference solution (a).

System suitability Reference solution (b):

— the chromatogram shows 2 spots which may, however, not be completely separated.

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C. Thin-layer chromatography (2.2.27).

Test solution (a) Dissolve 25 mg of the substance to be examined in methanol R with gentle heating and dilute to 5 mL with the same solvent (solution A). Dilute 2 mL of this solution to 10 mL with methylene chloride R.

Test solution (b) Transfer 2 mL of solution A to a 15 mL glass tube with a ground-glass stopper or a polytetrafluoroethylene cap. Add 10 mL of a 0.8 g/L solution of sodium hydroxide R in methanol R and immediately pass a stream of nitrogen R briskly through the solution for 5 min. Stopper the tube. Heat in a water-bath at 45 °C, protected from light, for 30 min. Allow to cool.

Reference solution (a) Dissolve 25 mg of hydrocortisone hydrogen succinate CRS in methanol R with gentle heating and dilute to 5 mL with the same solvent (solution B). Dilute 2 mL of this solution to 10 mL with methylene chloride R.

Reference solution (b) Transfer 2 mL of solution B to a 15 mL glass tube with a ground-glass stopper or a polytetrafluoroethylene cap. Add 10 mL of a 0.8 g/L solution of sodium hydroxide R in methanol R and immediately pass a stream of nitrogen R briskly through the solution for 5 min. Stopper the tube. Heat in a water-bath at 45 °C, protected from light, for 30 min. Allow to cool.

Plate TLC silica gel F_{254} plate R.

Mobile phase Add a mixture of 1.2 volumes of water R and 8 volumes of methanol R to a mixture of 15 volumes of ether R and 77 volumes of methylene chloride R.

Application 5 µL.

Developpement Over a path of 15 cm.

Drying In air.

Detection A Examine in ultraviolet light at 254 nm.

Results A The principal spot in each of the chromatograms obtained with the test solutions is similar in position and size to the principal spot in the chromatogram obtained with the corresponding reference solution.

Detection B Spray with alcoholic solution of sulfuric acid R. Heat at 120 °C for 10 min or until the spots appear. Allow to cool. Examine in daylight and in ultraviolet light at 365 nm.

Results B The principal spot in each of the chromatograms obtained with the test solutions is similar in position, colour in daylight, fluorescence in ultraviolet light at 365 nm and size to the principal spot in the chromatogram obtained with the corresponding reference solution. The principal spot in each of the chromatograms obtained with test solution (b) and reference solution (b) has an R_F value distinctly higher than that of the principal spot in each of the chromatograms obtained with test solution (a) and reference solution (a).

D. Add about 2 mg to 2 mL of sulfuric acid R and shake to dissolve. Within 5 min, an intense brownish-red colour develops with a green fluorescence which is particularly intense when viewed in ultraviolet light at 365 nm. Add this solution to 10 mL of water R and mix. The colour fades and a clear solution remains. The fluorescence in ultraviolet light does not disappear.

TESTS

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Appearance of solution

The solution is clear (*2.2.1*).

Dissolve 0.10 g in 5 mL of *sodium hydrogen carbonate solution R*.

Specific optical rotation (*2.2.7*)

+ 147 to + 153 (dried substance).

Dissolve 0.250 g in *anhydrous ethanol R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 25.0 mg of the substance to be examined in a mixture of equal volumes of *acetonitrile R* and *water R* and dilute to 10.0 mL with the same mixture of solvents.

Reference solution (a) Dissolve 2 mg of *hydrocortisone hydrogen succinate CRS* and 2 mg of *dexamethasone CRS* in 50 mL of *acetonitrile R*, then dilute to 100.0 mL with *water R*.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with a mixture of equal volumes of *acetonitrile R* and *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase In a 1000 mL volumetric flask mix 330 mL of *acetonitrile R* with 600 mL of *water R* and 1.0 mL of *phosphoric acid R*, then allow to equilibrate; dilute to 1000 mL with *water R* and mix again.

Flow rate 1 mL/min.

Detection Spectrophotometer at 254 nm.

Equilibration With the mobile phase for about 30 min.

Injection 20 µL.

Run time Twice the retention time of hydrocortisone hydrogen succinate.

Retention time Dexamethasone = about 12.5 min; hydrocortisone hydrogen succinate = about 15 min.

System suitability Reference solution (a):

— *resolution*: minimum 5.0 between the peaks due to dexamethasone and hydrocortisone hydrogen succinate; if necessary, adjust the concentration of acetonitrile in the mobile phase.

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Limits:

— *impurities A, B*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *total*: not more than 0.75 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.75 per cent);

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 4.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.100 g in *ethanol (96 per cent) R* and dilute to 100.0 mL with the same solvent. Dilute 2.0 mL of this solution to 100.0 mL with *ethanol (96 per cent) R*. Measure the absorbance (2.2.25) at the absorption maximum at 241.5 nm.

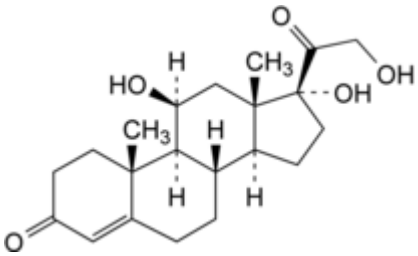
Calculate the content of $C_{25}H_{34}O_8$ taking the specific absorbance to be 353.

STORAGE

In an airtight container, protected from light.

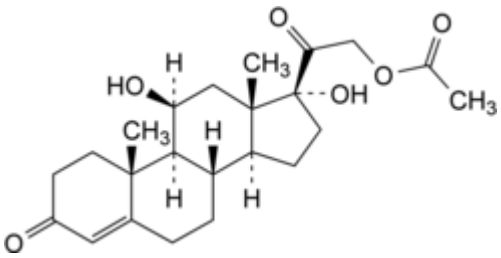
IMPURITIES

Specified impurities *A, B.*



A. 11β,17,21-trihydroxypregn-4-ene-3,20-dione (hydrocortisone),

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B. 11β,17-dihydroxy-3,20-dioxopregn-4-en-21-yl acetate (hydrocortisone acetate).

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Hydrocortisone Ointment

General Notices

Action and use

Corticosteroid.

DEFINITION

Hydrocortisone Ointment contains Hydrocortisone in a suitable basis.

The ointment complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of hydrocortisone, $C_{21}H_{30}O_5$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Complies with test A for Identification described under Hydrocortisone Cream but preparing solution (1) in the following manner. For ointments containing more than 0.5% w/w of Hydrocortisone, disperse a quantity containing 25 mg of Hydrocortisone in 5 mL of hot *hexane*, cool, extract with 10 mL of *methanol (90%)* and filter. For ointments containing 0.5% w/w or less of Hydrocortisone, disperse a quantity containing 5 mg of Hydrocortisone in 50 mL of hot *hexane*, cool, extract with 10 mL of *methanol (90%)* and filter.

B. In the Assay, the chromatogram obtained with solution (2) shows a peak with the same retention time as the peak due to hydrocortisone in the chromatogram obtained with solution (1).

ASSAY

Carry out the Assay described under Hydrocortisone Cream but prepare solution (2) in the following manner. For ointments containing more than 0.5% w/w of Hydrocortisone, disperse a quantity containing 25 mg of Hydrocortisone in 100 mL of hot *hexane*, cool and extract with 20 mL of a solution prepared by mixing 3 volumes of *methanol* with 1 volume of a 15% w/v solution of *sodium chloride*. Repeat the extraction using a further two 10 mL quantities of the methanolic sodium chloride solution. To the combined extracts add 5 mL of *methanol* and sufficient *water* to produce 100 mL, mix and filter through a glass microfibre filter (Whatman GF/C is suitable). For ointments containing 0.5% w/w or less of Hydrocortisone, prepare solution (2) in the same manner as solution (2) above but use a quantity containing 5 mg of Hydrocortisone.

STORAGE

Hydrocortisone Ointment should be protected from light.

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Hydrocortisone Oromucosal Tablets

General Notices

Action and use

Corticosteroid.

DEFINITION

Hydrocortisone Oromucosal Tablets are mucoadhesive buccal tablets containing hydrocortisone sodium succinate prepared by buffering Hydrocortisone Hydrogen Succinate.

The tablets comply with the requirements stated under Oromucosal Preparations and with the following requirements.

Content of hydrocortisone, $C_{21}H_{30}O_5$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

Carry out the method for *thin-layer chromatography*, Appendix III A, using a *TLC silica gel plate* (Merck silica gel 60 F_{254} plates are suitable) and a mixture of 20 volumes of *acetic anhydride*, 20 volumes of *water* and 60 volumes of *butan-1-ol* as the mobile phase. Apply separately to the plate 5 µL of each of the following solutions. For solution (1) shake a quantity of the tablets containing the equivalent of 25 mg of hydrocortisone with 10 mL of *methanol*, filter and use the filtrate. For solution (2) dissolve 50 mg of *hydrocortisone acetate* *BPCRS* in sufficient *methanol* to produce 20 mL. Solution (3) contains equal volumes of solutions (1) and (2). After removal of the plate, allow it to dry in air, spray with *ethanolic sulfuric acid (20%)*, heat at 120° for 10 minutes, allow to cool and examine under *ultraviolet light (365 nm)*. The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2). The test is not valid unless the chromatogram obtained with solution (3) shows a single compact spot.

TESTS

Disintegration

The tablets disintegrate in not less than 10 minutes when examined by the *disintegration test for tablets and capsules*, Appendix XII A1, but using *water* at 24° to 26°.

Free hydrocortisone

Not more than 15% of the stated amount when determined by the following method. Weigh and powder 20 tablets. For solution (1) disperse a quantity of the powdered tablets containing the equivalent of 7.5 mg of hydrocortisone in 15 mL of a phosphate buffer prepared by dissolving 5.8 g of *anhydrous disodium hydrogen orthophosphate* and 1.6 g of *sodium dihydrogen orthophosphate* in 1000 mL of *water* and

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adjusting the pH to 7.4, if necessary, by adding 10 mg quantities of either *anhydrous disodium hydrogen orthophosphate* or *sodium dihydrogen orthophosphate*. Shake and extract with three 25-mL quantities of *chloroform*, combine the extracts in a second separating funnel, wash the combined extracts with 2 mL of *water*, filter the chloroform layer through a plug of absorbent cotton, previously moistened with *chloroform*, into a 250-mL round-bottomed flask, wash the funnel and absorbent cotton plug with two 10-mL quantities of *chloroform* and add the washings to the flask; evaporate to dryness using a rotary evaporator, allow to cool and dissolve the residue in 50 mL of *aldehyde-free ethanol (96%)*. Solution (2) contains 0.00225% w/v of *hydrocortisone BPCRS* in *aldehyde-free ethanol (96%)*.

Protect all the solutions from light. Transfer 10 mL of solution (1) into a stoppered test-tube and repeat for solution (2). Place in a water bath at 35° for 10 minutes, add 1 mL of *triphenyltetrazolium chloride solution* and 1 mL of *dilute tetramethylammonium hydroxide solution* to each tube, stopper and mix well; allow the tubes to stand in the water bath at 35° for a further 25 minutes, remove from the water bath and allow to stand in water for 5 minutes at room temperature. Measure the *absorbance* of the resulting solutions in a stoppered cell at the maximum at 485 nm, Appendix II B, using in the reference cell a solution prepared at the same time and in the same manner using 10 mL of *aldehyde-free ethanol (96%)*.

Calculate the content of free hydrocortisone.

ASSAY

Weigh and powder 20 tablets. Shake a quantity of the powdered tablets containing the equivalent of 25 mg of hydrocortisone with 50 mL of *water* for 10 minutes, dilute to 100 mL with *water*, filter and discard the first 20 mL of the filtrate; dilute 4 mL of the remaining filtrate to 100 mL with *water* and measure the *absorbance*, Appendix II B, at the maximum at 248 nm using *water* in the reference cell. Calculate the content of hydrocortisone, $C_{21}H_{30}O_5$, in the tablets using 449 as the value of A(1%, 1 cm) at the maximum at 248 nm.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of hydrocortisone.

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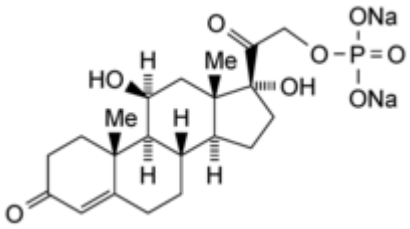
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Hydrocortisone Sodium Phosphate

General Notices



$C_{21}H_{29}Na_2O_8P$ 486.4 *6000-74-4*

Action and use

Corticosteroid.

Preparations

Hydrocortisone Sodium Phosphate Injection

Hydrocortisone Sodium Phosphate Oral Solution

DEFINITION

Hydrocortisone Sodium Phosphate is disodium 11β,17α-dihydroxy-3,20-dioxopregn-4-en-21-yl orthophosphate. It contains not less than 96.0% and not more than 103.0% of $C_{21}H_{29}Na_2O_8P$, calculated with reference to the anhydrous substance.

CHARACTERISTICS

A white or almost white powder; hygroscopic.

Freely soluble in *water*; practically insoluble in *absolute ethanol*.

IDENTIFICATION

Test A may be omitted if tests B, C and D are carried out. Tests B and C may be omitted if tests A and D are carried out.

A. The *infrared absorption spectrum*, Apppendix II A, is concordant with the *reference spectrum* of hydrocortisone sodium phosphate (*RS 386*).

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel G* as the coating substance and a freshly prepared mixture of 60 volumes of *butan-1-ol*, 20 volumes of *acetic anhydride* and 20 volumes of *water* as the mobile phase. Apply separately to the plate 2 µL of each of the following solutions. Solution (1) contains 0.25% w/v of the substance being examined in *methanol*. Solution (2)

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contains 0.25% w/v of *hydrocortisone sodium phosphate BPCRS* in *methanol*. Solution (3) is a mixture of equal volumes of solutions (1) and (2). Solution (4) is a mixture of equal volumes of solution (1) and a 0.25% w/v solution of *betamethasone sodium phosphate BPCRS* in *methanol*. After removal of the plate, allow it to dry in air until the solvent has evaporated, spray with *ethanolic sulfuric acid (20%)*, heat at 120° for 10 minutes and examine under *ultraviolet light (365 nm)*. The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2). The principal spot in the chromatogram obtained with solution (3) appears as a single, compact spot and the chromatogram obtained with solution (4) shows two principal spots with almost identical R_f values.

C. Dissolve 2 mg in 2 mL of *sulfuric acid*. A yellowish green fluorescence is produced immediately (distinction from betamethasone sodium phosphate, dexamethasone sodium phosphate and prednisolone sodium phosphate).

D. Heat gently 40 mg with 2 mL of *sulfuric acid* until white fumes are evolved, add *nitric acid* dropwise until oxidation is complete and cool. Add 2 mL of *water*, heat until white fumes are again evolved, cool, add 10 mL of *water* and neutralise to *litmus paper* with 5M *ammonia*. The resulting solution yields reaction A characteristic of *sodium salts* and reaction B characteristic of *phosphates*, Appendix VI.

TESTS

Alkalinity

pH of a 0.5% w/v solution, 7.5 to 9.0, Appendix V L.

Specific optical rotation

In a 1% w/v solution, +121 to +129, calculated with reference to the anhydrous substance, Appendix V F.

Inorganic phosphate

Dissolve 25 mg in 10 mL of *water*, add 4 mL of 1M *sulfuric acid*, 1 mL of a 10% w/v solution of *ammonium molybdate* and 2 mL of *methylaminophenol-sulfite reagent* and allow to stand for 15 minutes. Add sufficient *water* to produce 25 mL and allow to stand for a further 15 minutes. The *absorbance* of a 4-cm layer of the resulting solution at 730 nm, Appendix II B, is not more than that of a 4-cm layer of a solution prepared by treating 10 mL of a 0.0036% w/v solution of *potassium dihydrogen orthophosphate* in the same manner, beginning at the words ‘add 4 mL …’.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel* GF_{254} as the coating substance and a mixture of 77 volumes of *dichloromethane*, 15 volumes of *ether*, 8 volumes of *methanol* and 1.2 volumes of *water* as the mobile phase. Apply separately to the plate 2 µL of each of three solutions in *methanol* containing (1) 1.0% w/v of the substance being examined, (2) 1.0% w/v of *hydrocortisone sodium phosphate BPCRS* and (3) 0.020% w/v of *hydrocortisone BPCRS*. After removal of the plate, allow it to dry in air for 5 minutes and examine under *ultraviolet light (254 nm)*. Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (3) (2%).

Water

Not more than 10.0%, Appendix IX C. Use 0.4 g.

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ASSAY

Dissolve 0.1 g in sufficient *water* to produce 200 mL. Dilute 5 mL to 100 mL with *water* and measure the *absorbance* of the resulting solution at the maximum at 248 nm, Appendix II B. Calculate the content of $C_{21}H_{29}Na_2O_8P$ taking 333 as the value of A(1%, 1 cm) at the maximum at 248 nm.

STORAGE

Hydrocortisone Sodium Phosphate should be protected from light.

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Hydrocortisone Sodium Phosphate Injection

General Notices

Action and use

Corticosteroid.

DEFINITION

Hydrocortisone Sodium Phosphate Injection is a sterile solution of Hydrocortisone Sodium Phosphate in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of hydrocortisone, $C_{21}H_{30}O_5$

92.5 to 107.5% of the stated amount.

CHARACTERISTICS

A colourless or very pale yellow solution.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute a volume of the injection containing the equivalent of 0.25 g of hydrocortisone to 100 mL with *water*.

(2) 0.34% w/v of *hydrocortisone sodium phosphate BPCRS* in *methanol*.

(3) A mixture of equal volumes of solutions (1) and (2).

(4) A mixture of equal volumes of solution (1) and a 0.25% w/v solution of *betamethasone sodium phosphate BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow to dry in air until the solvent has evaporated, spray with *ethanolic sulfuric acid (20%)*, heat at 120° for 10 minutes and examine under *ultraviolet light (365 nm)*.

MOBILE PHASE

A freshly prepared mixture of 20 volumes of *acetic anhydride*, 20 volumes of *water* *and* 60 volumes of *butan-1-ol*.

CONFIRMATION

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The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

The principal spot in the chromatogram obtained with solution (3) appears as a single compact spot.

The chromatogram obtained with solution (4) exhibits two principal spots with almost identical Rf values.

B. Evaporate 0.1 mL to dryness on a water bath and dissolve the residue in 2 mL of *sulfuric acid*. A yellowish green fluorescence is produced immediately (distinction from betamethasone sodium phosphate, dexamethasone sodium phosphate and prednisolone sodium phosphate).

TESTS

Alkalinity

pH, 7.5 to 8.5, Appendix V L.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute a volume of the injection with *water* to contain the equivalent of 0.75% w/v of hydrocortisone.
(2) 1.0% w/v of *hydrocortisone sodium phosphate BPCRS* in *methanol*.
(3) 0.020% w/v of *hydrocortisone BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* GF_{254}.
(b) Use the mobile phase as described below.
(c) Apply 2 µL of each solution.
(d) Develop the plate to 15 cm.
(e) After removal of the plate, allow to dry in air for 5 minutes and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1.2 volumes of *water*, 8 volumes of *methanol*, 15 volumes of *ether* *and* 77 volumes of *dichloromethane*.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (3).

ASSAY

Dilute a volume containing the equivalent of 0.2 g of hydrocortisone to 1000 mL with *water*. To 5 mL add 15 mL of *water*, 2.5 g of *sodium chloride* and 0.5 mL of *hydrochloric acid* and extract with three 25-mL quantities of *chloroform*. Wash each chloroform layer with the same 1 mL quantity of 0.1M *hydrochloric acid*, add the washings to the aqueous solution and discard the chloroform. Extract the aqueous solution with two 10-mL quantities of *tributyl orthophosphate*, discard the aqueous phase and extract the combined tributyl phosphate solutions with

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two 25-mL quantities of a solution containing 10% w/v of *sodium chloride* and 1% w/v of *anhydrous disodium hydrogen orthophosphate*. Filter the extracts successively through absorbent cotton and wash the filter with 10 mL of the chloride–phosphate solution. Dilute the combined filtrates to 100 mL with the chloride–phosphate solution and measure the *absorbance* of the resulting solution at the maximum at 248 nm, Appendix II B, using in the reference cell a solution prepared in the same manner but using 20 mL of a solution containing 2.5 g of *sodium chloride* and 0.5 mL of *hydrochloric acid* and beginning at the words 'Extract the aqueous solution…'. Calculate the content of hydrocortisone sodium phosphate as $C_{21}H_{30}O_5$ taking 447 as the value of A(1%, 1 cm) at the maximum at 248 nm.

STORAGE

Hydrocortisone Sodium Phosphate Injection should be protected from light. The injection should not be allowed to freeze.

LABELLING

The strength is stated in terms of the equivalent amount of hydrocortisone in a suitable dose-volume.

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Hydrocortisone Sodium Phosphate Oral Solution

General Notices

NOTE: *This monograph has been developed to cover unlicensed formulations.*

Action and use

Corticosteroid.

DEFINITION

Hydrocortisone Sodium Phosphate Oral Solution is a solution containing Hydrocortisone Sodium Phosphate in a suitable flavoured vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral solution also complies with the requirements stated under Unlicensed Medicines.

Content of hydrocortisone, $C_{21}H_{30}O_5$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute a volume of the oral solution containing the equivalent of 0.25 g of hydrocortisone to 100 mL with *water*.

(2) 0.34% w/v of *hydrocortisone sodium phosphate BPCRS* in *methanol* .

(3) A mixture of equal volumes of solutions (1) and (2).

(4) A mixture of equal volumes of solution (1) and a 0.25% w/v solution of *betamethasone sodium phosphate BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air until the solvent has evaporated, spray with *ethanolic sulfuric acid (20%)*, heat at 120° for 10 minutes and examine under *ultraviolet light (365 nm)*.

MOBILE PHASE

A freshly prepared mixture of 20 volumes of *acetic anhydride*, 20 volumes of *water* and 60 volumes of *butan-1-ol*.

SYSTEM SUITABILITY

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The test is not valid unless the principal spot in the chromatogram obtained with solution (3) appears as a single compact spot and the chromatogram obtained with solution (4) exhibits two principal spots with almost identical Rf values.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. Evaporate 0.1 mL to dryness on a water bath and dissolve the residue in 2 mL of *sulfuric acid*. A yellowish green fluorescence is produced immediately (distinction from betamethasone sodium phosphate, dexamethasone sodium phosphate and prednisolone sodium phosphate).

TESTS

Alkalinity

pH, 7.5 to 8.5, Appendix V L.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute a suitable volume of the oral solution with *water* to contain the equivalent of 0.75% w/v of hydrocortisone.
(2) 1.0% w/v of *hydrocortisone sodium phosphate BPCRS* in *methanol*.
(3) Equal volumes of solutions (1) and (2).
(4) 0.020% w/v of *hydrocortisone BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* GF_{254}.
(b) Use the mobile phase described below.
(c) Apply 2 µL of each solution.
(d) Develop the plate to 15 cm.
(e) After removal of the plate, allow it to dry in air for 5 minutes and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1.2 volumes of *water*, 8 volumes of *methanol*, 15 volumes of *ether* and 77 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the principal spot in the chromatogram obtained with solution (3) appears as a single compact spot.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (4) (3%).

ASSAY

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Dilute a volume of the oral solution containing the equivalent of 20 mg of hydrocortisone to 100 mL with *water*. To 5 mL add 15 mL of *water*, 2.5 g of *sodium chloride* and 0.5 mL of *hydrochloric acid* and extract with three 25-mL quantities of *chloroform*. Wash each chloroform layer with the same 1 mL quantity of 0.1M *hydrochloric acid*, add the washings to the aqueous solution and discard the chloroform. Extract the aqueous solution with two 10-mL quantities of *tributyl orthophosphate*, discard the aqueous phase and extract the combined tributyl phosphate solutions with two 25-mL quantities of a solution containing 10% w/v of *sodium chloride* and 1% w/v of *anhydrous disodium hydrogen orthophosphate*. Filter the extracts successively through absorbent cotton and wash the filter with 10 mL of the chloride–phosphate solution. Dilute the combined filtrates to 100 mL with the chloride–phosphate solution and measure the *absorbance* of the resulting solution at the maximum at 248 nm, Appendix II B, using in the reference cell a solution prepared in the same manner but using 20 mL of a solution containing 2.5 g of *sodium chloride* and 0.5 mL of *hydrochloric acid* and beginning at the words 'Extract the aqueous solution …'. Calculate the content of hydrocortisone sodium phosphate as $C_{21}H_{30}O_5$ taking 447 as the value of A (1%, 1 cm) at the maximum at 248 nm.

STORAGE

Hydrocortisone Sodium Phosphate Oral Solution should be protected from light. The oral solution should not be allowed to freeze.

LABELLING

The strength is stated in terms of the equivalent amount of hydrocortisone in a suitable dose-volume.

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Hydrocortisone Sodium Succinate Injection

General Notices

Action and use

Corticosteroid.

DEFINITION

Hydrocortisone Sodium Succinate Injection is a sterile solution of Hydrocortisone Sodium Succinate in Water for Injections. It is prepared by dissolving Hydrocortisone Sodium Succinate for Injection in the requisite amount of Water for Injections immediately before use.

The injection complies with the requirements stated under Parenteral Preparations.

STORAGE

Hydrocortisone Sodium Succinate Injection deteriorates on storage and should be used immediately after preparation.

HYDROCORTISONE SODIUM SUCCINATE FOR INJECTION

DEFINITION

Hydrocortisone Sodium Succinate for Injection is a sterile material prepared from Hydrocortisone Hydrogen Succinate with the aid of a suitable alkali. It may contain excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of hydrocortisone, $C_{21}H_{30}O_5$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of hydrocortisone sodium succinate *(RS 180)*.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in 1 volume of *methanol* and 9 volumes of *dichloromethane*.

(1) 0.1% w/v solution of the contents of the sealed container.

(2) 0.1% w/v of *hydrocortisone hydrogen succinate BPCRS*.

(3) 0.1% w/v each of *hydrocortisone hydrogen succinate BPCRS* and *methylprednisolone hydrogen succinate EPCRS*.

CHROMATOGRAPHIC CONDITIONS

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(a) Use as the coating *silica gel GF_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow to dry in air and examine in daylight and under *ultraviolet light (365 nm)*.

MOBILE PHASE

1 volume of *anhydrous formic acid*, 10 volumes of *absolute ethanol* and 150 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless, by each method of visualisation, the chromatogram obtained with solution (3) shows two spots which may not be completely separated.

CONFIRMATION

By each method of visualisation, the principal spot in the chromatogram obtained with solution (1) corresponds in position to that in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity

pH of a solution containing the equivalent of 5% w/v of hydrocortisone, 6.5 to 8.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve a sufficient quantity of the contents of the sealed container in a mixture of equal volumes of *acetonitrile* and *water* to produce a solution containing the equivalent of 0.25% w/v of hydrocortisone.

(2) Dilute 2 volumes of solution (1) to 100 volumes with a mixture of equal volumes of *acetonitrile* and *water*.

(3) Dilute 1 volume of a 0.035% w/v solution of *hydrocortisone BPCRS* in *acetonitrile* to 2 volumes with *water*.

(4) Dilute a solution containing 0.04% w/v each of *hydrocortisone hydrogen succinate BPCRS* and *dexamethasone BPCRS* in *acetonitrile* with an equal volume of *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for twice the retention time of the principal peak.

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MOBILE PHASE

330 volumes of *acetonitrile*, 600 volumes of *water* and 1 volume of *orthophosphoric acid* which is allowed to equilibrate and then diluted to 1000 volumes with *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution factor* between the peaks corresponding to dexamethasone and hydrocortisone hydrogen succinate is at least 5.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to hydrocortisone is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (7%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (2%).

Uniformity of content

The content of hydrocortisone in each of 10 individual containers as determined in the Assay is not less than 92.5% and not more than 107.5% of the content of hydrocortisone stated on the label, except that in one container the weight may be not less than 85.0% and not more than 115.0% of the stated content.

ASSAY

Dissolve the contents of a sealed container in sufficient *water* to produce a solution containing the equivalent of 0.001% w/v of hydrocortisone. Measure the *absorbance* of the resulting solution at the maximum at 248 nm, Appendix II B, and calculate the content of $C_{21}H_{30}O_5$ taking 449 as the value of A(1%, 1 cm) at the maximum at 248 nm. Repeat the procedure with a further nine sealed containers and calculate the average content of $C_{21}H_{30}O_5$ per container from the ten individual results thus obtained.

LABELLING

The label of the sealed container states the quantity of hydrocortisone sodium succinate contained in it in terms of the equivalent amount of hydrocortisone.

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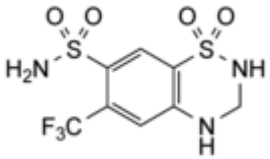
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Hydroflumethiazide

General Notices



$C_8H_8F_3N_3O_4S_2$ 331.3 *135-09-1*

Action and use

Thiazide diuretic.

DEFINITION

Hydroflumethiazide is 3,4-dihydro-6-trifluoromethyl-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. It contains not less than 98.0% and not more than 102.0% of $C_8H_8F_3N_3O_4S_2$, calculated with reference to the dried substance.

CHARACTERISTICS

White or almost white, glistening crystals or crystalline powder.

Practically insoluble in *water*; soluble in *ethanol (96%)*; practically insoluble in *ether*.

IDENTIFICATION

The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of hydroflumethiazide *(RS 181)*.

TESTS

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *acetone*.

(1) 1% w/v of the substance being examined.

(2) 0.01% w/v of the substance being examined.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

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(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it in a current of air and reveal the spots by *Method I*.

MOBILE PHASE

Ethyl acetate.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2).

Loss on drying

When dried to constant weight at 105°C, loses not more than 0.5% of its weight. Use 1 g.

Sulfated ash

Not more than 0.1%, Appendix IX A.

ASSAY

Dissolve 0.3 g in 50 mL of *anhydrous pyridine* and carry out Method II for *non-aqueous titration*, Appendix VIII A, using 0.1M *tetrabutylammonium hydroxide VS* as titrant and determining the end point potentiometrically. Each mL of 0.1M *tetrabutylammonium hydroxide VS* is equivalent to 16.56 mg of $C_8H_8F_3N_3O_4S_2$.

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Hydrogen Peroxide Mouthwash

General Notices

DEFINITION

Hydrogen Peroxide Mouthwash is Hydrogen Peroxide Solution (6 per cent).

The mouthwash complies with the requirements stated under Oromucosal Preparations and with the following requirements.

Content of hydrogen peroxide, H_2O_2

5.0 to 7.0% w/v.

IDENTIFICATION;

Acidity; Non-volatile matter; Organic stabilisers Complies with the requirements stated under Hydrogen Peroxide Solution (6 per cent).

ASSAY

Dilute 10 mL to 100 mL with *water*. To 10 mL of the resulting solution add 20 mL of 1M *sulfuric acid* and titrate with 0.02M *potassium permanganate VS*. Each mL of 0.02M *potassium permanganate VS* is equivalent to 1.701 mg of H_2O_2.

STORAGE

Hydrogen Peroxide Mouthwash should be protected from light.

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Hydrogen Peroxide Solution (3 per cent)

General Notices

Dilute Hydrogen Peroxide Solution

(Ph. Eur. monograph 0395)

Action and use

Antiseptic; deodorant.

When hydrogen peroxide is prescribed or demanded, Hydrogen Peroxide Solution (6 per cent) shall be dispensed or supplied.

Ph Eur

DEFINITION

Content

2.5 per cent *m/m* to 3.5 per cent *m/m* of H_2O_2 (M_r 34.01).

1 volume of hydrogen peroxide solution (3 per cent) corresponds to about 10 times its volume of oxygen. A suitable stabiliser may be added.

CHARACTERS

Appearance

Colourless, clear liquid.

IDENTIFICATION

A. To 2 mL, add 0.2 mL of *dilute sulfuric acid R* and 0.2 mL of *0.02 M potassium permanganate*. The solution becomes colourless or slightly pink within 2 min.

B. To 1 mL, add 0.1 mL of *dilute hydrochloric acid R* and 0.1 mL of *potassium iodide solution R*. A brown colour appears. Black particles may be formed.

C. It complies with the requirement for the content of H_2O_2.

TESTS

Acidity

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To 10 mL, add 20 mL of *water R* and 0.25 mL of *methyl red solution R*. Not less than 0.05 mL and not more than 1.0 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator.

Organic stabilisers

Maximum 250 ppm.

Shake 20 mL with 10 mL of *chloroform R* and then with 2 quantities, each of 5 mL, of *chloroform R*. Evaporate the combined chloroform layers under reduced pressure at a temperature not exceeding 25 °C and dry in a desiccator. The residue weighs a maximum of 5 mg.

Non-volatile residue

Maximum 2 g/L.

Allow 10 mL to stand in a platinum dish until all effervescence has ceased. Evaporate to dryness on a water-bath and dry at 100-105 °C. The residue weighs a maximum of 20 mg.

ASSAY

Dilute 10.0 g to 100.0 mL with *water R*. To 10.0 mL of this solution add 20 mL of *dilute sulfuric acid R*. Titrate with *0.02 M potassium permanganate* until a pink colour is obtained.

1 mL of *0.02 M potassium permanganate* is equivalent to 1.701 mg of H_2O_2 or 0.56 mL of oxygen.

STORAGE

Protected from light, and if the solution does not contain a stabiliser, at a temperature below 15 °C.

LABELLING

If the solution contains a stabiliser, the label states that the contents are stabilised. The competent authority may require that the name of the stabiliser be stated on the label.

CAUTION

It decomposes in contact with oxidisable organic matter and with certain metals and if allowed to become alkaline.

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Hydrogen Peroxide Solution (6 per cent)

General Notices

Hydrogen Peroxide Solution

Action and use

Antiseptic; deodorant.

Preparations

Hydrogen Peroxide Mouthwash

When hydrogen peroxide is prescribed or demanded, Hydrogen Peroxide Solution (6 per cent) shall be dispensed or supplied.

DEFINITION

Hydrogen Peroxide Solution (6 per cent) is an aqueous solution of hydrogen peroxide containing not less than 5.0% w/v and not more than 7.0% w/v of H_2O_2 (34.01), corresponding to about 20 times its volume of available oxygen. It may contain a suitable stabilising agent.

CHARACTERISTICS

A clear, colourless liquid. It decomposes in contact with oxidisable organic matter and with certain metals and if allowed to become alkaline.

IDENTIFICATION

A. To 1 mL add 0.2 mL of 1M *sulfuric acid* and 0.25 mL of 0.02M *potassium permanganate*. The solution becomes colourless with evolution of gas.

B. Shake 0.05 mL with 2 mL of 1M *sulfuric acid*, 2 mL of *ether* and 0.05 mL of *potassium chromate solution*. The ether layer is blue.

C. Complies with the requirement for the content of H_2O_2.

TESTS

Acidity

Dilute 10 mL with 20 mL of *water* and add 0.25 mL of *methyl red solution*. Not less than 0.05 mL and not more than 1.0 mL of *0.1M sodium hydroxide VS* is required to change the colour of the solution.

Organic stabilisers

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Shake 20 mL with successive quantities of 10, 5 and 5 mL of *chloroform*. Evaporate the combined chloroform extracts at a temperature not exceeding 25° at a pressure of 2 kPa and dry in a desiccator. Any residue weighs not more than 5 mg (250 ppm).

Non-volatile matter

Place 10 mL in a platinum dish and allow to stand until effervescence has ceased, cooling if necessary. Evaporate the solution on a water bath. Any residue, when dried at 100° to 105°, weighs not more than 20 mg (0.2% w/v).

ASSAY

Dilute 10 mL to 100 mL with *water*. To 10 mL of the resulting solution add 20 mL of 1M *sulfuric acid* and titrate with 0.02M *potassium permanganate VS*. Each mL of 0.02M *potassium permanganate VS* is equivalent to 1.701 mg of H_2O_2 or 0.56 mL of oxygen.

STORAGE

Hydrogen Peroxide Solution (6 per cent) should be protected from light. If the solution does not contain a stabilising agent, it should be stored at a temperature not exceeding 15°. It should not be stored for long periods.

LABELLING

The label states, where applicable, that the solution contains a stabilising agent.

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Hydrogen Peroxide Solution (30 per cent)

General Notices

(Ph. Eur. monograph 0396)

7722-84-1

Action and use

Antiseptic; deodorant.

When hydrogen peroxide is prescribed or demanded, Hydrogen Peroxide Solution (6 per cent) shall be dispensed or supplied.

Ph Eur

DEFINITION

Content

29.0 per cent *m/m* to 31.0 per cent *m/m* of H_2O_2 (M_r 34.01).

1 volume of hydrogen peroxide solution (30 per cent) corresponds to about 110 times its volume of oxygen. A suitable stabiliser may be added.

CHARACTERS

Appearance

Colourless, clear liquid.

IDENTIFICATION

A. To 1 mL, add 0.2 mL of *dilute sulfuric acid R* and 0.25 mL of *0.02 M potassium permanganate*. The solution becomes colourless with evolution of gas.

B. To 1 mL, add 0.1 mL of *dilute hydrochloric acid R* and 0.1 mL of *potassium iodide solution R*. A brown colour appears. Black particles may be formed.

C. It complies with the requirement for the content of H_2O_2.

TESTS

Acidity

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To 10 mL, add 100 mL of *water R* and 0.25 mL of *methyl red solution R*. Not less than 0.05 mL and not more than 0.5 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator.

Organic stabilisers

Maximum 500 ppm.

Shake 20 mL with 10 mL of *chloroform R* and then with 2 quantities, each of 5 mL, of *chloroform R*. Evaporate the combined chloroform layers under reduced pressure at a temperature not exceeding 25 °C and dry in a desiccator. The residue weighs a maximum of 10 mg.

Non-volatile residue

Maximum 2 g/L.

Allow 10 mL to stand in a platinum dish until all effervescence has ceased, cooling if necessary. Evaporate to dryness on a water-bath and dry at 100-105 °C. The residue weighs a maximum of 20 mg.

ASSAY

Dilute 1.00 g to 100.0 mL with *water R*. To 10.0 mL of this solution add 20 mL of *dilute sulfuric acid R*. Titrate with *0.02 M potassium permanganate* until a pink colour is obtained.

1 mL of *0.02 M potassium permanganate* is equivalent to 1.701 mg of H_2O_2 or 0.56 mL of oxygen.

STORAGE

Protected from light, and if the solution does not contain a stabiliser, at a temperature below 15 °C.

LABELLING

If the solution contains a stabiliser, the label states that the contents are stabilised. The competent authority may require that the name of the stabiliser be stated on the label.

CAUTION

It decomposes vigorously in contact with oxidisable organic matter and with certain metals and if allowed to become alkaline.

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Hydrogenated Arachis Oil

General Notices

Hydrogenated Peanut Oil

(Ph. Eur. monograph 1171)

Ph Eur

DEFINITION

Oil obtained by refining, bleaching, hydrogenating and deodorising oil obtained from the shelled seeds of *Arachis hypogaea* L. Each type of hydrogenated arachis oil is characterised by its nominal drop point.

CHARACTERS

Appearance

White or faintly yellowish, soft mass which melts to a clear, pale yellow liquid when heated.

Solubility

Practically insoluble in water, freely soluble in methylene chloride and in light petroleum (bp: 65-70 °C), very slightly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, C.

Second identification: A, B.

A. Drop point (see Tests).

B. Identification of fatty oils by thin-layer chromatography (*2.3.2*).

Results The chromatogram obtained is similar to the corresponding chromatogram shown in Figure 2.3.2.-1.

C. Composition of fatty acids (see Tests).

TESTS

Drop point (*2.2.17*)

32 °C to 43 °C, and within 3 °C of the nominal value.

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Acid value (2.5.1)

Maximum 0.5.

Dissolve 10.0 g in 50 mL of the prescribed solvent by heating on a water-bath.

Peroxide value (2.5.5, Method A)

Maximum 5.0.

Dissolve 5.0 g in 30 mL of the prescribed solvent by heating on a water-bath.

Unsaponifiable matter (2.5.7)

Maximum 1.0 per cent, determined on 5.0 g.

Alkaline impurities (2.4.19)

It complies with the test.

Composition of fatty acids

Gas chromatography (2.4.22, Method A) with the following modifications. Use the mixture of calibrating substances in Table 2.4.22.-3.

Column:

— *material*: fused silica;

— *size*: *l* = 25 m, Ø = 0.25 mm;

— *stationary phase*: cyanopropylpolysiloxane R (film thickness 0.2 µm).

Carrier gas helium for chromatography R.

Flow rate 0.7 mL/min.

Split ratio 1:100.

Temperature:

— *column*: 180 °C for 20 min;

— *injection port and detector*: 250 °C.

Detection Flame ionisation.

Composition of the fatty-acid fraction of the substance:

— *saturated fatty acids of chain length less than* C_{14}: maximum 0.5 per cent;

— *myristic acid*: maximum 0.5 per cent;

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— *palmitic acid*: 5.0 per cent to 16.0 per cent;

— *stearic acid*: 3.0 per cent to 19.0 per cent;

— *oleic acid and isomers*: 54.0 per cent to 78.0 per cent;

— *linoleic acid and isomers*: maximum 10.0 per cent;

— *arachidic acid*: 1.0 per cent to 3.0 per cent;

— *eicosenoic acids*: maximum 2.1 per cent;

— *behenic acid*: 1.0 per cent to 5.0 per cent;

— *erucic acid and isomers*: maximum 0.5 per cent;

— *lignoceric acid*: 0.5 per cent to 3.0 per cent.

STORAGE

Protected from light.

LABELLING

The label states the nominal drop point.

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Hydrogenated Castor Oil

General Notices

(Ph. Eur. monograph 1497)

Action and use

Excipient.

Ph Eur

DEFINITION

Fatty oil obtained by hydrogenation of *Virgin castor oil (0051)* or *Refined castor oil (2367)* or a mixture of both. It consists mainly of the triglyceride of 12-hydroxystearic ((12Ξ)-12-hydroxyoctadecanoic) acid.

CHARACTERS

Appearance

Fine, almost white or pale yellow powder or almost white or pale yellow masses or flakes.

Solubility

Practically insoluble in water, slightly soluble in methylene chloride, very slightly soluble in anhydrous ethanol, practically insoluble in light petroleum.

IDENTIFICATION

A. Melting point (*2.2.14*): 83 °C to 88 °C.

B. Hydroxyl value (see Tests).

C. Composition of fatty acids (see Tests).

TESTS

Acid value (*2.5.1*)

Maximum 4.0, determined on 10.0 g dissolved in 75 mL of hot *ethanol (96 per cent) R*.

Hydroxyl value (*2.5.3, Method A*)

145 to 165, determined on a warm solution.

Iodine value (*2.5.4, Method A*)

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Maximum 5.0.

Alkaline impurities

Dissolve 1.0 g with gentle heating in a mixture of 1.5 mL of *ethanol (96 per cent) R* and 3 mL of *toluene R*. Add 0.05 mL of a 0.4 g/L solution of *bromophenol blue R* in *ethanol (96 per cent) R*. Not more than 0.2 mL of *0.01 M hydrochloric acid* is required to change the colour of the indicator to yellow.

Composition of fatty acids

Gas chromatography (*2.4.22, Method A*) with the following modifications. Use the mixture of calibrating substances in Table 2.4.22.-3.

Test solution Introduce 75 mg of the substance to be examined into a 10 mL centrifuge tube with a screw cap. Dissolve in 2 mL of *1,1-dimethylethyl methyl ether R1* by shaking and heat gently (50-60 °C). Add, when still warm, 1 mL of a 12 g/L solution of *sodium R* in *anhydrous methanol R*, prepared with the necessary precautions, and mix vigorously for at least 5 min. Add 5 mL of *distilled water R* and mix vigorously for about 30 s. Centrifuge for 15 min at 1500 *g*. Use the upper layer.

Reference solution Dissolve 50 mg of *methyl 12-hydroxystearate CRS* and 50 mg of *methyl stearate CRS* in 10.0 mL of *1,1-dimethylethyl methyl ether R1*.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m; Ø = 0.25 mm;

— *stationary phase*: *macrogol 20 000 R* (film thickness 0.25 µm).

Carrier gas *helium for chromatography R*.

Flow rate 0.9 mL/min.

Split ratio 1:100.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 55	215
Injection port		250
Detector		250

Detection Flame ionisation.

Injection 1 µL.

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System suitability:

— *symmetry factor*: 0.7 to 1.5 for the peak due to methyl stearate in the chromatogram obtained with the test solution.

Calculate the fraction of each fatty acid using the following expression:

$$A_{x,s,c} / \sum A_{x,s,c} \times 100 \text{ per cent } m/m$$

$A_{x,s,c}$ = corrected peak area of the fatty acid in the test solution:

$$A_{x,s,c} = A_{x,s} \times R_c$$

$A_{x,s}$ = area of the peaks due to any specified or unspecified fatty acid methyl esters;

R_c = relative correction factor for the peak due to methyl 12-hydroxystearate:

$$R_c = \frac{m_{1,r} \times A_{2,r}}{A_{1,r} \times m_{2,r}}$$

R_c = 1 for peaks corresponding to each of the other specified fatty acids or any unspecified fatty acid;

$m_{1,r}$ = mass of methyl 12-hydroxystearate in the reference solution;

$m_{2,r}$ = mass of methyl stearate in the reference solution;

$A_{1,r}$ = area of the peak due to methyl 12-hydroxystearate in the chromatogram obtained with the reference solution;

$A_{2,r}$ = area of the peak due to methyl stearate in the chromatogram obtained with the reference solution.

Composition of the fatty-acid fraction of the oil:

— *palmitic acid*: maximum 2.0 per cent;

— *stearic acid*: 7.0 per cent to 14.0 per cent;

— *arachidic acid*: maximum 1.0 per cent;

— *12-oxostearic acid*: maximum 5.0 per cent;

— *12-hydroxystearic acid*: 78.0 per cent to 91.0 per cent;

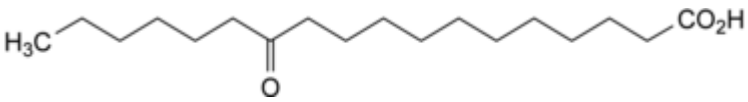
— *any other fatty acid*: for each fatty acid, maximum 3.0 per cent.

STORAGE

In a well-filled container.

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IMPURITIES



A. 12-oxooctadecanoic acid (12-oxostearic acid).

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Hydrogenated Cottonseed Oil

General Notices

(Ph. Eur. monograph 1305)

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DEFINITION

Product obtained by refining and hydrogenation of oil obtained from seeds of cultivated plants of various varieties of *Gossypium hirsutum* L. or of other species of *Gossypium*. The product consists mainly of triglycerides of palmitic and stearic acids.

CHARACTERS

Appearance

White or almost white mass or powder which melts to a clear, pale yellow liquid when heated.

Solubility

Practically insoluble in water, freely soluble in methylene chloride and in toluene, very slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Melting point (see Tests).

B. Composition of fatty acids (see Tests).

TESTS

Melting point (*2.2.14*)

57 °C to 70 °C.

Acid value (*2.5.1*)

Maximum 0.5.

Dissolve 10.0 g in 50 mL of a hot mixture of equal volumes of *ethanol (96 per cent) R* and *toluene R*, previously neutralised with *0.1 M potassium hydroxide* using 0.5 mL of *phenolphthalein solution R1* as indicator. Titrate the solution immediately while still hot.

Peroxide value (*2.5.5, Method A*)

Maximum 5.0.

Unsaponifiable matter (2.5.7)

Unsaponifiable matter (2.5.7)

Maximum 1.0 per cent, determined on 5.0 g.

Alkaline impurities

Dissolve with gentle heating 2.0 g in a mixture of 1.5 mL of *ethanol (96 per cent) R* and 3 mL of *toluene R*. Add 0.05 mL of a 0.4 g/L solution of *bromophenol blue R* in *ethanol (96 per cent) R*. Not more than 0.4 mL of *0.01 M hydrochloric acid* is required to change the colour to yellow.

Composition of fatty acids

Gas chromatography (*2.4.22, Method A*) with the following modifications. Use the mixture of calibrating substances in Table 2.4.22.-3.

Column:

— *material*: fused silica;

— *size*: *l* = 25 m, Ø = 0.25 mm;

— *stationary phase*: *cyanopropylpolysiloxane R* (film thickness 0.2 µm).

Carrier gas *helium for chromatography R*.

Flow rate 0.65 mL/min.

Split ratio 1:100.

Temperature:

— *column*: 180 °C for 35 min;

— *injection port and detector*: 250 °C.

Detection Flame ionisation.

Composition of the fatty-acid fraction of the substance:

— *saturated fatty acids of chain length less than* C_{14}: maximum 0.2 per cent;

— *myristic acid*: maximum 1.0 per cent;

— *palmitic acid*: 19.0 per cent to 26.0 per cent;

— *stearic acid*: 68.0 per cent to 80.0 per cent;

— *oleic acid and isomers*: maximum 4.0 per cent;

— *linoleic acid and isomers*: maximum 1.0 per cent;

— *arachidic acid*: maximum 1.0 per cent;

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— *behenic acid*: maximum 1.0 per cent;

— *lignoceric acid*: maximum 0.5 per cent.

STORAGE

Protected from light.

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Hydrogenated Polyoxyl Castor Oil

General Notices

(Macrogolglycerol Hydroxystearate, Ph. Eur. monograph 1083)

Ph Eur

DEFINITION

Contains mainly tris(12-hydroxystearyl) glycerol ethoxylated with 7 to 60 molecules of ethylene oxide (nominal value), with small amounts of macrogol hydroxystearate and of the corresponding free glycols. It results from the reaction of hydrogenated castor oil with ethylene oxide.

CHARACTERS

Appearance

— if less than 10 units of ethylene oxide per molecule: yellowish, turbid, viscous liquid;

— if more than 20 units of ethylene oxide per molecule: white or yellowish semi-liquid or pasty mass.

Solubility

— if less than 10 units of ethylene oxide per molecule: practically insoluble in water, soluble in acetone, dispersible in ethanol (96 per cent);

— if more than 20 units of ethylene oxide per molecule: freely soluble in water, in acetone and in ethanol (96 per cent), practically insoluble in light petroleum.

IDENTIFICATION

A. Iodine value (see Tests).
B. Saponification value (see Tests).
C. Thin-layer chromatography (*2.2.27*).

Test solution To 1 g of the substance to be examined, add 100 mL of a 100 g/L solution of *potassium hydroxide R* and boil under a reflux condenser for 30 min. Allow to cool. Acidify the solution with 20 mL of *hydrochloric acid R*. Shake the mixture with 50 mL of *ether R* and allow to stand until separation of the layers is obtained. Transfer the clear upper layer to a suitable tube, add 5 g of *anhydrous sodium sulfate R*, close the tube and allow to stand for 30 min. Filter and evaporate the filtrate to dryness on a water-bath. Dissolve 50 mg of the residue in 25 mL of *ether R*.

Reference solution Dissolve 50 mg of *12-hydroxystearic acid R* in *methylene chloride R* and dilute to 25 mL with the same solvent.

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Plate *TLC octadecylsilyl silica gel plate R*.

Mobile phase *methylene chloride R*, *glacial acetic acid R*, *acetone R* (10:40:50 *V/V/V*).

Application 2 µL.

Development Over a path of 8 cm.

Drying In a current of cold air.

Detection Spray with a 80 g/L solution of *phosphomolybdic acid R* in *2-propanol R* and heat at 120 °C for about 1-2 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and colour to the principal spot in the chromatogram obtained with the reference solution.

D. Place about 2 g in a test-tube and add 0.2 mL of *sulfuric acid R*. Close the tube using a stopper fitted with a glass tube bent twice at right angles. Heat the tube until white fumes appear. Collect the fumes in 1 mL of *mercuric chloride solution R*. A white precipitate is formed and the fumes turn a filter paper impregnated with *alkaline potassium tetraiodomercurate solution R* black.

TESTS

Solution S

Dissolve 5.0 g of macrogolglycerol hydroxystearate with less than 40 units of ethylene oxide per molecule in a mixture of 50 volumes of *acetone R* and 50 volumes of *anhydrous ethanol R* and dilute to 50 mL with the same mixture of solvents.

Dissolve 5.0 g of macrogolglycerol hydroxystearate with 40 units or more of ethylene oxide per molecule in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is not more opalescent than reference suspension III (*2.2.1*) and not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

Alkalinity

To 2 mL of solution S add 0.5 mL of *bromothymol blue solution R1*. The solution is not blue.

Acid value (*2.5.1*)

Maximum 2.0, determined on 5.0 g.

Hydroxyl value (*2.5.3, Method A*)

See Table 1083.-1.

Iodine value (*2.5.4*)

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Maximum 5.0.

Saponification value (*2.5.6*)

See Table 1083.-1.

Table 1083.-1

Ethylene oxide units per molecule (nominal value)	Hydroxyl value	Saponification value
7	115 - 135	125 - 140
25	70 - 90	70 - 90
40	57 - 80	45 - 69
60	45 - 67	40 - 51

Residual ethylene oxide and dioxan (*2.4.25*)

Maximum 1 ppm of residual ethylene oxide and 10 ppm of residual dioxan.

Water (*2.5.12*)

Maximum 3.0 per cent, determined on 2.000 g.

Total ash (*2.4.16*)

Maximum 0.3 per cent, determined on 2.0 g.

LABELLING

The label states the number of ethylene oxide units per molecule (nominal value).

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Hydrogenated Soya Oil

General Notices

Hydrogenated Soyabean Oil

(Hydrogenated Soya-bean Oil, Ph. Eur. monograph 1265)

Action and use

Excipient.

Ph Eur

DEFINITION

Product obtained by refining, bleaching, hydrogenation and deodorisation of oil obtained from seeds of *Glycine max* (L.) Merr. (*G. hispida* (Moench) Maxim.). The product consists mainly of triglycerides of palmitic and stearic acids.

CHARACTERS

Appearance

White or almost white mass or powder which melts to a clear, pale yellow liquid when heated.

Solubility

Practically insoluble in water, freely soluble in methylene chloride, in light petroleum (bp: 65-70 °C) after heating and in toluene, very slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Melting point (see Tests).

B. Composition of fatty acids (see Tests).

TESTS

Melting point (*2.2.15*)

66 °C to 72 °C.

Acid value (*2.5.1*)

Maximum 0.5.

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Dissolve 10.0 g in 50 mL of a hot mixture of equal volumes of *ethanol (96 per cent) R* and *toluene R*, previously neutralised with *0.1 M potassium hydroxide* using 0.5 mL of *phenolphthalein solution R1* as indicator. Titrate the solution immediately while still hot.

Peroxide value (*2.5.5, Method A*)

Maximum 5.0.

Unsaponifiable matter (*2.5.7*)

Maximum 1.0 per cent, determined on 5.0 g.

Alkaline impurities (*2.4.19*)

Dissolve 2.0 g with gentle heating in a mixture of 1.5 mL of *ethanol (96 per cent) R* and 3 mL of *toluene R*. Add 0.05 mL of a 0.4 g/L solution of *bromophenol blue R* in *ethanol (96 per cent) R*. Not more than 0.4 mL of *0.01 M hydrochloric acid* is required to change the colour to yellow.

Composition of fatty acids

Gas chromatography (*2.4.22, Method A*) with the following modifications. Use the mixture of calibrating substances in Table 2.4.22.-3.

Column:

— *material*: fused silica;

— *size*: *l* = 25 m, Ø = 0.25 mm;

— *stationary phase*: *cyanopropylpolysiloxane R* (film thickness 0.2 µm).

Carrier gas *helium for chromatography R*.

Flow rate 0.65 mL/min.

Split ratio 1:100.

Temperature:

— *column*: 180 °C for 20 min;

— *injection port and detector*: 250 °C.

Detection Flame ionisation.

Composition of the fatty-acid fraction of the substance:

— *saturated fatty acids of chain length less than* C_{14}: maximum 0.1 per cent;

— *myristic acid*: maximum 0.5 per cent;

— *palmitic acid*: 9.0 per cent to 16.0 per cent;

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— *stearic acid*: 79.0 per cent to 89.0 per cent;

— *oleic acid and isomers*: maximum 4.0 per cent;

— *linoleic acid and isomers*: maximum 1.0 per cent;

— *linolenic acid and isomers*: maximum 0.2 per cent;

— *arachidic acid*: maximum 1.0 per cent;

— *behenic acid*: maximum 1.0 per cent.

STORAGE

Protected from light.

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Hydrogenated Vegetable Oil

General Notices

68334-00-9

Action and use

Excipient.

DEFINITION

Hydrogenated Vegetable Oil is a mixture of triglycerides of fatty acids of vegetable origin.

CHARACTERISTICS

An almost white, fine powder at room temperature and a pale yellow, oily liquid above its melting point.

Practically insoluble in *water*; soluble in *hexane* and in hot *propan-2-ol*.

IDENTIFICATION

Complies with the tests for Acid value, Iodine value and Saponification value.

TESTS

Melting point

57° to 70°, Appendix V A.

Acid value

Not more than 4.0, Appendix X B.

Iodine value

Not more than 5, Appendix X E, Method B.

Saponification value

175 to 205, Appendix X G, Method II.

Unsaponifiable matter

Not more than 0.8% w/w, Appendix X H.

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Loss on drying

When dried at 105° for 4 hours, loses not more than 0.1% of its weight. Use 5 g.

STORAGE

Hydrogenated Vegetable Oil should be stored at a temperature of 8° to 25°.

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Hydrogenated Wool Fat

General Notices

(Ph. Eur. monograph 0969)

Ph Eur

DEFINITION

Mixture of higher aliphatic alcohols and sterols obtained from the direct, high-pressure, high-temperature hydrogenation of *wool fat (0134)* during which the esters and acids present are reduced to the corresponding alcohols. A suitable antioxidant may be added.

CHARACTERS

Appearance

White or pale yellow, unctuous substance.

Solubility

Practically insoluble in water, soluble in boiling anhydrous ethanol and in light petroleum.

IDENTIFICATION

First identification: B.

Second identification: A, C.

A. Melting point (see Tests).

B. Examine the chromatograms obtained in the test for fatty alcohols and sterols.

Results The principal peaks in the chromatogram obtained with the test solution are similar in retention time and size to the principal peaks in the chromatogram obtained with reference solution (a).

C. Dissolve 50 mg in 5 mL of *methylene chloride R* and add 1 mL of *acetic anhydride R* and 0.1 mL of *sulfuric acid R*. A green colour is produced.

TESTS

Melting point (*2.2.15*)

45 °C to 55 °C. Allow to stand at 20 °C for 16 h.

Acid value (*2.5.1*)

Maximum 1.0, determined on 5.0 g.

Hydroxyl value (*2.5.3, Method A*)

140 to 180.

Saponification value (*2.5.6*)

Maximum 8.0. Heat under reflux for 4 h.

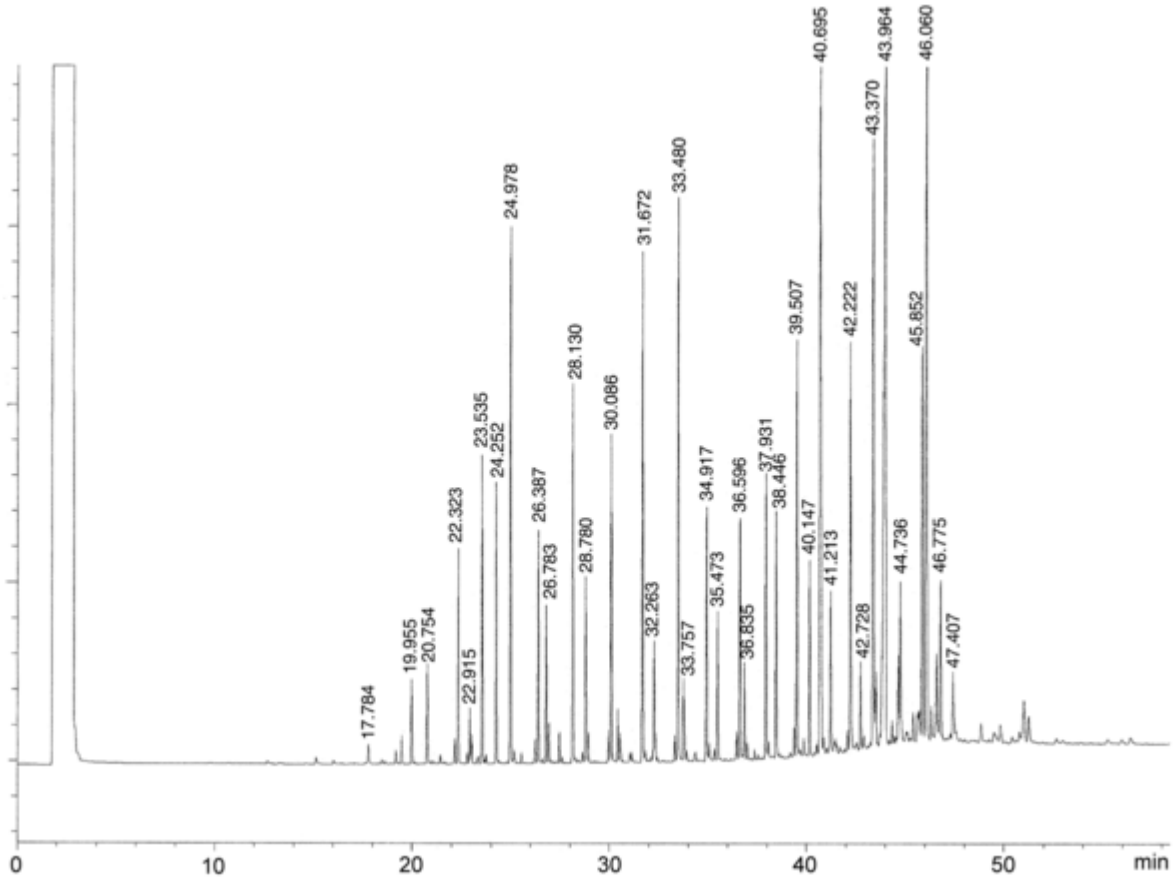


Figure 0969.-1. – *Chromatogram for the test for fatty alcohols and sterols in hydrogenated wool fat: reference solution (a)*

Fatty alcohols and sterols

Gas chromatography (*2.2.28*).

Test solution Dissolve 0.25 g of the substance to be examined in 60 mL of *anhydrous ethanol R* and dilute to 100.0 mL with the same solvent.

Reference solution (a) Dissolve 0.25 g of *hydrogenated wool fat CRS* in 60 mL of *anhydrous ethanol R* and dilute to 100.0 mL with the same solvent.

Reference solution (b) Dissolve 50 mg of *cetyl alcohol CRS* and 50 mg of *stearyl alcohol CRS* in 60 mL of *anhydrous ethanol R* and dilute to 100.0 mL with the same solvent.

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Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.25 mm;

— *stationary phase*: *methylpolysiloxane R* or another non-polar phase (film thickness 0.25 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1 mL/min.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 5	100
	5 - 45	100 → 300
	45 - 60	300
Injection port		325
Detector		350

Detection Flame ionisation.

Injection 1 µL.

Results The chromatogram obtained with the test solution does not differ significantly from the chromatogram obtained with reference solution (a) (Figure 0969.-1) and it does not show enhanced peaks with retention times corresponding to cetyl alcohol and stearyl alcohol present in the chromatogram obtained with reference solution (b).

Loss on drying (*2.2.32*)

Maximum 3.0 per cent, determined on 2.000 g by drying in an oven at 105 °C for 1 h.

Total ash (*2.4.16*)

Maximum 0.1 per cent, determined on 5.0 g.

STORAGE

In a well-filled container, protected from light.

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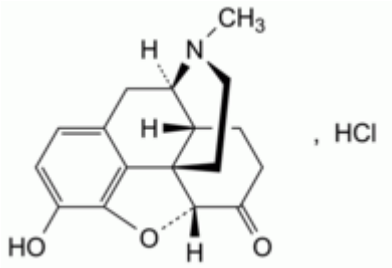
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Hydromorphone Hydrochloride

General Notices

(Ph. Eur. monograph 2099)



$C_{17}H_{20}ClNO_3$ 321.8 *71-68-1*

Action and use

Opioid receptor agonist; analgesic.

Ph Eur

DEFINITION

4,5α-Epoxy-3-hydroxy-17-methylmorphinan-6-one hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, very slightly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *hydromorphone hydrochloride CRS*.

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B. It gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 1.250 g in *carbon dioxide-free water R* and dilute to 25.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution BY_5 (2.2.2, *Method II*).

Acidity or alkalinity

To 2 mL of solution S add 0.1 mL of *methyl red solution R*. The solution is not yellow. To 2 mL of solution S add 0.05 mL of *bromocresol green solution R*. The solution is not yellow.

Specific optical rotation (2.2.7)

-136 to -140 (dried substance), determined on solution S.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.100 g of the substance to be examined in *water R*, sonicating if necessary and dilute to 100.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 10.0 mL with *water R*.

Reference solution (b) To 5 mL of the test solution add 5 mg of *naloxone hydrochloride dihydrate CRS* and dilute to 50 mL with *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Dissolve 18.29 g of *diethylamine R* and 2.88 g of *sodium laurilsulfate R* in *water R* and dilute to 1000 mL with the same solvent. Adjust 800 mL of this solution to pH 3.0 with *phosphoric acid R*. Add 100 mL of *acetonitrile R* and 100 mL of *methanol R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 284 nm.

Injection 20 µL.

Run time 4 times the retention time of hydromorphone.

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Relative retention With reference to hydromorphone (retention time = about 9 min): impurity D = about 0.72; impurity B = about 0.77; impurity C = about 0.82; impurity A = about 3.2.

System suitability Reference solution (b):

— *resolution*: minimum 4.0 between the peaks due to hydromorphone and naloxone.

Limits:

— *impurity A*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *impurities B, C, D*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on the residue obtained in the test for loss on drying.

ASSAY

Dissolve 0.250 g in 50 mL of *ethanol (96 per cent) R* and add 5.0 mL of *0.01 M hydrochloric acid*. Carry out a potentiometric titration (2.2.20), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 32.18 mg of $C_{17}H_{20}ClNO_3$.

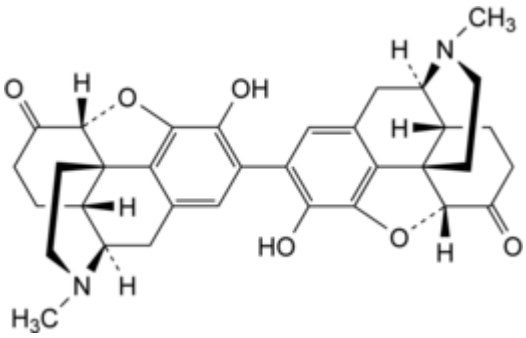
STORAGE

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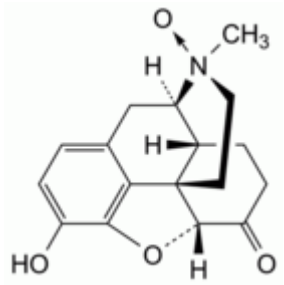
IMPURITIES

Specified impurities *A, B, C, D.*

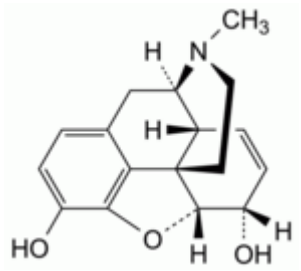
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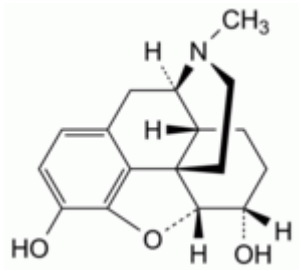
A. 4,5α:4′,5′α-diepoxy-3,3′-dihydroxy-17,17′-dimethyl-2,2′-bimorphinanyl-6,6′-dione (pseudohydromorphone),



B. 4,5α-epoxy-3-hydroxy-17-methylmorphinan-6-one 17-oxide (hydromorphone *N*-oxide),



C. 7,8-didehydro-4,5α-epoxy-17-methylmorphinan-3,6α-diol (morphine),



D. 4,5α-epoxy-17-methylmorphinan-3,6α-diol (dihydromorphine).

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Hydrophobic Colloidal Anhydrous Silica

General Notices

(Ph. Eur. monograph 2208)

Ph Eur

DEFINITION

Colloidal silicon dioxide partly alkylated for hydrophobation.

Content

99.0 per cent to 101.0 per cent SiO_2 (ignited substance).

CHARACTERS

Appearance

White or almost white, light, fine, amorphous powder, not wettable by water.

Solubility

Practically insoluble in water and mineral acids except hydrofluoric acid. It dissolves slowly in hot solutions of alkali hydroxides.

IDENTIFICATION

A. About 25 mg ignited in a platinum crucible at 900 ± 50 °C for 2 h gives the reaction of silicates (*2.3.1*).

B. Water-dispersible fraction (see Tests).

TESTS

Chlorides (*2.4.4*)

Maximum 250 ppm.

To 1.0 g add 30 mL of *methanol R* and 20 mL of *dilute nitric acid R*. Heat on a water-bath for 15 min stirring frequently. Cool, dilute to 50 mL with *water R* and filter. Dilute 10 mL of the filtrate to 15 mL with *water R*.

Water-dispersible fraction

Maximum 3.0 per cent.

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Place 0.400 g in a 500 mL separating funnel, add 100 mL of *water R* and shake for 1 min. Allow to stand for 1 h. Allow 90 mL of the aqueous phase to run out dropwise without filtration into a suitable dish dried at 140 °C and cooled in a desiccator. Evaporate to dryness at 140 °C, starting at a low temperature to avoid splashing. Cool in a desiccator. The residue weighs a maximum of 12 mg.

Loss on ignition

Maximum 6.0 per cent, determined on 0.200 g by ignition in a platinum crucible at 900 ± 50 °C for 2 h. It is advisable to place the crucible in a cold oven and then to heat up the oven. Allow to cool in a desiccator before weighing.

ASSAY

To the residue obtained in the test for loss on ignition add sufficient *ethanol (96 per cent) R* to moisten the residue completely and 0.2 mL of *sulfuric acid R*. Add 6 mL of *hydrofluoric acid R* and evaporate to dryness on a hot-plate at about 100 °C, taking care to avoid loss from sputtering. Wash down the sides of the platinum crucible with 6 mL of *hydrofluoric acid R* and evaporate to dryness. Ignite at 900 ± 50 °C, allow to cool in a desiccator and weigh.

The difference between the mass of the residue obtained in the test for loss on ignition and the mass of the final residue gives the amount of SiO_2 in the quantity of the substance to be examined.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristic may be relevant for hydrophobic colloidal silica used as glidant in tablets and capsules.

Specific surface area (*2.9.26, Method I*)

Determine the specific surface area in the P/P_0 range of 0.05 to 0.30.

Sample outgassing 20 min at 160 °C.

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Hydroquinone

General Notices



$C_6H_6O_2$ 110.11 *123-31-9*

Action and use

Depigmenting agent.

Preparation

Tretinoin, Hydrocortisone and Hydroquinone Cream

DEFINITION

Hydroquinone is 1,4-benzenediol. It contains not less than 99.0% and not more than 100.5% of $C_6H_6O_2$, calculated with reference to the anhydrous substance.

CHARACTERISTICS

Fine, white or almost white needles, which darken on exposure to light and air.

Freely soluble in *water*, in *ethanol (96%)* and in *ether*.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of hydroquinone *(RS 495)*.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dissolve the substance being examined in *methanol* to produce a solution containing 0.1% w/v of Hydroquinone.

(2) 0.1% w/v of *hydroquinone BPCRS* in *methanol*.

(3) Equal volumes of solutions (1) and (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

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(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air until the solvent has evaporated and heat at 105° for 15 minutes. Allow to cool and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

Equal volumes of *dichloromethane* and *methanol*.

SYSTEM SUITABILITY

The test is not valid unless the principal spot in the chromatogram obtained with solution (3) appears as a single, compact spot.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

TESTS

Melting point

172° to 174°, Appendix V A.

Water

Not more than 0.5%, Appendix IX C, Method I.

Sulfated ash

Not more than 0.5% w/w, Appendix IX A.

ASSAY

Dissolve 0.25 g in a mixture of 100 mL of *water* and 10 mL of 0.1M *sulfuric acid*, add 3 drops of *diphenylamine* and titrate with 0.1M *cerium(IV) sulfate VS* until a red-violet colour is reached. Each mL of 0.1M *cerium(IV) sulfate VS* is equivalent to 5.506 mg of $C_6H_6O_2$.

STORAGE

Hydroquinone should be protected from light.

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Hydrotalcite

General Notices

$Mg_6Al_2(OH)_{16}CO_3,4H_2O$ 604.0 *12304-65-3*

Action and use

Antacid.

Preparation

Hydrotalcite Tablets

DEFINITION

Hydrotalcite is a hydrated form of an aluminium magnesium basic carbonate corresponding to the formula $Mg_6Al_2(OH)_{16}CO_3,4H_2O$. It contains not less than 15.3% and not more than 18.7% of Al_2O_3 and not less than 36.0% and not more than 44.0% of MgO. The ratio of the content of Al_2O_3 to the content of MgO is not less than 0.40 and not more than 0.45.

CHARACTERISTICS

A white or almost white, free-flowing, granular powder.

Practically insoluble in *water*. It dissolves in dilute mineral acids with slight effervescence.

IDENTIFICATION

A. Dissolve 1.0 g in 20 mL of 2M *hydrochloric acid*. Effervescence occurs. Add 30 mL of *water*, boil, add 2M *ammonia* until just alkaline to *methyl red solution*, continue boiling for 2 minutes and filter, reserving the filtrate for test B. Wash the precipitate with 50 mL of a hot 2% w/v solution of *ammonium chloride* and dissolve in 15 mL of 2M *hydrochloric acid*. The resulting solution yields the reaction characteristic of *aluminium salts*, Appendix VI.

B. Dilute 1 mL of the filtrate obtained in test A to 10 mL with *water*. The resulting solution yields the reactions characteristic of *magnesium salts*, Appendix VI.

TESTS

Alkalinity

pH of a 4% w/v suspension in *carbon dioxide-free water*, 8.0 to 10.0, Appendix V L.

Neutralising capacity

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Mix 0.2 g with a small quantity of *water* to give a smooth paste and gradually add sufficient further quantities of *water* to produce 100 mL. Warm at 37°, add 100 mL of *0.1M hydrochloric acid VS* previously heated to 37° and stir continuously for 1 hour using a paddle stirrer at a rate of about 200 revolutions per minute, maintaining the temperature at 37°, and titrate with *0.1M sodium hydroxide VS* to pH 3.5. Subtract the volume of *0.1M sodium hydroxide VS* from 100 mL to obtain the number of mL of *0.1M hydrochloric acid VS* required for neutralisation. Not less than 260 mL of *0.1M hydrochloric acid VS* is required to neutralise 1 g.

Arsenic

Dissolve 0.33 g in 5 mL of *2M hydrochloric acid*. The resulting solution complies with the *limit test for arsenic*, Appendix VII (3 ppm).

Sodium

Not more than 0.1% of Na when determined by Method II for *atomic emission spectrophotometry*, Appendix II D, measuring at 589 nm. To prepare the test solution dissolve 0.1 g in 4 mL of 5M *hydrochloric acid*, dilute to 200 mL with *water* and use *sodium standard solution (200 ppm Na)*, diluted if necessary with *0.1M hydrochloric acid*, to prepare the standard solutions.

Chloride

Dissolve 0.18 g in 10 mL of 2M *nitric acid*, boil, allow to cool and dilute to 100 mL with *water*. To 10 mL add 5 mL of *water*. The resulting solution complies with the *limit test for chlorides*, Appendix VII (0.3%).

Sulfate

Dissolve 0.14 g in 15 mL of 1M *hydrochloric acid* and dilute to 100 mL with *water*. 15 mL of the resulting solution complies with the *limit test for sulfates*, Appendix VII (0.7%).

Loss on ignition

When ignited at 800°, loses 40.0 to 50.0% of its weight. Use 1 g.

ASSAY

For Al_2O_3

Dissolve 0.3 g in 2 mL of 7M *hydrochloric acid*, add 250 mL of *water* and 50 mL of 0.05M *disodium edetate VS* and neutralise with 1M *sodium hydroxide* using *methyl red solution* as indicator. Heat the solution on a water bath for 30 minutes and allow to cool. Add 3 g of *hexamine* and titrate the excess of disodium edetate with 0.05M *lead nitrate VS* using *xylenol orange solution* as indicator. Each mL of 0.05 M *disodium edetate VS* is equivalent to 2.549 mg of Al_2O_3.

For MgO

Dissolve 0.125 g in the minimum volume of 7M *hydrochloric acid*, add 30 mL of *water*, 1 g of *ammonium chloride*, 10 mL of *triethanolamine*, 150 mL of *water* and 5 mL of *ammonia buffer pH 10.9* and titrate immediately with 0.05M *disodium edetate VS* using *mordant black 11 solution* as indicator. Each mL of 0.05M *disodium edetate VS* is equivalent to 2.015 mg of MgO.

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Hydrotalcite Tablets

General Notices

Action and use

Antacid.

DEFINITION

Hydrotalcite Tablets contain Hydrotalcite.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of hydrotalcite, $Al_2Mg_6(OH)_{16}CO_3,4H_2O$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

Add 20 mL of 2M *hydrochloric acid* to a quantity of the powdered tablets containing 1.0 g of Hydrotalcite, shake and filter. Add 30 mL of *water* to the filtrate and boil. Add 2M *ammonia* until just alkaline to *methyl red*, continue boiling for 2 minutes and filter. Wash the precipitate with 50 mL of a hot 2% w/v solution of *ammonium chloride* and dissolve in 15 mL of 2M *hydrochloric acid*. The resulting solution yields the reaction characteristic of *aluminium salts*, Appendix VI.

Neutralising capacity

Weigh and powder 20 tablets, pass the powder as completely as possible through a sieve of nominal mesh aperture about 225 µm and remix the sifted powder. Mix a quantity equivalent to one tablet with a small quantity of *water*, added slowly with stirring, to give a smooth paste and add gradually sufficient further quantities of *water* to produce 100 mL. Warm to 37°, add 100 mL of *0.1M hydrochloric acid VS* previously heated to 37° and stir continuously using a paddle stirrer at a rate of about 200 revolutions per minute, maintaining the temperature at 37°. The pH of the solution at 37°, after 10 minutes and after 20 minutes, is 3.0 to 4.2, Appendix V L. Add 12 mL of *0.5M hydrochloric acid VS* at 37°, stir continuously for 1 hour, maintaining the temperature at 37°, and titrate with *0.1M sodium hydroxide VS* to pH 3.5. Subtract the number of mL of *0.1M sodium hydroxide VS* from 160 mL to obtain the number of mL of *0.1M hydrochloric acid VS* required for neutralisation. Not less than 130 mL of *0.1M hydrochloric acid VS* is required to neutralise one tablet.

ASSAY

Weigh and powder 20 tablets. To a quantity of the powder containing 0.3 g of Hydrotalcite add 2 mL of 7M *hydrochloric acid* and heat on a water bath for 15 minutes. Allow to cool, add 250 mL of *water* and 50 mL of 0.05M *disodium edetate VS* and neutralise with 1M *sodium hydroxide* using *methyl red solution* as indicator. Heat the solution on a water bath for 30 minutes and allow to cool. Add 3 g of *hexamine*

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and titrate the excess of disodium edetate with 0.05M *lead nitrate VS* using *xylenol orange solution* as indicator. Each mL of 0.05M *disodium edetate VS* is equivalent to 15.09 mg of $Al_2Mg_6(OH)_{16}CO_3,4H_2O$.

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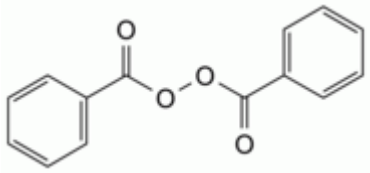
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Hydrous Benzoyl Peroxide

General Notices

(Ph. Eur. monograph 0704)



$C_{14}H_{10}O_4$ 242.2 (anhydrous substance)

Anhydrous benzoyl peroxide *94-36-0*

Action and use

Used topically in the treatment of acne.

Preparations

Benzoyl Peroxide and Clindamycin Gel

Benzoyl Peroxide Cream

Benzoyl Peroxide Gel

Benzoyl Peroxide Lotion

Potassium Hydroxyquinoline Sulfate and Benzoyl Peroxide Cream

Ph Eur

DEFINITION

Content

— *dibenzoyl peroxide (benzoic peroxyanhydride)*: 70.0 per cent to 77.0 per cent;

— *water*: minimum 20.0 per cent.

CHARACTERS

Appearance

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White or almost white, amorphous or granular powder.

Solubility

Practically insoluble in water, soluble in acetone, soluble in methylene chloride with the separation of water, slightly soluble in ethanol (96 per cent).

It loses water rapidly on exposure to air with a risk of explosion.

Mix the entire sample thoroughly before carrying out the following tests.

IDENTIFICATION

First identification: B.

Second identification: A, C, D.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution (a) Dissolve 80.0 mg in ethanol (96 per cent) R and dilute to 100.0 mL with the same solvent. Dilute 10.0 mL of the solution to 100.0 mL with ethanol (96 per cent) R.

Test solution (b) Dilute 10.0 mL of test solution (a) to 100.0 mL with ethanol (96 per cent) R.

Spectral ranges 250-300 nm for test solution (a); 220-250 nm for test solution (b).

Absorption maxima 274 nm for test solution (a); 235 nm for test solution (b).

Shoulder About 282 nm for test solution (a).

Absorbance ratio A_{235}/A_{274} = 1.17 to 1.21.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison Ph. Eur. reference spectrum of hydrous benzoyl peroxide.

The transmittance at about 2000 cm^{-1} (5 µm) is not less than 40 per cent without compensation.

C. Dissolve about 25 mg in 2 mL of acetone R. Add 1 mL of a 10 g/L solution of diethylphenylenediamine sulfate R and mix. A red colour develops which quickly darkens and becomes dark violet within 5 min.

D. To 1 g add 5 mL of ethanol (96 per cent) R, 5 mL of dilute sodium hydroxide solution R and 10 mL of water R. Boil the mixture under reflux for 20 min. Cool. The solution gives reaction (c) of benzoates (2.3.1).

TESTS

Acidity

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Dissolve a quantity of the substance to be examined containing the equivalent of 1.0 g of dibenzoyl peroxide in 25 mL of *acetone R*, add 75 mL of *water R* and filter. Wash the residue with 2 quantities, each of 10 mL, of *water R*. Combine the filtrate and the washings and add 0.25 mL of *phenolphthalein solution R1*. Not more than 1.25 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator. Carry out a blank test.

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use*.

Test solution Dissolve a quantity of the substance to be examined containing the equivalent of 0.10 g of dibenzoyl peroxide in *acetonitrile R* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *acetonitrile R*. Dilute 1.0 mL of this solution to 10.0 mL with *acetonitrile R*.

Reference solution (b) Dissolve 30.0 mg of *benzoic acid R* (impurity B) in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve 50.0 mg of *ethyl benzoate R* (impurity C) in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 100.0 mL with the mobile phase.

Reference solution (d) Dissolve 50.0 mg of *benzaldehyde R* (impurity A) in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 100.0 mL with the mobile phase.

Reference solution (e) Dissolve 30 mg of *benzoic acid R* (impurity B) and 30 mg of *benzaldehyde R* (impurity A) in the mobile phase and dilute to 100 mL with the mobile phase. Dilute 1 mL of the solution to 10 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (10 µm).

Mobile phase *glacial acetic acid R*, *acetonitrile for chromatography R*, *water for chromatography R* (1:500:500 *V/V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 235 nm.

Injection 20 µL.

Run time Twice the retention time of dibenzoyl peroxide.

Relative retention With reference to dibenzoyl peroxide (retention time = about 20 min): impurity B = about 0.2; impurity A = about 0.3; impurity C = about 0.5.

System suitability Reference solution (e):

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— *resolution*: minimum 6 between the peaks due to impurities B and A.

Limits:

— *impurity B*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.5 per cent);

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (d) (0.25 per cent);

— *impurity C*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.25 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.02 per cent).

Chlorides (2.4.4)

Maximum 0.4 per cent.

Dissolve a quantity of the substance to be examined containing the equivalent of 0.5 g of dibenzoyl peroxide in 15 mL of *acetone R*. Add, while stirring, 50 mL of *0.05 M nitric acid*. Allow to stand for 10 min and filter. Wash the residue with 2 quantities, each of 10 mL, of *0.05 M nitric acid*. Combine the filtrate and the washings and dilute to 100 mL with *0.05 M nitric acid*. Dilute 2.5 mL of the solution to 15.0 mL with *water R*.

ASSAY

Solution S

Dissolve 2.500 g immediately before use in 75 mL of *dimethylformamide R* and dilute to 100.0 mL with the same solvent.

Dibenzoyl peroxide

To 5.0 mL of solution S add 20 mL of *acetone R* and 3 mL of a 500 g/L solution of *potassium iodide R* and mix. Allow to stand for 1 min. Titrate with *0.1 M sodium thiosulfate*, determining the end-point potentiometrically (2.2.20) using a platinum electrode as indicator electrode. Carry out a blank titration.

1 mL of *0.1 M sodium thiosulfate* is equivalent to 12.11 mg of $C_{14}H_{10}O_4$.

Water (2.5.12)

Carry out the assay protected from light, using 5.0 mL of solution S. Use as the solvent a mixture of 20.0 mL of *anhydrous methanol R* and 3.0 mL of a 100 g/L solution of *potassium iodide R* in *dimethylformamide R*. After adding solution S, stir for 5 min before starting the titration. Carry out a blank determination.

Calculate the percentage content of water using the following expression:

$$\frac{\left(n_1 - n_2\right) \times w \times 2}{m} + (p \times 0.0744)$$

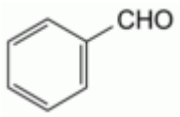
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n_1	=	volume of titrant used in the sample determination in millilitres;
n_2	=	volume of titrant used in the blank determination in millilitres;
w	=	water equivalent of titrant in milligrams of water per millilitre of reagent;
m	=	mass of the substance to be examined used for the preparation of solution S, in grams;
p	=	percentage content of dibenzoyl peroxide.

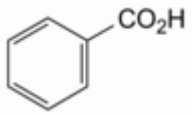
STORAGE

In a container that has been treated to reduce static discharge and that has a device for release of excess pressure, at a temperature of 2 °C to 8 °C, protected from light.

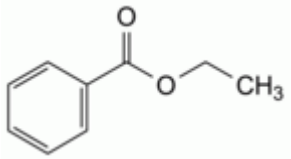
IMPURITIES



A. benzaldehyde,



B. benzoic acid,



C. ethyl benzoate.

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Hydrous Ointment

General Notices

Oily Cream

DEFINITION

Wool Alcohols Ointment	500 g
Phenoxyethanol	10 g
Dried Magnesium Sulfate	5 g
Purified Water, freshly boiled and cooled	Sufficient to produce 1000 g

In preparing Hydrous Ointment the proportions of Hard Paraffin, Soft Paraffin and Liquid Paraffin used to make the Wool Alcohols Ointment may be varied to produce Hydrous Ointment having suitable properties.

When Hydrous Ointment is used in a white ointment, it should be prepared from Wool Alcohols Ointment made with White Soft Paraffin; when used in a coloured ointment, it should be prepared from Wool Alcohols Ointment made with Yellow Soft Paraffin.

Extemporaneous preparation

The following directions apply.

Dissolve the Phenoxyethanol and the Dried Magnesium Sulfate in sufficient warm Purified Water to produce about 500 g. Melt the Wool Alcohols Ointment and heat to about 60°; gradually add the aqueous solution at about 60° with vigorous stirring until a smooth cream is obtained. Stir until cool, add sufficient Purified Water to produce 1000 g and mix.

The ointment complies with the requirements stated under Topical Semi-solid Preparations.

STORAGE

Hydrous Ointment should be kept in a container made from non-absorbent material. If, on storage, some aqueous liquid separates, it is readily reincorporated by stirring.

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Hydrous Wool Fat

General Notices

Lanolin

(Ph. Eur. monograph 0135)

Ph Eur

DEFINITION

Mixture of 75 per cent *m/m* of wool fat and 25 per cent *m/m* of water. It is obtained by the gradual addition of water to melted wool fat with continuous stirring. A suitable antioxidant may be added.

CHARACTERS

Appearance

Pale yellow, unctuous substance.

IDENTIFICATION

A. In a test-tube, dissolve 0.5 g in 5 mL of *methylene chloride R* and add 1 mL of *acetic anhydride R* and 0.1 mL of *sulfuric acid R*. A green colour develops.

B. Dissolve 50 mg in 5 mL of *methylene chloride R*, add 5 mL of *sulfuric acid R* and shake. A red colour develops and an intense green fluorescence appears in the lower layer when examined in daylight, with illumination from behind the observer.

TESTS

Water-soluble acid or alkaline substances

Melt 6.7 g on a water-bath and shake vigorously for 2 min with 75 mL of *water R* previously heated to 90-95 °C. Allow to cool and filter through filter paper previously rinsed with *water R*. To 60 mL of the filtrate (which may not be clear) add 0.25 mL of *bromothymol blue solution R1*. Not more than 0.2 mL of *0.02 M hydrochloric acid* or 0.15 mL of *0.02 M sodium hydroxide* is required to change the colour of the indicator.

Drop point (*2.2.17*)

38 °C to 44 °C.

To fill the metal cup, melt the residue obtained in the test for wool-fat content on a water-bath, cool to about 50 °C, pour into the cup and allow to stand at 15-20 °C for 24 h.

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Water-absorption capacity

Place 10 g of the residue obtained in the test for wool-fat content in a mortar. Add *water R* in portions of 0.2-0.5 mL from a burette, stirring vigorously after each addition to incorporate the *water R*. The end-point is reached when visible droplets remain which cannot be incorporated. Not less than 20 mL of *water R* is absorbed.

Acid value (*2.5.1*)

Maximum 0.8, determined on 5.0 g dissolved in 25 mL of the prescribed mixture of solvents.

Peroxide value (*2.5.5, Method A*)

Maximum 15.

Saponification value (*2.5.6*)

67 to 79, determined on 2.00 g while heating under reflux for 4 h.

Water-soluble oxidisable substances

To 10 mL of the filtrate obtained in the test for water-soluble acid or alkaline substances add 1 mL of *dilute sulfuric acid R* and 0.1 mL of *0.02 M potassium permanganate*. After 10 min, the solution is not completely decolourised.

Paraffins

Maximum 1.0 per cent.

The tap and cotton plugs used must be free from grease Prepare a column of anhydrous aluminium oxide 230 mm long and 20 mm in diameter by adding a slurry of *anhydrous aluminium oxide R* and *light petroleum R1* to a glass tube fitted with a tap and containing *light petroleum R1*. Allow to settle and reduce the depth of the layer of solvent above the column to about 40 mm. Dissolve 3.0 g of the residue obtained in the test for wool-fat content in 50 mL of warm *light petroleum R1*, cool, pass the solution through the column at a rate of 3 mL/min and wash with 250 mL of *light petroleum R1*. Concentrate the combined eluate and washings to low bulk by distillation, evaporate to dryness on a water-bath and heat the residue at 105 °C for periods of 10 min until 2 successive weighings do not differ by more than 1 mg. The residue weighs a maximum of 30 mg.

Chlorides

Maximum 115 ppm.

Boil 1.3 g with 20 mL of *ethanol (90 per cent V/V) R* under a reflux condenser for 5 min. Cool, add 40 mL of *water R* and 0.5 mL of *nitric acid R* and filter. To the filtrate add 0.15 mL of a 10 g/L solution of *silver nitrate R* in *ethanol (90 per cent V/V) R*. Allow to stand for 5 min, protected from light. Any opalescence in the solution is not more intense than that in a standard prepared at the same time by adding 0.15 mL of a 10 g/L solution of *silver nitrate R* in *ethanol (90 per cent V/V) R* to a mixture of 0.2 mL of *0.02 M hydrochloric acid*, 20 mL of *ethanol (90 per cent V/V) R*, 40 mL of *water R* and 0.5 mL of *nitric acid R*.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent.

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Ignite 5.0 g and use the residue.

Wool-fat content

72.5 per cent to 77.5 per cent.

In a suitable tared dish containing a glass rod, heat 30.0 g to constant mass on a water-bath, stirring continuously. Weigh the residue.

STORAGE

At a temperature not exceeding 25 °C.

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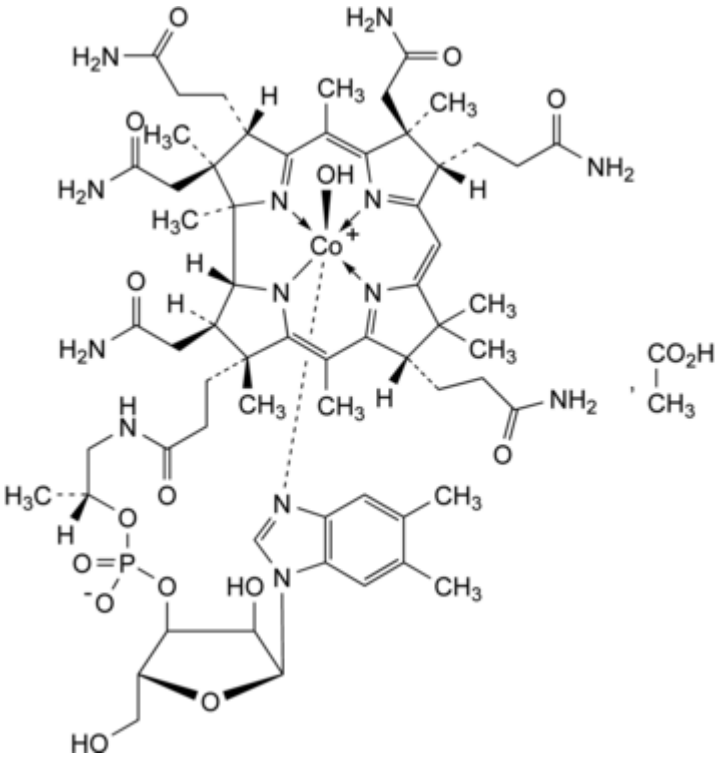
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Hydroxocobalamin Acetate

General Notices

(Ph. Eur. monograph 0913)



$C_{64}H_{93}CoN_{13}O_{17}P$ 1406 *22465-48-1*

Action and use

Vitamin B_{12} analogue.

Preparation

Hydroxocobalamin Injection

Ph Eur

DEFINITION

Coα-[α-(5,6-dimethylbenzimidazolyl)]-Coβ-hydroxocobamide acetate.

Content

96.0 per cent to 102.0 per cent (dried substance).

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This monograph applies to hydroxocobalamin acetate produced by fermentation.

CHARACTERS

Appearance

Dark red, crystalline powder or dark red crystals, very hygroscopic.

Solubility

Soluble in water.

Some decomposition may occur on drying.

IDENTIFICATION

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 2.5 mg in a solution containing 0.8 per cent *V/V* of *glacial acetic acid R* and 10.9 g/L of *sodium acetate R*, then dilute to 100 mL with the same solution.

Spectral range 260-610 nm.

Absorption maxima At 274 nm, 351 nm and 525 nm.

Absorbance ratio:

— A_{274}/A_{351} = 0.75 to 0.83;

— A_{525}/A_{351} = 0.31 to 0.35.

B. Thin-layer chromatography (2.2.27). *Carry out the test protected from light*.

Test solution Dissolve 2 mg of the substance to be examined in 1 mL of a mixture of equal volumes of *ethanol (96 per cent) R* and *water R*.

Reference solution Dissolve 2 mg of *hydroxocobalamin CRS* in 1 mL of a mixture of equal volumes of *ethanol (96 per cent) R* and *water R*.

Plate *TLC silica gel G plate R*.

Mobile phase *dilute ammonia R1*, *methanol R* (25:75 *V/V*).

Application 10 µL.

Development In an unlined tank, over a path of 12 cm.

Drying In air.

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Detection Examine in daylight.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. It gives reaction (a) of acetates (2.3.1).

TESTS

Related substances

Liquid chromatography (2.2.29). *Use freshly prepared solutions and protect them from bright light*.

Test solution Dissolve 10.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dilute 5.0 mL of the test solution to 100.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (c) Dissolve 25 mg of the substance to be examined in 10 mL of *water R*, warming if necessary. Allow to cool and add 1 mL of a 20 g/L solution of *chloramine R* and 0.5 mL of *0.05 M hydrochloric acid*. Dilute this solution to 25 mL with *water R*. Shake and allow to stand for 5 min. Inject immediately.

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 19.5 volumes of *methanol R* and 80.5 volumes of a solution containing 15 g/L of *citric acid monohydrate R* and 8.1 g/L of *disodium hydrogen phosphate dodecahydrate R*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 351 nm.

Injection 20 µL.

Run time 4 times the retention time of hydroxocobalamine.

System suitability:

— the chromatogram obtained with reference solution (c) shows 3 principal peaks;

— *resolution*: minimum 3.0 between each pair of adjacent peaks in the chromatogram obtained with reference solution (c);

— *signal-to-noise ratio*: minimum 5 for the principal peak in the chromatogram obtained with reference solution (b).

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Limits:

— *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (5 per cent);

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent).

Loss on drying (*2.2.32*)

8.0 per cent to 12.0 per cent, determined on 0.400 g by drying at 105 °C at a pressure not exceeding 0.7 kPa.

ASSAY

Protect the solutions from light throughout the assay Dissolve 25.0 mg in a solution containing 0.8 per cent *V/V* of *glacial acetic acid R* and 10.9 g/L of *sodium acetate R*, then dilute to 1000.0 mL with the same solution. Measure the absorbance (*2.2.25*) at the absorption maximum at 351 nm.

Calculate the content of $C_{64}H_{93}CoN_{13}O_{17}P$ taking the specific absorbance to be 187.

STORAGE

In an airtight container, protected from light, at a temperature of 2 °C to 8 °C.

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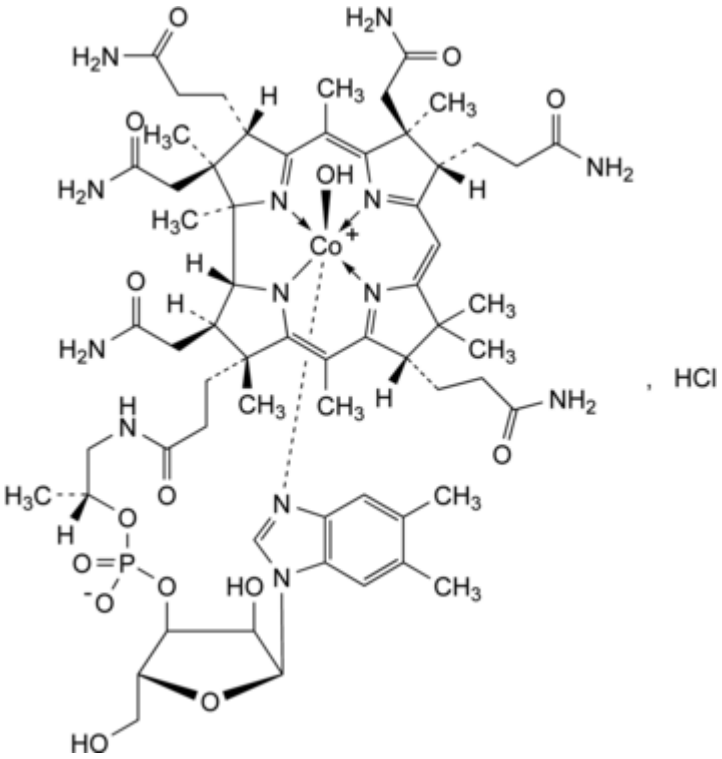
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Hydroxocobalamin Chloride

General Notices

(Ph. Eur. monograph 0914)



$C_{62}H_{90}ClCoN_{13}O_{15}P$ 1383 *58288-50-9*

Action and use

Vitamin B_{12} analogue.

Preparation

Hydroxocobalamin Injection

Ph Eur

DEFINITION

Coα-[α-(5,6-dimethylbenzimidazolyl)]-Coβ-hydroxocobamide chloride.

Fermentation product.

Content

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96.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

Dark red crystalline powder or dark red crystals, very hygroscopic.

Solubility

Soluble in water.

Some decomposition may occur on drying.

IDENTIFICATION

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 2.5 mg in a solution containing 0.8 per cent *V/V* of *glacial acetic acid R* and 10.9 g/L of *sodium acetate R*, then dilute to 100 mL with the same solution.

Spectral range 260-610 nm.

Absorption maxima At 274 nm, 351 nm and 525 nm.

Absorbance ratio:

— A_{274}/A_{351} = 0.75 to 0.83;

— A_{525}/A_{351} = 0.31 to 0.35.

B. Thin-layer chromatography (2.2.27). *Carry out the identification test protected from light*.

Test solution Dissolve 2 mg of the substance to be examined in 1 mL of a mixture of equal volumes of *ethanol (96 per cent) R* and *water R*.

Reference solution Dissolve 2 mg of *hydroxocobalamin CRS* in 1 mL of a mixture of equal volumes of *ethanol (96 per cent) R* and *water R*.

Plate *TLC silica gel G plate R*.

Mobile phase *dilute ammonia R1*, *methanol R* (25:75 *V/V*).

Application 10 µL.

Development In an unlined tank, over a path of 12 cm.

Drying In air.

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Detection Examine in daylight.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. It gives reaction (a) of chlorides (2.3.1).

TESTS

Related substances

Liquid chromatography (2.2.29). *Use freshly prepared solutions and protect them from bright light*.

Test solution Dissolve 10.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dilute 5.0 mL of the test solution to 100.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (c) Dissolve 25 mg of the substance to be examined in 10 mL of *water R*, warming if necessary. Allow to cool and add 1 mL of a 20 g/L solution of *chloramine R* and 0.5 mL of *0.05 M hydrochloric acid*. Dilute to 25 mL with *water R*. Shake and allow to stand for 5 min. Inject immediately.

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 19.5 volumes of *methanol R* and 80.5 volumes of a solution containing 15 g/L of *citric acid monohydrate R* and 8.1 g/L of *disodium hydrogen phosphate dodecahydrate R*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 351 nm.

Injection 20 µL.

Run time 4 times the retention time of hydroxocobalamin.

System suitability:

— the chromatogram obtained with reference solution (c) shows 3 principal peaks;

— *resolution*: minimum 3.0 between each pair of adjacent peaks in the chromatogram obtained with reference solution (c);

— *signal-to-noise ratio*: minimum 5 for the principal peak in the chromatogram obtained with reference solution (b).

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Limits:

— *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (5.0 per cent);

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent).

Loss on drying (*2.2.32*)

8.0 per cent to 12.0 per cent, determined on 0.400 g by drying at 105 °C at a pressure not exceeding 0.7 kPa.

ASSAY

Protect the solutions from light throughout the assay Dissolve 25.0 mg in a solution containing 0.8 per cent *V/V* of *glacial acetic acid R* and 10.9 g/L of *sodium acetate R*, then dilute to 1000.0 mL with the same solution. Measure the absorbance (*2.2.25*) at the absorption maximum at 351 nm.

Calculate the content of $C_{62}H_{90}ClCoN_{13}O_{15}P$ taking the specific absorbance to be 190.

STORAGE

In an airtight container protected from light, at a temperature of 2 °C to 8 °C.

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Hydroxocobalamin Injection

General Notices

Action and use

Vitamin B_{12} analogue.

DEFINITION

Hydroxocobalamin Injection is a sterile solution of Hydroxocobalamin Acetate, Hydroxocobalamin Chloride or Hydroxocobalamin Sulfate in Water for Injections containing sufficient Acetic Acid, Hydrochloric Acid or Sulfuric Acid respectively to adjust the pH to about 4.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of hydroxocobalamin, $C_{62}H_{89}CoN_{13}O_{15}P$

95.0 to 110.0% of the stated amount of anhydrous hydroxocobalamin.

IDENTIFICATION

Measure the *absorbance* at 351 nm and at 361 nm, Appendix II B. The ratio of the absorbance at 361 nm to that at 351 nm is about 0.65.

TESTS

Acidity

pH, 3.8 to 5.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. *Solutions (1) to (3) are freshly prepared; protect all the solutions from bright light*.

(1) Dilute a volume of the injection, if necessary, to produce a solution containing 0.10% w/v of hydroxocobalamin in the mobile phase.

(2) Dilute a volume of the injection, if necessary, to produce a solution containing 0.005% w/v of hydroxocobalamin in the mobile phase.

(3) Dilute a volume of the injection, if necessary, to produce a solution containing 0.00010% w/v of hydroxocobalamin in the mobile phase.

(4) Add 0.2 mL of a freshly prepared 2% w/v solution of *chloramine T* and 0.1 mL of 0.05M *hydrochloric acid* to a volume of the injection containing the equivalent of 5 mg of hydroxocobalamin, dilute to 10 mL with *water*, shake, allow to stand for 5 minutes and inject immediately.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (25 cm × 4 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Lichrosorb 100 CH8/11 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 351 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

19.5 volumes of *methanol* and 80.5 volumes of a solution containing 1.5% w/v of *citric acid* and 0.81% w/v of *disodium hydrogen orthophosphate*.

SYSTEM SUITABILITY

The test is not valid unless:

the chromatogram obtained with solution (4) shows three principal peaks and the *resolution factor* between each pair of adjacent peaks is not less than 3.0;

the chromatogram obtained with solution (3) shows one principal peak with a *signal-to-noise ratio* of not less than 5.

LIMITS

In the chromatogram obtained with solution (1):

the sum of the areas of any *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (10%).

Disregard any peak the area of which is less than that of the principal peak in the chromatogram obtained with solution (3) (0.1%).

ASSAY

Carry out the following procedure protected from light. Dilute a quantity containing the equivalent of 2.5 mg of anhydrous hydroxocobalamin to 100 mL with a solution containing 0.8% v/v of *glacial acetic acid* and 1.09% w/v of *sodium acetate* and measure the *absorbance* of the resulting solution at the maximum at 351 nm, Appendix II B. Calculate the content of $C_{62}H_{89}CoN_{13}O_{15}P$ taking 195 as the value of A(1%, 1 cm) at the maximum at 351 nm.

STORAGE

Hydroxocobalamin Injection should be protected from light.

LABELLING

The strength is stated in terms of the equivalent amount of anhydrous hydroxocobalamin in a suitable dose-volume.

When vitamin B_{12} injection is prescribed or demanded, Hydroxocobalamin Injection shall be dispensed or supplied.

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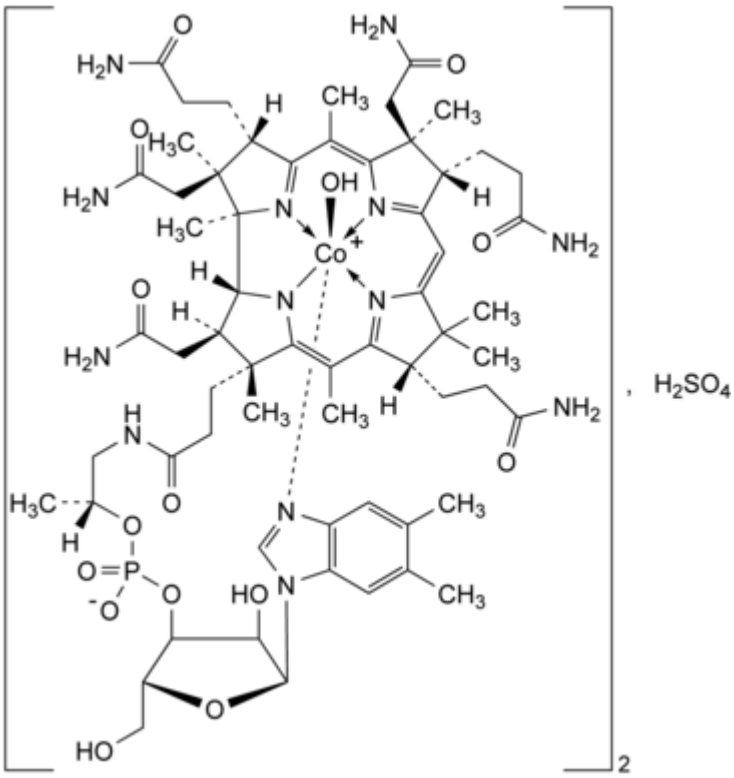
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Hydroxocobalamin Sulfate

General Notices

Hydroxocobalamin Sulphate

(Ph. Eur. monograph 0915)



$C_{124}H_{180}Co_2N_{26}O_{34}P_2S$ 2791

Action and use

Vitamin B_{12} analogue.

Preparation

Hydroxocobalamin Injection

Ph Eur

DEFINITION

Di-(Coα-[α-(5,6-dimethylbenzimidazolyl)]-Coβ-hydroxocobamide) sulfate.

Fermentation product.

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Content

96.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

Dark red crystalline powder or dark red crystals, very hygroscopic.

Solubility

Soluble in water.

Some decomposition may occur on drying.

IDENTIFICATION

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 2.5 mg in a solution containing 0.8 per cent *V/V* of glacial acetic acid R and 10.9 g/L of sodium acetate R, then dilute to 100 mL with the same solution.

Spectral range 260-610 nm.

Absorption maxima At 274 nm, 351 nm and 525 nm.

Absorbance ratios:

— A_{274}/A_{351} = 0.75 to 0.83;

— A_{525}/A_{351} = 0.31 to 0.35.

B. Thin-layer chromatography (2.2.27). *Carry out the test protected from light*.

Test solution Dissolve 2 mg of the substance to be examined in 1 mL of a mixture of equal volumes of ethanol (96 per cent) R and water R.

Reference solution Dissolve 2 mg of hydroxocobalamin CRS in 1 mL of a mixture of equal volumes of ethanol (96 per cent) R and water R.

Plate TLC silica gel G plate R.

Mobile phase dilute ammonia R1, methanol R (25:75 *V/V*).

Application 10 µL.

Development In an unlined tank, over a path of 12 cm.

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Drying In air.

Detection Examine in daylight.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. It gives reaction (a) of sulfates (2.3.1).

TESTS

Related substances

Liquid chromatography (2.2.29). *Use freshly prepared solutions and protect them from bright light*.

Test solution Dissolve 10.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dilute 5.0 mL of the test solution to 100.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (c) Dissolve 25 mg of the substance to be examined in 10 mL of *water R*, warming if necessary. Allow to cool and add 1 mL of a 20 g/L solution of *chloramine R* and 0.5 mL of *0.05 M hydrochloric acid*. Dilute to 25 mL with *water R*. Shake and allow to stand for 5 min. Inject immediately.

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 19.5 volumes of *methanol R* and 80.5 volumes of a solution containing 15 g/L of *citric acid monohydrate R* and 8.1 g/L of *disodium hydrogen phosphate dodecahydrate R*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 351 nm.

Injection 20 µL.

Run time 4 times the retention time of hydroxocobalamin.

System suitability:

— the chromatogram obtained with reference solution (c) shows 3 principal peaks;

— *resolution*: minimum 3.0 between each pair of adjacent peaks in the chromatogram obtained with reference solution (c);

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— *signal-to-noise ratio*: minimum 5 for the principal peak in the chromatogram obtained with reference solution (b).

Limits:

— *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (5.0 per cent);

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent).

Loss on drying (*2.2.32*)

8.0 per cent to 16.0 per cent, determined on 0.400 g by drying at 105 °C at a pressure not exceeding 0.7 kPa.

ASSAY

Protect the solutions from light throughout the assay Dissolve 25.0 mg in a solution containing 0.8 per cent *V/V* of *glacial acetic acid R* and 10.9 g/L of *sodium acetate R* and dilute to 1000.0 mL with the same solution. Measure the absorbance (*2.2.25*) at the absorption maximum at 351 nm.

Calculate the content of $C_{124}H_{180}Co_2N_{26}O_{34}P_2S$ taking the specific absorbance to be 188.

STORAGE

In an airtight container protected from light, at a temperature of 2 °C to 8 °C.

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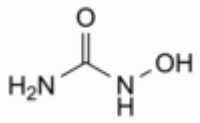
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Hydroxycarbamide

General Notices

(Ph. Eur. monograph 1616)



$CH_4N_2O_2$ 76.1 *127-07-1*

Action and use

Cytotoxic alkylating drug.

Preparation

Hydroxycarbamide Capsules

Ph Eur

DEFINITION

N-Hydroxyurea.

Content

97.5 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder, hygroscopic.

Solubility

Freely soluble in water, practically insoluble in ethanol (96 per cent).

It shows polymorphism (*5.9*).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *hydroxycarbamide CRS*.

If the spectra obtained in the solid state show differences dissolve the substance to be examined and the reference substance separately in *ethanol (96 per cent) R*, evaporate to dryness and record new spectra using the residues.

B. Examine the chromatograms obtained in the test for urea.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (c).

TESTS

Urea

Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 50 mg of the substance to be examined in *water R* and dilute to 1.0 mL with the same solvent.

Reference solution (a) Dissolve 12.5 mg of *urea R* in *water R* and dilute to 50 mL with the same solvent.

Reference solution (b) Dissolve 5 mg of the substance to be examined and 5 mg of *urea R* in *water R* and dilute to 20 mL with the same solvent.

Reference solution (c) Dissolve 50 mg of *hydroxycarbamide CRS* in *water R* and dilute to 1 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase *pyridine R*, *water R*, *ethyl acetate R* (2:2:10 *V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with a 10 g/L solution of *dimethylaminobenzaldehyde R* in *1 M hydrochloric acid*.

System suitability The test is not valid unless the chromatogram obtained with reference solution (b) shows 2 clearly separated spots.

Limit:

— *urea*: any spot corresponding to urea in the chromatogram obtained with the test solution is not more intense than the spot in the chromatogram obtained with the reference solution (a) (0.5 per cent).

Related substances

Liquid chromatography (*2.2.29*).

Test solution (a) Dissolve 0.100 g of the substance to be examined in the mobile phase and dilute to 10.0 mL with the same mobile phase.

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Test solution (b) Dilute 5.0 mL of test solution (a) to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 0.100 g of *hydroxylamine hydrochloride R* and 5 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase. Prepare immediately before use.

Reference solution (b) Dilute 0.1 mL of test solution (a) to 100.0 mL with the mobile phase.

Reference solution (c) Dissolve 0.100 g of *hydroxycarbamide CRS* in the mobile phase and dilute to 10.0 mL with the same solvent. Dilute 5.0 mL to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm,

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *methanol R*, *water R* (5:95 *V/V*).

Flow rate 0.5 mL/min.

Detection Spectrophotometer at 214 nm.

Injection 20 µL; inject test solution (a) and reference solutions (a) and (b).

Run time 3 times the retention time of hydroxycarbamide which is about 5 min.

System suitability Reference solution (a):

— *resolution*: minimum of 1.0 between the peaks due to impurity A and to hydroxycarbamide.

Limits:

— *any impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent),

— *total*: not more than 2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent),

— *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.02 per cent).

Chlorides (*2.4.4*)

Maximum 50 ppm.

Dissolve 1.0 g in *water R* and dilute to 15 mL with the same solvent.

Water (*2.5.12*)

Maximum 0.5 per cent, determined on 2.00 g.

Sulfated ash (*2.4.14*)

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Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances.

Injection Test solution (b) and reference solution (c).

STORAGE

In an airtight container, protected from light.

IMPURITIES

A. H_2N-OH: hydroxylamine.

Ph Eur

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Hydroxycarbamide Capsules

General Notices

Action and use

Cytotoxic alkylating drug.

DEFINITION

Hydroxycarbamide Capsules contain Hydroxycarbamide.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of hydroxycarbamide, $CH_4N_2O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the contents of the capsules containing 30 mg of Hydroxycarbamide with 10 mL of *methanol* and filter. Evaporate the filtrate to dryness and dry the residue at 60° at a pressure of 2 kPa for 3 hours. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of hydroxycarbamide *(RS 184)*.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Urea

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *water*.

(1) Shake a quantity of the contents of the capsules containing 0.5 g of Hydroxycarbamide with 10 mL of *water* for 15 minutes and filter through a glass-fibre filter (Whatman GF/C is suitable).

(2) 0.025% w/v of *urea*.

(3) 5.0% w/v of *hydroxycarbamide BPCRS* and 0.025% w/v of *urea*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, spray with a 1% w/v solution of *4-dimethylaminobenzaldehyde* in 1M *hydrochloric acid*.

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MOBILE PHASE

1 volume of *pyridine*, 1 volume of *water* and 5 volumes of *ethyl acetate*. Shake, allow to separate and use the upper layer.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

LIMITS

Any spot corresponding to urea in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%).

Hydroxylamine

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *water*.

(1) Shake a quantity of the contents of the capsules containing 0.1 g of Hydroxycarbamide with 8 mL of *water* for 5 minutes, add sufficient water to produce 10 mL and filter through a glass-fibre filter (Whatman GF/C is suitable).
(2) 1.0% w/v of *hydroxycarbamide BPCRS* and 0.02% w/v of *hydroxylamine hydrochloride*.
(3) 0.1% w/v of *hydroxycarbamide BPCRS* and 1.0% w/v of *hydroxylamine hydrochloride*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 0.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 214 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

5 volumes of *methanol* and 95 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to hydroxycarbamide and hydroxylamine is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to hydroxylamine is not greater than the area of the corresponding peak in the chromatogram obtained with solution (2) (1%).

ASSAY

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Weigh and powder the contents of 20 capsules. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *water*.

(1) Shake a quantity of the capsule contents containing 1 g of Hydroxycarbamide with 450 mL of *water* for 5 minutes, mix for 30 minutes with the aid of ultrasound, add sufficient *water* to produce 500 mL and mix well. Filter through a glass-fibre filter (Whatman GF/C is suitable) and dilute 1 volume of the filtrate with 1 volume of *water*.

(2) 0.10% w/v of *hydroxycarbamide BPCRS*

(3) 0.10% w/v of *hydroxycarbamide BPCRS* and 0.4% w/v of *hydroxylamine hydrochloride*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 214 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

water.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between hydroxycarbamide and hydroxylamine hydrochloride is at least 1.0.

DETERMINATION OF CONTENT

Calculate the content of $CH_4N_2O_2$ in the capsules using the declared content of $CH_4N_2O_2$ in *hydroxycarbamide BPCRS*.

STORAGE

Hydroxycarbamide Capsules should be protected from moisture.

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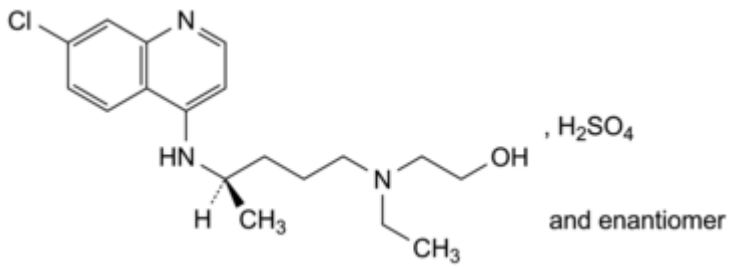
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Hydroxychloroquine Sulfate

General Notices

(Ph. Eur. monograph 2849)



$C_{18}H_{28}ClN_3O_5S$ 434.0 *747-36-4*

Action and use

Antiprotozoal (malaria).

Ph Eur

DEFINITION

2-[[(4*RS*)-4-[(7-Chloroquinolin-4-yl)amino]pentyl](ethyl)amino]ethan-1-ol sulfate.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or slightly yellowish, crystalline powder.

Solubility

Freely soluble in water, practically insoluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *hydroxychloroquine sulfate CRS*.

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B. It gives reaction (a) of sulfates (2.3.1).

TESTS

Appearance of solution

The solution is clear and not more intensely coloured than reference solution Y_7 (2.2.2, Method I).

Dissolve 1.0 g in water R and dilute to 10.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture Mix 500 mL of water R, 500 mL of methanol R and 4 mL of a 10 per cent *V/V* solution of sulfuric acid R.

Buffer solution Dissolve 1.36 g of potassium dihydrogen phosphate R in 900 mL of water for chromatography R. Add 0.15 g of sodium heptanesulfonate R, adjust to pH 7.0 with triethylamine R and dilute to 1000 mL with water for chromatography R.

Test solution (a) Dissolve 25.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with the solvent mixture.

Reference solution (a) Dissolve 5 mg of hydroxychloroquine for system suitability CRS (containing impurities B and C) in the solvent mixture and dilute to 10 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with the solvent mixture. Dilute 2.0 mL of this solution to 100.0 mL with the solvent mixture.

Reference solution (c) Dissolve 25.0 mg of hydroxychloroquine sulfate CRS in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.05 m, Ø = 2.1 mm;

— *stationary phase*: end-capped ethylene-bridged octadecylsilyl silica gel for chromatography (hybrid material) R (1.7 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: methanol R, buffer solution (10:90 *V/V*);

— *mobile phase B*: buffer solution, methanol R (15:85 *V/V*);

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 1	100	0
1 - 11	100 → 0	0 → 100

Flow rate 0.7 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 4 µL of test solution (a) and reference solutions (a) and (b).

Identification of impurities Use the chromatogram supplied with *hydroxychloroquine for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities B and C.

Relative retention With reference to hydroxychloroquine (retention time = about 6 min): impurity B = about 0.8; impurity C = about 0.9.

System suitability Reference solution (a):

— *resolution*: minimum 3.0 between the peaks due to impurity C and hydroxychloroquine; minimum 3.0 between the peaks due to impurities B and C.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity B by 1.6;

— for each impurity, use the concentration of hydroxychloroquine sulfate in reference solution (b).

Limits:

— *impurity C*: maximum 0.4 per cent;

— *impurity B*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.6 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 2.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

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Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

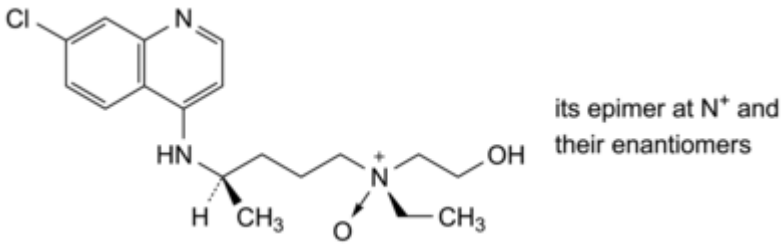
Injection 4 µL of test solution (b) and reference solution (c).

Calculate the percentage content of $C_{18}H_{28}ClN_3O_5S$ taking into account the assigned content of *hydroxychloroquine sulfate CRS*.

IMPURITIES

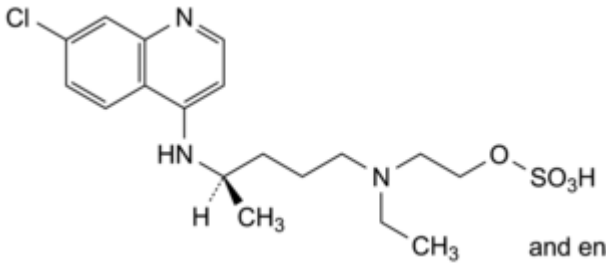
Specified impurities *B, C.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, D, E, F, G.*



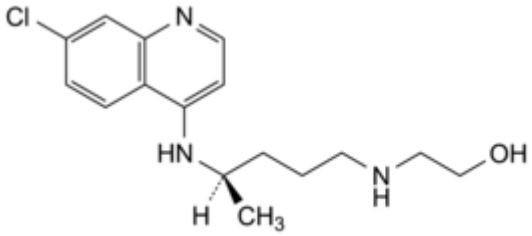
its epimer at N^+ and their enantiomers

A. mixture of diastereoisomers of 4-[(7-chloroquinolin-4-yl)amino]-*N*-ethyl-*N*-(hydroxyethyl)pentan-1-amine *N*-oxide,



and enantiomer

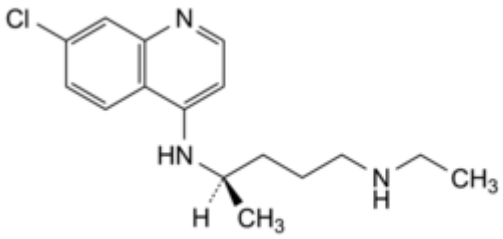
B. 2-[[(4*RS*)-4-[(7-chloroquinolin-4-yl)amino]pentyl](ethyl)amino]ethyl hydrogen sulfate,



and enantiomer

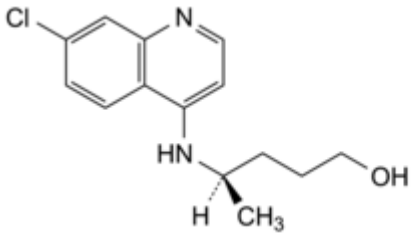
C. 2-[[(4*RS*)-4-[(7-chloroquinolin-4-yl)amino]pentyl]amino]ethan-1-ol,

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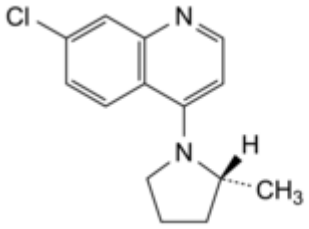
and enantiomer

D. (4*RS*)-N^4-(7-chloroquinolin-4-yl)-N^1-ethylpentane-1,4-diamine,



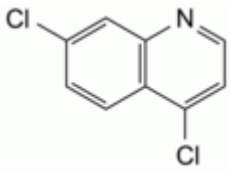
and enantiomer

E. (4*RS*)-4-[(7-chloroquinolin-4-yl)amino]pentan-1-ol,



and enantiomer

F. 7-chloro-4-[(2*RS*)-2-methylpyrrolidin-1-yl]quinoline,



G. 4,7-dichloroquinoline.

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Hydroxychloroquine Tablets

General Notices

Action and use

Antiprotozoal (malaria); used in the treatment of rheumatoid arthritis.

DEFINITION

Hydroxychloroquine Tablets contain Hydroxychloroquine Sulfate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of hydroxychloroquine sulfate, $C_{18}H_{26}ClN_3O,H_2SO_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Dissolve a quantity of the powdered tablets containing 0.1 g of Hydroxychloroquine Sulfate in a mixture of 10 mL of *water* and 2 mL of 2M *sodium hydroxide* and extract with two 20-mL quantities of *chloroform*. Wash the chloroform extracts with *water*, dry with *anhydrous sodium sulfate*, evaporate to dryness and dissolve the residue in 2 mL of *chloroform IR*. The *infrared absorption spectrum* of the resulting solution, Appendix II A, is concordant with the *reference spectrum* of hydroxychloroquine *(RS 182)*.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium, if necessary, to produce a solution expected to contain 0.022% w/v of Hydroxychloroquine Sulfate, at the maximum at 343 nm, Appendix II B, using dissolution medium in the reference cell.

(2) Measure the *absorbance* of a 0.022% w/v solution of *hydroxychloroquine sulfate BPCRS* in the dissolution medium using dissolution medium in the reference cell.

DETERMINATION OF CONTENT

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Calculate the total content of hydroxychloroquine sulfate, $C_{18}H_{26}ClN_3O,H_2SO_4$, in the medium from the absorbances obtained and using the declared content of $C_{18}H_{26}ClN_3O,H_2SO_4$ in *hydroxychloroquine sulfate BPCRS*.

LIMITS

The amount of hydroxychloroquine sulfate released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in mobile phase A.

(1) Shake a quantity of the powdered tablets containing 0.2 g of Hydroxychloroquine Sulfate in 150 mL of mobile phase A, dilute to 200 mL and filter. Dilute 1 volume of the resulting solution to 10 volumes.
(2) Dilute 1 volume of solution (1) to 100 volumes. Further dilute 1 volume to 5 volumes.
(3) 0.00004% w/v of *2-[4-[(7-chloro-4-quinolinyl)amino]pentyl] amino ethanol sulfate BPCRS* (impurity C).
(4) 0.0001% w/v of *hydroxychloroquine sulfate BPCRS* and 0.0001% w/v of *2-[4-[(7-chloro-4-quinolinyl)amino]pentyl] amino ethanol sulfate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5µm) (Inertsil ODS3 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 35°.
(e) Use a detection wavelength of 220 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 0.2 volumes of *orthophosphoric acid*, 10 volumes of *acetonitrile R1* and 90 volumes of *water*.

Mobile phase B 0.1 volumes of *orthophosphoric acid*, 20 volumes of *water* and 80 volumes of *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	100	0	isocratic
2-10	100→85	0→15	linear gradient
10-18	85→100	15→0	linear gradient
18-25	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to hydroxychloroquine (retention time about 5 minutes) are: impurity C, about 0.95; impurity B, about 1.5 and impurity G, about 2.9.

SYSTEM SUITABILITY

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The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity C and hydroxychloroquine is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.4%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%).

the sum of the areas of any *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in mobile phase A.

(1) Weigh and powder 20 tablets. Shake a quantity of the powdered tablets containing 0.2 g of Hydroxychloroquine Sulfate with 150 mL of mobile phase A, dilute to 200 mL and filter. Dilute 1 volume of the filtrate to 10 volumes.
(2) 0.01% w/v of *hydroxychloroquine sulfate BPCRS*.
(3) 0.0001% w/v of *hydroxychloroquine sulfate BPCRS* and 0.0001% w/v of *2-[4-[(7-chloro-4-quinolinyl)amino]pentyl] amino ethanol sulfate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity C and hydroxychloroquine is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of hydroxychloroquine sulfate, $C_{18}H_{26}ClN_3O,H_2SO_4$, in the tablets using the declared content of $C_{18}H_{26}ClN_3O,H_2SO_4$ in *hydroxychloroquine sulfate BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities B, C and G listed under Hydroxychloroquine Sulfate.

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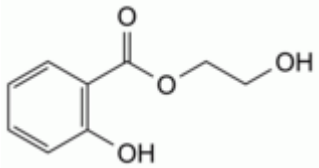
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This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Hydroxyethyl Salicylate

General Notices

(Ph. Eur. monograph 1225)



$C_9H_{10}O_4$ 182.2 *87-28-5*

Ph Eur

DEFINITION

2-Hydroxyethyl 2-hydroxybenzoate.

Content

98.0 per cent to 102.0 per cent.

CHARACTERS

Appearance

Oily, colourless or almost colourless liquid, or colourless crystals.

Solubility

Sparingly soluble in water, very soluble in acetone and in methylene chloride, freely soluble in ethanol (96 per cent).

mp

About 21 °C.

IDENTIFICATION

First identification: A, B.

Second identification: A, C.

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A. Refractive index (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Preparation Thin films.

Comparison *hydroxyethyl salicylate CRS*.

C. Examine the chromatograms obtained in the test for impurity B with the following modifications:

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with test solution (b) is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

TESTS

Solution S

Dissolve 2.5 g in 40 mL of *ethanol (96 per cent) R* and dilute to 50 mL with *distilled water R*.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, Method II).

Acidity or alkalinity

To 2 mL of solution S add 0.1 mL of *methyl red solution R* and 0.2 mL of *0.01 M sodium hydroxide*. The solution is yellow. Add 0.3 mL of *0.01 M hydrochloric acid*. The solution is red.

Relative density (2.2.5)

1.252 to 1.257.

Refractive index (2.2.6)

1.548 to 1.551.

Impurity B

Thin-layer chromatography (2.2.27).

Test solution (a) Dissolve 0.50 g of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Test solution (b) Dilute 2 mL of test solution (a) to 50 mL with *methanol R*.

Reference solution (a) Dissolve 50 mg of *hydroxyethyl salicylate CRS* in *methanol R* and dilute to 25 mL with the same solvent.

Reference solution (b) Dissolve 0.10 g of *ethylene glycol R* (impurity B) in *methanol R* and dilute to 50 mL with the same solvent. Dilute 1.25 mL of the solution to 10 mL with *methanol R*.

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Plate *TLC silica gel F_{254} plate R*.

Mobile phase *ethyl acetate R*, *glacial acetic acid R*, *cyclohexane R* (20:20:60 *V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In a current of cold air.

Detection Spray the plate with *ammonium vanadate solution R* and heat at 100 °C for 10 min. Allow to cool for 10 min and examine in daylight.

Retardation factor Impurity B = about 0.09.

System suitability Reference solution (b):

— the chromatogram shows a clearly visible spot.

Limit Test solution (a):

— *impurity B*: any spot due to impurity B is not more intense than the corresponding spot in the chromatogram obtained with reference solution (b) (0.5 per cent).

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 60.0 mg of the substance to be examined in *tetrahydrofuran R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *tetrahydrofuran R*. Dilute 1.0 mL of this solution to 10.0 mL with *tetrahydrofuran R*.

Reference solution (b) Dissolve 6.0 mg of *salicylic acid R* (impurity A) in *tetrahydrofuran R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of the solution to 10.0 mL with *tetrahydrofuran R*.

Reference solution (c) Dissolve 4.8 mg of *hydroxyethyl salicylate impurity C CRS* in *tetrahydrofuran R*, add 1 mL of the test solution and dilute to 100 mL with *tetrahydrofuran R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R1* (5 µm);

— *temperature*: 35 °C.

Mobile phase:

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— *mobile phase A*: *acetonitrile R*, 3.8 g/L solution of *ammonium acetate R* (20:80 *V/V*);

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	95	5
15 - 35	95 → 20	5 → 80
35 - 45	20	80

Flow rate 0.7 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 5 µL.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity C.

Relative retention With reference to hydroxyethyl salicylate (retention time = about 16 min): impurity A = about 0.2; impurity C = about 1.2.

System suitability Reference solution (c):

— *resolution*: minimum 4.0 between the peaks due to hydroxyethyl salicylate and impurity C.

Calculation of percentage contents:

— for impurity A, use the concentration of impurity A in reference solution (b);

— for impurities other than A, use the concentration of hydroxyethyl salicylate in reference solution (a).

Limits:

— *impurity C*: maximum 0.8 per cent;

— *impurity A*: maximum 0.10 per cent:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total (excluding impurity A)*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent.

Chlorides (2.4.4)

Maximum 100 ppm.

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Dilute 10 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 250 ppm.

Dilute 12 mL of solution S to 15 mL with *distilled water R*.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

In a flask with a ground-glass stopper, dissolve 0.125 g in 30 mL of *glacial acetic acid R*. Add 10 mL of *dilute sulfuric acid R*, 1.5 g of *potassium bromide R* and 50.0 mL of *0.0167 M potassium bromate*. Immediately close the flask and allow to stand protected from light for 15 min. Add 1.5 g of *potassium iodide R* immediately after removing the stopper and titrate with *0.1 M sodium thiosulfate*, adding 1 mL of *starch solution R* towards the end of the titration. Carry out a blank titration.

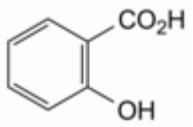
1 mL of *0.0167 M potassium bromate* is equivalent to 4.555 mg of $C_9H_{10}O_4$.

STORAGE

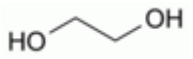
Protected from light.

IMPURITIES

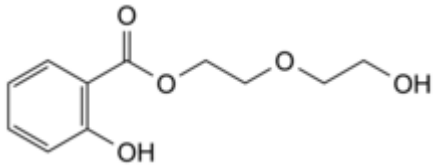
Specified impurities *A, B, C.*



A. 2-hydroxybenzoic acid (salicylic acid),



B. ethane-1,2-diol (ethylene glycol),



C. 2-(2-hydroxyethoxy)ethyl 2-hydroxybenzoate.

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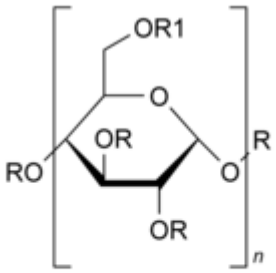
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Hydroxyethyl Starches

General Notices

(Ph. Eur. monograph 1785)



R = -[CH_2CH_2O]$_{n'}$H (*n'* = 0, 1, 2…)

R1 = -[CH_2CH_2O]$_{n''}$-H (*n''* = 0 or 1) or glucose

[$C_6H_{10}O_5(C_2H_4O)_X$]$_n$ with *x* = molar substitution *9005-27-0*

Ph Eur

DEFINITION

Hydroxyethyl starches are partially substituted poly(2-hydroxyethyl)ethers of waxy maize starch or potato starch, which primarily consist of amylopectine. The type of hydroxyethyl starch is defined by 2 numbers: the mean molecular weight (*Mw*) and the number of hydroxyethyl groups per anhydroglucose unit expressed as the molar substitution (*MS*). Hydroxyethyl starch is also characterised by the number of hydroxyethyl groups located at the C2 group over the number of hydroxyethyl groups located at C6, expressed as the C2/C6 ratio. The parameters *Mw*, *MS* and C2/C6 ratio are determined by the reaction conditions of the production.

PRODUCTION

Hydroxyethyl starches are produced from waxy maize starch or potato starch by acidic hydrolysis and reaction with ethylene oxide and purified by ultrafiltration.

CHARACTERS

Appearance

White or almost white powder.

Solubility

Freely soluble in water and in dimethyl sulfoxide, practically insoluble in anhydrous ethanol.

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Hydroxyethyl starches are hygroscopic until they reach a water content of about 12 per cent to 15 per cent.

IDENTIFICATION

First identification: A, C.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *medium Mw hydroxyethyl starch CRS*.

Results The spectrum obtained shows the same absorption bands as the spectrum obtained with *medium Mw hydroxyethyl starch CRS*. Due to the difference in the substitution of the substance, the intensity of some absorption bands can vary.

B. To 5 mL of solution S (see Tests), add 0.1 mL of *0.05 M iodine*. A reddish-brown or blue-violet colour appears.

C. Molecular weight (see Tests).

TESTS

Solution S

Dissolve 5.0 g of the substance to be examined (dried substance) in *carbon dioxide-free water R* and dilute to 100.0 mL with the same solvent.

Appearance of solution

Solution S is not more opalescent than reference suspension II (2.2.1).

pH (2.2.3)

4.5 to 7.0.

To 25 mL of solution S, add 0.2 mL of a saturated solution of *potassium chloride R*.

Absorbance (2.2.25)

Maximum 0.025, determined at 400 nm on solution S filtered through a 0.2 µm filter.

Molecular weight (*Mw*) and molecular weight distribution

Size-exclusion chromatography (2.2.30).

Buffer solution Dissolve 54.34 g of *sodium acetate R* in *water R*, add 100.0 mL of *glacial acetic acid R* and dilute to 1000.0 mL with *water R*.

Test stock solution Dissolve 2.0 g of the substance to be examined (dried substance) in *water R* and dilute to 50 mL with the same solvent. Add 10.0 mL of the buffer solution and dilute to 100.0 mL with *water R*.

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Reference solution (a) To prepare reference solution (a):

— if the nominal *Mw* of the substance to be examined is below 300 000, use *medium Mw hydroxyethyl starch CRS*;

— if the nominal *Mw* of the substance to be examined is above 300 000, use *high Mw hydroxyethyl starch CRS*.

Dissolve 0.4 g of *medium Mw hydroxyethyl starch CRS* or *high Mw hydroxyethyl starch CRS* in 10 mL of *water R*. Add 2.0 mL of the buffer solution and dilute to 20.0 mL with *water R*.

Reference solution (b) Dilute 10.0 mL of reference solution (a) to 20.0 mL with the mobile phase.

Reference solution (c) Dilute 10.0 mL of reference solution (b) to 20.0 mL with the mobile phase.

Reference solution (d) Dilute 10.0 mL of reference solution (c) to 20.0 mL with the mobile phase.

Column:

— *stationary phase*: *hydroxylated polymethacrylate gel R*;

— 4 columns to be connected in series:

Length in m	Internal diameter in mm	Particle size in µm	Pore size in nm
0.30	7.5	17	> 100
0.30	7.5	17	100
0.30	7.5	12	20
0.30	7.5	12	12.5

Mobile phase Dilute 100.0 mL of the buffer solution to 1000 mL with *water for chromatography R*.

Flow rate 0.5-1.0 mL/min.

Detection Multiple-angle light scattering (MALS) detector and refractometer maintained at a constant temperature, connected in series.

Injection volume 50 µL.

Determine the suitable working solution as follows: inject reference solutions (a) and (b), the mean *Mw* determined with reference solution (b) does not deviate by more than 3 per cent from the mean *Mw* determined with reference solution (a). If the deviation meets the requirement, use reference solution (a) to check the system suitability criterion.

If the deviation is higher, inject reference solution (c) and determine the mean *Mw*. The mean *Mw* determined with reference solution (c) does not deviate by more than 3 per cent from the mean *Mw* determined with reference solution (b). If the deviation meets the requirement, use reference solution (b) to check the system suitability criterion.

If the deviation is higher, inject reference solution (d) and determine the mean *Mw*. The mean *Mw* determined with reference solution (d) does not deviate by more than 3 per cent from the mean *Mw* determined with reference solution (c). If the deviation meets the requirement,

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use reference solution (c) to check the system suitability criterion.

System suitability:

— *mean Mw*: within 5 per cent of the value assigned to the *medium Mw hydroxyethyl starch CRS* or *high Mw hydroxyethyl starch CRS*.

If necessary, dilute the test stock solution in order to have the same concentration as that of the reference solution used to check the system suitability.

Results Use a suitable integrator to determine the mean *Mw* and the *Mw* of the lowest and highest 10 per cent mass fraction.

Low *Mw* **2000 - 100 000**	**Medium *Mw*** **100 000 - 300 000**	**High *Mw*** **300 000 - 900 000**
Determined *Mw* = nominal *Mw* ± 15 per cent		
Mw at 10 per cent lowest fraction > 10 per cent of nominal *Mw*	*Mw* at 10 per cent lowest fraction > 15 000	*Mw* at 10 per cent lowest fraction > 15 000
Mw at 10 per cent highest fraction < 300 per cent of nominal *Mw*	*Mw* at 10 per cent highest fraction < 300 per cent of nominal *Mw*	*Mw* at 10 per cent highest fraction < 500 per cent of nominal *Mw*

C2/C6 ratio

Gas chromatography (*2.2.28*).

Solution A Mix equal volumes of *dilute sulfuric acid R* and *water R*.

Test solution Introduce 0.18 g of the substance to be examined into a 5 mL vial. Add 3.0 mL of solution A, cap, seal the vial and shake until dissolution. Heat the vials for 4 h in a heating block already preheated to 100 °C, shaking them from time to time. Cool to room temperature. Open the vial and carefully add 0.9 g of *barium carbonate R*. Shake carefully and then centrifuge at about 9000 *g* for about 15 min. Test the clear supernatant for neutral pH with pH paper. If the solution is still acid, add more *barium carbonate R* in portions of 0.2 g until the solution is neutral. Filter the clear supernatant (pore size 0.45 µm). Introduce 0.5 mL of the filtrate into a autosampler vial and evaporate to dryness at 40 °C (several hours are usually needed). Take up the residue with 0.50 mL of *pyridine R*, 0.25 mL of *N,O-bis(trimethylsilyl)acetamide R* and 25 µL of *chlorotrimethylsilane R*. Seal the vial and heat to 40 °C for 1 h shaking from time to time. Cool to room temperature. Place the vial into the autosampler and perform 3 injections from each vial. Prepare in duplicate.

Reference solution Prepare as prescribed for the test solution but using *medium Mw hydroxyethyl starch CRS* instead of the substance to be examined.

Column:

— *size*: *l* = 15 m, Ø = 0.32 mm;

— *stationary phase*: *methylpolysiloxane R* (film thickness 0.25 µm).

Carrier gas *hydrogen for chromatography R* at a constant pressure of 69 kPa.

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Split ratio 1:20.

	Time (min)	Temperature (°C)
Column	0 - 1	150
	1 - 25	150 → 270
	25 - 28	270
Injection port		250
Detector		300

Detection Flame ionisation.

Injection 1 µL.

Identification of peaks Use the chromatogram supplied with *medium Mw hydroxyethyl starch CRS* and the chromatogram obtained with the reference solution to identify the peaks due to derivatised product 1, derivatised product 2, derivatised product 3, 2-*O*-hydroxyethyl-α-D-glucose, 6-*O*-hydroxyethyl-α-D-glucose, 2-*O*-hydroxyethyl-β-D-glucose and 6-*O*-hydroxyethyl-β-D-glucose.

System suitability Reference solution:

— *resolution*: minimum 1.5 between the peaks due to 2-*O*-hydroxyethyl-β-D-glucose and 6-*O*-hydroxyethyl-β-D-glucose;

— *symmetry factor*: 0.6 to 1.5 for the peak due to derivatised product 1;

— *repeatability*: maximum relative standard deviation of 5.0 per cent for derivatised product 1 after 3 injections.

Calculate the C2/C6 ratio using the following expression:

$$\frac{A_1+A_2+A_3+A_4+A_5}{A_6+A_7}$$

A_1 = area of the peak due to derivatised product 1;

A_2 = area of the peak due to derivatised product 2;

A_3 = area of the peak due to derivatised product 3;

A_4 = area of the peak due to 2-*O*-hydroxyethyl-α-D-glucose;

A_5 = area of the peak due to 2-*O*-hydroxyethyl-β-D-glucose;

A_6 = area of the peak due to 6-*O*-hydroxyethyl-α-D-glucose;

A_7 = area of the peak due to 6-*O*-hydroxyethyl-β-D-glucose.

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Calculate the mean C2/C6 ratio from the values obtained with the 2 test solutions.

The test is not valid unless the difference of the 2 values is not more than 5 per cent.

Limit Within 20.0 per cent of the nominal value.

Molar substitution (*MS*)

Gas chromatography (2.2.28).

The content of hydroxyethyl groups is determined after hydrolysis with hydriodic acid as iodoethane.

Internal standard solution Dilute 1.0 mL of *toluene R* to 200.0 mL with *xylene R*.

Test solution Introduce 50.0 mg of the substance to be examined and about 0.10-0.15 g of *adipic acid R* in a 5 mL vial. Add 1.0 mL of the internal standard solution and 2.0 mL of *hydriodic acid R*. Tightly seal and cap the vial with a septum and an aluminium, centre tear-off seal. Prepare the test solution 5 times.

Reference solutions In each of 7 vials of 5 mL, introduce about 0.10-0.15 g of *adipic acid R*. To each vial add 1.0 mL of the internal standard solution and 2.0 mL of *hydriodic acid R*. Tightly seal and cap the vials with a septum and an aluminium, centre tear-off seal. Weigh the vials with an accuracy of 0.01 mg. Introduce respectively 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg of *iodoethane R* with a 100 µL syringe piercing the septa carefully. Weigh the vials again with an accuracy of 0.01 mg and calculate the exact amount of *iodoethane R* added.

Determine the mass of the vials to the nearest 1 mg. Place the vials for 10 h into a heating block already preheated to 150 °C. After cooling to room temperature, determine the mass of each vial to the nearest 1 mg. Disregard any vial with a loss in mass of more than 5 mg. From 4 vials of the test solution and 5 of the reference solutions, take-up 100 µL of the upper layer. Introduce in an autosampler vial and dilute with 1.0 mL of *xylene R*. Seal immediately the vials and shortly shake.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.53 mm;

— *stationary phase*: *cyanopropyl(3)phenyl(3)methyl(94)polysiloxane R* (film thickness 3 µm).

Carrier gas *helium for chromatography R*.

Flow rate 8 mL/min.

Split ratio 1:20.

	Time (min)	Temperature (°C)
Column	0 - 4	50

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	Time (min)	Temperature (°C)
	4 - 16	50 → 230
	16 - 20	230
Injection port		200
Detector		280

Detection Flame ionisation.

Injection volume 1 µL; inject each solution twice.

Relative retention With reference to toluene (retention time = about 7.5 min): iodoethane = about 0.5.

System suitability Reference solutions:

— *resolution*: minimum 1.5 between the peaks due to iodoethane and toluene;

— calculate the ratio of the area of the peak due to *iodoethane R* to the area of the peak due to the internal standard for each chromatogram. Calculate the linear regression curve plotting the ratios calculated for the reference solutions against the quantity of *iodoethane R* added (in milligrams). The coefficient of determination R^2 is not less than 0.990.

Results Calculate the quantity (*T*) of iodoethane in milligrams present in the test solution using the following expression:

$$\frac{A - B}{M}$$

A = ratio of the area of the peak due to iodoethane to the area of the peak due to the internal standard in the chromatogram obtained with the test solution;

B = y-intercept of the curve;

M = slope of the curve.

Then calculate the percentage content of ethylene oxide (*C*) using the following expression:

$$\frac{44.05 \times T \times 100}{155.97 \times m}$$

m = mass of the substance to be examined, in milligrams;

44.05 = molecular mass of ethylene oxide;

155.97 = molecular mass of iodoethane.

Then calculate the *MS* using the following expression:

$$\frac{C \times 162.14}{(100 - C) \times 44.05}$$

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162.14	=	molecular mass of anhydroglucose;
44.05	=	molecular mass of ethylene oxide.

Calculate the mean *MS* from the values obtained with the 4 test solutions.

Limit 0.05 to 2.4, and within 8.0 per cent of the nominal value.

Ethylene glycol

Liquid chromatography (2.2.29).

Test solution Dissolve 1.0 g of the substance to be examined (dried substance) in *water R* and dilute to 50.0 mL with the same solvent.

Reference solution Dissolve 0.800 g of *ethylene glycol R* in *water R* and dilute to 100.0 mL with the same solvent. Dilute 2.0 mL of the solution to 200.0 mL with *water R*. Dilute 2.0 mL of this solution to 200.0 mL with *water R*.

Precolumn:

— *size*: *l* = 0.01 m, Ø = 4.0 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography compatible with 100 per cent aqueous mobile phases R* (5 µm).

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography compatible with 100 per cent aqueous mobile phases R* (5 µm);

— *temperature*: 30 °C.

Mobile phase *water for chromatography R*.

Flow rate 1.0 mL/min.

Post-column solution Dilute 750 mL of *2 M sodium hydroxide R* to 1000 mL with *water for chromatography R*.

Flow rate of post-column solution 0.2 mL/min.

Detection Pulsed amperometric detector.

Injection 20 µL.

Run time 2.5 times the retention time of ethylene glycol.

Retention time Ethylene glycol = about 4 min.

System suitability Reference solution:

— *signal-to-noise ratio*: minimum 10 for the principal peak;

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— *repeatability*: maximum relative standard deviation of 10.0 per cent determined on 6 injections.

After a maximum of 8 sample injections, wash the column using the following program.

Rinsing solution acetonitrile for chromatography R, water for chromatography R (20:80 *V/V*).

Time (min)	Mobile phase (per cent *V/V*)	Rinsing solution (per cent *V/V*)
0 - 15	75	25
15 - 20	75 → 0	25 → 100
20 - 25	0	100
25 - 30	0 → 100	100 → 0
30 - 100	100	0

Limit:

— ethylene glycol: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (40 ppm).

2-Chloroethanol

Gas chromatography (2.2.28).

Solvent mixture methanol R, acetonitrile R (25:75 *V/V*).

Internal standard solution Dissolve 0.250 g of 2,6-dimethylaniline R in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Dilute 0.5 mL of the solution to 50.0 mL with the solvent mixture.

Test solution Introduce 1.0 g of the substance to be examined into a 20 mL vial. Add 10.0 mL of the solvent mixture. Close tightly. Treat in an ultrasonic bath for 3.5 h. Allow to cool to room temperature. To 1.0 mL of this solution add 0.8 mL of the internal standard solution.

Reference solution Dissolve 0.250 g of 2-chloroethanol R in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 100.0 mL with the solvent mixture. To 1.0 mL of this solution add 0.8 mL of the internal standard solution.

Precolumn:

— *material*: fused silica;

— *size*: *l* = 10 m, Ø = 0.53 mm;

— *stationary phase*: polar-deactivated macrogol R.

Column:

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— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.32 mm;

— *stationary phase*: macrogol 20 000 R (film thickness 0.25 µm).

Carrier gas hydrogen for chromatography R.

Flow rate 2.9 mL/min.

Split program:

Time (min)	Split state	Split ratio
initial	on	1:20
0.01	off	1:20
0.50	on	1:20

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 4	45
	4 - 23.5	45 → 240
	23.5 - 28.5	240
Injection port		250
Detector		270

Detection Flame ionisation.

Injection 1 µL.

System suitability Reference solution:

— signal-to-noise ratio: minimum 10 for the peak due to 2-chloroethanol;

— *repeatability*: maximum relative standard deviation of 10.0 per cent after 6 injections.

Limit:

— 2-chloroethanol: calculate the ratio (*R*) of the area of the peak due to 2-chloroethanol to the area of the peak due to the internal standard from the chromatogram obtained with the reference solution; calculate the ratio of the area of the peak due to 2-chloroethanol

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to the area of the peak due to the internal standard from the chromatogram obtained with the test solution: this ratio is not greater than *R* (5 ppm).

Ethylene oxide

Head-space gas chromatography (2.2.28).

Test solution Dissolve 1.0 g of the substance to be examined in 1.0 mL of water R. Close the vial tightly. Prepare in duplicate.

Reference stock solution Introduce 80 mL of water R in a 100 mL volumetric flask. Cool at about 4 °C for at least 30 min. Place the flask on an analytical balance and slowly introduce 1.0 g of ethylene oxide R. Determine the precise quantity of ethylene oxide by differential weighing. Dilute to 100.0 mL with water R. Store in the refrigerator and use within 4 weeks.

Reference solution (a) Dilute 1.0 mL of the reference stock solution to 100.0 mL with water R. Dilute 1.0 mL of this solution to 100.0 mL with water R. Use within 24 h.

Reference solution (b) Dissolve 1.0 g of the substance to be examined in 1.0 mL of reference solution (a). Close the vial tightly. Prepare in duplicate.

Column:

— *material*: quartz;

— *size*: *l* = 30 m, Ø = 0.32 mm;

— *stationary phase*: cyanopropyl(3)phenyl(3)methyl(94)polysiloxane R (film thickness 1.5 µm).

Carrier gas helium for chromatography R at a pressure of 110.3 kPa.

Split ratio 1:35.

Static head-space conditions which may be used:

— *equilibration temperature*: 80 °C;

— *equilibration time*: 40 min;

— *transfer-line temperature*: 150 °C;

— *pressurisation time*: 2.0 min;

— *injection time*: 3 s.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 20	40

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	Time (min)	Temperature (°C)
	20 - 30	40 → 240
	30 - 40	240
Injection port		140
Detector		250

Detection Flame ionisation.

Injection Inject a suitable volume of the gaseous phase of the test solution and reference solution (b).

System suitability:

— *signal-to-noise ratio*: minimum 10 for the peak due to ethylene oxide in the chromatogram obtained with reference solution (b).

Limit:

— *ethylene oxide*: not more than 0.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (b) (1 ppm).

Sodium chloride

Maximum 0.1 per cent.

Test solution In a 250 mL conical flask, dissolve 10.0 g of the substance to be examined in 100 mL of *water R*. Add 2 mL of *dilute nitric acid R* and 5.0 mL of a 9 g/L solution of *sodium chloride R*.

Reference solution In a 250 mL conical flask, dilute 5.0 mL of a 9 g/L solution of *sodium chloride R* with 100 mL of *water R*. Add 2 mL of *dilute nitric acid R*.

Carry out a potentiometric titration (*2.2.20*) with *0.1 M silver nitrate*. Calculate the percentage content of sodium chloride using the following expression:

$$\frac{\left(n_1 - n_2\right) \times 5.844 \times 100}{m}$$

n_1 = volume of *0.1 M silver nitrate* used for the test solution, in millilitres;

n_2 = volume of *0.1 M silver nitrate* used for the reference solution, in millilitres;

m = mass of the substance to be examined in the test solution, in milligrams.

Loss on drying (*2.2.32*)

Maximum 15.0 per cent, determined on 1.000 g by drying at 105 °C.

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Bacterial endotoxins (*2.6.14*)

Less than 2.5 IU/g.

Microbial contamination

TAMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

LABELLING

The label states the mean molecular weight, molar substitution and C2/C6 ratio (nominal values).

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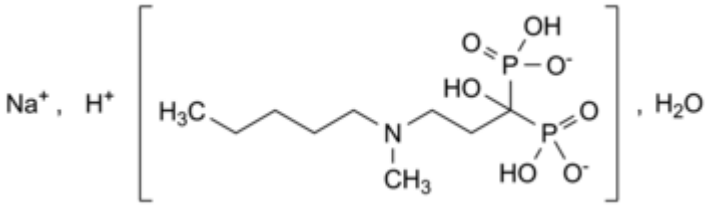
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Ibandronate Sodium Monohydrate

General Notices

(Ph. Eur. monograph 2771)



$C_9H_{22}NNaO_7P_2,H_2O$ 359.2 *138926-19-9*

Action and use

Bisphosphonate; treatment of osteolytic lesions; osteoporosis; hypercalcaemia in malignancy

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DEFINITION

Monosodium trihydrogen [1-hydroxy-3-[methyl(pentyl)amino]propane-1,1-diyl]bisphosphonate monohydrate.

Content

98.5 per cent to 101.5 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white or yellowish powder.

Solubility

Freely soluble in water, very slightly soluble in ethanol (96 per cent), practically insoluble in acetone.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *ibandronate sodium monohydrate CRS*.

B. Dissolve 0.1 g in 2 mL of *water R*. The solution gives reaction (a) of sodium (2.3.1).

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TESTS

Solution S

Dissolve 0.5 g in *water R* and dilute to 10 mL with the same solvent.

Appearance of solution

Solution S is not more opalescent than reference suspension IV (*2.2.1*) and not more intensely coloured than reference solution B_4 (*2.2.2, Method II*).

pH (*2.2.3*)

3.9 to 4.2 for solution S.

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture *acetonitrile R*, *ethanol (96 per cent) R* (50:50 *V/V*).

Buffer solution pH 2.3 Dissolve 0.25 g of *sodium edetate R* in 900 mL of *water for chromatography R*, add 1 mL of *trifluoroacetic acid R* and 1 mL of *triethylamine R*; adjust to pH 2.3 with *trifluoroacetic acid R* or *triethylamine R* and dilute to 1000 mL with *water for chromatography R*.

Solution A Dissolve 0.25 g of *sodium edetate R* in *water R*, add 10 mL of *trifluoroacetic acid R* and dilute to 1000 mL with *water R*.

Test solution Dissolve 0.40 g of the substance to be examined in solution A and dilute to 10.0 mL with solution A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with solution A. Dilute 1.0 mL of this solution to 10.0 mL with solution A.

Reference solution (b) Dilute 25 µL of *acetone R* to 50 mL with solution A (solution B). Dissolve 40 mg of the substance to be examined in 1 mL of solution B.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped phenylhexylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 35 °C.

Mobile phase Solvent mixture, buffer solution pH 2.3 (6:94 *V/V*).

Flow rate 1.2 mL/min.

Detection Differential refractometer maintained at 40 °C.

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Injection 30 µL.

Run time 4 times the retention time of ibandronate.

Relative retention With reference to ibandronate (retention time = about 6.5 min): acetone = about 0.7.

System suitability Reference solution (b):

— *resolution*: minimum 3.0 between the peaks due to acetone and ibandronate.

Calculation of percentage contents:

— for each impurity, use the concentration of ibandronate sodium monohydrate in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Water (2.5.32)

4.4 per cent to 5.6 per cent, determined on 50.0 mg using the evaporation technique at 150 °C.

ASSAY

Dissolve 0.500 g in 50 mL of *water R*. Carry out a potentiometric titration (2.2.20), using *0.1 M sodium hydroxide*. Read the volume added at the 1st inflexion point (not systematically detected) and continue the titration to the 2nd inflexion point.

Calculate the percentage content of $C_9H_{22}NNaO_7P_2$ using the following expression:

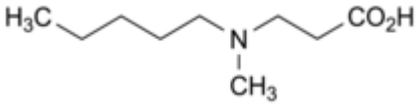
$$\frac{\left(V_2 - 2V_1\right) \times 341.24 \times 10 \times M}{m \times (100 - w)}$$

V_1	=	volume of *0.1 M sodium hydroxide* added at the 1st inflexion point (at about pH about 2 to 5), in millilitres (only detected if free phosphates and phosphites are present);
V_2	=	volume of *0.1 M sodium hydroxide* added at the 2nd inflexion point (at pH of about 11), in millilitres;
341.24	=	relative molecular mass of anhydrous ibandronate sodium;
m	=	mass of the substance to be examined, in grams;
M	=	molarity of the sodium hydroxide solution, in moles per litre;
w	=	percentage content of water.

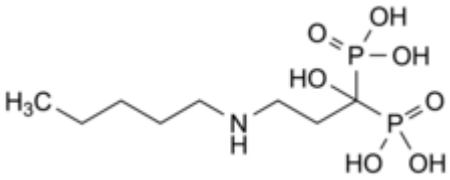
IMPURITIES

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Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, C.



A. 3-[methyl(pentyl)amino]propanoic acid,



C. [1-hydroxy-3-(pentylamino)propane-1,1-diyl]bis(phosphonic acid).

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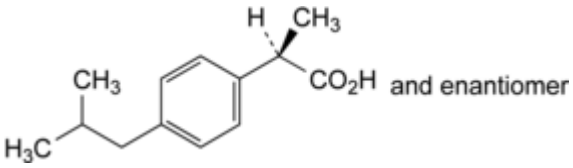
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Ibuprofen

General Notices

(Ph. Eur. monograph 0721)



$C_{13}H_{18}O_2$ 206.3 *15687-27-1*

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

Preparations

Ibuprofen Capsules

Ibuprofen Effervescent Granules

Ibuprofen Gel

Ibuprofen Oral Suspension

Ibuprofen Orodispersible Tablets

Ibuprofen Prolonged-release Capsules

Ibuprofen Prolonged-release Tablets

Ibuprofen Tablets

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DEFINITION

(2*RS*)-2-[4-(2-Methylpropyl)phenyl]propanoic acid.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

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Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Practically insoluble in water, freely soluble in acetone, in methanol and in methylene chloride. It dissolves in dilute solutions of alkali hydroxides and carbonates.

IDENTIFICATION

First identification: A, C.

Second identification: A, B, D.

A. Melting point (2.2.14): 75 °C to 78 °C.

B. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 50.0 mg in a 4 g/L solution of *sodium hydroxide R* and dilute to 100.0 mL with the same alkaline solution.

Spectral range 240-300 nm, using a spectrophotometer with a band width of 1.0 nm and a scan speed of not more than 50 nm/min.

Absorption maxima At 264 nm and 272 nm.

Shoulder At 258 nm.

Absorbance ratio:

— A_{264} / A_{258} = 1.20 to 1.30;

— A_{272} / A_{258} = 1.00 to 1.10.

C. Infrared absorption spectrophotometry (2.2.24).

Comparison *ibuprofen CRS*.

D. Thin-layer chromatography (2.2.27).

Test solution Dissolve 50 mg of the substance to be examined in *methylene chloride R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 50 mg of *ibuprofen CRS* in *methylene chloride R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase *anhydrous acetic acid R*, *ethyl acetate R*, *hexane R* (5:24:71 *V/V/V*).

Application 5 µL.

Development Over a path of 10 cm.

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Drying At 120 °C for 30 min.

Detection Lightly spray with a 10 g/L solution of *potassium permanganate R* in *dilute sulfuric acid R* and heat at 120 °C for 20 min; examine in ultraviolet light at 365 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Solution S

Dissolve 2.0 g in *methanol R* and dilute to 20 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Optical rotation (*2.2.7*)

-0.05° to + 0.05°.

Dissolve 0.50 g in *methanol R* and dilute to 20.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 20 mg of the substance to be examined in 2 mL of *acetonitrile R* and dilute to 10.0 mL with mobile phase A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (b) Dilute 1.0 mL of *ibuprofen impurity B CRS* to 10.0 mL with *acetonitrile R* (solution A). Dissolve 20 mg of *ibuprofen CRS* in 2 mL of *acetonitrile R*, add 1.0 mL of solution A and dilute to 10.0 mL with mobile phase A.

Reference solution (c) Dissolve the contents of a vial of *ibuprofen for peak identification CRS* (mixture of impurities A, J and N) in 1 mL of *acetonitrile R* and dilute to 5 mL with mobile phase A.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl amorphous organosilica polymer for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: mix 0.5 volumes of *phosphoric acid R*, 340 volumes of *acetonitrile R1* and 600 volumes of *water for chromatography R*; allow to equilibrate and dilute to 1000 volumes with *water for chromatography R*;

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— *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 25	100	0
25 - 55	100 → 15	0 → 85
55 - 70	15	85

Flow rate 2 mL/min.

Detection Spectrophotometer at 214 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *ibuprofen for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, J and N.

Relative retention With reference to ibuprofen (retention time = about 21 min): impurity J = about 0.2; impurity N = about 0.3; impurity A = about 0.9; impurity B = about 1.1.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity B, and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to ibuprofen. If necessary, adjust the concentration of acetonitrile in mobile phase A.

Limits:

— *impurities A, J, N*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *disregard limit*: 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.03 per cent).

Impurity F

Gas chromatography (*2.2.28*): use the normalisation procedure.

Methylating solution Dilute 1 mL of *N,N-dimethylformamide dimethylacetal R* and 1 mL of *pyridine R* to 10 mL with *ethyl acetate R*.

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Test solution Weigh about 50.0 mg of the substance to be examined into a sealable vial, dissolve in 1.0 mL of *ethyl acetate R*, add 1 mL of the methylating solution, seal and heat at 100 °C in a block heater for 20 min. Allow to cool. Remove the reagents under a stream of nitrogen at room temperature. Dissolve the residue in 5 mL of *ethyl acetate R*.

Reference solution (a) Dissolve 0.5 mg of *ibuprofen impurity F CRS* in *ethyl acetate R* and dilute to 10.0 mL with the same solvent.

Reference solution (b) Weigh about 50.0 mg of *ibuprofen CRS* into a sealable vial, dissolve in 1.0 mL of reference solution (a), add 1 mL of the methylating solution, seal and heat at 100 °C in a block heater for 20 min. Allow to cool. Remove the reagents under a stream of nitrogen at room temperature. Dissolve the residue in 5 mL of *ethyl acetate R*.

Column:

— *material*: fused silica;

— *size*: *l* = 25 m, Ø = 0.53 mm;

— *stationary phase*: *macrogol 20 000 R* (film thickness 2 µm).

Carrier gas *helium for chromatography R*.

Flow rate 5.0 mL/min.

Temperature:

— *column*: 150 °C;

— *injection port*: 200 °C;

— *detector*: 250 °C.

Detection Flame ionisation.

Injection 1 µL of the test solution and reference solution (b).

Run time Twice the retention time of ibuprofen.

System suitability:

— *relative retention* with reference to ibuprofen (retention time = about 17 min): impurity F = about 1.5.

Limit:

— *impurity F*: maximum 0.1 per cent.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo*.

Sulfated ash (*2.4.14*)

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Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

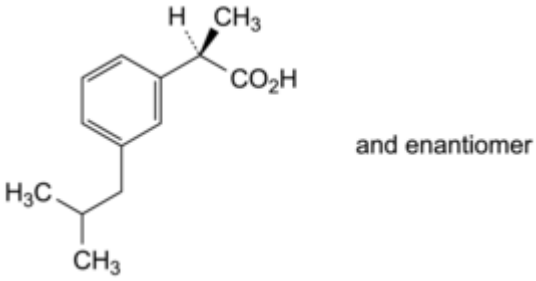
Dissolve 0.450 g in 50 mL of *methanol R*. Add 0.4 mL of *phenolphthalein solution R1*. Titrate with *0.1 M sodium hydroxide* until a red colour is obtained. Carry out a blank titration.

1 mL of *0.1 M sodium hydroxide* is equivalent to 20.63 mg of $C_{13}H_{18}O_2$.

IMPURITIES

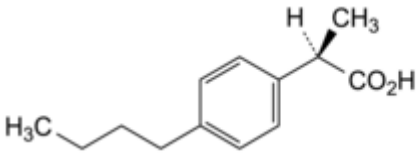
Specified impurities *A, F, J, N.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D, E, G, H, I, K, L, M, O, P, Q, R.*



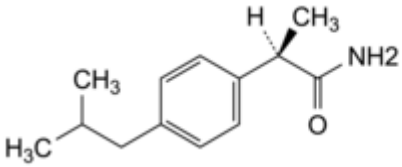
and enantiomer

A. (2*RS*)-2-[3-(2-methylpropyl)phenyl]propanoic acid,



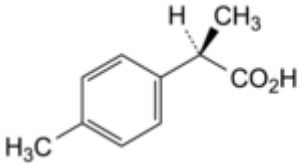
and enantiomer

B. (2*RS*)-2-(4-butylphenyl)propanoic acid,



and enantiomer

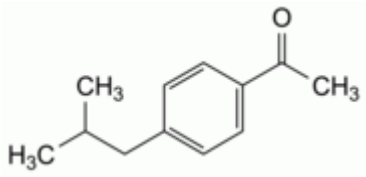
C. (2*RS*)-2-[4-(2-methylpropyl)phenyl]propanamide,



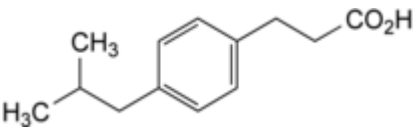
and enantiomer

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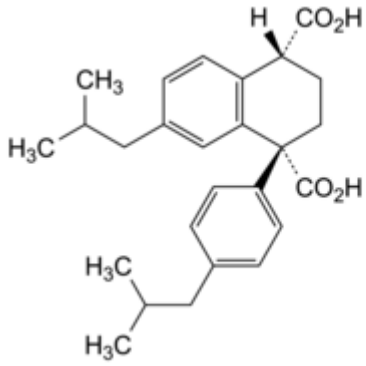
D. (2*RS*)-2-(4-methylphenyl)propanoic acid,



E. 1-[4-(2-methylpropyl)phenyl]ethanone,

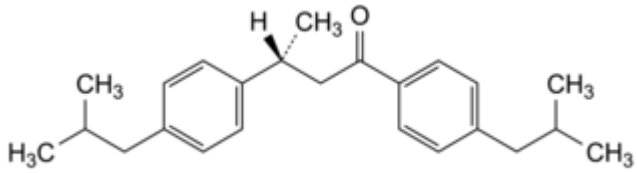


F. 3-[4-(2-methylpropyl)phenyl]propanoic acid,



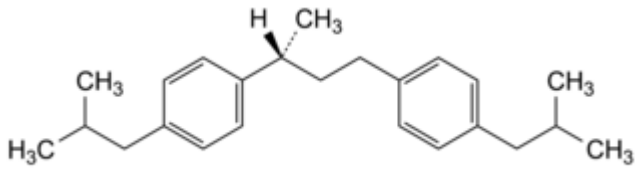
and enantiomer

G. (1*RS*,4*RS*)-7-(2-methylpropyl)-1-[4-(2-methylpropyl)phenyl]-1,2,3,4-tetrahydronaphthalene-1,4-dicarboxylic acid,



and enantiomer

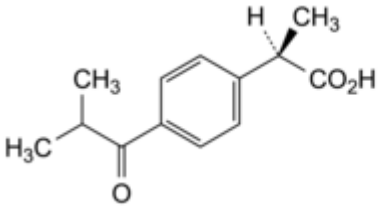
H. (3*RS*)-1,3-bis[4-(2-methylpropyl)phenyl]butan-1-one,



and enantiomer

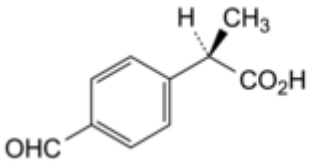
I. 1-(2-methylpropyl)-4-[(3*RS*)-3-[4-(2-methylpropyl)phenyl]butyl]benzene,

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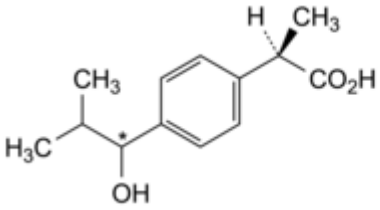
and enantiomer

J. (2*RS*)-2-[4-(2-methylpropanoyl)phenyl]propanoic acid,



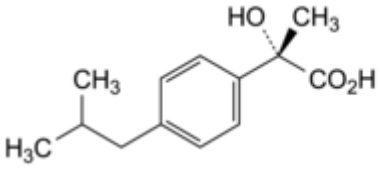
and enantiomer

K. (2*RS*)-2-(4-formylphenyl)propanoic acid,



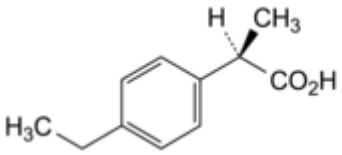
and enantiomer

L. (2*RS*)-2-[4-(1-hydroxy-2-methylpropyl)phenyl]propanoic acid,



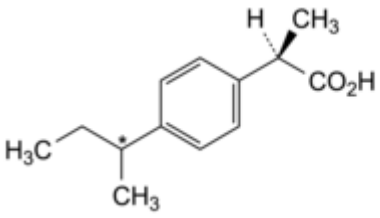
and enantiomer

M. (2*RS*)-2-hydroxy-2-[4-(2-methylpropyl)phenyl]propanoic acid,



and enantiomer

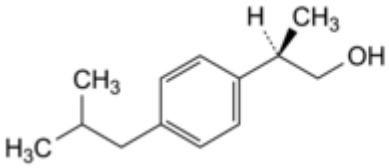
N. (2*RS*)-2-(4-ethylphenyl)propanoic acid,



and enantiomer

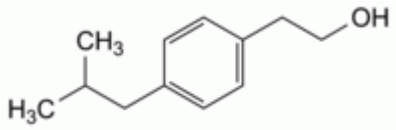
O. (2*RS*)-2-[4-(1-methylpropyl)phenyl]propanoic acid,

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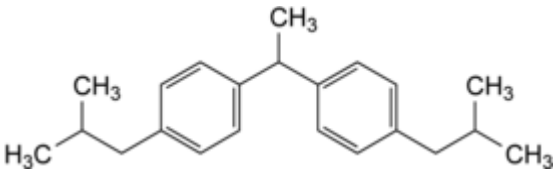


and enantiomer

P. (2*RS*)-2-[4-(2-methylpropyl)phenyl]propan-1-ol,



Q. 2-[4-(2-methylpropyl)phenyl]ethanol,



R. 1,1′-(ethane-1,1-diyl)-4,4′-(2-methylpropyl)dibenzene.

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Ibuprofen Capsules

General Notices

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

DEFINITION

Ibuprofen Capsules contain Ibuprofen.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of ibuprofen, $C_{13}H_{18}O_2$

92.5 to 105.0% of the stated amount.

IDENTIFICATION

Mix with the aid of ultrasound a quantity of the capsule contents containing 0.5 g of Ibuprofen with 20 mL of *water* and filter. Dissolve the residue in 20 mL of *acetone* and evaporate to dryness under a stream of nitrogen. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of ibuprofen (*RS 186*).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of *phosphate buffer pH 7.2*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix II D, using the following solutions.

(1) After 45 minutes, withdraw a sample of the medium, filter and dilute, if necessary, with the dissolution medium to produce a solution expected to contain 0.011% w/v of ibuprofen.

(2) 0.011% w/v of *ibuprofen BPCRS* in the dissolution medium.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 264 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

3 volumes of *orthophosphoric acid*, 247 volumes of *water* and 750 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions the retention time of ibuprofen is about 7 minutes.

DETERMINATION OF CONTENT

Calculate the total content of ibuprofen, $C_{13}H_{18}O_2$, in the medium using the declared content of $C_{13}H_{18}O_2$ in *ibuprofen BPCRS*.

LIMITS

The amount of ibuprofen released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the capsule contents containing 0.2 g of Ibuprofen in 20 mL of *acetonitrile R1*, add sufficient mobile phase A to produce 100 mL and filter (Whatman GF/C is suitable).

(2) Dilute 1 volume of solution (1) to 100 volumes with mobile phase A.

(3) Dissolve 20 mg of *ibuprofen BPCRS* in 2 mL of *acetonitrile R1* , add 1 mL of a 0.006% w/v solution of *ibuprofen impurity B BPCRS* in *acetonitrile R1* and dilute to 10 mL with mobile phase A.

(4) 0.0006% w/v of *4'-isobutylacetophenone BPCRS* (impurity E) in mobile phase A.

(5) To 10 mg of *ibuprofen BPCRS*, add 2 mL of *polyethylene glycol* and a drop of *sulfuric acid*. Heat gently for 1 hour and cool. Make up to 20 mL with mobile phase A (generation of impurity 1).

(6) Dissolve the contents of a vial of *ibuprofen for peak identification EPCRS* in 1 mL of *acetonitrile R1* and dilute to 5 mL with mobile phase A.

(7) Dilute 1 volume of solution (2) to 10 volumes with mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl amorphous organosilica polymer for chromatography* (5 µm) (XTerra MS C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 214 nm.

(f) Inject 20 µL of each solution.

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MOBILE PHASE

Mobile phase A 0.5 volume of *orthophosphoric acid*, 340 volumes of *acetonitrile R1* and sufficient *water* to produce 1000 volumes.

Mobile phase B 0.5 volume of *orthophosphoric acid*, 100 volumes of *water* and sufficient *acetonitrile R1* to produce 1000 volumes.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-25	100	0	isocratic
25-55	100→0	0→100	linear gradient
55-70	0	100	isocratic
70-71	0→100	100→0	linear gradient
71-85	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to ibuprofen (retention time about 26 minutes) are: impurity J, about 0.2; impurity N, about 0.3; impurity A, about 0.9; impurity B, about 1.08; impurity E, about 1.11 and impurity 1, about 1.2.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* is at least 5.0, where *Hp* is the height above the baseline of the peak due to impurity B and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to ibuprofen.

LIMITS

Use the chromatogram supplied with *ibuprofen for peak identification EPCRS* and the chromatogram obtained with solution (6) to identify the peaks due to impurities A, J, and N. Use the chromatogram obtained with solution (4) to identify the peaks due to impurity E. Use the chromatogram obtained with solution (5) to identify the peak due to impurity 1.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity 1 is not greater than 3.6 times the area of the principal peak in the chromatogram obtained with solution (2) (3.6%);

the area of any peak corresponding to impurity A, J or N is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (7) (0.15% of each);

the area of any peak corresponding to impurity E is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (7) (0.3%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (7) (0.10%);

the sum of the areas of any *secondary peaks*, excluding impurity 1, is not greater than 0.7 times the area of the principal peak in the chromatogram obtained with solution (2) (0.7%).

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Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (7) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the capsule contents containing 0.1 g of Ibuprofen with 50 mL of the mobile phase, add sufficient mobile phase to produce 100 mL and mix. Centrifuge and dilute 1 volume of the supernatant liquid to 10 volumes with the mobile phase.

(2) 0.01% w/v of *ibuprofen BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

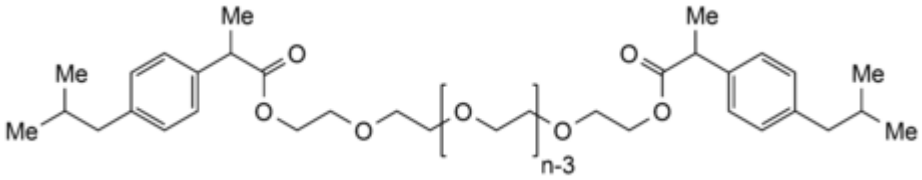
The chromatographic conditions described under Dissolution may be used.

DETERMINATION OF CONTENT

Calculate the content of ibuprofen, $C_{13}H_{18}O_2$, in the capsules from the chromatograms obtained and using the declared content of $C_{13}H_{18}O_2$ in *ibuprofen BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Ibuprofen and the following:



1. *rac*-α-({2-[4-(propan-2-yl)phenyl]propanoyloxy}methyl)poly(oxyethylene)-ω-yl 2-[4-(propan-2-yl)phenyl]propanoate (PEG-ibuprofen ester)

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Ibuprofen Effervescent Granules

General Notices

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

DEFINITION

Ibuprofen Effervescent Granules contain Ibuprofen in a suitable effervescent basis.

The granules comply with the requirements stated under Granules and with the following requirements.

Content of ibuprofen, $C_{13}H_{18}O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Extract a quantity of the powdered granules containing 0.5 g of Ibuprofen with 20 mL of *acetone*, filter and evaporate the filtrate to dryness. Wash the residue with 20 mL of *water*, filter, and discard the filtrate. Wash the resulting residue with 20 mL of *acetone*, and evaporate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of ibuprofen (*RS 186*).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix with the aid of ultrasound a quantity of the powdered granules containing 0.2 g of Ibuprofen with 20 mL of mobile phase A. Add sufficient mobile phase A to produce 100 mL and filter (Whatman GF/C is suitable).

(2) Dilute 1 volume of solution (1) to 100 volumes with mobile phase A. Further dilute 1 volume to 10 volumes with mobile phase A.

(3) Dissolve 20 mg of *ibuprofen BPCRS* in 2 mL of *acetonitrile R1* , add 1 mL of a 0.006% w/v solution of *ibuprofen impurity B BPCRS* in *acetonitrile R1* and dilute to 10 mL with mobile phase A.

(4) 0.0006% w/v of *4'-isobutylacetophenone BPCRS* (impurity E) in mobile phase A.

(5) Dissolve the contents of a vial of *ibuprofen for peak identification EPCRS* in 1 mL of *acetonitrile R1* and dilute to 5 mL with mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl amorphous organosilica polymer for chromatography* (5 µm) (XTerra MS C18 is suitable).

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(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 214 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 0.5 volume of *orthophosphoric acid*, 340 volumes of *acetonitrile R1* and sufficient *water* to produce 1000 volumes.

Mobile phase B 0.5 volume of *orthophosphoric acid*, 100 volumes of *water* and sufficient *acetonitrile R1* to produce 1000 volumes.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-25	100	0	isocratic
25-55	100→0	0→100	linear gradient
55-70	0	100	isocratic
70-71	0→100	100→0	linear gradient
71-85	100	0	re-equilibration

When chromatograms are recorded under the prescribed conditions, the relative retentions with reference to ibuprofen (retention time about 26 minutes) are: impurity J, about 0.18; impurity N, about 0.3; impurity A, about 0.9; impurity B, about 1.08 and impurity E, about 1.11.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* is at least 5.0, where *Hp* is the height above the baseline of the peak due to impurity B and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to ibuprofen.

LIMITS

Use the chromatogram supplied with *ibuprofen for peak identification EPCRS* and the chromatogram obtained with solution (5) to identify the peaks due to impurities A, J, and N. Use the chromatogram obtained with solution (4) to identify the peaks due to impurity E.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity E is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any peak corresponding to impurity A, J or N is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15% of each);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

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the sum of the areas of any *secondary peaks* is not greater than 7 times the area of the principal peak in the chromatogram obtained with solution (2) (0.7%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 35 volumes of 0.1 % w/v of *formic acid* and 65 volumes of *methanol* (solution A).

(1) Shake a quantity of the powdered granules containing 3 g of Ibuprofen with 500 mL of solution A. Add sufficient solution A to produce 1000 mL and mix thoroughly. Filter the solution (a Whatman GF/C 1.2-µm filter is suitable) and dilute 0.5 volume of the filtrate to 15 volumes.

(2) 0.01% w/v of *ibuprofen BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 264 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

3 volumes of *orthophosphoric acid*, 247 volumes of *water* and 750 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions, the retention time of ibuprofen is about 7 minutes.

DETERMINATION OF CONTENT

Calculate the content of ibuprofen, $C_{13}H_{18}O_2$, in the granules from the chromatograms obtained and using the declared content of $C_{13}H_{18}O_2$ in *ibuprofen BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Ibuprofen.

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Ibuprofen Gel

General Notices

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

DEFINITION

Ibuprofen Gel is a solution of Ibuprofen in a suitable water-miscible basis.

The gel complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of ibuprofen, $C_{13}H_{18}O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Disperse a quantity of the gel containing 0.5 g of Ibuprofen with 20 mL of *methanol* and prepare a solid phase extraction cartridge containing a silica sorbent (Discovery DSC-18 SPE cartridges are suitable) by passing through 2 mL of *methanol* and 3 mL of *water*. Mix 1 mL of the sample solution with 1.5 mL of *acetic acid (2%)* to produce a solution of pH 3.0. Pass the resulting solution through the cartridge, wash the cartridge with 1 mL of a 2% w/v solution of *acetic acid* and discard the eluent. Pass three 1-mL aliquots of *methanol*, collect the eluent and evaporate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of ibuprofen (RS 186).

TESTS

Acidity or alkalinity

The pH of the gel is 5.5 to 7.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse with the aid of ultrasound a quantity of the gel containing 0.2 g of Ibuprofen in 50 mL of mobile phase A, dilute to 100 mL with mobile phase A and filter (Whatman GF/C filter is suitable).

(2) Dilute 1 volume of solution (1) to 100 volumes with mobile phase A. Further dilute 1 volume to 10 volumes with mobile phase A.

(3) Dissolve 20 mg of *ibuprofen BPCRS* in 2 mL of *acetonitrile R1*, add 1 mL of a 0.006% w/v solution of *ibuprofen impurity B BPCRS* in *acetonitrile R1*, and dilute to 10 mL with mobile phase A.

(4) 0.0006% w/v of *4'-isobutylacetophenone BPCRS* (impurity E) in mobile phase A.

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(5) Dissolve the contents of a vial of *ibuprofen for peak identification EPCRS* in 1 mL of *acetonitrile R1* and dilute to 5 mL with mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl amorphous organosilica polymer for chromatography* (5 µm) (XTerra MS C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 214 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 0.5 volume of *orthophosphoric acid*, 340 volumes of *acetonitrile R1* and sufficient *water* to produce 1000 volumes.

Mobile phase B 0.5 volume of *orthophosphoric acid*, 100 volumes of *water* and sufficient *acetonitrile R1* to produce 1000 volumes.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-25	100	0	isocratic
25-55	100→0	0→100	linear gradient
55-70	0	100	isocratic
70-71	0→100	100→0	linear gradient
71-85	100	0	re-equilibration

When chromatograms are recorded under the prescribed conditions, the relative retentions with reference to ibuprofen (retention time about 26 minutes) are: impurity J, about 0.2; impurity N, about 0.3; impurity A, about 0.9; impurity B, about 1.08 and impurity E, about 1.11.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* is at least 5.0, where *Hp* is the height above the baseline of the peak due to impurity B and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to ibuprofen.

LIMITS

Use the chromatogram supplied with *ibuprofen for peak identification EPCRS* and the chromatogram obtained with solution (5) to identify the peaks due to impurities A, J, and N. Use the chromatogram obtained with solution (4) to identify the peak due to impurity E.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity E is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

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the area of any peak corresponding to impurity A, J or N is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15% of each);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of any *secondary peaks* is not greater than 7 times the area of the principal peak in the chromatogram obtained with solution (2) (0.7%).

Disregard any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse with the aid of ultrasound a weighed quantity of the gel containing 50 mg of Ibuprofen in 50 mL of *methanol*, dilute to 100 mL with *methanol* and filter (Whatman GF/C filter is suitable). Dilute 1 volume to 2 volumes with the mobile phase.
(2) 0.05% w/v of *ibuprofen BPCRS* in *methanol*. Dilute 1 volume to 2 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 264 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

3 volumes of *orthophosphoric acid*, 247 volumes of *water* and 750 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions, the retention time of ibuprofen is about 7 minutes.

DETERMINATION OF CONTENT

Calculate the content of $C_{13}H_{18}O_2$ in the gel using the declared content of $C_{13}H_{18}O_2$ in *ibuprofen BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Ibuprofen.

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Ibuprofen Oral Suspension

General Notices

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

DEFINITION

Ibuprofen Oral Suspension is a suspension of Ibuprofen in a suitable flavoured vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements.

Content of ibuprofen, $C_{13}H_{18}O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the oral suspension containing 0.5 g of Ibuprofen with 25 mL of *dichloromethane* and 15 mL of *water*. Allow to stand until the layers have separated and discard the upper layer. Shake the lower layer with 5 mL of *water* and discard the upper layer. Evaporate the lower layer to dryness, add 20 mL of *water* to the residue and filter (Whatman GF/C filter is suitable). Wash the residue with 20 mL of *dichloromethane* and evaporate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of ibuprofen *(RS 186)*.

TESTS

Acidity

pH, 3.6 to 4.6, Appendix V L.

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of *phosphate buffer pH 7.2*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix II D, using the following solutions.

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(1) Shake the oral suspension for 30 seconds and place a volume of the oral suspension containing 0.2 g of Ibuprofen into each dissolution vessel. After 30 minutes, withdraw a sample of the medium, filter and dilute, if necessary, with the dissolution medium to produce a solution expected to contain 0.022% w/v of Ibuprofen.

(2) 0.022% w/v of *ibuprofen BPCRS* in the dissolution medium.

(3) 0.15% w/v each of *benzophenone* and *ibuprofen BPCRS* in *acetonitrile*. Dilute 1 volume to 10 volumes with the dissolution medium.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

37 volumes of *acetonitrile* and 63 volumes of 0.01M *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to benzophenone and ibuprofen is at least 1.5.

DETERMINATION OF CONTENT

Calculate the total content of ibuprofen, $C_{13}H_{18}O_2$, in the medium using the declared content of $C_{13}H_{18}O_2$ in *ibuprofen BPCRS*.

LIMITS

The amount of ibuprofen released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions immediately after preparation.

(1) Disperse with the aid of ultrasound a quantity of the oral suspension containing 0.2 g of Ibuprofen with 20 mL of *acetonitrile R1*. Add sufficient mobile phase A to produce 100 mL and filter (Whatman GF/C is suitable).

(2) Dilute 1 volume of solution (1) to 100 volumes with mobile phase A. Further dilute 1 volume to 10 volumes with mobile phase A.

(3) Dissolve 20 mg of *ibuprofen BPCRS* in 2 mL of *acetonitrile R1* , add 1 mL of a 0.006% w/v solution of *ibuprofen impurity B BPCRS* in *acetonitrile R1*, and dilute to 10 mL with mobile phase A.

(4) 0.0006% w/v of *4'-isobutylacetophenone BPCRS* (impurity E) in mobile phase A.

(5) Dissolve the contents of a vial of *ibuprofen for peak identification EPCRS* in 1 mL of *acetonitrile R1*, and dilute to 5 mL with mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl amorphous organosilica polymer for chromatography* (5 µm) (XTerra MS C18 is suitable).

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(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 214 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 0.5 volume of *orthophosphoric acid*, 340 volumes of *acetonitrile R1* and sufficient *water* to produce 1000 volumes.

Mobile phase B 0.5 volume of *orthophosphoric acid*, 100 volumes of *water* and sufficient *acetonitrile R1* to produce 1000 volumes.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-25	100	0	isocratic
25-55	100→0	0→100	linear gradient
55-70	0	100	isocratic
70-71	0→100	100→0	linear gradient
71-85	100	0	re-equilibration

When chromatograms are recorded under the prescribed conditions, the relative retentions with reference to ibuprofen (retention time about 26 minutes) are: impurity J, about 0.2; impurity N, about 0.3; impurity A, about 0.9; impurity B, about 1.08 and impurity E, about 1.11.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* is at least 5.0, where *Hp* is the height above the baseline of the peak due to impurity B and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to ibuprofen.

LIMITS

Use the chromatogram supplied with *ibuprofen for peak identification EPCRS* and the chromatogram obtained with solution (5) to identify the peaks due to impurities A, J, and N. Use the chromatogram obtained with solution (4) to identify the peaks due to impurity E.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity E is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any peak corresponding to impurity A, J or N is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15% of each);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

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the sum of the areas of any *secondary peaks* is not greater than 7 times the area of the principal peak in the chromatogram obtained with solution (2) (0.7%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions immediately after preparation.

(1) Mix a weighed quantity of the mixed oral suspension containing 0.1 g of Ibuprofen with 30 mL of *acetonitrile*, add a further 10 mL of *acetonitrile* and 10 mL of 0.01M *orthophosphoric acid*, shake vigorously, dilute to 100 mL with 0.01M *orthophosphoric acid* and filter (Whatman GF/C paper is suitable).

(2) 0.1% w/v of *ibuprofen BPCRS* prepared by dissolving a suitable quantity in 40 volumes of *acetonitrile* and adding 60 volumes of 0.01M *orthophosphoric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (30 cm × 3.9 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (µBondapak C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

4 volumes of *acetonitrile* and 6 volumes of 0.01M *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions the retention time of ibuprofen is about 21 minutes.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_{13}H_{18}O_2$, weight in volume, from the declared content of $C_{13}H_{18}O_2$ in *ibuprofen BPCRS*.

STORAGE

Ibuprofen Oral Suspension should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Ibuprofen.

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Ibuprofen Orodispersible Tablets

General Notices

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

DEFINITION

Ibuprofen Orodispersible Tablets contain Ibuprofen.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of ibuprofen, $C_{13}H_{18}O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Extract a quantity of the powdered tablets containing 0.5 g of Ibuprofen with 20 mL of *acetone*, filter (Whatman GF/C is suitable) and evaporate the filtrate to dryness. Wash the residue with 20 mL of *water*, filter and discard the filtrate. Wash the resulting residue with 20 mL of *acetone* and evaporate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of ibuprofen (*RS 186*).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of *phosphate buffer pH 7.2*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix II D, using the following solutions.

(1) After 30 minutes, withdraw a sample of the medium, filter and dilute, if necessary, with the dissolution medium to produce a solution expected to contain 0.02% w/v of Ibuprofen.

(2) 0.02% w/v of *ibuprofen BPCRS* in the dissolution medium.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 264 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

3 volumes of *orthophosphoric acid*, 247 volumes of *water* and 750 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions, the retention time of ibuprofen is about 7 minutes.

DETERMINATION OF CONTENT

Calculate the total content of ibuprofen, $C_{13}H_{18}O_2$, in the medium using the declared content of $C_{13}H_{18}O_2$ in *ibuprofen BPCRS*.

LIMITS

The amount of ibuprofen released is not less than 80% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing 0.2 g of Ibuprofen with 20 mL of *acetonitrile R1*. Add sufficient mobile phase A to produce 100 mL and filter (Whatman GF/C is suitable).

(2) Dilute 1 volume of solution (1) to 100 volumes with mobile phase A. Further dilute 1 volume to 10 volumes with mobile phase A.

(3) Dissolve 20 mg of *ibuprofen BPCRS* in 2 volumes of *acetonitrile R1*, add 1 volume of a 0.006% w/v solution of *ibuprofen impurity B BPCRS* in *acetonitrile R1* and dilute to 10 volumes with mobile phase A.

(4) 0.0006% w/v of *4'-isobutylacetophenone BPCRS* (impurity E) in mobile phase A.

(5) Dissolve the contents of a vial of *ibuprofen for peak identification EPCRS* in 1 mL of *acetonitrile R1* and dilute to 5 mL with mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl amorphous organosilica polymer for chromatography* (5 µm) (XTerra MS C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 214 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 0.5 volume of *orthophosphoric acid*, 340 volumes of *acetonitrile R1* and sufficient *water* to produce 1000 volumes.

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Mobile phase B 0.5 volume of *orthophosphoric acid*, 100 volumes of *water* and sufficient *acetonitrile R1* to produce 1000 volumes.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-25	100	0	isocratic
25-55	100→0	0→100	linear gradient
55-70	0	100	isocratic
70-71	0→100	100→0	linear gradient
71-85	100	0	re-equilibration

When chromatograms are recorded under the prescribed conditions, the relative retentions with reference to ibuprofen (retention time about 26 minutes) are: impurity J, about 0.2; impurity N, about 0.3; impurity A, about 0.9; impurity B, about 1.08; impurity E, about 1.11 and impurity 1, about 1.6.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* is at least 5.0, where *Hp* is the height above the baseline of the peak due to impurity B and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to ibuprofen.

LIMITS

Use the chromatogram supplied with *ibuprofen for peak identification EPCRS* and the chromatogram obtained with solution (5) to identify the peaks due to impurities A, J, and N. Use the chromatogram obtained with solution (4) to identify the peak due to impurity E.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity E is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any peak corresponding to impurity 1 is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the area of any peak corresponding to impurity A, J or N is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15% of each);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of any *secondary peaks* is not greater than 7 times the area of the principal peak in the chromatogram obtained with solution (2) (0.7%).

Disregard any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

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Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.1 g of Ibuprofen with 50 mL of the mobile phase, add sufficient of the mobile phase to produce 100 mL and mix. Centrifuge and dilute 1 volume of the supernatant liquid to 10 volumes with the mobile phase.

(2) 0.01% w/v of *ibuprofen BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

DETERMINATION OF CONTENT

Calculate the content of ibuprofen, $C_{13}H_{18}O_2$, in the tablets from the chromatograms obtained and using the declared content of $C_{13}H_{18}O_2$ in *ibuprofen BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Ibuprofen and the following:

1. Unknown structure

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Ibuprofen Prolonged-release Capsules

General Notices

Prolonged-release Ibuprofen Capsules

Ibuprofen Prolonged-release Capsules from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

DEFINITION

Ibuprofen Prolonged-release Capsules contain Ibuprofen. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Ibuprofen. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of ibuprofen, $C_{13}H_{18}O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Extract a quantity of the capsule contents containing 0.5 g of Ibuprofen with 20 mL of *acetone*, filter and evaporate the filtrate to dryness in a current of air without heating. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of ibuprofen *(RS 186)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse a quantity of the capsule contents containing 0.2 g of Ibuprofen with 20 mL of *acetonitrile R1*, add sufficient mobile phase A to produce 100 mL and filter (Whatman GF/C is suitable).

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(2) Dilute 1 volume of solution (1) to 100 volumes with mobile phase A. Further dilute 1 volume to 10 volumes with mobile phase A.

(3) Dissolve 20 mg of *ibuprofen BPCRS* in 2 mL of *acetonitrile R1*, add 1 mL of a 0.006% w/v solution of *ibuprofen impurity B BPCRS* in *acetonitrile R1* and dilute to 10 mL with mobile phase A.

(4) 0.0006% w/v of *4'-isobutylacetophenone BPCRS* (impurity E) in mobile phase A.

(5) Dissolve the contents of a vial of *ibuprofen for peak identification EPCRS* in 1 mL of *acetonitrile R1* and dilute to 5 mL with mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl amorphous organosilica polymer for chromatography* (5 µm) (XTerra MS C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 214 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 0.5 volume of *orthophosphoric acid*, 340 volumes of *acetonitrile R1* and sufficient *water* to produce 1000 volumes.

Mobile phase B 0.5 volume of *orthophosphoric acid*, 100 volumes of *water* and sufficient *acetonitrile R1* to produce 1000 volumes.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-25	100	0	isocratic
25-55	100→0	0→100	linear gradient
55-70	0	100	isocratic
70-71	0→100	100→0	linear gradient
71-85	100	0	re-equilibration

When chromatograms are recorded under the prescribed conditions, the relative retentions with reference to ibuprofen (retention time about 26 minutes) are: impurity J, about 0.2; impurity N, about 0.3; impurity A, about 0.9; impurity B, about 1.08 and impurity E, about 1.11.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* is at least 5.0, where *Hp* is the height above the baseline of the peak due to impurity B and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to ibuprofen.

LIMITS

Use the chromatogram supplied with *ibuprofen for peak identification EPCRS* and the chromatogram obtained with solution (5) to identify the peaks due to impurities A, J, and N. Use the chromatogram obtained with solution (4) to identify the peak due to impurity E.

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In the chromatogram obtained with solution (1):

the area of any peak corresponding to ibuprofen impurity E is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any peak corresponding to impurity A, J or N is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15% of each);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of any *secondary peaks* is not greater than 7 times the area of the principal peak in the chromatogram obtained with solution (2) (0.7%).

Disregard any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Weigh the contents of 20 capsules. Mix, and powder if necessary. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the capsule contents containing 0.1 g of Ibuprofen in 50 mL of the mobile phase, add sufficient mobile phase to produce 100 mL and mix. Centrifuge and dilute 1 volume of the supernatant liquid to 10 volumes with the mobile phase.
(2) 0.01% w/v of *ibuprofen BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 264 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

3 volumes of *orthophosphoric acid*, 247 volumes of *water* and 750 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions the retention time of ibuprofen is about 7 minutes.

DETERMINATION OF CONTENT

Calculate the content of ibuprofen, $C_{13}H_{18}O_2$, in the capsules using the declared content of $C_{13}H_{18}O_2$ in *ibuprofen BPCRS* .

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Ibuprofen.

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Ibuprofen Prolonged-release Tablets

General Notices

Prolonged-release Ibuprofen Tablets

Ibuprofen Prolonged-release Tablets from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised..

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

DEFINITION

Ibuprofen Prolonged-release Tablets contain Ibuprofen. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Ibuprofen. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of ibuprofen, $C_{13}H_{18}O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Extract a quantity of the powdered tablets containing 0.5 g of Ibuprofen with 20 mL of *acetone*, filter and evaporate the filtrate to dryness in a current of air without heating. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of ibuprofen *(RS 186)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse a quantity of the powdered tablets containing 0.2 g of Ibuprofen with 20 mL of *acetonitrile R1* and add sufficient mobile phase A to produce 100 mL.

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(2) Dilute 1 volume of solution (1) to 100 volumes with mobile phase A. Further dilute 1 volume to 10 volumes with mobile phase A.

(3) Dissolve 20 mg of *ibuprofen BPCRS* in 2 mL of *acetonitrile R1*, add 1 mL of a 0.006% w/v solution of *ibuprofen impurity B BPCRS* in *acetonitrile R1* and dilute to 10 mL with mobile phase A.

(4) 0.0006% w/v of *4'-isobutylacetophenone BPCRS* (impurity E) in mobile phase A.

(5) Dissolve the contents of a vial of *ibuprofen for peak identification EPCRS* in 1 mL of *acetonitrile R1* and dilute to 5 mL with mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl amorphous organosilica polymer for chromatography* (5 µm) (XTerra MS C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 214 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 0.5 volume of *orthophosphoric acid*, 340 volumes of *acetonitrile R1* and sufficient *water* to produce 1000 volumes.

Mobile phase B 0.5 volume of *orthophosphoric acid*, 100 volumes of *water* and sufficient *acetonitrile R1* to produce 1000 volumes.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-25	100	0	isocratic
25-55	100→0	0→100	linear gradient
55-70	0	100	isocratic
70-71	0→100	100→0	linear gradient
71-85	100	0	re-equilibration

When chromatograms are recorded under the prescribed conditions, the relative retentions with reference to ibuprofen (retention time about 26 minutes) are: impurity J, about 0.2; impurity N, about 0.3; impurity A, about 0.9; impurity B, about 1.08 and impurity E, about 1.11.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* is at least 5.0, where *Hp* is the height above the baseline of the peak due to impurity B and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to ibuprofen.

LIMITS

Use the chromatogram supplied with *ibuprofen for peak identification EPCRS* and the chromatogram obtained with solution (5) to identify the peaks due to impurities A, J, and N. Use the chromatogram obtained with solution (4) to identify the peak due to impurity E.

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In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity E is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any peak corresponding to impurity A, J or N is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15% of each);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of any other *secondary peaks* is not greater than 7 times the area of the principal peak in the chromatogram obtained with solution (2) (0.7%).

Disregard any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.1 g of Ibuprofen in 50 mL of mobile phase, add sufficient mobile phase to product 100 mL and mix. Centrifuge and dilute 1 volume of the supernatant liquid to 10 volumes with the mobile phase.
(2) 0.01% w/v of *ibuprofen BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 264 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

3 volumes of *orthophosphoric acid*, 247 volumes of *water* and 750 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions, the retention time of ibuprofen is about 7 minutes.

DETERMINATION OF CONTENT

Calculate the content of $C_{13}H_{18}O_2$ in the tablets using the declared content of $C_{13}H_{18}O_2$ in *ibuprofen BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Ibuprofen.

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Ibuprofen Tablets

General Notices

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

DEFINITION

Ibuprofen Tablets contain Ibuprofen. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of ibuprofen, $C_{13}H_{18}O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Extract a quantity of the powdered tablets containing 0.5 g of Ibuprofen with 20 mL of *acetone*, filter and evaporate the filtrate to dryness in a current of air without heating. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of ibuprofen *(RS 186)*.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of *phosphate buffer pH 7.2*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix II D, using the following solutions.

(1) After 45 minutes, withdraw a sample of the medium, filter and dilute, if necessary, with the dissolution medium to produce a solution expected to contain 0.02% w/v of Ibuprofen.

(2) 0.02% w/v of *ibuprofen BPCRS* in the dissolution medium.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 264 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

3 volumes of *orthophosphoric acid*, 247 volumes of *water* and 750 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions, the retention time of ibuprofen is about 7 minutes.

DETERMINATION OF CONTENT

Calculate the total content of ibuprofen, $C_{13}H_{18}O_2$, in the medium using the declared content of $C_{13}H_{18}O_2$ in *ibuprofen BPCRS*.

LIMITS

The amount of ibuprofen released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing 0.2 g of Ibuprofen with 20 mL of *acetonitrile R1*, add sufficient mobile phase A to produce 100 mL and filter (Whatman GF/C is suitable).

(2) Dilute 1 volume of solution (1) to 100 volumes with mobile phase A. Further dilute 1 volume to 10 volumes with mobile phase A.

(3) Dissolve 20 mg of *ibuprofen BPCRS* in 2 mL of *acetonitrile R1*, add 1 mL of a 0.006% w/v solution of *ibuprofen impurity B BPCRS* in *acetonitrile R1* and dilute to 10 mL with mobile phase A.

(4) 0.0006% w/v of *4'-isobutylacetophenone BPCRS* (impurity E) in mobile phase A.

(5) Dissolve the contents of a vial of *ibuprofen for peak identification EPCRS* in 1 mL of *acetonitrile R1* and dilute to 5 mL with mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl amorphous organosilica polymer for chromatography* (5 µm) (XTerra MS C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 214 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 0.5 volume of *orthophosphoric acid*, 340 volumes of *acetonitrile R1* and sufficient *water* to produce 1000 volumes.

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Mobile phase B 0.5 volume of *orthophosphoric acid*, 100 volumes of *water* and sufficient *acetonitrile R1* to produce 1000 volumes.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-25	100	0	isocratic
25-55	100→0	0→100	linear gradient
55-70	0	100	isocratic
70-71	0→100	100→0	linear gradient
71-85	100	0	re-equilibration

When chromatograms are recorded under the prescribed conditions, the relative retentions with reference to ibuprofen (retention time about 26 minutes) are: impurity J, about 0.2; impurity N, about 0.3; impurity A, about 0.9; impurity B, about 1.08 and impurity E, about 1.11.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* is at least 5.0, where *Hp* is the height above the baseline of the peak due to impurity B and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to ibuprofen.

LIMITS

Use the chromatogram supplied with *ibuprofen for peak identification EPCRS* and the chromatogram obtained with solution (5) to identify the peaks due to impurities A, J, and N. Use the chromatogram obtained with solution (4) to identify the peak due to impurity E.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity E is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any peak corresponding to impurity A, J or N, is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15% of each);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of any *secondary peaks* is not greater than 7 times the area of the principal peak in the chromatogram obtained with solution (2) (0.7%).

Disregard any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.1 g of Ibuprofen with 50 mL of the mobile phase, add sufficient of the mobile phase to produce 100 mL and mix. Centrifuge and dilute 1 volume of the supernatant liquid to 10 volumes with the mobile phase.

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(2) 0.01% w/v of *ibuprofen BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{13}H_{18}O_2$ in the tablets using the declared content of $C_{13}H_{18}O_2$ in *ibuprofen BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Ibuprofen.

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Ichthammol

General Notices

Ammonium Ichthosulphonate

(Ph. Eur. monograph 0917)

Action and use

Chronic lichenified eczema.

Preparation

Zinc and Ichthammol Cream

Ph Eur

DEFINITION

Ichthammol is obtained by distillation from certain bituminous schists, sulfonation of the distillate and neutralisation of the product with ammonia.

Content

— *dry matter*: 50.0 per cent *m/m* to 56.0 per cent *m/m*;

— *total ammonia* (NH_3; M_r 17.03): 4.5 per cent *m/m* to 7.0 per cent *m/m* (dried substance);

— *organically combined sulfur*: minimum 10.5 per cent *m/m* (dried substance);

— *sulfur in the form of sulfate*: maximum 20.0 per cent *m/m* of the total sulfur.

CHARACTERS

Appearance

Dense, blackish-brown liquid.

Solubility

Miscible with water and with glycerol, slightly soluble in ethanol (96 per cent), in fatty oils and in liquid paraffin. It forms homogeneous mixtures with wool fat and soft paraffin.

IDENTIFICATION

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A. Dissolve 1.5 g in 15 mL of *water R* (solution A). To 2 mL of solution A add 2 mL of *hydrochloric acid R*. A resinous precipitate is formed. Decant the supernatant. The precipitate is partly soluble in *ether R*.

B. 2 mL of solution A, obtained in identification test A, gives the reaction of ammonium salts and salts of volatile bases (*2.3.1*).

C. Evaporate and ignite the mixture of solution A and *dilute sodium hydroxide solution R* obtained in identification test B. Take up the residue with 5 mL of *dilute hydrochloric acid R*. Gas is evolved which turns *lead acetate paper R* brown or black. Filter the solution. The filtrate gives reaction (a) of sulfates (*2.3.1*).

TESTS

Acidity or alkalinity

To 10.0 mL of the clear filtrate obtained in the assay of total ammonia add 0.05 mL of *methyl red solution R*. Not more than 0.2 mL of *0.02 M hydrochloric acid* or *0.02 M sodium hydroxide* is required to change the colour of the indicator.

Relative density (*2.2.5*)

1.040 to 1.085, determined on a mixture of equal volumes of the substance to be examined and *water R*.

Sulfated ash (*2.4.14*)

Maximum 0.3 per cent, determined on 1.00 g.

ASSAY

Dry matter

Weigh 1.000 g in a tared flask containing 2 g of *sand R*, previously dried to constant mass, and a small glass rod. Heat on a water-bath for 2 h with frequent stirring and dry in an oven at 100-105 °C until 2 consecutive weighings do not differ by more than 2.0 mg; the 2nd weighing is carried out after drying again for 1 h.

Total ammonia

Dissolve 2.50 g in 25 mL of warm *water R*. Rinse the solution into a 250 mL volumetric flask, add 200 mL of *sodium chloride solution R* and dilute to 250.0 mL with *water R*. Filter the solution, discarding the first 20 mL of filtrate. To 100.0 mL of the clear filtrate add 25 mL of *formaldehyde solution R*, neutralised to *phenolphthalein solution R1*. Titrate with *0.1 M sodium hydroxide* until a faint pink colour is obtained.

1 mL of *0.1 M sodium hydroxide* is equivalent to 1.703 mg of NH_3.

Organically combined sulfur

Mix 0.500 g with 4 g of *anhydrous sodium carbonate R* and 3 mL of *methylene chloride R* in a porcelain crucible of about 50 mL capacity, warm and stir until all the methylene chloride has evaporated. Add 10 g of coarsely powdered copper nitrate R, mix thoroughly and heat the mixture very gently using a small flame. When the initial reaction has subsided, increase the temperature slightly until most of the material has blackened. Cool, place the crucible in a large beaker, add 20 mL of *hydrochloric acid R* and, when the reaction has ceased, add

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100 mL of *water R* and boil until all the copper oxide has dissolved. Filter the solution, add 400 mL of *water R*, heat to boiling and add 20 mL of *barium chloride solution R1*. Allow to stand for 2 h, filter, wash with *water R*, dry and ignite at about 600 ± 50 °C until 2 successive weighings do not differ by more than 0.2 per cent of the mass of the residue.

1 g of residue is equivalent to 0.1374 g of total sulfur.

Calculate the percentage content of total sulfur and subtract the percentage content of sulfur in the form of sulfate.

Sulfur in the form of sulfate

Dissolve 2.000 g in 100 mL of *water R*, add 2 g of *cupric chloride R* dissolved in 80 mL of *water R* and dilute to 200.0 mL with *water R*. Shake and filter. Heat 100.0 mL of the filtrate almost to boiling, add 1 mL of *hydrochloric acid R* and 5 mL of *barium chloride solution R1* dropwise and heat on a water-bath. Filter, wash the precipitate with *water R*, dry and ignite at about 600 ± 50 °C until 2 successive weighings do not differ by more than 0.2 per cent of the mass of the residue.

1 g of residue is equivalent to 0.1374 g of sulfur present in the form of sulfate.

Calculate the percentage content of sulfur in the form of sulfate.

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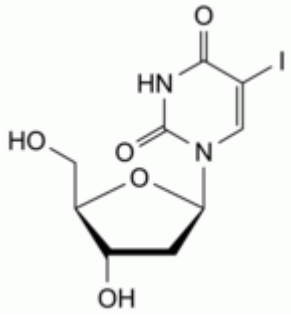
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Idoxuridine

General Notices

(Ph. Eur. monograph 0669)



$C_9H_{11}IN_2O_5$ 354.1 *54-42-2*

Action and use

Pyrimidine nucleoside analogue; antiviral (herpes viruses).

Ph Eur

DEFINITION

Idoxuridine contains not less than 98.0 per cent and not more than the equivalent of 101.0 per cent of 5-iodo-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyrimidine-2,4(1*H*,3*H*)-dione, calculated with reference to the dried substance.

CHARACTERS

A white or almost white, crystalline powder, slightly soluble in water and in ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides.

It melts at about 180 °C, with decomposition.

IDENTIFICATION

First identification: A.

Second identification: B, C, D.

A. Examine by infrared absorption spectrophotometry (2.2.24), comparing with the spectrum obtained with *idoxuridine CRS*. Examine the substances as discs prepared using 1 mg of the substance to be examined and of the reference substance each in 0.3 g of *potassium*

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bromide R.

B. Examine the chromatograms obtained in the test for related substances. The principal spot in the chromatogram obtained with test solution (b) is similar in position and size to the principal spot in the chromatogram obtained with reference solution (c).

C. Heat about 5 mg in a test-tube over a naked flame. Violet vapour is evolved.

D. Disperse about 2 mg in 1 mL of *water R* and add 2 mL of *diphenylamine solution R2*. Heat in a water-bath for 10 min. A persistent light-blue colour develops.

TESTS

Solution S

Dissolve 0.500 g in *1 M sodium hydroxide* and dilute to 50.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

Dissolve 0.10 g in *carbon dioxide-free water R* and dilute to 100 mL with the same solvent. The pH of the solution is 5.5 to 6.5.

Specific optical rotation (*2.2.7*)

+ 28 to + 32, determined on solution S and calculated with reference to the dried substance.

Related substances

Examine by thin-layer chromatography (*2.2.27*), using as coating substance a suitable silica gel with a fluorescent indicator having an optimal intensity at 254 nm.

Test solution (a) Dissolve 0.20 g of the substance to be examined in a mixture of 1 volume of *concentrated ammonia R* and 5 volumes of *methanol R* and dilute to 5 mL with the same mixture of solvents.

Test solution (b) Dilute 1 mL of test solution (a) to 10 mL with a mixture of 1 volume of *concentrated ammonia R* and 5 volumes of *methanol R*.

Reference solution (a) Dissolve 20 mg of *5-iodouracil R*, 20 mg of *2'-deoxyuridine R* and 20 mg of *5-bromo-2'-deoxyuridine R* in a mixture of 1 volume of *concentrated ammonia R* and 5 volumes of *methanol R* and dilute to 100 mL with the same mixture of solvents.

Reference solution (b) Dissolve 0.20 g of the substance to be examined in 5 mL of reference solution (a).

Reference solution (c) Dissolve 20 mg of *idoxuridine CRS* in a mixture of 1 volume of *concentrated ammonia R* and 5 volumes of *methanol R* and dilute to 5 mL with the same mixture of solvents.

Reference solution (d) Dilute 1 mL of test solution (b) to 20 mL with a mixture of 1 volume of *concentrated ammonia R* and 5 volumes of *methanol R*.

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Apply separately to the plate 5 µL of each solution. Develop twice over a path of 15 cm using a mixture of 10 volumes of *concentrated ammonia R*, 40 volumes of *chloroform R* and 50 volumes of *2-propanol R*, drying the plate in a current of cold air after each development. Examine in ultraviolet light at 254 nm. In the chromatogram obtained with test solution (a): any spots corresponding to 5-iodouracil, 2′-deoxyuridine and 5-bromo-2′-deoxyuridine are not more intense than the corresponding spots in the chromatogram obtained with reference solution (a) (0.5 per cent); any spot, apart from the principal spot and the spots corresponding to 5-iodouracil, 2′-deoxyuridine and 5-bromo-2′-deoxyuridine, is not more intense than the spot in the chromatogram obtained with reference solution (d) (0.5 per cent). The test is not valid unless the chromatogram obtained with reference solution (b) shows four clearly separated spots.

Iodide

Dissolve 0.25 g in 25 mL of *0.1 M sodium hydroxide*, add 5 mL of *dilute hydrochloric acid R* and dilute to 50 mL with *water R*. Allow to stand for 10 min and filter. To 25 mL of the filtrate add 5 mL of *dilute hydrogen peroxide solution R* and 10 mL of *chloroform R* and shake. Any pink colour in the organic layer is not more intense than that in a standard prepared at the same time in the same manner using 1 mL of a 0.33 g/L solution of *potassium iodide R* instead of the substance to be examined (0.1 per cent).

Loss on drying (*2.2.32*)

Not more than 1.0 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C.

Sulfated ash (*2.4.14*)

Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.3000 g in 20 mL of *dimethylformamide R*. Titrate with 0.1 M tetrabutylammonium hydroxide, determining the end-point potentiometrically (*2.2.20*).

1 mL of 0.1 M tetrabutylammonium hydroxide is equivalent to 35.41 mg of $C_9H_{11}IN_2O_5$.

STORAGE

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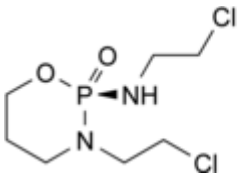
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Ifosfamide

General Notices

(Ph. Eur. monograph 1529)



and enantiomer

$C_7H_{15}Cl_2N_2O_2P$ 261.1 *3778-73-2*

Action and use

Cytotoxic alkylating agent.

Preparation

Ifosfamide Injection

Ph Eur

DEFINITION

Ifosfamide contains not less than 98.0 per cent and not more than the equivalent of 102.0 per cent of (*RS*)-*N*,3-bis(2-chloroethyl)-1,3,2-oxazaphosphinan-2-amine 2-oxide, calculated with reference to the anhydrous substance.

CHARACTERS

A white or almost white, fine, crystalline powder, hygroscopic, soluble in water, freely soluble in methylene chloride.

IDENTIFICATION

Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the *Ph. Eur. reference spectrum of ifosfamide*. Examine the substance prepared as a disc.

TESTS

Solution S

Dissolve 5.0 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

Appearance of solution

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Solution S is clear (2.2.1) and not more intensely coloured than reference solution Y_7 (2.2.2, Method II).

Acidity or alkalinity

Dilute 5 mL of solution S to 50 mL with *carbon dioxide-free water R*. To 10 mL of this solution add 0.1 mL of *methyl red solution R*. Not more than 0.1 mL of *0.01 M hydrochloric acid* is required to change the colour of the indicator to red. To another 10 mL of the solution add 0.1 mL of *phenolphthalein solution R*. Not more than 0.3 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to pink.

Optical rotation (2.2.7)

The angle of optical rotation, determined on solution S, is -0.10° to + 0.10°.

Related substances

A. Examine by thin-layer chromatography (2.2.27), using a *TLC silica gel plate R*.

Test solution Dissolve 1.00 g of the substance to be examined in a mixture of equal volumes of *methanol R* and *water R* and dilute to 10 mL with the same mixture of solvents.

Reference solution (a) Dissolve 25 mg of *ifosfamide impurity A CRS* and 25 mg of *chloroethylamine hydrochloride R* (impurity C) ina mixture of equal volumes of *methanol R* and *water R* and dilute to 100 mL with the same mixture of solvents.

Reference solution (b) Dissolve 15 mg of *ifosfamide impurity B CRS* ina mixture of equal volumes of *methanol R* and *water R* and dilute to 100 mL with the same mixture of solvents.

Reference solution (c) Dissolve 5 mg of *ethanolamine R* (impurity D), 20 mg of *ifosfamide impurity A CRS* and 80 mg of *chloroethylamine hydrochloride R* (impurity C) in a mixture of equal volumes of *methanol R* and *water R* and dilute to 100 mL with the same mixture of solvents.

Apply to the plate 10 µL of each solution. Develop over a path of 15 cm using a mixture of 10 volumes of *water R*, 15 volumes of *methanol R*, 25 volumes of *anhydrous acetic acid R* and 50 volumes of *methylene chloride R*. Dry the plate at 115 °C for 45 min. At the bottom of a chromatographic tank, place an evaporating dish containing a 3.2 g/L solution of *potassium permanganate R* and add an equal volume of *dilute hydrochloric acid R*, close the tank and allow to stand for 10 min. Place the plate whilst still hot in the tank, avoiding contact of the stationary phase with the solution, and close the tank. Leave the plate in contact with the chlorine vapour for 20 min. Withdraw the plate and place it in a current of cold air until the excess of chlorine is removed (about 20 min) and an area of coating below the points of application does not give a blue colour with a drop of *potassium iodide and starch solution R*. Avoid prolonged exposure to cold air. Immerse the plate in a 1 g/L solution of *tetramethylbenzidine R* in *alcohol R* for 5 s. Allow the plate to dry and examine. In the chromatogram obtained with the test solution: any spot corresponding to impurity A or impurity C is not more intense than the corresponding spot in the chromatogram obtained with reference solution (a) (0.25 per cent); any spot corresponding to impurity B is not more intense than the corresponding spot in the chromatogram obtained with reference solution (b) (0.15 per cent); any other spot is not more intense than the principal spot in the chromatogram obtained with reference solution (b) (0.15 per cent). The test is not valid unless the chromatogram obtained with reference solution (c) shows 3 clearly separated spots.

B. Examine by thin-layer chromatography (2.2.27), using a *TLC silica gel plate R*.

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Test solution Dissolve 0.200 g of the substance to be examined in a mixture of equal volumes of *methanol R* and *methylene chloride R* and dilute to 10 mL with the same mixture of solvents.

Reference solution (a) Dissolve 5 mg of *ifosfamide impurity E CRS* and 5 mg of *ifosfamide impurity F CRS* in a mixture of equal volumes of *methanol R* and *methylene chloride R* and dilute to 100 mL with the same mixture of solvents.

Reference solution (b) Dissolve 10 mg of *ifosfamide impurity E CRS* and 10 mg of *ifosfamide CRS* in a mixture of equal volumes of *methanol R* and *methylene chloride R* and dilute to 100 mL with the same mixture of solvents.

Apply to the plate 5 µL of each solution. Develop over a path of 15 cm using a mixture of 1 volume of *methylene chloride R* and 10 volumes of *acetone R*. Dry the plate at 115 °C for 45 min. Proceed as described in test A for related substances. Any spot corresponding to impurity E or impurity F in the chromatogram obtained with the test solution is not more intense than the corresponding spot in the chromatogram obtained with reference solution (a) (0.25 per cent). The test is not valid unless the chromatogram obtained with reference solution (b) shows 2 clearly separated spots.

Chlorides (*2.4.4*)

Dilute 5 mL of solution S to 15 mL with *water R*. The freshly prepared solution complies with the limit test for chlorides (100 ppm).

Water (*2.5.12*)

Not more than 0.5 per cent, determined on 1.00 g by the semi-micro determination of water.

ASSAY

Examine by liquid chromatography (*2.2.29*). *Use the solutions within 24 h.*

Solution A Dissolve 50.0 mg of *ethyl parahydroxybenzoate R* in 25 mL of *alcohol R*, dilute to 100.0 mL with *water R* and mix.

Test solution To 0.150 g of the substance to be examined add 10.0 mL of solution A and dilute to 250.0 mL with *water R*.

Reference solution To 15.0 mg of *ifosfamide CRS* add 1.0 mL of solution A and dilute to 25.0 mL with *water R*.

The chromatography may be carried out using:

— a stainless steel column 0.25 m long and 4.6 mm in internal diameter packed with *octadecylsilyl silica gel for chromatography R* (5 µm),

— as mobile phase at a flow rate of 1.5 mL/min a mixture of 30 volumes of *acetonitrile R* and 70 volumes of *water R*,

— as detector a spectrophotometer set at 195 nm.

Inject 1 µL of the reference solution six times. The assay is not valid unless the resolution between the peaks due to ifosfamide and to ethyl parahydroxybenzoate is not less than 6.0 and the relative standard deviation of the peak area for ifosfamide is at most 2.0 per cent.

Inject 1 µL of the test solution. Calculate the percentage content of $C_7H_{15}Cl_2N_2O_2P$ from the area of the corresponding peak in the chromatogram obtained and the declared content of *ifosfamide CRS*.

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STORAGE

Store in an airtight container.

IMPURITIES

Test A for related substances

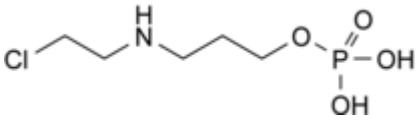
A, B, C, D.

Test B for related substances

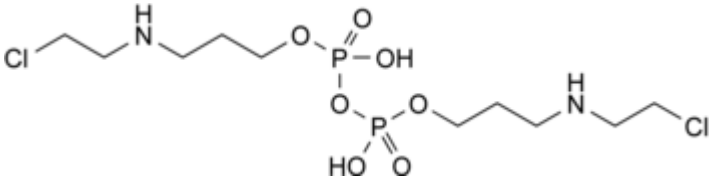
E, F.

Specified impurities *A, B, C, E, F.*

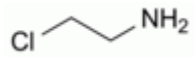
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *D.*



A. 3-[(2-chloroethyl)amino]propyl dihydrogen phosphate,



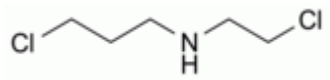
B. bis[3-[(2-chloroethyl)amino]propyl] dihydrogen diphosphate,



C. 2-chloroethanamine,

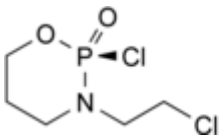


D. 2-aminoethanol.



E. 3-chloro-*N*-(2-chloroethyl)propan-1-amine,

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and enantiomer

F. (*RS*)-2-chloro-3-(2-chloroethyl)-1,3,2-oxazaphosphinane 2-oxide.

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Ifosfamide Injection

General Notices

Action and use

Cytotoxic alkylating agent.

DEFINITION

Ifosfamide Injection is a sterile solution of Ifosfamide in Water for Injections or a suitable liquid. It is prepared by dissolving Ifosfamide for Injection in the requisite amount of a suitable liquid immediately before use.

The injection complies with the requirements stated under Parenteral Preparations.

STORAGE

Ifosfamide Injection should be used immediately after preparation but, in any case, within the period recommended by the manufacturer when prepared and stored strictly in accordance with the manufacturer's instructions.

IFOSFAMIDE FOR INJECTION

Ifosfamide for Injection is a sterile material consisting of Ifosfamide with or without excipients. It is supplied in a sealed container.

CAUTION *Ifosfamide is Cytotoxic. Carry out the procedures described below exercising appropriate precautions.*

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of ifosfamide, $C_7H_{15}Cl_2N_2O_2P$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of ifosfamide (*RS 428*).

TESTS

Solution A

Dissolve 5.0 g in *carbon dioxide-free water* and dilute to 50.0 mL with the same solvent.

Appearance of solution

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Solution A is clear, Appendix IV A, and not more intensely coloured than *reference solution* Y_7, Appendix IV B.

Acidity or alkalinity

pH of an 8% w/v solution, 4.0 to 7.0, Appendix V L.

Related substances

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dissolve a sufficient quantity of the contents of the sealed container in a mixture of equal volumes of *methanol* and *water* to produce a solution containing 10.0% w/v of Ifosfamide.

(2) 0.025% w/v of *ifosfamide impurity A EPCRS* and 0.025% w/v of *chloroethylamine hydrochloride* (impurity C) in a mixture of equal volumes of *methanol* and *water*.

(3) 0.015% w/v of *ifosfamide impurity B EPCRS* in a mixture of equal volumes of *methanol* and *water*.

(4) 0.005% w/v of *ethanolamine*, 0.02% w/v of *ifosfamide impurity A EPCRS* and 0.08% w/v of *chloroethylamine hydrochloride* (impurity C) in a mixture of equal volumes of *methanol* and *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry at 115° for 45 minutes. At the bottom of a chromatography tank, place an evaporating dish containing a 0.32% w/v solution of *potassium permanganate* and add an equal volume of *dilute hydrochloric acid*, close the tank and allow to stand for 10 minutes. Place the plate whilst still hot in the tank, avoiding contact of the stationary phase with the solution, and close the tank. Leave the plate in contact with the chlorine vapour for 20 minutes. Withdraw the plate and place it in a current of cold air until the excess of chlorine is removed (about 20 minutes) and an area of coating below the points of application does not give a blue colour with a drop of *potassium iodide and starch solution*. Avoid prolonged exposure to cold air. Immerse the plate in a 0.1% w/v solution of *tetramethylbenzidine* in *ethanol (96%)* for 5 seconds. Allow the plate to dry and examine.

MOBILE PHASE

10 volumes of *water*, 15 volumes of *methanol*, 25 volumes of *acetic acid* and 50 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (4) shows three clearly separated spots.

LIMITS

In the chromatogram obtained with solution (1) any spot corresponding to impurity A or impurity C is not more intense than the corresponding spot in the chromatogram obtained with solution (2) (0.25%); any spot corresponding to impurity B is not more intense than the corresponding spot in the chromatogram obtained with solution (3) (0.15 %); any other spot is not more intense than the principal spot in the chromatogram obtained with solution (3) (0.15%).

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

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(1) Dissolve a sufficient quantity of the contents of the sealed container in a mixture of equal volumes of *methanol* and *water* to produce a solution containing 2.0% w/v of Ifosfamide.

(2) 0.005% w/v of *ifosfamide impurity E EPCRS* and 0.005% w/v of *ifosfamide impurity F EPCRS* in a mixture of equal volumes of *methanol* and *water*.

(3) 0.01% w/v of *ifosfamide impurity E EPCRS* and 0.01% w/v of *ifosfamide impurity F EPCRS* in a mixture of equal volumes of *methanol* and *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate dry at 115° for 45 minutes. At the bottom of a chromatography tank, place an evaporating dish containing a 0.32% w/v solution of *potassium permanganate* and add an equal volume of *dilute hydrochloric acid*, close the tank and allow to stand for 10 minutes. Place the plate whilst still hot in the tank, avoiding contact of the stationary phase with the solution, and close the tank. Leave the plate in contact with the chlorine vapour for 20 minutes. Withdraw the plate and place it in a current of cold air until the excess of chlorine is removed (about 20 minutes) and an area of coating below the points of application does not give a blue colour with a drop of *potassium iodide and starch solution*. Avoid prolonged exposure to cold air. Immerse the plate in a 0.1% w/v solution of *tetramethylbenzidine* in *ethanol (96%)* for 5 seconds. Allow the plate to dry and examine.

MOBILE PHASE

1 volume of *dichloromethane* and 10 volumes of *acetone*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

LIMITS

In the chromatogram obtained with solution (1) any spot corresponding to impurity E or impurity F is not more intense than the corresponding spot in the chromatogram obtained with solution (2) (0.25%).

Water

Not more than 0.5% w/w, Appendix IX C. Use 1g.

ASSAY

Determine the weight of the contents of 10 containers as described in the test for *uniformity of weight*, Appendix XII C1, Powders for Parenteral Use.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dissolve a sufficient quantity of the contents of the sealed container to produce a solution containing 0.060% w/v of Ifosfamide.

(2) 0.060% w/v of *ifosfamide BPCRS*.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Zorbax SB-C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 195 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

A mixture of 30 volumes of *acetonitrile R1* and 70 volumes of *carbon dioxide-free water*.

DETERMINATION OF CONTENT

Calculate the content of $C_7H_{15}Cl_2N_2O_2P$ in a container of average content weight using the declared content of $C_7H_{15}Cl_2N_2O_2P$ in *ifosfamide BPCRS*.

STORAGE

The sealed container should be kept protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Ifosfamide. Related substances test A is intended to control degradation impurities and Related substances test B is intended to control synthetic impurities.

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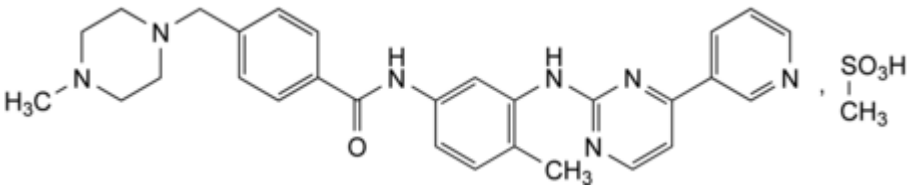
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Imatinib Mesilate

General Notices

(Ph. Eur. monograph 2736)



$C_{30}H_{35}N_7SO_4$ 589.7 *220127-57-1*

Action and use

Cytotoxic.

Ph Eur

DEFINITION

4-[(4-Methylpiperazin-1-yl)methyl]-*N*-[4-methyl-3-[[4-(pyridin-3-yl)pyrimidin-2-yl]amino]phenyl]benzamide methanesulfonate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

PRODUCTION

It is considered that alkyl methanesulfonate esters are genotoxic and are potential impurities in imatinib mesilate. The manufacturing process should be developed taking into consideration the principles of quality risk management, together with considerations of the quality of starting materials, process capability and validation. The general methods 2.5.37. *Methyl, ethyl and isopropyl methanesulfonate in methanesulfonic acid*, 2.5.38. *Methyl, ethyl and isopropyl methanesulfonate in active substances* and 2.5.39. *Methanesulfonyl chloride in methanesulfonic acid* are available to assist manufacturers.

CHARACTERS

Appearance

White or almost white, slightly brownish or yellowish powder; yellow or pale yellow, very hygroscopic, for the amorphous form.

Solubility

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Freely soluble in water, slightly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

It shows polymorphism (5.9).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *imatinib mesilate CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *anhydrous ethanol R*, evaporate to dryness and record new spectra using the residues.

TESTS

Impurity F

Liquid chromatography (2.2.29) coupled with mass spectrometry (2.2.43).

Solvent mixture *acetonitrile R1*, *water for chromatography R* (30:70 *V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution Dissolve 2.0 mg of *imatinib impurity F CRS* in the solvent mixture and dilute to 100.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 200.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 3.0 mm;

— *stationary phase*: *end-capped octadecylsilyl amorphous organosilica polymer for chromatography R* (3.5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: 1.26 g/L solution of *ammonium formate R* in *water for chromatography R* adjusted to pH 3.4-3.5 with *anhydrous formic acid R*;

— *mobile phase B*: 0.05 per cent *V/V* solution of *anhydrous formic acid R* in *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 6	80	20
6 - 10	80 → 20	20 → 80
10 - 15	20	80

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NOTE: MS acquisition can be started at 3.5 min and stopped at 6 min; during non-acquisition the eluent is directed to waste.

Flow rate 0.5 mL/min.

Detection Mass detector: the following settings have been found to be suitable and are given as examples; if the detector has different setting parameters, adjust the detector settings so as to comply with the system suitability criterion:

— *ionisation*: ESI-positive;

— *detection m/z (SIM)*: 278.2;

— *gas temperature*: 350 °C;

— *drying gas flow*: 12 L/min;

— *nebuliser pressure*: 414 kPa;

— *capillary voltage (Vcap)*: 3 kV.

Injection 10 µL.

System suitability Reference solution:

— *signal-to-noise ratio*: minimum 20 for the principal peak;

— *repeatability*: maximum relative standard deviation of 10 per cent determined on 6 injections.

Calculation of percentage content:

— for impurity F, use the concentration of impurity F in the reference solution.

Limit:

— *impurity F*: maximum 20 ppm.

Impurity H

Liquid chromatography (2.2.29).

Solvent mixture acetonitrile R1, water for chromatography R (30:70 *V/V*).

Test solution Dissolve 75.0 mg of the substance to be examined in the solvent mixture and dilute to 5.0 mL with the solvent mixture.

Reference solution (a) Dissolve the contents of a vial of imatinib impurity A CRS in 1.0 mL of the solvent mixture.

Reference solution (b) Dissolve 60.0 mg of imatinib impurity H CRS in the solvent mixture and dilute to 20.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 100.0 mL with the solvent mixture.

Reference solution (c) Dilute 5.0 mL of reference solution (b) to 50.0 mL with the solvent mixture.

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Reference solution (d) Dissolve 0.150 g of the substance to be examined in the solvent mixture, add 1.0 mL each of reference solutions (a) and (b) and dilute to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 35 °C.

Mobile phase:

— *mobile phase A*: dissolve 2.3 g of *sodium octanesulfonate monohydrate R* in 700 mL of *water for chromatography R* and add 300 mL of *acetonitrile R1* and 1.2 mL of *dilute phosphoric acid R*;

— *mobile phase B*: dissolve 2.3 g of *sodium octanesulfonate monohydrate R* in 100 mL of *water for chromatography R* and add 900 mL of *acetonitrile R1* and 1.2 mL of *dilute phosphoric acid R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 6	98	2
6 - 8	98 → 20	2 → 80
8 - 10	20	80

Flow rate 2.3 mL/min.

Detection Spectrophotometer at 227 nm.

Injection 10 µL of the test solution and reference solutions (c) and (d).

Identification of impurities Use the chromatogram obtained with reference solution (d) to identify the peaks due to impurities A and H.

Relative retention With reference to imatinib (retention time = about 8 min): impurity A = about 0.17; impurity H = about 0.2.

System suitability Reference solution (d):

— *resolution*: minimum 1.5 between the peaks due to impurities A and H.

Calculation of percentage content:

— for impurity H, use the concentration of impurity H in reference solution (c).

Limit:

— *impurity H*: maximum 0.02 per cent.

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Related substances

Liquid chromatography (2.2.29).

Solvent mixture acetonitrile R1, water for chromatography R (30:70 *V/V*).

Test solution Dissolve 25.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 1 mg of imatinib for system suitability CRS (containing impurities A, B, C, D and J) in the solvent mixture and dilute to 2 mL with the solvent mixture.

Reference solution (c) Dissolve 25.0 mg of imatinib mesilate CRS in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 35 °C.

Mobile phase:

— *mobile phase A*: dissolve 2.3 g of sodium octanesulfonate monohydrate R in 700 mL of water for chromatography R and add 300 mL of acetonitrile R1 and 1.2 mL of dilute phosphoric acid R;

— *mobile phase B*: dissolve 2.3 g of sodium octanesulfonate monohydrate R in 100 mL of water for chromatography R and add 900 mL of acetonitrile R1 and 1.2 mL of dilute phosphoric acid R;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 16	98	2
16 - 30	98 → 50	2 → 50

Flow rate 2.3 mL/min.

Detection Spectrophotometer at 267 nm.

Injection 10 µL of the test solution and reference solutions (a) and (b).

Identification of impurities Use the chromatogram supplied with imatinib for system suitability CRS and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C, D and J.

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Relative retention With reference to imatinib (retention time = about 11 min): impurity A = about 0.2; impurity B = about 0.6; impurity J = about 0.9; impurity C = about 1.2; impurity D = about 2.3.

System suitability:

— *resolution*: minimum 3.0 between the peaks due to imatinib and impurity C in the chromatogram obtained with reference solution (b);

— *signal-to-noise ratio*: minimum 45 for the principal peak in the chromatogram obtained with reference solution (a);

— *peak-to-valley ratio*: minimum 1.3, where H_p = height above the baseline of the peak due to impurity J and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to imatinib in the chromatogram obtained with reference solution (b).

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 2.2; impurity B = 2.0;

— for each impurity, use the concentration of imatinib mesilate in reference solution (a).

Limits:

— *impurity C*: maximum 0.3 per cent;

— *impurity D*: maximum 0.2 per cent;

— *impurities A, B*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.8 per cent;

— *reporting threshold*: 0.05 per cent.

Water (2.5.12)

Maximum 3.0 per cent, determined on 1.00 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (c).

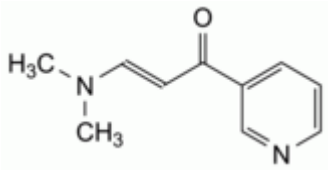
Calculate the percentage content of $C_{30}H_{35}N_7SO_4$ taking into account the assigned content of *imatinib mesilate CRS*.

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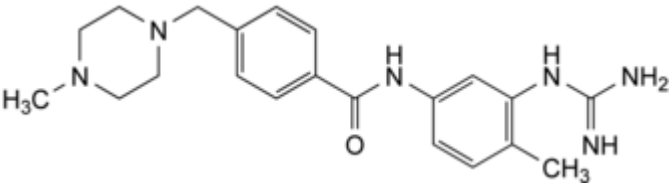
IMPURITIES

Specified impurities A, B, C, D, F, H.

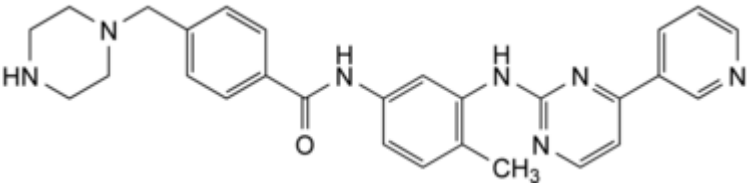
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) J.



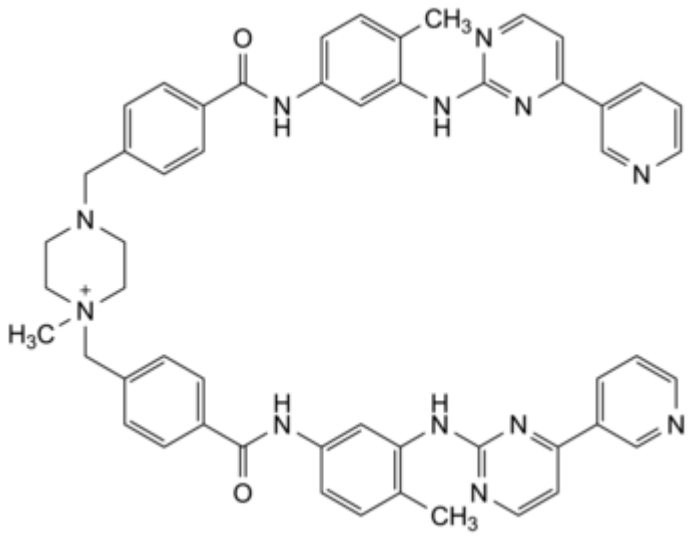
A. (2*E*)-3-(dimethylamino)-1-(pyridin-3-yl)prop-2-en-1-one,



B. *N*-(3-carbamimidamido-4-methylphenyl)-4-[(4-methylpiperazin-1-yl)methyl]benzamide,

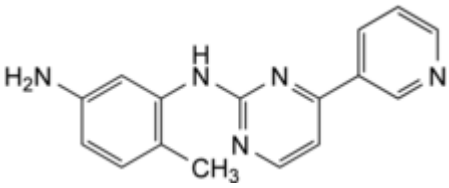


C. *N*-[4-methyl-3-[[4-(pyridin-3-yl)pyrimidin-2-yl]amino]phenyl]-4-(piperazin-1-ylmethyl)benzamide (desmethylimatinib),

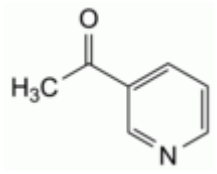


D. 1-methyl-1,4-bis[4-[[4-methyl-3-[[4-(pyridin-3-yl)pyrimidin-2-yl]amino]phenyl]carbamoyl]benzyl]piperazin-1-ium (imatinib dimer),

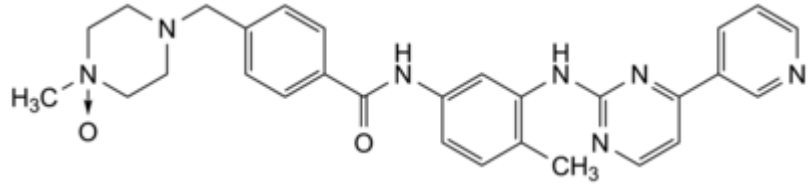
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F. 4-methyl-N^3-[4-(pyridin-3-yl)pyrimidin-2-yl]benzene-1,3-diamine,



H. 1-(pyridin-3-yl)ethan-1-one,



J. 4-[(4-methyl-4-oxidopiperazin-1-yl)methyl]-*N*-[4-methyl-3-[[4-(pyridin-3-yl)pyrimidin-2-yl]amino]phenyl]benzamide.

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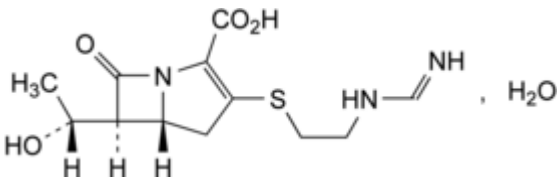
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Imipenem Monohydrate

General Notices

Imipenem

(Ph. Eur. monograph 1226)



$C_{12}H_{17}N_3O_4S,H_2O$ 317.4 *74431-23-5*

Action and use

Carbapenem antibacterial.

Preparation

Cilastatin and Imipenem for Infusion

Ph Eur

DEFINITION

(5*R*,6*S*)-6-[(*R*)-1-Hydroxyethyl]-3-[[2-[(iminomethyl)amino]ethyl]sulfanyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monohydrate.

Semi-synthetic product derived from a fermentation product or obtained by any other means.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white or pale yellow powder, slightly hygroscopic.

Solubility

Slightly soluble in water and in methanol.

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IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *imipenem CRS*.

TESTS

Appearance of solution

The solution is not more opalescent than reference suspension II (2.2.1) and not more intensely coloured than intensity 6 of the range of the reference solutions of the most appropriate colour (2.2.2, *Method II*).

Dissolve 0.500 g in *phosphate buffer solution pH 7.0 R3* and dilute to 50 mL with the same solution.

pH (2.2.3)

4.5 to 7.5.

Dissolve 0.500 g in *carbon dioxide-free water R* and dilute to 100.0 mL with the same solvent.

Specific optical rotation (2.2.7)

+ 90 to + 95 (anhydrous substance), measured at 25 °C. *Prepare the solutions immediately before use.*

Dissolve 0.125 g in *phosphate buffer solution pH 7.0 R3* and dilute to 25.0 mL with the same solution.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Buffer solution A Dissolve 0.32 g of *anhydrous sodium dihydrogen phosphate R* and 1.04 g of *anhydrous disodium hydrogen phosphate R* in 900 mL of *water for chromatography R*. Adjust to pH 7.3 with *dilute phosphoric acid R* and dilute to 1000 mL with *water for chromatography R*.

Buffer solution B Dissolve 0.11 g of *anhydrous disodium hydrogen phosphate R* in 900 mL of *water R*. Adjust to pH 6.8 with *dilute phosphoric acid R* and dilute to 1000 mL with *water R*.

Solvent mixture *acetonitrile R*, buffer solution B (0.7:99.3 *V/V*).

Test solution Dissolve 25.0 mg of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Reference solution (a) Dissolve 25.0 mg of *imipenem CRS* in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture.

Reference solution (c) Dissolve 5 mg of the substance to be examined in 8 mL of a mixture of 1 volume of *dilute sulfuric acid R* and 200 volumes of *water R*. After 5 min, add 10 mg of *sodium carbonate R* and dilute to 10.0 mL with *water R*.

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Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: *acetonitrile R1*, buffer solution A (0.7:99.3 *V/V*);

— *mobile phase B*: *acetonitrile R1*, buffer solution A (25:75 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 9	100	0
9 - 24	100 → 68	0 → 32
24 - 24.5	68 → 50	32 → 50
24.5 - 29	50	50

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Autosampler Set at 5 °C.

Injection 10 µL of the test solution and reference solutions (b) and (c).

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peaks due to the epimers of impurity B.

Relative retention With reference to imipenem (retention time = about 8 min): epimer I of impurity B = about 0.33; epimer II of impurity B = about 0.35; impurity A = about 0.8.

System suitability Reference solution (c):

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to epimer I of impurity B and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to epimer II of impurity B.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity A by 2.4;

— for each impurity, use the concentration of imipenem monohydrate in reference solution (b).

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Limits:

— *impurity A*: maximum 1.0 per cent;

— *impurity B*: for each epimer, maximum 0.3 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.5 per cent;

— *reporting threshold*: 0.05 per cent.

Water (2.5.12)

5.0 per cent to 8.0 per cent, determined on 0.100 g. Use an iodosulfurous reagent containing imidazole instead of pyridine and a clean container for each determination.

Sulfated ash (2.4.14)

Maximum 0.2 per cent, determined on 1.0 g.

Bacterial endotoxins (2.6.14)

Less than 0.17 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for removal of bacterial endotoxins.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

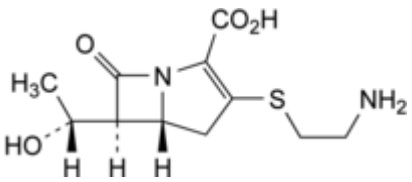
Calculate the percentage content of $C_{12}H_{17}N_3O_4S$ taking into account the assigned content of *imipenem CRS*.

STORAGE

In an airtight container, at a temperature of 2 °C to 8 °C. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

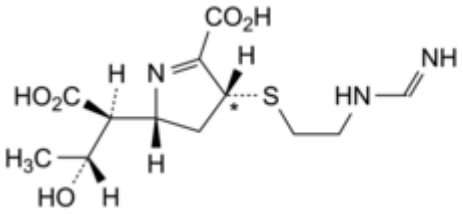
IMPURITIES

Specified impurities *A, B.*



A. (5*R*,6*S*)-3-[(2-aminoethyl)sulfanyl]-6-[(*R*)-1-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene- 2-carboxylic acid (thienamycin),

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and epimer at C*

B. (2*R*,4*RS*)-2-[(1*S*,2*R*)-1-carboxy-2-hydroxypropyl]-4-[[2-[(iminomethyl)amino]ethyl]sulfanyl]-3,4-dihydro-2*H*-pyrrole-5-carboxylic acid (imipenemoic acid).

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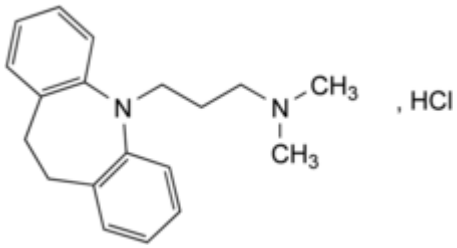
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Imipramine Hydrochloride

General Notices

(Ph. Eur. monograph 0029)



$C_{19}H_{25}ClN_2$ 316.9 *113-52-0*

Action and use

Monoamine reuptake inhibitor; tricyclic antidepressant.

Preparation

Imipramine Tablets

Ph Eur

DEFINITION

3-(10,11-Dihydro-5*H*-dibenzo[*b,f*]azepin-5-yl)-*N*,*N*-dimethylpropan-1-amine hydrochloride.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or slightly yellow, crystalline powder.

Solubility

Freely soluble in water and in ethanol (96 per cent).

IDENTIFICATION

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First identification: B, D.

Second identification: A, C, D.

A. Melting point (2.2.14): 170 °C to 174 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *imipramine hydrochloride CRS*.

C. Dissolve about 5 mg in 2 mL of *nitric acid R*. An intense blue colour develops.

D. About 20 mg gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

To 3.0 g add 20 mL of *carbon dioxide-free water R*, dissolve rapidly by shaking and triturating with a glass rod and dilute to 30 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1). Immediately after preparation, dilute solution S with an equal volume of *water R*. This solution is not more intensely coloured than reference solution BY_6 (2.2.2, Method II).

pH (2.2.3)

3.6 to 5.0 for solution S, measured immediately after preparation.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 5.0 mg of *imipramine for system suitability CRS* (containing impurity B) in the mobile phase and dilute to 5.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer R* (5 µm);

— *temperature*: 40 °C.

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Mobile phase Mix 40 volumes of *acetonitrile R1* with 60 volumes of a 5.2 g/L solution of *dipotassium hydrogen phosphate R* previously adjusted to pH 7.0 with *phosphoric acid R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 10 µL.

Run time 2.5 times the retention time of imipramine.

Relative retention With reference to imipramine (retention time = about 7 min): impurity B = about 0.7.

System suitability Reference solution (a):

— *resolution*: minimum 5.0 between the peaks due to impurity B and imipramine.

Limits:

— *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the peak due to imipramine in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 3 times the area of the peak due to imipramine in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the peak due to imipramine in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 50 mL of *ethanol (96 per cent) R* and add 5.0 mL of *0.01 M hydrochloric acid*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 31.69 mg of $C_{19}H_{25}ClN_2$.

STORAGE

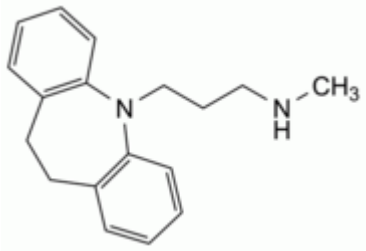
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Protected from light.

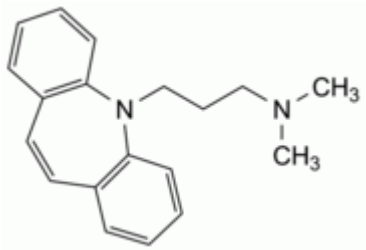
IMPURITIES

Specified impurities B.

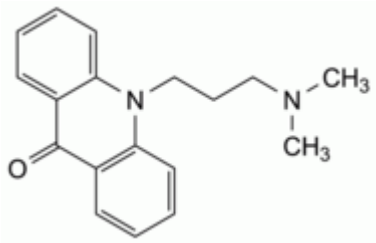
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, C.



A. 3-(10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepin-5-yl)-*N*-methylpropan-1-amine (desipramine),



B. 3-(5*H*-dibenzo[*b*,*f*]azepin-5-yl)-*N*,*N*-dimethylpropan-1-amine (depramine),



C. 10-[3-(dimethylamino)propyl]acridin-9(10*H*)-one.

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Imipramine Tablets

General Notices

Action and use

Monoamine reuptake inhibitor; tricyclic antidepressant.

DEFINITION

Imipramine Tablets contain Imipramine Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of imipramine hydrochloride, $C_{19}H_{24}N_2,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Dissolve a quantity of powdered tablets containing 100 mg of Imipramine Hydrochloride in 10 mL of *acetone* and filter. Evaporate the filtrate to approximately 3 mL under a stream of *nitrogen* and add *diethyl ether* until a precipitate is formed and filter. Wash the precipitate with *diethyl ether* and dry under vacuum at 105 °C for 30 minutes. Dissolve the precipitate in 10 mL of *acetone*, add *diethyl ether* until a precipitate is formed and filter. Dry the precipitate under vacuum at 105 °C for 30 minutes. The *infrared absorption* spectrum of the dried residue, Appendix II A, is concordant with the reference spectrum of imipramine hydrochloride (*RS 509*).

TESTS

Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with 0.1M *hydrochloric acid* if necessary, expected to contain 0.0011% w/v of Imipramine Hydrochloride.

(2) 0.0011% w/v of imipramine hydrochloride BPCRS in 0.1M *hydrochloric acid*.

(3) 0.1% w/v *imipramine for system suitability EPCRS* (containing impurity B) in 0.1M *hydrochloric acid*

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CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm x 4.6 mm) packed with *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer* (5µm) (X-Terra RP18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 220 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

40 volumes of *acetonitrile* and 60 volumes of a 0.52% w/v solution of *dipotassium hydrogen orthophosphate*, previously adjusted to pH 7.0 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to impurity B and imipramine is at least 4.5.

the *symmetry factor* is between 0.8 to 2.0.

DETERMINATION OF CONTENT

Calculate the total content of imipramine hydrochloride, $C_{19}H_{24}N_2$,HCl in the medium from the chromatograms obtained using the declared content of $C_{19}H_{24}N_2$,HCl in *imipramine hydrochloride BPCRS*.

LIMITS

The amount of imipramine hydrochloride released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using following solutions.

(1) To 80 mL of the mobile phase add 10 whole tablets and mix with the aid of ultrasound for 30 minutes. Shake for a further 30 minutes and add sufficient of the mobile phase to produce a solution containing 0.1% w/v of Imipramine Hydrochloride and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase and dilute 1 volume of this solution to 5 volumes with the same solvent.

(3) 0.0003% w/v of *iminodibenzyl* in the mobile phase.

(4) 0.1% w/v *imipramine for system suitability EPCRS* (containing impurity B) in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used allowing the chromatography to proceed for 2.5 times the retention time of imipramine for solution (1).

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When the chromatograms are recorded under the prescribed conditions, the *relative retention* of impurity B with respect to Imipramine (retention time, about 7 minutes) is about 0.7.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity B and imipramine is at least 4.5.

in the chromatogram obtained with solution (2), the *symmetry factor* of the principal peak is between 0.8 to 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to iminodibenzyl is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.3%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of impurities is not greater than 1.0%.

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To 80 mL of the mobile phase add 10 whole tablets and mix with the aid of ultrasound for 30 minutes. Shake for a further 30 minutes and add sufficient of the mobile phase to produce a solution containing 0.1% w/v of Imipramine Hydrochloride and filter. Dilute 1 volume of the filtrate to 10 volumes with the mobile phase.

(2) 0.01% w/v of *imipramine hydrochloride BPCRS* in the mobile phase.

(3) 0.1% w/v *imipramine for system suitability EPCRS* (containing impurity B) in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity B and imipramine is at least 4.5.

in the chromatogram obtained with solution (2), the *symmetry factor* of the principal peak is between 0.8 to 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{19}H_{24}N_2$,HCl in the tablets from the chromatograms obtained and using the declared content of $C_{19}H_{24}N_2$,HCl in *imipramine hydrochloride BPCRS*.

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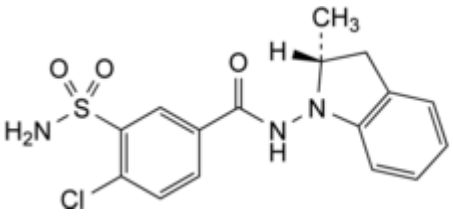
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Indapamide

General Notices

(Ph. Eur. monograph 1108)



and enantiomer

$C_{16}H_{16}ClN_3O_3S$ 365.8 *26807-65-8*

Action and use

Thiazide-like diuretic.

Preparations

Indapamide Tablets

Indapamide Prolonged-release Tablets

Ph Eur

DEFINITION

4-Chloro-*N*-[(2*RS*)-2-methyl-2,3-dihydro-1*H*-indol-1-yl]-3-sulfamoylbenzamide.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, soluble in ethanol (96 per cent).

IDENTIFICATION

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First identification: B.

Second identification: A, C.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 50.0 mg in *ethanol (96 per cent) R* and dilute to 100.0 mL with the same solvent. Dilute 2.0 mL of the solution to 100.0 mL with *ethanol (96 per cent) R*.

Spectral range 220-350 nm.

Absorption maximum At 242 nm.

Shoulders At 279 nm and 287 nm.

Specific absorbance at the absorption maximum 590 to 630.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *indapamide CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 20 mg of the substance to be examined in *ethanol (96 per cent) R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 20 mg of *indapamide CRS* in *ethanol (96 per cent) R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of *indometacin R* in 5 mL of reference solution (a) and dilute to 10 mL with *ethanol (96 per cent) R*.

Plate *TLC silica gel GF_{254} plate R*.

Mobile phase *glacial acetic acid R*, *acetone R*, *toluene R* (1:20:79 *V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

TESTS

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Optical rotation (2.2.7)

-0.02° to + 0.02°.

Dissolve 0.250 g in *anhydrous ethanol R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light and prepare the solutions immediately before use or maintain them at 4 °C.*

Solvent mixture *acetonitrile R*, *methanol R* (50:50 *V/V*).

Test solution Dissolve 20.0 mg of the substance to be examined in 7 mL of the solvent mixture and dilute to 20.0 mL with a 0.2 g/L solution of *sodium edetate R*.

Reference solution (a) Dissolve 3.0 mg of *indapamide impurity B CRS* in 3.5 mL of the solvent mixture and dilute to 10.0 mL with a 0.2 g/L solution of *sodium edetate R*. To 1.0 mL of the solution add 35 mL of the solvent mixture and dilute to 100.0 mL with a 0.2 g/L solution of *sodium edetate R*.

Reference solution (b) To 1.0 mL of the test solution add 17.5 mL of the solvent mixture and dilute to 50.0 mL with a 0.2 g/L solution of *sodium edetate R*. To 1.0 mL of this solution add 7 mL of the solvent mixture and dilute to 20.0 mL with a 0.2 g/L solution of *sodium edetate R*.

Reference solution (c) Dissolve 20.0 mg of *indapamide CRS* in 7 mL of the solvent mixture and dilute to 20.0 mL with a 0.2 g/L solution of *sodium edetate R*.

Reference solution (d) Dissolve 25 mg of *indapamide CRS* and 45 mg of *methylnitrosoindoline CRS* (impurity A) in 17.5 mL of the solvent mixture and dilute to 50 mL with a 0.2 g/L solution of *sodium edetate R*.

Column:

— *size*: *l* = 0.20 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase *glacial acetic acid R*, *acetonitrile R*, *methanol R*, 0.2 g/L solution of *sodium edetate R* (0.1:17.5:17.5:65 *V/V/V/V*).

Flow rate 2 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL of the test solution and reference solutions (a), (b) and (d).

Run time 2.5 times the retention time of indapamide.

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Identification of impurities Use the chromatogram obtained with reference solution (d) to identify the peak due to impurity A, use the chromatogram obtained with reference solution (a) to identify the peak due to impurity B.

Relative retention With reference to indapamide (retention time = about 11 min): impurity A = about 1.4; impurity B = about 1.7.

System suitability:

— *resolution*: minimum 4.0 between the peaks due to indapamide and impurity A in the chromatogram obtained with reference solution (d).

Limits:

— *impurity B*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Impurity A

Liquid chromatography (2.2.29). *Carry out the test protected from light*.

Test solution Dissolve 25.0 mg of the substance to be examined in 1 mL of *acetonitrile R* and dilute to 10.0 mL with *water R*. Shake for 15 min. Allow to stand at 4 °C for 1 h and filter.

Reference solution Dissolve 25.0 mg of the substance to be examined in 1.0 mL of a 0.125 mg/L solution of *methylnitrosoindoline CRS* (impurity A) in *acetonitrile R* and dilute to 10.0 mL with *water R*. Shake for 15 min. Allow to stand at 4 °C for 1 h and filter.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase Mix 7 volumes of *acetonitrile R*, 20 volumes of *tetrahydrofuran R* and 73 volumes of a 1.5 g/L solution of *triethylamine R* adjusted to pH 2.8 with *phosphoric acid R*.

Flow rate 1.4 mL/min.

Detection Spectrophotometer at 305 nm.

Injection 0.1 mL.

System suitability Reference solution:

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— *signal-to-noise ratio*: minimum 3 for the peak due to impurity A appearing just before the peak due to indapamide;

— *peak-to-valley-ratio*: minimum 6.7, where H_p = height above the baseline of the peak due to impurity A and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to indapamide.

Limit:

— *impurity A*: the area of the peak due to impurity A in the chromatogram obtained with the test solution is not more than the difference between the area of the peak due to impurity A in the chromatogram obtained with the reference solution and the area of the peak due to impurity A in the chromatogram obtained with the test solution (5 ppm).

Impurity C

Liquid chromatography (2.2.29). *Maintain the solutions at 10 °C after preparation.*

Solution A Dissolve 0.20 g of *sodium edetate R* in *water for chromatography R*, add 1.5 mL of *anhydrous acetic acid R* and dilute to 1000 mL with *water for chromatography R*.

Test solution Dissolve 75.0 mg of the substance to be examined in 7.5 mL of *acetonitrile R* and dilute to 25.0 mL with *water R*.

Reference solution (a) Dissolve 9.0 mg of *indapamide impurity C CRS* in 1.0 mL of *water R*, add 6.0 mL of *acetonitrile R* and dilute to 20.0 mL with *water R*. To 1.0 mL of the solution add 7.5 mL of *acetonitrile R* and dilute to 25.0 mL with *water R*.

Reference solution (b) To 1.0 mL of reference solution (a) add 3.0 mL of *acetonitrile R* and dilute to 10.0 mL with *water R*.

Reference solution (c) To 1 mL of reference solution (a) add 3 mL of *acetonitrile R* and dilute to 10 mL with the test solution.

Column:

— *size*: *l* = 0.05 m, Ø = 2.1 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography compatible with 100 per cent aqueous mobile phases R* (1.8 µm);

— *temperature*: 50 °C.

Mobile phase *acetonitrile for chromatography R*, solution A (30:70 *V/V*).

Flow rate 0.7 mL/min.

Detection Spectrophotometer at 235 nm.

Injection 2 µL of the test solution and reference solutions (b) and (c).

Run time 3 times the retention time of indapamide.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity C.

Relative retention With reference to indapamide (retention time = about 1.3 min): impurity C = about 0.5.

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System suitability Reference solution (c):

— *resolution*: minimum 4.0 between the peaks due to impurity C and indapamide;

— *signal-to-noise ratio*: minimum 20 for the peak due to impurity C.

Calculation of content:

— for impurity C, use the concentration of impurity C in reference solution (b).

Limit:

— *impurity C*: maximum 600 ppm.

Water (2.5.12)

Maximum 3.0 per cent, determined on 0.100 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (c).

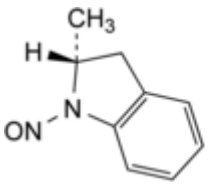
Calculate the percentage content of $C_{16}H_{16}ClN_3O_3S$ taking into account the assigned content of *indapamide CRS*.

STORAGE

Protected from light.

IMPURITIES

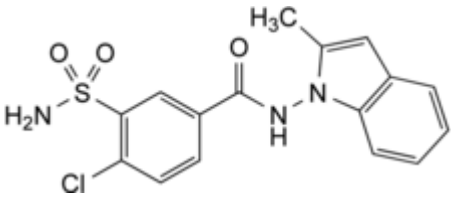
Specified impurities *A, B, C.*



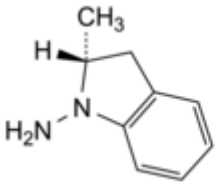
and enantiomer

A. (2*RS*)-2-methyl-1-nitroso-2,3-dihydro-1*H*-indole,

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B. 4-chloro-*N*-(2-methyl-1*H*-indol-1-yl)-3-sulfamoylbenzamide,



and enantiomer

C. (2*RS*)-2-methyl-2,3-dihydro-1*H*-indol-1-amine.

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Indapamide Prolonged-release Tablets

General Notices

Prolonged-release Indapamide Tablets

Indapamide Prolonged-release Tablets from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Thiazide-like diuretic.

DEFINITION

Indapamide Prolonged-release Tablets contain Indapamide. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Indapamide. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

A suitable test is carried out to demonstrate that the content of (2*RS*)-2-methyl-2,3-dihydro-1*H*-indol-1-amine (impurity C) is not more than 600 ppm.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of indapamide, $C_{16}H_{16}ClN_3O_3S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Grind a quantity of the powdered tablets containing 50 mg of Indapamide with 10 mL of *acetone*, mix for 15 minutes, filter (Whatman 42 is suitable) and use the filtrate.

(2) 0.5% w/v of *indapamide BPCRS* in *acetone*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *TLC silica gel* F_{254} (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

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(d) Develop the plate to 12 cm.

(e) After removal of the plate, allow it to dry until the solvent has evaporated and examine under *ultraviolet light (254 nm)*. Spray the plate with a solution prepared by mixing 10 volumes of *potassium iodobismuthate solution* and 20 volumes of *glacial acetic acid* and diluting to 100 volumes with *water* and examine again. Finally, spray the plate with a 5% w/v solution of *sodium nitrite* in a mixture of equal volumes of *water* and *ethanol (96%)* and examine again.

MOBILE PHASE

20 volumes of *acetone* and 80 volumes of *toluene*.

CONFIRMATION

By each method of visualisation, the principal spot in the chromatogram obtained with solution (1) is similar in position, colour and intensity to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, protected from light, using the following solutions prepared immediately before use.

(1) To a quantity of the powdered tablets containing 25 mg of Indapamide add 70 mL of *ethanol (96%)* and mix mechanically for 2 hours. Add sufficient *ethanol (96%)* to produce 100 mL, mix and centrifuge. Dilute the supernatant liquid with the mobile phase to produce a solution containing 0.005% w/v of Indapamide.
(2) Dilute 1 volume of solution (1) to 10 volumes with the mobile phase and further dilute 1 volume of this solution to 100 volumes with the mobile phase.
(3) Dilute 1 volume of a 0.00025% w/v solution of *indapamide impurity B BPCRS* in *ethanol (96%)* to 10 volumes with the mobile phase.
(4) Dilute 1 volume of a 0.00025% w/v solution of *4-chloro-3-sulfamoylbenzoic acid* in *ethanol (96%)* to 10 volumes with the mobile phase.
(5) Mix 1 volume of solution (1), 1 volume of a 0.00025% w/v solution of *indapamide impurity B BPCRS* in *ethanol (96%)* and 1 volume of a 0.00025% w/v solution of *4-chloro-3-sulfamoylbenzoic acid* in *ethanol (96%)* and add 7 volumes of the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.6 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 240 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

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6 volumes of a solution containing 5% w/v of *sodium dodecyl sulfate* and 3% v/v of *glacial acetic acid*, 10 volumes of *triethylamine*, 20 volumes of *butan-2-ol*, 310 volumes of *acetonitrile* and 690 volumes of *water*, the mixture being adjusted to pH 3.0 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5), the retention time of impurity B relative to indapamide is about 1.7 and the retention time of 4-chloro-3-sulfamoylbenzoic acid relative to indapamide is about 0.3.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity B is not greater than twice the area of the peak in the chromatogram obtained with solution (3) (1.0%);

the area of any peak corresponding to 4-chloro-3-sulfamoylbenzoic acid is not greater than the area of the peak in the chromatogram obtained with solution (4) (0.5%);

the area of any other *secondary peak* is not greater than 5 times the area of the peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the impurities is not greater than 1.5%.

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

Uniformity of Content

Tablets containing less than 2 mg of Indapamide comply with the requirement stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, protected from light, using the following solutions.

(1) Add 5 mL of *ethanol (96%)* to one whole tablet and mix mechanically for 2 hours and centrifuge. Dilute 1 volume of the supernatant liquid to 5 volumes with the mobile phase.
(2) Dilute 1 volume of a 0.03% w/v solution of *indapamide BPCRS* in *ethanol (96%)* to 5 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{16}H_{16}ClN_3O_3S$ in each tablet using the declared content of $C_{16}H_{16}ClN_3O_3S$ in *indapamide BPCRS.*

ASSAY

For tablets containing less than 2 mg and/or less than 2% w/w of Indapamide

Use the average of the individual results determined in the test for Uniformity of content.

For tablets containing 2 mg or more and 2% w/w or more of Indapamide

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Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, protected from light, using the following solutions.

(1) To a quantity of the powdered tablets containing 25 mg of Indapamide add 70 mL of *ethanol (96%)* and mix mechanically for 2 hours. Add sufficient *ethanol (96%)* to produce 100 mL, mix and centrifuge. Dilute the supernatant liquid with the mobile phase to produce a solution containing 0.005% w/v of Indapamide.

(2) Dilute 1 volume of a 0.025% w/v solution of *indapamide BPCRS* in *ethanol (96%)* to 5 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

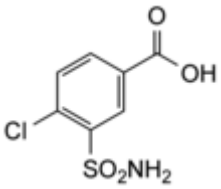
Calculate the content of $C_{16}H_{16}ClN_3O_3S$ in each tablet using the declared content of $C_{16}H_{16}ClN_3O_3S$ in *indapamide BPCRS*.

STORAGE

Indapamide Prolonged-release Tablets should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities B and C listed under Indapamide and the following:



1. 4-chloro-3-sulfamoylbenzoic acid

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Indapamide Tablets

General Notices

Action and use

Thiazide-like diuretic.

DEFINITION

Indapamide Tablets contain Indapamide. They are coated.

PRODUCTION

A suitable test is carried out to demonstrate that the content of (2*RS*)-2-methyl-2,3-dihydro-1*H*-indol-1-amine (impurity C) is not more than 600 ppm.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of indapamide hemihydrate, $C_{16}H_{16}ClN_3O_3S,½H_2O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Grind a quantity of the powdered tablets containing 50 mg of Indapamide with 10 mL of *acetone*, mix for 15 minutes, filter through a fine filter paper (Whatman 42 is suitable) and use the filtrate.
(2) 0.5% w/v of *indapamide BPCRS* in *acetone*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 12 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*. Spray the plate with a solution prepared by mixing 10 volumes of *potassium iodobismuthate solution* and 20 volumes of *glacial acetic acid* and diluting to 100 volumes with *water* and examine again. Finally, spray the plate with a 5% w/v solution of *sodium nitrite* in a mixture of equal volumes of *water* and *ethanol (96%)* and examine again.

MOBILE PHASE

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20 volumes of *acetone* and 80 volumes of *toluene*

CONFIRMATION

By each method of visualisation, the principal spot in the chromatogram obtained with solution (1) is similar in position, colour and intensity to that in the chromatogram obtained with solution (2).

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 100 revolutions per minute.

(b) Use 500 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 60 minutes withdraw a 10-mL sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maxima at 240 nm and at 275 nm, Appendix II B, using 0.1M *hydrochloric acid* in the reference cell.

(2) Measure the *absorbance* of a reference solution prepared by diluting 1 volume of a 0.10% w/v solution of *indapamide BPCRS* in *methanol* to 200 volumes with 0.1M *hydrochloric acid* using 0.1M *hydrochloric acid* in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of indapamide hemihydrate, $C_{16}H_{16}ClN_3O_3S,½H_2O$, in the medium using the differences in absorbance at 240 nm and at 275 nm and using the declared content of $C_{16}H_{16}ClN_3O_3S$ in *indapamide BPCRS*.Each mg of $C_{16}H_{16}ClN_3O_3S$ is equivalent to 1.0246 mg of $C_{16}H_{16}ClN_3O_3S,½H_2O$. The amount of indapamide hemihydrate released is not less than 75% of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, protected from light, using the following solutions.

(1) Mix 10 whole tablets with 70 mL of *ethanol (96%)*, mix mechanically until the tablets have disintegrated and continue mixing for 2 hours. Add sufficient *ethanol (96%)* to produce 100 mL, mix and centrifuge. Dilute the supernatant liquid with the mobile phase to produce a solution containing 0.005% w/v of Indapamide.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase and further dilute 1 volume of this solution to 10 volumes with the mobile phase.

(3) Dilute 1 volume of a 0.00025% w/v solution of *indapamide impurity B BPCRS* in *ethanol (96%)* to 10 volumes with the mobile phase.

(4) Dilute 1 volume of a 0.00025% w/v solution of *4-chloro-3-sulfamoylbenzoic acid* in *ethanol (96%)* to 10 volumes with the mobile phase.

(5) Mix one volume of solution (1), one volume of a 0.00025% w/v solution of *indapamide impurity B BPCRS* in *ethanol (96%)* and 1 volume of a 0.00025% w/v solution of *4-chloro-3-sulfamoylbenzoic acid* in *ethanol (96%)* and add 7 volumes of the mobile phase.

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CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.6 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 240 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

6 volumes of a solution containing 5% w/v of *sodium dodecyl sulfate* and 3% v/v of *glacial acetic acid*, 10 volumes of *triethylamine*, 20 volumes of *butan-2-ol*, 310 volumes of *acetonitrile* and 690 volumes of *water*, the mixture being adjusted to pH 3.0 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5), the retention of impurity B relative to indapamide is about 1.7 and the retention of 4-chloro-3-sulfamoylbenzoic acid relative to indapamide is about 0.3.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity B is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.5%);

the area of any peak corresponding to 4-chloro-3-sulfamoylbenzoic acid is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (4) (0.2%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

The sum of the impurities, excluding impurity B, is not greater than 0.3%.

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, protected from light, using the following solutions.

(1) Mix 10 whole tablets with 70 mL of *ethanol (96%)*, mix mechanically until the tablets have disintegrated and continue mixing for 2 hours. Add sufficient *ethanol (96%)* to produce 100 mL, mix and centrifuge. Dilute the supernatant liquid with the mobile phase to produce a solution containing 0.005% w/v of Indapamide.

(2) Dilute 1 volume of a 0.025% w/v solution of *indapamide BPCRS* in *ethanol (96%)* to 5 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Related substances may be used.

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DETERMINATION OF CONTENT

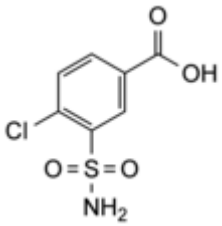
Calculate the content of $C_{16}H_{16}ClN_3O_3S,½H_2O$ in the tablets from the chromatogram obtained using the declared content of $C_{16}H_{16}ClN_3O_3S$ in *indapamide BPCRS*. Each mg of $C_{16}H_{16}ClN_3O_3S$ is equivalent to 1.0246 mg of $C_{16}H_{16}ClN_3O_3S,½H_2O$.

STORAGE

Indapamide Tablets should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities B and C listed under Indapamide and the following:



1. 4-chloro-3-sulfamoylbenzoic acid

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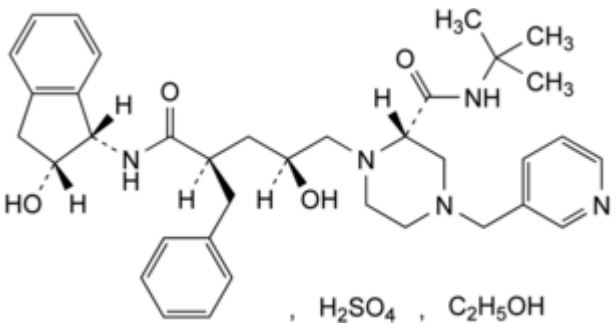
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Indinavir Sulfate

General Notices

Indinavir Sulphate

(Ph. Eur. monograph 2214)



$C_{36}H_{49}N_5O_8S,C_2H_6O$ 758 *157810-81-6*

Action and use

Protease inhibitor; antiviral (HIV).

Ph Eur

DEFINITION

(2*S*)-1-[(2*S*,4*R*)-4-Benzyl-2-hydroxy-5-[[(1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl]amino]-5-oxopentyl]-*N*-(1,1-dimethylethyl)-4-(pyridin-3-ylmethyl)piperazine-2-carboxamide sulfate ethanolate.

Content

98.0 per cent to 102.0 per cent (anhydrous and ethanol-free substance).

PRODUCTION

A test for enantiomeric purity is carried out unless it has been demonstrated that the manufacturing process is enantioselective for the substance.

CHARACTERS

Appearance

White or almost white, hygroscopic powder.

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Solubility

Freely soluble in water, soluble in methanol, practically insoluble in heptane.

IDENTIFICATION

A. Specific optical rotation (2.2.7): + 122 to + 129 (anhydrous and ethanol-free substance), determined at 365 nm and at 25 °C. Dissolve 0.500 g in *water R* and dilute to 50.0 mL with the same solvent.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of indinavir sulfate*.

C. It gives reaction (a) of sulfates (2.3.1).

D. Ethanol (see Tests).

TESTS

Related substances

Liquid chromatography (2.2.29).

Solution A Thoroughly mix equal volumes of mobile phase A and *acetonitrile R1*.

Test solution Dissolve 50.0 mg of the substance to be examined in solution A and dilute to 100.0 mL with the same solution.

Reference solution (a) Dissolve 4 mg of *indinavir for system suitability CRS* (containing impurities B, C and E) in solution A and dilute to 10 mL with the same solution.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with solution A. Dilute 1.0 mL of this solution to 10.0 mL with solution A.

Reference solution (c) Dissolve 5.0 mg of *cis-aminoindanol R* (impurity A) in solution A and dilute to 10.0 mL with the same solution. Dilute 1.0 mL of the solution to 100.0 mL with solution A. Dilute 1.0 mL of this solution to 10.0 mL with solution A.

Reference solution (d) To 30 mg of the substance to be examined add 0.25 mL of *2 M hydrochloric acid R* and allow to stand at room temperature for 1 h. Dilute to 100 mL with a mixture of 2 volumes of *acetonitrile R1* and 3 volumes of mobile phase A and mix (*in situ* degradation to obtain impurity D).

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: solution containing 0.27 g/L of *potassium dihydrogen phosphate R* and 1.40 g/L of *dipotassium hydrogen phosphate R*; filter and degas;

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— *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	80	20
5 - 40	80 → 30	20 → 70
40 - 45	30	70
45 - 47	30 → 80	70 → 20
47 - 52	80	20

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *indinavir for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities B, C and E; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity D.

Relative retention With reference to indinavir (retention time = about 25 min): impurity A = about 0.2; impurity B = about 0.8; impurity C = about 0.98; impurity D = about 1.1; impurity E = about 1.3.

System suitability Reference solution (a):

— *resolution*: minimum 1.8 between the peaks due to impurity C and indinavir.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity D by 1.8;

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent);

— *impurity D*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *impurities B, C, E*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

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— *disregard limit*: 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.03 per cent).

Ethanol

Gas chromatography (2.2.28).

Internal standard solution Dilute 1.0 mL of propanol R to 200.0 mL with water R.

Test solution Dissolve 0.400 g of the substance to be examined in 50.0 mL of water R, add 8.0 mL of the internal standard solution and dilute to 100.0 mL with water R.

Reference solution Dilute 1.0 mL of anhydrous ethanol R to 200.0 mL. Dilute 2.0 mL of this solution and 2.0 mL of the internal standard solution to 25.0 mL with water R.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.53 mm;

— *stationary phase*: macrogol 20 000 R (film thickness 1.0 µm).

Carrier gas helium for chromatography R.

Flow rate 10 mL/min.

Split ratio 1:10.

Temperature:

— *column*: 35 °C;

— *injection port*: 140 °C;

— *detector*: 220 °C.

Detection Flame ionisation.

Injection 1.0 µL.

System suitability Reference solution:

— *retention time*: ethanol = 2 min to 4 min;

— *resolution*: minimum 5.0 between the peaks due to ethanol and propanol.

Calculate the percentage content of ethanol taking the density (2.2.5) to be 0.790 g/mL.

Limit:

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— *ethanol*: 5.0 per cent to 8.0 per cent *m/m*.

Water (2.5.12)

Maximum 1.5 per cent, determined on 0.500 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29).

Solution B Add 20 mL of *dibutylammonium phosphate for ion-pairing R* to 1000 mL of *water R*. Adjust to pH 6.5 with *1 M sodium hydroxide*.

Test solution Dissolve 60.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution Dissolve 50.0 mg of *indinavir CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase *acetonitrile R*, solution B (45:55 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 260 nm.

Injection 10 µL.

Run time Twice the retention time of indinavir.

Retention time Indinavir = about 10 min.

Calculate the percentage content of $C_{36}H_{49}N_5O_8S$ using the declared content of *indinavir CRS* and multiplying by a correction factor of 1.1598.

STORAGE

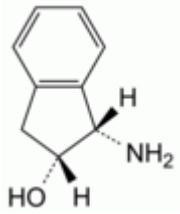
In an airtight container, protected from light.

IMPURITIES

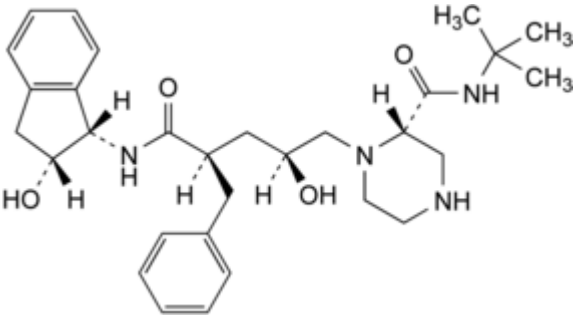
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Specified impurities *A, B, C, D, E.*

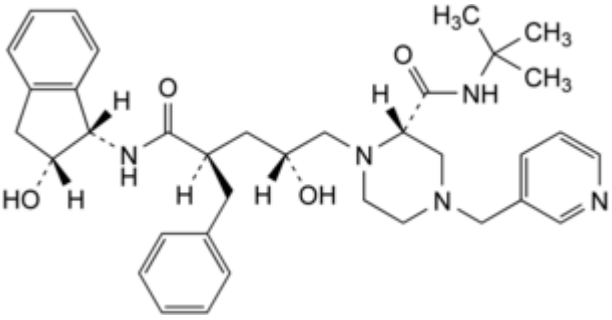
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *F.*



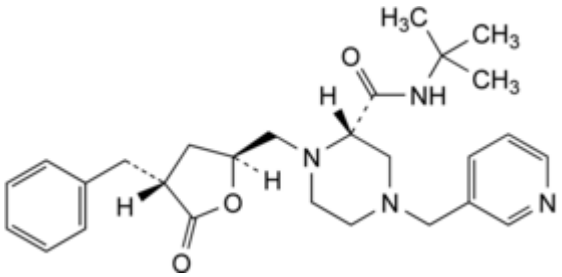
A. (1*S*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-ol (*cis*-aminoindanol),



B. (2*S*)-1-[(2*S*,4*R*)-4-benzyl-2-hydroxy-5-[[(1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl]amino]-5-oxopentyl]-*N*-(1,1-dimethylethyl)piperazine-2-carboxamide,

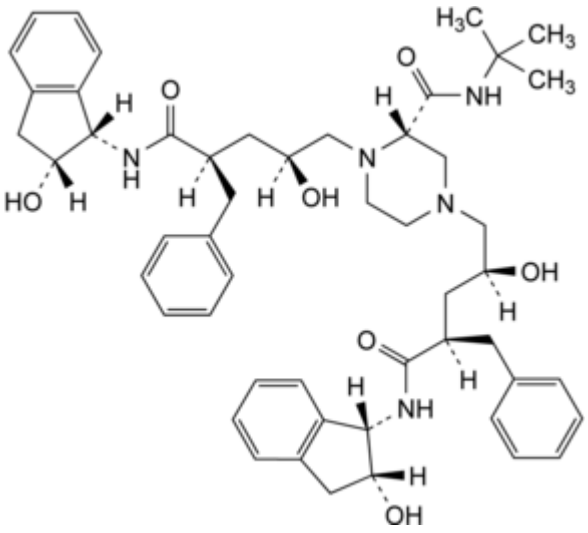


C. (2*S*)-1-[(2*R*,4*R*)-4-benzyl-2-hydroxy-5-[[(1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl]amino]-5-oxopentyl]-*N*-(1,1-dimethylethyl)-4-(pyridin-3-ylmethyl)piperazine-2-carboxamide,

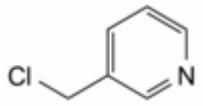


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D. (3*R*,5*S*)-3-benzyl-5-[[(2*S*)-2-[(1,1-dimethylethyl)carbamoyl]-4-(pyridin-3-ylmethyl)piperazin-1-yl]methyl]-4,5-dihydrofuran-2(3*H*)-one,



E. (2*S*)-1,4-bis[(2*S*,4*R*)-4-benzyl-2-hydroxy-5-[[(1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl]amino]-5-oxopentyl]-*N*-(1,1-dimethylethyl)piperazine-2-carboxamide,



F. 3-(chloromethyl)pyridine (nicotinyl chloride).

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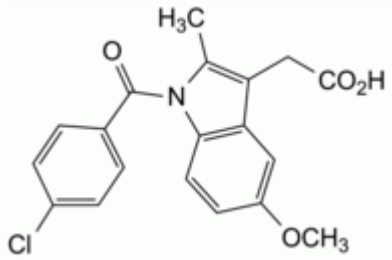
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Indometacin

General Notices

(Ph. Eur. monograph 0092)



$C_{19}H_{16}ClNO_4$ 357.8 *53-86-1*

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

Preparations

Indometacin Capsules

Indometacin Suppositories

Ph Eur

DEFINITION

[1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or yellow, crystalline powder.

Solubility

Practically insoluble in water, sparingly soluble in ethanol (96 per cent).

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It shows polymorphism (5.9). The acceptable crystalline form corresponds to *indometacin CRS*.

IDENTIFICATION

First identification: A, C.

Second identification: A, B, D, E.

A. Melting point (2.2.14): 158 °C to 162 °C.

B. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 25 mg in a mixture of 1 volume of a 103.0 g/L solution of *hydrochloric acid R* and 9 volumes of *methanol R* and dilute to 100.0 mL with the same mixture of solvents. Dilute 10.0 mL of the solution to 100.0 mL with a mixture of 1 volume of a 103.0 g/L solution of *hydrochloric acid R* and 9 volumes of *methanol R*.

Spectral range 300-350 nm.

Absorption maximum At 318 nm.

Specific absorbance at the absorption maximum 170 to 190.

C. Infrared absorption spectrophotometry (2.2.24), without recrystallisation.

Comparison *indometacin CRS*.

D. Dissolve 0.1 g in 10 mL of *ethanol (96 per cent) R*, heating slightly if necessary. To 0.1 mL of the solution add 2 mL of a freshly prepared mixture of 1 volume of a 250 g/L solution of *hydroxylamine hydrochloride R* and 3 volumes of *dilute sodium hydroxide solution R*. Add 2 mL of *dilute hydrochloric acid R* and 1 mL of *ferric chloride solution R2* and mix. A violet-pink colour develops.

E. To 0.5 mL of the solution in ethanol (96 per cent) prepared in identification test D, add 0.5 mL of *dimethylaminobenzaldehyde solution R2*. A precipitate is formed that dissolves on shaking. Heat on a water-bath. A bluish-green colour is produced. Continue to heat for 5 min and cool in iced water for 2 min. A precipitate is formed and the colour changes to light greyish-green. Add 3 mL of *ethanol (96 per cent) R*. The solution is clear and violet-pink in colour.

TESTS

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Solvent mixture *acetonitrile R*, *water R* (50:50 *V/V*).

Test solution Dissolve 25.0 mg of the substance to be examined in the solvent mixture, using sonication if necessary, and dilute to 25.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

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Reference solution (b) Dissolve the contents of a vial of *indometacin impurity mixture CRS* (impurities I and J) in 1 mL of the solvent mixture.

Column:

— *size*: *l* = 0.10 m, Ø = 2.1 mm;

— *stationary phase*: *end-capped ethylene-bridged phenylsilyl silica gel for chromatography (hybrid material) R* (1.7 µm);

— *temperature*: 50 °C.

Mobile phase:

— *mobile phase A*: 5 g/L solution of *anhydrous formic acid R*;

— *mobile phase B*: 5 g/L solution of *anhydrous formic acid R* in *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5.5	60	40
5.5 - 5.6	60 → 30	40 → 70
5.6 - 9	30	70

Flow rate 0.3 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 1.4 µL.

Identification of impurities Use the chromatogram supplied with *indometacin impurity mixture CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities I and J.

Relative retention With reference to indometacin (retention time = about 6 min): impurity I = about 1.3; impurity J = about 1.4.

System suitability Reference solution (b):

— *resolution*: minimum 3.0 between the peaks due to impurities I and J.

Calculation of percentage contents:

— for each impurity, use the concentration of indometacin in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

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— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29).

Solvent mixture acetonitrile R, water R (50:50 *V/V*).

Test solution Dissolve 25.0 mg of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 10.0 mL with the solvent mixture.

Reference solution Dissolve 25.0 mg of indometacin CRS in the solvent mixture and dilute to 25.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: end-capped solid core octadecylsilyl silica gel for chromatography R (2.6 µm);

— *temperature*: 50 °C.

Mobile phase:

— *mobile phase A*: 10 g/L solution of acetic acid R;

— *mobile phase B*: 10 g/L solution of acetic acid R in acetonitrile R;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	50	50
5 - 5.5	50 → 0	50 → 100
5.5 - 8	0	100

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

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Retention time Indometacin = about 4 min.

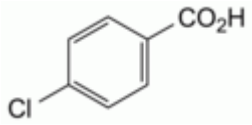
Calculate the percentage content of $C_{19}H_{16}ClNO_4$ taking into account the assigned content of *indometacin CRS*.

STORAGE

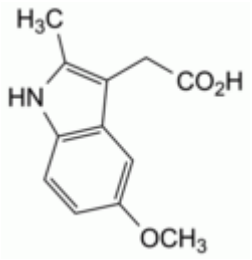
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IMPURITIES

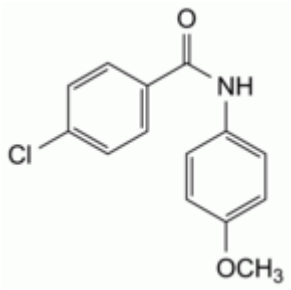
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D, E, F, G, H, I, J.



A. 4-chlorobenzoic acid,

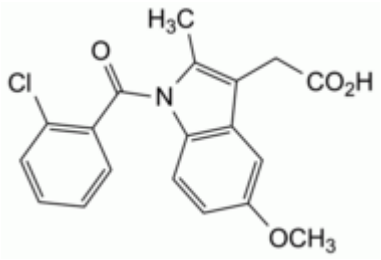


B. (5-methoxy-2-methyl-1*H*-indol-3-yl)acetic acid,

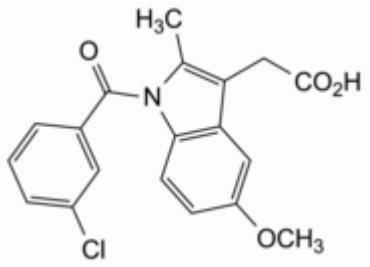


C. 4-chloro-*N*-(4-methoxyphenyl)benzamide,

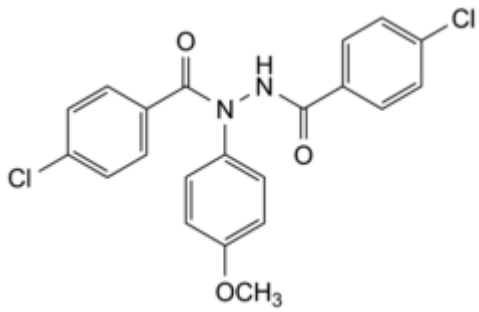
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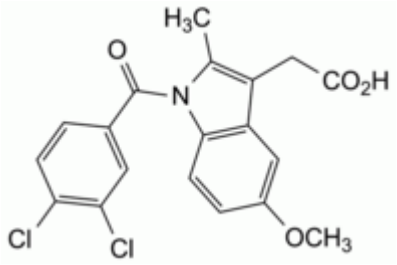
D. [1-(2-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid,



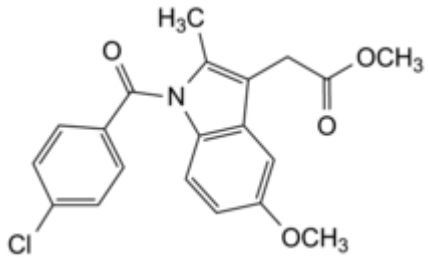
E. [1-(3-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid,



F. 4-chloro-*N*′-(4-chlorobenzoyl)-*N*-(4-methoxyphenyl)benzohydrazide,

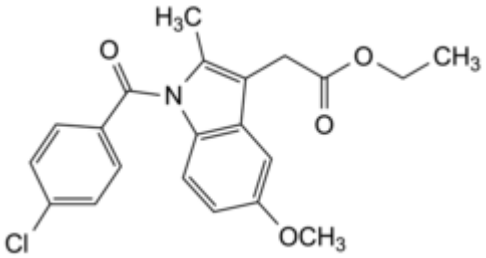


G. [1-(3,4-dichlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid,

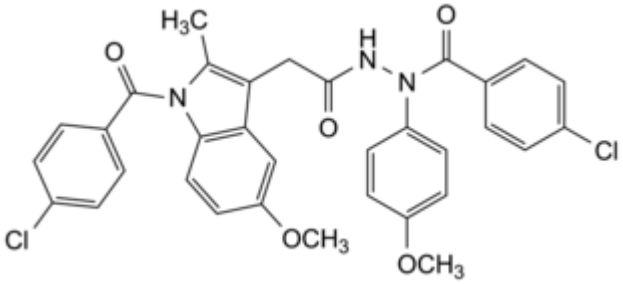


H. methyl [1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetate,

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I. ethyl [1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetate,



J. 4-chloro-*N*′-[[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetyl]-*N*-(4-methoxyphenyl)benzohydrazide.

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Indometacin Capsules

General Notices

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

DEFINITION

Indometacin Capsules contain Indometacin.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of indometacin, $C_{19}H_{16}ClNO_4$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the contents of the capsules containing 0.1 g of Indometacin with 5 mL of *chloroform*, filter and evaporate the filtrate to dryness. Dry the residue at 60° at a pressure not exceeding 0.7 kPa for 1 hour. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of indometacin *(RS 187)*.

B. The *light absorption*, Appendix II B, in the range 300 to 350 nm of the solution obtained in the Assay exhibits a maximum only at 320 nm.

C. Mix a quantity of the contents of the capsules containing 25 mg of Indometacin with 2 mL of *water* and add 2 mL of 2M *sodium hydroxide*. A bright yellow colour is produced which fades rapidly.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of *phosphate buffer pH 7.2*, at a temperature of 37°, as the medium.

PROCEDURE

(1) Withdraw a 10 mL sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 320 nm, Appendix II B using *phosphate buffer pH 7.2* in the reference cell.

DETERMINATION OF CONTENT

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DETERMINATION OF CONTENT

Calculate the total content of indometacin, $C_{19}H_{16}ClNO_4$, in the medium taking 196 as the value of A(1%, 1 cm) at the maximum at 320 nm.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the contents of the capsules containing 0.10 g of Indometacin with 5 mL of *chloroform*, filter and use the filtrate.

(2) Dilute 1 volume of solution (1) to 200 volumes with *chloroform*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a suspension of *silica gel* HF_{254} in a 4.68% w/v solution of *sodium dihydrogen orthophosphate* to coat the plate.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

30 volumes of *petroleum spirit (boiling range, 60° to 80°)* and 70 volumes of *ether*.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2).

ASSAY

To a quantity of the mixed contents of 20 capsules containing 50 mg of Indometacin add 10 mL of *water* and allow to stand for 10 minutes, swirling occasionally. Add 75 mL of *methanol*, shake well, add sufficient *methanol* to produce 100 mL and filter if necessary. To 5 mL of the filtrate add sufficient of a mixture of equal volumes of *methanol* and *phosphate buffer pH 7.2* to produce 100 mL. Measure the *absorbance* of the resulting solution at the maximum at 320 nm, Appendix II B. Calculate the content of $C_{19}H_{16}ClNO_4$ taking 193 as the value of A(1%, 1 cm) at the maximum at 320 nm.

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Indometacin Suppositories

General Notices

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

DEFINITION

Indometacin Suppositories contain Indometacin in a suitable suppository basis.

The suppositories comply with the requirements stated under Rectal Preparations and with the following requirements.

Content of indometacin, $C_{19}H_{16}ClNO_4$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Dissolve a quantity of the suppositories containing 0.1 g of Indometacin as completely as possible in 50 mL of hot *water*, filter, wash the residue with hot *water* and allow to dry in air. Dissolve the residue in 5 mL of *chloroform* and evaporate to dryness. The *infrared absorption spectrum* of the final residue, Appendix II A, is concordant with the *reference spectrum* of indometacin *(RS 187)*.

B. Shake a quantity of the suppositories containing 25 mg of Indometacin with 5 mL of *water* until the basis dissolves; a white suspension is produced. Add 2 mL of 2M *sodium hydroxide*; a bright yellow colour is produced which fades rapidly.

TESTS

Disintegration

Carry out the *disintegration test for suppositories and pessaries*, Appendix XII A2, using a weighed suppository and *phosphate buffer pH 6.8* in place of *water* and operating the apparatus for 90 minutes. At the end of this period remove the suppository, dry with filter paper and weigh. Repeat the operation with two further weighed suppositories. Not less than 75% of each suppository is dissolved.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following freshly prepared solutions. For solution (1) dilute 3 volumes of solution (2) to 100 volumes with the mobile phase. For solution (2) powder or cut into small pieces a suitable number of the suppositories, dissolve a quantity containing 0.1 g of Indometacin in sufficient *methanol* to produce 50 mL.

The chromatographic procedure may be carried out using (a) a stainless steel column (30 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (µBondapak C18 is suitable), (b) a mixture of 40 volumes of 0.2% v/v solution of *orthophosphoric acid* and 60 volumes of *methanol* as the mobile phase with a flow rate of 2 mL per minute and (c) a detection wavelength of 320 nm.

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The *column efficiency*, determined using the principal peak in the chromatogram obtained with solution (1), should be not less than 7500 theoretical plates per metre.

The sum of the areas of any *secondary peaks* that elute before the principal peak in the chromatogram obtained with solution (2) is not greater than the area of the peak in the chromatogram obtained with solution (1).

Repeat the procedure but using the following freshly prepared solutions and a detection wavelength of 240 nm. For solution (3) dilute 10 volumes of solution (2) to 20 volumes with the mobile phase. Solution (4) contains 0.001% w/v of *4-chlorobenzoic acid* in the mobile phase. In the chromatogram obtained with solution (3) the sum of the areas of any *secondary peaks* that elute before the principal peak, other than those determined in solution (2), is not greater than the area of the peak in the chromatogram obtained with solution (4).

ASSAY

Weigh 10 suppositories and powder or cut into small pieces. To a quantity containing 0.1 g of Indometacin add 50 mL of *methanol*, shake until dispersion is complete and, if necessary, filter. To 2 mL add sufficient of a mixture of equal volumes of *methanol* and *phosphate buffer pH 7.2* to produce 100 mL. Measure the *absorbance* of the resulting solution at the maximum at 318 nm, Appendix II B. Calculate the content of $C_{19}H_{16}ClNO_4$ taking 193 as the value of A(1%, 1 cm) at the maximum at 318 nm.

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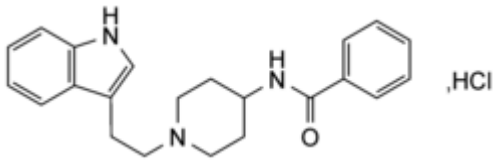
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Indoramin Hydrochloride

General Notices



$C_{22}H_{25}N_3O$,HCl 383.9 *33124-53-7*

Action and use

Alpha$_1$-adrenoceptor antagonist.

Preparation

Indoramin Tablets

DEFINITION

Indoramin Hydrochloride is *N*-1-[2-(indol-3-yl)ethyl]-4-piperidylbenzamide hydrochloride. It contains not less than 98.5% and not more than 100.5% of $C_{22}H_{25}N_3O$,HCl, calculated with reference to the dried substance.

CHARACTERISTICS

A white or almost white powder. It exhibits polymorphism.

Slightly soluble in *water*; sparingly soluble in *ethanol (96%)*; soluble in *methanol*; very slightly soluble in *ether*.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 230 to 350 nm of a 0.0045% w/v solution in *ethanol (96%)* exhibits three maxima, at 273, 280 and 290 nm. The *absorbances* at the maxima are about 0.76, 0.77 and 0.64, respectively.

B. Dissolve 50 mg in 30 mL of *water*, make the solution alkaline by the addition of 5M *ammonia* and shake with 50 mL of *dichloromethane*. Dry the dichloromethane layer with *anhydrous sodium sulfate*, filter and evaporate the filtrate to dryness using a rotary evaporator. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of indoramin *(RS 188)*.

C. Yields reaction A characteristic of *chlorides*, Appendix VI.

TESTS

Acidity

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pH of a 2% w/v suspension in *water*, 4.0 to 5.5, Appendix V L.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using a *silica gel* F_{254} precoated plate (Merck silica gel 60 F_{254} plates are suitable)and a mixture of 1 volume of 18M *ammonia*, 20 volumes of *absolute ethanol* and 79 volumes of *toluene* as the mobile phase. Apply separately to the plate 10 µL of each of three solutions of the substance being examined in *ethanol (96%)* containing (1) 1.0% w/v, (2) 0.0050% w/v and (3) 0.0010% w/v. After removal of the plate, allow it to dry in a current of warm air and examine under *ultraviolet light (254 nm)*. Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%) and not more than one such spot is more intense than the spot in the chromatogram obtained with solution (3) (0.1%).

Loss on drying

When dried at 100° to 105° for 4 hours, loses not more than 0.5% of its weight. Use 1 g.

Sulfated ash

Not more than 0.1%, Appendix IX A.

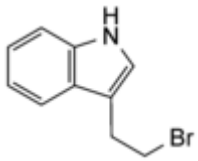
ASSAY

Dissolve 0.2 g in 30 mL of *anhydrous acetic acid*, add 6 mL of *acetic anhydride* and 6 mL of *mercury(II) acetate* solution. Titrate with *0.1M perchloric acid VS* determining the end point potentiometrically. Each mL of *0.1M perchloric acid VS* is equivalent to 38.39 mg of $C_{22}H_{25}N_3O,HCl$.

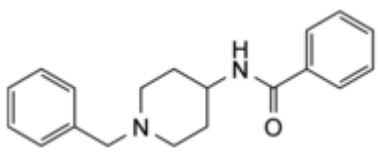
STORAGE

Indoramin Hydrochloride should be protected from light.

IMPURITIES

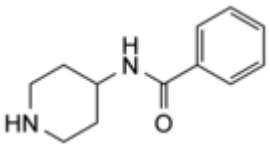


A. 3-(2-bromoethyl)indole



B. *N*-(1-benzyl-4-piperidyl)benzamide

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C. *N*-(4-piperidyl)benzamide

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Indoramin Tablets

General Notices

Action and use

Alpha$_1$-adrenoceptor antagonist.

DEFINITION

Indoramin Tablets contain Indoramin Hydrochloride. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of indoramin, $C_{22}H_{25}N_3O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing the equivalent of 0.1 g of indoramin with 25 mL of *water* for 5 minutes, filter (Whatman GF/C paper is suitable), make the filtrate alkaline with 2M *sodium hydroxide* and extract with 20 mL of *dichloromethane*. Wash the extracts with two 10 mL quantities of *water*, dry by shaking with *anhydrous sodium sulfate* and evaporate to dryness using a rotary evaporator. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of indoramin *(RS 188)*.

TESTS

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using a silica gel F_{254} precoated plate (Merck silica gel 60 F_{254} plates are suitable) and a mixture of 1 volume of 18M *ammonia*, 20 volumes of *absolute ethanol* and 79 volumes of *toluene* as the mobile phase. Apply separately to the plate 10 µL of each of the following solutions. For solution (1) add 10 mL of *ethanol (96%)* to a quantity of the powdered tablets containing the equivalent of 0.1 g of indoramin, shake for 30 minutes and filter. For solution (2) dilute 1 volume of solution (1) to 200 volumes with *ethanol (96%)*. For solution (3) dilute 1 volume of solution (2) to 5 volumes with *ethanol (96%)*. After removal of the plate, allow it to dry in a current of warm air and examine it under *ultraviolet light (254 nm)*. Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%) and not more than one such spot is more intense than the spot in the chromatogram obtained with solution (3) (0.1%). Disregard any spot remaining on the line of application.

Dissolution

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Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1, using Apparatus 2. Use 900 mL of *0.1M hydrochloric acid* as the medium and rotate the paddle at 50 revolutions per minute. Withdraw a sample of 10 mL of the medium. Measure the *absorbance* of a layer of suitable thickness of the filtered sample, suitably diluted if necessary, at the maximum at 280 nm, Appendix II B. Calculate the total content of indoramin, $C_{22}H_{25}N_3O$, in the medium taking 186 as the value of A(1%, 1 cm) at the maximum at 280 nm.

ASSAY

Shake 10 whole tablets with 50 mL of 0.1M *hydrochloric acid* until the tablets have disintegrated, add 300 mL of *ethanol (96%)* and mix with the aid of ultrasound for 10 minutes, shaking occasionally. Add sufficient *ethanol (96%)* to produce 500 mL, filter (Whatman GF/C paper is suitable), dilute the filtrate with *ethanol (96%)* to contain 0.005% w/v of indoramin and measure the *absorbance* of the resulting solution at the maximum at 280 nm, Appendix II B. Calculate the content of $C_{22}H_{25}N_3O$ taking 186 as the value of A(1%, 1 cm) at the maximum at 280 nm.

STORAGE

Indoramin Tablets should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of indoramin.

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Industrial Methylated Spirit

General Notices

Industrial Methylated Spirits; IMS

Industrial Denatured Alcohol

DEFINITION

Industrial Methylated Spirit is a mixture of nineteen volumes of ethanol of an appropriate strength with one volume of approved wood naphtha. Two strengths are available containing 99% by volume and 95% by volume of alcohol (also known as 74 OP and 66 OP respectively).

CHARACTERISTICS

A colourless, clear, mobile, volatile liquid, boiling at about 78°.

IDENTIFICATION

Mix 0.1 mL with 0.05 mL of an 11% w/w solution of *orthophosphoric acid* and 0.25 mL of *dilute potassium permanganate solution*. After 1 minute add a few mg of *sodium metabisulfite* and shake until the mixture is decolorised. Add 1.5 mL of a 50% v/v solution of *sulfuric acid* and a few mg of finely powdered *chromotropic acid sodium salt*, shake well and heat on a water bath for 5 minutes. A deep violet colour is produced.

TESTS

Acidity or alkalinity

25 mL requires not more than 0.2 mL of *0.1M sodium hydroxide VS* to produce a pink colour with *phenolphthalein solution R1* and not more than 1.0 mL of *0.1M hydrochloric acid VS* to produce a red colour with *methyl red solution*.

Clarity of solution

Dilute 5.0 mL to 100 mL with *water*. The solution is *clear*, Appendix IV A.

Apparent density

For '66 OP' grade, not greater than 811.6 kg m^{-3}, and for '74 OP' grade, not greater than 792.8 kg m^{-3}, Appendix V G.

Aldehydes

To 5.0 mL add 5 mL of *water* and 1 mL of *decolorised fuchsin solution* and allow to stand for 30 minutes. Any colour produced is not more intense than that obtained by treating in the same manner 5 mL of a 0.005% w/v solution of redistilled *acetaldehyde* in *aldehyde-free*

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ethanol (96%) (50 ppm).

Non-volatile matter

When evaporated and dried at 105°, leaves not more than 0.01% w/v of residue.

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Industrial Methylated Spirit (Ketone-free)

General Notices

Industrial Denatured Alcohol (Ketone-free)

DEFINITION

Industrial Methylated Spirit (Ketone-free) is a mixture of nineteen volumes of ethanol of an appropriate strength with one volume of approved wood naphtha substantially free from ketones. Two strengths are available containing 99% by volume and 95% by volume of alcohol (also known as 74 OP and 66 OP respectively).

CHARACTERISTICS; IDENTIFICATION; TESTS

Acidity or alkalinity; Clarity of solution; Apparent density; Aldehydes; Non-volatile matter

Complies with the requirements stated under Industrial Methylated Spirit.

Ketones

Dilute 5 mL to 10 mL with *water*, add 1 mL of a 1.0% w/v solution of *2-nitrobenzaldehyde* in *ethanol (50%)* followed by 1 mL of a 15% w/v solution of *sodium hydroxide* in *water* and allow to stand for 15 minutes. Any colour produced is not more intense than that produced by treating in the same manner 10 mL of a 0.025% v/v solution of *acetone* in *ethanol (50%)* (500 ppm).

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This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Infliximab Concentrated Solution

General Notices

(Ph. Eur. monograph 2928)

heavy chain

```
EVKLEESGGG  LVQPGGSMKL  SCVASGFIFS  NHWMNWVRQS   40
PEKGLEWVAE  IRSKSINSAT  HYAESVKGRF  TISRDDSKSA   80
VYLQMTDLRT  EDTGVYYCSR  NYYGSTYDYW  GQGTTLTVSS  120
ASTKGPSVFP  LAPSSKSTSG  GTAALGCLVK  DYFPEPVTVS  160
WNSGALTSGV  HTFPAVLQSS  GLYSLSSVVT  VPSSSLGTQT  200
YICNVNHKPS  NTKVDKKVEP  KSCDKTHTCP  PCPAPELLGG  240
PSVFLFPPKP  KDTLMISRTP  EVTCVVVDVS  HEDPEVKFNW  280
YVDGVEVHNA  KTKPREEQYN  STYRVVSVLT  VLHQDWLNGK  320
EYKCKVSNKA  LPAPIEKTIS  KAKGQPREPQ  VYTLPPSRDE  360
LTKNQVSLTC  LVKGFYPSDI  AVEWESNGQP  ENNYKTTPPV  400
LDSDGSFFLY  SKLTVDKSRW  QQGNVFSCSV  MHEALHNHYT  440
QKSLSLSPGK                                    450
```

light chain

```
DILLTQSPAI  LSVSPGERVS  FSCRASQFVG  SSIHWYQQRT   40
NGSPRLLIKY  ASESMSGIPS  RFSGSGSGTD  FTLSINTVES   80
EDIADYYCQQ  SHSWPFTFGS  GTNLEVKRTV  AAPSVFIFPP  120
SDEQLKSGTA  SVVCLLNNFY  PREAKVQWKV  DNALQSGNSQ  160
ESVTEQDSKD  STYSLSSTLT  LSKADYEKHK  VYACEVTHQG  200
LSSPVTKSFN  RGEC                              214
```

disulfide bridges:

Intra-H	22-98	147-203	264-324	370-428
	22''-98''	147''-203''	264''-324''	370''-428''
Intra-L	23'-88'	134'-194'		
	23'''-88'''	134'''-194'''		
Inter-H-L	223-214'			
	223''-214'''			
Inter-H-H	229-229''	232-232''		

N-glycosylation sites:
300, 300''

M_r approx. 145 kDa (dimer without glycosylation)

$C_{6462}H_{9960}N_{1728}O_{2036}S_{44}$ (dimer without glycosylation)

Action and use

Monoclonal antibody (TNF alfa).

Ph Eur

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DEFINITION

Solution of a monoclonal antibody consisting of a bisdisulfide dimer of 1328 amino acid residues with a molecular weight of approximately 145 kDa, which binds with high affinity to both soluble and transmembrane forms of TNF-α.

Infliximab is a chimeric human-murine IgG1 kappa monoclonal antibody representing a glycosylated immunoglobulin with 1 *N*-linked glycosylation site (Asn 300) in the CH2 domain of each heavy chain. The detected oligosaccharides are mostly G0F (absence of terminal galactose) and G1F (1 terminal galactose) structures. Each heavy chain consists of 450 amino acids with 11 cysteine residues, and each light chain consists of 214 amino acids with 5 cysteine residues. All cysteine residues in heavy and light chains are involved in either intra- or inter-disulfide bonding.

Content (milligrams of protein per millilitre) As approved by the competent authority.

Potency

8×10^3 to 12×10^3 IU per milligram of protein.

PRODUCTION

Infliximab is produced in a suitable mammalian cell expression system by a method based on recombinant DNA (rDNA) technology. In the course of product development, it must be demonstrated that the manufacturing process consistently produces a product with the expected *N*-glycan occupancy and Fc-effector functions (antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC)) using suitably qualified assay(s).

Prior to release, the following tests are carried out on each batch of infliximab concentrated solution, unless an exemption has been granted by the competent authority.

Host-cell-derived proteins (*2.6.34*)

The limit is approved by the competent authority.

Host-cell- and vector-derived DNA

The limit is approved by the competent authority.

Residual Protein A

Use a suitable immunochemical method (*2.7.1*) based on an ELISA. To determine residual Protein A, the preparation to be examined is transferred to an ELISA microplate coated with an anti-protein A capture antibody. Peroxidase-conjugated polyclonal anti-protein A antibody is added followed by a peroxidase substrate. Optical density is measured and the amount of residual Protein A is calculated using a standard curve and the usual statistical methods (for example, *5.3*).

Limit As approved by the competent authority.

Glycan analysis

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Use a suitable procedure developed according to general chapter 2.2.59. *Glycan analysis of glycoproteins*, section 2-3:

— after desalting, release the glycans using one of the agents described in Table 2.2.59.-1, for example peptide *N*-glycosidase F (PNGase F);

— if needed, label the released glycans with one of the fluorescent labelling agents described in Table 2.2.59.-2;

— analyse the labelled or unlabelled glycans using a suitable technique.

The following procedure is given as an example.

Solution A Dissolve 0.17 g of anhydrous sodium dihydrogen phosphate R and 0.53 g of anhydrous disodium hydrogen phosphate R in water R. Adjust to pH 7.6 with sodium hydroxide solution R or hydrochloric acid R and dilute to 1000.0 mL with water R.

Test solution Desalt a volume of the preparation to be examined by a suitable method (for example, using a suitable centrifugal filter with water for chromatography R as elution buffer), and dilute with solution A to obtain a concentration of about 1 mg/mL. To 200 µL of this solution add 0.3 µL of a 500 000 U/mL solution of peptide N-glycosidase F R. Incubate at 37 °C for at least 16 hours.

Reference solution (a) Dissolve the contents of a vial of infliximab CRS in water R. Desalt a volume of this preparation and carry out the glycan release at the same time and in the same manner as for the test solution.

Reference solution (b) Use a suitable infliximab in-house reference preparation shown to be representative of batches tested clinically and batches used to demonstrate consistency of production. Desalt a volume of this preparation and carry out the glycan release at the same time and in the same manner as for the test solution.

Blank solution Use 200 µL of solution A to proceed to glycan release.

Analyse the native glycans by liquid chromatography (2.2.29).

Precolumn:

— *size*: *l* = 0.05 m, Ø = 3.0 mm;

— *stationary phase*: strongly basic anion-exchange resin for chromatography R2 (5.5 µm).

Column:

— *size*: *l* = 0.25 m, Ø = 3.0 mm;

— *stationary phase*: strongly basic anion-exchange resin for chromatography R2 (5.5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: 2 g/L solution of sodium hydroxide R;

— *mobile phase B*: solution containing 2 g/L of sodium hydroxide R and 10.25 g/L of anhydrous sodium acetate R;

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— *mobile phase C*: solution containing 2 g/L of *sodium hydroxide R* and 41 g/L of *anhydrous sodium acetate R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Mobile phase C (per cent *V/V*)	Flow rate (mL/min)
0 - 5	99.2	0.8	0	0.35
5 - 45	99.2 → 95.2	0.8 → 4.8	0	0.35
45 - 50	95.2 → 72	4.8 → 28	0	0.35
50 - 77	72 → 4	28 → 96	0	0.35
77 - 77.1	4 → 0	96 → 0	0 → 100	0.35
77.1 - 87	0	0	100	0.40

Detection Electrochemical detector (pulsed amperometry).

Autosampler Set at 2-8 °C.

Injection 25 µL.

Identification of peaks Use the chromatogram in Figure 2928.-1 to identify the 7 peaks corresponding to fucosylated (peaks 1, 4 and 5), afucosylated (peaks 2 and 3) and sialylated (peaks 6 and 7) glycans; record the retention time of each peak.

System suitability:

— the chromatogram obtained with reference solution (a) is qualitatively similar to the chromatogram supplied with *infliximab CRS* and peaks 1 to 7 are clearly visible;

— no significant peaks are observed in the chromatogram obtained with the blank solution.

Results:

— the profile of the chromatogram obtained with the test solution corresponds to that of the chromatogram obtained with reference solution (b);

— the retention times of the peaks in the chromatogram obtained with the test solution correspond to those in the chromatogram obtained with reference solution (b);

— no additional peaks are observed in the chromatogram obtained with the test solution in comparison with the chromatogram obtained with reference solution (b).

Calculate the relative peak areas of the individual peaks corresponding to fucosylated, afucosylated and sialylated glycans with reference to the sum of the areas of all retained glycan peaks.

Calculate the percentage contents of fucosylated, afucosylated and sialylated glycans, using the following expressions:

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$$\frac{A}{A+B+C} \times 100$$

$$\frac{B}{A+B+C} \times 100$$

$$\frac{C}{A+B+C} \times 100$$

A	=	sum of the areas of the peaks due to fucosylated glycans;
B	=	sum of the areas of the peaks due to afucosylated glycans;
C	=	sum of the areas of the peaks due to sialylated glycans.

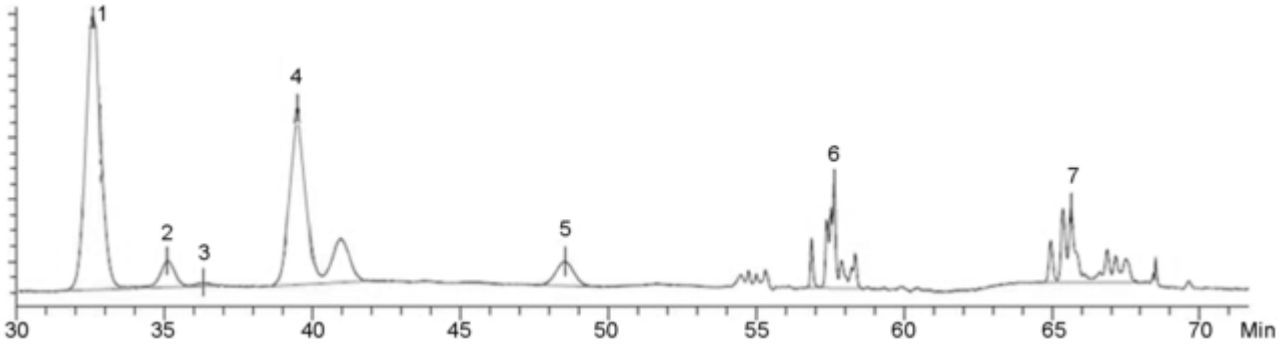
NOTE: sialylated glycans elute as peak clusters and are integrated as such.

Limits:

— *percentage of fucosylated glycans*: as authorised by the competent authority;

— *percentage of afucosylated glycans*: as authorised by the competent authority;

— *percentage of sialylated glycans*: as authorised by the competent authority.



Peak	*Charged*	*Glycoform*	*Peak*	*Charged*	*Glycoform*
1.	No	Fucosylated G0F (absence of terminal galactose)	5.	No	Fucosylated G2F (2 terminal galactoses)
2.	No	Afucosylated Man5 (addition of 2 mannoses instead of terminal *N*-acetylglucosamine)	6.	Yes	Sialylated SA1 (addition of 1 sialic acid)
3.	No	Afucosylated G0 (absence of fucose)	7.	Yes	Sialylated SA2 (addition of 2 sialic acids)
4.	No	Fucosylated G1F (1 terminal galactose)			

Figure 2928.-1. – *Chromatogram for glycan analysis of infliximab*

Charged variants

A. Isoelectric focusing (2.2.54): use suitable agarose gels.

The following procedure is given as an example.

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Test solution Dilute the preparation to be examined with *water R* to obtain a concentration of 0.5 mg/mL.

Reference solution (a) Dissolve the contents of a vial of *infliximab CRS* in *water R* to obtain a concentration of 0.5 mg/mL.

Reference solution (b) Use a suitable infliximab in-house reference preparation shown to be representative of batches tested clinically and batches used to demonstrate consistency of production. Dilute with *water R* to obtain a concentration of 0.5 mg/mL.

Reference solution (c) Use an isoelectric point (pI) calibration solution, in the pI range of 3-10, prepared according to the manufacturer's instructions. Adjust the concentration to allow detection of all marker proteins.

Focusing:

— *pH gradient*: 3-10;

— *catholyte*: 40 g/L solution of *sodium hydroxide R*;

— *anolyte*: 2.87 per cent *V/V* solution of *glacial acetic acid R*;

— *application*: 15 µL.

For each gel, run 2 lanes with reference solution (a), 2 lanes with reference solution (b) and 2 lanes with reference solution (c); use the remaining lanes for the test solution. Proceed with the isoelectric focusing by applying the electrical parameters according to the manufacturer's instructions (the following parameters have been found suitable: 1500 V, 7 mA, 25 W and 80 min).

Detection As described in general chapter *2.2.54*, with the following modifications.

Immerse the gel in a solution containing 36 g/L of *sulfosalicylic acid R*, 60 g/L of *trichloroacetic acid R* and 285 g/L of *methanol R*. Incubate with gentle shaking at room temperature for 30 min. Drain off the solution and transfer the gel to a mixture of 80 volumes of *glacial acetic acid R*, 250 volumes of *anhydrous ethanol R* and 670 volumes of *water R* (mixture A); while shaking, rinse for 10 min at room temperature. Immerse the gel in a staining solution (1 g/L solution of *acid blue 83 R* in mixture A) and incubate for 20 min at room temperature. Destain the gel by passive diffusion (for at least 6 h) with mixture A until the bands are well visualised against a clear background. Soak and wash the gel for 1 h with *water R*.

System suitability:

— in the electropherogram obtained with reference solution (a), 7 bands (4 major and 3 minor) in the pI region 7.35-8.30 are clearly visible;

— in the electropherogram obtained with reference solution (c), the relevant pI markers are distributed along the entire length of the gel.

Results:

— the electropherogram obtained with the test solution is similar to the electropherogram obtained with reference solution (b). Plot the migration distances of the relevant pI markers versus their pI and determine the isoelectric points of the principal components of the test solution and reference solution (b); they do not differ by more than 0.05 pI units;

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— no additional bands are observed in the electropherogram obtained with the test solution in comparison to the electropherogram obtained with reference solution (b).

Alternatively, use a suitable capillary isoelectric focusing procedure developed according to general chapter 2.2.47. *Capillary electrophoresis*.

B. Liquid chromatography (2.2.29): use the normalisation procedure.

Test solution Dilute the preparation to be examined with mobile phase A to obtain a concentration of about 1 mg/mL.

Reference solution (a) Dissolve the contents of a vial of *infliximab CRS* in mobile phase A to obtain a concentration of about 1 mg/mL.

Reference solution (b) Use a suitable infliximab in-house reference preparation shown to be representative of batches tested clinically and batches used to demonstrate consistency of production. Dilute with mobile phase A to obtain a concentration of about 1 mg/mL.

Precolumn:

— *size*: *l* = 0.05 m, Ø = 4 mm;

— *stationary phase*: *weak cation-exchange resin R* (10 µm).

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm;

— *stationary phase*: *weak cation-exchange resin R* (10 µm).

Mobile phase:

— *mobile phase A*: dissolve 0.56 g of *sodium dihydrogen phosphate R* and 1.14 g of *disodium hydrogen phosphate dihydrate R* in 800 mL of *water for chromatography R*, and adjust to pH 7.25, if necessary, with *sodium hydroxide solution R* or *hydrochloric acid R*; dilute to 1000.0 mL with *water for chromatography R* and degas;

— *mobile phase B*: dissolve 0.56 g of *sodium dihydrogen phosphate R*, 1.14 g of *disodium hydrogen phosphate dihydrate R* and 58.44 g of *sodium chloride R* in 800 mL of *water for chromatography R*, and adjust to pH 7.25, if necessary, with *sodium hydroxide solution R* or *hydrochloric acid R*; dilute to 1000.0 mL with *water for chromatography R* and degas;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	100 → 92	0 → 8
15 - 16	92 → 60	8 → 40
16 - 21	60	40

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 214 nm.

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Autosampler Set at 10 °C.

Injection 50 µL.

Relative retention With reference to the peak due to isoform 6 (retention time = about 9.2 min): isoform 1 = 0.68; isoform 2 = 0.74; isoform 3 = 0.80; isoform 4 = 0.87; isoform 5 = 0.95.

System suitability Reference solution (a):

— the chromatogram obtained is similar to the chromatogram supplied with *infliximab CRS*;

— *resolution*: minimum 1.5 between the peaks due to isoforms 3 and 4.

Results:

— the profile of the chromatogram obtained with the test solution corresponds to that of the chromatogram obtained with reference solution (b);

— the relative retentions of the peaks due to isoforms 2, 3 and 4 in the chromatogram obtained with the test solution are within 1 per cent of those of the corresponding peaks in the chromatogram obtained with reference solution (b).

Calculate the relative peak areas of the individual peaks due to isoforms with reference to the total area of all peaks eluting between 3 min and 11 min.

Limits:

— *sum of isoforms 1 and 2*: as authorised by the competent authority;

— *sum of isoforms 3, 4 and 6*: as authorised by the competent authority;

— *isoform 5*: as authorised by the competent authority.

CHARACTERS

Appearance

Opalescent or slightly opalescent, colourless or light yellow liquid.

IDENTIFICATION

A. It complies with the limits of the assay (potency).

B. Peptide mapping (*2.2.55*).

SELECTIVE CLEAVAGE OF THE PEPTIDE BONDS

Dilution buffer Dissolve 50.00 g of *sucrose R*, 0.22 g of *sodium dihydrogen phosphate monohydrate R*, 0.61 g of *disodium hydrogen phosphate dihydrate R* and 0.05 g of *polysorbate 80 R* in *water R*. Adjust to pH 7.2, if necessary, and dilute to 500.0 mL with *water R*.

Test solution Dilute the preparation to be examined with the dilution buffer to obtain a concentration of about 5 mg/mL.

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Reference solution Dissolve the contents of a vial of *infliximab CRS* in the dilution buffer to obtain a concentration of about 5 mg/mL.

Reduction and alkylation Dilute the test solution with *guanidine-tris(hydroxymethyl)aminomethane-EDTA buffer solution pH 8.6 R* to obtain a concentration of 2 mg/mL. To 1 mL of this solution add 10 µL of a 154 g/L solution of *dithiothreitol R* and incubate at 37 °C for 1 h. Add 20 µL of a freshly prepared 185 g/L solution of *iodoacetamide R* and incubate at room temperature for 15 min, protected from light. Add 10 µL of a 154 g/L of solution of *dithiothreitol R* and mix well.

Digestion Desalt a volume of the reduced solution prepared previously by a suitable method (for example, using a suitable centrifugal filter unit with *tris(hydroxymethyl)aminomethane buffer solution pH 7.5 R1* as elution buffer), and adjust the concentration to 1 mg/mL with *tris(hydroxymethyl)aminomethane buffer solution pH 7.5 R1*. Prepare a 0.5 mg/mL solution of *trypsin for peptide mapping R*, and add 10 µL of the solution to 100 µL of the desalted solution. Incubate at 37 °C for 16 h. Add 2 µL of a 150 g/L solution of *trifluoroacetic acid R* and mix gently using a vortex mixer.

NOTE: a protease/protein ratio of 1:20 (m/m) is recommended.

Carry out the reduction/alkylation and digestion steps for the reference solution in the same manner as for the test solution.

CHROMATOGRAPHIC SEPARATION

Liquid chromatography (*2.2.29*).

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm) with a pore size of 30 nm;

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: add 0.6 mL of *trifluoroacetic acid R* to 1000 mL of *water for chromatography R*; degas;

— *mobile phase B*: add 0.6 mL of *trifluoroacetic acid R* to a mixture of 100 mL of *water for chromatography R* and 900 mL of *acetonitrile R1*; degas;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	100	0
3 - 115	100 → 50	0 → 50
115 - 115.5	50 → 10	50 → 90
115.5 - 135	10	90

Flow rate 1 mL/min.

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Detection Spectrophotometer at 214 nm.

Autosampler Set at 2-8 °C.

Injection 80 µL.

Identification of peaks Use the chromatogram supplied with *infliximab CRS* to identify peaks 1 to 20.

System suitability Reference solution:

— the chromatogram obtained is qualitatively similar to the chromatogram supplied with *infliximab CRS* and peaks 1 to 20 are clearly visible;

— peaks 5 and 6 are separated as shown in the chromatogram supplied with *infliximab CRS*.

Results:

— the profile of the chromatogram obtained with the test solution corresponds to that of the chromatogram obtained with the reference solution;

— no additional peak in the chromatogram obtained with the test solution has an area greater than 0.5 per cent of the sum of the areas of peaks 1 to 20.

TESTS

pH (2.2.3)

As approved by the competent authority.

Related proteins

Capillary electrophoresis (2.2.47) under both reducing and non-reducing conditions.

Sample buffer Dissolve 1 g of *sodium dodecyl sulfate R* in *tris(hydroxymethyl)aminomethane buffer solution pH 9.0 R1* and dilute to 100.0 mL with the same solution.

Test solution Dilute the preparation to be examined with *water R* to obtain a concentration of 2 mg/mL. Mix 27 µL of this solution and 30 µL of sample buffer.

— *reducing conditions*: add 3 µL of *2-mercaptoethanol R* and incubate at 80 °C for 10 min; allow to cool for 5 min and transfer 60 µL to the autosampler vial;

— *non-reducing conditions*: add 3 µL of a 46.3 g/L solution of *iodoacetamide R* and incubate at 60-65 °C for 5 min; allow to cool for 5 min and transfer 60 µL to the autosampler vial.

Reference solution Dissolve the contents of a vial of *infliximab CRS* in *water R* to obtain a concentration of 2 mg/mL. Mix 27 µL of the solution and 30 µL of sample buffer. Proceed at the same time and in the same manner as for the test solution.

Capillary:

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— *material*: uncoated fused silica;

— *size*: total length = about 30 cm, effective length = 20 cm, Ø = 50 µm.

Temperature 25 °C.

Gel buffer Use a formulation suitable for a sieving range of approximately 10-225 kDa.

Acidic wash solution *dilute hydrochloric acid R3*.

Basic wash solution 4 g/L solution of *sodium hydroxide R*.

Detection Spectrophotometer at 220 nm.

Autosampler Set at 25 °C.

Preconditioning of the capillary Rinse the capillary with the basic wash solution for 10 min at 138 kPa, with the acidic wash solution for 5 min at 138 kPa, with *water R* for 2 min at 138 kPa and with the gel buffer for 10 min at 483 kPa. Apply voltage for 10 min (15 kV reversed polarity).

Between-run rinsing Rinse the capillary with the basic wash solution for 3 min at 483 kPa, with the acidic wash solution for 1 min at 483 kPa, with *water R* for 1 min at 483 kPa and with the gel buffer for 10 min at 483 kPa.

Injection Electrokinetically at 5 kV reversed polarity for 20 s.

Migration Apply a voltage of 15 kV reversed polarity for 35 min using the gel buffer as the electrolyte in both buffer reservoirs.

Migration time:

— *reducing conditions*: light chain = 14 min to 17 min; non-glycosylated heavy chain = 17 min to 20 min; heavy chain = 18 min to 21 min;

— *non-reducing conditions*: intact IgG = 26 min to 32 min.

Calculate corrected areas of all peaks with a migration time greater than 11 min, using the following expression:

$$\frac{L_d \times A}{t}$$

L_d = capillary length to detector;

A = uncorrected peak area;

t = migration time.

System suitability Reference solution:

— *reducing conditions*: the electropherogram obtained is qualitatively similar to the electropherogram supplied with *infliximab CRS*;

— *non-reducing conditions*: the electropherogram obtained is qualitatively similar to the electropherogram supplied with *infliximab CRS*.

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Result:

— the profile of the electropherogram obtained with the test solution corresponds to that of the electropherogram obtained with the reference solution, except for minor peaks, that may be absent in the electropherogram obtained with the test solution.

Calculate individual peak areas expressed as a percentage of the sum of all corrected peak areas with a migration time greater than 11 min.

Limits:

Reducing conditions:

— *sum of all peaks other than heavy chain and light chain*: maximum 2 per cent, unless otherwise justified and authorised;

Non-reducing conditions:

— *sum of all peaks other than the principal peak*: maximum 8 per cent.

Impurities with molecular masses differing from that of infliximab

Size-exclusion chromatography (*2.2.30*): use the normalisation procedure.

Test solution Dilute the preparation to be examined with the mobile phase to obtain a concentration of 8 mg/mL.

Reference solution (a) Dissolve the contents of a vial of *infliximab CRS* in the mobile phase to obtain a concentration of 8 mg/mL.

Reference solution (b) Reconstitute a mixture of thyroglobulin, gamma-globulin, ovalbumin, myoglobin and vitamin B_{12} in *water R* to obtain an 18 mg/mL solution of molecular mass markers suitable for calibration in the range of 1350-670 000 Da. Further dilute 10 µL of the solution with *water for chromatography R* to obtain a concentration of 0.9 mg/mL.

Column:

— *size*: *l* = 0.30 m, Ø = 7.8 mm;

— *stationary phase*: *hydrophilic silica gel for chromatography R* (5 µm) with a pore size of 25 nm and of a grade suitable for fractionation of globular proteins in the relative molecular mass range of 10 000 to 500 000.

Mobile phase Dissolve 0.78 g of *anhydrous sodium dihydrogen phosphate R*, 1.92 g of *anhydrous disodium hydrogen phosphate R* and 8.77 g of *sodium chloride R* in 900 mL of *water for chromatography R* and dilute to 1000.0 mL with *water for chromatography R*; filter and degas.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 214 nm.

Autosampler Set at 10 °C.

Injection 10 µL.

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Relative retention With reference to infliximab monomer (retention time = about 8 min): high molecular weight species = about 0.88; low molecular weight species = about 1.28.

Calculate individual peak areas expressed as a percentage relative to the sum of the areas of all peaks eluting between 5 min and 11 min. Individual relative per cent peak areas are calculated as the average of 3 injections.

NOTE: protein species that elute between 5 min and the monomer peak are classified as high molecular weight species, while those that elute after the monomer peak and before 11 min are classified as low molecular weight species.

System suitability:

— the chromatogram obtained with reference solution (a) is qualitatively similar to the chromatogram supplied with *infliximab CRS*;

— *resolution*: minimum 1.2 between the peaks due to gamma-globulin and ovalbumin in the chromatogram obtained with reference solution (b).

Result:

— the retention time of the principal peak in the chromatogram obtained with the test solution corresponds to that of the principal peak in the chromatogram obtained with reference solution (a).

Limit:

— *sum of all peaks other than the monomer peak*: maximum 2 per cent.

ASSAY

Protein (*2.5.33, Method 1*)

Test solution Dilute the preparation to be examined with a suitable buffer to obtain a concentration of about 1 mg/mL. Prepare and analyse each preparation in duplicate.

Record the UV spectrum between 280 nm and 350 nm. Measure the value at the absorbance maximum of 280 nm, after correction for any light scattering measured up to 350 nm. Calculate the protein content, taking the specific absorbance to be 14.5.

Potency

The potency of infliximab is determined by comparison of dilutions of the test preparation with dilutions of *infliximab BRP* using a suitable cell-based assay based on the inhibitory action of infliximab on the biological activity of TNF-α with a suitable readout for assessing this inhibitory effect.

The following procedure is given as an example.

WEHI-164 cytotoxicity assay (*2.7.26, Procedure B*)

Carry out the assay as described with the following modifications.

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Reference solution Reconstitute the contents of 1 vial of *infliximab BRP* with sterilised *water for injections R* to obtain a concentration of 500 IU/mL. Further dilute with assay medium to obtain a concentration of 6.4 IU/mL. Analyse 2 independent dilutions per plate.

Result The estimated potency is not less than 80 per cent and not more than 120 per cent relative to the reference solution. The confidence limits (P = 0.95) are not less than 80 per cent and not more than 125 per cent of the estimated potency.

In addition, the following procedures have been found suitable:

U937 apoptosis assay (*2.7.26, Procedure A*)

Carry out the assay as described with the following modifications.

Reference solution Reconstitute the contents of 1 vial of *infliximab BRP* with sterilised *water for injections R* to obtain a concentration of 500 IU/mL. Further dilute with assay medium to obtain a concentration of 12.5 IU/mL. Use this solution to prepare 10 additional reference sample dilutions on a dilution plate to generate the standard curve (a dilution step of 2 has been found suitable). Analyse 2 independent dilutions per plate.

NF-κB-inducible reporter gene assay (*2.7.26, Procedure C*)

Carry out the assay as described with the following modifications.

Reference solution Reconstitute the contents of 1 vial of *infliximab BRP* with sterilised *water for injections R* to obtain a concentration of 500 IU/mL. Further dilute with assay medium to obtain a concentration of 8 IU/mL. Use this solution to prepare 10 additional reference sample dilutions (a dilution step of 1.7 has been found suitable) on a dilution plate. Analyse 2 independent dilutions per plate.

L929 cytotoxicity assay (*2.7.26, Procedure D*)

Carry out the assay as described with the following modifications.

Reference solution Reconstitute the contents of 1 vial of *infliximab BRP* with sterilised *water for injections R* to obtain a concentration of 500 IU/mL. Further dilute with assay medium to obtain a concentration of 1.0 IU/mL. Use this solution to prepare 10 additional reference sample dilutions (a dilution step of 1.7 has been found suitable) on a dilution plate. Analyse 2 independent dilutions per plate.

STORAGE

In an airtight container, under approved conditions.

LABELLING

The label states the content in milligrams of protein per millilitre.

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Injectable Insulin Preparations

General Notices

Insulin Preparations

(Ph. Eur. monograph 0854)

The provisions of this monograph apply to sterile preparations of Human Insulin and its analogues, Bovine Insulin and Porcine Insulin.

The provisions of this monograph apply to Injectable Insulin Preparations listed below.

For preparations of Human Insulin, the label states the approved code in lower case letters indicative of the method of production.

Preparations

Biphasic Isophane Insulin Injection

Insulin Injection

Insulin Aspart Injection

Insulin Lispro Injection

Insulin Zinc Suspension

Insulin Zinc Suspension (Amorphous)

Insulin Zinc Suspension (Crystalline)

Isophane Insulin Injection

Protamine Zinc Insulin Injection

Biphasic Insulin Aspart Injection

Ph Eur

Injectable insulin preparations comply with the requirements for Injections prescribed in the monograph Parenteral preparations (0520).

DEFINITION

Injectable insulin preparations are sterile preparations of *Insulin, human (0838)* or *Insulin, porcine (1638)*. They contain not less than 90.0 per cent and not more than the equivalent of 110.0 per cent of the amount of insulin stated on the label. They are either solutions or suspensions or they are prepared by combining solutions and suspensions.

PRODUCTION

PRODUCTION

The methods of preparation are designed to confer suitable properties with respect to the onset and duration of therapeutic action.

The following procedures are carried out in a suitable sequence, depending on the method of preparation:

— addition of suitable antimicrobial preservatives;

— addition of a suitable substance or substances to render the preparation isotonic with blood;

— addition of a suitable substance or substances to adjust the pH to the appropriate value;

— determination of the strength of the insulin-containing component or components followed, where necessary, by adjustment so that the final preparation contains the requisite number of International Units per millilitre;

— sterilisation by filtration of the insulin-containing component or components; once this procedure has been carried out all subsequent procedures are carried out aseptically using materials that have been sterilised by a suitable method.

In addition, where appropriate, suitable excipients are added and suitable procedures carried out to confer the appropriate physical form on the insulin-containing component or components. The final preparation is distributed aseptically into sterile containers which are closed so as to exclude microbial contamination.

TESTS

pH (2.2.3)

The pH of the solution or suspension is 6.9 to 7.8, unless otherwise prescribed in the specific monograph.

Insulin in the supernatant

For injectable insulin preparations that are suspensions, not more than 2.5 per cent of the total insulin content, unless otherwise stated. Centrifuge 10 mL of the suspension at 1500 *g* for 10 min and carefully separate the supernatant and the residue. Determine the insulin content of the supernatant (*S*) by a suitable method, for example using the chromatographic conditions described under Assay. Calculate the percentage of insulin in solution using the following expression:

$$\frac{100S}{T}$$

where *T* is the total insulin content determined as described under Assay.

Impurities with molecular masses greater than that of insulin

Examine by size-exclusion chromatography (2.2.30).

Test solution Add 4 µL of 6 M hydrochloric acid R per millilitre of the preparation to be examined, whether a suspension or a solution, to obtain a clear acid insulin solution. When sampling a suspension, agitate the material prior to sampling in order to obtain a homogeneous sample. If a suspension does not turn clear within 5 min of the initial addition of hydrochloric acid, add small aliquots of acid (less than 4 µL per millilitre) until a solution is obtained. Preparations with concentrations higher than 100 IU/mL need to be diluted with 0.01 M hydrochloric acid to avoid overloading the column with insulin monomer.

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Resolution solution Use a solution of insulin (approximately 4 mg/mL), containing more than 0.4 per cent of high molecular mass proteins. An injectable insulin preparation, whether a solution or a suspension, that has been clarified with a sufficient amount of *6 M hydrochloric acid R*, containing the indicated percentage of high molecular mass proteins, or a solution prepared from insulin, dissolved in *0.01 M hydrochloric acid*, may be used. Insulin containing the indicated percentage of high molecular mass proteins may be prepared by allowing insulin powder to stand at room temperature for about ten days.

Maintain the solutions at 2 °C to 10 °C and use within 30 h (soluble insulin injection) or 7 days (other insulin preparations). If an automatic injector is used, maintain the temperature at 2 °C to 10 °C.

The chromatographic procedure may be carried out using:

— a column 0.3 m long and at least 7.5 mm in internal diameter packed with *hydrophilic silica gel for chromatography R* (5 µm to 10 µm), of a grade suitable for the separation of insulin monomer from dimers and polymers;

— as mobile phase at a flow rate of 0.5 mL/min a mixture consisting of 15 volumes of *glacial acetic acid R*, 20 volumes of *acetonitrile R* and 65 volumes of a 1.0 g/L solution of *arginine R*; filter and degas;

— as detector a spectrophotometer set at 276 nm.

Equilibration of the column Before using a new column for chromatographic analysis, equilibrate by repeated injections of an insulin solution containing high molecular mass proteins. This can be done by at least 3 injections of the resolution solution. The column is equilibrated when repeatable results are obtained from 2 subsequent injections. If protamine-containing samples are to be analysed, the equilibration of the column is performed using a solution containing protamine.

Inject 100 µL of the resolution solution. When the chromatograms are recorded under the prescribed conditions, the retention times are: polymeric insulin complexes or covalent insulin-protamine complex: about 13 min to 17 min, covalent insulin dimer: about 17.5 min, insulin monomer: about 20 min, salts: about 22 min. If the sample solution contains preservatives, for example methyl paraben, *m*-cresol or phenol, these compounds elute later. The test is not valid unless the resolution, defined by the ratio of the height of the dimer peak to the height above the baseline of the valley separating the monomer and dimer peaks, is at least 2.0.

Inject 100 µL of the test solution. Record the chromatogram for approximately 35 min. In the chromatogram obtained, the sum of the areas of any peak with a retention time less than that of the insulin peak is not greater than 3.0 per cent (protamine containing preparations) or 2.0 per cent (non-protamine containing preparations) of the total area of the peaks. Disregard any peak with a retention time greater than that of the insulin peak.

Related proteins

Examine by liquid chromatography (*2.2.29*) as described under Assay, following the elution conditions as described in the table below:

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Comment
0 - 30	42	58	isocratic
30 - 44	42 → 11	58 → 89	linear gradient

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Comment
44 - 50	11	89	isocratic

Maintain the solutions at 2 °C to 10 °C and use within 24 h. Perform a system suitability check (resolution, linearity) as described under Assay. If necessary, the relative proportions of the mobile phases may be adjusted to ensure complete elution of A21 desamido porcine insulin before commencement of the gradient. The profile of the gradient may also be adjusted to ensure complete elution of all insulin related impurities.

Inject 20 µL of the test solution and 20 µL of either reference solution (a), for insulin preparations containing 100 IU/mL, or reference solution (b), for insulin preparations containing 40 IU/mL. If necessary, adjust the injection volume to a volume between 10 µL and 20 µL in accordance with the results obtained in the test for linearity as described under Assay. Record the chromatograms for about 50 min. If necessary, make further adjustments to the mobile phase in order to ensure that the antimicrobial preservatives present in the test solution are well separated from the insulin and show a shorter retention time. A small reduction in the concentration of acetonitrile increases the retention time of the insulin peaks relatively more than those of the preservatives. In the chromatogram obtained with either reference solution (a), or reference solution (b), as appropriate, A21 desamido insulin appears as a small peak after the principal peak and has a retention time of about 1.3 relative to the principal peak, due to insulin. In the chromatogram obtained with the test solution, the area of the peak due to A21 desamido insulin is not greater than 5.0 per cent of the total area of the peaks; the sum of the areas of any other peaks, apart from those due to insulin and A21 desamido insulin is not greater than 6.0 per cent of the total area of the peaks. Disregard the peaks due to the preservatives and protamine (early eluting peaks).

Total zinc

Not more than the amount stated in the individual monograph, determined by atomic absorption spectrometry (*2.2.23, Method I*).

Use the following method, unless otherwise prescribed in the specific monograph.

Test solution Shake the preparation gently and dilute a volume containing 200 IU of insulin to 25.0 mL with *0.01 M hydrochloric acid*. Dilute if necessary to a suitable concentration of zinc (for example, 0.4 µg to 1.6 µg of Zn per millilitre) with *0.01 M hydrochloric acid*.

Reference solutions Use solutions containing 0.40 µg, 0.80 µg, 1.00 µg, 1.20 µg and 1.60 µg of Zn per millilitre, freshly prepared by diluting *zinc standard solution (5 mg/mL Zn) R* with *0.01 M hydrochloric acid*.

Measure the absorbance at 213.9 nm using a zinc hollow-cathode lamp as source of radiation and an air-acetylene flame of suitable composition (for example 11 L of air and 2 L of acetylene per minute).

Zinc in solution

Where applicable, not more than the amount stated in the individual monograph, determined by atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Centrifuge the preparation to be examined and dilute 1 mL of the clear supernatant obtained to 25.0 mL with *water R*. Dilute if necessary to a suitable concentration of zinc (for example 0.4 µg to 1.6 µg of Zn per millilitre) with *water R*.

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Reference solutions Use solutions containing 0.40 µg, 0.80 µg, 1.00 µg, 1.20 µg and 1.60 µg of Zn per millilitre, freshly prepared by diluting *zinc standard solution (5 mg/mL Zn) R* with *0.01 M hydrochloric acid*.

Measure the absorbance at 213.9 nm using a zinc hollow-cathode lamp as source of radiation and an air-acetylene flame of suitable composition (for example 11 L of air and 2 L of acetylene per minute).

Bacterial endotoxins (*2.6.14*)

Less than 80 IU per 100 IU of insulin.

ASSAY

Examine by liquid chromatography (*2.2.29*).

Test solution Add 4 µL of *6 M hydrochloric acid R* per millilitre of the preparation to be examined, whether a suspension or a solution, to obtain a clear solution. When sampling a suspension, shake the material prior to sampling in order to obtain a homogeneous sample. If a suspension does not turn clear within 5 min of the initial addition of acid, add small aliquots of acid (less than 4 µL per millilitre) until a solution is obtained. For a preparation containing more than 100 IU/mL, an additional dilution with *0.01 M hydrochloric acid* is necessary to avoid overloading the column.

Reference solution (a) Dissolve, as appropriate, the contents of a vial of *human insulin CRS* or *porcine insulin CRS* in *0.01 M hydrochloric acid* to obtain a concentration of 4.0 mg/mL. *Reference solution (a) is used for the assay of insulin preparations containing 100 IU/mL.*

Reference solution (b) Dilute 4.0 mL of reference solution (a) to 10.0 mL with *0.01 M hydrochloric acid*. *Reference solution (b) is used for the assay of insulin preparations containing 40 IU/mL*.

Reference solution (c) Dissolve the contents of a vial of *human insulin CRS* in *0.01 M hydrochloric acid* to obtain a concentration of 4.0 mg/mL.

Reference solution (d) Dissolve the contents of a vial of *insulin porcine for system suitability CRS* in *0.01 M hydrochloric acid* to obtain a concentration of 4 mg/mL.

Reference solution (e) Dilute 1.0 mL of reference solution (a) to 10.0 mL with *0.01 M hydrochloric acid*.

Reference solution (f) Dilute 1.0 mL of reference solution (b) to 10.0 mL with *0.01 M hydrochloric acid*.

Resolution solution Mix 1.0 mL of reference solution (c) and 1.0 mL of reference solution (d).

Maintain the solutions at 2 °C to 10 °C and use within 48 h. If an automatic injector is used, maintain the temperature at 2 °C to 10 °C.

The chromatographic procedure may be carried out using:

— a stainless steel column 0.25 m long and 4.6 mm in internal diameter packed with *octadecylsilyl silica gel for chromatography R* (5 µm);

— as mobile phase at a flow rate of 1 mL/min the following solutions prepared and maintained at a temperature not lower than 20 °C:

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Mobile phase A Dissolve 28.4 g of *anhydrous sodium sulfate R* in *water for chromatography R* and dilute to 1000 mL with the same solvent; add 2.7 mL of *phosphoric acid R*; adjust the pH to 2.3, if necessary, with *ethanolamine R*; filter and degas;

Mobile phase B Mix 550 mL of mobile phase A with 450 mL of *acetonitrile R1*. Warm the solution to a temperature not lower than 20 °C in order to avoid precipitation (mixing of mobile phase A with acetonitrile is endothermic); filter and degas;

— as detector a spectrophotometer set at 214 nm;

maintaining the temperature of the column at 40 °C.

Elute with a mixture of 42 volumes of mobile phase A and 58 volumes of mobile phase B, adjusted if necessary.

Inject 20 µL of the resolution solution and 20 µL of reference solution (d). Record the chromatogram of the resolution solution until the peak corresponding to the principal peak in the chromatogram obtained with reference solution (d) is clearly visible. In the chromatogram obtained with the resolution solution, identify the peaks due to porcine insulin and human insulin. The test is not valid unless the resolution between the peaks due to human insulin and porcine insulin is at least 1.2. If necessary, adjust the concentration of acetonitrile in the mobile phase until this resolution is achieved.

Inject 20 µL of the test solution and 20 µL of either reference solutions (a) and (e), for insulin preparations containing 100 IU/mL, or 20 µL of reference solutions (b) and (f), for insulin preparations containing 40 IU/mL. If necessary, make further adjustments of the mobile phase in order to ensure that the antimicrobial preservatives present in the test solution are well separated from the insulin and show shorter retention times. A small reduction in the concentration of acetonitrile increases the retention time of the insulin peaks relatively more than those of the preservatives. If necessary, after having carried out the chromatography of a solution wash the column with a mixture of equal volumes of *acetonitrile R1* and *water for chromatography R* for a sufficient time to ensure elution of any interfering substances before injecting the next solution. The test is not valid unless the area of the principal peak in the chromatogram obtained with reference solution (a) or (b) is 10 ± 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (e) or (f). If this test fails, adjust the injection volume between 10 µL and 20 µL, in order to be in the linearity range of the detector.

Calculate the content of insulin plus A21 desamido insulin from the area of the peak due to the human or porcine insulin and that of any peak due to the A21 desamido insulin, using the declared content of insulin plus A21 desamido insulin in , *human insulin CRS* or *porcine insulin CRS* as appropriate. [1]

STORAGE

Unless otherwise prescribed, store in a sterile, airtight, tamper-evident container, protected from light, at a temperature of 2 °C to 8 °C. Insulin preparations are not to be frozen.

LABELLING

The label states:

— the potency in International Units per millilitre;

— the concentration in terms of the number of milligrams of insulin per millilitre;

— where applicable, that the substance is produced by enzymatic modification of porcine insulin;

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— where applicable, that the substance is produced by recombinant DNA technology;

— where applicable, the animal species of origin;

— that the preparation must not be frozen;

— where applicable, that the preparation must be resuspended before use.

Ph Eur

1 100 IU are equivalent to 3.47 mg of human insulin and to 3.45 mg of porcine insulin.

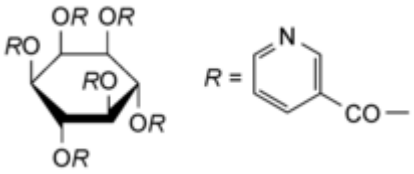
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Inositol Nicotinate

General Notices



$C_{42}H_{30}N_6O_{12}$ 810.7 *6556-11-2*

Action and use

Vasodilator.

Preparation

Inositol Nicotinate Tablets

DEFINITION

Inositol Nicotinate is *myo*-inositol hexanicotinate. It contains not less than 98.0% and not more than 101.0% of $C_{42}H_{30}N_6O_{12}$, calculated with reference to the dried substance.

CHARACTERISTICS

A white or almost white powder.

Practically insoluble in *water*; practically insoluble in *acetone*, in *ethanol (96%)* and in *ether*. It dissolves in dilute mineral acids.

IDENTIFICATION

The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of inositol nicotinate *(RS 190)*.

TESTS

Clarity and colour of solution

A 5.0% w/v solution in 0.5M *sulfuric acid* is *clear*, Appendix IV A, and not more intensely coloured than *reference solution* BY_6, Appendix IV B, Method II.

Chloride

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Dissolve 0.14 g in a sufficient quantity of 2M *nitric acid* and dilute to 16 mL with *water*. The resulting solution complies with the *limit test for chlorides*, Appendix VII, beginning at the words 'pour the mixture as a single addition...' (350 ppm).

Free nicotinic acid

To 1 g add 75 mL of *water*, shake for 15 minutes and titrate with *0.02M sodium hydroxide VS* using *phenolphthalein solution R1* as indicator. Not more than 0.8 mL of *0.02M sodium hydroxide VS* is required to produce the first pink colour.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using a plate 200 mm × 200 mm in size and *silica gel* GF_{254} as the coating substance. For the first development use a mixture of 90 volumes of *chloroform* and 10 volumes of *methanol* as the mobile phase. Apply to the bottom right-hand corner of the plate 5 µL of solution (1) containing 5.0% w/v of the substance being examined in a mixture of 9 volumes of *chloroform* and 1 volume of *methanol* and develop over a path of 12 cm. After removal of the plate, allow it to dry in air and turn the plate through 90° in a clockwise direction. Apply separately to the bottom right-hand corner of the plate, and to the right of the solvent front, 5 µL of each of two solutions of the substance being examined in a mixture of 9 volumes of *chloroform* and 1 volume of *methanol* containing (2) 0.075% w/v and (3) 0.050% w/v. For the second development use a mixture of 50 volumes of *ethyl acetate* and 5 volumes each of *glacial acetic acid*, *ethanol (96%)* and *water* as the mobile phase. After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. In the chromatogram obtained with solution (1) any *secondary spot* is not more intense than the spot in the chromatogram obtained with solution (2) (1.5%) and not more than one such spot is more intense than the spot in the chromatogram obtained with solution (3) (1%).

Acetone

Prepare a 0.020% v/v solution of *butan-2-one* (internal standard) in *dimethylformamide* (solution A). Carry out the method for *gas chromatography*, Appendix III B, using the following solutions. Solution (1) contains 0.020% v/v of *acetone* in solution A. For solution (2) add 5 mL of *dimethylformamide* to 0.20 g of the substance being examined contained in a suitable vessel, stopper securely, suspend in a water bath until solution is complete and allow to cool. Prepare solution (3) in the same manner as solution (2) but using 5 mL of solution A in place of the dimethylformamide.

The chromatographic procedure may be carried out using a glass column (1.5 m × 4 mm) packed with *acid-washed, silanised diatomaceous support* coated with 10% w/w of polyethylene glycol 1000 and maintained at 60°.

In the chromatogram obtained with solution (3) the ratio of the area of any peak corresponding to acetone to the area of the peak due to the internal standard is not greater than the corresponding ratio in the chromatogram obtained with solution (1).

Loss on drying

When dried to constant weight at 105°, loses not more than 0.5% of its weight. Use 1 g.

Sulfated ash

Not more than 0.1%, Appendix IX A.

ASSAY

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Carry out Method I for *non-aqueous titration*, Appendix VIII A, using 0.2 g and *1-naphtholbenzein solution* as indicator. Each mL of *0.1M perchloric acid VS* is equivalent to 13.51 mg of $C_{42}H_{30}N_6O_{12}$.

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Inositol Nicotinate Tablets

General Notices

Action and use

Vasodilator.

DEFINITION

Inositol Nicotinate Tablets contain Inositol Nicotinate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of inositol nicotinate, $C_{42}H_{30}N_6O_{12}$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 1 g of Inositol Nicotinate with 30 mL of a mixture of 9 volumes of *chloroform* and 1 volume of *methanol*, filter and evaporate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of inositol nicotinate *(RS 190)*. Retain the remainder of the residue for use in the Related substances test.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a 20 mL sample of the medium and filter.

(2) Measure the *absorbance* of the filtrate, Appendix II B, diluted with 1M *hydrochloric acid* if necessary, at the maximum at 262 nm using 1M *hydrochloric acid* in the reference cell.

DETERMINATION OF CONTENT

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Calculate the total content of inositol nicotinate, $C_{42}H_{30}N_6O_{12}$, in the medium taking 398 as the value of A(1%, 1 cm) at the maximum at 262 nm.

Free nicotinic acid

To a quantity of the powdered tablets containing 1 g of Inositol Nicotinate add 75 mL of *water*, shake for 15 minutes and titrate with *0.02M sodium hydroxide VS* using *phenolphthalein solution R1* as indicator. Not more than 1.0 mL of *0.02M sodium hydroxide VS* is required to produce the first pink colour.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) 5.0% w/v of the residue obtained in test A for Identification in a mixture of 1 volume of *methanol* and 9 volumes of *chloroform*.
(2) 0.075% w/v of the residue obtained in test A for Identification in a mixture of 1 volume of *methanol* and 9 volumes of *chloroform*.
(3) 0.050% w/v of the residue obtained in test A for Identification in a mixture of 1 volume of *methanol* and 9 volumes of *chloroform*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as a plate 200 mm × 200 mm in size and *silica gel GF_{254}* as the coating substance.
(b) Use the mobile phase as described below for the first development.
(c) Apply to the bottom right-hand corner of the plate 5 µL of solution (1).
(d) Develop the plate to 12 cm.
(e) After removal of the plate, allow it to dry in air and turn the plate through 90° in a clockwise direction.
(f) Use the mobile phase as described below for the second development.
(g) Apply separately to the bottom right-hand corner of the plate, and to the right of the solvent front, 5 µL of solutions (2) and (3).
(h) After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

For the first development: 10 volumes of *methanol* and 90 volumes of *chloroform*.

For the second development: 5 volumes each of *glacial acetic acid*, *ethanol (96%)* and *water* and 50 volumes of *ethyl acetate*.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (1.5%) and not more than one such spot is more intense than the spot in the chromatogram obtained with solution (3) (1%).

ASSAY

Weigh and powder 20 tablets. To a quantity of the powdered tablets containing 0.25 g of Inositol Nicotinate add 50 mL of *anhydrous acetic acid*, heat to boiling and allow to cool. Carry out Method I for *non-aqueous titration*, Appendix VIII A, using *1-naphtholbenzein solution* as indicator. Each mL of *0.1M perchloric acid VS* is equivalent to 13.51 mg of $C_{42}H_{30}N_6O_{12}$.

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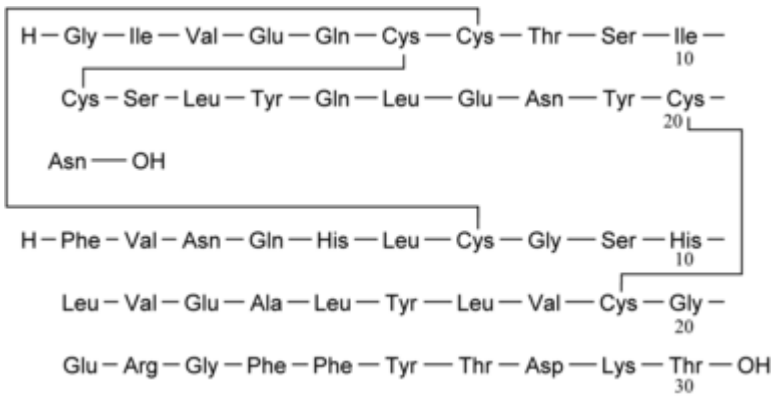
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Insulin Aspart

General Notices

(Ph. Eur. monograph 2084)



$C_{256}H_{381}N_{65}O_{79}S_6$ 5826

Action and use

Hormone; treatment of diabetes mellitus.

Preparation

Biphasic Insulin Aspart Injection

Ph Eur

DEFINITION

28^{B}-L-Aspartate insulin (human).

Insulin aspart 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.

Content

90.0 per cent to 104.0 per cent of insulin aspart $C_{256}H_{381}N_{65}O_{79}S_6$ plus A21Asp insulin aspart, B3Asp insulin aspart, B3isoAsp insulin aspart and B28isoAsp insulin aspart (dried substance).

By convention, for the purpose of labelling insulin aspart preparations, 0.0350 mg of insulin aspart is equivalent to 1 unit.

PRODUCTION

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PRODUCTION

Insulin aspart is produced by a method based on recombinant DNA (rDNA) technology under conditions designed to minimise the degree of microbial contamination.

Prior to release, the following tests are carried out on each batch of insulin aspart, unless exemption has been granted by the competent authority.

Host-cell-derived proteins

The limit is approved by the competent authority.

Single-chain precursor

The limit is approved by the competent authority. Use a suitably sensitive method.

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in ethanol (96 per cent), in methanol and 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.

IDENTIFICATION

A. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with reference solution (a).

B. Peptide mapping (2.2.55).

SELECTIVE CLEAVAGE OF THE PEPTIDE BONDS

Test solution Prepare a 2.0 mg/mL solution of the substance to be examined in *0.01 M hydrochloric acid* and transfer 25 µL of this solution to a clean tube. Add 100 µL of *HEPES buffer solution pH 7.5 R* and 20 µL of a 1 mg/mL solution of *Staphylococcus aureus strain V8 protease, type XVII-B R*. Cap the tube and incubate at 25 °C for 6 h. Stop the reaction by adding 145 µL of *sulfate buffer solution pH 2.0 R*.

Reference solution Prepare at the same time and in the same manner as for the test solution, but using *insulin aspart CRS* instead of the substance to be examined.

CHROMATOGRAPHIC SEPARATION. Liquid chromatography (2.2.29).

Column:

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— *size*: *l* = 0.10 m, Ø = 4.6 mm,

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (3 µm) with a pore size of 8 nm,

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: mix 100 mL of *acetonitrile for chromatography R*, 200 mL of *sulfate buffer solution pH 2.0 R* and 700 mL of *water R*; filter and degas;

— *mobile phase B*: mix 200 mL of *sulfate buffer solution pH 2.0 R*, 400 mL of *acetonitrile for chromatography R* and 400 mL of *water R*; filter and degas;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 60	90 → 30	10 → 70
60 - 65	30 → 0	70 → 100
65 - 70	0	100

Flow rate 1 mL/min.

Detection Spectrophotometer at 214 nm.

Equilibration At initial conditions for at least 15 min. Carry out a blank run using the above-mentioned gradient.

Injection 50 µL.

System suitability:

— the chromatogram obtained with the reference solution is qualitatively similar to the chromatogram of insulin aspart digest supplied with *insulin aspart CRS*,

— in the chromatogram obtained with the reference solution, identify the peaks due to digest fragments I, II and III:

symmetry factor Maximum 1.5, for the peaks due to fragments II and III,

resolution Minimum 8.0, between the peaks due to fragments II and III.

Results The profile of the chromatogram obtained with the test solution corresponds to that of the chromatogram obtained with the reference solution.

NOTE: the retention times of fragments I, II and IV are the same as for human insulin. The retention time of fragment III differs from human insulin due to substitution of proline by aspartic acid.

TESTS

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Impurities with molecular masses greater than that of insulin aspart

Size-exclusion chromatography (2.2.30): use the normalisation procedure.

Test solution Prepare a solution containing 4 mg/mL of the substance to be examined in *0.01 M hydrochloric acid*. Maintain the solution at 2-8 °C and use within 48 h.

Resolution solution Use a solution of insulin (about 4 mg/mL), containing more than 0.4 per cent of high molecular mass proteins. An injectable insulin preparation, whether a solution or a suspension, that has been clarified with a sufficient amount of *6 M hydrochloric acid R*, containing the indicated percentage of high molecular mass proteins, or a solution prepared from insulin, dissolved in *0.01 M hydrochloric acid* may be used. Insulin containing the indicated percentage of high molecular mass proteins may be prepared by allowing insulin powder to stand at room temperature for about 10 days. Maintain the solution at 2-8 °C and use within 7 days.

Column:

— *size*: *l* = 0.3 m, Ø = 7.8 mm,

— *stationary phase*: *hydrophilic silica gel for chromatography R* (5-10 µm) with a pore size of 12-12.5 nm, of a grade suitable for the separation of insulin monomer from dimer and polymers.

Mobile phase Mix 15 volumes of *glacial acetic acid R*, 20 volumes of *acetonitrile for chromatography R* and 65 volumes of a 1.0 g/L solution of *arginine R*; filter and degas.

Flow rate 0.5 mL/min.

Detection Spectrophotometer at 276 nm.

Equilibration At least 3 injections of the resolution solution; the column is equilibrated when repeatable results are obtained from 2 subsequent injections.

Injection 100 µL.

Run time About 35 min.

Retention time Insulin aspart polymers = 13-17 min; insulin aspart dimer = about 17.5 min; insulin aspart monomer = about 20 min; salts = about 22 min.

System suitability Resolution solution:

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to the dimer and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to the monomer.

Limits The sum of the areas of the peaks with a retention time less than that of the principal peak is not more than 0.5 per cent of the total area of the peaks. Disregard any peak with a retention time greater than that of the peak due to insulin aspart monomer.

Related proteins

Liquid chromatography (2.2.29) as described under Assay: use the normalisation procedure.

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Limits:

— *B28isoAsp insulin aspart*: maximum 1.0 per cent,

— *total of the peaks due to A21Asp insulin aspart, B3Asp insulin aspart and B3isoAsp insulin aspart*: maximum 2.0 per cent,

— *total of other impurities*: maximum 1.5 per cent.

Loss on drying (2.2.32)

Maximum 10.0 per cent, determined on 0.200 g by drying in an oven at 105 °C for 24 h.

Sulfated ash (2.4.14)

Maximum 6.0 per cent, determined on 0.200 g (dried substance).

Bacterial endotoxins (2.6.14)

Less than 10 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (2.2.29).

Test solution Dissolve the substance to be examined in *0.01 M hydrochloric acid* to obtain a concentration of 4.0 mg/mL. Maintain the solution at 2-8 °C and use within 24 h.

Reference solution Dissolve the contents of a vial of *insulin aspart CRS* in *0.01 M hydrochloric acid* to obtain a concentration of 4.0 mg/mL. Maintain the solution at 2-8 °C and use within 48 h.

Resolution solution Use an appropriate solution with a content of B3Asp insulin aspart and A21Asp insulin aspart of not less than 1 per cent. This may be achieved by storing reference solution at room temperature for about 1-3 days. Maintain the solution at 2-8 °C and use within 72 h.

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm,

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm),

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: dissolve 142.0 g of *anhydrous sodium sulfate R* in *water R*; add 13.5 mL of *phosphoric acid R* and dilute to 5000 mL with *water R*; adjust to pH 3.6, if necessary, with *strong sodium hydroxide solution R*; filter and degas; mix 9 volumes of the solution with 1 volume of *acetonitrile for chromatography R*; filter and degas;

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— *mobile phase B*: mix equal volumes of *water R* and *acetonitrile for chromatography R*; filter and degas;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 35	58	42
35 - 40	58 → 20	42 → 80
40 - 45	20	80
45 - 46	20 → 58	80 → 42
46 - 60	58	42

Flow rate 1 mL/min.

Detection Spectrophotometer at 214 nm.

Injection 10 µL.

Relative retention With reference to insulin aspart (retention time = 20-24 min): B28isoAsp insulin aspart = about 0.9; B3Asp insulin aspart plus A21Asp insulin aspart (generally coeluted) = about 1.3; B3isoAsp insulin aspart = about 1.5.

System suitability Resolution solution:

— *resolution*: minimum 2.0 between the peak due to insulin aspart and the peak due to A21Asp insulin aspart and to B3Asp insulin aspart.

Calculate the content of insulin aspart $C_{256}H_{381}N_{65}O_{79}S_6$, plus B28isoAsp insulin aspart, A21Asp insulin aspart, B3Asp insulin aspart and B3isoAsp insulin aspart using the areas of the corresponding peaks in the chromatograms obtained with the test solution and reference solution and the declared content of insulin aspart plus B28isoAsp insulin aspart, A21Asp insulin aspart, B3Asp insulin aspart and B3isoAsp insulin aspart in *insulin aspart CRS*.

STORAGE

In an airtight container, protected from light, at or below -18 °C until released by the manufacturer. When thawed, insulin aspart is stored at 5 ± 3 °C and used for manufacturing preparations 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

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Insulin Aspart Injection

General Notices

Action and use

Hormone; treatment of diabetes mellitus.

DEFINITION

Insulin Aspart Injection is a sterile, neutral, aqueous solution of Insulin Aspart.

The injection complies with the requirements stated under Injectable Insulin Preparations with the modifications described below.

Content of insulin aspart, $C_{256}H_{381}N_{65}O_{79}S_6$

90.0 to 110.0% of the stated amount.

CHARACTERISTICS

A colourless liquid, free from turbidity and foreign matter; during storage traces of a very fine sediment may be deposited.

IDENTIFICATION

In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

TESTS

Related proteins

Carry out the method for *liquid chromatography*, Appendix III D, as described under Assay using the *normalisation procedure*.

LIMITS

In the chromatogram obtained with solution (1), the area of the peak corresponding to B28isoAsp insulin aspart is not more than 2.5%, the total area of the peaks corresponding to A21Asp insulin aspart, B3Asp insulin aspart and B3isoAsp insulin aspart is not more than 5%, and the total area of other peaks corresponding to impurities is not more than 3.5%.

Total zinc

Not more than 40 µg per 100 units of insulin aspart, determined by *atomic absorption spectrometry*, Appendix II D Method I.

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Test solution Shake the preparation gently and dilute a volume containing 100 units of insulin aspart to 25.0 mL with 0.01M *hydrochloric acid*. Dilute, if necessary, to a suitable concentration of zinc (for example 0.1 µg to 1.0 µg of Zn per millilitre) with 0.01M *hydrochloric acid*.

Reference solutions Use solutions containing a suitable range of concentrations, for example 0.20 µg, 0.40 µg, 0.60 µg, 0.80 µg and 1.00 µg of Zn per millilitre, freshly prepared by diluting *zinc standard solution (5 mg/mL Zn)* with 0.01M *hydrochloric acid*.

Measure the absorbance at 213.9 nm using a zinc hollow-cathode lamp as source of radiation and an air-acetylene flame of suitable composition (for example 11 litres of air and 2 litres of acetylene per minute).

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. The endotoxin limit concentration is less than 80 IU of endotoxin per 100 units of insulin aspart.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute, if necessary, the preparation being examined with 0.01M *hydrochloric acid* to produce a solution containing 100 units/mL of insulin aspart (equivalent to approximately 0.35% w/v insulin aspart). Add 4 µL of *6M hydrochloric acid* per mL to this solution to obtain a clear acid solution. Maintain the solution at 2° to 8° and use within 48 hours.

(2) Dissolve the contents of a vial of *insulin aspart EPCRS* in 0.01M *hydrochloric acid* to produce a solution containing 0.4% w/v insulin aspart. Maintain the solution at 2° to 8° and use within 48 hours.

(3) Use an appropriate solution with a content of B3Asp insulin aspart and A21Asp insulin aspart of not less than 1%. This may be achieved by storing solution (2) at room temperature for 1 to 3 days. Maintain the solution at 2° to 8° and use within 72 hours.

CHROMATOGRAPHIC CONDITIONS

(a) Stainless steel column (25 cm x 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Lichrosorb RP18 is suitable).

(b) Use gradient elution and the mobile phases described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 214 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A Dissolve 70 g of *anhydrous sodium sulfate* in approximately 4500 mL of *water*; add 6.5 mL of *orthophosphoric acid* and adjust to pH 3.4, if necessary, with *dilute sodium hydroxide solution*. Dilute to 5000 mL with *water*; filter and degas. Mix 9 volumes of the solution with 1 volume of *acetonitrile R1*.

Mobile phase B Mix equal volumes of *water* and *acetonitrile R1*.

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Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0-35	58	42	Isocratic
35-40	58 → 20	42 → 80	Linear gradient
40-45	20	80	Isocratic
45-46	20 → 58	80 → 42	Linear gradient
46-60	58	42	Re-equilibration

When the chromatograms are recorded under the prescribed conditions the relative retention times with reference to insulin aspart (retention time, 20 to 26 minutes) are: B28isoAsp insulin aspart, approximately 0.9; B3Asp insulin aspart plus A21Asp insulin aspart (generally co eluted), approximately 1.3; B3isoAsp insulin aspart, approximately 1.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peak due to insulin aspart and the peak due to A21Asp insulin aspart plus B3Asp insulin aspart is greater than 1.6.

The test is not valid unless the *symmetry factor* of the principal peak in the chromatogram obtained with solution (2) is less than 1.8.

DETERMINATION OF CONTENT

Calculate the content of insulin aspart $C_{256}H_{381}N_{65}O_{79}S_6$, together with the content of B28isoAsp insulin aspart, A21Asp insulin aspart, B3Asp insulin aspart and B3isoAsp insulin aspart using the areas of the corresponding peaks in the chromatograms obtained with solution (1) and solution (2) and the declared content of insulin aspart together with the content of B28isoAsp insulin aspart, A21Asp insulin aspart, B3Asp insulin aspart and B3isoAsp insulin aspart[1] in *insulin aspart EPCRS*.

LABELLING

The label states the potency in units per mL.

1 100 units are equivalent to 3.50 mg of insulin aspart.

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Insulin Glargine

General Notices

(Ph. Eur. monograph 2571)



$C_{267}H_{404}N_{72}O_{78}S_6$ 6063

Action and use

Hormone; treatment of diabetes mellitus.

Preparation

Insulin Glargine Injection

Ph Eur

DEFINITION

21^{A}-Glycine-30^{B}a-L-arginine-30^{B}b-L-arginine-insulin (human).

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.

Content

94.0 per cent to 105.0 per cent (anhydrous substance).

By convention, for the purpose of labelling insulin glargine preparations, 0.0364 mg of insulin glargine is equivalent to 1 unit.

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PRODUCTION

Insulin glargine is produced by a method based on recombinant DNA (rDNA) technology under conditions designed to minimise the degree of microbial contamination.

Prior to release, the following tests are carried out on each batch of insulin glargine, unless exemption has been granted by the competent authority.

Host-cell-derived proteins

The limit is approved by the competent authority.

Single-chain precursor

The limit is approved by the competent authority. Use a suitably sensitive method.

CHARACTERS

Appearance

White or almost white, hygroscopic powder.

Solubility

Practically insoluble in water and in anhydrous ethanol, soluble in dilute mineral acids.

IDENTIFICATION

A. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with the reference solution.

B. Peptide mapping (2.2.55).

SELECTIVE CLEAVAGE OF THE PEPTIDE BONDS

Test solution Prepare a 10.0 mg/mL solution of the substance to be examined in a 1 g/L solution of *hydrochloric acid R* and transfer 5 µL of the solution to a clean tube. Add 1.0 mL of *1 M tris-hydrochloride buffer solution pH 7.5 R* and 100 µL of a 20 U/mL solution of *Staphylococcus aureus strain V8 protease, type XVII-B R* in *1 M tris-hydrochloride buffer solution pH 7.5 R*. Mix and incubate at 45 °C for about 2 h. Stop the reaction by adding 2 µL of *phosphoric acid R*.

Reference solution Prepare at the same time and in the same manner as for the test solution but using *insulin glargine CRS* instead of the substance to be examined.

CHROMATOGRAPHIC SEPARATION. Liquid chromatography (2.2.29).

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Buffer solution Dissolve 11.6 g of *phosphoric acid R* and 42.1 g of *sodium perchlorate R* in 1600 mL of *water for chromatography R*, adjust to pH 2.3 with *triethylamine R* and dilute to 2000 mL with *water for chromatography R*.

Column:

— *size*: *l* = 0.125 m, Ø = 3.0 mm;

— *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (4 µm);

— *temperature*: 35 °C.

Mobile phase:

— *mobile phase A*: *acetonitrile R1*, buffer solution (7:93 *V/V*);

— *mobile phase B*: buffer solution, *acetonitrile R1* (43:57 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 30	90 → 20	10 → 80
30 - 35	20	80

Flow rate 0.6 mL/min.

Detection Spectrophotometer at 214 nm.

Equilibration At initial conditions for at least 15 min.

Injection 50 µL.

Retention time Insulin glargine fragment II = about 14 min; insulin glargine fragment III = about 15 min.

System suitability:

— the chromatogram obtained with the reference solution is qualitatively similar to the chromatogram of insulin glargine digest supplied with *insulin glargine CRS*;

— in the chromatogram obtained with the reference solution, identify the peaks due to digest fragments II and III:

symmetry factor Maximum 1.5 for the peaks due to fragments II and III;

resolution Minimum 3.4 between the peaks due to fragments II and III.

Results The profile of the chromatogram obtained with the test solution corresponds to that of the chromatogram obtained with the reference solution.

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NOTE: the retention times of fragments I and IV are the same as for human insulin; the retention times of fragments II and III differ from human insulin due to the difference in the sequence at position 21 of the A-chain and to the 2 additional amino acids of the B-chain.

TESTS

Impurities with molecular masses greater than that of insulin glargine

Size-exclusion chromatography (2.2.30): use the normalisation procedure.

Test solution Prepare a 4 mg/mL solution of the substance to be examined in a 1 g/L solution of *hydrochloric acid R*.

Resolution solution Dry about 200 mg of the substance to be examined in an oven at 100 °C for 1.5-3 h. Dissolve 15.0 mg of the dried substance in 1.5 mL of a 1 g/L solution of *hydrochloric acid R* and dilute to 10.0 mL with *water R*.

Reference solution Dilute 1.0 mL of the test solution to 100.0 mL with *water R*. Dilute 3.0 mL of this solution to 20.0 mL with *water R*.

Column:

— *size*: *l* = 0.3 m, Ø = 7.8 mm;

— *stationary phase*: *hydrophilic silica gel for chromatography R* (10 µm) with a pore size of 12.5 nm, of a grade suitable for fractionation of globular proteins in the relative molecular mass range of 5000 to 150 000.

Mobile phase Mix 15 volumes of *glacial acetic acid R*, 20 volumes of *acetonitrile R* and 65 volumes of a 1.0 g/L solution of *arginine R*; filter and degas.

Flow rate 0.5 mL/min.

Detection Spectrophotometer at 276 nm.

Injection 100 µL.

Run time About 35 min.

Retention time Insulin glargine = about 18 min.

System suitability:

— *signal-to-noise ratio*: minimum 10 for the principal peak in the chromatogram obtained with the reference solution;

— *symmetry factor*: maximum 2.0 for the peak due to insulin glargine in the chromatogram obtained with the resolution solution;

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to high molecular mass proteins and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to insulin glargine in the chromatogram obtained with the resolution solution.

Limits:

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— *total of impurities with a retention time less than that of insulin glargine*: maximum 0.3 per cent of the total area of the peaks; disregard any peak with a retention time greater than that of the peak due to insulin glargine.

Related proteins

Liquid chromatography (2.2.29): use the normalisation procedure. *Maintain the solutions at 2-8 °C.*

Test solution Dissolve 15.0 mg of the substance to be examined in 1.5 mL of a 1 g/L solution of *hydrochloric acid R* and dilute to 10.0 mL with *water R*.

Reference solution Dissolve the contents of a vial of *insulin glargine CRS* in 1.5 mL of a 1 g/L solution of *hydrochloric acid R*, transfer the solution with *water R* to a 10 mL volumetric flask and dilute to 10.0 mL with *water R*.

Resolution solution Dissolve the contents of a vial of *insulin glargine for peak identification CRS* (containing 0^{A}-Arg-insulin glargine) in 0.3 mL of a 1 g/L solution of *hydrochloric acid R* and add 1.7 mL of *water R*.

Buffer solution Dissolve 20.7 g of *anhydrous sodium dihydrogen phosphate R* in 900 mL of *water for chromatography R*, adjust to pH 2.5 with *phosphoric acid R* and dilute to 1000 mL with *water for chromatography R*.

Column:

— *size*: *l* = 0.25 m, Ø = 3.0 mm;

— *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (4 µm);

— *temperature*: 35 °C.

Mobile phase:

— *mobile phase A*: dissolve 18.4 g of *sodium chloride R* in 250 mL of the buffer solution, add 250 mL of *acetonitrile R1* and mix; dilute to 1000 mL with *water for chromatography R*;

— *mobile phase B*: dissolve 3.2 g of *sodium chloride R* in 250 mL of the buffer solution, add 650 mL of *acetonitrile R1* and mix; dilute to 1000 mL with *water for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 20	96 → 83	4 → 17
20 - 30	83 → 63	17 → 37
30 - 33	63 → 96	37 → 4
33 - 40	96	4

Flow rate 0.6 mL/min.

Detection Spectrophotometer at 214 nm.

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Injection 5 µL of the test solution and the resolution solution.

Retention time Insulin glargine = about 20 min.

System suitability Resolution solution:

— *peak-to-valley ratio*: minimum 2, where H_p = height above the baseline of the peak due to 0^A-Arg-insulin glargine and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to insulin glargine.

Limits:

— *any impurity*: for each impurity, maximum 0.4 per cent;

— *total*: maximum 1.0 per cent.

Zinc

Maximum 0.80 per cent.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Dissolve 45.0 mg of the substance to be examined in a 1 g/L solution of *hydrochloric acid R* and dilute to 50.0 mL with the same solution. Dilute 10.0 mL of the solution to 100.0 mL with a 1 g/L solution of *hydrochloric acid R*.

Reference solutions Prepare reference solutions containing 0.2 µg, 0.4 µg and 0.6 µg of zinc per millilitre by diluting *zinc standard solution (10 ppm Zn) R* with a 1 g/L solution of *hydrochloric acid R*.

Source Zinc hollow-cathode lamp.

Wavelength 213.9 nm.

Atomisation device Air-acetylene flame of suitable composition (for example, 11 L of air and 2 L of acetylene per minute).

Water (*2.5.32*)

Maximum 8.0 per cent, determined on 30.0 mg.

Bacterial endotoxins (*2.6.14, Method D*)

Less than 10 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related proteins with the following modification.

Injection 5 µL of the test solution and the reference solution.

Calculate the content of insulin glargine ($C_{267}H_{404}N_{72}O_{78}S_6$) taking into account the assigned content of *insulin glargine CRS*.

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STORAGE

In an airtight container, protected from light, at a temperature of -20 ± 5 °C.

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Insulin Glargine Injection

General Notices

Action and use

Hormone; treatment of diabetes mellitus.

DEFINITION

Insulin Glargine Injection is a sterile, acidic, aqueous solution of Insulin Glargine.

The injection complies with the requirements stated under Injectable Insulin Preparations with the modifications described below.

Content of insulin glargine, $C_{267}H_{404}N_{72}O_{78}S_6$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 3.5 to 4.5, Appendix V L.

Impurities with molecular masses greater than that of insulin glargine

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute the injection, if necessary, with sufficient *water* to produce a solution containing 0.15% w/v of Insulin Glargine.

(2) Dry 1 vial of *insulin glargine EPCRS* in an oven at 100° for 1.5 to 3 hours. Dissolve the contents of the vial in 1.5 mL of 0.01M *hydrochloric acid* and dilute to 10.0 mL with *water*.

(3) Dilute 1 volume of solution (1) to 100 volumes with *water*, dilute 3 volumes of this solution to 20 volumes with *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use two stainless steel columns (30 cm × 8.0 mm) coupled in series and packed with *hydrophilic silica gel for chromatography* (5 µm) with a pore size of 15 nm of a grade suitable for the fractionation of globular proteins in the relative molecular mass range of 2000 to 80,000 (Shodex PROTEIN KW-802.5 is suitable).

(b) Use isocratic elution and the mobile phase described below.

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(c) Use a flow rate of 0.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 276 nm.

(f) Inject 100 µL of each solution. If splitting of the principal peak is observed, the injection volume may be decreased according to the provisions given in Appendix III.

(g) Allow the chromatography to proceed for 1.8 times the retention time of insulin glargine.

MOBILE PHASE

Mix 200 volumes of *anhydrous acetic acid*, 300 volumes of *acetonitrile for chromatography* and 400 volumes of *water*, adjust to pH 3.0 with *concentrated ammonia* and dilute to 1000 volumes with *water*.

When the chromatograms are recorded under the prescribed conditions the retention time of insulin glargine is about 35 minutes.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (2), the *symmetry factor* of the peak due to insulin glargine is not more than 2.0;

in the chromatogram obtained with solution (2), the *peak-to-valley ratio* is at least 2, where H_p = height above the baseline due to high molecular mass proteins and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to insulin glargine;

in the chromatogram obtained with solution (3), the *signal-to-noise ratio* of the principal peak is at least 10.

LIMITS

In the chromatogram obtained with solution (1) the sum of the areas of any *secondary peaks* with a retention time less than that of the peak due to insulin glargine is not greater than 0.3% by normalisation.

Disregard any peaks with a retention time greater than that of the peak due to insulin glargine.

Related proteins

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Store the solutions at a temperature of 2° to 8°.

(1) Dilute the injection, if necessary, with sufficient *water* to produce a solution containing 0.15% w/v of Insulin Glargine.

(2) Dissolve the contents of a vial of *insulin glargine for peak identification EPCRS* (containing 0^A-Arg-insulin glargine) in 0.3 mL of 0.01M *hydrochloric acid* and add 1.7 mL of *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 3.0 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (4 µm) (Merck Superspher 100-RP-18e is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 0.6 mL per minute.

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(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 214 nm.

(f) Inject 5 µL of each solution.

MOBILE PHASE

Mobile phase A Dissolve 18.4 g of *sodium chloride* in 250 mL of buffer solution prepared as described below; add 250 mL of *acetonitrile R1* and mix; dilute to 1000 mL with *water*.

To prepare the buffer solution, dissolve 20.7 g of *anhydrous sodium dihydrogen phosphate* in 900 mL of *water*, adjust to pH 2.5 with *orthophosphoric acid* and dilute to 1000 mL with *water*.

Mobile phase B Dissolve 3.2 g of *sodium chloride* in 250 mL of the buffer solution prepared as described above; add 650 mL of *acetonitrile R1* and mix; dilute to 1000 mL with *water for chromatography*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-20	96→83	4→17	linear gradient
20-30	83→63	17→37	linear gradient
30-40	63→96	37→4	linear gradient
40-48	96	4	re-equilibration

When the chromatograms are recorded under the prescribed conditions the relative retention time of insulin glargine is about 20 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *peak-to-valley ratio* is at least 2, where H_p = height above the baseline due to 0^A-Arg-insulin glargine and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to insulin glargine.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than 0.5% by *normalisation*;

the sum of the areas of all *secondary peaks* is not greater than 2.0% by *normalisation*.

Total zinc

27 to 33 µg per 100 units of insulin glargine, determined by *atomic absorption spectrometry*, Appendix II D, Method I.

Test solution Dilute, if necessary, to a suitable concentration of zinc (for example 0.2 µg to 0.6 µg of Zn per mL) with 0.01M *hydrochloric acid*.

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Reference solutions Use solutions containing a suitable range of concentrations, for example 0.20 µg, 0.40 µg and 0.60 µg of Zn per mL, freshly prepared by diluting *zinc standard solution (10 ppm Zn)* with 0.01M *hydrochloric acid*.

Measure the *absorbance* at 213.9 nm using a zinc hollow-cathode lamp as source of radiation and an air-acetylene flame of suitable composition (for example 11 litres of air and 2 litres of acetylene per minute).

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. The endotoxin limit concentration is less than 80 IU of endoxtoxin per 100 units of insulin glargine.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Store the solutions at a temperature of 2° to 8°.

(1) Dilute the injection, if necessary, with sufficient *water* to produce a solution containing 0.15% w/v of Insulin Glargine.

(2) Dissolve the contents of a vial of *insulin glargine EPCRS* in 1.5 mL of 0.01M *hydrochloric acid* and dilute to 10.0 mL with *water*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related proteins may be used.

DETERMINATION OF CONTENT

Calculate the content of insulin glargine, $C_{267}H_{404}N_{72}O_{78}S_6$, in the injection from the chromatograms obtained and the declared content of $C_{267}H_{404}N_{72}O_{78}S_6$[1] in *insulin glargine EPCRS*.

LABELLING

The label states the potency in units per mL.

1 100 IU are equivalent to 3.64 mg of insulin glargine.

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Insulin Injection

General Notices

Neutral Insulin

Neutral Insulin Injection

Soluble Insulin

(Soluble Insulin Injection, Ph. Eur. monograph 0834)

Action and use

Hormone; treatment of diabetes mellitus.

Ph Eur

Soluble insulin injection complies with the monograph Insulin preparations, injectable (0854) with the amendments prescribed below.

DEFINITION

Soluble insulin injection is a neutral, sterile solution of human or porcine insulin.

CHARACTERS

A colourless liquid, free from turbidity and foreign matter; during storage, traces of a very fine sediment may be deposited.

IDENTIFICATION

Examine the chromatograms obtained in the assay. The position of the peak due to insulin in the chromatogram obtained with the test solution corresponds to that of the principal peak in the chromatogram obtained with the appropriate reference solution.

TESTS

Total zinc

Not more than 40.0 µg per 100 IU of insulin.

Determine by the method described in the monograph on *Insulin preparations, injectable (0854)*.

Use the following test solution.

Test solution Dilute a volume of the gently shaken preparation containing 200 IU to 25.0 mL with *water R*. Dilute if necessary to a suitable concentration (for example, 0.4 µg to 1.6 µg of Zn per millilitre) with *water R*.

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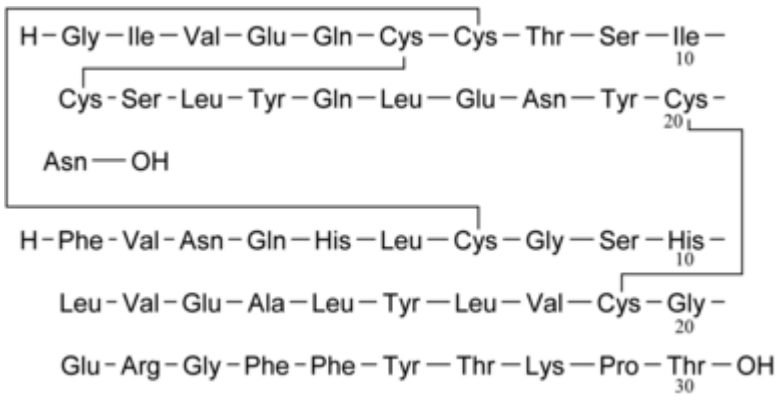
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Insulin Lispro

General Notices

(Ph. Eur. monograph 2085)



$C_{257}H_{383}N_{65}O_{77}S_6$ 5808

Action and use

Hormone; treatment of diabetes mellitus.

Preparation

Biphasic Insulin Lispro Injection

Ph Eur

DEFINITION

28^{B}-L-Lysine-29^{B}-L-proline insulin (human).

Insulin lispro 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.

Content

94.0 per cent to 104.0 per cent (dried substance).

By convention, for the purpose of labelling insulin lispro preparations, 0.0347 mg of insulin lispro is equivalent to 1 unit.

PRODUCTION

PRODUCTION

Insulin lispro is produced by a method based on recombinant DNA (rDNA) technology under conditions designed to minimise the degree of microbial contamination.

Prior to release, the following tests are carried out on each batch of insulin lispro, unless exemption has been granted by the competent authority.

Host-cell-derived proteins

The limit is approved by the competent authority.

Single-chain precursor

The limit is approved by the competent authority. Use a suitably sensitive method.

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water and in ethanol (96 per cent). It dissolves in dilute mineral acids and with decomposition in dilute solutions of alkali hydroxides.

IDENTIFICATION

A. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with the reference solution.

B. Peptide mapping (*2.2.55*).

SELECTIVE CLEAVAGE OF THE PEPTIDE BONDS

Test solution Prepare a 2.0 mg/mL solution of the substance to be examined in *0.01 M hydrochloric acid* and transfer 500 µL of this solution to a clean tube. Add 2.0 mL of *HEPES buffer solution pH 7.5 R* and 400 µL of a 1 mg/mL solution of *Staphylococcus aureus strain V8 protease, type XVII-B R*. Cap the tube and incubate at 25 °C for 6 h. Stop the reaction by adding 2.9 mL of *sulfate buffer solution pH 2.0 R*.

Reference solution Prepare at the same time and in the same manner as for the test solution but using *insulin lispro CRS* instead of the substance to be examined.

CHROMATOGRAPHIC SEPARATION. Liquid chromatography (*2.2.29*).

Column:

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— *size*: *l* = 0.10 m, Ø = 4.6 mm,

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (3 µm) with a pore size of 8 nm,

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: mix 100 mL of *acetonitrile for chromatography R*, 200 mL of *sulfate buffer solution pH 2.0 R* and 700 mL of *water R*; filter and degas;

— *mobile phase B*: mix 200 mL of *sulfate buffer solution pH 2.0 R*, 400 mL of *acetonitrile for chromatography R* and 400 mL of *water R*; filter and degas;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 60	90 → 30	10 → 70
60 - 65	30 → 0	70 → 100
65 - 70	0	100

Flow rate 1 mL/min.

Detection Spectrophotometer at 214 nm.

Equilibration At initial conditions for at least 15 min. Carry out a blank run using the above-mentioned gradient.

Injection 50 µL.

System suitability:

— the chromatogram obtained with the reference solution is qualitatively similar to the chromatogram of insulin lispro digest supplied with *insulin lispro CRS*,

— in the chromatogram obtained with the reference solution, identify the peaks due to digest fragments I, II and III:

symmetry factor Maximum 1.5 for the peaks due to fragments II and III,

resolution Minimum 8.0 between the peaks due to fragments II and III.

Results The profile of the chromatogram obtained with the test solution corresponds to that of the chromatogram obtained with the reference solution.

NOTE: the retention times of fragments I, II and IV are the same as for human insulin. The retention time of fragment III differs from human insulin due to differences in sequence at positions 28 and 29 of the B-chain.

TESTS

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Impurities with molecular masses greater than that of insulin lispro

Size-exclusion chromatography (2.2.30): use the normalisation procedure.

Test solution Prepare a solution containing 4 mg/mL of the substance to be examined in *0.01 M hydrochloric acid*. Maintain the solution at 2-8 °C and use within 48 h.

Resolution solution Use a solution of insulin (about 4 mg/mL), containing more than 0.4 per cent of high molecular mass proteins. An injectable insulin preparation, whether a solution or a suspension, that has been clarified with a sufficient amount of *6 M hydrochloric acid R*, containing the indicated percentage of high molecular mass proteins, or a solution prepared from insulin, dissolved in *0.01 M hydrochloric acid*, may be used. Insulin containing the indicated percentage of high molecular mass proteins may be prepared by allowing insulin powder to stand at room temperature for about 10 days. Maintain the solution at 2-8 °C and use within 8 days.

Column:

— *size*: *l* = 0.30 m, Ø = 7.8 mm,

— *stationary phase*: *hydrophilic silica gel for chromatography R* (5-10 µm) with a pore size of 12-12.5 nm, of a grade suitable for the separation of insulin monomer from dimer and polymers.

Mobile phase Mix 15 volumes of *glacial acetic acid R*, 20 volumes of *acetonitrile for chromatography R* and 65 volumes of a 1.0 g/L solution of *arginine R*; filter and degas.

Flow rate 0.5 mL/min.

Detection Spectrophotometer at 276 nm.

Equilibration At least 3 injections of the resolution solution; the column is equilibrated when repeatable results are obtained for 2 subsequent injections.

Injection 100 µL.

Run time About 35 min.

Retention time Insulin lispro polymers = 13-17 min; insulin lispro dimer = about 17.5 min; insulin lispro monomer = about 20 min; salts = about 22 min.

System suitability Resolution solution:

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to the dimer and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to the monomer,

— *symmetry factor*: maximum 2.0 for the peak due to insulin lispro.

Limits The sum of the areas of the peaks with a retention time less than that of the principal peak is not more than 0.25 per cent of the total area of the peaks. Disregard any peak with a retention time greater than that of the peak due to insulin lispro monomer.

Related proteins

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Liquid chromatography (2.2.29): use the normalisation procedure.

Test solution Dissolve 3.5 mg of the substance to be examined in 1.0 mL of *0.01 M hydrochloric acid*. Maintain the solution at 2-8 °C and use within 56 h.

Resolution solution Dissolve 3.5 mg of the substance to be examined in 1.0 mL of *0.01 M hydrochloric acid*. Allow to stand at room temperature to obtain a solution containing between 0.8 per cent and 11 per cent of A21 desamido insulin lispro.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm,

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm) with a pore size of 30 nm,

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: mix 82 volumes of a 28.4 g/L solution of *anhydrous sodium sulfate R* adjusted to pH 2.3 with *phosphoric acid R* and 18 volumes of *acetonitrile for chromatography R*; filter and degas;

— *mobile phase B*: mix equal volumes of a 28.4 g/L solution of *anhydrous sodium sulfate R* adjusted to pH 2.3 with *phosphoric acid R* and *acetonitrile for chromatography R*; filter and degas;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 60	81	19
60 - 83	81 → 51	19 → 49
83 - 84	51 → 81	49 → 19
84 - 94	81	19

Flow rate 1 mL/min.

Detection Spectrophotometer at 214 nm.

Injection 20 µL.

Retention time Adjust the mobile phase composition to obtain a retention time of about 41 min for insulin lispro; A21 desamido insulin lispro elutes near the start of the gradient elution.

System suitability Resolution solution:

— *resolution*: minimum 1.5 between the 1st peak (insulin lispro) and the 2nd peak (A21 desamido insulin lispro),

— *symmetry factor*: maximum 2.0 for the peak due to insulin lispro.

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Limits:

— *A21 desamido insulin lispro*: maximum 1.0 per cent,

— *any other impurity*: maximum 0.50 per cent,

— *total (excluding A21)*: maximum 2.0 per cent.

Zinc

Maximum 1.0 per cent (dried substance).

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Dissolve at least 50 mg of the substance to be examined in *0.01 M hydrochloric acid* and dilute to 25 mL with the same acid. Dilute if necessary to a suitable concentration (for example 0.4-0.6 µg of Zn per millilitre) with *0.01 M hydrochloric acid*.

Reference solutions Use solutions of concentrations which bracket the expected zinc concentration of the samples, for example, 0.2-0.8 µg of Zn per millilitre, freshly prepared by diluting *zinc standard solution (5 mg/mL Zn) R* with *0.01 M hydrochloric acid*.

Source Zinc hollow-cathode lamp.

Wavelength 213.9 nm.

Atomisation device Air-acetylene flame of suitable composition (for example, 11 L of air and 2 L of acetylene per minute).

Loss on drying (*2.2.32*)

Maximum 10.0 per cent, determined on 0.200 g by drying in an oven at 105 °C for 16 h.

Sulfated ash (*2.4.14*)

Maximum 2.5 per cent, determined on 0.200 g (dried substance).

Bacterial endotoxins (*2.6.14, Method D*)

Less than 10 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (*2.2.29*).

Test solution Dissolve the substance to be examined in *0.01 M hydrochloric acid* to obtain a concentration of 0.8 mg/mL. Maintain the solution at 2-8 °C and use within 48 h.

Reference solution Dissolve the contents of a vial of *insulin lispro CRS* in *0.01 M hydrochloric acid* to obtain a concentration of 0.8 mg/mL. Maintain the solution at 2-8 °C and use within 48 h.

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Resolution solution Dissolve about 10 mg of the substance to be examined in 10 mL of *0.01 M hydrochloric acid*. Allow to stand at room temperature to obtain a solution containing between 0.8 per cent and 11 per cent of A21 desamido insulin lispro. Maintain the solution at 2-8 °C and use within 14 days.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm,

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (3 µm) with a pore size of 8 nm,

— *temperature*: 40 °C.

Mobile phase Mix 745 volumes of a 28.4 g/L solution of *anhydrous sodium sulfate R* adjusted to pH 2.3 with *phosphoric acid R* and 255 volumes of *acetonitrile for chromatography R*; filter and degas.

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 214 nm.

Injection 20 µL.

Retention time Insulin lispro = about 24 min.

System suitability:

— *resolution*: minimum 1.8 between the 1st peak (insulin lispro) and the 2nd peak (A21 desamido insulin lispro), in the chromatogram obtained with the resolution solution,

— *repeatability*: maximum relative standard deviation of 1.1 per cent after 3 injections of the reference solution.

Calculate the content of insulin lispro $C_{257}H_{383}N_{65}O_{77}S_6$ using the chromatograms obtained with the test solution and the reference solution and the declared content of $C_{257}H_{383}N_{65}O_{77}S_6$ in *insulin lispro CRS*.

STORAGE

In an airtight container, protected from light, at or below -18 °C. When thawed, insulin lispro is stored and weighed under conditions defined by the manufacturer to maintain the quality attributes of the drug substance and is used for manufacturing preparations within a short period of time. To avoid absorption of humidity from the air during weighing, insulin lispro must be at room temperature before opening the container.

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Insulin Lispro Injection

General Notices

Action and use

Hormone; treatment of diabetes mellitus.

DEFINITION

Insulin Lispro Injection is a sterile, aqueous solution of Insulin Lispro.

The injection complies with the requirements stated under Injectable Insulin Preparations, with the exception of the test for Insulin in the supernatant, and with the modifications described below.

Content of insulin lispro, $C_{257}H_{383}N_{65}O_{77}S_6$

90.0 to 105.0% of the stated amount.

CHARACTERISTICS

A clear and colourless solution, free from turbidity and foreign matter.

IDENTIFICATION

In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

TESTS

Impurities with molecular masses greater than that of insulin lispro

The sum of the areas of the peaks in the chromatogram obtained with the test solution with a retention time less than that of the principal peak is not more than 1.5% of the total area of the peaks. Disregard any peak with a retention time greater than that of the peak due to insulin lispro monomer.

Related proteins

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute, if necessary, the preparation being examined with 0.01M *hydrochloric acid* to produce a solution containing 0.35% w/v of Insulin Lispro. Add 4 µL of *6M hydrochloric acid* per mL of this solution. Maintain the solution at 2° to 8° and use within 56 hours.

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(2) Prepare a 0.35% w/v solution of Insulin Lispro in 0.01M *hydrochloric acid* and add 4 µL of *6M hydrochloric acid* per mL. Allow to stand at room temperature to obtain a solution containing between 0.8% and 11% of A21 desamido insulin lispro.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm x 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) with a pore size of 30 nm (Vydac Protein and Peptide C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 214 nm.

(f) Inject 20 µL for each solution.

MOBILE PHASE

Mobile phase A Mix 82 volumes of a 2.84% w/v solution of *anhydrous sodium sulfate* adjusted to pH 2.3 with *orthophosphoric acid* and 18 volumes of *acetonitrile for chromatography*.

Mobile phase B Mix equal volumes of a 2.84% w/v solution of *anhydrous sodium sulfate*, adjusted to pH 2.3 with *orthophosphoric acid*, and *acetonitrile for chromatography*.

Use the following gradient.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0-60	81	19	Isocratic
60-83	81 → 51	19 → 49	Linear gradient
83-84	51 → 81	49 → 19	Linear gradient
84-94	81	19	Re-equilibration

SYSTEM SUITABILITY

Adjust the mobile phase composition to obtain a retention time of about 41 minutes for insulin lispro; A21 desamido insulin lispro elutes near the start of the gradient elution. The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the first peak (insulin lispro) and the second peak (A21 desamido insulin lispro) is at least 1.5 and the *symmetry factor* for the peak due to insulin lispro is less than 2.0.

LIMITS

In the chromatogram obtained with solution (1), the amount of A21 desamido insulin lispro is not more than 1.5%. The total amount of related proteins (excluding A21) is not greater than 4.0%.

Total zinc

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14 to 35 µg per 100 units of insulin lispro, determined by *atomic absorption spectrometry*, Appendix II D, Method I.

Test solution Shake the preparation gently and dilute a volume containing 200 units of insulin lispro to 25.0 mL with 0.01M *hydrochloric acid*. Dilute if necessary to a suitable concentration of zinc (for example 0.4 µg to 1.6 µg of Zn per mL) with 0.01M *hydrochloric acid*.

Reference solutions Use solutions containing a suitable range of concentrations, for example 0.40 µg, 0.80 µg, 1.00 µg, 1.20 µg and 1.60 µg of Zn per mL, freshly prepared by diluting *zinc standard solution (5 mg per mL Zn)* with 0.01M *hydrochloric acid*.

Measure the absorbance at 213.9 nm using a zinc hollow-cathode lamp as source of radiation and an air-acetylene flame of suitable composition (for example 11 litres of air and 2 litres of acetylene per minute).

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. The endotoxin limit concentration is less than 80 IU of endotoxin per 100 units of insulin lispro.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute, if necessary, the preparation being examined with 0.01M *hydrochloric acid* to obtain a 0.08% w/v solution. Add 4 µL of *6M hydrochloric acid* per mL of this solution. Maintain the solution at 2 to 8° and use within 48 hours.
(2) Dissolve the contents of a vial of *insulin lispro EPCRS* in 0.01M *hydrochloric acid* to obtain a 0.08% w/v solution. Maintain the solution at 2° to 8° and use within 48 hours.
(3) Prepare a 0.1% w/v solution of the preparation being examined in 0.01M *hydrochloric acid* and add 4 µL of *6M hydrochloric acid* per mL. Allow to stand at room temperature to obtain a solution containing between 0.8% and 11% of A21 desamido insulin lispro. Maintain the solution at 2° to 8° and use within 14 days.

CHROMATOGRAPHIC CONDITIONS

(a) Stainless steel column (10 cm x 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (3 µm) (Spherisorb ODS 2 is suitable).
(b) Isocratic elution using the mobile phase described below.
(c) Flow rate of 0.8 mL per minute.
(d) Column temperature of 40°.
(e) Detection wavelength of 214 nm.
(f) Injection volume of 20 µL for each solution.

MOBILE PHASE

Mix 255 volumes of *acetonitrile for chromatography* and 745 volumes of a 2.84% w/v solution of *anhydrous sodium sulfate* adjusted to pH 2.3 with *orthophosphoric acid*.

SYSTEM SUITABILITY

When the chromatograms are recorded in the prescribed conditions, the retention time of insulin lispro is approximately 24 minutes. The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the first peak (insulin lispro) and the second

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peak (A21 desamido insulin lispro), is greater than 1.8, and the maximum relative standard deviation for replicate injections is 1.1% after 3 injections.

DETERMINATION OF CONTENT

Calculate the content of insulin lispro $C_{257}H_{383}N_{65}O_{77}S_6$ from the chromatograms obtained and the declared content of $C_{257}H_{383}N_{65}O_{77}S_6$[1] in *insulin lispro EPCRS*.

LABELLING

The label states the potency in units per mL.

1 100 IU are equivalent to 3.47 mg of insulin lispro.

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Insulin Zinc Suspension

General Notices

Insulin Zinc Suspension, Mixed

(Insulin Zinc Injectable Suspension, Ph. Eur. monograph 0837)

Action and use

Hormone; treatment of diabetes mellitus.

Ph Eur

Insulin zinc injectable suspension complies with the monograph Insulin preparations, injectable (0854) with the amendments prescribed below.

DEFINITION

Insulin zinc injectable suspension is a sterile, neutral suspension of human or of porcine insulin with a suitable zinc salt; the insulin is in a form which is practically insoluble in water.

PRODUCTION

Insulin zinc injectable suspension is prepared by carrying out the procedures described in the monograph *Insulin preparations, injectable (0854)*.

Insulin zinc injectable suspension is produced by mixing insulin zinc injectable suspension (crystalline) and insulin zinc injectable suspension (amorphous) in a ratio of 7 to 3.

CHARACTERS

A white or almost white suspension which on standing deposits a white or almost white sediment and leaves a colourless or almost colourless supernatant; the sediment is readily resuspended by gently shaking. When examined under a microscope, the majority of the particles are seen to be rhombohedral crystals with a maximum dimension when measured from corner to corner through the crystal greater than 10 µm but rarely exceeding 40 µm; a considerable proportion of the particles are seen to have no uniform shape and a maximum dimension rarely exceeding 2 µm.

IDENTIFICATION

Examine the chromatograms obtained in the assay.

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The position of the peak due to insulin in the chromatogram obtained with the test solution corresponds to that of the principal peak in the chromatogram obtained with the appropriate reference solution.

TESTS

Insulin not extractable with buffered acetone solution

63 per cent to 77 per cent of the total insulin content. Centrifuge a volume of the substance to be examined containing 200 IU of insulin and discard the supernatant. Suspend the residue in 1.65 mL of *water R*, add 3.3 mL of *buffered acetone solution R*, stir for 3 min, again centrifuge, discard the supernatant and repeat all the operations with the residue. Dissolve the residue using a suitable procedure, for example dissolve in *0.1 M hydrochloric acid* to give a final volume of 2.0 mL. Determine the insulin content of the residue (*R*) and determine the total insulin content (*T*) of an equal volume of the suspension by a suitable method. Calculate the percentage of insulin not extractable with buffered acetone solution from the expression:

$$\frac{100R}{T}$$

Total zinc

0.12 mg to 0.25 mg per 100 IU of insulin, determined as described in the monograph *Insulin preparations, injectable (0854)*.

Zinc in solution

20 per cent to 65 per cent of the total zinc is in the form of zinc in solution. Determine by the method described in the monograph *Insulin preparations, injectable (0854)*.

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Insulin Zinc Suspension (Amorphous)

General Notices

(Insulin Zinc Injectable Suspension (Amorphous), Ph. Eur. monograph 0835)

Action and use

Hormone; treatment of diabetes mellitus.

Ph Eur

Insulin zinc injectable suspension (amorphous) complies with the monograph Insulin preparations, injectable (0854) with the amendments prescribed below.

DEFINITION

Insulin zinc injectable suspension (amorphous) is a sterile, neutral suspension of human or porcine insulin complexed with a suitable zinc salt; the insulin is in a form which is practically insoluble in water.

CHARACTERS

A white or almost white suspension which on standing deposits a white or almost white sediment and leaves a colourless or almost colourless supernatant; the sediment is readily resuspended by gently shaking. When examined under a microscope, the particles are seen to have no uniform shape and a maximum dimension rarely exceeding 2 µm.

IDENTIFICATION

Examine the chromatograms obtained in the assay. The position of the peak due to insulin in the chromatogram obtained with the test solution corresponds to that of the principal peak in the chromatogram obtained with the appropriate reference solution.

TESTS

Total zinc

0.12 mg to 0.25 mg per 100 IU of insulin, determined as described in the monograph *Insulin preparations, injectable (0854)*.

Zinc in solution

20 per cent to 65 per cent of the total zinc is in the form of zinc in solution. Determine by the method described in the monograph *Insulin preparations, injectable (0854)*.

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Insulin Zinc Suspension (Crystalline)

General Notices

(Insulin Zinc Injectable Suspension (Crystalline), Ph. Eur. monograph 0836)

Action and use

Hormone; treatment of diabetes mellitus.

Ph Eur

Insulin zinc injectable suspension (crystalline) complies with the monograph Insulin preparations, injectable (0854) with the amendments prescribed below.

DEFINITION

Insulin zinc injectable suspension (crystalline) is a sterile, neutral suspension of human or porcine insulin, complexed with a suitable zinc salt; the insulin is in a form which is practically insoluble in water.

CHARACTERS

A white or almost white suspension which on standing deposits a white or almost white sediment and leaves a colourless or almost colourless supernatant; the sediment is readily resuspended by gently shaking. When examined under a microscope, the particles are seen to be rhombohedral crystals, the majority having a maximum dimension when measured from corner to corner through the crystal greater than 10 µm but rarely exceeding 40 µm.

IDENTIFICATION

Examine the chromatograms obtained in the assay. The position of the peak due to insulin in the chromatogram obtained with the test solution corresponds to that of the principal peak in the chromatogram obtained with the appropriate reference solution.

TESTS

Insulin not extractable with buffered acetone solution

Not less than 90 per cent of the total insulin content. Centrifuge a volume of the substance to be examined containing 200 IU of insulin and discard the supernatant. Suspend the residue in 1.65 mL of *water R*, add 3.3 mL of *buffered acetone solution R*, stir for 3 min, again centrifuge, discard the supernatant and repeat all the operations with the residue. Dissolve the residue using a suitable procedure, for example dissolve in *0.1 M hydrochloric acid* to give a final volume of 2.0 mL. Determine the insulin content of the residue (*R*) and determine the total insulin content (*T*) of an equal volume of the suspension by a suitable method. Calculate the percentage of insulin not extractable with buffered acetone solution from the expression:

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$$\frac{100R}{T}$$

Total zinc

0.12 mg to 0.25 mg per 100 IU of insulin, determined as described in the monograph *Insulin preparations, injectable (0854)*.

Zinc in solution

20 per cent to 65 per cent of the total zinc is in the form of zinc in solution. Determine by the method described in the monograph *Insulin preparations, injectable (0854)*.

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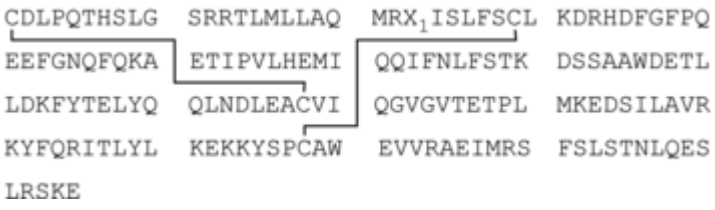
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Interferon Alfa-2 Concentrated Solution

General Notices

(Ph. Eur. monograph 1110)



Action and use

Cytokine.

Preparation

Interferon Alfa-2a Injection

Ph Eur

DEFINITION

Interferon alfa-2 concentrated solution is a solution of a protein that is produced according to the information coded by the alfa-2 sub-species of interferon alfa gene and that exerts non-specific antiviral activity, at least in homologous cells, through cellular metabolic processes involving synthesis of both ribonucleic acid and protein. Interferon alfa-2 concentrated solution also exerts antiproliferative activity. Different types of alfa-2 interferon, varying in the amino acid residue at position 23, are designated by a letter in lower case.

Designation	Residue at position 23 (X_1)
alfa-2a	Lys
alfa-2b	Arg

This monograph applies to interferon alfa-2a and -2b concentrated solutions.

The potency of interferon alfa-2 concentrated solution is not less than 1.4×10^8 IU per milligram of protein. Interferon alfa-2 concentrated solution contains not less than 2×10^8 IU of interferon alfa-2 per millilitre.

PRODUCTION

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Interferon alfa-2 concentrated solution is produced by a method based on recombinant DNA (rDNA) technology using bacteria as host cells. It is produced under conditions designed to minimise microbial contamination of the product.

Interferon alfa-2 concentrated solution complies with the following additional requirements.

Host-cell-derived proteins

The limit is approved by the competent authority.

Host-cell- or vector-derived DNA

The limit is approved by the competent authority.

CHARACTERS

A clear, colourless or slightly yellowish liquid.

IDENTIFICATION

A. It shows the expected biological activity (see Assay).

B. Examine by isoelectric focusing.

Test solution Dilute the preparation to be examined with *water R* to a protein concentration of 1 mg/mL.

Reference solution Prepare a 1 mg/mL solution of *interferon alfa-2b CRS* in *water R*.

Isoelectric point calibration solution pI range 3.0 to 10.0 Prepare and use according to the manufacturer's instructions.

Use a suitable apparatus connected with a recirculating temperature controlled water-bath set at 10 °C and gels for isoelectric focusing with a pH gradient from 3.5 to 9.5. Operate the apparatus in accordance with the manufacturer's instructions. Use as the anode solution *phosphoric acid R* (98 g/L H_3PO_4) and as the cathode solution *1 M sodium hydroxide*. Samples are applied to the gel by filter papers. Place sample application filters on the gel close to the cathode.

Apply 15 µL of the test solution and 15 µL of the reference solution. Start the isoelectric focusing at 1500 V and 50 mA. Turn off the power after 30 min, remove the application filters and reconnect the power supply for 1 h. Keep the power constant during the focusing process. After focusing, immerse the gel in a suitable volume of a solution containing 115 g/L of *trichloroacetic acid R* and 34.5 g/L of *sulfosalicylic acid R* in *water R* and agitate the container gently for 60 min. Transfer the gel to a mixture of 32 volumes of *glacial acetic acid R*, 100 volumes of *anhydrous ethanol R* and 268 volumes of *water R*, and soak for 5 min. Immerse the gel for 10 min in a staining solution prewarmed to 60 °C in which 1.2 g/L of *acid blue 83 R* has been added to the previous mixture of glacial acetic acid, ethanol and water. Wash the gel in several containers with the previous mixture of glacial acetic acid, ethanol and water and keep the gel in this mixture until the background is clear (12 h to 24 h). After adequate destaining, soak the gel for 1 h in a 10 per cent *V/V* solution of *glycerol R* in the previous mixture of glacial acetic acid, ethanol and water.

The principal bands of the electropherogram obtained with the test solution correspond in position to the principal bands of the electropherogram obtained with the reference solution. Plot the migration distances of the isoelectric point markers versus their isoelectric points and determine the isoelectric points of the principal components of the test solution and the reference solution. They do not differ by

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more than 0.2 pI units. The test is not valid unless the isoelectric point markers are distributed along the entire length of the gel and the isoelectric points of the principal bands in the electropherogram obtained with the reference solution are between 5.8 and 6.3.

C. Examine the electropherograms obtained under reducing conditions in the test for impurities of molecular masses differing from that of interferon alfa-2. The principal band in the electropherogram obtained with test solution (a) corresponds in position to the principal band in the electropherogram obtained with reference solution (a).

D. Examine by peptide mapping.

Test solution Dilute the preparation to be examined in *water R* to a protein concentration of 1.5 mg/mL. Transfer 25 µL to a polypropylene or glass tube of 1.5 mL capacity. Add 1.6 µL of *1 M phosphate buffer solution pH 8.0 R*, 2.8 µL of a freshly prepared 1.0 mg/mL solution of *trypsin for peptide mapping R* in *water R* and 3.6 µL of *water R* and mix vigorously. Cap the tube and place it in a water-bath at 37 °C for 18 h, then add 100 µL of a 573 g/L solution of *guanidine hydrochloride R* and mix well. Add 7 µL of 154.2 g/L solution of *dithiothreitol R* and mix well. Place the capped tube in boiling water for 1 min. Cool to room temperature.

Reference solution Prepare at the same time and in the same manner as for the test solution but use a 1.5 mg/mL solution of *interferon alfa-2b CRS* in *water R*.

Examine by liquid chromatography (*2.2.29*).

The chromatographic procedure may be carried out using:

— a stainless steel column 0.10 m long and 4.6 mm in internal diameter packed with *octadecylsilyl silica gel for chromatography R* (5 µm) with a pore size of 30 nm,

— as mobile phase at a flow rate of 1.0 mL/min:

Mobile phase A Dilute 1 mL of *trifluoroacetic acid R* to 1000 mL with *water R*,

Mobile phase B To 100 mL of *water R* add 1 mL of *trifluoroacetic acid R* and dilute to 1000 mL with *acetonitrile for chromatography R*,

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Comment
0 - 8	100	0	isocratic
8 - 68	100 → 40	0 → 60	linear gradient
68 - 72	40	60	isocratic
72 - 75	40 → 100	60 → 0	linear gradient
75 - 80	100	0	re-equilibration

— as detector a spectrophotometer set at 214 nm,

maintaining the temperature of the column at 30 °C.

Equilibrate the column with mobile phase A for at least 15 min.

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Inject 100 µL of the test solution and 100 µL of the reference solution.

System suitability The chromatogram obtained with the reference solution is qualitatively similar to the chromatogram of interferon alfa-2 digest supplied with *interferon alfa-2b CRS*.

Results The profile of the chromatogram obtained with the test solution corresponds to that of the chromatogram obtained with the reference solution.

TESTS

Impurities of molecular masses differing from that of interferon alfa-2

Examine by SDS polyacrylamide gel electrophoresis (*2.2.31*). The test is performed under both reducing and non-reducing conditions, using resolving gels of 14 per cent acrylamide and silver staining as the detection method.

Sample buffer (non-reducing conditions) Mix equal volumes of *water R* and *concentrated SDS-PAGE sample buffer R*.

Sample buffer (reducing conditions) Mix equal volumes of *water R* and *concentrated SDS-PAGE sample buffer for reducing conditions R* containing 2-mercaptoethanol as the reducing agent.

Test solution (a) Dilute the preparation to be examined in sample buffer to a protein concentration of 0.5 mg/mL.

Test solution (b) Dilute 0.20 mL of test solution (a) to 1 mL with sample buffer.

Reference solution (a) Prepare a 0.625 mg/mL solution of *interferon alfa-2b CRS* in sample buffer.

Reference solution (b) Dilute 0.20 mL of reference solution (a) to 1 mL with sample buffer.

Reference solution (c) Dilute 0.20 mL of reference solution (b) to 1 mL with sample buffer.

Reference solution (d) Dilute 0.20 mL of reference solution (c) to 1 mL with sample buffer.

Reference solution (e) Dilute 0.20 mL of reference solution (d) to 1 mL with sample buffer.

Reference solution (f) Use a solution of molecular mass standards suitable for calibrating SDS-PAGE gels in the range 15 kDa to 67 kDa.

Place test and reference solutions, contained in covered test-tubes, on a water-bath for 2 min.

Apply 10 µL of reference solution (f) and 50 µL of each of the other solutions to the stacking gel wells. Perform the electrophoresis under the conditions recommended by the manufacturer of the equipment. Detect proteins in the gel by silver staining.

The test is not valid unless: the validation criteria are met (*2.2.31*); a band is seen in the electropherogram obtained with reference solution (e); and a gradation of intensity of staining is seen in the electropherograms obtained, respectively, with test solution (a) and test solution (b) and with reference solutions (a) to (e).

The electropherogram obtained with test solution (a) under reducing conditions may show, in addition to the principal band, less intense bands with molecular masses lower than the principal band. No such band is more intense than the principal band in the electropherogram

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obtained with reference solution (d) (1.0 per cent) and not more than 3 such bands are more intense than the principal band in the electropherogram obtained with reference solution (e) (0.2 per cent).

The electropherogram obtained with test solution (a) under non-reducing conditions may show, in addition to the principal band, less intense bands with molecular masses higher than the principal band. No such band is more intense than the principal band in the electropherogram obtained with reference solution (d) (1.0 per cent) and not more than 3 such bands are more intense than the principal band in the electropherogram obtained with reference solution (e) (0.2 per cent).

Related proteins

Examine by liquid chromatography (2.2.29).

Test solution Dilute the preparation to be examined with water R to a protein concentration of 1 mg/mL.

0.25 per cent m/m hydrogen peroxide solution Dilute dilute hydrogen peroxide solution R in water R in order to obtain a 0.25 per cent *m/m* solution.

Reference solution To a volume of the test solution, add a suitable volume of 0.25 per cent *m/m* hydrogen peroxide solution to give a final hydrogen peroxide concentration of 0.005 per cent *m/m*, and allow to stand at room temperature for 1 h, or for the length of time that will generate about 5 per cent oxidised interferon. Add 12.5 mg of L-methionine R per millilitre of solution. Allow to stand at room temperature for 1 h. Store the solutions for not longer than 24 h at a temperature of 2-8 °C.

The chromatographic procedure may be carried out using:

— a stainless steel column 0.25 m long and 4.6 mm in internal diameter packed with octadecylsilyl silica gel for chromatography R (5 µm) with a pore size of 30 nm,

— as mobile phase at a flow rate of 1.0 mL/min:

Mobile phase A To 700 mL of water R add 2 mL of trifluoroacetic acid R and 300 mL of acetonitrile for chromatography R,

Mobile phase B To 200 mL of water R add 2 mL of trifluoroacetic acid R and 800 mL of acetonitrile for chromatography R,

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Comment
0 - 1	72	28	isocratic
1 - 5	72 → 67	28 → 33	linear gradient
5 - 20	67 → 63	33 → 37	linear gradient
20 - 30	63 → 57	37 → 43	linear gradient
30 - 40	57 → 40	43 → 60	linear gradient
40 - 42	40	60	isocratic
42 - 50	40 → 72	60 → 28	linear gradient

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Comment
50 - 60	72	28	re-equilibration

— as detector a spectrophotometer set at 210 nm.

Equilibrate the column with the mobile phases in the initial gradient ratio for at least 15 min. Inject 50 µL of each solution.

In the chromatograms obtained, interferon alfa-2 elutes at a retention time of about 20 min. In the chromatogram obtained with the reference solution a peak related to oxidised interferon appears at a relative retention of about 0.9 with reference to the principal peak. The test is not valid unless the resolution between the peaks due to oxidised interferon and interferon is at least 1.0. Consider only the peaks whose relative retention is 0.7 to 1.4 with reference to the principal peak. In the chromatogram obtained with the test solution, the area of any peak, apart from the principal peak, is not greater than 3.0 per cent of the total area of all of the peaks. The sum of the areas of any peaks other than the principal peak is not greater than 5.0 per cent of the total area of all of the peaks.

Bacterial endotoxins (*2.6.14*)

Less than 100 IU in the volume that contains 1.0 mg of protein.

ASSAY

Protein

Test solution Dilute the preparation to be examined with *water R* to obtain a concentration of about 0.5 mg/mL of interferon alfa-2.

Reference solutions Prepare a stock solution of 0.5 mg/mL of *bovine albumin R*. Prepare 8 dilutions of the stock solution containing between 3 µg/mL and 30 µg/mL of *bovine albumin R*.

Prepare 30-fold and 50-fold dilutions of the test solution. Add 1.25 mL of a mixture prepared the same day by combining 2.0 mL of a 20 g/L solution of *copper sulfate pentahydrate R* in *water R*, 2.0 mL of a 40 g/L solution of *sodium tartrate R* in *water R* and 96.0 mL of a 40 g/L solution of *sodium carbonate R* in *0.2 M sodium hydroxide* to test-tubes containing 1.5 mL of *water R* (blank), 1.5 mL of the different dilutions of the test solution or 1.5 mL of the reference solutions. Mix after each addition. After approximately 10 min, add to each test-tube 0.25 mL of a mixture of equal volumes of *water R* and *phosphomolybdotungstic reagent R*. Mix after each addition. After approximately 30 min, measure the absorbance (*2.2.25*) of each solution at 750 nm using the blank as the compensation liquid. Draw a calibration curve from the absorbances of the 8 reference solutions and the corresponding protein contents and read from the curve the content of protein in the test solution.

Potency

The potency of interferon alfa-2 is estimated by comparing its effect to protect cells against a viral cytopathic effect with the same effect of the appropriate International Standard of human recombinant interferon alfa-2 or of a reference preparation calibrated in International Units.

The International Unit is the activity contained in a stated amount of the appropriate International Standard. The equivalence in International Units of the International Standard is stated by the World Health Organization.

Carry out the assay by a suitable method, based on the following design.

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Use, in standard culture conditions, an established cell line sensitive to the cytopathic effect of a suitable virus (a human diploid fibroblast cell line, free of microbial contamination, responsive to interferon and sensitive to encephalomyocarditis virus, is suitable).

The following cell cultures and virus have been shown to be suitable: MDBK cells (ATCC No. CCL22), or Mouse L cells (NCTC clone 929; ATCC No. CCL 1) as the cell culture and vesicular stomatitis virus VSV, Indiana strain (ATCC No. VR-158) as the infective agent; or A-549 cells (ATCC No. CCL-185) responsive to interferon as the cell culture, and encephalomyocarditis virus (ATCC No. VR-129B) as the infective agent.

Incubate in at least 4 series, cells with 3 or more different concentrations of the preparation to be examined and the reference preparation in a microplate and include in each series appropriate controls of untreated cells. Choose the concentrations of the preparations such that the lowest concentration produces some protection and the largest concentration produces less than maximal protection against the viral cytopathic effect. Add at a suitable time the cytopathic virus to all wells with the exception of a sufficient number of wells in all series, which are left with uninfected control cells. Determine the cytopathic effect of virus quantitatively with a suitable method. Calculate the potency of the preparation to be examined by the usual statistical methods for a parallel line assay.

The estimated potency is not less than 80 per cent and not more than 125 per cent of the stated potency. The confidence limits of the estimated potency (P = 0.95) are not less than 64 per cent and not more than 156 per cent of the stated potency.

STORAGE

Store in an airtight container, protected from light, at or below -20 °C.

LABELLING

The label states:

— the type of interferon (alfa-2a or alfa-2b),

— the type of production.

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Interferon Alfa-2a Injection

General Notices

Action and use

Cytokine.

DEFINITION

Interferon Alfa-2a Injection is a dilution of Interferon Alfa-2a Concentrated Solution in a suitable liquid. It is supplied as a ready-to-use solution.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Potency

The estimated potency is not less than 80% and not more than 125% of the stated potency.

CHARACTERISTICS

A clear, colourless or slightly yellowish solution virtually free from particles.

IDENTIFICATION

A. It gives the appropriate response when examined using the conditions under the Assay.

B. In the test for Related proteins, the retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that of the principal peak in the chromatogram obtained with solution (2).

C. In the test for Impurities of molecular weights differing from that of Interferon Alfa-2a, the principal band in the gel obtained with solution (1) corresponds to that in the gel obtained with solution (3).

TESTS

Acidity

pH 4.7 to 5.3, Appendix V L.

Impurities of molecular weights differing from that of Interferon Alfa-2a

Carry out the method for *polyacrylamide gel electrophoresis*, Appendix III F, under reducing and non-reducing conditions, using slab gels 1.0 mm thick and 14% *acrylamide* as the resolving gel.

For the test under non-reducing conditions, the sample buffer consists of equal volumes of *water* and *SDS PAGE sample buffer (concentrated)*. For the test under reducing conditions, the sample buffer consists of equal volumes of *water* and *SDS PAGE sample buffer*

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solution for reducing conditions (concentrated) containing *2-mercaptoethanol* as the reducing agent.

For solution (1) dilute, if necessary, the injection being examined in sample buffer to a concentration of 5.5 MIU of Interferon Alfa-2a per mL. For solution (2) dilute 0.20 mL of solution (1) to 1 mL with sample buffer. For solution (3) prepare a 25 µg per mL solution of the *interferon alfa-2a EPCRS* in sample buffer. For solution (4) dilute 0.2 mL of solution (3) to 1 mL with sample buffer. For solution (5) dilute 0.2 mL of solution (4) to 1 mL with sample buffer. For solution (6) dilute 0.2 mL of solution (5) to 1 mL with sample buffer. For solution (7) dilute 0.4 mL of solution (6) to 1 mL with sample buffer. Solution (8) is a solution of molecular weight markers suitable for calibrating SDS-polyacrylamide gels in the range of 15 kDa to 67 kDa.

Place solutions (1) to (8), contained in covered test-tubes, on a water-bath for 2 minutes prior to application. Apply 10 µL of solution (8) and 50 µL of each of the other solutions to the stacking gel wells. Perform the electrophoresis under the conditions recommended by the manufacturer of the equipment. Proteins in the gel are visualised by silver staining.

The test is not valid unless:

there is compliance with the validation criteria for solution (8);

a band is seen in the electrophoretogram obtained with solution (7);

a gradation of intensity of staining is seen in the electrophoretograms obtained, respectively, with solutions (1) and (2) and with solutions (3) to (7).

The electrophoretogram obtained with solution (1) under reducing conditions may show, in addition to the principal band, less intense bands with molecular weights lower than the principal band. No such band is more intense than the principal band in the electrophoretogram obtained with solution (6) (1%) and not more than three such bands are more intense than the principal band in the electrophoretogram obtained with solution (7) (0.4%).

The electrophoretogram obtained with solution (1) under non-reducing conditions may show, in addition to the principal band, less intense bands with molecular weights higher than the principal band. No such band is more intense than the principal band in the electrophoretogram obtained with solution (6) (1%) and not more than three such bands are more intense than the principal band in the electrophoretogram obtained with solution (7) (0.4%).

Related proteins

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions and the *normalisation procedure*. Store the solutions for not longer than 24 hours at a temperature of 2° to 8°.

(1) Dilute the injection, if necessary, with *water* to give a solution containing 5.5 MIU of Interferon Alfa-2a per mL.
(2) Add a suitable volume of 0.25% w/w *hydrogen peroxide solution* to a volume of the solution (1) to give a final hydrogen peroxide concentration of 0.005% w/w and allow to stand at room temperature for 1 hour or for the length of time that will generate about 5% oxidised interferon. Add 12.5 mg of *L-methionine* per mL of solution. Allow to stand at room temperature for 1 hour.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Bakerbond C18 is suitable).

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(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 210 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

Mobile phase A 0.2 volumes of *trifluoroacetic acid*, 30 volumes of *acetonitrile* and 70 volumes of *water*.

Mobile phase B 0.2 volumes of *trifluoroacetic acid*, 20 volumes of *water* and 80 volumes of *acetonitrile*.

Equilibrate the column with the mobile phases in the initial gradient ratio for at least 15 minutes.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-1	72	28	isocratic
1-5	72→67	28→33	linear gradient
5-20	67→63	33→37	linear gradient
20-30	63→57	37→43	linear gradient
30-40	57→40	43→60	linear gradient
40-42	40	60	isocratic
42-50	40→72	60→28	linear gradient
50-60	72	28	re-equilibration

When the chromatograms are recorded using the prescribed conditions the retention time of the peak due to interferon alfa-2a is about 20 minutes. The relative retention times with reference to interferon alfa-2a are: impurity A (oxidised interferon alfa-2a), about 0.7; impurity B (*N*-acetyl interferon), about 1.1; impurity C (interferon with broken disulfide bridge), about 1.3.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution factor* between the peaks corresponding to oxidised interferon (impurity A) and interferon is at least 1.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than 5.0%;

the area of any peak corresponding to impurity B is not greater than 3.0%;

the sum of the areas of any other *secondary peaks* is not greater than 5.0%;

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the sum of the areas of any *secondary peaks* is not greater than 12.0%.

Disregard any peak with a retention time less than 0.7 times, or greater than 1.4 times, of that of the principal peak in the chromatogram obtained with solution (2).

Bacterial endotoxins

Carry out the *test for Bacterial endotoxins*, Appendix XIV C. The endotoxin limit is not more than 2 IU in a volume containing 1 MIU of Interferon Alfa-2a.

ASSAY

The potency of interferon alfa-2a is calculated by comparing its effect to protect cells against a viral cytopathic effect with the same effect of the appropriate International Standard of human recombinant interferon alfa-2a or of a reference preparation calibrated in International Units.

The International Unit is the activity contained in a stated amount of the appropriate International Standard. The equivalence in International Units of the International Standard is stated by the World Health Organization.

Carry out the assay by a suitable method, based on the following design.

Use, in standard culture conditions, an established cell line sensitive to the cytopathic effect of a suitable virus (a human diploid fibroblast cell line, free of microbial contamination, responsive to interferon and sensitive to encephalomyocarditis virus, is suitable).

The following cell cultures and virus have shown to be suitable: MDBK cells (ATCC No. CCL22), or Mouse L cells (NCTC clone 929; ATCC No. CCL 1) as the cell culture and vesicular stomatitis virus VSV, Indiana strain (ATCC No. VR-158) as the infective agent; or A-549 cells (ATCC No. CCL-185) responsive to interferon as the cell culture, and encephalomyocarditis virus (ATCC No. VR-129B) as the infective agent.

Incubate in at least four series, cells with three or more different concentrations of the preparation being examined and the reference preparation in a microtitre plate and include in each series appropriate controls of untreated cells. Choose the concentrations of the preparations such that the lowest concentration produces some protection and the largest concentration produces less than maximal protection against the viral cytopathic effect. Add at a suitable time the cytopathic virus to all wells with the exception of a sufficient number of wells in all series, which are left with uninfected control cells. Determine the cytopathic effect of virus quantitatively with a suitable method. Calculate the potency of the preparation being examined by the standard statistical methods for a parallel line assay.

The fiducial limits of error are not less than 64% and not more than 156% of the stated potency.

STORAGE

Interferon Alfa-2a Injection should be stored at a temperature of 2° to 8°. It should not be allowed to freeze.

LABELLING

The label of the sealed container states the number of MIU (Million Units) contained in it.

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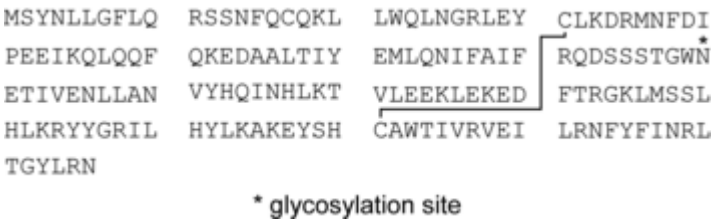
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This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Interferon Beta-1a Concentrated Solution

General Notices

(Ph. Eur. monograph 1639)



$C_{908}H_{1406}N_{246}O_{252}S_7$ M_r approx. 22 500

Action and use

Cytokine.

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DEFINITION

Solution of a glycosylated protein having the same amino acid sequence and disulfide bridge and a similar glycosylation pattern as interferon beta produced by human diploid fibroblasts in response to viral infections and various other inducers. It exerts antiviral, antiproliferative and immunomodulatory activity.

Content

Minimum 0.20 mg of protein per millilitre.

Potency

Minimum 1.5×10^8 IU per milligram of protein.

It may contain buffer salts.

PRODUCTION

Interferon beta-1a concentrated solution is produced by a method based on recombinant DNA (rDNA) technology, using mammalian cells in culture.

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Prior to release, the following tests are carried out on each batch of interferon beta-1a concentrated solution, unless exemption has been granted by the competent authority.

Host-cell-derived proteins

The limit is approved by the competent authority.

Host-cell or vector-derived DNA

The limit is approved by the competent authority.

N-terminal truncated forms

Examination for specific *N*-terminal truncated forms should be performed using a suitable technique such as *N*-terminal sequence determination. The limits are approved by the competent authority.

Dimer and related substances of higher molecular mass

Not more than the amount approved by the competent authority, using an appropriate validated liquid chromatography method.

CHARACTERS

Appearance

Clear or slightly opalescent, colourless or slightly yellowish liquid.

IDENTIFICATION

A. It shows the expected biological activity (see Assay).

B. Isoform distribution. Mass spectrometry (*2.2.43*).

Introduction of the sample Direct inflow of a desalted preparation to be examined or liquid chromatography-mass spectrometry combination.

Mode of ionisation Electrospray.

Signal acquisition Complete spectrum mode from 1100 to 2400.

Calibration Use myoglobin in the *m/z* range of 600-2400; set the instrument within validated instrumental settings and analyse the sample; the deviation of the measured mass does not exceed 0.02 per cent of the reported mass.

Interpretation of results A typical spectrum consists of 6 major glycoforms (A to F), which differ in their degree of sialylation and/or antennarity type as shown in Table 1639.-1.

Table 1639.-1.

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MS peak	Glycoform*	Expected M_r	Sialylation level
A	2A2S1F	22 375	Disialylated
B	2A1S1F	22 084	Monosialylated
C	3A2S1F and/or 2A2S1F + 1 HexNacHex repeat	22 739	Disialylated
D	3A3S1F	23 031	Trisialylated
E	4A3S1F and/or 3A3S1F + 1 HexNacHex repeat	23 400	Trisialylated
F	2A0S1F	21 793	Non-sialylated

* 2A = biantennary complex type oligosaccharide; 3A = triantennary complex type oligosaccharide; 4A = tetraantennary complex type oligosaccharide; 0S = non-sialylated; 1S = monosialylated; 2S = disialylated; 3S = trisialylated; 1F = fucosylated.

Results The mass spectrum obtained with the preparation to be examined corresponds, with respect to the 6 major peaks, to the mass spectrum obtained with *interferon beta-1a CRS*.

C. Peptide mapping (*2.2.55*) and liquid chromatography (*2.2.29*).

Test solution Add 5 µL of a 242 g/L solution of *tris(hydroxymethyl)aminomethane R* and a volume of the preparation to be examined containing 20 µg of protein to a polypropylene tube of 0.5 mL capacity. Add 4 µL of a 1 mg/mL solution of *endoprotease LysC R* in *0.05 M tris-hydrochloride buffer solution pH 9.0 R*. Mix gently and incubate at 30 °C for 2 h. Add 10 µL of a 15.4 g/L solution of *dithiothreitol R*. Dilute the solution with the same volume of a 573 g/L solution of *guanidine hydrochloride R*. Incubate at 4 °C for 3-4 h.

Reference solution Prepare at the same time and in the same manner as for the test solution but using *interferon beta-1a CRS* instead of the preparation to be examined.

Precolumn:

— *size*: *l* = 0.02 m, Ø = 2.1 mm;

— *stationary phase*: spherical *octadecylsilyl silica gel for chromatography R* (5 µm) with a pore size of 30 nm.

Column:

— *size*: *l* = 0.25 m, Ø = 2.1 mm;

— *stationary phase*: spherical *octadecylsilyl silica gel for chromatography R* (5 µm) with a pore size of 30 nm.

Mobile phase:

— *mobile phase A*: dilute 1 mL of *trifluoroacetic acid R* to 1000 mL with *water for chromatography R*;

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— *mobile phase B*: dilute 1 mL of *trifluoroacetic acid R* in 700 mL of *acetonitrile R1*, then dilute to 1000 mL with *water for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 30	100 → 64	0 → 36
30 - 45	64 → 55	36 → 45
45 - 50	55 → 40	45 → 60
50 - 70	40 → 0	60 → 100
70 - 83	0	100
83 - 85	0 → 100	100 → 0

Flow rate 0.2 mL/min.

Detection Spectrophotometer at 214 nm.

Injection Volume that contains 20 µg of digested protein.

System suitability The chromatogram obtained with the reference solution is qualitatively similar to the chromatogram of interferon beta-1a digest supplied with *interferon beta-1a CRS*.

Results The profile of the chromatogram obtained with the test solution corresponds to that of the chromatogram obtained with the reference solution.

TESTS

Impurities of molecular masses differing from that of interferon beta-1a

Polyacrylamide gel electrophoresis (*2.2.31*) under reducing conditions.

Resolving gel 12 per cent acrylamide.

Concentrated sample buffer *concentrated SDS-PAGE sample buffer for reducing conditions R* containing 2-mercaptoethanol as the reducing agent.

Sample buffer Mixture of equal volumes of *concentrated SDS-PAGE sample buffer for reducing conditions R* and *water R*.

Test solution (a) Concentrate the preparation to be examined using a suitable method to obtain a protein concentration of 1.5 mg/mL.

Test solution (b) Mixture of equal volumes of test solution (a) and the concentrated sample buffer.

Test solution (c) Dilute test solution (a) to obtain a protein concentration of 0.6 mg/mL. Mix equal volumes of this solution and the concentrated sample buffer.

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Test solution (d) Mix 8 µL of test solution (c) and 40 µL of the sample buffer.

Test solution (e) Mix 15 µL of test solution (d) and 35 µL of the sample buffer.

Test solution (f) Mix 18 µL of test solution (e) and 18 µL of the sample buffer.

Test solution (g) Mix 12 µL of test solution (f) and 12 µL of the sample buffer.

Reference solution Solution of relative molecular mass markers suitable for calibrating SDS-PAGE gels in the range of 15-67 kDa. Dissolve in the sample buffer.

Sample treatment Boil for 3 min.

Application 20 µL of test solutions (b) to (g) and the reference solution.

Detection Coomassie staining, carried out as follows: immerse the gel in *Coomassie staining solution R1* at 33-37 °C for 90 min with gentle shaking, then remove the staining solution; destain the gel with a large excess of a mixture of 1 volume of *glacial acetic acid R*, 1 volume of *2-propanol R* and 8 volumes of *water R*.

Apparent molecular masses Interferon beta-1a = about 23 000; underglycosylated interferon beta-1a = about 21 000; deglycosylated interferon beta-1a = about 20 000; interferon beta-1a dimer = about 46 000.

Identification of bands Use the electropherogram provided with *interferon beta-1a CRS*.

System suitability:

— the validation criteria are met (*2.2.31*);

— a band is seen in the electropherogram obtained with test solution (g);

— a gradation of intensity of staining is seen in the electropherograms obtained with test solutions (b) to (g).

Limits:

— in the electropherogram obtained with test solution (c), the band corresponding to underglycosylated interferon beta-1a is not more intense than the principal band in the electropherogram obtained with test solution (e) (5 per cent);

— in the electropherogram obtained with test solution (b), the band corresponding to deglycosylated interferon beta-1a is not more intense than the principal band in the electropherogram obtained with test solution (e) (2 per cent); any other band corresponding to an impurity of a molecular mass lower than that of interferon beta-1a, apart from the band corresponding to underglycosylated interferon beta-1a is not more intense than the principal band in the electropherogram obtained with test solution (f) (1 per cent).

Oxidised interferon beta-1a

Maximum 6 per cent.

Use the chromatogram obtained with the test solution in identification C. Locate the peaks due to the peptide fragment comprising amino acids 34-45 and its oxidised form using the chromatogram of oxidised interferon beta-1a digest supplied with *interferon beta-1a CRS*.

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Calculate the percentage of oxidation of interferon beta-1a using the following expression:

$$\frac{A_{34\text{-}45ox}}{A_{34\text{-}45}+A_{34\text{-}45ox}} \times 100$$

$A_{34\text{-}45ox}$ = area of the peak due to the oxidised peptide fragment 34-45;

$A_{34\text{-}45}$ = area of the peak due to the peptide fragment 34-45.

Bacterial endotoxins (2.6.14)

Less than 0.7 IU in the volume that contains 1×10^6 IU of interferon beta-1a, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for removal of bacterial endotoxins.

ASSAY

Protein

Liquid chromatography (2.2.29). Prepare 3 independent dilutions for each solution.

Test solution Dilute the preparation to be examined to obtain a concentration of 100 µg/mL.

Reference solution Dissolve the contents of a vial of interferon beta-1a CRS to obtain a concentration of 100 µg/mL.

Precolumn:

— *size*: *l* = 0.02 m, Ø = 2.1 mm;

— *stationary phase*: end-capped butylsilyl silica gel for chromatography R (5 µm) with a pore size of 30 nm.

Column:

— *size*: *l* = 0.25 m, Ø = 2.1 mm;

— *stationary phase*: end-capped butylsilyl silica gel for chromatography R (5 µm) with a pore size of 30 nm.

Mobile phase:

— *mobile phase A*: 0.1 per cent *V/V* solution of trifluoroacetic acid R;

— *mobile phase B*: to 300 mL of water for chromatography R, add 1 mL of trifluoroacetic acid R and dilute to 1000 mL with acetonitrile R1;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 20	100 → 0	0 → 100
20 - 25	0	100

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
25 - 26	0 → 100	100 → 0
26 - 40	100	0

Flow rate 0.2 mL/min.

Detection Spectrophotometer at 214 nm.

Injection 50 µL.

Retention time Interferon beta-1a = about 20 min.

System suitability Reference solution:

— *symmetry factor*: 0.8 to 2.0 for the peak due to interferon beta-1a;

— *repeatability*: maximum relative standard deviation of 3.0 per cent between the peak areas obtained after injection of the 3 independent dilutions.

Calculate the content of interferon beta-1a ($C_{908}H_{1406}N_{246}O_{252}S_7$) taking into account the assigned content of $C_{908}H_{1406}N_{246}O_{252}S_7$ in *interferon beta-1a CRS*.

Potency

The potency of interferon beta-1a is estimated by comparing its ability to protect cells against a viral cytopathic effect with the same ability of the appropriate International Standard of human recombinant interferon beta-1a or of a reference preparation calibrated in International Units.

The International Unit is the activity contained in a stated amount of the appropriate International Standard. The equivalence in International Units of the International Standard is stated by the World Health Organization.

Carry out the assay using a suitable method, based on the following design.

Use, in standard culture conditions, an established cell line sensitive to the cytopathic effect of a suitable virus and responsive to interferon. The cell cultures and viruses that have been shown to be suitable include the following:

— WISH cells (ATCC No. CCL-25) and vesicular stomatitis virus VSV, Indiana strain (ATCC No. VR-158) as infective agent;

— A549 cells (ATCC No. CCL-185) and encephalomyocarditis virus EMC (ATCC No. VR-129B) as infective agent.

Incubate in at least 4 series, cells with 3 or more different concentrations of the preparation to be examined and the reference preparation in a microplate and include in each series appropriate controls of untreated cells. Choose the concentrations of the preparations such that the lowest concentration produces some protection and the largest concentration produces less than maximal protection against the viral cytopathic effect. Add at a suitable time the cytopathic virus to all wells with the exception of a sufficient number of wells in all series, which

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are left with uninfected control cells. Determine the cytopathic effect of the virus quantitatively with a suitable method. Calculate the potency of the preparation to be examined by the usual statistical methods (for example, 5.3).

The estimated potency is not less than 80 per cent and not more than 125 per cent of the stated potency. The confidence limits (P = 0.95) are not less than 64 per cent and not more than 156 per cent of the estimated potency.

STORAGE

In an airtight container, protected from light, at a temperature below -70 °C. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

LABELLING

The label states:

— the interferon beta-1a content, in milligrams per millilitre;

— the antiviral activity, in International Units per millilitre;

— where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

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Interferon Beta-1a Injection

General Notices

Action and use

Cytokine.

DEFINITION

Interferon Beta-1a Injection is a sterile solution of Interferon Beta-1a Concentrated Solution in a suitable liquid. It is supplied as a ready-to-use solution.

PRODUCTION

Glycoforms

Interferon beta-1a Injection is manufactured and tested using methods which produce a product containing not less than 50% of the main active di-sialylated form. The method of analysis used should be capable of resolving, identifying and quantifying all of the main glycoforms present, with specific limits for each form being set by the competent regulatory authority.

Acidity

The pH of the injection is controlled, Appendix V L, so as to ensure the stability and quality of the product throughout its shelf-life. The limits are approved by the competent authority.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of interferon beta-1a, $C_{908}H_{1406}N_{246}O_{252}S_7$

For products containing 8.8 µg or less of interferon beta-1a

80.0 to 120.0% of the stated amount.

For products containing more than 8.8 µg of interferon beta-1a

90.0 to 110.0% of the stated amount.

Potency

The estimated potency is not less than 80% and not more than 125% of the stated potency.

CHARACTERISTICS

Clear or slightly opalescent, colourless or slightly yellowish liquid.

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IDENTIFICATION

A. It gives the appropriate response when examined using the conditions under the Assay for potency.

B. Isoform distribution. Carry out the method for *mass spectrometry*, Appendix II G.

Introduction of the sample Direct inflow of a desalted preparation to be examined or liquid chromatography-mass spectrometry combination.

Mode of ionisation Electrospray Positive.

Signal acquisition Complete spectrum mode from m/z 1100 to 2400.

Calibration Use myoglobin in the *m/z* range of 600-2400; set the instrument within validated instrumental settings and analyse the sample; the deviation of the measured mass does not exceed 0.02 per cent of the reported mass.

Interpretation of results A typical deconvoluted spectrum consists of 6 major glycoforms (A to F), which differ in their degree of sialylation and/or antennarity type as shown in the table below.

MS Peak	Glycoform(1)	Expected M_r	Sialylation level
A	2A2S1F	22,375	Disialylated
B	2A1S1F	22,084	Monosialylated
C	3A2S1F and/or 2A2S1F + 1 HexNacHex repeat	22,739	Disialylated
D	3A3S1F	23,031	Trisialylated
E	4A3S1F and/or 3A3S1F + 1 HexNacHex repeat	23,400	Trisialylated
F	2A0S1F	21,793	Non-sialylated

(1) 2A = biantennary complex type oligosaccharide; 3A = triantennary complex type oligosaccharide; 4A = tetraantennary complex type oligosaccharide; 0S = non-sialylated; 1S = monosialylated; 2S = disialylated; 3S = trisialylated; 1F = fucosylated.

Results The deconvoluted mass spectrum obtained with the preparation to be examined corresponds, with respect to the 6 major peaks, to the mass spectrum obtained with *interferon beta-1a EPCRS*.

C. Carry out the method for *peptide mapping*, Appendix III K, and *liquid chromatography*, Appendix III D, using the following solutions.

(1) If necessary, concentrate the injection by an appropriate procedure, such as membrane ultrafiltration, to a suitable concentration. Add 5 µL of a 24.2% w/v solution of *tris(hydroxymethyl)methylamine* and a volume of the concentrated injection containing 20 µg of protein to a polypropylene tube of 0.5-mL capacity. Add 4 µL of a 0.1% w/v solution of *endoprotease LysC* in *0.05M tris-hydrochloride buffer solution pH 9.0*. Mix gently and incubate at 30° for 2 h. Add 10 µL of a 1.54% w/v solution of *dithiothreitol*. Dilute the solution with the same volume of a 57.3% w/v solution of *guanidine hydrochloride*. Incubate at 4° for 3 to 4 hours.

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(2) Prepare at the same time and in the same manner as for solution (1) but using *interferon beta-1a EPCRS* instead of the injection being examined.

(3) 2.0 w/v % of*Interferon beta-1a oxidised peptide BPCRS* in *water* (for use in the Oxidised forms test).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 2.1 mm) and a stainless steel pre-column (2 cm × 2.1 mm) both packed with spherical *octadecylsilyl silica gel for chromatography* (5 µm) with a pore size of 30 nm (Vydac 218TP52 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 0.2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 214 nm.

(f) Inject a volume of each of solution (1) and (2) containing 20 µg of digested protein. For use in the test for Oxidised forms, inject 70 µl of solution (3).

MOBILE PHASE

Mobile phase A 0.1% v/v of *trifluoroacetic acid*

Mobile phase B Mix 1 volume of *trifluoroacetic acid* with 700 volumes of *acetonitrile R1* and dilute to 1000 volumes with *water*

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-30	100→64	0→36	linear gradient
30-45	64→55	36→45	linear gradient
45-50	55→40	45→60	linear gradient
50-70	40→0	60→100	linear gradient
70-83	0	100	isocratic
83-85	0→100	100→0	linear gradient
85-100	100	0	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (2) is qualitatively similar to the chromatogram of interferon beta-1a digest supplied with *interferon beta-1a EPCRS*.

CONFIRMATION

The profile of the chromatogram obtained with solution (1) resembles that of the chromatogram obtained with solution (2).

TESTS

Impurities of molecular masses differing from that of interferon beta-1a

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Carry out the method for *polyacrylamide gel electrophoresis*, Appendix III F, under reducing conditions, using 12% *acrylamide* as the resolving gel.

The concentrated sample buffer consists of *concentrated SDS-PAGE sample buffer for reducing conditions* containing 2-mercaptoethanol as the reducing agent. The sample buffer consists of equal volumes of *concentrated SDS-PAGE sample buffer for reducing conditions* and *water*.

For solution (1) concentrate the injection using a suitable method to obtain a protein concentration of 0.15% w/v. For solution (2) mix equal volumes of solution (1) and the concentrated sample buffer. For solution (3) dilute solution (1) to obtain a protein concentration of 0.06% w/v and mix equal volumes of this solution and the concentrated sample buffer. For solution (4) mix 8 µL of solution (3) and 40 µL of the sample buffer. For solution (5) mix 15 µL of solution (4) and 35 µL of the sample buffer. For solution (6) mix 18 µL of solution (5) and 18 µL of the sample buffer. For solution (7) mix 12 µL of solution (6) and 12 µL of the sample buffer. Solution (8) is a solution of relative molecular weight markers suitable for calibrating SDS-PAGE gels in the range of 15 to 67 kDa dissolved in the sample buffer.

Boil solutions (2) to (8) for 3 minutes and apply 20 µL of each solution to the gel. Perform the electrophoresis under the conditions recommended by the manufacturer of the equipment. Proteins in the gel are visualised by Coomassie staining, carried out as follows: immerse the gel in *Coomassie staining solution R1* at 33° to 37° for 90 minutes with gentle shaking, then remove the staining solution; destain the gel with a large excess of a mixture of 1 volume of *glacial acetic acid*, 1 volume of *propan-2-ol* and 8 volumes of *water*.

The apparent molecular weights of: interferon beta-1a, about 23 000; underglycosylated interferon beta-1a, about 21 000; deglycosylated interferon beta-1a, about 20 000; interferon beta-1a dimer, about 46 000. Use the electrophoretogram provided with *interferon beta-1a EPCRS* to identify the bands.

SYSTEM SUITABILITY

The test is not valid unless:

the validation criteria in Appendix III F are met;

a band is seen in the electrophoretogram obtained with solution (7);

a gradation of intensity of staining is seen in the electrophoretograms obtained with solutions (2) to (7).

LIMITS

The electrophoretogram obtained with solution (3) may show, in addition to the principal band, less intense bands with molecular weights lower than the principal band. The band corresponding to underglycosylated interferon beta-1a is not more intense than the principal band in the electrophoretogram obtained with solution (5) (5 per cent).

The electrophoretogram obtained with solution (2) may show, in addition to the principal band, less intense bands with molecular weights lower than the principal band. The band corresponding to deglycosylated interferon beta-1a is not more intense than the principal band in the electrophoretogram obtained with solution (5) (2 per cent); any other band corresponding to an impurity of a molecular weight lower than that of interferon beta-1a, apart from the band corresponding to underglycosylated interferon beta-1a is not more intense than the principal band in the electrophoretogram obtained with solution (6) (1 per cent).

Oxidised forms

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Maximum 9.0% of fragment 34-45.

Use the chromatogram obtained with solution (1) in identification C. Locate the peaks due to the peptide fragment comprising amino acids 34 to 45 and its oxidised form using the chromatogram obtained with solution (3) in identification C.

Calculate the percentage of oxidation of interferon beta-1a using the following expression:

$$\frac{A_{34\text{-}45ox}}{A_{34\text{-}45}}$$

$A_{34\text{-}45ox}$	=	area of the peak corresponding to the oxidised peptide fragment 34-45;
$A_{34\text{-}45}$	=	area of the peak corresponding to the peptide fragment 34-45.

Dimers and related substances of higher molecular weight

Use method A or method B. The choice of method A or method B should be based on compliance with the system suitability requirements.

A. Carry out the method for *size-exclusion chromatography*, Appendix III C, using the following solutions. Store the solutions at a temperature of 5°.

(1) Inject a quantity of injection containing approximately 8.8 µg of interferon beta-1a.
(2) Inject a quantity of solution containing approximately 25 µg *interferon beta-1 EPCRS* that, following a number of freeze-thaw cycles (usually 3) at -20°, has a percentage content of aggregation products (dimers and aggregates) of at least 3%.
(3) Inject 100 µL of a buffer prepared as follows. Transfer 450 mL, of purified water to a 500 mL, graduated cylinder. With the magnetic stirrer on, mix 286 µL of *glacial acetic acid* with 450 mL of *water*, adjust the pH to 3.8 with a 50% w/v solution of *sodium hydroxide* in *water* and dilute to 500 mL with *water* (blank solution).

CHROMATOGRAPHIC CONDITIONS

(a) Use a column (30 cm × 7.8 mm) packed with appropriate porous silica beads (5 µm) with a fractionation range for proteins of approximately 5,000 to 150,000 (Tosoh Biosciences TSK G2000 SW_{XL} is suitable). New columns should be conditioned prior to first use and previously conditioned columns saturated prior to the test with saturation solution. To prepare the saturation solution dilute Interferon Beta-1a Concentrated Solution that, following freeze-thaw cycles, contains a percentage of degradation products (dimers and aggregates) of at least 20%, to contain 0.03% w/v of interferon beta-1a using a buffer prepared as follows. Mix 1.43 mL of *glacial acetic acid* to 400 mL with *water*, adjust the pH to 3.8 with 50% w/v solution of *sodium hydroxide* in *water* and dilute to 500 mL with *water*.
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 0.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 215 nm.
(f) Inject the volumes prescribed above for each solution.

MOBILE PHASE

Mix 2.86 mL of *glacial acetic acid* and 2.92 g of *sodium chloride* with 900 mL of *water*, adjust the pH to 3.8 with 50% w/v solution of *sodium hydroxide* in *water* and dilute to 1 L with *water*.

SYSTEM SUITABILITY

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Inject solution (2) two times. The test is not valid unless the relative standard deviation of the percentage content for the aggregate and dimer peaks is less than 5%.

LIMITS

For products containing 8.8 µg or less of interferon beta-1a

In the chromatogram obtained with solution (1) the sum of the areas of any peaks eluting before the principal peak is not greater than 2% by normalisation.

For products containing more than 8.8 µg of interferon beta-1a

In the chromatogram obtained with solution (1) the sum of the areas of any peaks eluting before the principal peak is not greater than 1% by normalisation.

B. Carry out the method for *size-exclusion chromatography*, Appendix III C, using the following solutions. Store the solutions at a temperature of 2° to 8°.

(1) A quantity of the injection.
(2) 0.05% w/v of *bovine albumin* and 0.02% w/v of *cytochrome C* in the mobile phase.
(3) Mobile phase (blank solution)

CHROMATOGRAPHIC CONDITIONS

(a) Use a column (30 cm × 7.8 mm) packed with appropriate porous silica beads (5 µm) with a fractionation range for proteins of approximately 5,000 to 150,000 (Tosoh Biosciences TSK G2000 SW_{XL} is suitable) fitted with a guard column (4 cm × 6 mm) packed with the same material.
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 280 nm.
(f) Inject 40 µL of solution (2), 100 µL of solution (3) and a quantity of solution (1) containing 25 µg of interferon beta-1a.

MOBILE PHASE

To 800 mL of *water* add 2.77 g *sodium dihydrogen orthophosphate monohydrate*, 21.9 g *disodium hydrogen orthophosphate heptahydrate* and 12.0 g *sodium chloride*, then dilute with *water* to 1000 mL. Adjust to pH 7.2.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the peaks due to bovine albumin and cytochrome C is at least 4.0.

The test is not valid unless, in the chromatogram obtained with solution (3), no peaks are observed between the retention time of the peak due to bovine albumin and the retention time of the peak due to cytochrome C. Initial blank injections may contain peaks as the solution is used to condition the column.

LIMITS

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In the chromatogram obtained with solution (1) the sum of the areas of any peaks eluting before the principal peak is not greater than 2% by *normalisation*.

ASSAY

For protein

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Prepare 3 independent dilutions for each solution.

(1) Inject a quantity of the injection containing 5 µg of interferon beta-1a.

(2) Dilute the contents of a vial of *interferon beta-1a EPCRS* to obtain a solution containing 0.01% w/v of interferon beta-1a and inject a quantity containing 5 µg of interferon beta-1a.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 2.1 mm) and a stainless steel pre-column (2 cm × 2.1 mm) both packed with *butylsilyl silica gel for chromatography* (5 µm) with a pore size of 30 nm (Vydac 214TP52 and Vydac 214GD52 are suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 0.2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 214 nm.

(f) Inject the volumes prescribed above for each solution.

MOBILE PHASE

Mobile phase A 0.1% v/v of *trifluoroacetic acid*.

Mobile phase B Dilute 1 volume of *trifluoroacetic acid* and 300 volumes of *water* to 1000 volumes with *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-20	100→0	0→100	linear gradient
20-25	0	100	isocratic
25-26	0→100	100→0	linear gradient
26-40	100	0	re-equilibration

SYSTEM SUITABILITY

Inject the three independent dilutions of solution (2). The Assay is not valid unless:

the relative standard deviation of the area of the principal peak is not more than 3.0%;

the *symmetry factor* of the peak due to interferon beta-1a is between 0.8 and 2.0.

DETERMINATION OF CONTENT

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Calculate the content of $C_{908}H_{1406}N_{246}O_{252}S_7$ in the injection from the chromatograms obtained and using the declared content of $C_{908}H_{1406}N_{246}O_{252}S_7$ in *interferon beta-1a EPCRS*.

For potency

The potency of interferon beta-1a is estimated by comparing its ability to protect cells against a viral cytopathic effect with the same ability of the appropriate International Standard of human recombinant interferon beta-1a or of a reference preparation calibrated in International Units.

The International Unit is the activity contained in a stated amount of the appropriate International Standard. The equivalence in International Units of the International Standard is stated by the World Health Organisation.

Carry out the assay using a suitable method, based on the following design.

Use, in standard culture conditions, an established cell line sensitive to the cytopathic effect of a suitable virus and responsive to interferon. The cell cultures and viruses that have been shown to be suitable include the following:

— WISH cells (ATCC No. CCL-25) and vesicular stomatitis virus VSV, Indiana strain (ATCC No. VR-158) as infective agent;

— A549 cells (ATCC No. CCL-185) and encephalomyocarditis virus EMC (ATCC No. VR-129B) as infective agent.

Incubate in at least 4 series, cells with 3 or more different concentrations of the preparation to be examined and the reference preparation in a microtitre plate and include in each series appropriate controls of untreated cells. Choose the concentrations of the preparations such that the lowest concentration produces some protection and the largest concentration produces less than maximal protection against the viral cytopathic effect. Add at a suitable time the cytopathic virus to all wells with the exception of a sufficient number of wells in all series, which are left with uninfected control cells. Determine the cytopathic effect of the virus quantitatively with a suitable method. Calculate the potency of the preparation to be examined by a suitable method (for example, Supplementary Chapter IV G).

The confidence limits (P = 0.95) are not less than 64 per cent and not more than 156 per cent of the estimated potency.

STORAGE

Interferon Beta-1a Injection should be protected from light and stored at a temperature of 2° to 8°. It should not be allowed to freeze.

LABELLING

The label of the sealed container states the micrograms per millilitre, and the number of MIU (Million International Units).

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Interferon Gamma-1b Concentrated Solution

General Notices

(Ph. Eur. monograph 1440)

$C_{734}H_{1166}N_{204}O_{216}S_5$ 16 465

Action and use

Cytokine.

Ph Eur

DEFINITION

Interferon gamma-1b concentrated solution is a solution of the *N*-terminal methionyl form of interferon gamma, a protein which is produced and secreted by human antigen-stimulated T lymphocytes in response to viral infections and various other inducers. It has specific immunomodulatory properties, such as potent phagocyte-activating effects. The protein consists of non-covalent dimers of two identical monomers. The formula of the monomer is as follows:

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                                                M
QDPYVKEAEN  LKKYFNAGHS  DVADNGTLFL  GILKNWKEES
DRKIMQSQIV  SFYFKLFKNF  KDDQSIQKSV  ETIKEDMNVK
FFNSNKKKRD  DFEKLTNYSV  TDLNVQRKAI  HELIQVMAEL
SPAAKTGKRK  RSQMLFRGR
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The potency of interferon gamma-1b is not less than 20×10^6 IU per milligram of protein. Interferon gamma-1b concentrated solution contains not less than 30×10^6 IU of interferon gamma-1b per millilitre.

PRODUCTION

Interferon gamma-1b concentrated solution is produced by a method based on recombinant DNA technology, using bacteria as host-cells. It is produced under conditions designed to minimise microbial contamination.

Interferon gamma-1b concentrated solution complies with the following additional requirements.

Host-cell derived proteins

The limit is approved by the competent authority.

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Host-cell- and vector-derived DNA

The limit is approved by the competent authority.

CHARACTERS

A clear, colourless or slightly yellowish liquid.

IDENTIFICATION

A. It shows the expected biological activity when tested as prescribed in the assay.

B. Examine the electropherograms obtained in the test for impurities of molecular masses differing from that of interferon gamma-1b. The principal bands in the electropherogram obtained with the test solution correspond in position to the principal bands in the electropherogram obtained with reference solution (a).

C. Examine by peptide mapping.

Solution A Prepare a solution containing 1.2 g/L of *tris(hydroxymethyl)aminomethane R*, 8.2 g/L of *anhydrous sodium acetate R*, 0.02 g/L of *calcium chloride R* and adjust to pH 8.3 with *dilute acetic acid R*. Add *polysorbate 20 R* to a concentration of 0.1 per cent *V/V*.

Test solution Desalt a volume of the preparation to be examined containing 1 mg of protein by a suitable procedure. For example, filter in a microcentrifuge tube and reconstitute with 500 µL of solution A. Add 10 µL of a freshly prepared 1 mg/mL solution of *trypsin for peptide mapping R* in *water R* and mix gently by inversion. Incubate at 30 °C to 37 °C for 24 h, add 100 µL of *phosphoric acid R* per millilitre of digested sample and mix by inversion.

Reference solution Dilute *interferon gamma-1b CRS* in *water R* to obtain a concentration of 1 mg/mL. Prepare as for the test solution, ensuring that all procedures are carried out simultaneously and under identical conditions.

Examine by liquid chromatography (*2.2.29*).

The chromatographic procedure may be carried out using:

— a stainless steel column, 0.15 m long and 4.6 mm in internal diameter packed with *octadecylsilyl silica gel for chromatography R* (10 µm),

— as mobile phase at a flow rate of 1.0 mL/min:

Mobile phase A (*0.05 M sodium phosphate buffer solution pH 3.3*). Solution I: dissolve 7.80 g of *sodium dihydrogen phosphate R* in *water R* and dilute to 1000.0 mL with the same solvent. Solution II: dilute 0.33 mL of *phosphoric acid R* to 100.0 mL with *water R*. Mix 920 mL of solution I and 80 mL of solution II. Adjust the pH if necessary,

Mobile phase B *Acetonitrile for chromatography R*, with the following elution conditions (if necessary, the gradient may be modified to improve the separation of the digest):

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 30	100 → 80	0 → 20

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
30 - 50	80 → 60	20 → 40
50 - 51	60 → 30	40 → 70
51 - 59	30	70

— as detector a spectrophotometer set at 214 nm,

maintaining the temperature of the column at 40 °C.

Equilibrate the column for at least 15 min at the initial elution composition. Carry out a blank run using the above-mentioned gradient.

Inject 100 µL of the test solution and 100 µL of the reference solution.

System suitability The chromatogram obtained with the reference solution is qualitatively similar to the chromatogram of interferon gamma-1b digest supplied with *interferon gamma-1b CRS*.

Results The profile of the chromatogram obtained with the test solution corresponds to that of the chromatogram obtained with the reference solution.

D. Examine by *N*-terminal sequence analysis.
Use an automated solid-phase sequencer, operated in accordance with the manufacturer's instructions.

Equilibrate by a suitable procedure the equivalent of 100 µg of interferon gamma-1b in a 10 g/L solution of *ammonium hydrogen carbonate R*, pH 9.0.

Identify the phenylthiohydantoin (PTH)-amino acids released at each sequencing cycle by reverse-phase liquid chromatography. The procedure may be carried out using the column and reagents recommended by the manufacturer of the sequencing equipment for the separation of PTH-amino acids.

The separation procedure is calibrated using:

— the mixture of PTH-amino acids provided by the manufacturer, with the gradient conditions adjusted as indicated to achieve optimum resolution of all amino acids,

— a sample from a blank sequencing cycle, obtained as recommended by the equipment manufacturer.

The first fifteen amino acids are:

Met-Gln-Asp-Pro-Tyr-Val-Lys-Glu-Ala-Glu-Asn-Leu-Lys-Lys-Tyr.

TESTS

Appearance

The preparation to be examined is clear (*2.2.1*) and not more intensely coloured than reference solution Y_7 (*2.2.2, Method II*).

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pH (*2.2.3*)

The pH of the preparation to be examined is 4.5 to 5.5.

Covalent dimers and oligomers

Not greater than 2 per cent, determined by size-exclusion chromatography (*2.2.30*).

Test solution Dilute the preparation to be examined with the mobile phase to a protein concentration of 0.1 mg/mL.

Reference solution (a) Dilute *interferon gamma-1b CRS* with the mobile phase to a protein concentration of 0.1 mg/mL.

Reference solution (b) Prepare a mixture of the following molecular mass standards: bovine albumin, ovalbumin, trypsinogen, lysozyme, at a concentration of 0.1 mg/mL to 0.2 mg/mL for each standard.

The chromatographic procedure may be carried out using:

— a stainless steel column 0.3 m long and 7.8 mm in internal diameter packed with *hydrophilic silica gel for chromatography R*, of a grade suitable for fractionation of globular proteins in the molecular weight range of 10 000 to 500 000 (5 µm),

— as mobile phase at a flow rate of 1.0 mL/min a mixture prepared as follows (0.2 M sodium phosphate buffer solution pH 6.8). Solution I: dissolve 31.2 g of *sodium dihydrogen phosphate R* and 1.0 g of *sodium dodecyl sulfate R* in *water R* and dilute to 1000.0 mL with the same solvent. Solution II: dissolve 28.4 g of *anhydrous disodium hydrogen phosphate R* and 1.0 g of *sodium dodecyl sulfate R* in *water R* and dilute to 1000.0 mL with the same solvent. Mix 450 mL of solution I and 550 mL of solution II. Adjust the pH if necessary,

— as detector a spectrophotometer set at 210 nm to 214 nm.

Inject 200 µL of each solution. The test is not valid unless: the molecular mass standards in reference solution (b) are well separated; the retention time of the principal peak in the chromatogram obtained with reference solution (a) is between the retention time of trypsinogen and lysozyme in the chromatogram obtained with reference solution (b).

Compare the chromatograms obtained with the test solution and with reference solution (a). There are no additional shoulders or peaks in the chromatogram obtained with the test solution compared with the chromatogram obtained with reference solution (a).

Calculate the percentage content of covalent dimers and oligomers.

Monomer and aggregates

Examine by size-exclusion chromatography (*2.2.30*). The content of monomer and aggregates is not greater than 2 per cent.

Solution A Prepare a solution of the following composition: 0.59 g/L of *succinic acid R* and 40 g/L of *mannitol R*, adjusted to pH 5.0 with *sodium hydroxide solution R*.

Test solution Dilute the preparation to be examined with solution A to a protein concentration of 1 mg/mL.

Reference solution Dilute *interferon gamma-1b CRS* with solution A to a protein concentration of 1 mg/mL.

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Resolution solution Prepare 500 µL of a mixture consisting of 0.04 mg/mL of *bovine albumin R* and 0.2 mg/mL of *interferon gamma-1b CRS* in solution A. Use this solution within 24 h of preparation.

The chromatographic procedure may be carried out using:

— a stainless steel column 0.3 m long and 7.8 mm in internal diameter packed with *hydrophilic silica gel for chromatography R*, of a grade suitable for fractionation of globular proteins in the molecular weight range of 10 000 - 300 000 (5 µm),

— as mobile phase at a flow rate of 0.8 mL/min a 89.5 g/L solution of *potassium chloride R* (1.2 M),

— as detector a spectrophotometer set at 214 nm.

Inject 20 µL of the resolution solution. In the chromatogram obtained, the retention time of the principal peak, corresponding to the native interferon gamma-1b dimer, is about 10 min. Bovine albumin elutes at a relative retention of about 0.85 with reference to the main peak. The test is not valid unless the resolution between the peaks due to bovine albumin and interferon gamma-1b is at least 1.5.

Inject 20 µL of the test solution and 20 µL of the reference solution. The chromatograms obtained show principal peaks with identical retention times. Calculate the percentage content of monomer and aggregates from the peak area of the monomer peak and of peaks which elute prior to the native interferon gamma-1b peak in the chromatogram obtained with the test solution, by the normalisation procedure, disregarding any peak due to the solvent.

Deamidated and oxidised forms and heterodimers

Examine by liquid chromatography (*2.2.29*). The content of deamidated and oxidised forms is not greater than 10 per cent. The content of heterodimers is not greater than 3 per cent.

Test solution Dilute the preparation to be examined with *water R* to a protein concentration of 1 mg/mL.

Reference solution (a) Dilute *interferon gamma-1b CRS* with *water R* to a protein concentration of 1 mg/mL.

Reference solution (b) Dissolve the contents of a vial of *interferon gamma-1b for system suitability CRS* in *water R* to obtain a protein concentration of about 1 mg/mL.

The chromatographic procedure may be carried out using:

— a stainless steel column 0.075 m long and 7.5 mm in internal diameter packed with an appropriate hydrophilic polymethacrylate, strong cation-exchange gel (10 µm, 100 nm),

— as mobile phase at a flow rate of 1.2 mL/min:

Mobile phase A (*0.05 M ammonium acetate buffer pH 6.5*). A 3.86 g/L solution of *ammonium acetate R*, adjusted to pH 6.5 with *dilute acetic acid R*,

Mobile phase B (*1.2 M ammonium acetate buffer pH 6.5*). A 92.5 g/L solution of *ammonium acetate R*, adjusted to pH 6.5 with *dilute acetic acid R*,

with the following elution conditions (if necessary, the slope of the gradient may be modified to improve the separation).

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 1	100	0
2 - 30	100 → 0	0 → 100
31 - 35	0	100

— as detector a spectrophotometer set at 280 nm,

maintaining the temperature of the column at 35 °C.

Inject 25 µL of reference solution (b). In the chromatogram obtained, the retention time of the principal peak is about 26 min. Deamidated and oxidised forms co-elute at a relative retention of about 0.95 with reference to the principal peak. The test is not valid unless the resolution, defined by the ratio of the height of the peak corresponding to the deamidated and oxidised forms to the height above the baseline of the valley separating the two peaks, is at least 1.2.

Inject 25 µL of the test solution and 25 µL of reference solution (a). The chromatograms obtained show principal peaks with identical retention times. Calculate the percentage content of deamidated and oxidised interferon gamma-1b as a percentage of the area of the main peak. Heterodimers have relative retentions of 0.7 and 0.85 with reference to the main peak. Calculate the percentage of heterodimers as a percentage of the sum of the areas of all peaks.

Impurities of molecular masses differing from that of interferon gamma-1b

Examine by polyacrylamide gel electrophoresis (2.2.31). The test is performed under both reducing and non-reducing conditions, using resolving gels of 15 per cent acrylamide and silver staining as the detection method.

Sample buffer (non-reducing conditions) Dissolve 3.78 g of *tris(hydroxymethyl)aminomethane R*, 10.0 g of *sodium dodecyl sulfate R* and 0.100 g of *bromophenol blue R* in *water R*. Add 50.0 mL of *glycerol R* and dilute to 80 mL with *water R*. Adjust the pH to 6.8 with *hydrochloric acid R* and dilute to 100 mL with *water R*.

Sample buffer (reducing conditions) Dissolve 3.78 g of *tris(hydroxymethyl)aminomethane R*, 10.0 g of *sodium dodecyl sulfate R* and 0.100 g of *bromophenol blue R* in *water R*. Add 50.0 mL of *glycerol R* and dilute to 80 mL with *water R*. Adjust the pH to 6.8 with *hydrochloric acid R* and dilute to 100 mL with *water R*. Immediately before use, add *dithiothreitol R* to a final concentration of 250 mM.

Test solution Dilute the preparation to be examined in *water R* to a protein concentration of 1 mg/mL. Dilute 150 µL of the solution with 38 µL of sample buffer.

Reference solution (a) Prepare in the same manner as for the test solution, but using *interferon gamma-1b CRS* instead of the preparation to be examined.

Reference solution (b) (5 ng control) Mix 50 µL of a 0.01 mg/mL solution of *bovine albumin R* with 2000 µL of *water R* and 450 µL of sample buffer.

Reference solution (c) (2 ng control) Mix 20 µL of a 0.01 mg/mL solution of *bovine albumin R* with 2000 µL of *water R* and 450 µL of sample buffer.

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Reference solution (d) Use a solution of molecular mass standards suitable for calibrating SDS-polyacrylamide gels in the range of 10 kDa to 70 kDa.

Leave each solution, contained in a test tube, at ambient temperature for 15 min, then store on ice.

Apply 25 µL of each solution to the stacking gel wells. Perform the electrophoresis under the conditions recommended by the manufacturer of the equipment. Detect proteins in the gel by silver staining.

The test is not valid unless: the validation criteria are met (2.2.31); a band is seen in the electropherograms obtained with reference solutions (b) and (c).

The principal band in the electropherogram obtained with the test solution is similar in intensity to the principal band in the electropherogram obtained with reference solution (a). In the electropherogram obtained with the test solution, no significant bands are observed that are not present in the electropherogram obtained with reference solution (a) (0.01 per cent). A significant band is defined as any band whose intensity is greater than or equal to that of the band in the electropherogram obtained with reference solution (c).

Norleucine

Not more than 0.2 mole of norleucine per mole of interferon gamma-1b, determined by amino acid analysis.

Test solution Add 2.5 mL of the preparation to be examined onto a column suitable for the desalting of proteins previously equilibrated with 25 mL of a 10 per cent *V/V* solution of *acetic acid R*. Elute the sample with another 2.5 mL of a 10 per cent *V/V* solution of *acetic acid R*. Determine the protein content by measuring the absorbance of this solution as described under Protein, in the Assay section. Pipette a volume containing the equivalent of 100 µg of interferon gamma-1b into each of three reaction vials. Evaporate to dryness under reduced pressure.

Perform the hydrolysis of the three samples as follows. Add to each reaction vial 200 µL of a 50 per cent *V/V* solution of *hydrochloric acid R* containing 1 per cent *V/V* of *phenol R*, evacuate the samples, purge with nitrogen and hydrolyse in the gas phase. Heat the reaction vials at 110 °C for 22 h. After hydrolysis evaporate to dryness under reduced pressure.

Perform the derivatisation of the samples as follows. Prepare immediately before use a mixture consisting of two volumes of *ethanol R*, one volume of *water R* and one volume of *triethylamine R*. Add 50 µL of this solution to each reaction vial and shake lightly. Evaporate to dryness under reduced pressure. Add to each vial 50 µL of a mixture consisting of 7 volumes of *ethanol R*, one volume of *water R*, one volume of *triethylamine R* and one volume of *phenyl isothiocyanate R*. Shake lightly and allow to stand at room temperature for about 15 min. Evaporate to dryness under reduced pressure. Reconstitute the samples in 250 µL of mobile phase A.

Norleucine stock solution Prepare a 250 nmol/mL solution of *DL-norleucine R* in *0.01 M hydrochloric acid*. *This solution may be kept for two months at 4 °C*.

Leucine stock solution Prepare a 250 nmol/mL solution of *leucine R* in *0.01 M hydrochloric acid*. *This solution may be kept at 4 °C for two months*.

Reference solution Mix 10 µL of norleucine stock solution with 100 µL of leucine stock solution in each of the three reaction vials. Evaporate to dryness under reduced pressure. Perform the derivatisation of the samples as described for the preparation of the test solution.

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Examine by liquid chromatography (2.2.29).

The chromatographic procedure may be carried out using:

— a stainless steel column 0.15 m long and 3.9 mm in diameter packed with *octadecylsilyl silica gel for chromatography R* (4 µm),

— as mobile phase at a flow rate of 1.0 mL/min:

Mobile phase A Mix 70 volumes of a 19 g/L solution of *sodium acetate R* containing 0.05 per cent *V/V* of *triethylamine R* and adjusted to pH 6.4 with *dilute acetic acid R* and 30 volumes of mobile phase B,

Mobile phase B Mix 40 volumes of *water R* and 60 volumes of *acetonitrile R*,

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Comment
0 - 7	100	0	isocratic
7 - 7.1	100 → 0	0 → 100	linear gradient
7.1 - 10	0	100	washing step
10 - 10.1	0 → 100	100 → 0	linear gradient
10.1 - 15	100	0	re-equilibration

— as detector a spectrophotometer set at 254 nm,

maintaining the temperature of the column at 43 °C.

Inject 50 µL of each solution.

In the chromatograms obtained with the test solution, identify the peaks corresponding to leucine and norleucine. The retention time of norleucine is 6.2 min to 7 min.

Calculate the content of norleucine (in moles of norleucine per mole of interferon gamma-1b) from the peak areas of leucine and norleucine in the chromatograms obtained with the reference and test solutions, considering that there are 10 moles of leucine per mole of interferon gamma-1b.

Bacterial endotoxins (2.6.14)

Less than 5 IU in the volume that contains 20×10^6 IU of interferon gamma-1b.

ASSAY

Protein (2.2.25)

Dilute the substance to be examined in *water R* to obtain a concentration of 1 mg/mL. Record the absorbance spectrum between 220 nm and 340 nm. Measure the value at the absorbance maximum of 280 nm, after correction for any light scattering due to turbidity measured at 316 nm. Calculate the concentration of interferon gamma-1b using a specific absorbance value of 7.5.

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Potency

The potency of interferon gamma-1b is estimated by evaluating the increase of the expression of human-leukocyte-antigen-DR (HLA-DR) due to the interferon gamma-1b present in test solutions during cultivation of the cells, and comparing this increase with the same effect of the appropriate International Standard of human recombinant interferon gamma or of a reference preparation calibrated in International Units.

The International Unit is the activity contained in a stated amount of the appropriate International Standard. The equivalence in International Units of the International Standard is stated by the World Health Organization.

Carry out the assay by a suitable method, based on the following design.

Use COLO 205 cells under standard culture conditions. Trypsinise a 3- to 5-day-old flask of COLO 205 cells and prepare a cell suspension at a concentration of 1.0×10^6 cells/mL.

Add 100 µL of the dilution medium to all wells of a 96-well microplate. Add an additional 100 µL of this solution to the wells designed for the blanks. Add 100 µL of each solution to be tested onto the plate and carry out a series of twofold dilution steps in order to obtain a standard curve. Then add 100 µL of the cell suspension to all wells and incubate the plate under appropriate conditions for cell cultivation.

After cultivation remove the growth medium and wash and fix cells to the plate. Add an antibody able to detect HLA-DR expressed due to the presence of interferon gamma-1b and incubate under appropriate conditions. After washing the plate, incubate with an antibody conjugated to a marker enzyme which is able to detect the anti-HLA-DR antibody. After this incubation step, wash the plate and add an appropriate substrate solution. Stop the reaction. Measure the absorbance of the solution and calculate the potency of the preparation to be examined by the usual statistical methods.

The estimated specific activity is not less than 80 per cent and not more than 125 per cent of the stated potency. The confidence limits (P = 0.95) are not less than 70 per cent and not more than 140 per cent of the estimated potency.

STORAGE

Store in an airtight container, protected from light and at a temperature of -70 °C.

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Invert Syrup

General Notices

DEFINITION

Invert Syrup is a mixture of glucose and fructose prepared by hydrolysing a 66.7% w/w solution of Sucrose with a suitable mineral acid, such as hydrochloric acid, and neutralising the resulting solution using, for example, calcium carbonate or sodium carbonate. The degree of inversion is at least 95%.

The syrup complies with the requirements stated under Oral Liquids and with the following requirements.

Content of reducing sugars, expressed as invert sugar

Not less than 67.0% w/w.

CHARACTERISTICS

A clear, colourless to pale straw-coloured syrupy liquid.

Miscible with *water*, producing a clear solution; it dissolves in *ethanol (96%)* with the formation of an insoluble residue.

IDENTIFICATION

A. Heat 1 g with 10 mL of *water* and 5 mL of *cupri-tartaric solution*. A red precipitate is produced.

B. A solution in *water* is laevorotatory.

TESTS

Acidity

pH, 5.0 to 6.0, Appendix V L.

Arsenic

To 4.0 g add 50 mL of *water* and 10 mL of *brominated hydrochloric acid*, allow to stand for 5 minutes and remove the excess of bromine by adding *tin(II) chloride solution AsT* and dilute to 100 mL with *water*. 25 mL of the resulting solution complies with the *limit test for arsenic*, Appendix VII (1 ppm).

Lead

Prepare two solutions as follows. For solution (1) add 5 mL of 6M *acetic acid* to 12 g of the syrup. For solution (2) add 5 mL of 6M *acetic acid* and 2 mL of *lead standard solution (10 ppm Pb)* to 2.0 g of the syrup. Make solutions (1) and (2) alkaline with 5M *ammonia*, if necessary, and to each add 1 mL of *potassium cyanide solution PbT*. The solutions should not be more than faintly opalescent. If the colours of the

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solutions differ, equalise by the addition of a few drops of a highly diluted solution of burnt sugar or other non-reactive substance. Dilute each solution to 50 mL with *water*, add 0.1 mL of a 10% w/v solution of *sodium sulfide* to each and mix thoroughly. When viewed against a white background, the colour produced in solution (1) is not more intense than that produced in solution (2) (2 ppm).

Refractive index

1.4608 to 1.4630, Appendix V E.

Sulfur dioxide

Not more than 70 ppm, Appendix IX B.

Weight per mL

1.338 to 1.344 g, Appendix V G.

Sulfated ash

Not more than 0.1%, Appendix IX A.

ASSAY

Dilute the syrup so that the volume of the diluted solution required in the following method is between 15 and 50 mL. Add 10.00 mL of *cupri-tartaric solution R1* to a 300 mL conical flask, add from a burette 15 mL of the diluted solution, heat to boiling over wire gauze covered with insulating material and continue adding the diluted solution in quantities of about 5 mL at 15-second intervals until the colour of the mixture indicates that the reduction appears to be almost complete. Boil for 2 minutes, add 0.2 mL of a 1% w/v solution of *methylene blue* and continue the titration until the blue colour is discharged. Repeat the operation, but, before heating, add almost the full quantity of the diluted solution required to reduce all the copper and then boil moderately for 2 minutes. Without removing the flask from either the gauze or the flame during the remainder of the titration, add 0.2 mL of the methylene blue solution and continue the titration so that it is just complete in a total boiling time of exactly 3 minutes; the end point is indicated by the disappearance of the blue colour, the solution becoming orange. From the Table calculate the content of reducing sugars (expressed as invert sugar) in 100 mL of the diluted solution and hence the percentage weight in weight in the substance being examined.

STORAGE

Invert Syrup should be stored at a temperature of 35° to 45°.

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Quantity of prepared solution required ml	Invert sugar factor*	Quantity of invert sugar per 100 ml mg	Quantity of prepared solution required ml	Invert sugar factor*	Quantity of invert sugar per 100 ml mg
15	50.5	336.0	33	51.7	156.6
16	50.6	316.0	34	51.7	152.2
17	50.7	298.0	35	51.8	147.9
18	50.8	282.0	36	51.8	143.9
19	50.8	267.0	37	51.9	140.2
20	50.9	254.5	38	51.9	136.6
21	51.0	242.9	39	52.0	133.3
22	51.0	231.8	40	52.0	130.1
23	51.1	222.2	41	52.1	127.1
24	51.2	213.3	42	52.1	124.2
25	51.2	204.8	43	52.2	121.4
26	51.3	197.4	44	52.2	118.7
27	51.4	190.4	45	52.3	116.1
28	51.4	183.7	46	52.3	113.7
29	51.5	177.6	47	52.4	111.4
30	51.5	171.7	48	52.4	109.2
31	51.6	166.3	49	52.5	107.1
32	51.6	161.2	50	52.5	105.1

* mg of invert sugar corresponding to 10.00 mL of *cupri-tartaric solution R1*.

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Iodinated Povidone

General Notices

(Ph. Eur. monograph 1142)

Action and use

Antiseptic.

Preparations

Povidone-Iodine Eye Drops

Povidone-Iodine Mouthwash

Povidone-Iodine Solution

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DEFINITION

Complex of iodine and povidone.

Content

9.0 per cent to 12.0 per cent of available iodine (dried substance).

PRODUCTION

It is produced using povidone that complies with the monograph on *Povidone (0685)*, except that the povidone used may contain not more than 2.0 per cent of formic acid and not more than 8.0 per cent of water.

CHARACTERS

Appearance

Yellowish-brown or reddish-brown, amorphous powder.

Solubility

Soluble in water and in ethanol (96 per cent), practically insoluble in acetone.

IDENTIFICATION

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A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *iodinated povidone CRS*.

B. Dissolve 10 mg in 10 mL of *water R* and add 1 mL of *starch solution R*. An intense blue colour is produced.

TESTS

pH (*2.2.3*)

1.5 to 5.0.

Dissolve 1.0 g in 10 mL of *carbon dioxide-free water R*.

Iodide

Maximum 6.0 per cent (dried substance).

Dissolve 0.500 g in 100 mL of *water R*. Add *sodium metabisulfite R* until the colour of the iodine has disappeared. Add 25.0 mL of *0.1 M silver nitrate*, 10 mL of *nitric acid R* and 5 mL of *ferric ammonium sulfate solution R2*. Titrate with *0.1 M ammonium thiocyanate*. Carry out a blank titration.

1 mL of *0.1 M silver nitrate* is equivalent to 12.69 mg of total iodine. From the percentage of total iodine, calculated with reference to the dried substance, subtract the percentage of available iodine as determined in the assay to obtain the percentage of iodide.

Loss on drying (*2.2.32*)

Maximum 8.0 per cent, determined on 0.500 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Transfer 1.000 g into a ground-glass-stoppered flask containing 150 mL of *water R* and stir for 1 h. Add 0.1 mL of *dilute acetic acid R* and titrate with *0.1 M sodium thiosulfate* using *starch solution R* as indicator.

1 mL of *0.1 M sodium thiosulfate* is equivalent to 12.69 mg of available iodine.

STORAGE

Protected from light.

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Iodine

General Notices

(Ph. Eur. monograph 0031)

I_2 253.8 *7553-56-2*

Action and use

Antiseptic; antithyroid.

Preparations

Alcoholic Iodine Solution

Aqueous Iodine Oral Solution

Povidone-Iodine Eye Drops

Povidone-Iodine Mouthwash

Povidone-Iodine Solution

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DEFINITION

Content

99.5 per cent to 100.5 per cent of I.

CHARACTERS

Appearance

Greyish-violet, brittle plates or fine crystals with a metallic sheen.

Solubility

Very slightly soluble in water, very soluble in concentrated solutions of iodides, soluble in ethanol (96 per cent), slightly soluble in glycerol.

It volatilises slowly at room temperature.

IDENTIFICATION

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A. Heat a few fragments in a test-tube. Violet vapour is evolved and a bluish-black crystalline sublimate is formed.

B. To a saturated solution add *starch solution R*. A blue colour is produced. Heat until decolourised. On cooling, the colour reappears.

TESTS

Solution S

Triturate 3.0 g with 20 mL of *water R*, filter, wash the filter with *water R* and dilute the filtrate to 30 mL with the same solvent. To the solution add 1 g of *zinc powder R*. When the solution is decolourised, filter, wash the filter with *water R* and dilute to 40 mL with the same solvent.

Bromides and chlorides

Maximum 250 ppm.

To 10 mL of solution S add 3 mL of *ammonia R* and 6 mL of *silver nitrate solution R2*. Filter, wash the filter with *water R* and dilute the filtrate to 20 mL with the same solvent. To 10 mL of the solution add 1.5 mL of *nitric acid R*. After 1 min, any opalescence in the solution is not more intense than that in a standard prepared at the same time by mixing 10.75 mL of *water R*, 0.25 mL of *0.01 M hydrochloric acid*, 0.2 mL of *dilute nitric acid R* and 0.3 mL of *silver nitrate solution R2*.

Non-volatile substances

Maximum 0.1 per cent.

Heat 1.00 g in a porcelain dish on a water-bath until the iodine has volatilised. Dry the residue at 100-105 °C. The residue weighs a maximum of 1 mg.

ASSAY

Introduce 0.200 g into a flask containing 1 g of *potassium iodide R* and 2 mL of *water R* and add 1 mL of *dilute acetic acid R*. When dissolution is complete, add 50 mL of *water R* and titrate with *0.1 M sodium thiosulfate*, using *starch solution R* as indicator.

1 mL of *0.1 M sodium thiosulfate* is equivalent to 12.69 mg of I.

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Iodised Oil Fluid Injection

General Notices

Action and use

Radio-opaque injection.

DEFINITION

Iodised Oil Fluid Injection is a sterile iodine addition product of the ethyl esters of the fatty acids obtained from poppy-seed oil.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of combined iodine

37.0 to 39.0% w/w.

CHARACTERISTICS

A straw-coloured or yellow, oily liquid.

Practically insoluble in *water*; soluble in *chloroform*, in *ether* and in *petroleum spirit (boiling range, 40° to 60°)*.

IDENTIFICATION

Boil 0.05 mL with 2 mL of *glacial acetic acid* and 0.1 g of *zinc powder* for 2 minutes, add 5 mL of *water*, shake, decant from any undissolved zinc and add 1 mL of *hydrogen peroxide solution (20 vol)*. Iodine vapour is evolved.

TESTS

Acidity

To 5 mL of *chloroform* add 5 mL of *ethanol (96%)* previously neutralised to *phenolphthalein solution R1* with 0.1M *ethanolic sodium hydroxide VS*, add 5 g of the injection, shake and titrate with 0.1M *ethanolic sodium hydroxide VS* using *phenolphthalein solution R1* as indicator. Not more than 1.0 mL is required to change the colour of the solution.

Weight per mL

1.28 to 1.30 g, Appendix V G.

Free iodine

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Shake 1 g with 1 mL of *starch mucilage* and 1 mL of *cadmium iodide solution*. Any blue colour disappears on the addition of 0.4 mL of 0.01 M *sodium thiosulfate*.

ASSAY

Boil 1 g with 10 mL of *glacial acetic acid* and 1 g of *zinc powder* under a reflux condenser for 1 hour. Add through the condenser 30 mL of hot *water*, filter through absorbent cotton, wash the flask with two 20 mL quantities of hot *water* and pass the washings through the filter. Cool the filtrate, add 25 mL of *hydrochloric acid* and 8 mL of *potassium cyanide solution* and titrate with *0.05M potassium iodate VS* until the dark brown solution which is produced becomes light brown; add 5 mL of *starch mucilage* and continue the titration until the blue colour disappears. Each mL of *0.05M potassium iodate VS* is equivalent to 12.69 mg of combined iodine.

STORAGE

Iodised Oil Fluid Injection should be kept in an atmosphere of carbon dioxide or nitrogen and protected from light.

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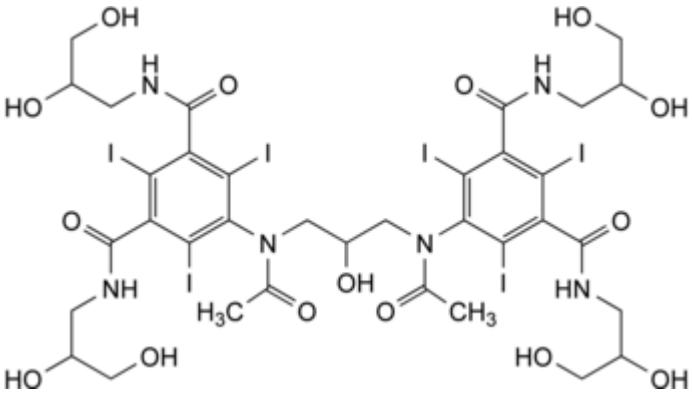
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Iodixanol

General Notices

(Ph. Eur. monograph 2215)



$C_{35}H_{44}I_6N_6O_{15}$ 1550 *92339-11-2*

Action and use

Iodinated contrast medium.

Ph Eur

DEFINITION

Mixture of stereoisomers of 5,5′-[(2-hydroxypropane-1,3-diyl)bis(acetylimino)]bis[*N*,*N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide].

Content

98.5 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder, hygroscopic.

Solubility

Freely soluble in water, sparingly soluble in methanol, practically insoluble in methylene chloride.

IDENTIFICATION

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A. Infrared absorption spectrophotometry (2.2.24).

Comparison *iodixanol CRS*.

B. Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Injection Test solution and reference solution (b).

Results The 3 principal peaks in the chromatogram obtained with the test solution are similar in retention time to the 3 principal peaks in the chromatogram obtained with reference solution (b).

TESTS

Solution S

Dissolve 5.0 g in *water R* and dilute to 50.0 mL with the same solvent.

Appearance of solution

Heat solution S at about 98 °C for 30 min without boiling then allow to cool to room temperature. The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_7 (2.2.2, *Method II*).

Impurities E and H

Liquid chromatography (2.2.29).

Test solution Dissolve 0.250 g of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *water R*.

Reference solution (b) Dissolve 5 mg of *iodixanol impurity E CRS* and 5 mg of *iodixanol impurity H CRS* in *water R* and dilute to 20.0 mL with the same solvent.

Reference solution (c) Mix 5.0 mL of the test solution with 5.0 mL of reference solution (b) and dilute to 50.0 mL with *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *aminopropylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: *acetonitrile R*, *water R* (50:50 *V/V*);

— *mobile phase B*: *acetonitrile R*;

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	30	70
2 - 27	30 → 68	70 → 32

Flow rate 1.7 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL of the test solution and reference solutions (a) and (c).

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities E and H.

Relative retention With reference to iodixanol (1st peak) (retention time = about 16 min): impurity E (1st peak) = about 0.7; impurity E (2nd peak) = about 0.8; impurity H = about 1.4.

System suitability Reference solution (c):

— *resolution*: minimum 5.0 between the 1st peak due to impurity E and the 1st peak due to iodixanol.

Limits:

— *correction factor*: for the calculation of total content of impurity E, multiply the peak area of the 1st peak due to impurity E by 1.7;

— *impurity H*: not more than 0.6 times the sum of the areas of the 2 principal peaks in the chromatogram obtained with reference solution (a) (0.6 per cent);

— *impurity E*: not more than 0.3 times the sum of the areas of the 2 principal peaks in the chromatogram obtained with reference solution (a) (0.3 per cent).

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.250 g of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *water R*.

Reference solution (b) Dissolve 25 mg of *iodixanol CRS* in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution (c) Dissolve 5 mg of *iodixanol impurity C CRS* and 5 mg of *iopentol CRS* in *water R* and dilute to 10.0 mL with the same solvent. Dilute 5.0 mL of this solution to 100.0 mL with *water R*.

Reference solution (d) Mix 5.0 mL of the test solution with 5.0 mL of reference solution (c) and dilute to 50.0 mL with *water R*.

Column:

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— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: *water R*;

— *mobile phase B*: *acetonitrile R*, *water R* (50:50 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	94	6
2 - 32	94 → 80	6 → 20
32 - 72	80 → 0	20 → 100
72 - 82	0	100

Flow rate 1 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL of the test solution and reference solutions (a), (c) and (d).

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peaks due to impurity C and iopentol.

Relative retention With reference to iodixanol (1^{st} peak) (retention time = about 27 min): iopentol (1^{st} peak) = about 0.8; iopentol (2^{nd} peak) = about 0.9; impurity C (1^{st} peak) = about 1.04; overalkylated impurities (a group of peaks) = 1.33-1.70.

System suitability Reference solution (d):

— *resolution*: baseline separation between the 2 peaks due to iopentol;

— *peak-to-valley ratio*: minimum 1.3, where H_p = height above the baseline of the 1^{st} peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the 1^{st} peak due to iodixanol.

Limits:

— *correction factor*: for the calculation of total content of impurity C, multiply the peak area of the 1^{st} peak due to impurity C by 1.3;

— *impurity C*: not more than 0.4 times the sum of the areas of the 2 principal peaks in the chromatogram obtained with reference solution (a) (0.4 per cent);

— *overalkylated impurities (such as impurity I)*: not more than the sum of the areas of the 2 principal peaks in the chromatogram obtained with reference solution (a) (1.0 per cent);

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— *unspecified impurities*: for each impurity, not more than 0.1 times the sum of the areas of the 2 principal peaks in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 1.5 times the sum of the areas of the 2 principal peaks in the chromatogram obtained with reference solution (a) (1.5 per cent);

— *disregard limit*: 0.05 times the sum of the areas of the 2 principal peaks in the chromatogram obtained with reference solution (a) (0.05 per cent).

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

Free aromatic amine

Maximum 500 ppm.

Test solution Transfer 0.200 g of the substance to be examined to a 25 mL volumetric flask and dissolve in 15.0 mL of *water R*.

Reference solution Dissolve 5.0 mg of *iohexol impurity J CRS* in *water R* and dilute to 5.0 mL with the same solvent. Dilute 1.0 mL of this solution to 100.0 mL with *water R*. Mix 10.0 mL of this solution with 5.0 mL of *water R* in a 25 mL volumetric flask.

Blank solution Transfer 15.0 mL of *water R* to a 25 mL volumetric flask.

In conducting the following steps, keep the flasks in iced water and protected as much as possible from light until all the reagents have been added.

Place the 3 flasks containing respectively the test solution, the reference solution and the blank solution in iced water, protected from light, for 5 min. Add 1.5 mL of *hydrochloric acid R1* and mix by swirling. Add 1.0 mL of a 20 g/L solution of *sodium nitrite R*, mix and allow to stand for 4 min. Add 1.0 mL of a 40 g/L solution of *sulfamic acid R*, swirl gently until gas liberation has ceased and allow to stand for 1 min. (*CAUTION: considerable pressure is produced*). Add 1.0 mL of a freshly prepared 3 g/L solution of *naphthylethylenediamine dihydrochloride R* in a mixture of 30 volumes of *water R* and 70 volumes of *propylene glycol R* and mix. Remove the flasks from the iced water, dilute to 25.0 mL with *water R*, mix and examine the solutions after 5 min. The solution obtained from the test solution is less coloured than the solution obtained from the reference solution. If the solution obtained from the test solution is about the same colour or darker than the solution obtained from the reference solution, proceed as follows. Concomitantly determine the absorbance (*2.2.25*) at 495 nm of the solution obtained from the test solution and the reference solution in 5 cm cells, using the blank solution as the compensation liquid. The absorbance of the solution obtained from the test solution is not greater than that of the solution obtained from the reference solution.

Free iodine

Transfer 2.0 g to a glass-stoppered tube, add 20 mL of *water R*, 5 mL of *toluene R* and 5 mL of *dilute sulfuric acid R*, shake vigorously and allow the phases to separate: the toluene layer shows no red or pink colour.

Iodide

Maximum 10 ppm.

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Dissolve 5.000 g in *water R* and dilute to 20.0 mL with the same solvent. Titrate with *0.001 M silver nitrate*. Determine the end-point potentiometrically (*2.2.20*) using a silver indicator electrode and an appropriate reference electrode.

1 mL of *0.001 M silver nitrate* is equivalent to 126.9 µg of iodide.

Ionic compounds (*2.2.38*)

Maximum 0.02 per cent *m/m* calculated as sodium chloride.

Rinse all glassware with distilled water R 5 times before use.

Test solution Dissolve 1.0 g of the substance to be examined in *water R* and dilute to 50.0 mL with the same solvent.

Reference solution Dissolve 20.0 mg of *sodium chloride R* in *water R* and dilute to 50.0 mL with the same solvent. Dilute 1.0 mL of this solution to 100.0 mL with *water R*.

Measure the specific conductivity of the test solution and the reference solution using a suitable conductivity meter. The specific conductivity of the test solution is not greater than that of the reference solution.

Water (*2.5.12*)

Maximum 4.0 per cent, determined on 0.500 g.

ASSAY

In a 125 mL round-bottomed flask, dissolve 0.200 g in 25 mL of a 50 g/L solution of *sodium hydroxide R*, add 0.5 g of *zinc powder R* and a few glass beads. Boil under a reflux condenser for 1 h. Allow to cool and rinse the condenser with 20 mL of *water R*, adding the rinsings to the flask. Filter through a sintered-glass filter (40) (*2.1.2*) and wash the filter with several quantities of *water R*. Collect the filtrate and washings. Add 5 mL of *glacial acetic acid R* and titrate immediately with *0.1 M silver nitrate*. Determine the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M silver nitrate* is equivalent to 25.84 mg of $C_{35}H_{44}I_6N_6O_{15}$.

STORAGE

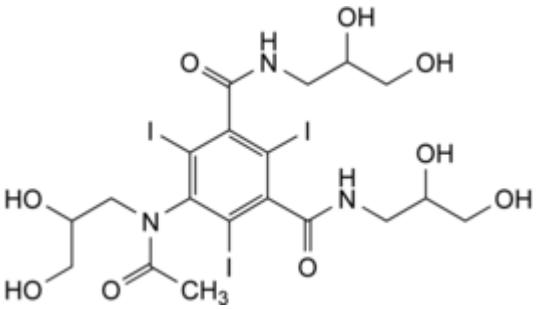
In an airtight container, protected from light.

IMPURITIES

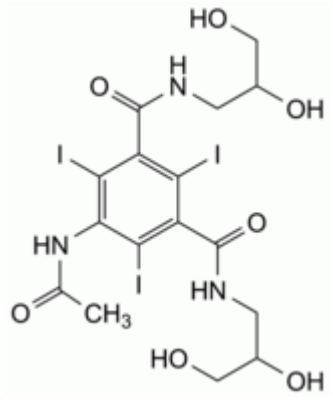
Specified impurities *C, E, H, overalkylated impurities.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also *5.10*. *Control of impurities in substances for pharmaceutical use: A, B, F, G.*

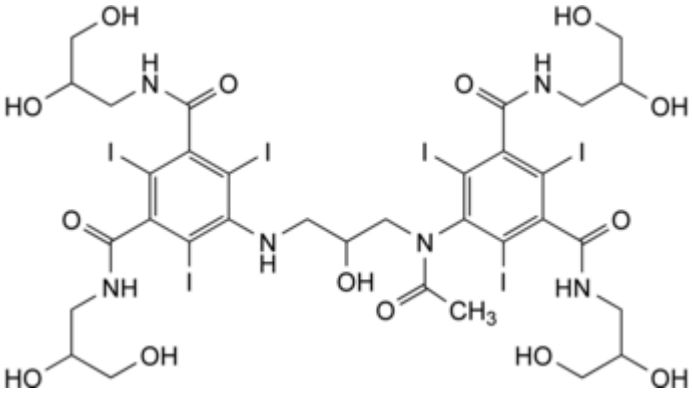
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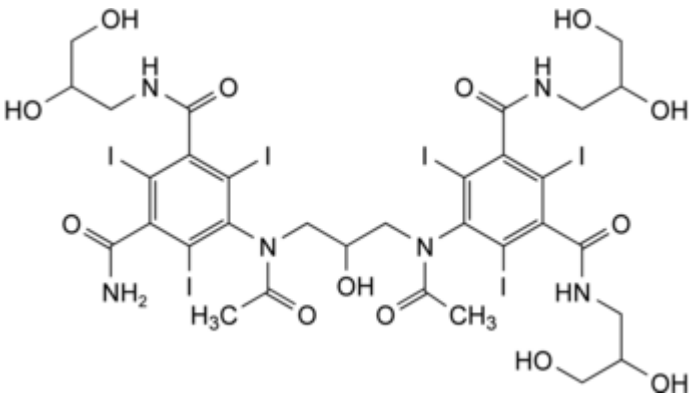
A. 5-[acetyl(2,3-dihydroxypropyl)amino]-*N*,*N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide (iohexol),



B. 5-acetamido-*N*,*N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide,

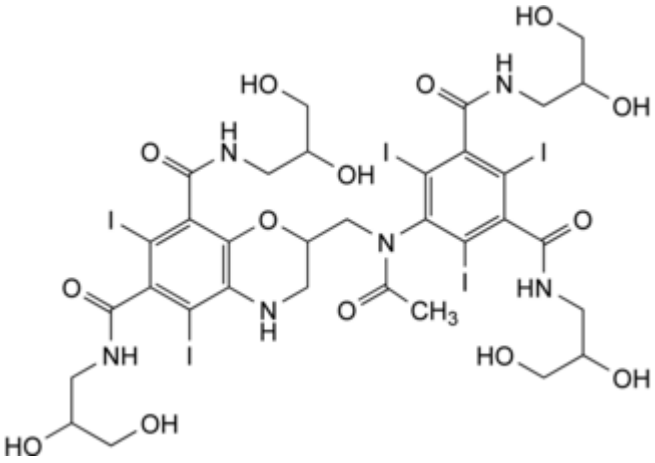


C. 5-[acetyl[3-[[3,5-bis[(2,3-dihydroxypropyl)carbamoyl]-2,4,6-triiodophenyl]amino]-2-hydroxypropyl]amino]-*N*,*N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide,

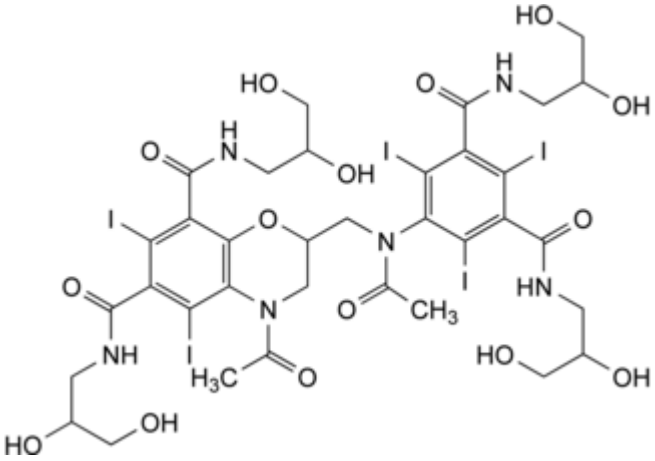


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E. 5-[acetyl[3-[acetyl[3-carbamoyl-5-[(2,3-dihydroxypropyl)carbamoyl]-2,4,6-triiodophenyl]amino]-2-hydroxypropyl]amino]-*N*,*N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide,

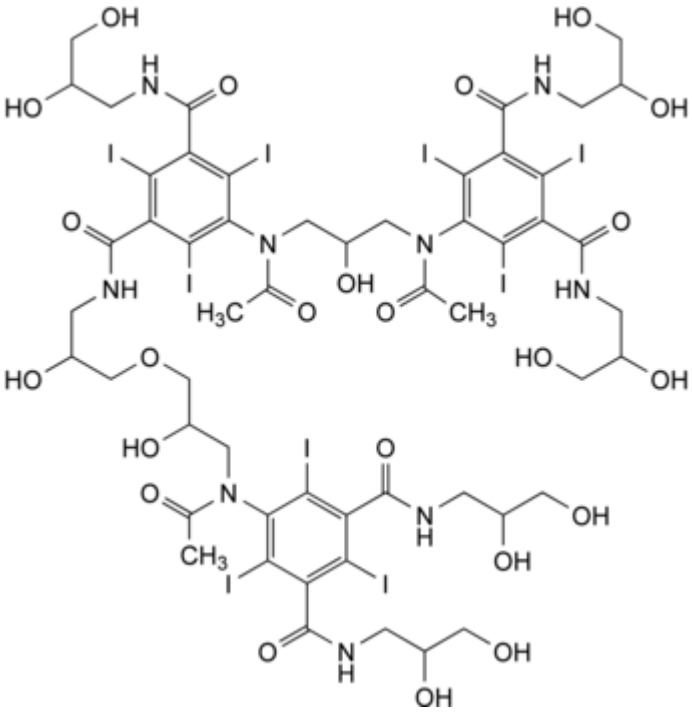


F. 2-[[acetyl[3,5-bis[(2,3-dihydroxypropyl)carbamoyl]-2,4,6-triiodophenyl]amino]methyl]-*N*,*N*′-bis(2,3-dihydroxypropyl)-5,7-diiodo-3,4-dihydro-2*H*-1,4-benzoxazine-6,8-dicarboxamide,

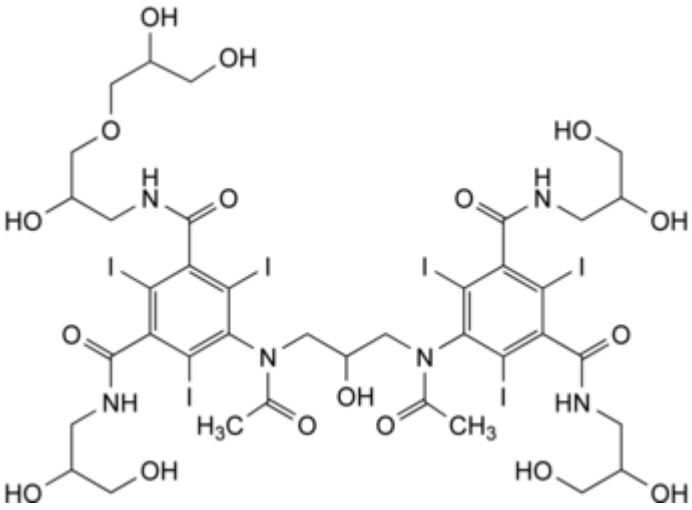


G. 4-acetyl-2-[[acetyl[3,5-bis[(2,3-dihydroxypropyl)carbamoyl]-2,4,6-triiodophenyl]amino]methyl]-*N*,*N*′-bis(2,3-dihydroxypropyl)-5,7-diiodo-3,4-dihydro-2*H*-1,4-benzoxazine-6,8-dicarboxamide,

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H. 5-[acetyl[3-[acetyl[3-[[3-[3-[acetyl[3,5-bis[(2,3-dihydroxypropyl)carbamoyl]-2,4,6-triiodophenyl]amino]-2-hydroxypropoxy]-2-hydroxypropyl]carbamoyl]-5-[(2,3-dihydroxypropyl)carbamoyl]-2,4,6-triiodophenyl]amino]-2-hydroxypropyl]amino]-*N*,*N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide.



I. overalkylated impurities (an example): 5-[acetyl[3-[acetyl[3,5-bis[(2,3-dihydroxypropyl)carbamoyl]-2,4,6-triiodophenyl]amino]-2-hydroxypropyl]amino]-*N*-[3-(2,3-dihydroxypropoxy)-2-hydroxypropyl]-*N*′-(2,3-dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide.

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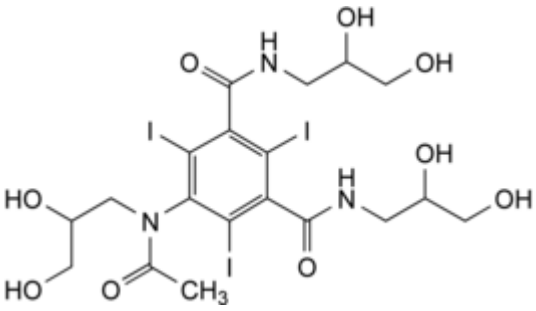
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You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Iohexol

General Notices

(Ph. Eur. monograph 1114)



$C_{19}H_{26}I_3N_3O_9$ 821 *66108-95-0*

Action and use

Iodinated contrast medium.

Ph Eur

DEFINITION

5-[Acetyl(2,3-dihydroxypropyl)amino]-*N,N'*-bis(2,3-dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide.

The substance is a mixture of diastereoisomers and atropisomers.

Content

98.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or greyish-white, hygroscopic powder.

Solubility

Very soluble in water, freely soluble in methanol, practically insoluble in methylene chloride.

IDENTIFICATION

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A. Infrared absorption spectrophotometry (2.2.24).

Comparison *iohexol CRS*.

B. Examine the chromatograms obtained in test A for related substances.

Results The principal peaks in the chromatogram obtained with reference solution (b) are similar in retention time and size to the peaks due to iohexol in the chromatogram obtained with reference solution (a).

TESTS

Solution S

Dissolve 5.0 g in *water R* and dilute to 50.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution Y_7 (2.2.2, *Method II*).

Related substances

A. Liquid chromatography (2.2.29).

NOTE: iohexol gives rise to 2 non-resolved peaks in the chromatogram due to endo-exo isomerism. In addition, a small peak (also due to iohexol) usually appears at the leading edge of the 1st principal peak. This small peak has a retention time about 1.2 min less than the 1st principal peak.

Test solution Dissolve 0.150 g of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (a) Dissolve 15.0 mg of *iohexol CRS* and 15.0 mg of *iohexol impurity A CRS* in a mixture of 0.05-0.1 mL of *dilute sodium hydroxide solution R* and 10 mL of *water R* and dilute to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 10.0 mL with *water R*.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *water R*.

Reference solution (c) Dissolve 5.0 mg of *iohexol for peak identification CRS* (containing impurities B, C, D and E) in *water R* and dilute to 5.0 mL with the same solvent.

Blank solution *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: *water R*;

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— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 60	99 → 87	1 → 13

Flow rate 1 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

Retention time Impurities A and H = about 17 min; iohexol (peaks corresponding to *endo-exo* isomerism) = about 20 min.

System suitability Reference solution (a):

— *resolution*: minimum 5.0 between the peak due to impurity A and the 2nd and greater peak due to iohexol.

Limits:

— *sum of impurities B, C, D and E* (relative retention with reference to the 2nd and greater peak due to iohexol between 1.1 and 1.4): not more than 0.6 times the total area of the principal peaks in the chromatogram obtained with reference solution (b) (0.6 per cent); use the chromatogram obtained with reference solution (c) to identify the corresponding peaks;

— *sum of impurities A and H*: not more than 0.5 times the total area of the principal peaks in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than 0.1 times the total area of the principal peaks in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 1.5 times the total area of the principal peaks in the chromatogram obtained with reference solution (b) (1.5 per cent);

— *disregard limit*: 0.03 times the total area of the principal peaks in the chromatogram obtained with reference solution (b) (0.03 per cent).

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

B. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 1.0 g of the substance to be examined in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 50 mg of *iohexol impurity J CRS* and 50 mg of *iohexol CRS* in *water R* and dilute to 10.0 mL with the same solvent.

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Reference solution (b) Dilute 1.0 mL of the test solution to 10.0 mL with *water R*. Dilute 1.0 mL of this solution to 50.0 mL with *water R*.

Plate *TLC silica gel F_{254} plate R*.

Pretreatment Wash the plate with the mobile phase, dry at room temperature for 30 min, then at 90 °C for 1 h.

Mobile phase *concentrated ammonia R*, *methanol R*, *2-propanol R*, *acetone R* (16:16:28:40 *V/V/V/V*).

Application 10 µL.

Development Over 1/2 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (a):

— the chromatogram shows 2 clearly separated spots.

Limits:

— *any impurity*: any spot in the chromatogram obtained with the test solution, apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.2 per cent).

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

3-Chloropropane-1,2-diol

Gas chromatography (*2.2.28*).

Test solution Dissolve 1.0 g of the substance to be examined in 1.0 mL of *water R*. Shake with 4 quantities, each of 2 mL, of *methyl acetate R*. Dry the combined upper layers over *anhydrous sodium sulfate R*. Filter and concentrate to about 0.7 mL using a warm water-bath at 60 °C and a stream of nitrogen and dilute to 1.0 mL with *methyl acetate R*.

Reference solution Dissolve 0.25 g of *3-chloropropane-1,2-diol R* in 100.0 mL of *methyl acetate R*. Dilute 1.0 mL of this solution to 100.0 mL with *methyl acetate R*.

Column:

— *material*: fused silica;

— *size*: *l* = 25 m, Ø = 0.33 mm;

— *stationary phase*: *phenyl(50)methyl(50)polysiloxane R* (film thickness 1 µm).

Carrier gas *helium for chromatography R*.

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Flow rate 1 mL/min.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 2	80
	2 - 8	80 → 170
	8 - 10	170
Injection port		230
Detector		250

Detection Flame ionisation.

Injection 2 µL (splitless for 30 s).

System suitability Reference solution:

— *retention time*: 3-chloropropane-1,2-diol = about 8 min.

Limit:

— *3-chloropropane-1,2-diol*: not more than the area of the principal peak in the chromatogram obtained with the reference solution (25 ppm).

Free aromatic amine

Maximum 500 ppm.

Test solution Transfer 0.200 g of the substance to be examined to a 25 mL volumetric flask and dissolve in 15.0 mL of *water R*.

Reference solution Dissolve 5.0 mg of *iohexol impurity J CRS* in *water R* and dilute to 5.0 mL with *water R*. Dilute 1.0 mL of the solution to 100.0 mL with *water R*. Mix 10.0 mL of this solution with 5.0 mL of *water R* in a 25 mL volumetric flask.

Blank solution Transfer 15.0 mL of *water R* to a 25 mL volumetric flask.

In conducting the following steps, keep the flasks in iced water and protected as much as possible from light until all of the reagents have been added.

Place the 3 flasks containing respectively the test solution, the reference solution and the blank solution in iced water, protected from light, for 5 min. Add 1.5 mL of *hydrochloric acid R1* and mix by swirling. Add 1.0 mL of a 20 g/L solution of *sodium nitrite R*, mix and allow to stand for 4 min. Add 1.0 mL of a 40 g/L solution of *sulfamic acid R*, swirl gently until gas liberation has ceased and allow to stand for 1 min. *(CAUTION: considerable pressure is produced)*. Add 1.0 mL of a freshly prepared 3 g/L solution of *naphthylethylenediamine dihydrochloride R* in a mixture of 30 volumes of *water R* and 70 volumes of *propylene glycol R* and mix. Remove the flasks from the iced

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water, dilute to 25.0 mL with *water R*, mix and allow to stand for 5 min. Simultaneously determine the absorbance (*2.2.25*) at 495 nm of the solutions obtained from the test solution and the reference solution in 5 cm cells, using the blank as the compensation liquid. The absorbance of the test solution is not greater than that of the reference solution.

Iodide

Maximum 10 ppm.

Dissolve 6.000 g in *water R* and dilute to 20 mL with the same solvent. Add 2.0 mL of *0.001 M potassium iodide*. Titrate with *0.001 M silver nitrate*. Determine the end-point potentiometrically (*2.2.20*), using a silver indicator electrode and an appropriate reference electrode. Subtract the volume of titrant corresponding to the 2.0 mL of *0.001 M potassium iodide*, determined by titrating a blank to which is added 2.0 mL of *0.001 M potassium iodide* and use the residual value to calculate the iodide content.

1 mL of *0.001 M silver nitrate* is equivalent to 126.9 µg of I^-.

Ionic compounds (*2.2.38*)

Maximum 0.01 per cent *m/m* calculated as sodium chloride.

Rinse all glassware with distilled water R 5 times before use.

Test solution Dissolve 1.0 g of the substance to be examined in *water R* and dilute to 50.0 mL with the same solvent.

Reference solution Dissolve 20.0 mg of *sodium chloride R* in *water R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of this solution to 100.0 mL with *water R*.

Measure the conductivity of the test solution and the reference solution using a suitable conductivity meter. The conductivity of the test solution is not greater than that of the reference solution.

Water (*2.5.12*)

Maximum 4.0 per cent, determined on 1.00 g.

ASSAY

To 0.500 g in a 125 mL round-bottomed flask add 25 mL of a 50 g/L solution of *sodium hydroxide R*, 0.5 g of *zinc powder R* and a few glass beads. Boil under a reflux condenser for 30 min. Allow to cool and rinse the condenser with 20 mL of *water R*, adding the rinsings to the flask. Filter through a sintered-glass filter (*2.1.2*) and wash the filter with several quantities of *water R*. Collect the filtrate and washings. Add 5 mL of *glacial acetic acid R* and titrate immediately with *0.1 M silver nitrate*. Determine the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M silver nitrate* is equivalent to 27.37 mg of $C_{19}H_{26}I_3N_3O_9$.

STORAGE

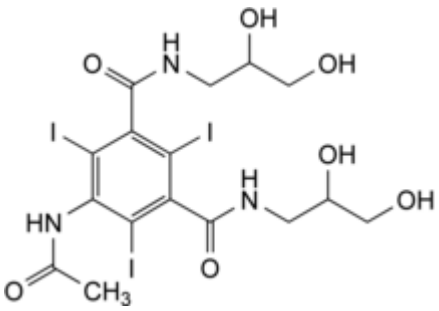
In an airtight container, protected from light and moisture.

IMPURITIES

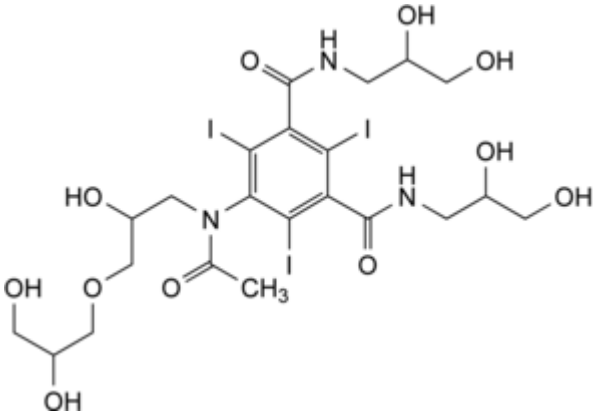
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Specified impurities *A, B, C, D, E, H.*

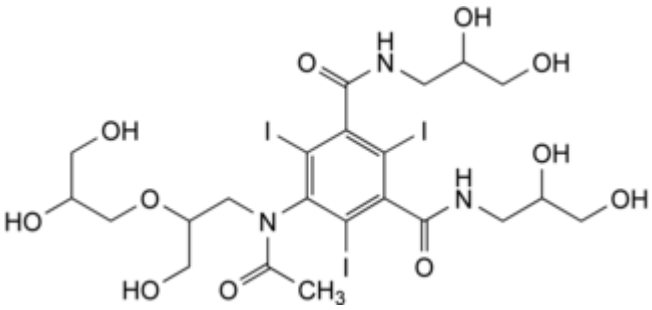
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *F, G, I, J, K, L, M, N, O, P, Q.*



A. 5-(acetylamino)-*N,N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide,

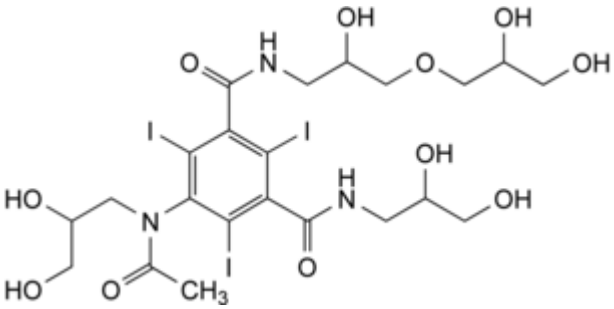


B. 5-[acetyl[3-(2,3-dihydroxypropoxy)-2-hydroxypropyl]amino]-*N,N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide,

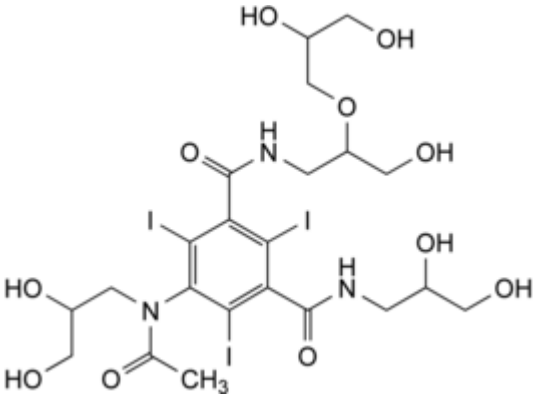


C. 5-[acetyl[2-(2,3-dihydroxypropoxy)-3-hydroxypropyl]amino]-*N,N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide,

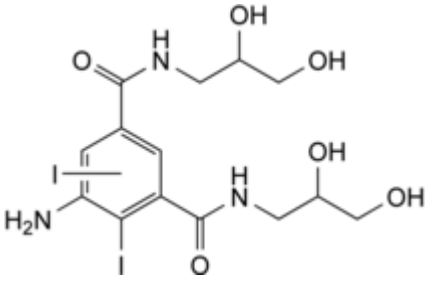
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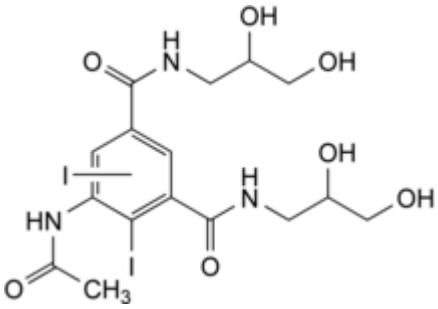
D. 5-[acetyl(2,3-dihydroxypropyl)amino]-*N*-[3-(2,3-dihydroxypropoxy)-2-hydroxypropyl]-*N*′-(2,3-dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide,



E. 5-[acetyl(2,3-dihydroxypropyl)amino]-*N*-[2-(2,3-dihydroxypropoxy)-3-hydroxypropyl]-*N*′-(2,3-dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide,

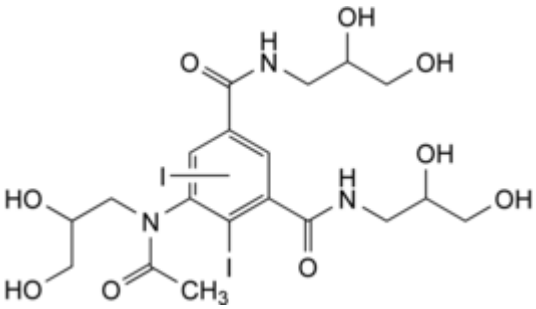


F. 5-amino-*N*,*N*′-bis(2,3-dihydroxypropyl)diiodobenzene-1,3-dicarboxamide,

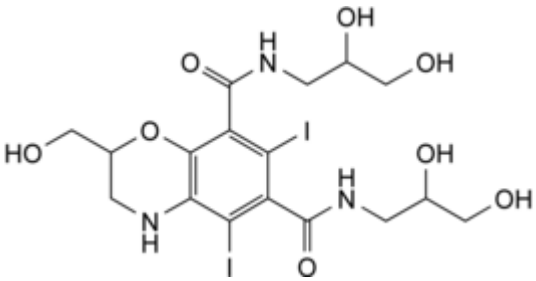


G. 5-(acetylamino)-*N*,*N*′-bis(2,3-dihydroxypropyl)diiodobenzene-1,3-dicarboxamide,

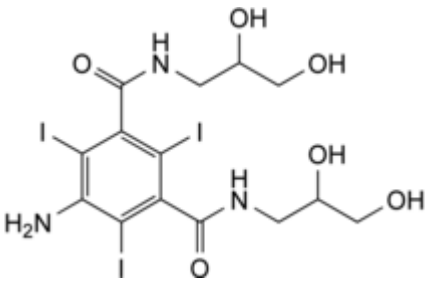
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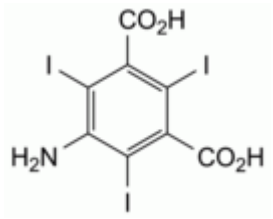
H. 5-[acetyl(2,3-dihydroxypropyl)amino]-*N,N*′-bis(2,3-dihydroxypropyl)diiodobenzene-1,3-dicarboxamide,



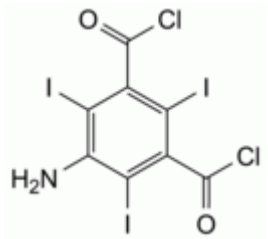
I. *N,N*′-bis(2,3-dihydroxypropyl)-2-(hydroxymethyl)-5,7-diiodo-3,4-dihydro-2*H*-1,4-benzoxazine-6,8-dicarboxamide,



J. 5-amino-*N,N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide,

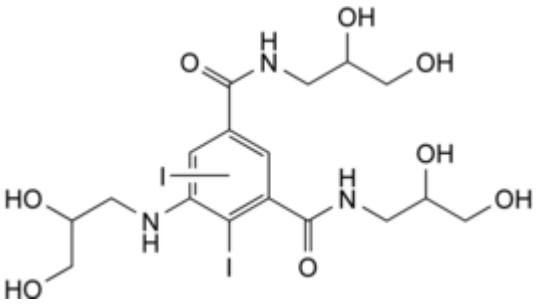


K. 5-amino-2,4,6-triiodobenzene-1,3-dicarboxylic acid,

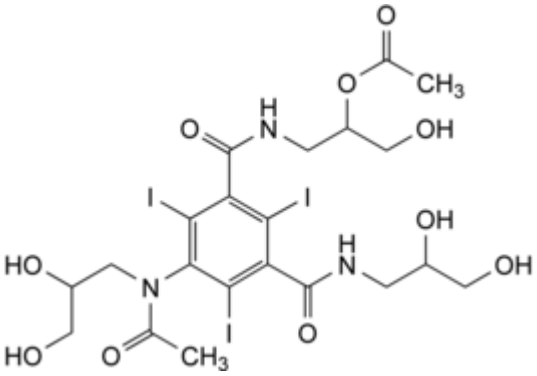


L. 3,5-bis(chlorocarbonyl)-2,4,6-triiodobenzenamine,

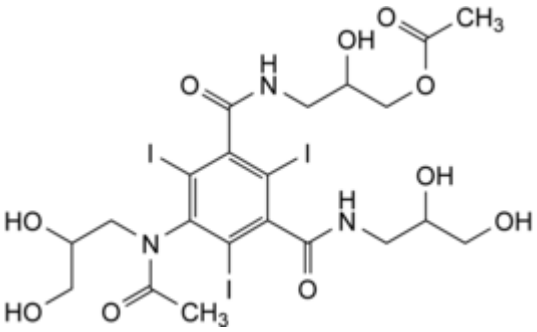
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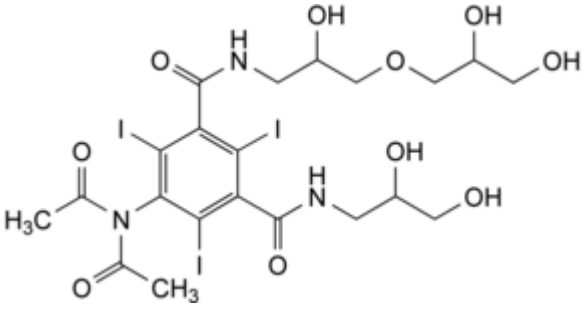
M. *N,N′*-bis(2,3-dihydroxypropyl)-5-[(2,3-dihydroxypropyl)amino]diiodobenzene-1,3-dicarboxamide,



N. 5-[acetyl(2,3-dihydroxypropyl)amino]-*N*-[2-(acetyloxy)-3-hydroxypropyl]-*N′*-(2,3-dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide,

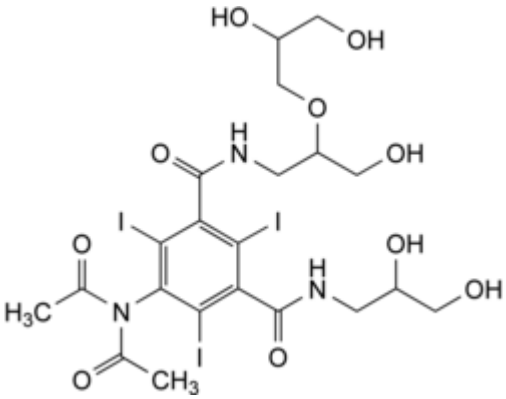


O. 5-[acetyl(2,3-dihydroxypropyl)amino]-*N*-[3-(acetyloxy)-2-hydroxypropyl]-*N′*-(2,3-dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide,



P. 5-(diacetylamino)-*N*-[3-(2,3-dihydroxypropoxy)-2-hydroxypropyl]-*N′*-(2,3-dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide,

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Q. 5-(diacetylamino)-*N*-[2-(2,3-dihydroxypropoxy)-3-hydroxypropyl]-*N*′-(2,3-dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide.

Ph Eur

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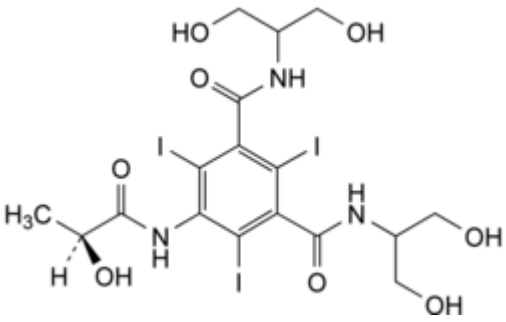
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You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Iopamidol

General Notices

(Ph. Eur. monograph 1115)



$C_{17}H_{22}I_3N_3O_8$ *777* *60166-93-0*

Action and use

Iodinated contrast medium.

Preparations

Iopamidol Injection

Iopamidol Oral Solution

Ph Eur

DEFINITION

N,*N*′-Bis[2-hydroxy-1-(hydroxymethyl)ethyl]-5-[[(2*S*)-2-hydroxypropanoyl]amino]-2,4,6-triiodobenzene-1,3-dicarboxamide.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

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Freely soluble in water, very slightly soluble in methanol, practically insoluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *iopamidol CRS*.

B. Loss on drying (see Tests).

C. Specific optical rotation (see Tests).

TESTS

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, *Method II*).

Dissolve 1 g in *water R* and dilute to 50 mL with the same solvent.

Acidity or alkalinity

Dissolve 10.0 g in *carbon dioxide-free water R* and dilute to 100 mL with the same solvent. Not more than 0.75 mL of *0.01 M hydrochloric acid* or 1.4 mL of *0.01 M sodium hydroxide* is required to adjust to pH 7.0 (2.2.3).

Specific optical rotation (2.2.7)

-4.6 to -5.2 (dried substance), determined at 436 nm.

Dissolve 10.0 g, with heating if necessary, in *water R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.50 g of the substance to be examined in *water R* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dissolve 5.0 mg of *iopamidol impurity H CRS* in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (b) Dilute 2.0 mL of the test solution to 20.0 mL with *water R*. Dilute 1.0 mL of this solution to 50.0 mL with *water R*.

Reference solution (c) Add 0.1 mL of the test solution to 20 mL of reference solution (a) and dilute to 50 mL with *water R*.

Column 2 columns coupled in series,

— *size*: *l* = 0.25 m, Ø = 4.6 mm,

— *stationary phase*: *phenylsilyl silica gel for chromatography R* (5 µm),

— *temperature*: 60 °C.

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Mobile phase:

— *mobile phase A*: *water R*,

— *mobile phase B*: *acetonitrile R*, *water R* (50:50 *V/V*),

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 18	100	0
18 - 40	100 - 62	0 - 38
40 - 45	62 - 50	38 - 50
45 - 50	50 - 100	50 - 0
50 - 60	100	0

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 20 µL.

Relative retention With reference to iopamidol (retention time = about 14.6 min): impurity D = about 0.1; impurity B = about 0.6; impurities I and H = about 0.9; impurity G = about 1.1; impurity K = about 1.2; impurity C = about 1.3; impurity J = about 1.5; impurity A = about 1.8; impurity E = about 2.2; impurity F = about 2.3.

System suitability Reference solution (c):

— *resolution*: minimum 2.0 between the peaks due to impurity H and iopamidol.

Limits:

— *sum of impurities H and I*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent),

— *impurities A, B, C, D, E, F, G, J, K*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent),

— *any other impurity*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent),

— *sum of impurities other than H and I*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent),

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.01 per cent).

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Free aromatic amines

Maximum 200 ppm.

Keep the solutions and reagents in iced water, protected from bright light.

Test solution In a 25 mL volumetric flask, dissolve 0.500 g of the substance to be examined in 20.0 mL of *water R*.

Reference solution In a 25 mL volumetric flask, mix 4.0 mL of a 25.0 mg/L solution of *iopamidol impurity A CRS* with 16.0 mL of *water R*.

Blank solution Place 20.0 mL of *water R* in a 25 mL volumetric flask.

Place the flasks in iced water, protected from light, for 5 min. Add 1.0 mL of *hydrochloric acid R* to each flask, mix and allow to stand for 5 min. Add 1.0 mL of a 20 g/L solution of *sodium nitrite R* prepared immediately before use, mix and allow to stand for 5 min. Add 1.0 mL of a 120 g/L solution of *ammonium sulfamate R*, swirl gently until gas liberation has ceased, and allow to stand for 5 min. *(CAUTION: considerable pressure is produced)*. Add 1.0 mL of a freshly prepared 1 g/L solution of *naphthylethylenediamine dihydrochloride R* and mix. Remove the flasks from the iced water and allow to stand for 10 min. Dilute to 25.0 mL with *water R* and mix. Measure immediately the absorbance (*2.2.25*) at 500 nm of the solutions obtained from the test solution and the reference solution using, as the compensation liquid, the solution obtained from the blank solution.

The absorbance of the test solution is not greater than that of the reference solution.

Free iodine

Maximum 10 ppm.

Dissolve 2.0 g in 25 mL of *water R* in a ground-glass stoppered centrifuge tube. Add 5 mL of *toluene R* and 5 mL of *dilute sulfuric acid R*. Shake and centrifuge. Any red colour of the upper layer is not more intense than that of the upper phase obtained in the same way from 22 mL of *water R*, 2 mL of *iodide standard solution (10 ppm I) R*, 5 mL of *dilute sulfuric acid R*, 1 mL of *strong hydrogen peroxide solution R* and 5 mL of *toluene R*.

Iodide

Maximum 10 ppm.

Dissolve 6.000 g in *water R* and dilute to 20 mL with the same solvent. Add 2.0 mL of *0.001 M potassium iodide*. Carry out a potentiometric titration (*2.2.20*) with *0.001 M silver nitrate* using a silver indicator electrode and an appropriate reference electrode. Subtract the volume of titrant corresponding to the 2.0 mL of *0.001 M potassium iodide*, determined by titrating a blank to which is added 2.0 mL of *0.001 M potassium iodide* and use the residual value to calculate the iodide content.

1 mL of *0.001 M silver nitrate* is equivalent to 126.9 µg of iodide.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

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Maximum 0.1 per cent, determined on 1.0 g.

Bacterial endotoxins (2.6.14)

Less than 1.4 IU/g, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

To 0.300 g in a 250 mL round-bottomed flask add 5 mL of *strong sodium hydroxide solution R*, 20 mL of *water R*, 1 g of *zinc powder R* and a few glass beads. Boil under a reflux condenser for 30 min. Allow to cool and rinse the condenser with 20 mL of *water R*, adding the rinsings to the flask. Filter through a sintered-glass filter (2.1.2) and wash the filter with several quantities of *water R*. Collect the filtrate and washings. Add 5 mL of *glacial acetic acid R* and titrate immediately with *0.1 M silver nitrate*. Determine the end-point potentiometrically (2.2.20) using a suitable electrode system such as silver-silver chloride.

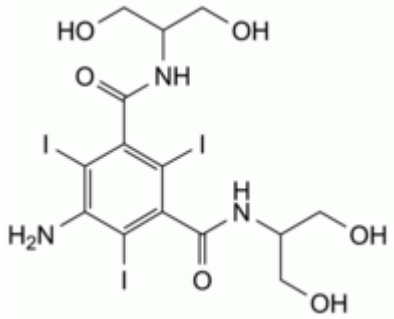
1 mL of *0.1 M silver nitrate* is equivalent to 25.90 mg of $C_{17}H_{22}I_3N_3O_8$.

STORAGE

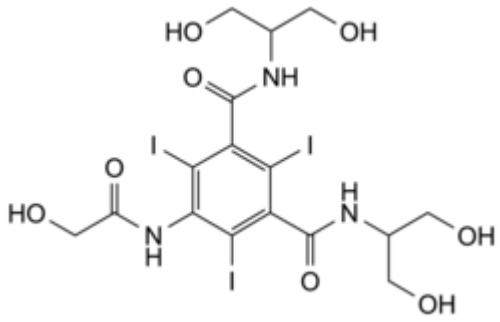
Protected from light. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

IMPURITIES

Specified impurities *A, B, C, D, E, F, G, H, I, J, K.*

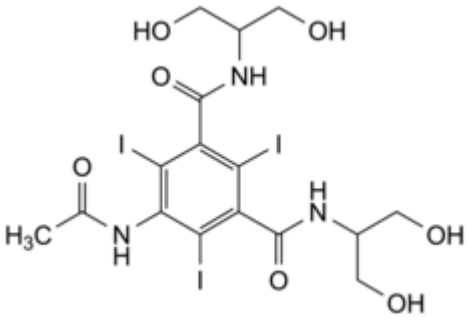


A. 5-amino-*N*,*N*′-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-2,4,6-triiodobenzene-1,3-dicarboxamide,

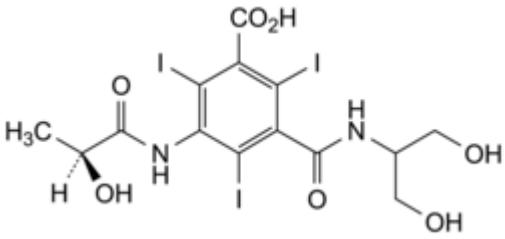


B. 5-[(hydroxyacetyl)amino]-*N*,*N*′-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-2,4,6-triiodobenzene-1,3-dicarboxamide,

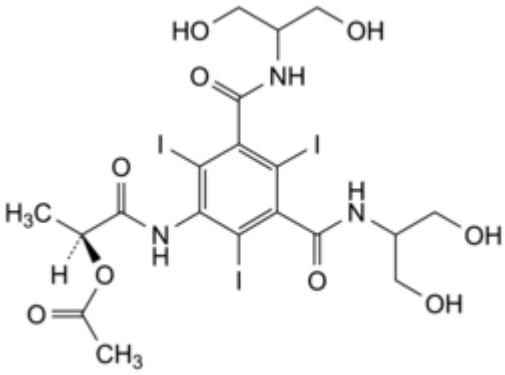
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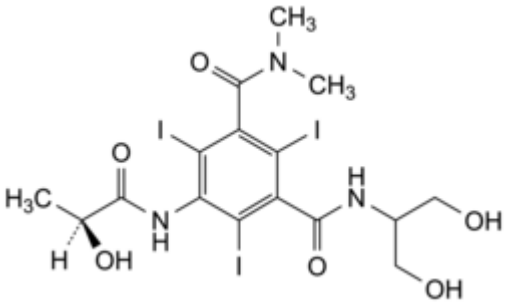
C. 5-(acetylamino)-*N*,*N*′-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-2,4,6-triiodobenzene-1,3-dicarboxamide,



D. 3-[[2-hydroxy-1-(hydroxymethyl)ethyl]carbamoyl]-5-[[(2*S*)-2-hydroxypropanoyl]amino]-2,4,6-triiodobenzoic acid,

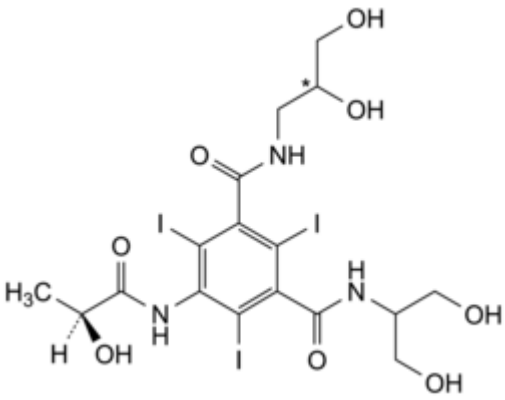


E. (1*S*)-2-[[3,5-bis[[2-hydroxy-1-(hydroxymethyl)ethyl]carbamoyl]-2,4,6-triiodophenyl]amino]-1-methyl-2-oxoethyl acetate,

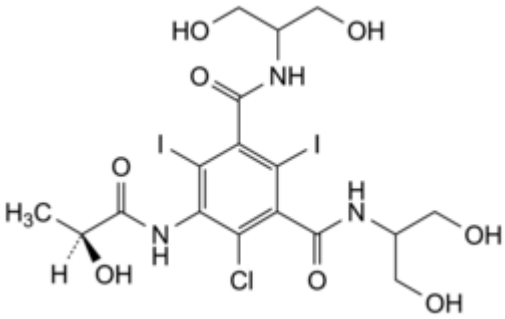


F. *N*′-[2-hydroxy-1-(hydroxymethyl)ethyl]-5-[[(2*S*)-2-hydroxypropanoyl]amino]-2,4,6-triiodo-*N*,*N*-dimethylbenzene-1,3-dicarboxamide,

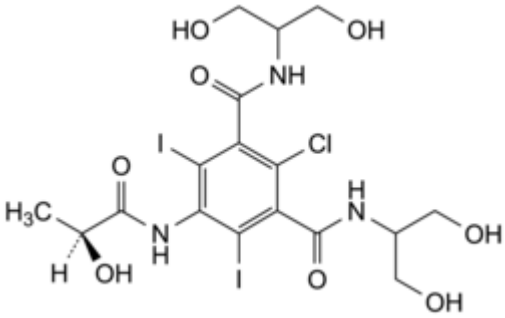
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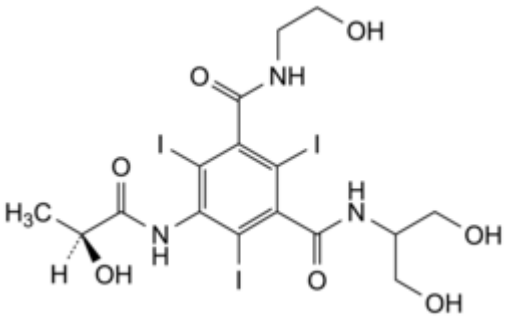
G. *N*-(2,3-dihydroxypropyl)-*N*′-[2-hydroxy-1-(hydroxymethyl)ethyl]-5-[[(2*S*)-2-hydroxypropanoyl]amino]-2,4,6-triiodobenzene-1,3-dicarboxamide,



H. 4-chloro-*N*,*N*′-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-5-[[(2*S*)-2-hydroxypropanoyl]amino]-2,6-diiodobenzene-1,3-dicarboxamide,

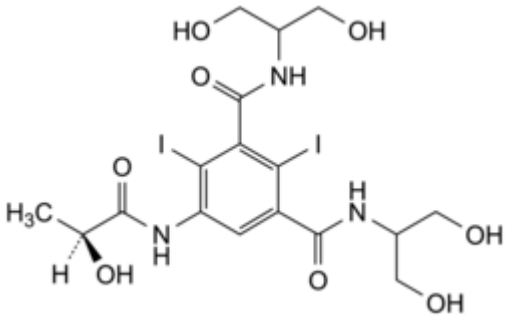


I. 2-chloro-*N*,*N*′-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-5-[[(2*S*)-2-hydroxypropanoyl]amino]-4,6-diiodobenzene-1,3-dicarboxamide,



J. *N*-(2-hydroxyethyl)-*N*′-[2-hydroxy-1-(hydroxymethyl)ethyl]-5-[[(2*S*)-2-hydroxypropanoyl]amino]-2,4,6-triiodobenzene-1,3-dicarboxamide,

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K. *N*,*N*′-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-5-[[(2*S*)-2-hydroxypropanoyl]amino]-2,4-diiodobenzene-1,3-dicarboxamide.

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Iopamidol Injection

General Notices

Action and use

Iodinated contrast medium.

DEFINITION

Iopamidol Injection is a solution of Iopamidol in Water for Injections with or without excipients.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of iopamidol, $C_{17}H_{22}I_3N_3O_8$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Dry 1 mL of the injection over *phosphorus pentoxide* at a pressure of 2 kPa for 16 hours. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of iopamidol (*RS 441*).

B. In the test for Related substances, the principal peak in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (5).

TESTS

Acidity or alkalinity

pH, 6.5 to 7.5, Appendix V L.

Light absorption

The *light absorption* of a 4-cm layer of the injection, Appendix II B at 450 nm is not more than 0.120.

Free aromatic amines

The following solutions and reagents are stored in ice-water and protected from bright light.

Mix a volume of the injection containing 0.5 g of Iopamidol with *water* and add sufficient *water* to produce 20 mL. Place the solution in ice-water, protected from light, for 5 minutes. Add 1.0 mL of *hydrochloric acid*, mix and allow to stand for 5 minutes. Add 1.0 mL of a 2% w/v solution of *sodium nitrite* prepared immediately before use, mix and allow to stand for 5 minutes. Add 1.0 mL of a 12% w/v solution of *ammonium sulfamate*, swirl gently until gas liberation has ceased and allow to stand for 5 minutes. Add 1.0 mL of a freshly prepared 0.1% w/v solution of *naphthylethylenediamine dihydrochloride* and mix. Remove from the ice-water and allow to stand for 10 minutes. Add

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sufficient *water* to produce 25 mL and mix. Immediately measure the *absorbance* at 500 nm, Appendix II B, using in the reference cell a solution prepared by treating 20 mL of *water* in the same manner.

The *absorbance* is not greater than that obtained by treating 20 mL of a 0.00125% w/v solution of *iopamidol impurity A EPCRS* in *water* in the same manner and beginning at the words “Place the solution…”.(500 ppm).

Free iodine

Mix a volume of the injection containing 2.0 g of Iopamidol with *water* and add sufficient *water* to produce 25 mL. Add 5 mL of *toluene* and 5 mL of *dilute sulfuric acid*, shake and centrifuge. Any red colour in the upper phase is not more intense than that of the upper phase obtained in the same manner from a mixture of 22 mL of *water*, 2 mL of *iodide standard solution (10 ppm I)*, 5 mL of *dilute sulfuric acid*, 1 mL of *hydrogen peroxide solution (100 vol)* and 5 mL of *toluene* (10 ppm).

Iodide

To 10 mL of the injection add sufficient *water* to produce 50 mL. Add 2.0 mL of *0.001M potassium iodide*. Carry out the method for *potentiometric titration*, Appendix VIII B, using 0.001M *silver nitrate VS*, a silver indicator electrode and an appropriate reference electrode. Subtract the volume of titrant corresponding to the 2.0 mL of *0.001M potassium iodide*, determined by titrating a blank to which is added 2.0 mL of 0.001M *potassium iodide*, and use the residual value to calculate the iodide content.

1 mL of *0.001M silver nitrate VS* is equivalent to 126.9 µg of iodide.

Not more than 2.0 mL of *0.001M silver nitrate VS* is required (40 ppm).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix a volume of the injection containing 0.5 g of Iopamidol with *water* and add sufficient *water* to produce 50 mL.
(2) 0.005% w/v of *iopamidol impurity H EPCRS* in *water*.
(3) Dilute 1 volume of solution (1) to 500 volumes with *water*.
(4) To 200 volumes of solution (2) add 1 volume of solution (1) and add sufficient *water* to produce 500 volumes.
(5) 1.0% w/v of *iopamidol EPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use two stainless steel columns (25 cm × 4.6 mm) coupled in series and packed with *phenylsilyl silica gel for chromatography* (5 µm) (Zorbax SB-Phenyl 80 Å is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 2.0 mL per minute.
(d) Use a column temperature of 60°.
(e) Use a detection wavelength of 240 nm.
(f) Inject 20 µL of each solution.

The retention time of iopamidol is about 15 minutes and the retention time of the peak due to impurity H is about 13 minutes. Impurity H and impurity I have identical retention times.

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MOBILE PHASE

Mobile phase A *water*.

Mobile phase B Equal volumes of *acetonitrile* and *water*.

Equilibrate the column for at least 20 minutes with mobile phase A.

Time (Minutes)	Mobile phase A (%v/v)	Mobile phase B (%v/v)	Comment
0-18	100	0	isocratic
18-40	100→62	0→38	linear gradient
40-45	62→50	38→50	linear gradient
45-50	50→100	50→0	linear gradient
50-60	100	0	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution factor* between the peaks corresponding to iopamidol and iopamidol impurity H is at least 2.0. If necessary, adjust the composition of the mobile phase or the time programme of the gradient.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity H or impurity I is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (3) (0.5%);

the area of any other *secondary peak* is not greater than half the area of the principal peak in the chromatogram obtained with solution (3) (0.1%);

the sum of the areas of any *secondary peaks* other than impurites H and I is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%).

Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (3) (0.05%).

Sterility

Complies with the *test for sterility*, Appendix XVI A.

Bacterial endotoxins

The endotoxin limit concentration is 0.7 IU per mL, Appendix XIV C.

ASSAY

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Mix a volume of the injection containing 0.220 g of Iopamidol with *water* and add sufficient *water* to produce 20 mL. Add 5 mL of *strong sodium hydroxide solution*, 1 g of *zinc powder* and a few glass beads. Boil under a reflux condenser for 30 minutes. Allow to cool and rinse the condenser with 20 mL of *water*, adding the rinsings to the flask. Filter through a sintered-glass filter and wash the filter with several quantities of *water*. Collect the filtrate and washings. Add 5 mL of *glacial acetic acid* and titrate immediately with *0.1M silver nitrate VS*. Carry out the method for *potentiometric titration*, Appendix VIII B, using a suitable electrode system such as silver-silver chloride.

Each mL of *0.1M silver nitrate VS* is equivalent to 25.90 mg of $C_{17}H_{22}I_3N_3O_8$.

STORAGE

Iopamidol Injection should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of Iopamidol and as the equivalent amount of iodine.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Iopamidol.

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Iopamidol Oral Solution

General Notices

Action and use

Iodinated contrast medium.

DEFINITION

Iopamidol Oral Solution is a solution of Iopamidol in a suitable aqueous vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of iopamidol, $C_{17}H_{22}I_3N_3O_8$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Dry 1 mL of the oral solution over *phosphorus pentoxide* at a pressure of 2 kPa for 16 hours. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of iopamidol (*RS 441*).

B. In the test for Related substances, the principal peak in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (5).

TESTS

Acidity

pH, 4.0 to 5.5, Appendix V L.

Free aromatic amines

The following solutions and reagents are stored in ice-water and protected from bright light.

Mix a volume of the oral solution containing 0.5 g of Iopamidol with *water* and add sufficient *water* to produce 20 mL. Place the solution in ice-water, protected from light, for 5 minutes. Add 1.0 mL of *hydrochloric acid*, mix and allow to stand for 5 minutes. Add 1.0 mL of a 2% w/v solution of *sodium nitrite* prepared immediately before use, mix and allow to stand for 5 minutes. Add 1.0 mL of a 12% w/v solution of *ammonium sulfamate*, swirl gently until gas liberation has ceased and allow to stand for 5 minutes. Add 1.0 mL of a freshly prepared 0.1% w/v solution of *naphthylethylenediamine dihydrochloride* and mix. Remove from the ice-water and allow to stand for 10 minutes. Add sufficient *water* to produce 25 mL and mix. Immediately measure the *absorbance* at 500 nm, Appendix II B, using in the reference cell a solution prepared by treating 20 mL of *water* in the same manner.

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The *absorbance* is not greater than that obtained by treating 20 mL of a 0.00125% w/v solution of *iopamidol impurity A EPCRS* in *water* in the same manner and beginning at the words “Place the solution…”.(500 ppm).

Free iodine

Mix a volume of the oral solution containing 2.0 g of Iopamidol with *water* and add sufficient *water* to produce 25 mL. Add 5 mL of *toluene* and 5 mL of *dilute sulfuric acid*. Shake and centrifuge. Any red colour in the upper phase is not more intense than that of the upper phase obtained in the same manner from a mixture of 22 mL of *water*, 2 mL of *iodide standard solution (10 ppm I)*, 5 mL of *dilute sulfuric acid*, 1 mL of *hydrogen peroxide solution (100 vol)* and 5 mL of *toluene* (10 ppm).

Iodide

Mix a volume of the oral solution containing 6.0 g of Iopamidol with *water* and add sufficient *water* to produce 20 mL. Add 2.0 mL of *0.001M potassium iodide*. Carry out the method for *potentiometric titration*, Appendix VIII B, using *0.001M silver nitrate VS*, a silver indicator electrode and an appropriate reference electrode. Subtract the volume of titrant corresponding to the 2.0 mL of *0.001M potassium iodide*, determined by titrating a blank to which is added 2.0 mL of *0.001M potassium iodide* and use the residual value to calculate the iodide content.

Not more than 2.0 mL of *0.001M silver nitrate VS* is required (65 ppm).

Each mL of *0.001M silver nitrate VS* is equivalent to 126.9 µg of iodide.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix a volume of the oral solution containing 0.5 g of Iopamidol with *water* and add sufficient *water* to produce 50 mL.
(2) 0.005% w/v of *iopamidol impurity H EPCRS* in *water*.
(3) Dilute 1 volume of solution (1) to 500 volumes with *water*.
(4) To 200 volumes of solution (2) add 1 volume of solution (1) and add sufficient *water* to produce 500 volumes.
(5) 1.0% w/v of *iopamidol EPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use two stainless steel columns (25 cm × 4.6 mm) coupled in series and packed with *phenylsilyl silica gel for chromatography* (5 µm) (Zorbax SB-Phenyl 80 Å is suitable).
(b) Use gradient elution and the mobile phases described below.
(c) Use a flow rate of 2.0 mL per minute.
(d) Use a column temperature of 60°.
(e) Use a detection wavelength of 240 nm.
(f) Inject 20 µL of each solution.

The retention time of iopamidol is about 15 minutes and the retention time of the peak due to impurity H is about 13 minutes. Impurity H and impurity I have identical retention times.

MOBILE PHASE

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Mobile phase A *water*.

Mobile phase B Equal volumes of *acetonitrile* and *water*.

Equilibrate the column for at least 20 minutes with mobile phase A.

Time (Minutes)	Mobile phase A (%v/v)	Mobile phase B (%v/v)	Comment
0-18	100	0	isocratic
18-40	100→62	0→38	linear gradient
40-45	62→50	38→50	linear gradient
45-50	50→100	50→0	linear gradient
50-60	100	0	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution factor* between the peaks corresponding to iopamidol and iopamidol impurity H is at least 2.0. If necessary, adjust the composition of the mobile phase or the time programme of the gradient.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity H or impurity I is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (3) (0.5%);

the area of any other *secondary peak* is not greater than half the area of the principal peak in the chromatogram obtained with solution (3) (0.1%);

the sum of the areas of any *secondary peaks* other than impurities H and I is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%).

Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (3) (0.05%).

ASSAY

Mix a volume of the oral solution containing 0.220 g of Iopamidol with *water* and add sufficient *water* to produce 20 mL. Add 5 mL of *strong sodium hydroxide solution*, 1 g of *zinc powder* and a few glass beads. Boil under a reflux condenser for 30 minutes. Allow to cool and rinse the condenser with 20 mL of *water*, adding the rinsings to the flask. Filter through a sintered-glass filter and wash the filter with several quantities of *water*. Collect the filtrate and washings. Add 5 mL of *glacial acetic acid* and titrate immediately with *0.1M silver nitrate VS*. Carry out the method for *potentiometric titration*, Appendix VIII B, using a suitable electrode system such as silver-silver chloride.

Each mL of *0.1M silver nitrate VS* is equivalent to 25.90 mg of $C_{17}H_{22}I_3N_3O_8$.

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STORAGE

Iopamidol Oral Solution should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of Iopamidol and as the equivalent amount of iodine.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Iopamidol.

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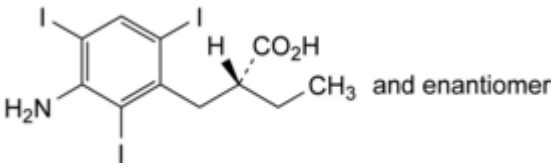
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Iopanoic Acid

General Notices

(Ph. Eur. monograph 0700)



$C_{11}H_{12}I_3NO_2$ 571 *96-83-3*

Action and use

Iodinated contrast medium.

Ph Eur

DEFINITION

Iopanoic acid contains not less than 98.5 per cent and not more than the equivalent of 101.0 per cent of (*RS*)-2-(3-amino-2,4,6-tri-iodobenzyl)butanoic acid, calculated with reference to the dried substance.

CHARACTERS

A white or yellowish-white powder, practically insoluble in water, soluble in anhydrous ethanol and in methanol. It dissolves in dilute solutions of alkali hydroxides.

IDENTIFICATION

First identification: B.

Second identification: A, C, D.

A. Melting point (*2.2.14*): about 155 °C, with decomposition.

B. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *iopanoic acid CRS*.

C. Examine the chromatograms obtained in the test for related substances (see Tests). Spray the plate with a 1 g/L solution of *4-dimethylaminocinnamaldehyde R* in a mixture of 1 volume of *hydrochloric acid R* and 99 volumes of *ethanol (96 per cent) R*. The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

D. Heat 50 mg carefully in a small porcelain dish over a flame. Violet vapour is evolved.

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TESTS

Appearance of solution

Dissolve 1.0 g in *1 M sodium hydroxide* and dilute to 20 mL with the same solvent. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_3 (*2.2.2, Method II*).

Related substances

Examine by thin-layer chromatography (*2.2.27*), using *silica gel GF_{254} R* as the coating substance.

Test solution (a) Dissolve 1.0 g of the substance to be examined in a mixture of 3 volumes of *ammonia R* and 97 volumes of *methanol R* and dilute to 10 mL with the same mixture of solvents.

Test solution (b) Dilute 1 mL of test solution (a) to 10 mL with a mixture of 3 volumes of *ammonia R* and 97 volumes of *methanol R*.

Reference solution (a) Dissolve 50 mg of *iopanoic acid CRS* in a mixture of 3 volumes of *ammonia R* and 97 volumes of *methanol R* and dilute to 5 mL with the same mixture of solvents.

Reference solution (b) Dilute 1 mL of test solution (b) to 50 mL with a mixture of 3 volumes of *ammonia R* and 97 volumes of *methanol R*.

Apply separately to the plate 5 µL of each solution. Develop over a path of 10 cm using a mixture of 10 volumes of *concentrated ammonia R*, 20 volumes of *methanol R*, 20 volumes of *toluene R* and 50 volumes of *dioxan R*. Examine in ultraviolet light at 254 nm. Any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.2 per cent).

Halides

To 0.46 g add 10 mL of *nitric acid R* and 15 mL of *water R*. Shake for 5 min and filter. 15 mL of the filtrate complies with the limit test for chlorides (*2.4.4*) (180 ppm, expressed as chloride).

Loss on drying (*2.2.32*)

Not more than 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 1 h.

Sulfated ash (*2.4.14*)

Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

To 0.150 g in a 250 mL round-bottomed flask add 5 mL of *strong sodium hydroxide solution R*, 20 mL of *water R*, 1 g of *zinc powder R* and a few glass beads. Boil under a reflux condenser for 60 min. Allow to cool and rinse the condenser with 20 mL of *water R*, adding the rinsings to the flask. Filter through a sintered-glass filter (*2.1.2*) and wash the filter with several quantities of *water R*. Collect the filtrate and washings. Add 40 mL of *dilute sulfuric acid R* and titrate immediately with *0.1 M silver nitrate*. Determine the end-point potentiometrically (*2.2.20*).

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1 mL of *0.1 M silver nitrate* is equivalent to 19.03 mg of $C_{11}H_{12}I_3NO_2$.

STORAGE

Store protected from light.

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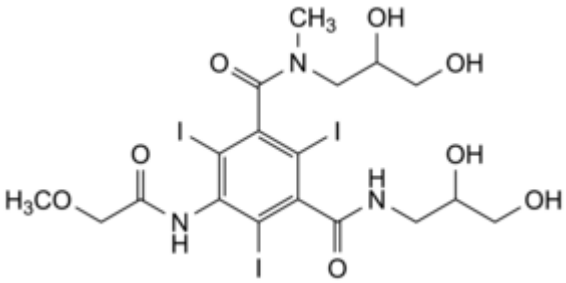
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Iopromide

General Notices

(Ph. Eur. monograph 1753)



$C_{18}H_{24}I_3N_3O_8$ 791 *73334-07-3*

Action and use

Iodinated contrast medium.

Ph Eur

DEFINITION

N,*N*′-Bis(2,3-dihydroxypropyl)-2,4,6-triiodo-5-[(methoxyacetyl)amino]-*N*-methylbenzene-1,3-dicarboxamide.

Mixture of diastereoisomers and atropisomers.

Content

97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or slightly yellowish powder.

Solubility

Freely soluble in water and in dimethyl sulfoxide, practically insoluble in ethanol (96 per cent) and in acetone.

IDENTIFICATION

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Infrared absorption spectrophotometry (2.2.24).

Comparison *iopromide CRS*.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solutions BY_6, B_6 and Y_6 (2.2.2, *Method I*).

Dissolve 16.5 g in 20 mL of *carbon dioxide-free water R* while heating on a water-bath at a temperature not exceeding 70 °C. Allow to cool to room temperature.

Conductivity (2.2.38)

Maximum 50 $\mu S \cdot cm^{-1}$.

Dissolve 1.000 g in *water R* and dilute to 50.0 mL with the same solvent.

Impurity A and related primary aromatic amines

Maximum 0.01 per cent.

Protect the solutions from light throughout the test. All given times are critical for the test results. The test solution, reference solution and blank solution must be processed in parallel.

Test solution Dissolve 0.500 g of the substance to be examined in 20.0 mL of *water R* in a 25 mL volumetric flask.

Reference solution Dissolve the contents of a vial of *iopromide impurity A CRS* in 5.0 mL of *water R*. Transfer 2.0 mL of this solution to a 25 mL volumetric flask and add 18.0 mL of *water R*.

Blank solution Place 20.0 mL of *water R* in a 25 mL volumetric flask.

Cool the test solution, reference solution and blank solution in a bath of iced water for 5 min. Add 1.0 mL of *hydrochloric acid R1* to each solution and cool again for 5 min in a bath of iced water. Add 1.0 mL of a 20 g/L solution of *sodium nitrite R*, shake vigorously and cool for another 5 min in a bath of iced water. To each solution add 0.50 mL of an 80 g/L solution of *sulfamic acid R*. Over the next 5 min, shake vigorously several times, raising the stoppers to vent the gas that evolves. Afterwards, add to each solution 1.0 mL of a 1 g/L solution of *naphthylethylenediamine dihydrochloride R* in a mixture of 300 volumes of *water R* and 700 volumes of *propylene glycol R*, shake, allow to cool to room temperature for 10 min and dilute to 25.0 mL with *water R*. Degas the solutions in an ultrasonic bath for 1 min and measure the absorbance (2.2.25) of the test solution and the reference solution at 495 nm against the blank, within 5 min. The test is not valid unless the absorbance of the reference solution is at least 0.08. The absorbance of the test solution is not greater than the absorbance of the reference solution.

Impurity B

Liquid chromatography (2.2.29).

Solvent mixture *methanol R*, *water R* (50:50 *V/V*).

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Test solution Dissolve 40.0 mg of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Reference solution (a) Dissolve 40.0 mg of *iopromide CRS* in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Reference solution (b) Introduce several millilitres of reference solution (a) into a vial sealed with a crimp-top. Heat at 121 °C for 15 min.

Reference solution (c) Dilute 1.5 mL of the test solution to 100.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 20 °C.

Mobile phase Mix 6 g of *chloroform R* with 59 g of *methanol R*. Add 900 g of *water for chromatography R* in small portions to the chloroform/methanol mixture and stir for at least 2 h to obtain a homogeneous solution.

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL of the test solution and reference solutions (a) and (c).

Run time 50 min.

Identification of impurities Use the chromatogram supplied with *iopromide CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurity B isomers Y_1 and Y_2.

Relative retention With reference to iopromide isomer Z_2 (retention time = about 34 min): impurity B isomer Y_1 = about 0.28; impurity B isomer Y_2 = about 0.31.

System suitability Reference solution (a):

— the chromatogram obtained shows 2 peaks due to impurity B isomers Y_1 and Y_2.

Limit:

— *sum of impurity B isomers Y_1 and Y_2*: not more than the sum of the areas of the 2 principal peaks due to the iopromide in the chromatogram obtained with reference solution (c) (1.5 per cent).

Related substances

Thin-layer chromatography (*2.2.27*).

Solvent mixture *methanol R*, *water R* (50:50 *V/V*).

Test solution Dissolve 1.0 g of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

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Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture.

Reference solution (b) Dilute 5.0 mL of reference solution (a) to 10.0 mL with the solvent mixture.

Reference solution (c) Dilute 2.0 mL of reference solution (a) to 10.0 mL with the solvent mixture.

Reference solution (d) Dilute 1.0 mL of reference solution (a) to 10.0 mL with the solvent mixture.

Reference solution (e) Dissolve the contents of a vial of *iopromide for system suitability 1 CRS* (containing impurities B and E) in 50 µL of the solvent mixture.

Reference solution (f) Dissolve the contents of a vial of *iopromide for system suitability 2 CRS* (containing impurities B, C, D and F) in 50 µL of the solvent mixture.

Plates *TLC silica gel F_{254} plate R* (2 plates).

A. *Mobile phase*: *concentrated ammonia R*, *water R*, *dioxan R* (4:15:85 *V/V/V*).

Application 2 µL of the test solution and reference solutions (b), (d) and (e).

Development Over 3/4 of the plate.

Drying In a current of air, until complete evaporation of the solvents, then at 120 °C for 30 min.

Detection Examine immediately in ultraviolet light at 254 nm; expose to ultraviolet light for 2-5 min until the principal spots appear clearly as yellow spots, then spray with *ferric chloride-ferricyanide-arsenite reagent R* and examine immediately in daylight.

Retardation factors Impurity B = about 0.26; iopromide = about 0.34; impurity E = about 0.41.

System suitability Reference solution (e):

— the chromatogram shows 3 clearly separated spots.

Limits:

— *impurity E*: any spot due to impurity E is not more intense than the principal spot in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *unspecified impurities*: any other spot is not more intense than the principal spot in the chromatogram obtained with reference solution (d) (0.10 per cent); disregard any spot due to impurity B.

B. *Mobile phase*: *anhydrous formic acid R*, *water R*, *methanol R*, *chloroform R* (2:6:32:62 *V/V/V/V*).

Application 2 µL of the test solution and reference solutions (a), (b) ,(c), (d) and (f).

Development Over 3/4 of the plate.

Drying In a current of air, until complete evaporation of the solvents, then at 120 °C for 30 min.

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Detection Examine immediately in ultraviolet light at 254 nm; expose to an ammonia vapour for 30 min, dry in a current of air for 10 min, then expose to ultraviolet light for 2-5 min until the principal spots appear clearly as yellow spots, then spray with *ferric chloride-ferricyanide-arsenite reagent R* and examine immediately in daylight.

Retardation factors Impurity C = about 0.23; impurity D = about 0.29; impurity B = about 0.36; iopromide = about 0.43; impurity F = about 0.71.

System suitability Reference solution (f):

— the chromatogram shows 5 clearly separated spots.

Limits:

— *impurity D*: any spot due to impurity D is not more intense than the principal spot in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *impurity C*: any spot due to impurity C is not more intense than the principal spot in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *impurity F*: any spot due to impurity F is not more intense than the principal spot in the chromatogram obtained with reference solution (c) (0.2 per cent);

— *unspecified impurities*: any other spot is not more intense than the principal spot in the chromatogram obtained with reference solution (d) (0.10 per cent); disregard any spot due to impurity B.

Isomer distribution

Liquid chromatography (*2.2.29*) as described in the test for impurity B with the following modifications.

Calculate the percentage content of the isomer groups with reference to the total area of all the peaks due to the 4 iopromide isomers, using the chromatogram obtained with the test solution.

Limits:

— *sum of iopromide isomers E_1 and Z_1*: 40.0 per cent to 51.0 per cent;

— *sum of iopromide isomers E_2 and Z_2*: 49.0 per cent to 60.0 per cent.

Free iodine

Dissolve 2.0 g in 20 mL of *water R* in a glass-stoppered test tube. Add 2 mL of *dilute sulfuric acid R* and 2 mL of *toluene R*, close and shake vigorously. The upper layer remains colourless (*2.2.2, Method II*).

Iodide

Maximum 2 ppm.

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Dissolve 10.0 g in 50 mL of *carbon dioxide-free water R*. Adjust to pH 3-4 adding about 0.15 mL of *0.1 M sulfuric acid*. Titrate with *0.001 M silver nitrate*. Determine the end-point potentiometrically (*2.2.20*) using a combined metal electrode. Not more than 0.15 mL of *0.001 M silver nitrate* is required to reach the end-point.

Water (*2.5.12*)

Maximum 1.5 per cent, determined on 1.00 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

Bacterial endotoxins (*2.6.14*)

Less than 1.0 IU/g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for impurity B with the following modifications.

Injection Test solution and reference solutions (a) and (b).

Identification of the isomers The 2 principal peaks in the chromatogram obtained with reference solution (a) are due to iopromide isomers Z_1 and Z_2 . The 2 peaks that have an increased size in the chromatogram obtained with reference solution (b) in comparison to the chromatogram obtained with reference solution (a), are due to iopromide isomers E_1 and E_2.

Relative retention With reference to iopromide isomer Z_2 (retention time = about 34 min): iopromide isomer E_1 = about 0.70; iopromide isomer E_2 = about 0.75; iopromide isomer Z_1 = about 0.85.

System suitability Reference solution (a):

— *resolution*: minimum 2.0 between the peaks due to iopromide isomers Z_1 and Z_2.

Calculate the percentage content of iopromide from the declared content of *iopromide CRS* and from the sum of the areas of all of the peaks due to isomer groups E and Z.

STORAGE

Protected from light.

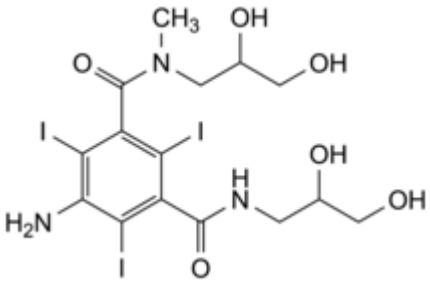
IMPURITIES

Specified impurities *A, B, C, D, E, F.*

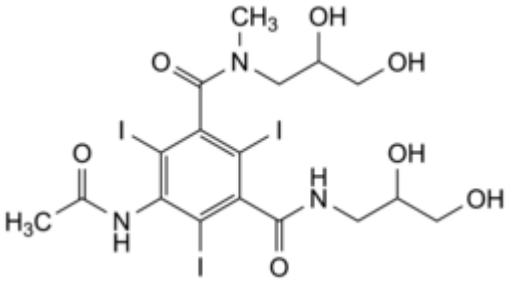
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph

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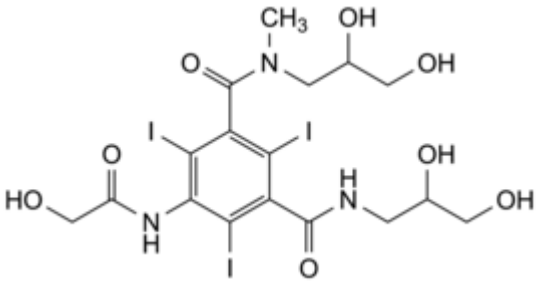
Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) G, H.



A. 5-amino-*N*,*N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-*N*-methylbenzene-1,3-dicarboxamide,

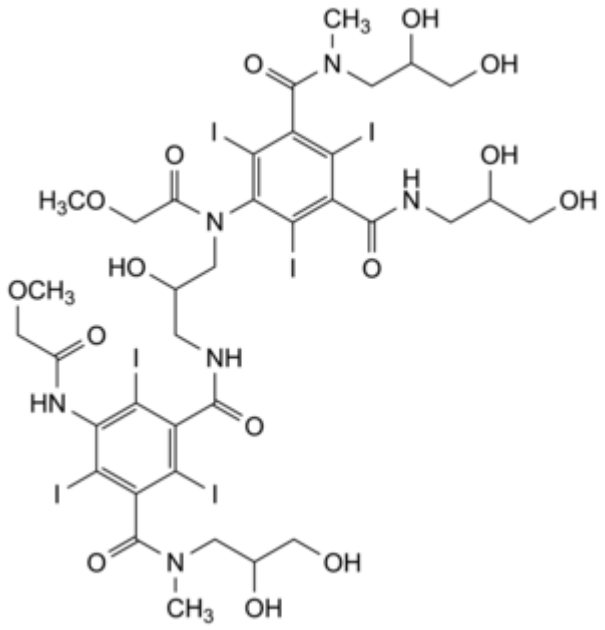


B. 5-(acetylamino)-*N*,*N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-*N*-methylbenzene-1,3-dicarboxamide,

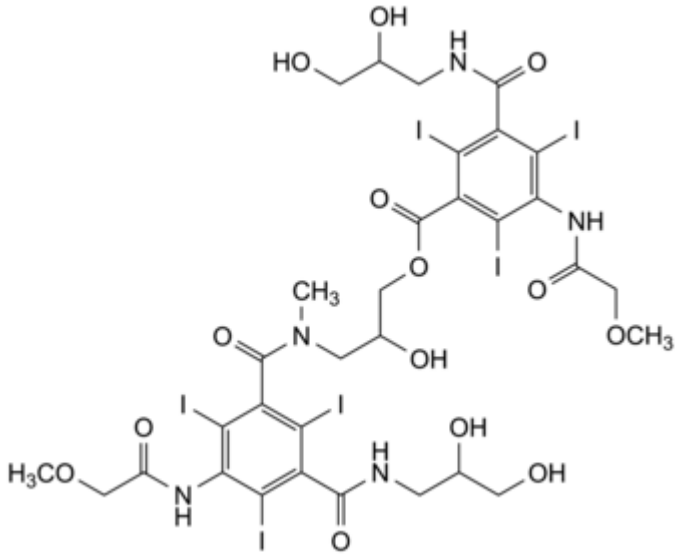


C. *N*,*N*′-bis(2,3-dihydroxypropyl)-5-[(hydroxyacetyl)amino]-2,4,6-triiodo-*N*-methylbenzene-1,3-dicarboxamide,

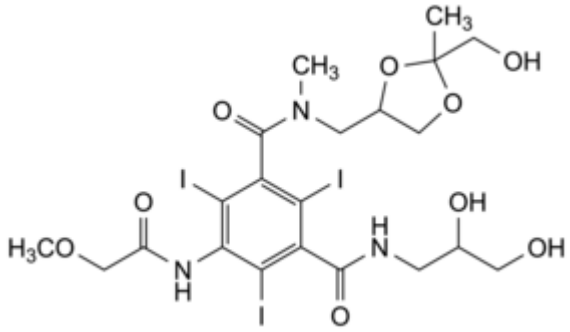
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D. *N*-(2,3-dihydroxypropyl)-*N'*-[3-[[3-[(2,3-dihydroxypropyl)carbamoyl]-5-[(2,3-dihydroxypropyl)methylcarbamoyl]-2,4,6-triiodophenyl](methoxyacetyl)amino]-2-hydroxypropyl]-2,4,6-triiodo-5-[(methoxyacetyl)amino]-*N*-methylbenzene-1,3-dicarboxamide,

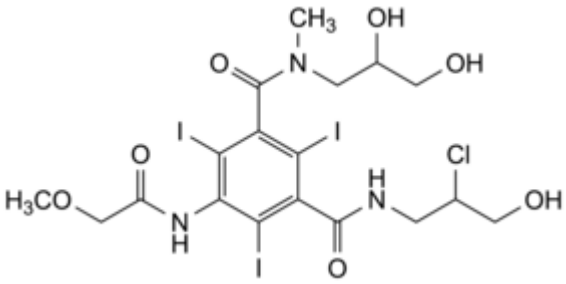


E. 3-[[3-[(2,3-dihydroxypropyl)carbamoyl]-2,4,6-triiodo-5-[(methoxyacetyl)amino]benzoyl]methylamino]-2-hydroxypropyl 3-[(2,3-dihydroxypropyl)carbamoyl]-2,4,6-triiodo-5-[(methoxyacetyl)amino]benzoate,

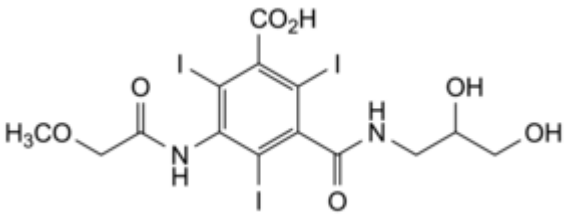


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F. *N*′-(2,3-dihydroxypropyl)-*N*-[[2-(hydroxymethyl)-2-methyl-1,3-dioxolan-4-yl]methyl]-2,4,6-triiodo-5-[(methoxyacetyl)amino]-*N*-methylbenzene-1,3-dicarboxamide,



G. *N*′-(2-chloro-3-hydroxypropyl)-*N*-(2,3-dihydroxypropyl)-2,4,6-triiodo-5-[(methoxyacetyl)amino]-*N*-methylbenzene-1,3-dicarboxamide,



H. 3-[(2,3-dihydroxypropyl)carbamoyl]-2,4,6-triiodo-5-[(methoxyacetyl)amino]benzoic acid.

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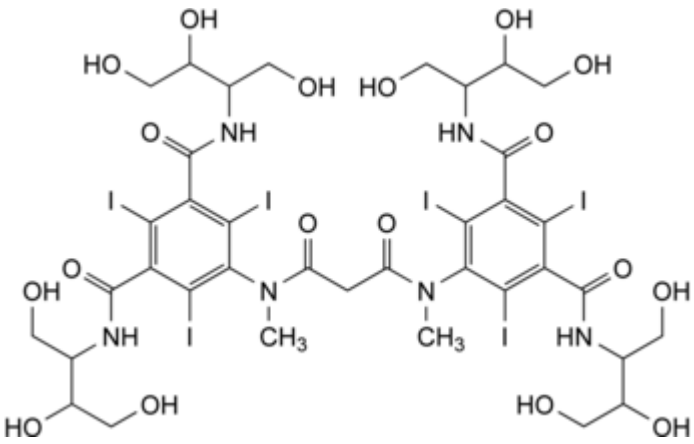
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You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Iotrolan

General Notices

(Ph. Eur. monograph 1754)



$C_{37}H_{48}I_6N_6O_{18}$ 1626 *79770-24-4*

Action and use

Iodinated contrast medium.

Ph Eur

DEFINITION

Mixture of stereoisomers of 5,5′-[propanedioylbis(methylimino)]bis[*N*,*N*′-bis[2,3-dihydroxy-1-(hydroxymethyl)propyl]2,4,6-triiodobenzene-1,3-dicarboxamide].

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or yellowish-white powder, hygroscopic.

Solubility

Very soluble in water, freely soluble in dimethyl sulfoxide, practically insoluble in ethanol (96 per cent).

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IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *iotrolan CRS*.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution BY_6 (2.2.2, *Method II*).

Dissolve 18.0 g in *carbon dioxide-free water R* and dilute to 20.0 mL with the same solvent.

Conductivity (2.2.38)

Maximum 25 $\mu S \cdot cm^{-1}$.

Dissolve 1.000 g in *water R* and dilute to 50.0 mL with the same solvent.

Primary aromatic amines

Protect the solutions from light throughout the test. All given times are critical for the test results. The test solution, the reference solution and the blank solution must be processed in parallel.

Test solution Dissolve 0.500 g of the substance to be examined in 20.0 mL of *water R* in a 25 mL volumetric flask.

Reference solution Dissolve 5.0 mg of *iopamidol impurity A CRS* in *water R* and dilute to 20.0 mL with the same solvent. Transfer 1.0 mL of this solution to a 25 mL volumetric flask and add 19.0 mL of *water R*.

Blank solution Place 20.0 mL of *water R* in a 25 mL volumetric flask.

Procedure Cool the test solution, reference solution and blank solution in a bath of iced water for 5 min. Add 1.0 mL of *hydrochloric acid R1* to each solution and cool again for 5 min in a bath of iced water. Add 1.0 mL of a 20 g/L solution of *sodium nitrite R*, shake vigorously and cool for another 5 min in a bath of iced water. To each solution add 0.50 mL of an 80 g/L solution of *sulfamic acid R*. Over the next 5 min, shake vigorously several times, raising the stoppers to vent the gas that evolves. Afterwards add to each solution 1.0 mL of a 1 g/L solution of *naphthylethylenediamine dihydrochloride R* in a mixture of 300 volumes of *water R* and 700 volumes of *propylene glycol R*, shake, allow to cool to room temperature for 10 min and dilute to 25.0 mL with *water R*. Degas the solutions in an ultrasonic bath for 1 min and measure the absorbance (2.2.25) of the test solution and the reference solution at 495 nm against the blank, within 5 min.

System suitability:

— *absorbance of the reference solution*: minimum 0.40.

Limit:

— *absorbance of the test solution*: not more than the absorbance of the reference solution (0.05 per cent).

Related substances

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Thin-layer chromatography (2.2.27). *Prepare the solutions immediately before use*.

Test solution Dissolve 1.0 g of the substance to be examined in a mixture of equal volumes of *methanol R* and *water R* and dilute to 10.0 mL with the same mixture of solvents.

Reference solution (a) Dilute 1.0 mL of the test solution to 200.0 mL with a mixture of equal volumes of *methanol R* and *water R*.

Reference solution (b) Dilute 2.0 mL of reference solution (a) to 10.0 mL with a mixture of equal volumes of *methanol R* and *water R*.

Reference solution (c) Dissolve the contents of a vial of *iotrolan for system suitability CRS* (containing about 0.05 per cent of each of impurities A and B) in 50 µL of a mixture of equal volumes of *methanol R* and *water R*.

Plate *TLC silica gel F_{254} plate R*.

Pretreatment Over 3/4 of the plate with *methylene chloride R*.

Mobile phase *concentrated ammonia R*, *water R*, *dioxan R* (4:20:80 *V/V/V*).

Application 2 µL.

Development Over 3/4 of the plate.

Drying In a current of air until the solvents have evaporated.

Detection Examine in ultraviolet light at 254 nm. Expose the plate to the ultraviolet light for 2-5 min until the principal spots appear clearly as yellow spots. Spray with *ferric chloride-ferricyanide-arsenite reagent R* and examine in daylight.

R_F values Iotrolan = about 0.25; impurity A = about 0.4; impurity B = about 0.5.

System suitability Reference solution (c):

— the chromatogram shows 3 clearly separated spots.

Limits:

— *impurities A, B*: any spot due to impurity A or B is not more intense than the principal spot in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *unspecified impurities*: any other spot is not more intense than the principal spot in the chromatogram obtained with reference solution (b) (0.10 per cent).

Isomer distribution

Liquid chromatography (2.2.29) as described under Assay. Use the normalisation procedure.

Identification of peaks Use the chromatogram supplied with *iotrolan CRS* and the chromatogram obtained with the reference solution to identify the peaks due to the 3 isomer groups.

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Calculate the percentage content of each of the isomer groups G1, G2 and G3, with reference to the total area of all of the peaks due to the 3 isomer groups, using the chromatogram obtained with the test solution.

Limits:

— *isomer group G1*: 53.0 per cent to 70.0 per cent;

— *isomer group G2*: 3.0 per cent to 11.0 per cent;

— *isomer group G3*: 25.0 per cent to 39.0 per cent.

Free iodine

Dissolve 0.20 g in 1 mL of *water R* in a glass-stoppered test tube. Add 4 mL of a 370 g/L solution of *sulfuric acid R* and 5 mL of *toluene R*, close and shake vigorously. The upper layer remains colourless (*2.2.2, Method II*).

Iodide

Maximum 20 ppm.

Dissolve 10.0 g in 50 mL of *carbon dioxide-free water R*. Adjust to pH 3-4 adding about 0.15 mL of *dilute sulfuric acid R*. Titrate with *0.001 M silver nitrate*, determining the end-point potentiometrically (*2.2.20*). Not more than 1.5 mL of *0.001 M silver nitrate* is required to reach the end-point.

Water (*2.5.12*)

Maximum 3.5 per cent, determined on 0.250 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

Bacterial endotoxins (*2.6.14*)

Less than 0.7 IU/g.

ASSAY

Liquid chromatography (*2.2.29*).

Test solution Dissolve 40.0 mg of the substance to be examined in *water R* and dilute to 25.0 mL with the same solvent.

Reference solution Dissolve 40.0 mg of *iotrolan CRS* in *water R* and dilute to 25.0 mL with the same solvent.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

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— *temperature*: 40 °C.

Mobile phase *methanol R*, *water for chromatography R* (10:90 *V/V*).

Flow rate 0.5 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

Run time 40 min.

Retention time Isomer group G1 = about 8 min to 12 min; isomer group G2 = about 15 min to 22 min; isomer group G3 = about 22 min to 32 min.

System suitability Reference solution:

— the chromatogram obtained is similar to the chromatogram supplied with *iotrolan CRS*.

Calculate the percentage content of iotrolan from the total area of all of the peaks of the 3 isomer groups G1, G2 and G3 and the declared content of *iotrolan CRS*.

STORAGE

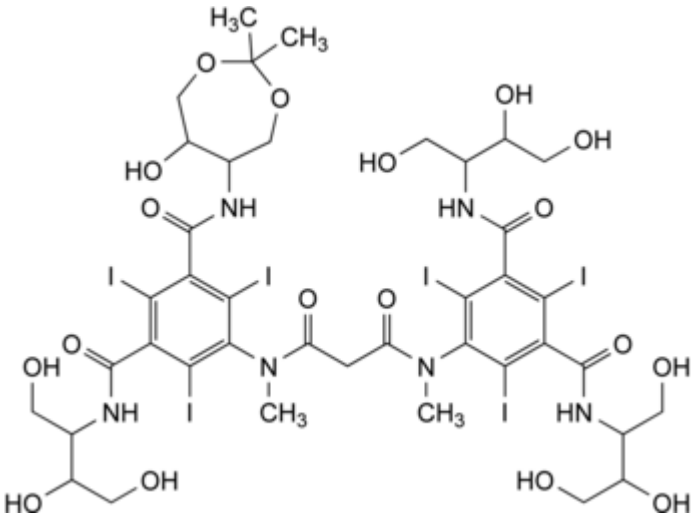
In an airtight container, protected from light.

IMPURITIES

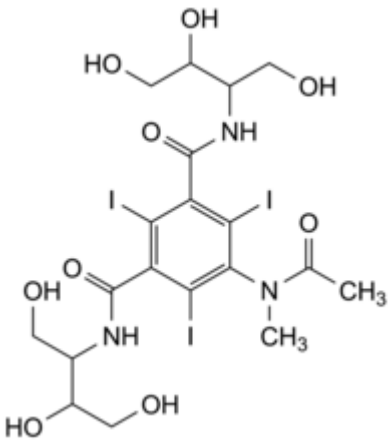
Specified impurities *A, B.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, D, E, F, G, H, I, J.*

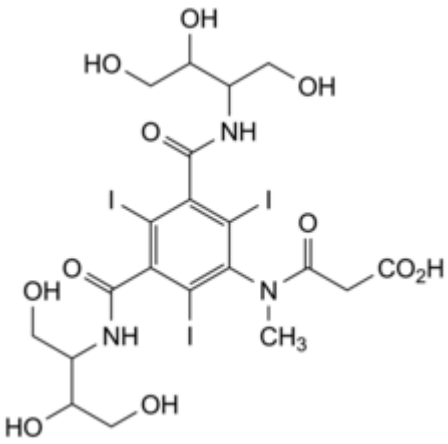
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A. *N*,*N*′-bis[2,3-dihydroxy-1-(hydroxymethyl)propyl]-5-[[3-[[3-[[2,3-dihydroxy-1-(hydroxymethyl)propyl]carbamoyl]-5-[(6-hydroxy-2,2-dimethyl-1,3-dioxepan-5-yl)carbamoyl]-2,4,6-triiodophenyl]methylamino]-3-oxopropanoyl]methylamino]-2,4,6-triiodobenzene-1,3-dicarboxamide,

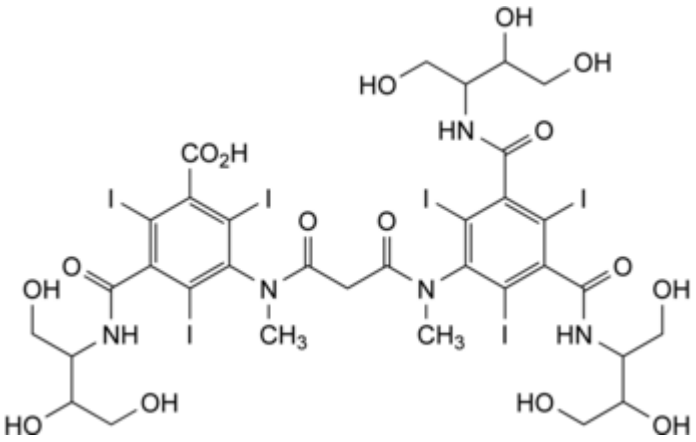


B. 5-(acetylmethylamino)-*N*,*N*′-bis[2,3-dihydroxy-1-(hydroxymethyl)propyl]-2,4,6-triiodobenzene-1,3-dicarboxamide,

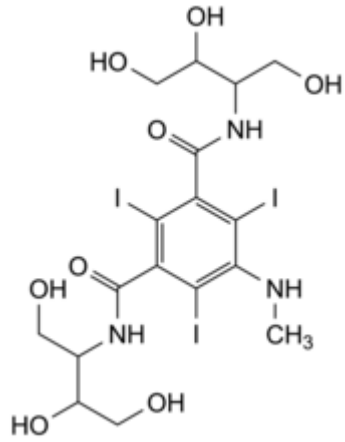


C. 3-[[3,5-bis[[2,3-dihydroxy-1-(hydroxymethyl)propyl]carbamoyl]-2,4,6-triiodophenyl]methylamino]-3-oxopropanoic acid,

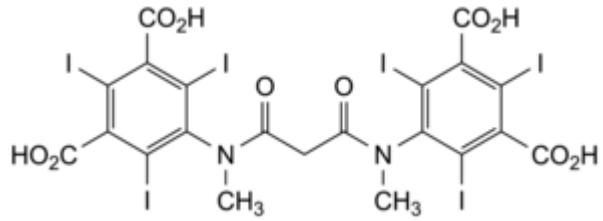
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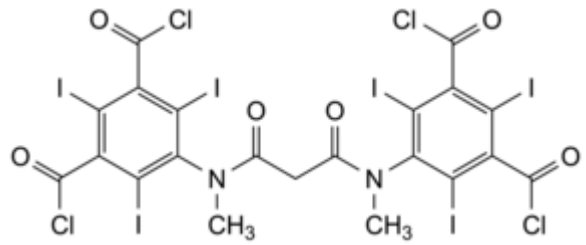
D. 3-[[3-[[3,5-bis[[2,3-dihydroxy-1-(hydroxymethyl)propyl]carbamoyl]-2,4,6-triiodophenyl]methylamino]-3-oxopropanoyl]methylamino]-5-[[2,3-dihydroxy-1-(hydroxymethyl)propyl]carbamoyl]-2,4,6-triiodobenzoic acid,



E. *N,N′*-bis[2,3-dihydroxy-1-(hydroxymethyl)propyl]-2,4,6-triiodo-5-(methylamino)benzene-1,3-dicarboxamide,

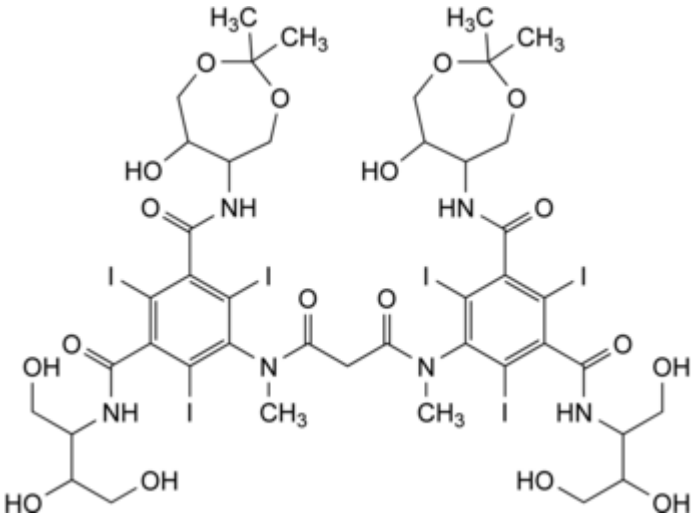


F. 5,5′-[propanedioylbis(methylimino)]bis[2,4,6-triiodobenzene-1,3-dicarboxylic] acid,

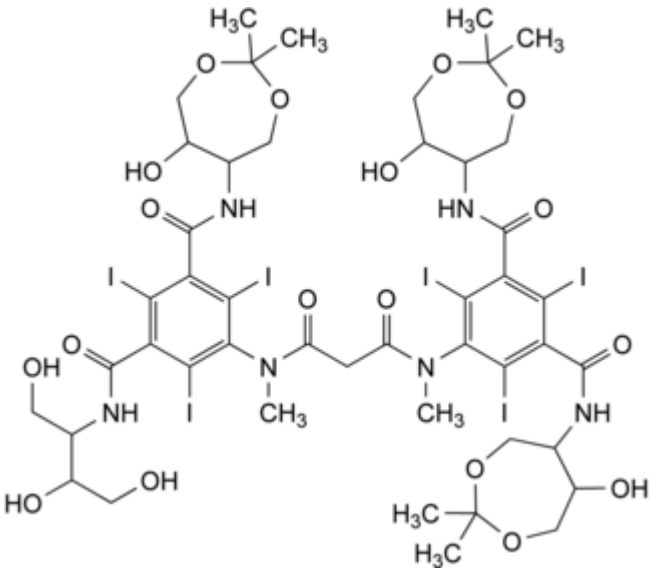


G. 5,5′-[propanedioylbis(methylimino)]bis[2,4,6-triiodobenzene-1,3-dicarbonyl] tetrachloride,

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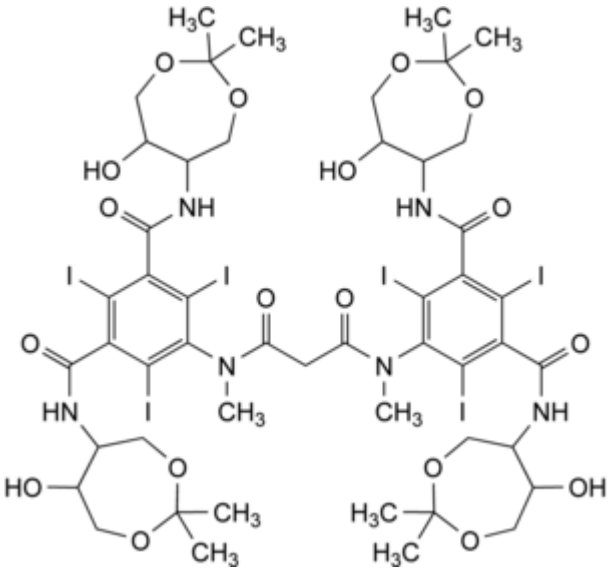


H. 5,5′-[propanedioylbis(methylimino)]bis[*N*-[2,3-dihydroxy-1-(hydroxymethyl)propyl]-*N*′-(6-hydroxy-2,2-dimethyl-1,3-dioxepan-5-yl)-2,4,6-triiodobenzene-1,3-dicarboxamide],



I. 5-[[3-[[3-[[2,3-dihydroxy-1-(hydroxymethyl)propyl]carbamoyl]-5-[(6-hydroxy-2,2-dimethyl-1,3-dioxepan-5-yl)carbamoyl]-2,4,6-triiodophenyl]methylamino]-3-oxopropanoyl]methylamino]-*N*,*N*′-bis(6-hydroxy-2,2-dimethyl-1,3-dioxepan-5-yl)-2,4,6-triiodobenzene-1,3-dicarboxamide,

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J. 5,5′-[propanedioylbis(methylimino)]bis[*N*,*N*′-bis(6-hydroxy-2,2-dimethyl-1,3-dioxepan-5-yl)-2,4,6-triiodobenzene-1,3-dicarboxamide].

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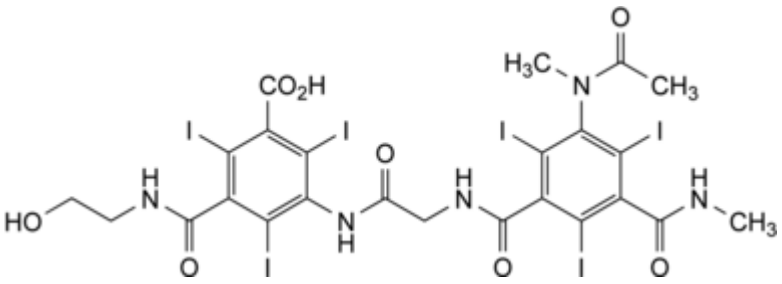
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Ioxaglic Acid

General Notices

(Ph. Eur. monograph 2009)



$C_{24}H_{21}I_6N_5O_8$ 1269 *59017-64-0*

Action and use

Iodinated contrast medium.

Ph Eur

DEFINITION

3-[[[[3-(Acetylmethylamino)-2,4,6-triiodo-5-(methylcarbamoyl)benzoyl]amino]acetyl]amino]-5-[(2-hydroxyethyl)carbamoyl]-2,4,6-triiodobenzoic acid.

Content

98.5 per cent to 101.5 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, hygroscopic powder.

Solubility

Very slightly soluble in water, slightly soluble in ethanol (96 per cent), very slightly soluble in methylene chloride. It dissolves in dilute solutions of alkali hydroxides.

IDENTIFICATION

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Infrared absorption spectrophotometry (2.2.24).

Comparison ioxaglic acid CRS.

TESTS

Appearance of solution

The solution is clear (2.2.1).

Dissolve 1.0 g in a 40 g/L solution of sodium hydroxide R and dilute to 20 mL with the same solution.

Absorbance (2.2.25)

Maximum 0.18, calculated for a solution containing 40 per cent of anhydrous ioxaglic acid.

Dissolve 10.0 g in about 8 mL of a 40 g/L solution of sodium hydroxide R. Adjust to pH 7.2-7.6 with a 40 g/L solution of sodium hydroxide R or 1 M hydrochloric acid. Dilute to 25 mL with water R. Filter through a membrane filter (nominal pore size 0.45 µm). Measure the absorbance at 450 nm using water R as the compensation liquid.

Related substances

Liquid chromatography (2.2.29): use the normalisation procedure.

Solvent mixture acetonitrile R, water R (5:95 *V/V*).

Test solution Dissolve 0.10 g of the substance to be examined in about 40 mL of the solvent mixture. Add 0.5 ± 0.1 mL of a 4 g/L solution of sodium hydroxide R and dilute to 50.0 mL with the solvent mixture. Shake until dissolution is complete, using ultrasound if necessary.

Reference solution (a) Dissolve 0.10 g of ioxaglic acid CRS in about 40 mL of the solvent mixture. Add 0.5 ± 0.1 mL of a 4 g/L solution of sodium hydroxide R and dilute to 50.0 mL with the solvent mixture. Shake until dissolution is complete, using ultrasound if necessary.

Reference solution (b) Dissolve 5 mg of ioxaglic acid impurity A CRS in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 50.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 25 °C.

Mobile phase:

— *mobile phase A*: 0.136 g/L solution of potassium dihydrogen phosphate R previously adjusted to pH 3.0 with phosphoric acid R;

— *mobile phase B*: acetonitrile R;

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	95 → 90	5 → 10
5 - 40	90	10
40 - 85	90 → 70	10 → 30
85 - 115	70	30
115 - 120	70 → 50	30 → 50
120 - 125	50	50

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 242 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *ioxaglic acid CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities B, C, D1, D2, D3, D4, E and F; use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A.

Relative retention With reference to ioxaglic acid (retention time = about 65 min): impurity A = about 0.3; impurity B = about 0.7; impurity C = about 0.9; impurity D1 = about 1.09; impurity E = about 1.12; impurity D2 = about 1.20; impurity D3 = about 1.26; impurity D4 = about 1.28; impurity F = about 1.6.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 1.3, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to ioxaglic acid.

Limits:

— *impurity D (sum of the peaks due to impurities D1, D2, D3 and D4)*: maximum 0.7 per cent;

— *impurity E*: maximum 0.7 per cent;

— *impurity F*: maximum 0.4 per cent;

— *impurity B*: maximum 0.3 per cent;

— *impurity C*: maximum 0.3 per cent;

— *impurity A*: maximum 0.1 per cent;

— *unspecified impurities*: for each impurity, maximum 0.2 per cent;

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— *total*: maximum 2.0 per cent;

— *reporting threshold*: 0.05 per cent; disregard any peak with a retention time greater than 125 min.

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

Iodides

Maximum 50 ppm.

Disperse 10.0 g in 50 mL of *water R*. Add 8 mL of *1 M sodium hydroxide*. After dissolution and homogenisation, add 1.0 mL of *glacial acetic acid R*. Immediately titrate with *0.001 M silver nitrate*, determining the end-point potentiometrically (*2.2.20*), using a silver indicator electrode and a suitable reference electrode.

1 mL of *0.001 M silver nitrate* is equivalent to 0.1269 mg of iodides.

Water (*2.5.12*)

Maximum 5.0 per cent, determined on 0.100 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

In a round-bottomed flask place 0.100 g of the substance to be examined and add 5 mL of *strong sodium hydroxide solution R*, 20 mL of *water R*, 1 g of *zinc powder R* and a few glass beads. Fit the flask with a reflux condenser and boil for 30 min. Cool and rinse the condenser with 20 mL of *water R*. Add the rinsings to the contents of the flask. Filter, wash the filter with 3 quantities, each of 15 mL, of *water R* and add the washings to the filtrate. Add 40 mL of *dilute sulfuric acid R* and titrate immediately with *0.05 M silver nitrate*. Determine the end-point potentiometrically (*2.2.20*).

1 mL of *0.05 M silver nitrate* is equivalent to 10.58 mg of $C_{24}H_{21}I_6N_5O_8$.

STORAGE

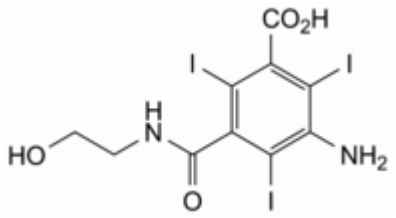
In an airtight container, protected from light.

IMPURITIES

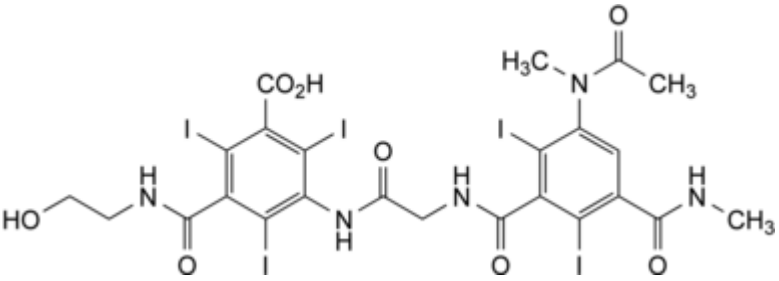
Specified impurities *A, B, C, D, E, F.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *G, H.*

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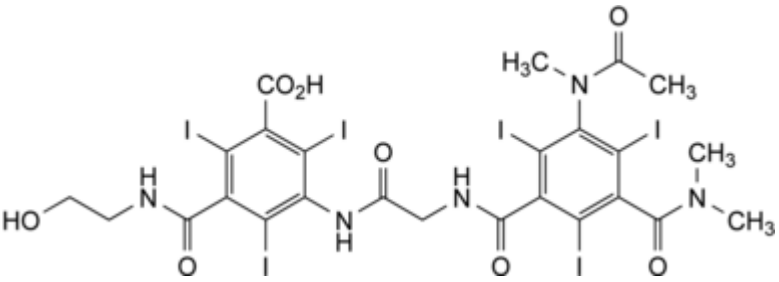


A. 3-amino-5-[(2-hydroxyethyl)carbamoyl]-2,4,6-triiodobenzoic acid,

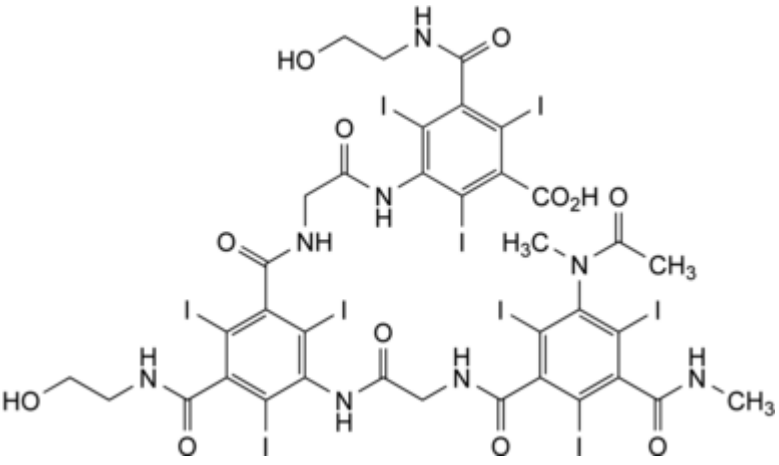


B. 3-[[[[3-(acetylmethylamino)-2,6-diiodo-5-(methylcarbamoyl)benzoyl]amino]acetyl]amino]-5-[(2-hydroxyethyl)carbamoyl]-2,4,6-triiodobenzoic acid,

C. unknown structure,



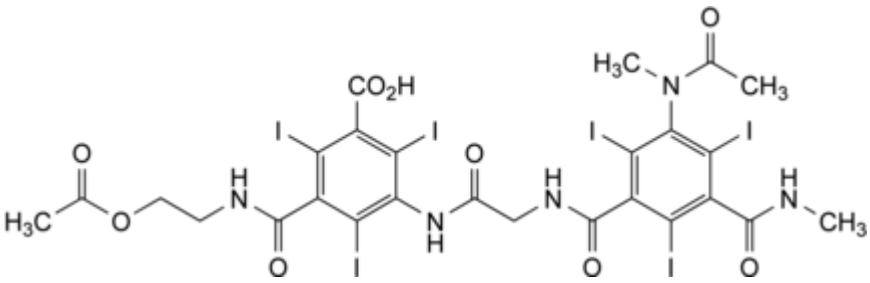
D. D1, D2, D3 and D4: 3-[[[[3-(acetylmethylamino)-5-(dimethylcarbamoyl)-2,4,6-triiodobenzoyl]amino]acetyl]amino]-5-[(2-hydroxyethyl)carbamoyl]-2,4,6-triiodobenzoic acid,



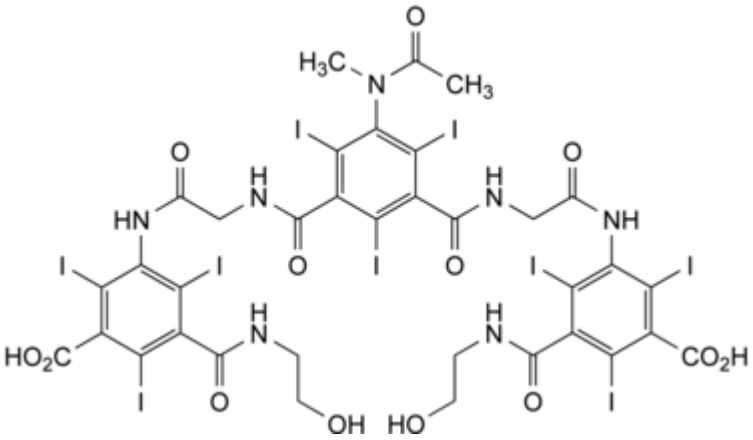
E. 3-[[[[3-[[[[3-(acetylmethylamino)-2,4,6-triiodo-5-(methylcarbamoyl)benzoyl]amino]acetyl]amino]-5-[(2-hydroxyethyl)carbamoyl]-2,4,6-triiodobenzoyl]amino]acetyl]amino]-5-[(2-hydroxyethyl)carbamoyl]-2,4,6-triiodobenzoic acid,

F. unknown structure,

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G. 3-[[[[3-(acetylmethylamino)-2,4,6-triiodo-5-(methylcarbamoyl)benzoyl]amino]acetyl]amino]-5-[[2-(acetyloxy)ethyl]carbamoyl]-2,4,6-triiodobenzoic acid,



H. 3,3′-[[5-(acetylmethylamino)-2,4,6-triiodo-1,3-phenylene]bis(carbonyliminomethylenecarbonylimino)]bis[5-[(2-hydroxyethyl)carbamoyl]-2,4,6-triiodobenzoic] acid.

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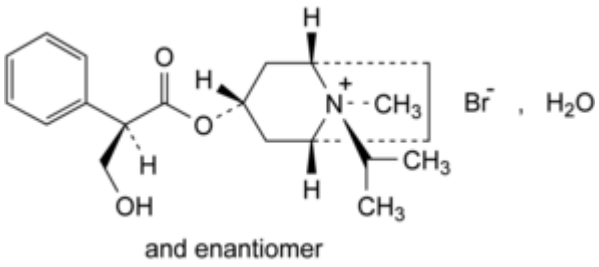
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Ipratropium Bromide

General Notices

(Ph. Eur. monograph 0919)



$C_{20}H_{30}BrNO_3,H_2O$ 430.4 *66985-17-9*

Action and use

Anticholinergic (antimuscarinic) bronchodilator.

Preparations

Ipratropium Nebuliser Solution

Ipratropium Pressurised Inhalation

Ph Eur

DEFINITION

(1*R*,3*r*,5*S*,8*r*)-3-[[(2*RS*)-3-Hydroxy-2-phenylpropanoyl]oxy]-8-methyl-8-(1-methylethyl)-8-azoniabicyclo[3.2.1]octane bromide monohydrate.

Content

99.0 per cent to 100.5 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Soluble in water, freely soluble in methanol, slightly soluble in ethanol (96 per cent).

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About 230 °C, with decomposition.

IDENTIFICATION

First identification: A, E.

Second identification: B, C, D, E.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *ipratropium bromide CRS*.

B. Examine the chromatograms obtained in the test for impurity A.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. To 5 mL of solution S (see Tests), add 2 mL of *dilute sodium hydroxide solution R*. No precipitate is formed.

D. To about 1 mg add 0.2 mL of *nitric acid R* and evaporate to dryness on a water-bath. Dissolve the residue in 2 mL of *acetone R* and add 0.1 mL of a 30 g/L solution of *potassium hydroxide R* in *methanol R*. A violet colour develops.

E. It gives reaction (a) of bromides (2.3.1).

TESTS

Solution S

Dissolve 0.50 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution GY_7 (2.2.2, Method II).

pH (2.2.3)

5.0 to 7.5 for solution S.

Impurity A

Thin-layer chromatography (2.2.27).

Test solution Dissolve 20 mg of the substance to be examined in *methanol R* and dilute to 1.0 mL with the same solvent.

Reference solution (a) Dissolve 20 mg of *ipratropium bromide CRS* in *methanol R* and dilute to 1.0 mL with the same solvent.

Reference solution (b) Dissolve 20 mg of *methylatropine bromide CRS* in 1.0 mL of reference solution (a).

Reference solution (c) Dissolve 5 mg of *ipratropium impurity A CRS* in 100.0 mL of *methanol R*. Dilute 2.0 mL of the solution to 5.0 mL with *methanol R*.

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Plate TLC silica gel plate R (2-10 µm).

Mobile phase *anhydrous formic acid R*, water R, ethanol (96 per cent) R, methylene chloride R (1:3:18:18 *V/V/V/V*).

Application 1 µL.

Development Over a path of 6 cm.

Drying At 60 °C for 15 min.

Detection Spray with potassium iodobismuthate solution R5, allow the plate to dry in air, spray with a 50 g/L solution of sodium nitrite R and protect immediately with a sheet of glass.

System suitability The chromatogram obtained with reference solution (b) shows 2 clearly separated principal spots.

Limit:

— *impurity A*: any spot due to impurity A is not more intense than the principal spot in the chromatogram obtained with reference solution (c) (0.1 per cent).

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.200 g of the substance to be examined in the mobile phase and dilute to 20.0 mL with the mobile phase.

Reference solution (a) Dissolve 10.0 mg of ipratropium bromide CRS in the mobile phase and dilute to 20.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 50.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of ipratropium bromide CRS and 5 mg of ipratropium impurity B CRS in 1 mL of methanol R and dilute to 25.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 20.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

— *stationary phase*: octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 30 °C.

Mobile phase Dissolve 12.4 g of sodium dihydrogen phosphate R and 1.7 g of tetrapropylammonium chloride R in 870 mL of water for chromatography R; adjust to pH 5.5 with a 180 g/L solution of disodium hydrogen phosphate dodecahydrate R and add 130 mL of methanol R1.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 5 µL.

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Run time 6 times the retention time of ipratropium.

Relative retention With reference to ipratropium (retention time = about 4.9 min): impurity C = about 0.7; impurity B = about 1.2; impurity D = about 1.8; impurity E = about 2.3; impurity F = about 5.1.

System suitability Reference solution (b):

— *resolution*: minimum 3.0 between the peaks due to impurity B and ipratropium;

— *symmetry factor*: maximum 2.5 for the principal peak.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity C = 0.3; impurity D = 0.2; impurity F = 0.5;

— *impurity D*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent);

— *impurities B, C*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.25 per cent);

— *disregard limit*: one-third of the area of the principal peak in the chromatogram obtained with reference solution (a) (0.03 per cent); disregard the peak due to the bromide ion.

Water (*2.5.12*)

3.9 per cent to 4.4 per cent, determined on 0.50 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.350 g in 50 mL of *water R* and add 3 mL of *dilute nitric acid R*. Titrate with *0.1 M silver nitrate*, determining the end-point potentiometrically (*2.2.20*).

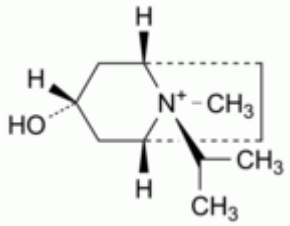
1 mL of *0.1 M silver nitrate* is equivalent to 41.24 mg of $C_{20}H_{30}BrNO_3$.

IMPURITIES

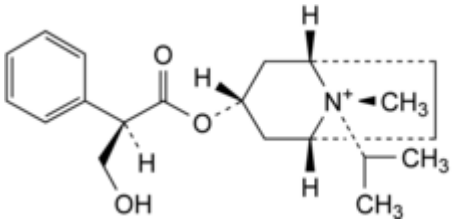
Specified impurities *A, B, C, D*.

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Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *E, F.*

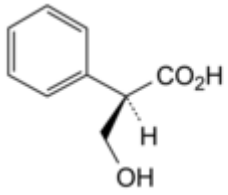


A. (1*R*,3*r*,5*S*,8*r*)-3-hydroxy-8-methyl-8-(1-methylethyl)-8-azoniabicyclo[3.2.1]octane,



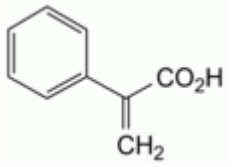
and enantiomer

B. (1*R*,3*r*,5*S*,8*s*)-3-[[(2*RS*)-3-hydroxy-2-phenylpropanoyl]oxy]-8-methyl-8-(1-methylethyl)-8-azoniabicyclo[3.2.1]octane,

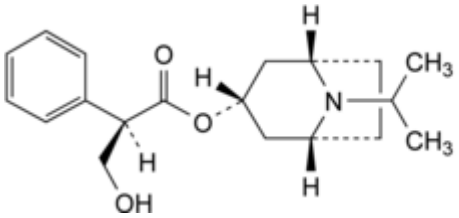


and enantiomer

C. (2*RS*)-3-hydroxy-2-phenylpropanoic acid (DL-tropic acid),



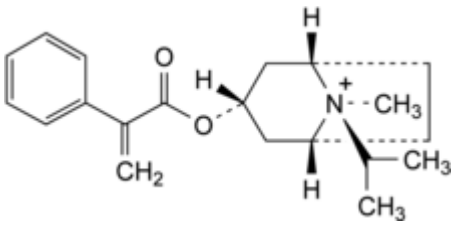
D. 2-phenylpropenoic acid (atropic acid),



and enantiomer

E. (1*R*,3*r*,5*S*)-8-(1-methylethyl)-8-azabicyclo[3.2.1]oct-3-yl (2*RS*)-3-hydroxy-2-phenylpropanoate,

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F. (1*R*,3*r*,5*S*,8*r*)-8-methyl-8-(1-methylethyl)-3-[(2-phenylpropenoyl)oxy]-8-azoniabicyclo[3.2.1]octane.

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Ipratropium Nebuliser Solution

General Notices

Action and use

Anticholinergic (antimuscarinic) bronchodilator.

DEFINITION

Ipratropium Nebuliser Solution is a solution of Ipratropium Bromide in Water for Injections and may contain sodium chloride.

The nebuliser solution complies with the requirements stated under Preparations for Inhalation and with the following requirements.

Content of ipratropium bromide, $C_{20}H_{30}NO_3Br,H_2O$

95.0 to 110.0% of the stated amount.

IDENTIFICATION

Evaporate a volume of the nebuliser solution containing 1.5 mg of Ipratropium Bromide to dryness on a water bath. Shake the residue with 5 mL of *methanol* and filter (Whatman GF/C is suitable). Evaporate the filtrate to dryness on a water bath and dry the residue at room temperature at a pressure of 1 kPa for 15 minutes. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with a spectrum prepared from a mixture of 5 mg of *ipratropium bromide BPCRS* and 45 mg of *sodium chloride* dissolved in the minimum quantity of *water*, evaporated to dryness on a water bath and treated in a similar manner to the substance being examined beginning at the words “Shake the residue with 5 mL of *methanol*,…”.

TESTS

Acidity

pH, 3.0 to 4.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a quantity of the nebuliser solution, if necessary, with sufficient 0.001M *hydrochloric acid* to produce a solution containing 0.02% w/v of Ipratropium Bromide.

(2) Dilute 1 volume of solution (1) to 200 volumes with 0.001M *hydrochloric acid*.

(3) 0.005% w/v of *ipratropium bromide impurity B EPCRS* and 0.005% w/v of *ipratropium bromide BPCRS* in 0.001M *hydrochloric acid*.

(4) Dilute 1 volume of solution (2) to 5 volumes with 0.001M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

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(a) Stainless steel column (12.5 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Columbus C8 is suitable).

(b) Use isocratic elution using the mobile phase described below.

(c) Use a flow rate of 0.5 mL per minute.

(d) Use an ambient column temperature.

(e) Detection wavelength of 210 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for 6 times the retention time of ipratropium.

MOBILE PHASE

A mixture of 4 volumes of freshly distilled *triethylamine*, 50 volumes of *propan-2-ol R1*, 100 volumes of *acetonitrile R1* and 850 volumes of a 0.1% w/v solution of *sodium methanesulfonate* adjusted to pH 3.0 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions, the retention time of ipratropium is about 11 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to ipratropium bromide and impurity B is at least 1.2.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of any such peaks is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a quantity of the nebuliser solution, if necessary, with sufficient 0.001M *hydrochloric acid* to produce a solution containing 0.02% w/v of Ipratropium Bromide.

(2) 0.02% w/v of *ipratropium bromide BPCRS* in 0.001M *hydrochloric acid*.

(3) 0.005% w/v of *ipratropium bromide impurity B EPCRS* and 0.005% w/v of *ipratropium bromide BPCRS* in 0.001M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks is at least 1.2.

DETERMINATION OF CONTENT

Calculate the content of $C_{20}H_{30}NO_3Br,H_2O$ in the solution using the declared content of $C_{20}H_{30}NO_3Br,H_2O$ in *ipratropium bromide BPCRS*.

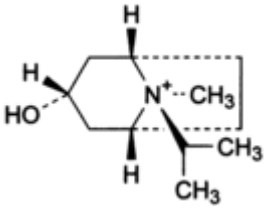
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STORAGE

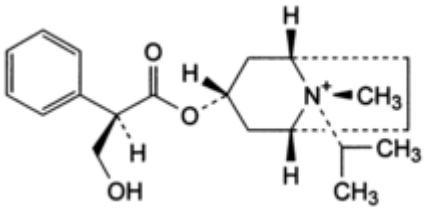
Ipratropium Nebuliser Solution should be stored protected from light in a sealed container.

IMPURITIES

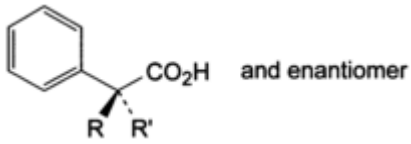
The impurities limited by the requirements of this monograph include.



A. (1*R*,3*r*,5*S*,8*r*)-3-hydroxy-8-methyl-8-(1-methylethyl)-8-azoniabicyclo[3.2.1]octane,



B. (1*R*,3*r*,5*S*,8*s*)-3-[[(2*RS*)-3-hydroxy-2-phenylpropanoyl]oxy]-8-methyl-8-(1-methylethyl)-8- azoniabicyclo[3.2.1]octane,



C. R = CH_2-OH, R′ = H: (2*RS*)-3-hydroxy-2-phenylpropanoic acid (DL-tropic acid),

D. R + R′ = CH_2: 2-phenylpropenoic acid (atropic acid).

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Ipratropium Pressurised Inhalation, Solution

General Notices

Ipratropium Pressurised Inhalation

Action and use

Anticholinergic (antimuscarinic) bronchodilator.

DEFINITION

Ipratropium Pressurised Inhalation, Solution is a solution of Ipratropium Bromide in a suitable liquid in a pressurised container fitted with a metering dose valve.

The pressurised inhalation complies with the requirements stated under Preparations for Inhalation and with the following requirements.

PRODUCTION

The size of aerosol particles to be inhaled is controlled so that a consistent portion is deposited in the lungs. The fine-particle characteristics of preparations for inhalation are determined using the method described in Appendix XII C7. Preparations for inhalation: Aerodynamic Assessment of Fine Particles. The test and limits should be agreed with the competent authority.

The water content is controlled to ensure the performance of the product as justified and authorised by the competent authority.

Content of ipratropium bromide, $C_{20}H_{30}NO_3Br,H_2O$

85.0 to 115.0% of the stated delivered dose (ex-actuator).

IDENTIFICATION

A. In the test for Impurity A, the principal spot in the chromatogram obtained with solution (2) corresponds to that in the chromatogram obtained with solution (4).
B. In the Uniformity of delivered dose, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to ipratropium bromide in the chromatogram obtained with solution (2).

TESTS

Impurity A

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

Solution A To one volume of *potassium iodobismuthate solution*, add 2 volumes of *glacial acetic acid* and 10 volumes of *water*.

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(1) Place three containers into a freezer for about 20 minutes and punch a small hole in the can wall of each frozen container, allow the propellant to evaporate for about 1 minute and open the containers. Evaporate the contents under a stream of nitrogen and dissolve the residues in sufficient 0.01M *hydrochloric acid* to make a solution expected to contain 0.6% w/v of ipratropium bromide.

(2) Dilute 1 volume of solution (1) to 50 volumes with 0.01M *hydrochloric acid*.

(3) 0.08% w/v of *8s-isopropyl-3β-hydroxytropanium bromide BPCRS* (impurity A) in 0.01M *hydrochloric acid*.

(4) 0.08% w/v of *ipratropium bromide BPCRS* in 0.01M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* F_{254} (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 15 µL of each solution.

(d) Develop the plate to 6 cm.

(e) After removal of the plate, dry it in a current of warm air for about 30 minutes. Spray the plate with Solution A, allow to dry briefly, spray with *sodium nitrite solution* and immediately examine the plate.

MOBILE PHASE

5 volumes of *water*, 8 volumes of *formic acid*, 28 volumes of *methanol* and 70 volumes of *dichloromethane*.

LIMITS

In the chromatogram obtained with solution (1):

any spot corresponding to impurity A is not more intense than the spot in the chromatogram obtained with solution (2) (2%).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A *Water*, adjusted to pH 2.6 with *orthophosphoric acid*.

(1) Empty the contents of one container into a 50 mL-volumetric flask, wash the container with 5 mL of solution A and add the washing to the flask. Make up to volume with solution A. Dilute, if necessary, with sufficient solution A to make a solution containing 0.04% w/v of ipratropium bromide.

(2) Dilute 1 volume of solution (1) to 100 volumes with solution A.

(3) 0.0002% w/v of *ipratropium bromide impurity D BPCRS* and 0.0002% w/v of *ipratropium bromide BPCRS* in solution A.

(4) Dilute 1 volume of solution (2) to 10 volumes with solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *base-deactivated octadecylsilyl silica gel for chromatography* (5 µm) (Zorbax SB-C18 is suitable).

(b) Use isocratic elution using the mobile phase described below.

(c) Use a flow rate of 1.3 mL per minute.

(d) Use a column temperature of 45°.

(e) Use a detection wavelength of 210 nm.

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(f) Inject 50 µL of each solution.

(g) Allow the chromatography to proceed for six times the retention time of ipratropium bromide.

MOBILE PHASE

185 volumes of *acetonitrile R1* and 815 volumes of a 0.16% w/v of *sodium butanesulfonate*, adjusted to pH 2.6 with *orthophosphoric acid.*

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to ipratropium bromide (retention time about 4 minutes) are: for impurity C, about 0.7; impurity D, about 3.5 and impurity F, about 5.0.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the resolution between the peak due to ipratropium bromide and the peak due to impurity D, is not less than 4.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any other *secondary peak* is not greater than half the area of the corresponding peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of any *secondary peaks* is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

Uniformity of delivered dose

Complies with the requirements stated under Pressurised Metered-dose Preparations for Inhalation using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A *water*, adjusted to pH 2.6 with *orthophosphoric acid*.

(1) Collect single doses of the preparation being examined using the procedure described under Pressurised Metered-dose Preparations for Inhalation, Uniformity of delivered dose and dissolve the collected dose in sufficient solution A to produce a solution containing the equivalent of 0.0002% w/v of ipratropium bromide.

(2) 0.0002% w/v of *ipratropium bromide BPCRS* in solution A.

(3) Mix 1 volume of solution (2) with 1 volume of 0.0002% w/v of *ipratropium bromide impurity D BPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *base-deactivated octadecylsilyl silica gel for chromatography* (5 µm) (Zorbax SB-C18 is suitable).

(b) Use isocratic elution using the mobile phase described below.

(c) Use a flow rate of 2.0 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 210 nm.

(f) Inject 100 µL of each solution.

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(g) Allow the chromatography to proceed for 1.6 times the retention time of ipratropium bromide.

MOBILE PHASE

225 volumes of *acetonitrile* and 775 volumes of a 0.209% w/v solution of *sodium heptanesulfonate*, and adjusted to pH 2.6 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peak due to ipratropium bromide and the peak due to impurity D, is not less than 4.0.

DETERMINATION OF CONTENT

Calculate the content of ipratropium bromide $C_{20}H_{30}BrNO_3,H_2O$ per delivered dose using the declared content of $C_{20}H_{30}BrNO_3,H_2O$ in *ipratropium bromide BPCRS*. Repeat the procedure as described under *Pressurised Metered-dose Preparations for Inhalation, Uniformity of Delivered Dose*.

ASSAY

Use the average of the individual results obtained in the test for Uniformity of delivered dose.

LABELLING

The label states the content of active ingredient in terms of the equivalent delivered dose.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, C, D and F listed under Ipratropium Bromide.

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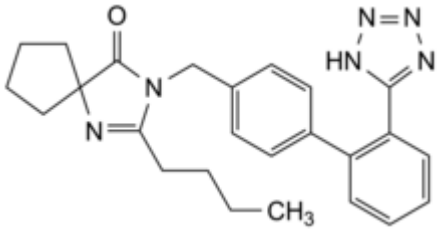
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Irbesartan

General Notices

(Ph. Eur. monograph 2465)



$C_{25}H_{28}N_6O$ 428.5 *138402-11-6*

Action and use

Angiotensis II (AT_1) receptor antagonist.

Preparation

Irbesartan Tablets

Ph Eur

DEFINITION

2-Butyl-3-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1,3-diazaspiro[4.4]non-1-en-4-one.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

PRODUCTION

As *N*-nitrosamines are classified as probable human carcinogens, their presence in irbesartan should be avoided or limited as much as possible. For this reason, manufacturers of irbesartan for human use are expected to perform an assessment of the risk of *N*-nitrosamine formation and contamination during their manufacturing process; if this assessment identifies a potential risk, the manufacturing process should be modified to minimise contamination and a control strategy implemented to detect and control *N*-nitrosamine impurities in irbesartan. The general chapter *2.5.42. N-Nitrosamines in active substances* is available to assist manufacturers.

CHARACTERS

Appearance

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White or almost white, crystalline powder.

Solubility

Practically insoluble in water, sparingly soluble in methanol, slightly soluble in methylene chloride.

It shows polymorphism (5.9).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *irbesartan CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness at 60 °C and record new spectra using the residues.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution B_7 (2.2.2, *Method II*).

Dissolve 0.50 g in a mixture of 1 volume of *2 M sodium hydroxide R* and 9 volumes of *methanol R2* and dilute to 10 mL with the same mixture of solvents.

Impurity B

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Test solution Dissolve 0.100 g of the substance to be examined in the mobile phase and dilute to 5.0 mL with the mobile phase.

Reference solution Dissolve 25.0 mg of *sodium azide R* (sodium salt of impurity B) in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 0.25 mL of the solution to 200.0 mL with the mobile phase.

Precolumn (used to prevent saturation of the column with irbesartan):

— *size*: *l* = 0.05 m, Ø = 4 mm;

— *stationary phase*: *strongly basic anion-exchange resin for chromatography R* (8.5 µm).

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm;

— *stationary phase*: *strongly basic anion-exchange resin for chromatography R* (8.5 µm).

Mobile phase 4.2 g/L solution of *sodium hydroxide R* in *carbon dioxide-free water R*.

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Flow rate 1.0 mL/min.

Detection Conductivity detector with a sensitivity of 3 µS; use a self-regenerating anion suppressor.

Neutralisation of the eluent Either chemical or electrochemical:

— *chemical*: by continuous countercurrent circulation in a neutralising micromembrane, performed before detection:

— *neutralising solvent*: *0.025 M sulfuric acid*;

— *flow rate*: 10 mL/min;

— *pressure*: about 100 kPa.

— *electrochemical*: 300 mA (for example).

Injection 200 µL; after each injection of the test solution, rinse the precolumn with a mixture of mobile phase and *methanol R* (40:60 *V/V*) for 10 min; equilibrate to initial conditions as necessary; a switch valve can be used to avoid disconnecting the precolumn from the column.

Run time 25 min.

Retention time Impurity B = about 14 min.

System suitability Reference solution:

— *signal-to-noise ratio*: minimum 10 for the peak due to impurity B.

Limit:

— *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (10 ppm).

Related substances

Liquid chromatography (*2.2.29*).

Buffer solution pH 3.2 Mix 5.5 mL of *phosphoric acid R* and 950 mL of *water for chromatography R* and adjust to pH 3.2 with *triethylamine R*.

Test solution Dissolve 50 mg of the substance to be examined in *methanol R2* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R2*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R2*.

Reference solution (b) Dissolve 5 mg of the substance to be examined and 5 mg of *irbesartan impurity A CRS* in *methanol R2* and dilute to 10 mL with the same solvent. Dilute 1 mL of the solution to 10 mL with *methanol R2*.

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm;

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— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *acetonitrile R1*, buffer solution pH 3.2 (33:67 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 10 µL.

Run time 1.4 times the retention time of irbesartan.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A.

Relative retention With reference to irbesartan (retention time = about 23 min): impurity A = about 0.7.

System suitability Reference solution (b):

— *resolution*: minimum 3.0 between the peaks due to impurity A and irbesartan.

Limits:

— *impurity A*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (2.5.12)

Maximum 0.5 per cent, determined on 1.00 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

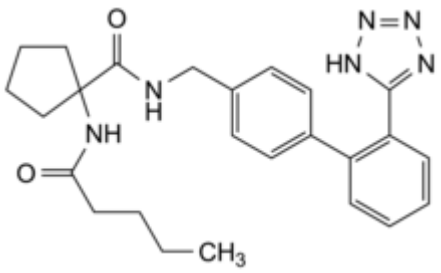
Dissolve 0.300 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 42.85 mg of $C_{25}H_{28}N_6O$.

IMPURITIES

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Specified impurities *A, B.*



A. 1-(pentanoylamino)-*N*-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]cyclopentane-1-carboxamide,

B. N_3^-: trinitride (azide).

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Irbesartan Tablets

General Notices

Action and use

Angiotensin II (AT_1) receptor antagonist.

DEFINITION

Irbesartan Tablets contain Irbesartan.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of irbesartan, $C_{25}H_{28}N_6O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Dissolve a quantity of the powdered tablets containing 0.3 g of Irbesartan in 10 mL of *methanol* with the aid of ultrasound. Filter through a Whatman GF/C filter and then through a 0.45-µm filter. Evaporate the filtrate to dryness under a stream of nitrogen and dry the residue at 60° for 1 hour. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of Irbesartan (*RS 467*). Disregard any bands occurring between 1125 and 1000 cm^{-1}.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a 10 mL sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary to produce a solution containing 0.0083% w/v of Irbesartan, at the maximum at 254 nm, Appendix II B using 0.1M *hydrochloric acid* in the reference cell.

(2) Measure the *absorbance* of a 0.0083% w/v solution of *irbesartan BPCRS* using 0.1M *hydrochloric acid* in the reference cell.

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DETERMINATION OF CONTENT

Calculate the total content of irbesartan, $C_{25}H_{28}N_6O$ in the medium from the absorbances obtained and using the declared content of $C_{25}H_{28}N_6O$ in *irbesartan BPCRS*.

LIMITS

The amount of irbesartan released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Prepare a 0.025M solution of *sodium dihydrogen orthophosphate monohydrate*, adjusted to pH 3.2 with *orthophosphoric acid* (solvent A).

(1) To a quantity of the powdered tablets containing 62.5 mg of Irbesartan, add 125 mL of *methanol* and mix with the aid of ultrasound. Add 100 mL of solvent A and shake. Dilute to 250 mL with solvent A, mix and filter (a 0.45-µm filter is suitable).

(2) Dilute 1 volume of solution (1) to 50 volumes with equal volumes of *methanol* and solvent A. Dilute 1 volume of this solution to 10 volumes with solvent A.

(3) 0.025% w/v of *irbesartan impurity A BPCRS* in *methanol*.

(4) To 25 mg of *irbesartan BPCRS*, add 50 mL of *methanol* and mix with the aid of ultrasound, add sufficient solvent A to produce 100 mL.

(5) Dilute 1 volume of solution (3) to 200 volumes with solution (4).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.0 mm) packed with *octadecylsilyl silica gel for chromatography* (3.5 µm) (Waters SunFire C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 0.6 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 10 µL of solutions 1, 2 and 5.

MOBILE PHASE

Mobile phase A 42 volumes of *acetonitrile R1* and 58 volumes of solvent A.

Mobile phase B 20 volumes of solvent A and 80 volumes of *acetonitrile R1*.

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Time (Minutes)	Mobile phase A%	Mobile phase B%	Comment
0-6	100	0	isocratic
6-11	100→0	0→100	linear gradient
11-12	0	100	isocratic
12-13	0→100	100→0	linear gradient
13-15	100	0	Re-equilibration

When the chromatograms are recorded under the prescribed conditions the relative retention, with reference to Irbesartan (retention time = about 5 minutes), of impurity A is about 0.8.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5), the *resolution factor* between the peaks due to irbesartan and irbesartan impurity A is at least 4.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to irbesartan impurity A is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any other *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Prepare a 0.025M solution of *sodium dihydrogen orthophosphate monohydrate*, adjusted to pH 3.2 with *orthophosphoric acid* (solvent B).

(1) To a quantity of the powdered tablets containing 62.5 mg of irbesartan, add 125 mL of *methanol* and mix with the aid of ultrasound. Add 100 mL of solvent B and shake. Dilute to 250 mL with solvent B, mix and filter (a 0.45-µm filter is suitable).
(2) To 25 mg of *irbesartan BPCRS*, add 50 mL of *methanol* and mix with the aid of ultrasound. Dilute to 100 mL with solvent B.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used with a detection wavelength of 250 nm.

SYSTEM SUITABILITY

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The test is not valid unless, in the chromatogram obtained with solution (2), the *symmetry factor* of the peak due to irbesartan is between 0.8 and 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{25}H_{28}N_6O$ in the tablets using the declared content of $C_{25}H_{28}N_6O$ in *irbesartan BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurity A listed under Irbesartan.

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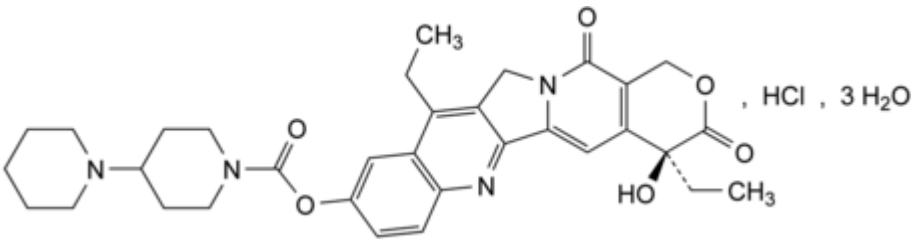
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This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Irinotecan Hydrochloride Trihydrate

General Notices

(Ph. Eur. monograph 2675)



$C_{33}H_{39}ClN_4O_6,3H_2O$ 677 *136572-09-3*

Action and use

Inhibitor of DNA topoisomerase type I; antineoplastic.

Ph Eur

DEFINITION

(4*S*)-4,11-Diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinolin-9-yl 1,4′-bipiperidine-1′-carboxylate hydrochloride trihydrate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Pale yellow or yellow, crystalline powder.

Solubility

Sparingly soluble in water, in ethanol (96 per cent) and in methanol.

It shows polymorphism (5.9).

IDENTIFICATION

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IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *irinotecan hydrochloride trihydrate CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

B. Water (see Tests).

C. It gives reaction (a) of chlorides (2.3.1).

Dissolve 0.10 g in *water R* and dilute to 50 mL with the same solvent.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution GY_2 (2.2.2, *Method II*).

Dissolve 0.200 g in *water R* with heating at 80 °C and dilute to 20 mL with the same solvent.

Enantiomeric purity

Liquid chromatography (2.2.29).

Solvent mixture *diethylamine R*, *anhydrous ethanol R* (0.4:100 *V/V*).

Test solution Dissolve 15.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve the contents of a vial of *irinotecan for system suitability 1 CRS* (containing impurity L) in 1 mL of the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *cellulose derivative of silica gel for chiral separation R* (10 µm).

Mobile phase *diethylamine R*, *anhydrous ethanol R*, *hexane R* (0.2:50:50 *V/V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 370 nm.

Injection 20 µL.

Run time 1.5 times the retention time of irinotecan.

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Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity L.

Relative retention With reference to irinotecan (retention time = about 15 min): impurity L = about 0.7.

System suitability:

— *resolution*: minimum 1.5 between the peaks due to impurity L and irinotecan in the chromatogram obtained with reference solution (b).

Calculation of percentage content:

— for impurity L, use the concentration of irinotecan hydrochloride trihydrate in reference solution (a).

Limit:

— *impurity L*: maximum 0.15 per cent.

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light.*

Solvent mixture acetonitrile R, methanol R, mobile phase A (25:25:50 *V/V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dissolve 50.0 mg of irinotecan hydrochloride trihydrate CRS in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve the contents of a vial of irinotecan for peak identification CRS (containing impurities C and E) in 1 mL of the solvent mixture.

Reference solution (d) Dissolve 5 mg of irinotecan for system suitability 2 CRS (containing impurity M) in the solvent mixture and dilute to 10 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography with embedded polar groups R (5 µm).

Mobile phase:

— *mobile phase A*: dissolve 2.72 g of potassium dihydrogen phosphate R in 950 mL of water for chromatography R, adjust to pH 3.5 with dilute phosphoric acid R and dilute to 1000 mL with water for chromatography R;

— *mobile phase B*: methanol R2, acetonitrile R1 (40:60 *V/V*);

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	80	20
2 - 42	80 → 30	20 → 70
42 - 47	30	70

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 10 µL of the test solution and reference solutions (b), (c) and (d).

Identification of impurities Use the chromatogram supplied with *irinotecan for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities C and E; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity M.

Relative retention With reference to irinotecan (retention time = about 17 min): impurity M = about 0.9; impurity C = about 1.3; impurity E = about 1.5.

System suitability:

— *resolution*: minimum 2.0 between the peaks due to impurity M and irinotecan in the chromatogram obtained with reference solution (d).

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity M by 1.3;

— for each impurity, use the concentration of irinotecan hydrochloride trihydrate in reference solution (b).

Limits:

— *impurities C, E, M*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Water (*2.5.12*)

7.0 per cent to 9.0 per cent, determined on 0.100 g.

Sulfated ash (*2.4.14*)

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Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection 5 µL of the test solution and reference solution (a).

Calculate the percentage content of $C_{33}H_{39}ClN_4O_6$ taking into account the assigned content of *irinotecan hydrochloride trihydrate CRS*.

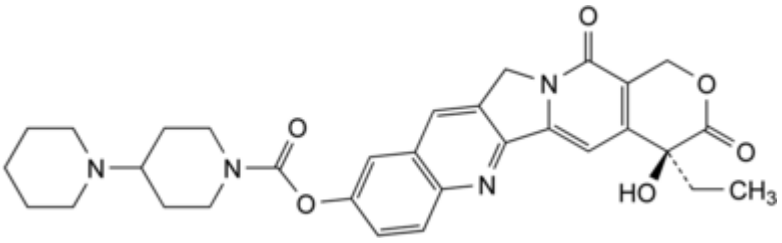
STORAGE

In an airtight container, protected from light.

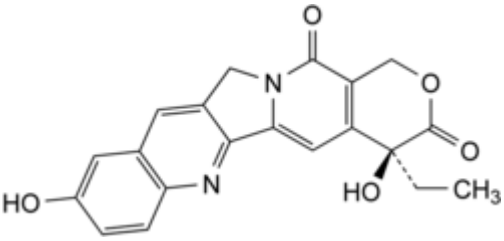
IMPURITIES

Specified impurities *C, E, L, M.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, D, F, G, H, K.*

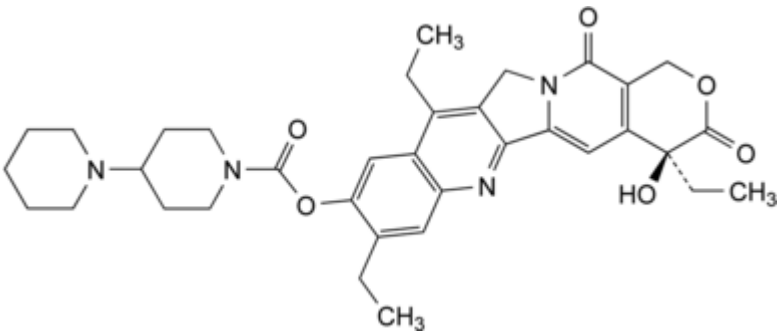


A. (4*S*)-4-ethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinolin-9-yl 1,4′-bipiperidine-1′-carboxylate (11-desethyl irinotecan),

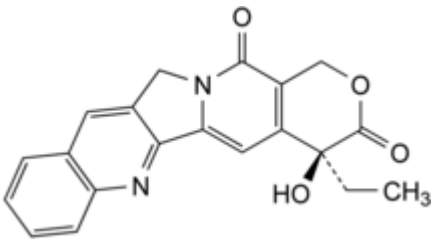


B. (4*S*)-4-ethyl-4,9-dihydroxy-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione (9-hydroxycamptothecin),

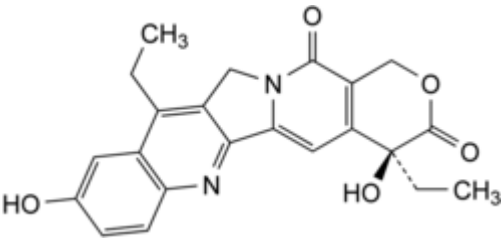
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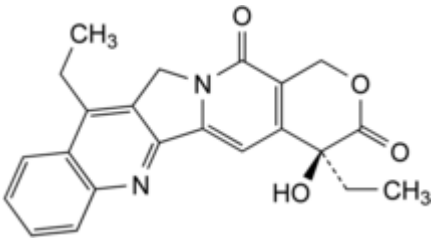
C. (4*S*)-4,8,11-triethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinolin-9-yl 1,4′-bipiperidine-1′-carboxylate (8-ethyl irinotecan),



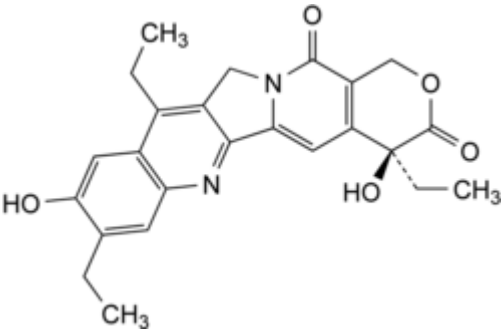
D. (4*S*)-4-ethyl-4-hydroxy-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione (camptothecin),



E. (4*S*)-4,11-diethyl-4,9-dihydroxy-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione (11-ethyl-9-hydroxycamptothecin),

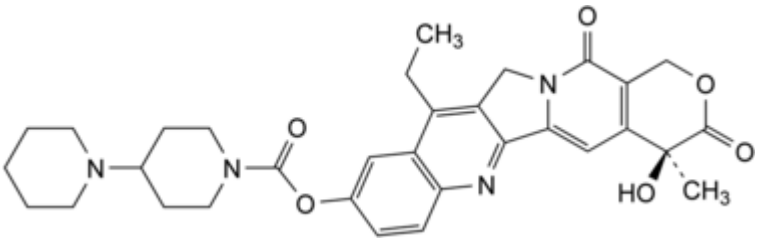


F. (4*S*)-4,11-diethyl-4-hydroxy-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione (11-ethylcamptothecin),

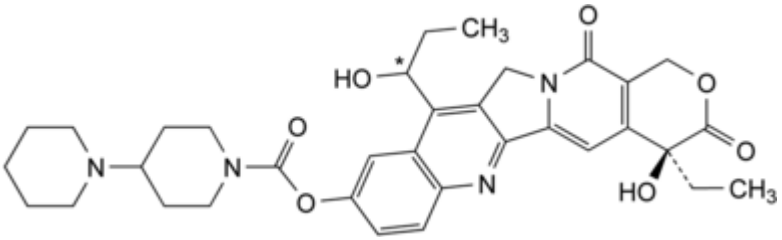


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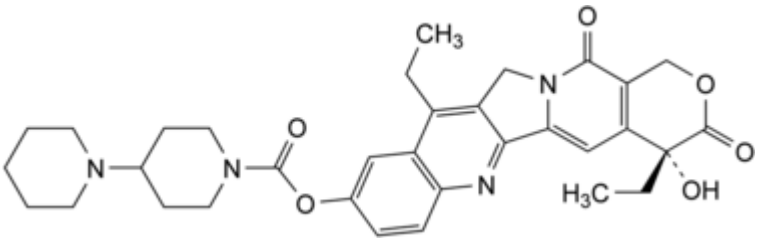
G. (4*S*)-4,8,11-triethyl-4,9-dihydroxy-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione (8,11-diethyl-9-hydroxycamptothecin),



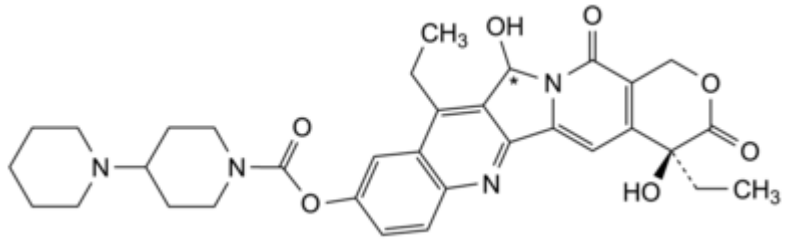
H. (4*S*)-11-ethyl-4-hydroxy-4-methyl-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinolin-9-yl 1,4′-bipiperidine-1′-carboxylate (4-methyl irinotecan analogue),



K. (4*S*)-4-ethyl-4-hydroxy-11-(1-hydroxypropyl)-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinolin-9-yl 1,4′-bipiperidine-1′-carboxylate,



L. (4*R*)-4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinolin-9-yl 1,4′-bipiperidine-1′-carboxylate (irinotecan enantiomer),



M. (4*S*)-4,11-diethyl-4,12-dihydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinolin-9-yl 1,4′-bipiperidine-1′-carboxylate (12-hydroxy irinotecan).

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Iron Dextran Injection

General Notices

Action and use

Treatment of iron-deficiency anaemia.

DEFINITION

Iron Dextran Injection is a sterile colloidal solution containing a complex of iron(III) hydroxide with dextrans of weight average molecular weight between 5000 and 7500.

PRODUCTION

Iron Dextran Injection is produced by a method of manufacture designed to provide an iron-dextran complex with appropriate iron absorption characteristics. This may be confirmed for routine control purposes by the use of an appropriate combination of physico-chemical tests, subject to the agreement of the competent authority.

The method of manufacture is validated to demonstrate that, if tested, the injection would comply with the following test.

Undue toxicity

Inject 0.10 mL into a tail vein of each of 10 mice; not more than three mice die within 5 days of injection. If more than three mice die within 5 days, repeat the test on another group of 20 mice. Not more than 10 of the 30 mice used in the combined tests die within 5 days of injection.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of iron, Fe

4.75 to 5.25% w/v.

Content of dextrans

17.0 to 23.0% w/v.

CHARACTERISTICS

A dark brown solution.

IDENTIFICATION

A. Add 5M *ammonia* to 0.2 mL of the injection previously diluted to 5 mL with *water*. No precipitate is produced.

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B. Mix 1 mL with 100 mL of *water*. To 10 mL of this solution add 0.2 mL of *hydrochloric acid*, boil for 30 seconds, cool rapidly, add 4 mL of 13.5M *ammonia* and 10 mL of *hydrogen sulfide solution*, boil for at least 4 minutes to remove hydrogen sulfide, cool and filter. Boil 5 mL of the filtrate with 5 mL of *cupri-tartaric solution R1*; the solution remains greenish in colour and no precipitate is produced. Boil a further 5 mL of the filtrate with 0.5 mL of *hydrochloric acid* for 5 minutes, cool, add 2.5 mL of 5M *sodium hydroxide* and 5 mL of *cupri-tartaric solution R1* and boil again; a reddish precipitate is produced.

C. To 1 mL add 20 mL of *water* and 5 mL of *hydrochloric acid* and boil for 5 minutes. Cool, add an excess of 13.5M *ammonia* and filter. Wash the precipitate with *water*, dissolve in the minimum volume of 2M *hydrochloric acid* and add sufficient *water* to produce 20 mL. The resulting solution yields reaction B characteristic of *iron salts*, Appendix VI.

TESTS

Acidity

pH, 5.2 to 6.5, Appendix V L.

Arsenic

To 5.0 mL in a Kjeldahl flask add 10 mL of *water* and 10 mL of *nitric acid* and heat until the vigorous evolution of brown fumes ceases. Cool, add 10 mL of *sulfuric acid* and heat again until fumes are evolved, adding *nitric acid* dropwise at intervals until oxidation is complete. Cool, add 30 mL of *water*, bring to the boil and continue boiling until the volume of liquid is reduced to about 20 mL. Cool and dilute to 50 mL with *water*. Reserve a portion of the solution for the test for Lead. To 5 mL of the solution add 10 mL of *water*, 15 mL of *stannated hydrochloric acid* and 3 mL of *tin(II) chloride solution AsT*. Connect to a condenser and distil 15 mL into 10 mL of *water*. To the distillate add 0.2 mL of *bromine water* and remove the excess of bromine with *tin(II) chloride solution AsT*. The solution complies with the *limit test for arsenic*, Appendix VII (2 µg per mL).

Copper

To 5.0 mL add 5 mL of *nitric acid* and heat until the vigorous evolution of brown fumes ceases. Cool, add 2 mL of *sulfuric acid* and heat again until fumes are evolved, adding *nitric acid* dropwise at intervals until oxidation is complete. Cool, add 25 mL of *hydrochloric acid*, warm to dissolve, cool and extract with four 25 mL quantities of *isobutyl acetate*, discarding the extracts. Evaporate the acid solution to dryness, adding *nitric acid* dropwise if charring occurs. Dissolve the residue in 10 mL of 1M *hydrochloric acid*, reserving a portion of the solution for the test for Zinc. To 1 mL add 25 mL of *water* and 1 g of *citric acid*, make alkaline to *litmus paper* with 5M *ammonia*, dilute to 50 mL with *water*, add 1 mL of *sodium diethyldithiocarbamate solution* and allow to stand for 5 minutes. Any colour produced is not more intense than that produced by treating in the same manner a mixture of 3 mL of *copper standard solution (10 ppm Cu)* and 1 mL of 1M *hydrochloric acid* beginning at the words ‘add 25 mL of *water*…’ (60 µg per mL).

Lead

Sample stock solution To 16.0 mL of the solution reserved in the test for Arsenic add 50 mL of *hydrochloric acid* and wash with four 20 mL quantities of *isobutyl acetate*, discarding the oraganic layer. Evaporate the acid solution to dryness and dissolve the residue in 20 mL of *water*.

Use the following solutions:

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(1) 12 mL of the sample stock solution.

(2) A mixture of 10 mL of *lead standard solution* (2 ppm Pb) and 2 mL of sample stock solution.

(3) (Blank solution) A mixture of 10 mL of *water* and 2 mL of the sample stock solution.

PROCEDURE

To solutions 1, 2 and 3: add 2 mL of *buffer solution pH 3.5*. Mix and add to 1.2 mL of *thioacetamide reagent*. Examine through Nessler cylinders after 2 minutes.

SYSTEM SUITABILITY

Solution (2) shows a slight brown colour compared to solution (3).

LIMITS

Any brown colour in solution (1) is not more intense than that in solution (2) (25 µg per mL).

Zinc

To 5.0 mL of the solution reserved in the test for Copper add 15 mL of 1M *sodium hydroxide*, boil, filter, wash the residue with *water* and dilute the combined filtrate and washings to 25 mL with *water*. To 5 mL add 5 mL of 1M *hydrochloric acid* and 2 g of *ammonium chloride*, dilute to 50 mL with *water*, add 1 mL of freshly prepared *dilute potassium hexacyanoferrate*(II) *solution* and allow to stand for 20 minutes. Any opalescence produced is not more than that produced when 1 mL of freshly prepared *dilute potassium hexacyanoferrate*(II) *solution* is added to a solution prepared from 3 mL of *zinc standard solution (25 ppm Zn)*, 3 mL of 1M *sodium hydroxide*, 6 mL of 1M *hydrochloric acid* and 2 g of *ammonium chloride* diluted to 50 mL with *water* and allowed to stand for 20 minutes (150 µg per mL).

Chloride

To 5 mL add 75 mL of *water* and 0.05 mL of *nitric acid* and titrate immediately with *0.1M silver nitrate VS* determining the end point potentiometrically. 6.8 to 9.6 mL of *0.1M silver nitrate VS* is required.

Iron absorption

Using at least two rabbits, each weighing between 1.5 and 2.5 kg, clip the right hind leg free from hair over the injection site and swab the area with a bactericidal solution. Inject into each rabbit 0.4 mL of the injection per kg of the rabbit's weight using a 2 mL syringe fitted with a No. 12 hypodermic needle [22 gauge × 1.25 inch (0.7 × 32 mm approx.)]. Insert the needle at the distal end of the semitendinosus muscle, passing through the sartorius and entering the vastus medialis; the angle of the needle must be such that the full length is used. After 7 days, kill the rabbits and remove the legs into which the injections were made. Carefully cut open the muscles and examine the site of injection; it should be only very lightly stained and should show no dark brown deposits and no evidence of leakage along fascial planes. Skin the leg, dissect the flesh from the bone and cut into small pieces. Transfer the pieces to a 1000 mL beaker, add 75 mL of 2M *sodium hydroxide* and sufficient *water* to cover the flesh, cover the beaker with a watch glass and boil until most of the solid matter has disintegrated. Cool, cautiously add 50 mL of *sulfuric acid*, heat the mixture almost to boiling and add carefully ten 1 mL quantities of *fuming nitric acid* until no charring occurs when the excess of nitric acid has been boiled off. Cool, add 170 mL of *water*, boil until solution is complete, cool and dilute to 250 mL with *water*. To 5 mL of this solution add 3 mL of *sulfuric acid*, heat to fuming and complete the oxidation by the addition of small quantities of *nitric acid* until the solution is colourless. Cool, add 20 mL of *water*, boil for 3 minutes and add 10 mL of *ammonium citrate solution*, 10 mL of *ammonium mercaptoacetate solution*, 5M *ammonia* dropwise until the iron colour is fully developed,

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1 mL of 5M *ammonia* in excess and sufficient *water* to produce 100 mL. Measure the *absorbance* of the resulting solution at 530 nm, Appendix II B.

Prepare a reference solution by adding 20 mL of *water* the same quantities of *ammonium citrate solution*, *ammonium mercaptoacetate solution* and 5M *ammonia* as used above, dilute to 100 mL with *water* and measure the *absorbance* at 530 nm. From the difference between the absorbances, calculate the amount of Fe present in the legs from a reference curve prepared by treating suitable aliquots of a solution of *ammonium iron*(III) *sulfate* containing 0.01% w/v of Fe by the procedure described above beginning at the words 'add 10 mL of *ammonium citrate solution*…'. Repeat the determination of Fe on the corresponding legs into which no injection was made, beginning at the words 'Carefully cut open the muscles…'. From the difference between the two amounts of iron, calculate the proportion of injected iron, as Fe, remaining in the leg tissues. Not more than 20% of the injected iron remains.

Bacterial endotoxins

The endotoxin limit concentration is 0.50 IU per mg of iron, Appendix XIV C.

ASSAY

For iron

To 2 g add 10 mL of *water* and 5 mL of *sulfuric acid* and stir for several minutes. Allow to stand for 5 minutes, cool and dilute to 50 mL with *water*. Prepare a suitable zinc amalgam by covering 300 g of *zinc shot* with a 2% w/v solution of *mercury*(II) *chloride* and stir for 10 minutes. Decant the solution, wash the residue three times with *water* and transfer it to a column (30 cm × 18 mm) fitted with a sintered-glass disc (ISO 4793, porosity grade 0, is suitable). Activate the zinc amalgam by passing through the column 200 mL of *sulfuric acid (5%)*. Pass the prepared solution slowly through the column and wash successively with 50 mL of *water*, four 25 mL quantities of *sulfuric acid (5%)* and 50 mL of *water*. Titrate the combined eluates with 0.1M *ammonium cerium*(IV) *sulfate VS* using *ferroin solution* as indicator. Each mL of 0.1M *ammonium cerium*(IV) *sulfate VS* is equivalent to 5.585 mg of Fe. Determine the *weight per mL* of the injection, Appendix V G, and calculate the percentage w/v of Fe.

For dextrans

Dilute 1 g to 500 mL with *water*, dilute 10 mL of the solution to 100 mL with *water*, transfer 3 mL of the resulting solution to a test tube and cool to 0°. Add, to form a lower layer, 6 mL of a solution prepared and maintained at 0° containing 0.2% w/v of *anthrone* in a mixture of 19 volumes of *sulfuric acid* and 1 volume of *water*, mix and immediately heat on a water bath for 5 minutes. Cool and measure the *absorbance* of the resulting solution at the maximum at 625 nm, Appendix II B. Repeat the operation using 3 mL of *water* in place of the dilution of the injection. From the difference between the absorbances calculate the content of glucose present using a calibration curve prepared by treating suitable amounts of D-*glucose* in the same manner. Each g of D-*glucose* is equivalent to 0.94 g of dextrans. Determine the *weight per mL* of the injection, Appendix V G, and calculate the percentage w/v of dextrans.

LABELLING

The strength is stated as the equivalent amount of iron, Fe, in a suitable dose-volume.

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Iron Sucrose Injection

General Notices

Action and use

Treatment of iron-deficiency anaemia.

DEFINITION

Iron Sucrose Injection is a sterile colloidal solution containing a complex of iron(III) hydroxide with sucrose of average molecular weight between 34000 and 60000.

PRODUCTION

Iron Sucrose Injection is produced by a method of manufacture designed to provide an iron-sucrose complex with appropriate iron absorption characteristics. This may be confirmed for routine control purposes by the use of an appropriate combination of physico-chemical tests, subject to the agreement of the competent authority.

A suitable test is carried out to demonstrate (1) the amount of iron(II) present in the injection is not more than 0.4% w/v of the total iron content and (2) there are no low molecular weight complexes in the injection.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of iron, Fe

95.0 to 105.0% of the stated amount.

Content of sucrose

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. To a quantity of the injection containing the equivalent of 20 mg of iron, add 20 mL of *water* and 5 mL of *hydrochloric acid* and boil for 5 minutes. Cool, add an excess of 13.5M *ammonia* and filter. Wash the precipitate with *water*, dissolve in the minimum volume of 2M *hydrochloric acid* and add sufficient *water* to produce 20 mL. The resulting solution yields reaction B characteristic of *iron salts*, Appendix VI.

B. In the Assay for Sucrose, the retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that of the principal peak in the chromatogram obtained with solution (2).

C. Complies with the test for Molecular weight determination.

TESTS

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Alkalinity

pH, 10.5 to 11.0, Appendix V L.

Osmolality

The osmolality, Appendix V N, of the injection is 1150 mosmol/kg to 1350 mosmol/kg.

Clarity of solution

Appendix IV A. To a quantity of the injection containing 10 mg of iron, add 100 mL of water and adjust to pH 6.0 with *0.1M hydrochloric acid*. The solution must not have any turbidity. Add *0.1M hydrochloric acid* dropwise until a faint turbidity develops, the pH of the solution is between 4.4 and 5.3.

Molecular weight determination

Carry out the method for *size-exclusion chromatography*, Appendix III C, using the following solutions in the mobile phase.

(1) Dilute a quantity of the injection with a sufficient volume of the mobile phase to produce a solution expected to contain 1% w/v of iron.
(2) 0.4% w/v of *polysaccharide molecular weight standard 5000 Da*. Allow to stand for a minimum of 12 hours and gently swirl to dissolve any agglomerated particles.
(3) 0.4% w/v of *polysaccharide molecular weight standard 25000 Da*. Allow to stand for a minimum of 12 hours and gently swirl to dissolve any agglomerated particles.
(4) 0.4% w/v of *polysaccharide molecular weight standard 50000 Da*. Allow to stand for a minimum of 12 hours and gently swirl to dissolve any agglomerated particles.
(5) 0.4% w/v of *polysaccharide molecular weight standard 150000 Da*. Allow to stand for a minimum of 12 hours and gently swirl to dissolve any agglomerated particles.
(6) 0.4% w/v of *polysaccharide molecular weight standard 270000 Da*. Allow to stand for a minimum of 12 hours and gently swirl to dissolve any agglomerated particles.
(7) 0.4% w/v of *polysaccharide molecular weight standard 410000 Da*. Allow to stand for a minimum of 12 hours and gently swirl to dissolve any agglomerated particles.
(8) 0.4% w/v of *polysaccharide molecular weight standards 12000 Da*. Allow to stand for a minimum of 12 hours and gently swirl to dissolve any agglomerated particles.

CHROMATOGRAPHIC CONDITIONS

(a) Use two columns (30 cm × 7.8 mm) packed with *hydrophilic polyhydroxymethacrylate gel of totally porous spherical resin for chromatography,* connected in series with pore sizes of 1000Å and 120Å respectively.
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 0.5 mL per minute.
(d) Use a column temperature of 45°.
(e) Use a refractive index detector, maintained at 45°.
(f) Inject 25 µL of each solution.

MOBILE PHASE

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A solution containing 0.02% w/v of *sodium azide*, 0.276% w/v of *sodium dihydrogen orthophosphate monohydrate* and 0.356% w/v of *disodium hydrogen orthophosphate dihydrate* *in* *water*. Adjust the pH to 6.8 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless:

the correlation coefficient of the calculated calibration curve is at least 0.98;

in the chromatogram obtained with solution (8), the calculated molecular weight is concordant with the value supplied with *polysaccharide molecular weight standard 12000 Da*.

DETERMINATION OF MOLECULAR WEIGHT

Determine the peak areas and retention times of the principal peaks in solutions (2), (3), (4), (5) (6) and (7). Plot the peak area for each solution as a function of concentration and peak area to create a cubic calibration curve.

From the calibration curve obtained with solutions (2) to (7), calculate the molecular weight of the complex in the injection.

The molecular weight distribution curve of solution (1) is split into fractions correlating to the molecular weight of solutions (2) to (7). Calculate:

the weight-average molecular weight (M_W):

$$M_w = \sum(A_T M_T)/\sum A_T$$

and the number-average molecular weight (M_N):

$$M_N = \sum(A_T)/\sum(A_T/M_T)$$

where

A_T	=	the area of each fraction of the sample distribution
M_T	=	the corresponding mean molecular weight of each fraction as determined from its retention time on the calibration curve.

The molecular weight distribution curve obtained for the Injection conforms to the following parameters:

M_W	=	34,000 to 60,000 Da
M_N	=	Not less than 24,000 Da
M_W/M_N	=	Not more than 1.7.

ASSAY

For iron

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To a quantity of the injection containing the equivalent of 100 mg of iron add 100 mL of 0.5M *hydrochloric acid* and 10 mL of *acetic acid*. Adjust the pH to 2.4 using *dilute sodium hydroxide*, add 0.5 mL of *hydrogen peroxide solution (20 vol)* and 2.5 mL of *tiron indicator solution*. Titrate with 0.1M *sodium edetate* *VS* until the dark green colour changes to yellow and remains yellow for at least one minute. Each mL of 0.1M *sodium edetate* *VS* is equivalent to 5.585 mg of iron.

For sucrose

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a volume of the injection containing 40mg of Iron Sucrose add 2.5 mL of a 3.0% w/v solution of *sodium dihydrogen orthophosphate monohydrate*, mix and allow to stand for 10 minutes, add sufficient *water* to produce 25 mL, centrifuge and filter discarding the first 2 mL of filtrate.

(2) 1.30% w/v of *sucrose BPCRS* in mobile phase.

(3) 1.60% w/v of *sucrose BPCRS* in mobile phase.

(4) 1.80% w/v of *sucrose BPCRS* in mobile phase.

(5) 2.10% w/v of *sucrose BPCRS* in mobile phase.

(6) 2.30% w/v of *sucrose BPCRS* in mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4 mm) packed with *aminopropylsilyl silica gel for chromatography* (3-10 µm).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a refractive index detector.

(f) Inject 20 µL of each solution.

MOBILE PHASE

21 volumes of *water* and 79 volumes of *acetonitrile*.

DETERMINATION OF CONTENT

Determine the peak areas of the principal peak in solutions (2), (3), (4), (5) and (6), plot the peak area for each solution as a function of concentration of sucrose and draw a straight line best fitting the five plotted points. From the graph obtained calculate the content of sucrose in the injection using the declared content of sucrose in *sucrose BPCRS*.

LABELLING

The strength is stated as the equivalent amount of iron, Fe, in a suitable dose-volume.

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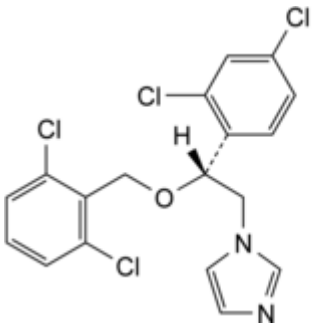
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Isoconazole

General Notices

(Ph. Eur. monograph 1018)



and enantiomer

$C_{18}H_{14}Cl_4N_2O$ 416.1 *27523-40-6*

Action and use

Antifungal.

Ph Eur

DEFINITION

1-[(2*RS*)-2-(2,4-Dichlorophenyl)-2-[(2,6-dichlorophenyl)methoxy]ethyl]-1*H*-imidazole.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, very soluble in methanol, freely soluble in ethanol (96 per cent).

IDENTIFICATION

A. Melting point (*2.2.14*): 111 °C to 115 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *isoconazole CRS*.

TESTS

Solution S

Dissolve 0.20 g in *methanol R* and dilute to 20.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

Optical rotation (*2.2.7*)

-0.10° to + 0.10°, determined on solution S.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.100 g of the substance to be examined in 3.2 mL of *methanol R*. Add 3.0 mL of *acetonitrile R* and dilute to 10.0 mL with a 15.78 g/L solution of *ammonium acetate R*.

Reference solution (a) Dissolve 2.5 mg of *isoconazole CRS* and 2.5 mg of *miconazole nitrate CRS* (impurity D) in the mobile phase, then dilute to 100 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase Dissolve 6.0 g of *ammonium acetate R* in a mixture of 300 mL of *acetonitrile for chromatography R*, 320 mL of *methanol R1* and 380 mL of *water for chromatography R*.

Flow rate 2 mL/min.

Detection Spectrophotometer at 235 nm.

Injection 10 µL.

Run time Twice the retention time of isoconazole.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity D.

Relative retention With reference to isoconazole (retention time = about 14 min): impurity D = about 1.4.

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System suitability Reference solution (a):

— *resolution*: minimum 5.0 between the peaks due to isoconazole and impurity D.

Calculation of percentage contents:

— for each impurity, use the concentration of isoconazole in reference solution (b).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in 50 mL of a mixture of 1 volume of *anhydrous acetic acid R* and 7 volumes of *methyl ethyl ketone R*. Using 0.2 mL of *naphtholbenzein solution R* as indicator, titrate with *0.1 M perchloric acid* until the colour changes from orange-yellow to green.

1 mL of *0.1 M perchloric acid* is equivalent to 41.61 mg of $C_{18}H_{14}Cl_4N_2O$.

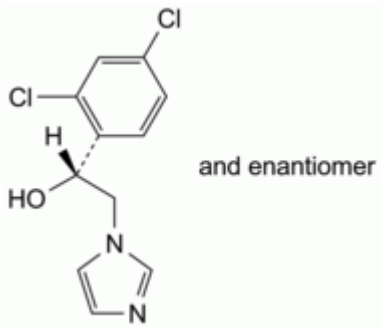
STORAGE

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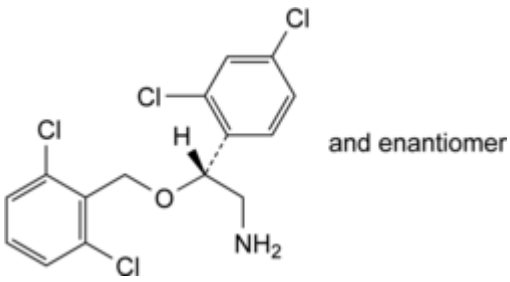
IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, C, D.

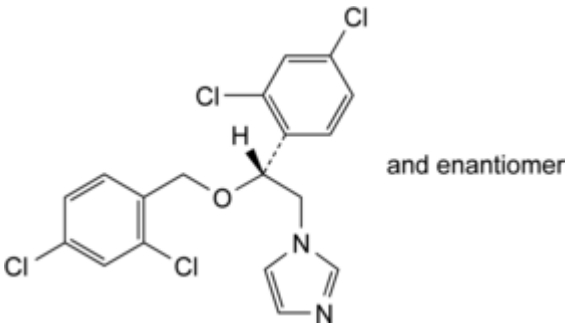
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B. (1*RS*)-1-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethan-1-ol,



C. (2*RS*)-2-(2,4-dichlorophenyl)-2-[(2,6-dichlorophenyl)methoxy]ethan-1-amine,



D. 1-[(2*RS*)-2-(2,4-dichlorophenyl)-2-[(2,4-dichlorophenyl)methoxy]ethyl]-1*H*-imidazole (miconazole).

Ph Eur

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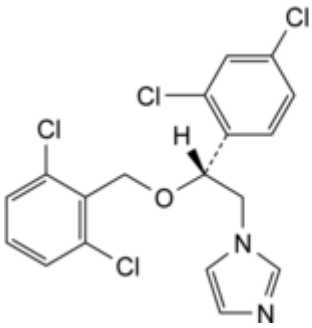
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Isoconazole Nitrate

General Notices

(Ph. Eur. monograph 1017)



and enantiomer , HNO_3

$C_{18}H_{15}Cl_4N_3O_4$ 479.1 *24168-96-5*

Action and use

Antifungal.

Ph Eur

DEFINITION

1-[(2*RS*)-2-(2,4-Dichlorophenyl)-2-[(2,6-dichlorophenyl)methoxy]ethyl]-1*H*-imidazole nitrate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Very slightly soluble in water, soluble in methanol, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Melting point (*2.2.14*): 178 °C to 182 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *isoconazole nitrate CRS*.

TESTS

Solution S

Dissolve 0.20 g in *methanol R* and dilute to 20.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution Y_7 (*2.2.2, Method II*).

Optical rotation (*2.2.7*)

-0.10° to + 0.10°, determined on solution S.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.100 g of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 2.5 mg of *isoconazole nitrate CRS* and 2.5 mg of *miconazole nitrate CRS* (impurity C) in the mobile phase, then dilute to 100 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase Dissolve 6.0 g of *ammonium acetate R* in a mixture of 300 mL of *acetonitrile for chromatography R*, 320 mL of *methanol R1* and 380 mL of *water for chromatography R*.

Flow rate 2 mL/min.

Detection Spectrophotometer at 235 nm.

Injection 10 µL.

Run time Twice the retention time of isoconazole.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity C.

Relative retention With reference to isoconazole (retention time = about 14 min): nitrate = about 0.04; impurity C = about 1.4.

System suitability Reference solution (a):

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— *resolution*: minimum 5.0 between the peaks due to isoconazole and impurity C.

Calculation of percentage contents:

— for each impurity, use the concentration of isoconazole nitrate in reference solution (b).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent; disregard the peak due to the nitrate ion.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.350 g in 75 mL of a mixture of 1 volume of *anhydrous acetic acid R* and 7 volumes of *methyl ethyl ketone R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 47.91 mg of $C_{18}H_{15}Cl_4N_3O_4$.

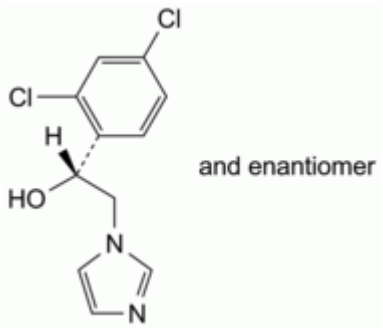
STORAGE

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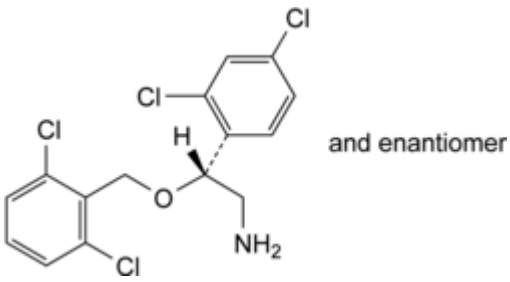
IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C.

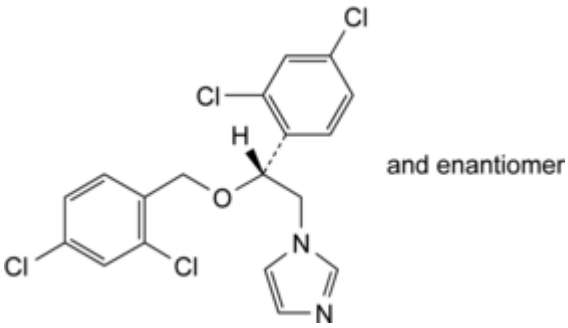
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A. (1*RS*)-1-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethan-1-ol,



B. (2*RS*)-2-(2,4-dichlorophenyl)-2-[(2,6-dichlorophenyl)methoxy]ethan-1-amine,



C. 1-[(2*RS*)-2-(2,4-dichlorophenyl)-2-[(2,4-dichlorophenyl)methoxy]ethyl]-1*H*-imidazole (miconazole).

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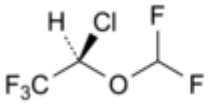
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Isoflurane

General Notices

(Ph. Eur. monograph 1673)



and enantiomer

$C_3H_2ClF_5O$ 184.5 *26675-46-7*

Action and use

General anaesthetic.

Ph Eur

DEFINITION

(2*RS*)-2-Chloro-2-(difluoromethoxy)-1,1,1-trifluoroethane.

CHARACTERS

Appearance

Clear, colourless, mobile, heavy liquid.

Solubility

Practically insoluble in water, miscible with ethanol.

bp

About 48 °C.

It is non-flammable.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Preparation Examine the substance in the gaseous state.

Comparison *Ph. Eur. reference spectrum of isoflurane*.

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TESTS

Acidity or alkalinity

To 20 mL add 20 mL of *carbon dioxide-free water R*, shake for 3 min and allow to stand. Collect the upper layer and add 0.2 mL of *bromocresol purple solution R*. Not more than 0.1 mL of *0.01 M sodium hydroxide* or 0.6 mL of *0.01 M hydrochloric acid* is required to change the colour of the indicator.

Related substances

Gas chromatography (*2.2.28*).

Test solution The substance to be examined.

Reference solution To 80 mL of *anhydrous ethanol R*, add 1.0 mL of the substance to be examined and 1.0 mL of *acetone R*, avoiding loss by evaporation. Dilute to 100.0 mL with *anhydrous ethanol R*. Dilute 1.0 mL of the solution to 100.0 mL with *anhydrous ethanol R*.

Column:

— *material*: fused silica,

— *size*: *l* = 30 m, Ø = 0.32 mm,

— *stationary phase*: *macrogol 20 000 R* (film thickness 0.25 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1.0 mL/min.

Split ratio 1:25.

Temperature:

— *column*: 35 °C,

— *injection port*: 150 °C,

— *detector*: 250 °C.

Detection Flame ionisation.

Injection 1.0 µL of each solution and 1.0 µL of *anhydrous ethanol R* as a blank.

Run time Until elution of the ethanol peak in the chromatogram obtained with the reference solution.

Relative retention With reference to isoflurane (retention time = about 3.8 min): acetone = about 0.75.

System suitability Reference solution:

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— *resolution*: minimum of 5 between the peaks due to acetone and to isoflurane,

— *repeatability*: maximum relative standard deviation 15.0 per cent for the peak due to isoflurane after 3 injections.

Limits:

— *acetone*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.01 per cent),

— *any other impurity*: not more than the area of the peak due to isoflurane in the chromatogram obtained with the reference solution (0.01 per cent),

— *total*: not more than 3 times the area of the peak due to isoflurane in the chromatogram obtained with the reference solution (0.03 per cent),

— *disregard limit*: 0.1 times the area of the peak due to isoflurane in the chromatogram obtained with the reference solution (0.001 per cent).

Chlorides (2.4.4)

Maximum 10 ppm.

To 10 mL add 10 mL of *0.01 M sodium hydroxide* and shake for 3 min. To 5 mL of the upper layer add 10 mL of *water R*.

Fluorides

Maximum 10 ppm.

Determine by potentiometry (*2.2.36, Method I*) using a fluoride-selective indicator-electrode and a silver-silver chloride reference electrode.

Test solution To 10.0 mL in a separating funnel, add 10 mL of a mixture of 30.0 mL of *dilute ammonia R2* and 70.0 mL of *distilled water R*. Shake for 1 min and collect the upper layer. Repeat this extraction procedure twice collecting the upper layer each time. Adjust the combined upper layers to pH 5.2 using *dilute hydrochloric acid R*. Add 5.0 mL of *fluoride standard solution (1 ppm F) R* and dilute to 50.0 mL with *distilled water R*. To 20.0 mL of the solution add 20.0 mL of *total-ionic-strength-adjustment buffer R* and dilute to 50.0 mL with *distilled water R*.

Reference solutions To each of 5.0 mL, 4.0 mL, 3.0 mL, 2.0 mL and 1.0 mL of *fluoride standard solution (10 ppm F) R* add 20.0 mL of *total-ionic-strength-adjustment buffer R* and dilute to 50.0 mL with *distilled water R*.

Carry out the measurements on 20 mL of each solution. Calculate the concentration of fluorides using the calibration curve, taking into account the addition of fluoride to the test solution.

Non-volatile matter

Maximum 200 mg/L.

Evaporate 10.0 mL to dryness with the aid of a stream of cold air and dry the residue at 50 °C for 2 h. The residue weighs a maximum of 2.0 mg.

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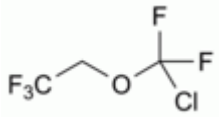
Water (*2.5.12*)

Maximum 1.0 mg/mL, determined on 10.0 mL.

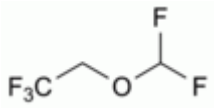
STORAGE

In an airtight container, protected from light.

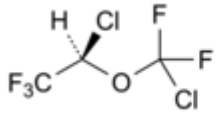
IMPURITIES



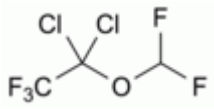
A. 2-(chlorodifluoromethoxy)-1,1,1-trifluoroethane,



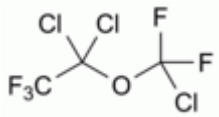
B. 2-(difluoromethoxy)-1,1,1-trifluoroethane,

 and enantiomer

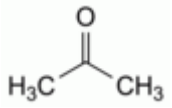
C. (2*RS*)-2-chloro-2-(chlorodifluoromethoxy)-1,1,1-trifluoroethane,



D. 1,1-dichloro-1-(difluoromethoxy)-2,2,2-trifluoroethane,



E. 1,1-dichloro-1-(chlorodifluoromethoxy)-2,2,2-trifluoroethane,



F. propanone (acetone).

Ph Eur

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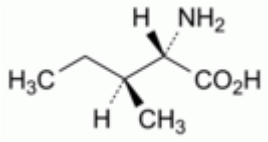
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Isoleucine

General Notices

(Ph. Eur. monograph 0770)



$C_6H_{13}NO_2$ 131.2 *73-32-5*

Action and use

Amino acid.

Ph Eur

DEFINITION

(2*S*,3*S*)-2-Amino-3-methylpentanoic acid.

Product of fermentation or of protein hydrolysis.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or flakes.

Solubility

Sparingly soluble in water, slightly soluble in ethanol (96 per cent). It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.

IDENTIFICATION

First identification: A, B.

Second identification: A, C.

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A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *isoleucine CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in a 10.3 g/L solution of *hydrochloric acid R* and dilute to 50 mL with the same solution.

Reference solution Dissolve 10 mg of *isoleucine CRS* in a 10.3 g/L solution of *hydrochloric acid R* and dilute to 50 mL with the same solution.

Plate *TLC silica gel plate R*.

Mobile phase *glacial acetic acid R*, *water R*, *butanol R* (20:20:60 *V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with *ninhydrin solution R* and heat at 105 °C for 15 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution BY_6 (2.2.2, *Method II*).

Dissolve 0.5 g in a 103 g/L solution of *hydrochloric acid R* and dilute to 10 mL with the same solution.

Specific optical rotation (2.2.7)

+ 40.0 to + 43.0 (dried substance).

Dissolve 1.00 g in *hydrochloric acid R1* and dilute to 25.0 mL with the same acid.

Ninhydrin-positive substances

Amino acid analysis (2.2.56). For analysis, use Method 1.

The concentrations of the test solution and the reference solutions may be adapted according to the sensitivity of the equipment used. The concentrations of all solutions are adjusted so that the system suitability requirements described in general chapter 2.2.46 are fulfilled, keeping the ratios of concentrations between all solutions as described.

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Solution A *dilute hydrochloric acid R1* or a sample preparation buffer suitable for the apparatus used.

Test solution Dissolve 30.0 mg of the substance to be examined in solution A and dilute to 50.0 mL with solution A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with solution A. Dilute 2.0 mL of this solution to 10.0 mL with solution A.

Reference solution (b) Dissolve 30.0 mg of *valine R* (impurity A) in solution A and dilute to 100.0 mL with solution A. Dilute 1.0 mL of the solution to 250.0 mL with solution A.

Reference solution (c) Dissolve 30.0 mg of *proline R* in solution A and dilute to 100.0 mL with solution A. Dilute 1.0 mL of the solution to 250.0 mL with solution A.

Reference solution (d) Dissolve 30.0 mg of *leucine R* (impurity C) in solution A and dilute to 100.0 mL with solution A. Dilute 1.0 mL of the solution to 250.0 mL with solution A.

Reference solution (e) Dilute 6.0 mL of *ammonium standard solution (100 ppm NH_4) R* to 50.0 mL with solution A. Dilute 1.0 mL of this solution to 100.0 mL with solution A.

Reference solution (f) Dissolve 30 mg of *isoleucine R* and 30 mg of *leucine R* (impurity C) in solution A and dilute to 50.0 mL with solution A. Dilute 1.0 mL of the solution to 200.0 mL with solution A.

Blank solution Solution A.

Inject suitable, equal amounts of the test solution, blank solution and reference solutions (a), (b), (c), (d) and (f) into the amino acid analyser. Run a program suitable for the determination of physiological amino acids.

System suitability Reference solution (f):

— *resolution*: minimum 1.5 between the peaks due to isoleucine and impurity C.

Calculation of percentage contents:

— for impurity A, use the concentration of impurity A in reference solution (b);

— for impurity C, use the concentration of impurity C in reference solution (d);

— for any ninhydrin-positive substance detected at 570 nm, use the concentration of isoleucine in reference solution (a);

— for any ninhydrin-positive substance detected at 440 nm, use the concentration of proline in reference solution (c); if a peak is above the reporting threshold at both wavelengths, use the result obtained at 570 nm for quantification.

Limits:

— *impurities A and C at 570 nm*: for each impurity, maximum 0.3 per cent;

— *any ninhydrin-positive substance*: for each impurity, maximum 0.2 per cent;

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— *total*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent.

The thresholds indicated under Related Substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

Chlorides (2.4.4)

Maximum 200 ppm.

Dissolve 0.25 g in *water R* and dilute to 15 mL with the same solvent.

Sulfates (2.4.13)

Maximum 300 ppm.

Dissolve 0.5 g in 3 mL of *dilute hydrochloric acid R* and dilute to 15 mL with *distilled water R*.

Ammonium

Amino acid analysis (2.2.56) as described in the test for ninhydrin-positive substances with the following modifications.

Injection Test solution, reference solution (e) and blank solution.

Limit:

— *ammonium at 570 nm*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (e) (0.02 per cent), taking into account the peak due to ammonium in the chromatogram obtained with the blank solution.

Iron (2.4.9)

Maximum 10 ppm.

In a separating funnel, dissolve 1.0 g in 10 mL of *dilute hydrochloric acid R*. Shake with 3 quantities, each of 10 mL, of *methyl isobutyl ketone R1*, shaking for 3 min each time. To the combined organic layers add 10 mL of *water R* and shake for 3 min. Use the aqueous layer.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.100 g in 3 mL of *anhydrous formic acid R*. Add 30 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

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1 mL of *0.1 M perchloric acid* is equivalent to 13.12 mg of $C_6H_{13}NO_2$.

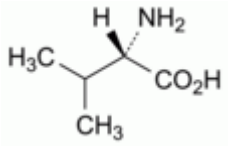
STORAGE

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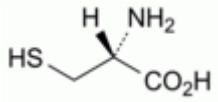
IMPURITIES

Specified impurities A, C.

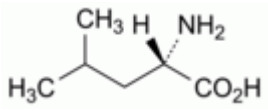
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, D.



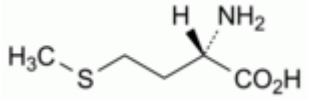
A. (2*S*)-2-amino-3-methylbutanoic acid (valine),



B. (2*R*)-2-amino-3-sulfanylpropanoic acid (cysteine),



C. (2*S*)-2-amino-4-methylpentanoic acid (leucine),



D. (2*S*)-2-amino-4-(methylsulfanyl)butanoic acid (methionine).

Ph Eur

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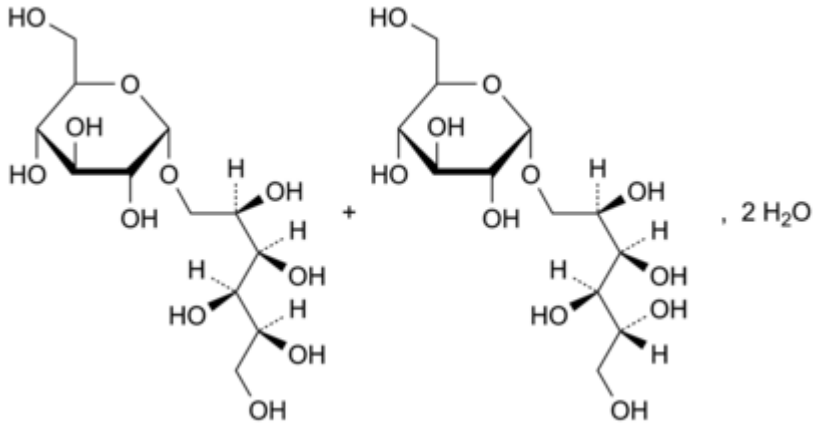
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Isomalt[1]

General Notices

(Ph. Eur. monograph 1531)



$C_{12}H_{24}O_{11}$ 344.3

$C_{12}H_{24}O_{11},2H_2O$ 380.3

Anhydrous isomalt *64519-82-0*

Action and use

Sweetening agent.

Ph Eur

DEFINITION

Mixture of 6-*O*-α-D-glucopyranosyl-D-glucitol (6-*O*-α-D-glucopyranosyl-D-sorbitol; 1,6-GPS) and 1-*O*-α-D-glucopyranosyl-D-mannitol (1,1-GPM).

Content

98.0 per cent to 102.0 per cent for the mixture of 1,6-GPS and 1,1-GPM and neither of the 2 components is less than 3.0 per cent (anhydrous substance).

♦ CHARACTERS

Appearance

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White or almost white powder or granules.

Solubility

Freely soluble in water, practically insoluble in anhydrous ethanol.♦

IDENTIFICATION

First identification: A.

◊ *Second identification: B, C.*◊

A. Examine the chromatograms obtained in the assay.

Results The 2 principal peaks in the chromatogram obtained with the test solution are similar in retention time to the 2 principal peaks in the chromatogram obtained with reference solution (a).

◊ B. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 50 mg of the substance to be examined in *water R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 50 mg of *isomalt CRS* in *water R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *acetic acid R*, *propionic acid R*, *water R*, *ethyl acetate R*, *pyridine R* (5:5:10:50:50 *V/V/V/V/V*).

Application 1 µL; thoroughly dry the points of application in warm air.

Development Over 1/2 of the plate.

Drying In a current of warm air.

Detection Dip for 3 s in a 1 g/L solution of *sodium periodate R* and dry in a current of hot air; dip for 3 s in a mixture of 1 volume of *acetic acid R*, 1 volume of *anisaldehyde R*, 5 volumes of *sulfuric acid R* and 90 volumes of *anhydrous ethanol R*; dry in a current of hot air until coloured spots become visible; the background colour may be brightened in warm steam; examine in daylight.

Results The chromatogram obtained with the reference solution shows 2 blue-grey spots with R_F values of about 0.13 (1,6-GPS) and 0.16 (1,1-GPM). The chromatogram obtained with the test solution shows principal spots similar in position and colour to the principal spots in the chromatogram obtained with the reference solution.

C. To 3 mL of a freshly prepared 100 g/L solution of *pyrocatechol R* add 6 mL of *sulfuric acid R* while cooling in iced water. To 3 mL of the cooled mixture add 0.3 mL of a 100 g/L solution of the substance to be examined. Heat gently over a naked flame for about 30 s. A pink colour develops.◊

TESTS

Conductivity (*2.2.38*)

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Maximum 20 µS·cm^{-1}.

Dissolve 20.0 g in *carbon dioxide-free water R* with gentle heating (40-50 °C) and dilute to 100.0 mL with the same solvent. Measure the conductivity of the solution while gently stirring with a magnetic stirrer.

Reducing sugars

Maximum 0.3 per cent, expressed as glucose equivalent.

Dissolve 3.3 g in 10 mL of *water R* with gentle heating. Cool and add 20 mL of *cupri-citric solution R* and a few glass beads. Heat so that boiling begins after 4 min and maintain boiling for 3 min. Cool rapidly and add 100 mL of a 2.4 per cent *V/V* solution of *glacial acetic acid R* and 20.0 mL of *0.025 M iodine*. With continuous shaking, add 25 mL of a mixture of 6 volumes of *hydrochloric acid R* and 94 volumes of *water R*. When the precipitate has dissolved, titrate the excess of iodine with *0.05 M sodium thiosulfate* using 1 mL of *starch solution R* as indicator, added towards the end of the titration. Not less than 12.8 mL of *0.05 M sodium thiosulfate* is required.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.200 g of the substance to be examined in 4 mL of *water R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 0.200 g of *isomalt CRS* in 4 mL of *water R* and dilute to 10.0 mL with the same solvent.

Reference solution (b) Dissolve 10.0 mg of *sorbitol CRS* (impurity C) and 10.0 mg of *mannitol CRS* (impurity B) in 20 mL of *water R* and dilute to 100.0 mL with the same solvent.

Precolumn:

— *size*: *l* = 30 mm, Ø = 4.6 mm;

— *stationary phase*: *strong cation-exchange resin (calcium form) R* (9 µm);

— *temperature*: 80 ± 3 °C.

Column:

— *size*: *l* = 0.3 m, Ø = 7.8 mm;

— *stationary phase*: *strong cation-exchange resin (calcium form) R* (9 µm);

— *temperature*: 80 ± 3 °C.

Mobile phase Degassed *water for chromatography R*.

Flow rate 0.5 mL/min.

Detection Differential refractometer maintained at a constant temperature (e.g. 40 °C).

Injection 20 µL.

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Run time 2.5 times the retention time of 1,1-GPM.

Relative retention With reference to 1,1-GPM (retention time = about 14 min): 1,6-GPS = about 1.2; impurity B = about 1.6; impurity C = about 2.0.

System suitability Reference solution (a):

— *resolution*: minimum 2.0 between the peaks due to 1,1-GPM and 1,6-GPS.

Limits:

— *impurities B, C*: for each impurity, not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the peak due to impurity C in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *total*: not more than 4 times the area of the peak due to impurity C in the chromatogram obtained with reference solution (b) (2.0 per cent);

— *disregard limit*: 0.2 times the area of the peak due to impurity C in the chromatogram obtained with reference solution (b) (0.1 per cent).

Water (2.5.12)

Maximum 7.0 per cent, determined on 0.300 g. As solvent, use a mixture of 20 mL of *anhydrous methanol R* and 20 mL of *formamide R1* at 50 ± 5 °C.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

Calculate the percentage content of isomalt (1,1-GPM and 1,6-GPS) taking into account the assigned contents of 1,1-GPM and 1,6-GPS in *isomalt CRS*.

LABELLING

The label states the percentage contents of 1,1-GPM and 1,6-GPS.

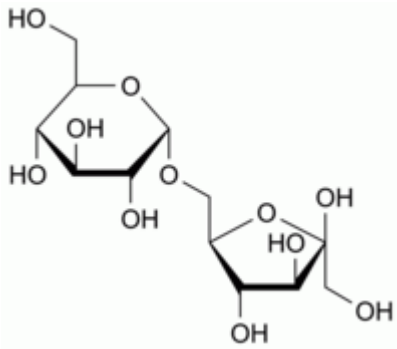
IMPURITIES

Specified impurities *B, C.*

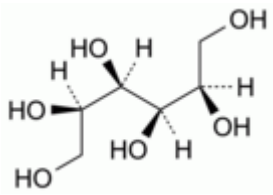
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify

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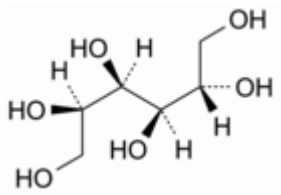
these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, D.



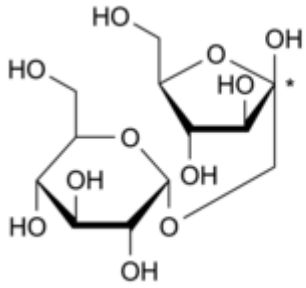
A. 6-*O*-α-D-glucopyranosyl-β-D-*arabino*-hex-2-ulofuranose (isomaltulose),



B. D-mannitol,



C. D-glucitol (D-sorbitol),



and epimer at C*

D. 1-*O*-α-D-glucopyranosyl-D-*arabino*-hex-2-ulofuranose (trehalulose).

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1 This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8 Pharmacopoeial harmonisation*.

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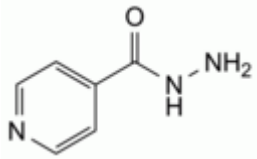
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This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Isoniazid

General Notices

(Ph. Eur. monograph 0146)



$C_6H_7N_3O$ 137.1 *54-85-3*

Action and use

Antituberculosis drug.

Preparations

Isoniazid Injection

Isoniazid Oral Solution

Isoniazid Tablets

Ph Eur

DEFINITION

Pyridine-4-carbohydrazide.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

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Freely soluble in water, sparingly soluble in ethanol (96 per cent), practically insoluble in heptane.

IDENTIFICATION

First identification: A, B.

Second identification: A, C.

A. Melting point (2.2.14): 170 °C to 174 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *isoniazid CRS*.

C. Dissolve 0.1 g in 2 mL of *water R* and add 10 mL of a warm 10 g/L solution of *vanillin R*. Allow to stand and scratch the wall of the test tube with a glass rod. A yellow precipitate is formed. Recrystallise from 5 mL of *ethanol (70 per cent V/V) R*. The crystals, dried at 100-105 °C, melt (2.2.14) at 226 °C to 231 °C.

TESTS

Solution S

Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution BY_7 (2.2.2, *Method II*).

pH (2.2.3)

6.0 to 8.0 for solution S.

Impurity E

Liquid chromatography (2.2.29). *Use freshly prepared solutions*.

Solvent mixture *acetonitrile R*, *water R* (50:50 *V/V*).

Solution A Dilute 1 mL of *benzaldehyde R* to 50 mL with *methanol R*. Use the solution within 4 h.

Test solution Dissolve 50.0 mg of the substance to be examined in 1 mL of *water R* and mix with 5 mL of solution A. Shake and allow to stand for 45 min to allow completion of the derivatisation reaction (hydrazine (impurity E) reacts with benzaldehyde to give benzaldehyde azine). Dilute to 10.0 mL with the solvent mixture.

Reference solution Dissolve 20.0 mg of *hydrazine sulfate R* (equivalent to 4.925 mg of hydrazine (impurity E)) in *water R* and dilute to 50.0 mL with the same solvent. Dilute 2.5 mL of the solution to 100.0 mL with *water R*. Mix 1.0 mL of this solution and 2.5 mL of solution A. Shake and allow to stand for 45 min to allow completion of the derivatisation reaction (hydrazine (impurity E) reacts with benzaldehyde to give benzaldehyde azine). Dilute to 25.0 mL with the solvent mixture. Dilute 7.5 mL of this solution to 10.0 mL with the solvent mixture.

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Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *water for chromatography R*, *acetonitrile R* (40:60 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 300 nm.

Injection 10 µL.

Run time 1.5 times the retention time of benzaldehyde azine.

Retention time Benzaldehyde azine = about 14 min.

System suitability Reference solution:

— *repeatability*: maximum relative standard deviation of 5.0 per cent for the area of the peak due to benzaldehyde azine determined on 6 injections.

Calculation of content:

— for impurity E, use the concentration of hydrazine in the reference solution and the peak areas due to benzaldehyde azine.

Limit:

— *impurity E*: maximum 15 ppm.

Related substances

Liquid chromatography (*2.2.29*). *Use freshly prepared solutions*.

Buffer solution Dissolve 13.6 g of *potassium dihydrogen phosphate R* in 950 mL of *water for chromatography R*, adjust to pH 6.9 with *strong sodium hydroxide solution R*, add 30 mg of *triethanolamine R* and dilute to 1000 mL with *water for chromatography R*.

Test solution Dissolve 25.0 mg of the substance to be examined in mobile phase A and dilute to 25.0 mL with mobile phase A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (b) Dissolve 5 mg of *isonicotinic acid R* (impurity A), 5 mg of *isonicotinamide R* (impurity B) and 5 mg of *nicotinoyl hydrazide R* (impurity D) in mobile phase A and dilute to 50 mL with mobile phase A. Dilute 1 mL of the solution to 10 mL with mobile phase A. Dilute 1 mL of the solution obtained to 10 mL with the test solution.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

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— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: *methanol R*, buffer solution (3:97 *V/V*);

— *mobile phase B*: *methanol R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 12	100	0
12 - 20	100 → 85	0 → 15
20 - 28	85	15

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 266 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B and D.

Relative retention With reference to isoniazid (retention time = about 9 min): impurity A = about 0.4; impurity D = about 1.15; impurity B = about 1.4.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 1.8, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to isoniazid.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 1.4; impurity B = 1.5;

— for each impurity, use the concentration of isoniazid in reference solution (a).

Limits:

— *impurities A, B*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

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Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

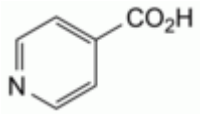
Dissolve 0.250 g in *water R* and dilute to 100.0 mL with the same solvent. To 20.0 mL of the solution add 100 mL of *water R*, 20 mL of *hydrochloric acid R*, 0.2 g of *potassium bromide R* and 0.05 mL of *methyl red solution R*. Titrate dropwise with *0.0167 M potassium bromate*, shaking continuously, until the red colour disappears.

1 mL of *0.0167 M potassium bromate* is equivalent to 3.429 mg of $C_6H_7N_3O$.

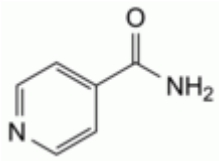
IMPURITIES

Specified impurities *A, B, E.*

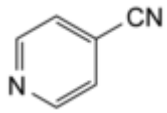
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, D.*



A. pyridine-4-carboxylic acid (isonicotinic acid),

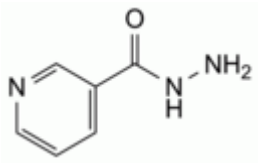


B. pyridine-4-carboxamide (isonicotinamide),

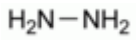


C. pyridine-4-carbonitrile (isonicotinonitrile),

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D. pyridine-3-carbohydrazide (nicotinoyl hydrazide),



E. hydrazine.

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Isoniazid Injection

General Notices

Action and use

Antituberculosis drug.

DEFINITION

Isoniazid Injection is a sterile solution of Isoniazid in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of isoniazid, $C_6H_7N_3O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Using a rotary evaporator, evaporate a volume of the injection containing 50 mg of Isoniazid to dryness, extract the residue with two 10 mL quantities of *ethanol (96%)*, filter and evaporate the combined ethanol extracts to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of isoniazid *(RS 196)*.

B. To a volume containing 25 mg of Isoniazid add 5 mL of *ethanol (96%)*, 0.1 g of *sodium tetraborate* and 5 mL of a 5.0% w/v solution of *1-chloro-2,4-dinitrobenzene* in *ethanol (96%)*, evaporate to dryness on a water bath, heat for a further 10 minutes and dissolve the residue in 10 mL of *methanol*. A reddish purple colour is produced.

TESTS

Acidity

pH, 5.6 to 6.0, Appendix V L.

ASSAY

Dilute a quantity containing 0.4 g of Isoniazid to 250 mL with *water*. To 25 mL of the solution in a glass-stoppered flask add 25 mL of 0.05M *bromine VS* and 5 mL of *hydrochloric acid*, shake for 1 minute, allow to stand for 15 minutes, add 1 g of *potassium iodide* and titrate with 0.1M *sodium thiosulfate VS* using *starch mucilage* as indicator. Repeat the operation without the injection. The difference between the titrations represents the amount of bromine required. Each mL of 0.05M *bromine VS* is equivalent to 3.429 mg of $C_6H_7N_3O$.

STORAGE

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Isoniazid Injection should be protected from light.

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Isoniazid Oral Solution

General Notices

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Antituberculosis drug.

DEFINITION

Isoniazid Oral Solution is a solution of Isoniazid in a suitable flavoured vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral solution also complies with the requirements stated under Unlicensed Medicines.

Content of isoniazid, $C_6H_7N_3O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in a mixture of equal volumes of *acetone* and *water*.

(1) Dilute a volume of the oral solution, if necessary, to contain 0.01% w/v of Isoniazid.

(2) 0.01% w/v of *isoniazid BPCRS*.

(3) 0.01% w/v of each of *isoniazid BPCRS* and *pyrazinamide BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 50 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

10 volumes of *water*, 20 volumes of *acetone*, 20 volumes of *methanol* and 50 volumes of *ethyl acetate*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

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The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. To a volume of the oral solution containing 25 mg of Isoniazid add 5 mL of *ethanol (96%)*, 0.1 g of *sodium tetraborate* and 5 mL of a 5.0% w/v solution of *1-chloro-2,4-dinitrobenzene* in *ethanol (96%)*. Evaporate to dryness on a water bath, heat for a further 10 minutes and dissolve the residue in 10 mL of *methanol*; a reddish purple colour is produced.

C. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 5.4 to 5.9, Appendix V L.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a weighed quantity of the oral solution with sufficient of the mobile phase to produce a solution containing 0.032% w/v of Isoniazid and filter through a 0.45-µm nylon filter.

(2) 0.032% w/v of *isoniazid BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 260 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Dissolve about 8.8 g of *sodium dodecyl sulfate* in a mixture of 840 volumes of *water* and 1160 volumes of *methanol*, mix with the aid of ultrasound and adjust the pH of the resulting solution to 2.5 using 1M *sulfuric acid*.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_6H_7N_3O$, weight in volume, using the declared content of $C_6H_7N_3O$ in *isoniazid BPCRS*.

STORAGE

Isoniazid Oral Solution should be protected from light.

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Isoniazid Tablets

General Notices

Action and use

Antituberculosis drug.

DEFINITION

Isoniazid Tablets contain Isoniazid.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of isoniazid, $C_6H_7N_3O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 0.1 g of Isoniazid with 10 mL of *ethanol (96%)* for 15 minutes, centrifuge and decant the supernatant liquid. Extract the residue with two further 10-mL quantities of *ethanol (96%)* and evaporate the combined extracts to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of isoniazid *(RS 196)*.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.

(b) Use 900 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

After 45 minutes withdraw a 10 mL sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted if necessary, at the maximum at 263 nm, Appendix II B.

DETERMINATION OF CONTENT

Calculate the total content of isoniazid, $C_6H_7N_3O$, in the medium taking 307 as the value of A(1%, 1 cm) at the maximum at 263 nm.

ASSAY

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Weigh and powder 20 tablets. Dissolve a quantity of the powder containing 150 mg of Isoniazid as completely as possible in *water*, filter and wash the residue with sufficient *water* to produce 250 mL. To 50 mL of the resulting solution add 50 mL of *water*, 20 mL of *hydrochloric acid* and 0.2 g of *potassium bromide* and titrate with *0.0167M potassium bromate VS* determining the end point electrometrically. Each mL of *0.0167M potassium bromate VS* is equivalent to 3.429 mg of $C_6H_7N_3O$.

STORAGE

Isoniazid Tablets should be protected from light.

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Isophane Insulin Injection

General Notices

Isophane Insulin

Isophane Insulin (NPH)

(Ph. Eur. monograph 0833)

Action and use

Hormone; treatment of diabetes mellitus.

Ph Eur

Isophane insulin injection complies with the monograph Insulin preparations, injectable (0854) with the modifications prescribed below.

DEFINITION

Isophane insulin injection is a sterile suspension of human or porcine insulin, complexed with protamine sulfate or another suitable protamine.

PRODUCTION

Isophane insulin injection is prepared by carrying out the procedures described in the monograph *Insulin preparations, injectable (0854)*.

The amount of protamine is based on the known isophane ratio and is not less than the equivalent of 0.3 mg and not more than the equivalent of 0.6 mg of protamine sulfate for each 100 IU of insulin in the insulin-protamine complex.

CHARACTERS

A white or almost white suspension which on standing deposits a white or almost white sediment and leaves a colourless or almost colourless supernatant; the sediment is readily resuspended by gently shaking. When examined under a microscope, the particles are seen to be rod-shaped crystals, the majority with a maximum dimension greater than 1 µm but rarely exceeding 60 µm, free from large aggregates.

IDENTIFICATION

Examine the chromatograms obtained in the assay. The position of the peak due to insulin in the chromatogram obtained with the test solution corresponds to that of the principal peak in the chromatogram obtained with the appropriate reference solution.

TESTS

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Total zinc

Not more than 40.0 µg per 100 IU of insulin, determined as described in the monograph *Insulin preparations, injectable (0854)*.

Ph Eur

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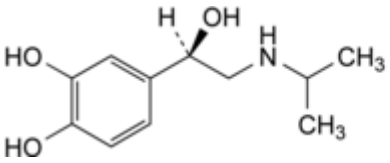
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Isoprenaline Hydrochloride

General Notices

(Ph. Eur. monograph 1332)



and enantiomer , HCl

$C_{11}H_{18}ClNO_3$ 247.7 *51-30-9*

Action and use

Adrenoceptor agonist.

Preparation

Isoprenaline Injection

Ph Eur

DEFINITION

(1*RS*)-1-(3,4-Dihydroxyphenyl)-2-[(1-methylethyl)amino]ethanol hydrochloride.

Content

98.0 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, sparingly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

First identification: B, C, E.

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Second identification: A, C, D, E.

A. Melting point (2.2.14): 165 °C to 170 °C, with decomposition.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *isoprenaline hydrochloride CRS*.

C. Optical rotation (see Tests).

D. To 0.1 mL of solution S (see Tests) add 0.05 mL of *ferric chloride solution R1* and 0.9 mL of *water R*. A green colour is produced. Add dropwise *sodium hydrogen carbonate solution R*. The colour becomes blue and then red.

E. To 0.5 mL of solution S add 1.5 mL of *water R*. The solution gives reaction (a) of chlorides (2.3.1).

TESTS

Prepare the solutions immediately before use.

Solution S

Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 25.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution B_7 or BY_7 (2.2.2, *Method II*).

pH (2.2.3)

4.3 to 5.5.

Mix 5 mL of solution S and 5 mL of *carbon dioxide-free water R*.

Optical rotation (2.2.7)

-0.10° to + 0.10°, determined on solution S.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 2.5 mg of *orciprenaline sulfate CRS* in the mobile phase and dilute to 100 mL with the mobile phase.

Reference solution (c) To 5 mL of reference solution (a) add 5 mL of reference solution (b).

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Reference solution (d) Dissolve 6.0 mg of *isoprenaline impurity A CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 10.0 mL of the solution to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.125 m, Ø = 4.0 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *methanol R*, 11.5 g/L solution of *phosphoric acid R* (5:95 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 20 µL.

Run time 7 times the retention time of isoprenaline.

Identification of impurities Use the chromatogram obtained with reference solution (d) to identify the peak due to impurity A; use the chromatogram obtained with reference solution (b) to identify the peak due to orciprenaline.

Relative retention With reference to isoprenaline (retention time = about 4 min): orciprenaline = about 1.5; impurity A = about 1.8. If necessary, adjust the concentration of methanol in the mobile phase.

System suitability Reference solution (c):

— *resolution*: minimum 3.0 between the peaks due to isoprenaline and orciprenaline.

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: maximum 1.0 per cent;

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying *in vacuo* at 15-25 °C for 4 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

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In order to avoid overheating in the reaction medium, mix thoroughly throughout and stop the titration immediately after the end-point has been reached.

Dissolve 0.150 g in 10 mL of *anhydrous formic acid R* and add 50 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

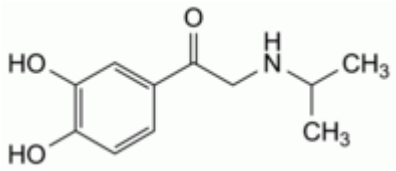
1 mL of *0.1 M perchloric acid* is equivalent to 24.77 mg of $C_{11}H_{18}ClNO_3$.

STORAGE

In an airtight container, protected from light.

IMPURITIES

Specified impurities *A.*



A. 1-(3,4-dihydroxyphenyl)-2-[(1-methylethyl)amino]ethanone.

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Isoprenaline Injection

General Notices

Action and use

Adrenoceptor agonist.

DEFINITION

Isoprenaline Injection is a sterile solution of Isoprenaline Hydrochloride in Water for Injections. It is supplied either as a ready-to-use solution or prepared immediately before use in accordance with the manufacturer's instructions from Isoprenaline Sterile Concentrate.

The injection complies with the requirements stated under Parenteral Preparations.

When supplied as a ready-to-use solution, the injection complies with the following requirements.

Content of isoprenaline hydrochloride, $C_{11}H_{17}NO_3$,HCl

90.0 to 115.0% of the stated amount.

CHARACTERISTICS

A colourless solution.

IDENTIFICATION

A. Record *second-derivative ultraviolet absorption spectra* of the following solutions, Appendix II B, in the range 250 to 330 nm. For solution (1) dilute the injection, if necessary, with *methanol* to contain 0.002% w/v of Isoprenaline Hydrochloride. Solution (2) is a 0.002% w/v solution of *isoprenaline hydrochloride BPCRS* in *methanol*. The spectrum obtained with solution (1) exhibits a maximum at 294 nm and a trough at 289 nm and is similar to the spectrum obtained with solution (2) in the range 280 to 298 nm.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Evaporate a suitable volume of the solution just to dryness and dissolve the residue in sufficient *methanol* to produce a solution containing 0.01% w/v of Isoprenaline Hydrochloride.

(2) 0.01% w/v of *isoprenaline hydrochloride BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *TLC octadecylsilyl silica gel* F_{254} (Merck HPTLC RP18 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, heat at 105° for 15 minutes and examine under *ultraviolet light (254 nm)*.

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MOBILE PHASE

0.1 volume of *glacial acetic acid*, 40 volumes of *water* and 60 volumes of *methanol*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

C. To 2 mL add 0.1 mL of *iron(III) chloride solution R1*. An emerald green colour is produced which, on the gradual addition of *sodium hydrogen carbonate solution*, changes first to blue and then to red.

TESTS

Acidity

pH, 2.5 to 3.0, Appendix V L.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Use the solution diluted, if necessary, with sufficient of a 0.1% w/v solution of *sodium metabisulfite* to produce a solution containing 0.002% w/v of Isoprenaline Hydrochloride.
(2) 0.002% w/v of *isoprenaline hydrochloride BPCRS* in a 0.1% w/v solution of *sodium metabisulfite*.
(3) A mixture of 1 volume of a 0.02% w/v solution of *adrenaline acid tartrate* in the mobile phase containing 1.0% w/v of *sodium metabisulfite* and 18 volumes of solution (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3 to 10 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 280 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

A solution prepared by dissolving 1.76 g of *sodium heptanesulfonate* in 800 mL of *water*, adding 200 mL of *methanol* and adjusting the pH to 3.0 with 1M *orthophosphoric acid*.

SYSTEM SUITABILITY

The assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 3.5.

DETERMINATION OF CONTENT

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Calculate the content of $C_{11}H_{17}NO_3$,HCl in the injection using the declared content of $C_{11}H_{17}NO_3$,HCl in *isoprenaline hydrochloride BPCRS*.

ISOPRENALINE STERILE CONCENTRATE

DEFINITION

Isoprenaline Sterile Concentrate is a sterile solution of Isoprenaline Hydrochloride in Water for Injections.

The concentrate complies with the requirements for Concentrates for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of isoprenaline hydrochloride, $C_{11}H_{17}NO_3$,HCl

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A colourless or very pale yellow solution.

IDENTIFICATION

A. Record *second-derivative ultraviolet absorption spectra* of the following solutions, Appendix II B, in the range 250 to 330 nm. For solution (1) dilute the concentrate with *methanol* to contain 0.002% w/v of Isoprenaline Hydrochloride. Solution (2) is a 0.002% w/v solution of *isoprenaline hydrochloride BPCRS* in *methanol*. The spectrum obtained with solution (1) exhibits a maximum at 294 nm and a trough at 289 nm and is similar to the spectrum obtained with solution (2) in the range 280 to 298 nm.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute the concentrate with *methanol* to produce a solution containing 0.01% w/v of Isoprenaline Hydrochloride.

(2) 0.01% w/v of *isoprenaline hydrochloride BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *TLC octadecylsilyl silica gel* F_{254} (Merck HPTLC RP18 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, heat at 105° for 15 minutes and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

0.1 volume of *glacial acetic acid*, 40 volumes of *water* and 60 volumes of *methanol*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

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C. To 2 mL add 0.1 mL of *iron(III) chloride solution R1*. An emerald green colour is produced which, on the gradual addition of *sodium hydrogen carbonate solution*, changes first to blue and then to red.

TESTS

Acidity

pH, 2.5 to 3.0, Appendix V L.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Use the concentrate diluted with sufficient of a 0.1% w/v solution of *sodium metabisulfite* to produce a solution containing 0.002% w/v of Isoprenaline Hydrochloride.

(2) 0.002% w/v of *isoprenaline hydrochloride BPCRS* in a 0.1% w/v solution of *sodium metabisulfite*.

(3) A mixture of 1 volume of a 0.02% w/v solution of *adrenaline acid tartrate* in the mobile phase containing 1.0% w/v of *sodium metabisulfite* and 18 volumes of solution (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3 to 10 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 280 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

A solution prepared by dissolving 1.76 g of *sodium heptanesulfonate* in 800 mL of *water*, adding 200 mL of *methanol* and adjusting the pH to 3.0 with 1M *orthophosphoric acid*.

SYSTEM SUITABILITY

The assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 3.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{11}H_{17}NO_3$,HCl in the concentrate using the declared content of $C_{11}H_{17}NO_3$,HCl in *isoprenaline hydrochloride BPCRS*.

STORAGE

Isoprenaline Sterile Concentrate should be protected from light.

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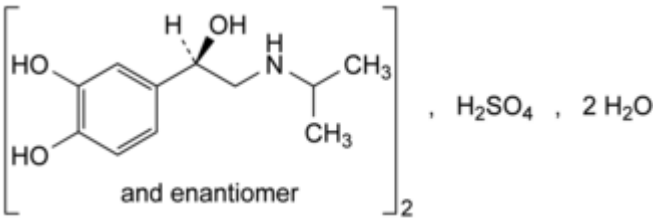
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Isoprenaline Sulfate

General Notices

Isoprenaline Sulphate

(Ph. Eur. monograph 0502)



$C_{22}H_{36}N_2O_{10}S,2H_2O$ 556.6 *6700-39-6*

Action and use

Adrenoceptor agonist.

Ph Eur

DEFINITION

Bis[(1*RS*)-1-(3,4-dihydroxyphenyl)-2-[(1-methylethyl)amino]ethanol] sulfate dihydrate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, very slightly soluble in ethanol (96 per cent).

mp

About 128 °C, with decomposition.

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).
Dissolve 0.5 g in 1.5 mL of *water R* and add 3.5 mL of *2-propanol R*. Scratch the wall of the tube with a glass rod to initiate crystallisation. Collect the crystals and dry *in vacuo* (2.2.32) at 60 °C.

Comparison Repeat the operations using 0.5 g of *isoprenaline sulfate CRS*.

B. To 0.1 mL of solution S (see Tests) add 0.9 mL of *water R* and 0.05 mL of *ferric chloride solution R1*. A green colour is produced. Add dropwise *sodium hydrogen carbonate solution R*. The colour becomes blue and then red.
C. Dilute 1 mL of solution S to 10 mL with *water R* and add 0.25 mL of *silver nitrate solution R1*. A shining, grey, fine precipitate is formed within 10 min and the solution becomes pink.
D. Solution S gives reaction (a) of sulfates (2.3.1).

TESTS

Solution S

Dissolve 5.0 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent. Use within 2 h of preparation.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (2.2.2, *Method II*).

pH (2.2.3)

4.3 to 5.5.

Dilute 5 mL of solution S to 10 mL with *carbon dioxide-free water R*.

Isoprenalone

The absorbance (2.2.25) is not greater than 0.20 at 310 nm.

Dissolve 0.20 g in *0.005 M sulfuric acid* and dilute to 100.0 mL with the same acid.

Water (2.5.12)

5.0 per cent to 7.5 per cent, determined on 0.200 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

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Dissolve 0.400 g in 20 mL of *anhydrous acetic acid R*, warming gently if necessary and add 20 mL of *methyl isobutyl ketone R*. Titrate with *0.1 M perchloric acid* determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 52.06 mg of $C_{22}H_{36}N_2O_{10}S$.

STORAGE

In an airtight container, protected from light.

Ph Eur

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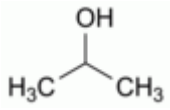
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Isopropyl Alcohol

General Notices

(Ph. Eur. monograph 0970)



C_3H_8O 60.1 *67-63-0*

Ph Eur

DEFINITION

Propan-2-ol.

CHARACTERS

Appearance

Clear, colourless liquid.

Solubility

Miscible with water and with ethanol (96 per cent).

IDENTIFICATION

First identification: B, C.

Second identification: A, B, D.

A. Relative density (2.2.5): 0.785 to 0.789.

B. Refractive index (2.2.6): 1.376 to 1.379.

C. Infrared absorption spectrophotometry (2.2.24).

Comparison *isopropyl alcohol CRS*.

D. To 1 mL add 4 mL of *water R* and mix. Carefully add 2 mL of a 10 g/L solution of *dimethylaminobenzaldehyde R* in *sulfuric acid R*, ensuring that the liquids do not mix; a bright reddish-violet ring forms immediately at the junction of the 2 liquids. After 2-5 min, the entire sulfuric acid layer turns violet.

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TESTS

Appearance

The substance to be examined is clear (2.2.1) and colourless (2.2.2, Method II). Dilute 1 mL to 20 mL with water R. After 5 min, the solution is clear (2.2.1).

Acidity or alkalinity

Gently boil 25 mL for 5 min. Add 25 mL of carbon dioxide-free water R and allow to cool protected from carbon dioxide in the air. Add 0.1 mL of phenolphthalein solution R. The solution is colourless. Not more than 0.6 mL of 0.01 M sodium hydroxide is required to change the colour of the indicator to pale pink.

Absorbance (2.2.25)

Maximum 0.30 at 230 nm, 0.10 at 250 nm, 0.03 at 270 nm, 0.02 at 290 nm and 0.01 at 310 nm.

The absorbance is measured between 230 nm and 310 nm using water R as the compensation liquid. The spectrum shows a steadily descending curve with no observable peaks or shoulders.

Benzene and related substances

Gas chromatography (2.2.28).

Test solution (a) The substance to be examined.

Test solution (b) Dilute 1.0 mL of 2-butanol R1 to 50.0 mL with test solution (a). Dilute 5.0 mL of this solution to 100.0 mL with test solution (a).

Reference solution (a) Dilute 0.5 mL of 2-butanol R1 and 0.5 mL of propanol R to 50.0 mL with test solution (a). Dilute 5.0 mL of this solution to 50.0 mL with test solution (a).

Reference solution (b) Dilute 100 µL of benzene R to 100.0 mL with test solution (a). Dilute 0.20 mL of this solution to 100.0 mL with test solution (a).

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.32 mm;

— *stationary phase*: cyanopropyl(3)phenyl(3)methyl(94)polysiloxane R (film thickness 1.8 µm).

Carrier gas helium for chromatography R.

Auxiliary gas nitrogen for chromatography R or helium for chromatography R.

Linear velocity 35 cm/s.

Split ratio 1:5.

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Temperature:

	Time (min)	Temperature (°C)
Column	0 - 12	40
	12 - 32	40 → 240
	32 - 42	240
Injection port		280
Detector		280

Detection Flame ionisation.

Injection 1 µL.

Retention time Benzene = about 10 min.

System suitability Reference solution (a):

— *resolution*: minimum 10 between the 1st peak (propanol) and the 2nd peak (2-butanol).

Limits:

— *benzene* (test solution (a)): not more than 0.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (b) (2 ppm), after the sensitivity has been adjusted so that the height of the peak due to benzene in the chromatogram obtained with reference solution (b) represents at least 10 per cent of the full scale of the recorder;

— *total of impurities apart from 2-butanol* (test solution (b)): not more than 3 times the area of the peak due to 2-butanol in the chromatogram obtained with test solution (b) (0.3 per cent), after the sensitivity has been adjusted so that the height of the 2 peaks following the principal peak in the chromatogram obtained with reference solution (a) represents at least 50 per cent of the full scale of the recorder.

Peroxides

In a 12 mL test-tube with a ground-glass stopper and a diameter of about 15 mm, introduce 8 mL of *potassium iodide and starch solution R*. Fill completely with the substance to be examined. Shake vigorously and allow to stand protected from light for 30 min. No colour develops.

Non-volatile substances

Maximum 20 ppm.

Evaporate 100 g to dryness on a water-bath *after having verified that it complies with the test for peroxides* and dry in an oven at 100-105 °C. The residue weighs a maximum of 2 mg.

Water (*2.5.12*)

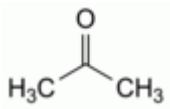
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Maximum 0.5 per cent, determined on 5.0 g.

STORAGE

Protected from light.

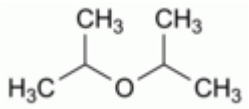
IMPURITIES



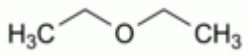
A. propanone (acetone),



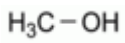
B. benzene,



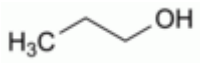
C. 2-(1-methylethoxy)propane (diisopropyl ether),



D. ethoxyethane (diethyl ether),



E. methanol,



F. propan-1-ol (*n*-propanol).

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Isopropyl Isostearate

General Notices

(Ph. Eur. monograph 2867)

Ph Eur

DEFINITION

Product obtained by esterification of isostearic acid (regioisomers mainly of octadecanoic acid, a complex mixture of branched and straight-chain fatty acids) with isopropyl alcohol. The monograph applies to isopropyl isostearate for cutaneous use.

CHARACTERS

Appearance

Clear, colourless or pale yellow liquid.

Solubility

Practically insoluble in water, miscible with ethanol (96 per cent) and with fatty oils.

Viscosity

About 11 mPa·s at 20 °C.

Relative density

About 0.866 at 20 °C.

Refractive index

About 1.447 at 20 °C.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *isopropyl isostearate CRS*.

An additional weak absorption band at 1780 cm^{-1} may be present.

B. Saponification value (see Tests).

C. Composition of fatty acids (see Tests).

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TESTS

Appearance of solution

The solution is not more intensely coloured than reference solution Y_7 (*2.2.2, Method II*).

Dissolve 10.0 g in *ethanol (96 per cent) R* and dilute to 20 mL with the same solvent.

Acid value (*2.5.1*)

Maximum 1.0, determined on 20.0 g.

Iodine value (*2.5.4, Method B*)

Maximum 3.0, determined on 3.0 g.

Peroxide value (*2.5.5, Method B*)

Maximum 5.0.

Saponification value (*2.5.6*)

165 to 180, determined on 2.0 g.

Composition of fatty acids (*2.4.22, Method B*)

Use the mixture of calibrating substances in Table 2.4.22.-1.

Composition of the fatty-acid fraction of the substance:

— *sum of the contents of the fatty acids eluting between palmitic acid and stearic acid*: minimum 65.0 per cent;

— *sum of the contents of myristic acid, palmitic acid and stearic acid*: maximum 11.0 per cent.

Water (*2.5.12*)

Maximum 0.1 per cent, determined on 5.00 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

STORAGE

In an airtight container.

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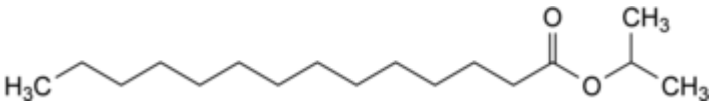
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Isopropyl Myristate

General Notices

(Ph. Eur. monograph 0725)



$C_{17}H_{34}O_2$ 270.5

Action and use

Excipient.

Ph Eur

DEFINITION

1-Methylethyl tetradecanoate together with variable amounts of other fatty acid isopropyl esters.

Content

Minimum 90.0 per cent of $C_{17}H_{34}O_2$.

CHARACTERS

Appearance

Clear, colourless, oily liquid.

Solubility

Immiscible with water, miscible with ethanol (96 per cent), with methylene chloride, with fatty oils and with liquid paraffin.

Relative density

About 0.853.

IDENTIFICATION

First identification: B.

Second identification: A, C.

A. Saponification value (see Tests).

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B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with the reference solution.

C. Superpose 2 mL of a 1 g/L solution in *ethanol (96 per cent) R* on a freshly prepared solution of 20 mg of *dimethylaminobenzaldehyde R* in 2 mL of *sulfuric acid R*. After 2 min, a yellowish-red colour appears at the junction of the 2 liquids and gradually becomes red.

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_7 (*2.2.2, Method II*).

Dissolve 2.0 g in *methanol R* and dilute to 20 mL with the same solvent.

Refractive index (*2.2.6*)

1.434 to 1.437.

Viscosity (*2.2.9*)

5 mPa·s to 6 mPa·s.

Acid value (*2.5.1*)

Maximum 1.0.

Iodine value (*2.5.4*)

Maximum 1.0.

Saponification value (*2.5.6*)

202 to 212.

Water (*2.5.12*)

Maximum 0.1 per cent, determined on 5.0 g.

Total ash (*2.4.16*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Gas chromatography (*2.2.28*).

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Internal standard solution Dissolve 50.0 mg of *tricosane R* in *heptane R* and dilute to 250.0 mL with the same solvent.

Test solution Dissolve 20.0 mg of the substance to be examined in the internal standard solution and dilute to 100.0 mL with the same solution.

Reference solution Dissolve 20.0 mg of *isopropyl tetradecanoate CRS* in the internal standard solution and dilute to 100.0 mL with the same solution.

Column:

— *material*: fused silica;

— *size*: *l* = 50 m, Ø = 0.2 mm;

— *stationary phase*: *cyanopropylpolysiloxane R* (film thickness 0.2 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1 mL/min.

Split ratio 1:40.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 6	125 → 185
	6 - 16	185
Injection port		250
Detector		250

Detection Flame ionisation.

Injection 2 µL.

Calculate the percentage content of $C_{17}H_{34}O_2$ in the substance to be examined.

STORAGE

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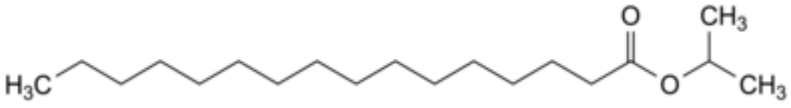
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Isopropyl Palmitate

General Notices

(Ph. Eur. monograph 0839)



$C_{19}H_{38}O_2$ 298.5

Action and use

Excipient.

Ph Eur

DEFINITION

1-Methylethyl hexadecanoate together with varying amounts of other fatty acid isopropyl esters.

Content

Minimum 90.0 per cent of $C_{19}H_{38}O_2$.

CHARACTERS

Appearance

Clear, colourless, oily liquid.

Solubility

Immiscible with water, miscible with ethanol (96 per cent), with methylene chloride, with fatty oils and with liquid paraffin.

Relative density

About 0.854.

IDENTIFICATION

First identification: B.

Second identification: A, C.

A. Saponification value (see Tests).

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B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with the reference solution.

C. Superpose 2 mL of a 1 g/L solution in *ethanol (96 per cent) R* on a freshly prepared solution of 20 mg of *dimethylaminobenzaldehyde R* in 2 mL of *sulfuric acid R*. After 2 min, a yellowish-red colour appears at the junction of the 2 liquids which gradually becomes red.

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_7 (*2.2.2, Method II*).

Dissolve 2.0 g in *methanol R* and dilute to 20 mL with the same solvent.

Refractive index (*2.2.6*)

1.436 to 1.440.

Viscosity (*2.2.9*)

5 mPa·s to 10 mPa·s.

Acid value (*2.5.1*)

Maximum 1.0.

Iodine value (*2.5.4*)

Maximum 1.0.

Saponification value (*2.5.6*)

183 to 193.

Water (*2.5.12*)

Maximum 0.1 per cent, determined on 5.0 g.

Total ash (*2.4.16*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Gas chromatography (*2.2.28*).

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Internal standard solution Dissolve 50.0 mg of *tricosane R* in *heptane R* and dilute to 250.0 mL with the same solvent.

Test solution Dissolve 20.0 mg of the substance to be examined in the internal standard solution and dilute to 100.0 mL with the same solution.

Reference solution Dissolve 20.0 mg of *isopropyl hexadecanoate CRS* in the internal standard solution and dilute to 100.0 mL with the same solution.

Column:

— *material*: fused silica,

— *size*: *l* = 50 m, Ø = 0.2 mm,

— *stationary phase*: *cyanopropylpolysiloxane R* (film thickness 0.2 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1 mL/min.

Split ratio 1:40.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 6	125 → 185
	6 - 16	185
Injection port		250
Detector		250

Detection Flame ionisation.

Injection 2 µL.

Calculate the percentage content of $C_{19}H_{38}O_2$ in the substance to be examined.

STORAGE

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Isosorbide Dinitrate Injection

General Notices

Action and use

Nitric oxide analogue; treatment of angina pectoris.

DEFINITION

Isosorbide Dinitrate Injection is a sterile solution of isosorbide dinitrate made isotonic with Sodium Chloride in Water for Injections. It is supplied as a ready-to-use solution.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of isosorbide dinitrate, $C_6H_8N_2O_8$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Evaporate a suitable volume of the injection under reduced pressure and below 40° to dryness. Shake a quantity of the residue containing 25 mg of isosorbide dinitrate with 10 mL of *dichloromethane* for 5 minutes, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of isosorbide dinitrate (*RS 412*).

B. Yields the reactions characteristic of *sodium salts* and reaction A characteristic of *chlorides*, Appendix VI.

Acidity or alkalinity

pH, 3.5 to 7.0, Appendix V L.

Nitrite

To 40 mL of the injection add 2 mL of *sulfanilic acid solution*, 2 mL of *aminonaphthalenesulfonic acid solution* and sufficient *water* to produce 50 mL. Allow to stand at room temperature for 1 hour. Measure the *absorbance* of the resulting solution at the maximum at 524 nm, Appendix II B, using in the reference cell a solution prepared by treating 40 mL of *water* in the same manner, beginning at the words “add 2 mL of *sulfanilic acid solution* ...”. The *absorbance* is not greater than that obtained by repeating the procedure using 2 mL of *nitrite standard solution (20 ppm)* diluted to 40 mL with *water* and treated at the same time and in the same manner, beginning at the words “add 2 mL of *sulfanilic acid solution* ...” (1 ppm, calculated with reference to the injection).

Isosorbide 5-nitrate and isosorbide 2-nitrate

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) evaporate a volume of the injection containing 50 mg of isosorbide dinitrate, under reduced pressure and below 40°, to dryness, triturate the residue with 50 mL of mobile phase, shake, filter through a glass-fibre filter (Whatman GF/C is suitable) and use the filtrate. Solution (2) contains 0.0005% w/v of

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isosorbide 2-nitrate BPCRS in the mobile phase. Solution (3) contains 0.0005% w/v of *isosorbide mononitrate BPCRS* in the mobile phase. Solution (4) contains 0.005% w/v each of *isosorbide mononitrate BPCRS* and *isosorbide 2-nitrate BPCRS* in the mobile phase.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 2 is suitable), (b) as the mobile phase with a flow rate of 1.0 mL per minute a mixture of 30 volumes of *methanol* and 70 volumes of *water* and (c) a detection wavelength of 220 nm.

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution factor* between the peaks corresponding to isosorbide mononitrate and isosorbide 2-nitrate is at least 2.4.

In the chromatogram obtained with solution (1) the area of any peak corresponding to isosorbide 2-nitrate is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%) and the area of any peak corresponding to isosorbide 5-nitrate is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.5%).

Bacterial endotoxins

The endotoxin limit concentration is 5.0 IU per mL, Appendix XIV C.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) use the injection, diluted, if necessary, with sufficient of a mixture of 25 volumes of *methanol* and 75 volumes of *water* to produce a solution containing 0.002% w/v of isosorbide dinitrate. For solution (2) prepare a 0.1% w/v solution of *isosorbide dinitrate BPCRS* in *methanol*. Filter and dilute 1 volume to 50 volumes with a mixture of 25 volumes of *methanol* and 75 volumes of *water*.

The chromatographic procedure may be carried out using (a) a stainless steel column (10 cm × 4.6 mm) packed with *trimethylsilyl silica gel for chromatography* (3 µm) (Hypersil SAS is suitable), (b) as the mobile phase with a flow rate of 1.3 mL per minute a mixture containing 0.039% w/v of *ammonium acetate* in 25 volumes of *methanol R2* and 75 volumes of *water* and (c) a detection wavelength of 214 nm.

Calculate the content of $C_6H_8N_2O_8$ in the injection using the declared content of $C_6H_8N_2O_8$ in *isosorbide dinitrate BPCRS*.

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Isosorbide Dinitrate Sublingual Tablets

General Notices

Action and use

Nitric oxide analogue; treatment of angina pectoris.

DEFINITION

Isosorbide Dinitrate Sublingual Tablets contain Diluted Isosorbide Dinitrate.

CAUTION *Undiluted isosorbide dinitrate can be exploded by percussion or excessive heat. Appropriate precautions should be exercised and only exceedingly small amounts should be isolated.*

The sublingual tablets comply with the requirements stated under Oromucosal Preparations and with the following requirements.

Content of isosorbide dinitrate, $C_6H_8N_2O_8$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Extract a quantity of the powdered tablets containing 2 mg of isosorbide dinitrate with 1 mL of *ether* and centrifuge.

(2) Prepare solution (2) in the same manner but use *isosorbide dinitrate BPCRS* in place of the powdered tablets.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel*.

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it in a current of air, spray with *diphenylamine solution R1* and irradiate for 15 minutes with *ultraviolet light (254* and *365 nm*).

MOBILE PHASE

toluene.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. Shake a quantity of the powdered tablets containing 50 mg of Isosorbide Dinitrate with warm *sulfuric acid (50%)* containing a trace of *diphenylamine*. An intense blue colour is produced.

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TESTS

Inorganic nitrates

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.1 g of Isosorbide Dinitrate with 5 mL of *ethanol (96%)* and filter.

(2) Dissolve 10 mg of *potassium nitrate* in 1 mL of *water* and dilute to 100 mL with *ethanol (96%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel H*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate thoroughly dry it in a current of air until the acetic acid is completely removed. Spray copiously with freshly prepared *potassium iodide and starch solution*. Expose the plate to *ultraviolet light (254 nm)* for 15 minutes. Examine in daylight.

MOBILE PHASE

15 volumes of *glacial acetic acid*, 30 volumes of *acetone* and 60 volumes of *toluene*.

LIMITS

In the chromatogram obtained with solution (1) any spot corresponding to potassium nitrate is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%, calculated as potassium nitrate).

Isosorbide 5-nitrate and isosorbide 2-nitrate

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 20 mL of the mobile phase to a quantity of the powdered tablets containing 25 mg of Isosorbide Dinitrate, mix with the aid of ultrasound for 15 minutes and dilute to 25 mL with the same solvent. Filter through a glass-fibre filter (Whatman GF/C is suitable) and use the filtrate.

(2) 0.0005% w/v *of isosorbide 2-nitrate BPCRS* in the mobile phase.

(3) 0.0005% w/v of *isosorbide mononitrate BPCRS* in the mobile phase.

(4) 0.005% w/v each of *isosorbide dinitrate BPCRS* and *isosorbide 2-nitrate BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *aminopropylsilyl silica gel for chromatography* (10 µm) (Lichrosorb NH_2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 215 nm.

(f) Inject 20 µL of each solution.

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MOBILE PHASE

15 volumes of *absolute ethanol* and 85 volumes of *2,2,4-trimethylpentane*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks corresponding to isosorbide dinitrate and isosorbide 2-nitrate is at least 6.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to isosorbide 2-nitrate is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to isosorbide 5-nitrate is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.5%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a quantity of the powdered tablets containing 25 mg of Isosorbide Dinitrate add 20 mL of the mobile phase mix with the aid of ultrasound for 15 minutes and dilute to 25 mL with the same solvent. Filter through a glass-fibre filter (Whatman GF/C is suitable) and dilute 1 volume to 10 volumes with the mobile phase.
(2) To a quantity of *isosorbide dinitrate BPCRS* containing 25 mg of Isosorbide Dinitrate add 20 mL of the mobile phase mix with the aid of ultrasound for 15 minutes and dilute to 25 mL with the mobile phase. Filter through a glass-fibre filter (Whatman GF/C is suitable) and dilute 1 volume to 10 volumes with the mobile phase.
(3) 0.005% w/v each *of isosorbide dinitrate BPCRS* and *isosorbide 2-nitrate BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Isosorbide 5-nitrate and isosorbide 2-nitrate may be used but using a detection wavelength of 230 nm.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks corresponding to isosorbide dinitrate and isosorbide 2-nitrate is at least 6.0.

DETERMINATION OF CONTENT

Calculate the content of $C_6H_8N_2O_8$ in the tablets from the chromatograms obtained and using the declared content of $C_6H_8N_2O_8$ in *isosorbide dinitrate BPCRS*.

LABELLING

The label states that the tablets should be placed under the tongue and allowed to dissolve slowly.

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Isosorbide Dinitrate Tablets

General Notices

Action and use

Nitric oxide analogue; treatment of angina pectoris.

DEFINITION

Isosorbide Dinitrate Tablets contain Diluted Isosorbide Dinitrate.

CAUTION *Undiluted isosorbide dinitrate can be exploded by percussion or excessive heat. Appropriate precautions should be exercised and only exceedingly small amounts should be isolated.*

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of isosorbide dinitrate, $C_6H_8N_2O_8$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Extract a quantity of the powdered tablets containing 2 mg of isosorbide dinitrate with 1 mL of *ether* and centrifuge.

(2) Prepare solution (2) in the same manner but use *isosorbide dinitrate BPCRS* in place of the powdered tablets.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel*.

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it in a current of air, spray with *diphenylamine solution R1* and irradiate for 15 minutes with *ultraviolet light (254* and *365 nm*).

MOBILE PHASE

toluene.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. Shake a quantity of the powdered tablets containing 50 mg of isosorbide dinitrate with warm *sulfuric acid (50%)* containing a trace of *diphenylamine*. An intense blue colour is produced.

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TESTS

Dissolution

Tablets intended to be swallowed whole comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter through a membrane filter with a nominal pore size not greater than 0.45 µm. Use the filtered medium, diluted with 0.1M *hydrochloric acid* if necessary, expected to contain 0.0011% w/v of isosorbide dinitrate.

(2) 0.0011% w/v of *isosorbide dinitrate BPCRS* in 0.1M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 222 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

Equal volumes of *methanol* and *water*.

DETERMINATION OF CONTENT

Calculate the total content of isosorbide dinitrate, $C_6H_8N_2O_8$, in the medium using the declared content of $C_6H_8N_2O_8$ in *isosorbide dinitrate BPCRS*.

Inorganic nitrates

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.1 g of Isosorbide Dinitrate with 5 mL of *ethanol (96%)* and filter.

(2) Dissolve 10 mg of *potassium nitrate* in 1 mL of *water* and dilute to 100 mL with *ethanol (96%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Analtech silica gel H plates are suitable).

(b) Use the mobile phase as described below.

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(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate thoroughly dry it in a current of air until the acetic acid is completely removed. Spray copiously with freshly prepared *potassium iodide and starch solution*. Expose the plate to *ultraviolet light (254 nm)* for 15 minutes. Examine in daylight.

MOBILE PHASE

15 volumes of *glacial acetic acid*, 30 volumes of *acetone* and 60 volumes of *toluene*.

LIMITS

In the chromatogram obtained with solution (1) any spot corresponding to potassium nitrate is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%, calculated as potassium nitrate).

Isosorbide 5-nitrate and isosorbide 2-nitrate

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 20 mL of the mobile phase to a quantity of the powdered tablets containing 25 mg of Isosorbide Dinitrate, mix with the aid of ultrasound for 15 minutes and dilute to 25 mL with the same solvent. Filter through a glass-fibre filter (Whatman GF/C is suitable) and use the filtrate.

(2) 0.0005% w/v of *isosorbide 2-nitrate BPCRS* in the mobile phase.

(3) 0.0005% w/v of *isosorbide mononitrate BPCRS* in the mobile phase.

(4) 0.005% w/v each of *isosorbide dinitrate BPCRS* and *isosorbide 2-nitrate BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *aminopropylsilyl silica gel for chromatography* (10 µm) (Lichrosorb NH_2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 215 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

15 volumes of *absolute ethanol* and 85 volumes of *2,2,4-trimethylpentane*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks corresponding to isosorbide dinitrate and isosorbide 2-nitrate is at least 6.0.

LIMITS

In the chromatogram obtained with solution (1):

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the area of any peak corresponding to isosorbide 2-nitrate is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to isosorbide 5-nitrate is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.5%).

Disintegration

The requirement for Disintegration does not apply to Isosorbide Dinitrate Tablets.

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a quantity of the powdered tablets containing 25 mg of Isosorbide Dinitrate add 20 mL of the mobile phase mix with the aid of ultrasound for 15 minutes and dilute to 25 mL with the same solvent. Filter through a glass-fibre filter (Whatman GF/C is suitable) and dilute 1 volume to 10 volumes with the mobile phase.
(2) To a quantity of *isosorbide dinitrate BPCRS* containing 25 mg of Isosorbide Dinitrate add 20 mL of the mobile phase mix with the aid of ultrasound for 15 minutes and dilute to 25 mL with the mobile phase. Filter through a glass-fibre filter (Whatman GF/C is suitable) and dilute 1 volume to 10 volumes with the mobile phase.
(3) 0.005% w/v each of *isosorbide dinitrate BPCRS* and *isosorbide 2-nitrate BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Isosorbide 5-nitrate and isosorbide 2-nitrate may be used but using a detection wavelength of 230 nm.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks corresponding to isosorbide dinitrate and isosorbide 2-nitrate is at least 6.0.

DETERMINATION OF CONTENT

Calculate the content of $C_6H_8N_2O_8$ in the tablets from the chromatograms obtained and using the declared content of $C_6H_8N_2O_8$ in *isosorbide dinitrate BPCRS*.

LABELLING

The label states whether the tablets are to be swallowed whole or chewed before being swallowed.

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Isosorbide Mononitrate Prolonged-release Capsules

General Notices

Prolonged-release Isosorbide Mononitrate Capsules

Isosorbide Mononitrate Prolonged-release Capsules from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Nitric oxide analogue; treatment of angina pectoris.

DEFINITION

Isosorbide Mononitrate Prolonged-release Capsules contain Diluted Isosorbide Mononitrate. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of isosorbide mononitrate. The dissolution profile reflects the *in vivo* performance, which in turn is compatible with the dosage schedule recommended by the manufacturer.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of isosorbide mononitrate, $C_6H_9NO_6$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the capsule contents containing the equivalent of 10 mg of isosorbide mononitrate with 10 mL of *ethanol (96%)* and filter.

(2) 0.1% w/v solution of *isosorbide mononitrate BPCRS* in *ethanol (96%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *silica gel plate* (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, spray with *diphenylamine solution R1* and irradiate for 15 minutes with *ultraviolet light (254* and *365 nm)*.

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MOBILE PHASE

5 volumes of *methanol* and 95 volumes of *dichloromethane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Inorganic nitrates

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the capsule contents containing the equivalent of 0.1 g of isosorbide mononitrate with 5 mL of *ethanol (96%)* and filter.

(2) Dissolve 10 mg of *potassium nitrate* in 1 mL of *water* and dilute to 100 mL with *ethanol (96%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *silica gel plate* (Analtech silica gel H plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, thoroughly dry it in a current of air until the acetic acid is completely removed. Spray copiously with freshly prepared *potassium iodide and starch solution*. Expose the plate to *ultraviolet light (254 nm)* for 15 minutes and examine in daylight.

MOBILE PHASE

15 volumes of *glacial acetic acid*, 30 volumes of *acetone* and 60 volumes of *toluene*.

CONFIRMATION

In the chromatogram obtained with solution (1) any spot corresponding to potassium nitrate is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%, calculated as potassium nitrate).

Isosorbide dinitrate and isosorbide 2-nitrate

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in mobile phase.

(1) Add 15 mL of mobile phase to a quantity of the capsule contents containing the equivalent of 50 mg of isosorbide mononitrate, mix with the aid of ultrasound for 15 minutes and dilute to 25 mL. Filter through a membrane filter with a nominal pore size not greater than 0.45-µm and use the filtrate.

(2) 0.001% w/v of *isosorbide 2-nitrate BPCRS*.

(3) 0.001% w/v of *isosorbide dinitrate BPCRS*.

(4) 0.001% w/v each of *isosorbide mononitrate BPCRS* and *isosorbide 2-nitrate BPCRS*.

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CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for five times the retention time of isosorbide mononitrate.

MOBILE PHASE

30 volumes of *methanol* and 70 volumes of *water*.

When the chromatograms are recorded under the prescribed conditions the retention time relative to isosorbide mononitrate (retention time = about 6 minutes) are: isosorbide 2-nitrate = about 0.9; isosorbide dinitrate = about 4.0.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks corresponding to isosorbide mononitrate and isosorbide 2-nitrate is at least 2.4.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to isosorbide 2-nitrate is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to isosorbide dinitrate is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.5%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Shake a quantity of the mixed contents of 20 capsules containing the equivalent of 50 mg of isosorbide mononitrate with 70 mL of the mobile phase, mix with the aid of ultrasound for 15 minutes, dilute to 100 mL with the same solvent and centrifuge. Dilute 1 volume of the supernatant liquid to 5 volumes with the mobile phase and filter through a membrane filter with a nominal pore size not greater than 0.45-µm.

(2) 0.01% w/v of *isosorbide mononitrate BPCRS*.

(3) 0.001% w/v each of *isosorbide mononitrate BPCRS* and *isosorbide 2-nitrate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Isosorbide dinitrate and isosorbide 2-nitrate may be used.

MOBILE PHASE

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30 volumes of *methanol* and 70 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks corresponding to isosorbide mononitrate and isosorbide 2-nitrate is at least 2.4.

DETERMINATION OF CONTENT

Calculate the content of $C_6H_9NO_6$ in the capsules from the chromatograms obtained and using the declared content of $C_6H_9NO_6$ in *isosorbide mononitrate BPCRS*.

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Isosorbide Mononitrate Prolonged-release Tablets

General Notices

Prolonged-release Isosorbide Mononitrate Tablets

Isosorbide Mononitrate Prolonged-release Tablets from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Nitric oxide analogue; treatment of angina pectoris.

DEFINITION

Isosorbide Mononitrate Prolonged-release Tablets contain Diluted Isosorbide Mononitrate. They are formulated so that the medicament is released over a period of several hours. They are coated.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of isosorbide mononitrate. The dissolution profile reflects the *in vivo* performance, which in turn is compatible with the dosage schedule recommended by the manufacturer.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of isosorbide mononitrate, $C_6H_9NO_6$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Filtered solution prepared from powdered tablets containing the equivalent of 0.1% w/v of isosorbide mononitrate in *ethanol (96%)*.

(2) 0.1% w/v solution of *isosorbide mononitrate BPCRS* in *ethanol (96%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *silica gel plate* (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, spray with *diphenylamine solution R1* and irradiate for 15 minutes with *ultraviolet light (254* and *365 nm)*.

MOBILE PHASE

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5 volumes of *methanol* and 95 volumes of *dichloromethane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Inorganic nitrates

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing the equivalent of 0.1 g of isosorbide mononitrate with 5 mL of *ethanol (96%)* and filter.

(2) Dissolve 10 mg of *potassium nitrate* in 1 mL of *water* and dilute to 100 mL with *ethanol (96%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *silica gel plate* (Analtech silica gel H plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, thoroughly dry it in a current of air until the acetic acid is completely removed. Spray copiously with freshly prepared *potassium iodide and starch solution*.

(f) Expose the plate to *ultraviolet light (254 nm)* for 15 minutes and examine in daylight.

MOBILE PHASE

15 volumes of *glacial acetic acid*, 30 volumes of *acetone* and 60 volumes of *toluene*.

CONFIRMATION

In the chromatogram obtained with solution (1) any spot corresponding to potassium nitrate is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%, calculated as potassium nitrate).

Isosorbide dinitrate and isosorbide 2-nitrate

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in mobile phase.

(1) Add 15 mL of mobile phase to a quantity of the powdered tablets containing the equivalent of 50 mg of isosorbide mononitrate, mix with the aid of ultrasound for 15 minutes and dilute to 25 mL. Filter through a membrane filter with a nominal pore size not greater than 0.45 µm and use the filtrate.

(2) 0.001% w/v of *isosorbide 2-nitrate BPCRS*.

(3) 0.001% w/v of *isosorbide dinitrate BPCRS*.

(4) 0.001% w/v each of *isosorbide mononitrate BPCRS* and *isosorbide 2-nitrate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

30 volumes of *methanol* and 70 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks corresponding to isosorbide mononitrate and isosorbide 2-nitrate is at least 2.4.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to isosorbide 2-nitrate is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to isosorbide dinitrate is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.5%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Add 70 mL of mobile phase to a quantity of the powdered tablets containing the equivalent of 50 mg of isosorbide mononitrate, mix with the aid of ultrasound for 15 minutes and dilute to 100 mL with the same solvent and centrifuge. Dilute 1 volume of the supernatant liquid to 5 volumes with the mobile phase and filter through a membrane filter with a nominal pore size not greater than 0.45 µm.

(2) 0.01% w/v of *isosorbide mononitrate BPCRS*.

(3) 0.001% w/v each of *isosorbide mononitrate BPCRS* and *isosorbide 2-nitrate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 20 µL of each solution.

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MOBILE PHASE

30 volumes of *methanol* and 70 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks corresponding to isosorbide mononitrate and isosorbide 2-nitrate is at least 2.4.

DETERMINATION OF CONTENT

Calculate the content of $C_6H_9NO_6$ in the tablets from the chromatograms obtained and using the declared content of $C_6H_9NO_6$ in *isosorbide mononitrate BPCRS*.

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Isosorbide Mononitrate Tablets

General Notices

Action and use

Nitric oxide analogue; angina pectoris.

DEFINITION

Isosorbide Mononitrate Tablets contain Diluted Isosorbide Mononitrate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of isosorbide mononitrate, $C_6H_9NO_6$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for thin-layer chromatography, Appendix III A, using the following solutions.

(1) Extract a quantity of the powdered tablets containing 10 mg of isosorbide mononitrate with 10 mL of *ethanol (96%)* and filter.

(2) 0.1% w/v solution of *isosorbide mononitrate BPCRS* in *ethanol (96%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *TLC silica gel plate* (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it in a current of air, spray with *diphenylamine solution R1* and irradiate for 15 minutes with *ultraviolet light (254* and *365 nm)*.

MOBILE PHASE

5 volumes of *methanol* and 95 volumes of *dichloromethane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

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Inorganic nitrates

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.1 g of isosorbide mononitrate with 5 mL of *ethanol (96%)* and filter.

(2) Dissolve 10 mg of *potassium nitrate* in 1 mL of *water* and dilute to 100 mL with *ethanol (96%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *TLC silica gel plate* (Analtech silica gel H plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate thoroughly dry it in a current of air until the acetic acid is completely removed. Spray copiously with freshly prepared *potassium iodide and starch solution*. Expose the plate to *ultraviolet light (254 nm)* for 15 minutes and examine in daylight.

MOBILE PHASE

15 volumes of *glacial acetic acid*, 30 volumes of *acetone* and 60 volumes of *toluene*.

LIMITS

In the chromatogram obtained with solution (1) any spot corresponding to potassium nitrate is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%, calculated as potassium nitrate).

Isosorbide dinitrate and isosorbide 2-nitrate

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 15 mL of mobile phase to a quantity of the powdered tablets containing 50 mg of isosorbide mononitrate, mix with the aid of ultrasound for 15 minutes and dilute to 25 mL with the same solvent. Filter through a membrane filter with a nominal pore size not greater than 0.45 µm and use the filtrate.

(2) 0.001% w/v of *isosorbide 2-nitrate BPCRS* in the mobile phase.

(3) 0.001% w/v of *isosorbide dinitrate BPCRS* in the mobile phase.

(4) 0.001% w/v each of *isosorbide mononitrate BPCRS* and *isosorbide 2-nitrate BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

30 volumes of *methanol* and 70 volumes of *water*.

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SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks corresponding to isosorbide mononitrate and isosorbide 2-nitrate is at least 2.4.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to isosorbide 2-nitrate is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to isosorbide dinitrate is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.5%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 70 mL of mobile phase to a quantity of the powdered tablets containing 50 mg of isosorbide mononitrate, mix with the aid of ultrasound for 15 minutes, dilute to 100 mL with the same solvent and centrifuge. Dilute 1 volume of the supernatant liquid to 5 volumes with mobile phase and filter through a membrane filter with a nominal pore size not greater than 0.45 µm.
(2) Add 20 mL of mobile phase to a quantity of *isosorbide mononitrate BPCRS* containing 25 mg of isosorbide mononitrate, mix with the aid of ultrasound for 15 minutes, dilute to 25 mL with the same solvent and centrifuge. Dilute 1 volume of the supernatant liquid to 10 volumes with the mobile phase and filter through a membrane filter with a nominal pore size not greater than 0.45 µm.
(3) 0.001% w/v each of *isosorbide mononitrate BPCRS* and *isosorbide 2-nitrate BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Isosorbide dinitrate and isosorbide 2-nitrate may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks corresponding to isosorbide mononitrate and isosorbide 2-nitrate is at least 2.4.

DETERMINATION OF CONTENT

Calculate the content of $C_6H_9NO_6$ in the tablets from the chromatograms obtained and using the declared content of $C_6H_9NO_6$ in *isosorbide mononitrate BPCRS*.

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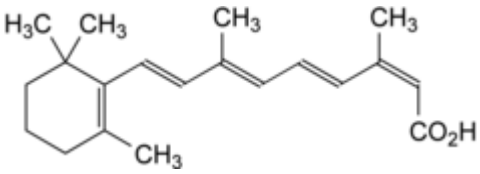
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Isotretinoin

General Notices

(Ph. Eur. monograph 1019)



$C_{20}H_{28}O_2$ 300.4 *4759-48-2*

Action and use

Vitamin A analogue (retinoid); treatment of acne.

Preparations

Isotretinoin Capsules

Isotretinoin Gel

Ph Eur

DEFINITION

(2*Z*,4*E*,6*E*,8*E*)-3,7-Dimethyl-9-(2,6,6-trimethylcyclohex-1-en-1-yl)nona-2,4,6,8-tetraenoic acid.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

Yellow or light orange, crystalline powder.

Solubility

Practically insoluble in water, soluble in methylene chloride, slightly soluble in ethanol (96 per cent).

It is sensitive to air, heat and light, especially in solution.

IDENTIFICATION

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IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *isotretinoin CRS*.

TESTS

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light and prepare the solutions immediately before use.*

Test solution Dissolve 0.100 g of the substance to be examined in *methanol R* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dissolve 5.0 mg of *tretinoin CRS* (impurity A) in *methanol R* and dilute to 5.0 mL with the same solvent.

Reference solution (b) Mix 0.5 mL of the test solution and 1 mL of reference solution (a) and dilute to 25 mL with *methanol R*.

Reference solution (c) Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase *glacial acetic acid R*, *water for chromatography R*, *methanol R* (5:225:770 *V/V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 355 nm.

Injection 10 µL of the test solution and reference solutions (b) and (c).

Run time 1.6 times the retention time of isotretinoin.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A.

Relative retention With reference to isotretinoin (retention time = about 26 min): impurity A = about 1.3.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to isotretinoin and impurity A.

Limits:

— *impurity A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent);

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— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* for 16 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 70 mL of *acetone R*. Titrate with *0.1 M tetrabutylammonium hydroxide in 2-propanol*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M tetrabutylammonium hydroxide in 2-propanol* is equivalent to 30.04 mg of $C_{20}H_{28}O_2$.

STORAGE

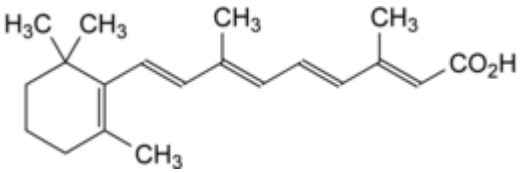
Under an inert gas, in an airtight container, protected from light.

It is recommended that the contents of an opened container be used as soon as possible and any unused part be protected by an atmosphere of inert gas.

IMPURITIES

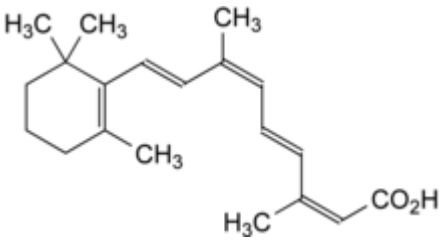
Specified impurities *A.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D, F, G, H, I.*

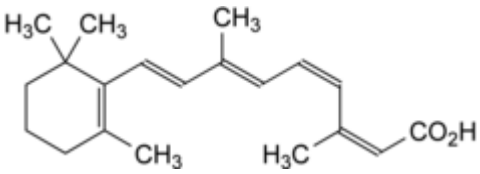


A. (2*E*,4*E*,6*E*,8*E*)-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-en-1-yl)nona-2,4,6,8-tetraenoic acid (tretinoin),

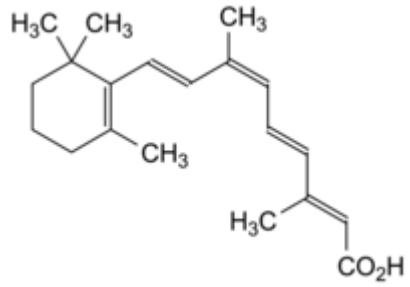
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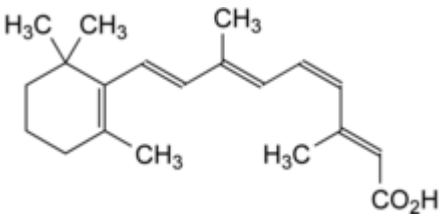
B. (2*Z*,4*E*,6*Z*,8*E*)-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-en-1-yl)nona-2,4,6,8-tetraenoic acid (9,13-di*cis*-retinoic acid),



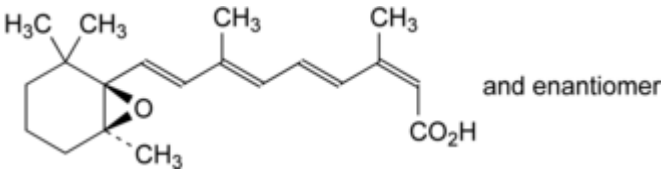
C. (2*Z*,4*Z*,6*E*,8*E*)-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-en-1-yl)nona-2,4,6,8-tetraenoic acid (11,13-di*cis*-retinoic acid),



D. (2*E*,4*E*,6*Z*,8*E*)-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-en-1-yl)nona-2,4,6,8-tetraenoic acid (9-*cis*-retinoic acid),

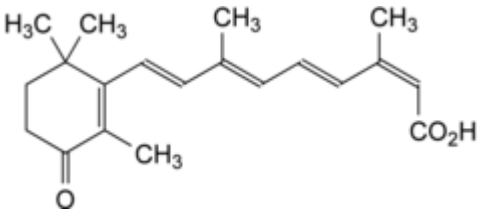


F. (2*E*,4*Z*,6*E*,8*E*)-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-en-1-yl)nona-2,4,6,8-tetraenoic acid (11-*cis*-retinoic acid),

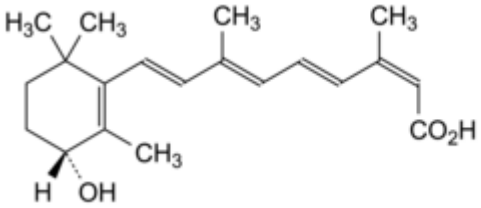


G. (2*Z*,4*E*,6*E*,8*E*)-3,7-dimethyl-9-[(1*RS*,6*SR*)-2,2,6-trimethyl-7-oxabicyclo[4.1.0]heptan-1-yl]nona-2,4,6,8-tetraenoic acid (13-*cis*-5,6-dihydro-5,6-epoxyretinoic acid),

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H. (2*Z*,4*E*,6*E*,8*E*)-3,7-dimethyl-9-(2,6,6-trimethyl-3-oxocyclohex-1-en-1-yl)nona-2,4,6,8-tetraenoic acid (13-*cis*-4-oxoretinoic acid),



and enantiomer

I. (2*Z*,4*E*,6*E*,8*E*)-9-[(3*RS*)-3-hydroxy-2,6,6-trimethylcyclohex-1-en-1-yl]-3,7-dimethylnona-2,4,6,8-tetraenoic acid (13-*cis*-4-hydroxyretinoic acid).

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Isotretinoin Capsules

General Notices

Action and use

Vitamin A analogue (retinoid); treatment of acne.

DEFINITION

Isotretinoin Capsules contain Isotretinoin.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of isotretinoin, $C_{20}H_{28}O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. In the test for Related substances, the chromatogram obtained with solution (2) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (4).

B. The *light absorption* of the final solution obtained in the Assay, Appendix II B, in the range 300 to 400 nm, exhibits a maximum at 356 nm.

TESTS

Dissolution

Protect the apparatus from light throughout the determination and flush the apparatus with nitrogen before use.

TEST CONDITIONS

(a) Carry out the test using the apparatus for the *disintegration test for tablets and capsules*, Appendix XII A1.

(b) Use 900 mL of 0.1M *sodium hydroxide* at a temperature of 37°, as the medium.

PROCEDURE

After 60 minutes withdraw a 20 mL sample of the medium, filter immediately through a 0.2-µm filter, discarding the first 5 mL of filtrate, and dilute the filtrate with 0.1M *sodium hydroxide* to give a solution expected to contain about 0.00025% w/v of Isotretinoin. Measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 343 nm, Appendix II B, using 0.1M *sodium hydroxide* in the reference cell.

DETERMINATION OF CONTENT

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Calculate the total content of isotretinoin, $C_{20}H_{28}O_2$, in the medium taking 1490 as the value of A(1%, 1 cm) at 343 nm and divide the result by 6 to obtain the amount per capsule.

LIMITS

Not less than 85% of the stated amount per capsule is released after 60 minutes.

Related substances

Protect the solutions from light throughout the procedure. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the contents of the capsules containing 10 mg of Isotretinoin with 10 mL of a mixture of 20 volumes of 0.1M *sodium hydroxide* and 80 volumes of *absolute ethanol* for 10 minutes, treat with ultrasound for 15 minutes and centrifuge for 5 minutes. Mix 5 mL of the supernatant liquid with 7.5 mL of 0.1M *hydrochloric acid* and extract with two 20-mL quantities of *dichloromethane*. Filter the combined extracts through phase separating paper (Whatman 1PS is suitable) and wash the filter with 5 mL of *dichloromethane*. Evaporate the combined filtrate and washing to dryness at 30° under reduced pressure and dissolve the residue in 5 mL of *methanol*.

(2) Dilute 1 volume of solution (1) to 100 volumes with *methanol*.

(3) 0.002% w/v of *tretinoin EPCRS* in *methanol*.

(4) 0.001% w/v of *isotretinoin EPCRS* in *methanol*.

(5) 0.001% w/v of each of *tretinoin EPCRS* and *isotretinoin EPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Spherisorb ODS 2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.4 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 353 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

A 0.5% w/v solution of *glacial acetic acid* in a mixture of *methanol* and *water*, the proportions adjusted to give a retention time for tretinoin of about 15 minutes (a mixture of 23 volumes of *water* and 77 volumes of *methanol* is usually suitable).

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5), the *resolution factor* between the peaks due to tretinoin and isotretinoin is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to tretinoin is not greater than twice the area of the peak in the chromatogram obtained with solution (3) (4%);

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the area of any other *secondary peak* is not greater than the area of the peak in the chromatogram obtained with solution (2) (1%);

the sum of the areas of any such peaks is not greater than 1.5 times the area of the peak in the chromatogram obtained with solution (2) (1.5%).

ASSAY

Carry out the following procedure in subdued light. Slit 10 capsules with a scalpel avoiding loss of the capsule contents, place the capsules in a 500-mL graduated flask washing any material adhering to the scalpel into the flask with 25 mL of *dichloromethane* per capsule and mix with the aid of ultrasound for 15 minutes. Add sufficient *dichloromethane* to produce 500 mL, shake for 2 minutes and dilute with a solution prepared by diluting 5 mL of 0.1M *hydrochloric acid* to 250 mL with *ethanol (96%)* to produce a solution containing 0.0008% w/v of Isotretinoin. Measure the *absorbance* of this solution at the maximum at 356 nm, Appendix II B, using the ethanolic hydrochloric acid solution in the reference cell. Calculate the content of $C_{20}H_{28}O_2$ in the capsules taking 1350 as the value of A(1%, 1 cm) at the maximum at 356 nm.

STORAGE

Isotretinoin Capsules should be protected from light.

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Isotretinoin Gel

General Notices

Action and use

Vitamin A analogue (retinoid); treatment of acne.

DEFINITION

Isotretinoin Gel is a solution of Isotretinoin in a suitable alcoholic basis.

The gel complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of isotretinoin, $C_{20}H_{28}O_2$

90.0 to 110.0% of the stated amount.

Carry out all the operations as rapidly as possible protected from light.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake to disperse a quantity of the gel containing 1 mg of Isotretinoin as completely as possible in 5 mL of *dichloromethane reagent* and 10 mL of *dichloromethane*, add 80 mL of *n-hexane* and shake the mixture vigorously; filter, evaporate the filtrate to dryness using a rotary evaporator at a temperature not exceeding 60° and dissolve the residue in 1 mL of *dichloromethane*.

(2) 0.1% w/v of *isotretinoin EPCRS* in *dichloromethane*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a silica gel F_{254} precoated plate (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

2 volumes of *glacial acetic acid*, 4 volumes of *acetone*, 40 volumes of *peroxide-free ether* and 54 volumes of *cyclohexane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. The *light absorption* of the final solution obtained in the Assay, Appendix II B, in the range 300 to 400 nm, exhibits a maximum at 356 nm.

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TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *n-hexane*, protected from light.

(1) Shake to disperse a quantity of the gel containing 2.5 mg of Isotretinoin as completely as possible in a mixture of 5 mL of *dichloromethane reagent* and 10 mL of *dichloromethane*, dilute to 50 mL with *n-hexane*, shake and filter.

(2) 0.0002% w/v of *tretinoin EPCRS*.

(3) Dilute 1 volume of solution (1) to 100 volumes.

(4) 0.0002% w/v each of *isotretinoin EPCRS* and *tretinoin EPCRS*.

(5) Dilute 1 volume of solution (3) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *silica gel for chromatography* (5 µm) (Lichrosorb Si60 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 365 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

1 volume of *glacial acetic acid*, 30 volumes of *ethyl acetate* and 970 volumes of *n-hexane*.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (4), the *resolution factor* between the peaks due to isotretinoin and tretinoin is at least 3.0;

in the chromatogram obtained with solution (5), *the signal-to-noise ratio* of the peak due to isotretinoin is at least 10.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak due to tretinoin is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (4%);

the sum of the areas of any other *secondary peaks* is not greater than the area of the peak in the chromatogram obtained with solution (3) (1%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

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Carry out the following procedure in subdued light. To a quantity of the gel containing 0.5 mg of Isotretinoin, add 10 mL of *dichloromethane*, shake until all the gel has dispersed and dilute the solution to 100 mL with a solution prepared by diluting 5 mL of 0.1M *hydrochloric acid* to 250 mL with *ethanol (96%)*. Measure the *absorbance* of this solution at the maximum at 356 nm, Appendix II B, using the ethanolic hydrochloric acid solution in the reference cell. Calculate the content of $C_{20}H_{28}O_2$ in the gel taking 1350 as the value of A(1%, 1 cm) at the maximum at 356 nm.

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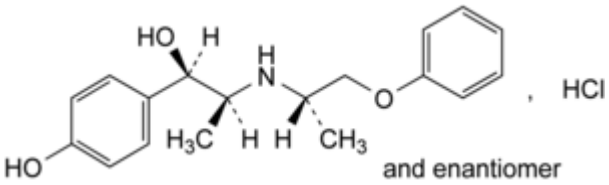
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Isoxsuprine Hydrochloride

General Notices

(Ph. Eur. monograph 1119)



$C_{18}H_{24}ClNO_3$ 337.8 *579-56-6*

Action and use

Beta$_2$-adrenoceptor agonist.

Ph Eur

DEFINITION

(1*RS*,2*SR*)-1-(4-Hydroxyphenyl)-2-[[(1*SR*)-1-methyl-2-phenoxyethyl]amino]propan-1-ol hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Sparingly soluble in water and in ethanol (96 per cent), practically insoluble in methylene chloride.

mp

About 205 °C, with decomposition.

IDENTIFICATION

First identification: B, E.

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Second identification: A, C, D, E.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 50.0 mg in *0.1 M hydrochloric acid* and dilute to 50.0 mL with the same acid. Dilute 10.0 mL of this solution to 100.0 mL with *0.1 M hydrochloric acid*.

Spectral range 230-350 nm.

Absorption maxima At 269 nm and 275 nm.

Resolution (2.2.25): minimum 1.7 for the absorbance ratio.

Specific absorbance at the absorption maxima:

— at 269 nm: 71 to 74;

— at 275 nm: 70 to 73.

B. Infrared absorption spectrophotometry (2.2.24).

Preparation Discs.

Comparison *isoxsuprine hydrochloride CRS*.

If the spectra obtained show differences, dissolve 50 mg of the substance to be examined and of the reference substance separately in 2 mL of *methanol R*, add 15 mL of *methylene chloride R*, evaporate to dryness and record new spectra using the residues.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 20 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 20 mg of *isoxsuprine hydrochloride CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel G plate R*.

Mobile phase *concentrated ammonia R*, *methanol R*, *methylene chloride R* (0.25:15:85 *V/V/V*).

Application 10 µL.

Development Over a path of 12 cm.

Drying In a current of warm air.

Detection Spray with a 10 g/L solution of *potassium permanganate R*.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

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D. To 1 mL of solution S (see Tests) add 0.05 mL of *copper sulfate solution R* and 0.5 mL of *strong sodium hydroxide solution R*. The solution becomes blue. Add 1 mL of *ether R* and shake. Allow to separate. The upper layer remains colourless.

E. 2 mL of solution S gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S

Dissolve 0.50 g, with gentle heating if necessary, in *carbon dioxide-free water R*, cool and dilute to 50.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

4.5 to 6.0 for solution S.

Optical rotation (*2.2.7*)

-0.05° to + 0.05°, determined on solution S.

Phenones

Maximum 1.0 per cent, calculated as impurity B.

Dissolve 10.0 mg in *water R* and dilute to 100.0 mL with the same solvent. The absorbance (*2.2.25*) of the solution measured at the absorption maximum at 310 nm is not greater than 0.10.

Related substances

Gas chromatography (*2.2.28*). *Prepare the solutions immediately before use*.

Internal standard solution (a) Dissolve 0.1 g of *hexacosane R* in *trimethylpentane R* and dilute to 20 mL with the same solvent.

Internal standard solution (b) Dilute 1 mL of internal standard solution (a) to 50 mL with *trimethylpentane R*.

Test solution To 10.0 mg of the substance to be examined, add 0.5 mL of *N-trimethylsilylimidazole R*. Heat to 65 °C for 10 min. Allow to cool, then add 2.0 mL of the internal standard solution (b) and 2.0 mL of *water R*. Shake. Use the upper layer.

Reference solution (a) To 10.0 mg of the substance to be examined, add 0.5 mL of *N-trimethylsilylimidazole R*. Heat to 65 °C for 10 min. Allow to cool, then add 2.0 mL of the internal standard solution (a) and 2.0 mL of *water R*. Shake. Dilute 1.0 mL of the upper layer to 50.0 mL with *trimethylpentane R*.

Reference solution (b) To 10.0 mg of the substance to be examined, add 0.5 mL of *N-trimethylsilylimidazole R*. Heat to 65 °C for 10 min. Allow to cool, then add 2.0 mL of *trimethylpentane R* and 2.0 mL of *water R*. Shake. Use the upper layer.

Column:

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— *material*: glass;

— *size*: *l* = 1.5 m, Ø = 4 mm;

— *stationary phase*: *silanised diatomaceous earth for gas chromatography R* (125-135 µm) impregnated with 3 per cent *m/m* of *methylpolysiloxane R*.

Carrier gas *nitrogen for chromatography R*.

Flow rate 30 mL/min.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 25	195
	25 - 29	195 → 215
	29 - 39	215
Injection port		225
Detector		225

Detection Flame ionisation.

Injection 1 µL.

Elution order Isoxsuprine, hexacosane.

System suitability:

— *resolution*: minimum 5.0 between the peaks due to isoxsurpine and hexacosane in the chromatogram obtained with reference solution (a);

— in the chromatogram obtained with reference solution (b), there is no peak with the same retention time as the internal standard.

Limit:

— *total*: calculate the ratio (*R*) of the area of the peak due to the trimethylsilyl derivative of isoxsuprine to the area of the peak due to the internal standard from the chromatogram obtained with reference solution (a); from the chromatogram obtained with the test solution, calculate the ratio of the sum of the areas of any peaks, apart from the principal peak and the peak due to the internal standard, to the area of the peak due to the internal standard: this ratio is not greater than *R* (2.0 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

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Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 80 mL of *ethanol (96 per cent) R* and add 1.0 mL of *0.1 M hydrochloric acid*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 33.78 mg of $C_{18}H_{24}ClNO_3$.

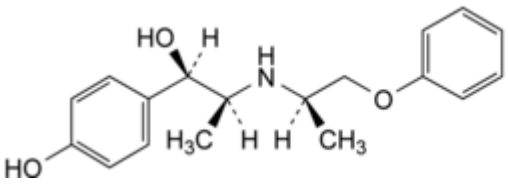
STORAGE

Protected from light.

IMPURITIES

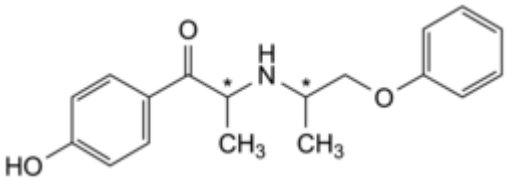
Specified impurities B.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A.



and enantiomer

A. (1*RS*,2*SR*)-1-(4-hydroxyphenyl)-2-[[(1*RS*)-1-methyl-2-phenoxyethyl]amino]propan-1-ol,



B. 1-(4-hydroxyphenyl)-2-[(1-methyl-2-phenoxyethyl)amino]propan-1-one.

Ph Eur

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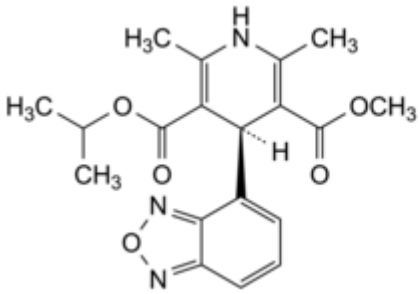
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This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Isradipine

General Notices

(Ph. Eur. monograph 2110)



and enantiomer

$C_{19}H_{21}N_3O_5$ 371.4 *75695-93-1*

Action and use

Calcium channel blocker.

Ph Eur

DEFINITION

3-Methyl 5-(propan-2-yl) (4*RS*)-4-(2,1,3-benzoxadiazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate.

Content

97.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

Yellow, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in acetone, soluble in methanol.

mp

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About 168 °C.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *isradipine CRS*.

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 50 mg of the substance to be examined in 1 mL of *methanol R*, using an ultrasonic bath if necessary, and dilute to 25.0 mL with the mobile phase.

Test solution (b) Dissolve 50.0 mg of the substance to be examined in 2 mL of *methanol R* and dilute to 250.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 2 mg of the substance to be examined and 2 mg of *isradipine impurity D CRS* in the mobile phase and dilute to 10 mL with the mobile phase. Dilute 1 mL of this solution to 10 mL with the mobile phase.

Reference solution (c) Dissolve 10 mg of *isradipine for peak identification CRS* (containing impurities A and B) in 2 mL of *methanol R*, using an ultrasonic bath if necessary, and dilute to 5 mL with the mobile phase.

Reference solution (d) Dissolve 50.0 mg of *isradipine CRS* in 2 mL of *methanol R* and dilute to 250.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *acetonitrile for chromatography R*, *tetrahydrofuran R*, *water for chromatography R* (125:270:625 *V/V/V*).

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 20 µL of test solution (a) and reference solutions (a), (b) and (c).

Run time 5 times the retention time of isradipine.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity D; use the chromatogram supplied with *isradipine for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and B.

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Relative retention With reference to isradipine (retention time = about 7 min): impurity A = about 0.8; impurity D = about 0.9; impurity B = about 1.8.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to isradipine and impurity D.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity D by 1.4;

— for each impurity, use the concentration of isradipine in reference solution (a).

Limits:

— *impurity B*: maximum 0.8 per cent;

— *impurity A*: maximum 0.2 per cent;

— *impurity D*: maximum 0.10 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 0.2 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Mobile phase *acetonitrile R*, *tetrahydrofuran R*, *water for chromatography R* (125:270:625 *V/V/V*).

Detection Spectrophotometer at 326 nm.

Injection Test solution (b) and reference solution (d).

Run time Twice the retention time of isradipine.

Calculate the percentage content of isradipine taking into account the assigned content of *isradipine CRS*.

STORAGE

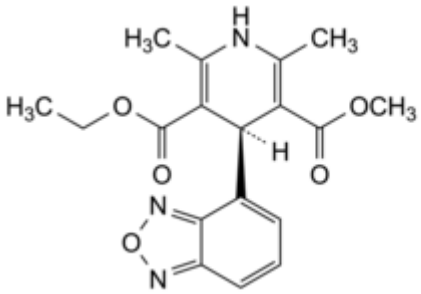
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Protected from light.

IMPURITIES

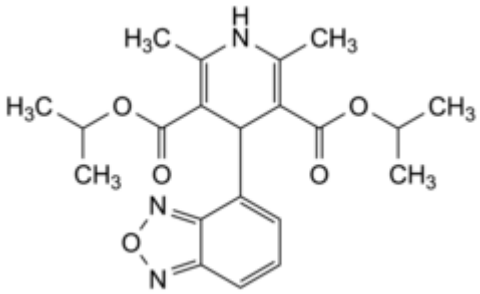
Specified impurities A, B, D.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) C, E.

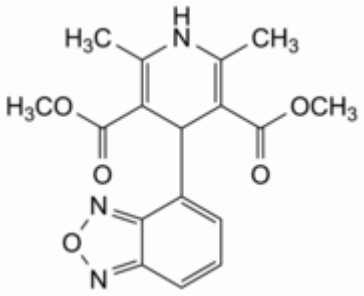


and enantiomer

A. 5-ethyl 3-methyl (4*RS*)-4-(2,1,3-benzoxadiazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate,

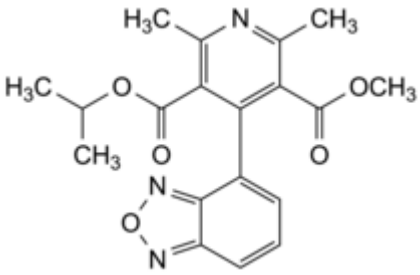


B. di(propan-2-yl) 4-(2,1,3-benzoxadiazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate,

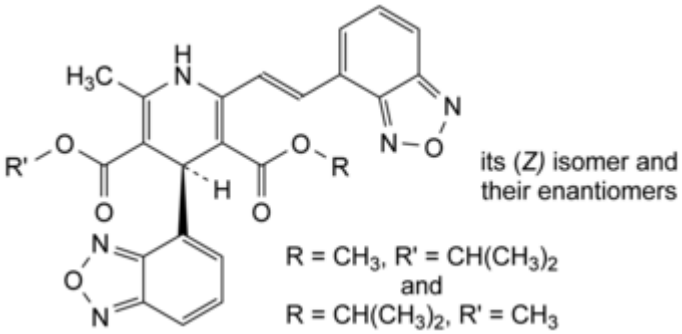


C. dimethyl 4-(2,1,3-benzoxadiazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate,

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D. 3-methyl 5-(propan-2-yl) 4-(2,1,3-benzoxadiazol-4-yl)-2,6-dimethylpyridine-3,5-dicarboxylate,



E. mixture of 3-methyl 5-(propan-2-yl) (4*RS*)-4-(2,1,3-benzoxadiazol-4-yl)-2-[(1*EZ*)-2-(2,1,3-benzoxadiazol-4-yl)ethen-1-yl]-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate and 5-methyl 3-(propan-2-yl) (4*RS*)-4-(2,1,3-benzoxadiazol-4-yl)-2-[(1*EZ*)-2-(2,1,3-benzoxadiazol-4-yl)ethen-1-yl]-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate.

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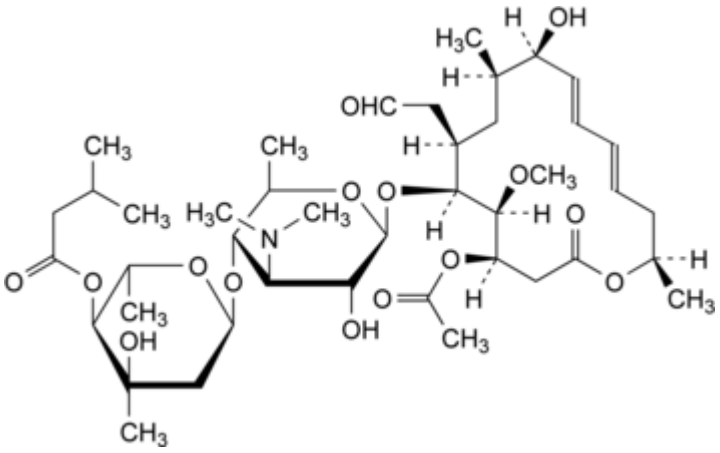
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Josamycin

General Notices

(Ph. Eur. monograph 1983)



$C_{42}H_{69}NO_{15}$ 828 *16846-24-5*

Action and use

Antibacterial.

Ph Eur

DEFINITION

Josamycin is a macrolide antibiotic obtained by fermentation using, for example, certain strains of *Streptomyces narbonensis* var. *josamyceticus* var. *nova*. The main component is (4*R*,5*S*,6*S*,7*R*,9*R*,10*R*,11*E*,13*E*,16*R*)-4-(acetyloxy)-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]-10-hydroxy-5-methoxy-9,16-dimethyl-7-(2-oxoethyl)oxacyclohexadeca-11,13-dien-2-one.

Content

Minimum 900 Ph. Eur. U./mg (dried substance).

CHARACTERS

Appearance

White or slightly yellowish powder, slightly hygroscopic.

Solubility

Very slightly soluble in water, freely soluble in methanol and in methylene chloride, soluble in acetone.

IDENTIFICATION

First identification: A, C.

Second identification: A, B.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 0.10 g in methanol R and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of this solution to 50.0 mL with methanol R.

Spectral range 220-350 nm.

Absorption maximum At 232 nm.

Specific absorbance at the absorption maximum 330 to 370.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in 2.5 mL of methanol R.

Reference solution (a) Dissolve 10 mg of josamycin CRS in 2.5 mL of methanol R.

Reference solution (b) Dissolve 10 mg of josamycin propionate CRS in 2.5 mL of methanol R.

Plate TLC silica gel GF_{254} plate R.

Mobile phase methanol R, acetone R, ethyl acetate R, toluene R, hexane R (8:10:20:25:30 *V/V/V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying At 100 °C for 10 min.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a) and different in position from the principal spot in the chromatogram obtained with reference solution (b).

C. Examine the chromatograms obtained in the test for related substances.

Results The principal peak in the chromatogram obtained with the test solution is similar in position and size to the principal peak in the chromatogram obtained with reference solution (a).

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution BY_4 (2.2.2, Method II).

Dissolve 2.0 g in *methanol R* and dilute to 20 mL with the same solvent.

Specific optical rotation (2.2.7)

-65 to -75 (dried substance).

Dissolve 1.000 g in *methanol R* and dilute to 100.0 mL with the same solvent. Allow to stand for 30 min before measuring the angle of rotation.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture *acetonitrile R*, *water R* (30:70 *V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 20.0 mL with the solvent mixture.

Reference solution (a) Dissolve 25.0 mg of *josamycin CRS* in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 20.0 mL with the solvent mixture.

Reference solution (c) Dilute 1.0 mL of reference solution (b) to 50.0 mL with the solvent mixture.

Reference solution (d) To 10 mL of the test solution add 0.1 mL of *strong hydrogen peroxide solution R* and heat in a water-bath for 10 min. Mix 1.0 mL of this solution and 1.0 mL of the test solution.

Reference solution (e) Dissolve 12.5 mg of *josamycin for peak identification CRS* (containing impurities A, B, C, D and E) in 5 mL of the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 45 °C.

Mobile phase:

— *mobile phase A*: mix 3 volumes of a 67.9 g/L solution of *tetrabutylammonium hydrogen sulfate R*, 5 volumes of a 27.6 g/L solution of *sodium dihydrogen phosphate monohydrate R* adjusted to pH 3.0 with *dilute phosphoric acid R*, and 21 volumes of *acetonitrile R*, and dilute to 100 volumes with *water R*;

— *mobile phase B*: mix 5 volumes of a 27.6 g/L solution of *sodium dihydrogen phosphate monohydrate R* adjusted to pH 3.0 with *dilute phosphoric acid R*, and 50 volumes of *acetonitrile R*, and dilute to 100 volumes with *water R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 38	100	0
38 - 55	100 → 0	0 → 100

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 232 nm.

Injection 10 µL of the test solution and reference solutions (b), (c), (d) and (e).

Identification of impurities Use the chromatogram supplied with *josamycin for peak identification CRS* and the chromatogram obtained with reference solution (e) to identify the peaks due to impurities A, B, C, D and E.

Relative retention With reference to josamycin (retention time = about 35 min): impurity A = about 0.5; impurity B = about 0.8; impurity C = about 0.9; impurity D = about 1.2; impurity E = about 1.4.

System suitability Reference solution (d):

— *resolution*: minimum 1.7 between the 2 peaks due to josamycin and the peak eluted with a relative retention with reference to josamycin of about 1.1;

— *retention time of josamycin*: between 32 min and 38 min.

If necessary, adjust the concentration of acetonitrile in the mobile phases.

Limits:

— *impurities A, B, C, D, E* (any shoulder observed on the peak due to impurity A and/or the peak due to impurity B is not to be integrated separately): for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (5.0 per cent);

— *any other impurity*: not more than 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (b) (3.0 per cent);

— *total*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (20.0 per cent);

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent).

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.2 per cent, determined on 1.0 g.

ASSAY

Dissolve 30.0 mg in 5 mL of *methanol R* and dilute to 100.0 mL with *water R*.

Carry out the microbiological assay of antibiotics (2.7.2).Use *josamycin CRS* as the chemical reference substance.

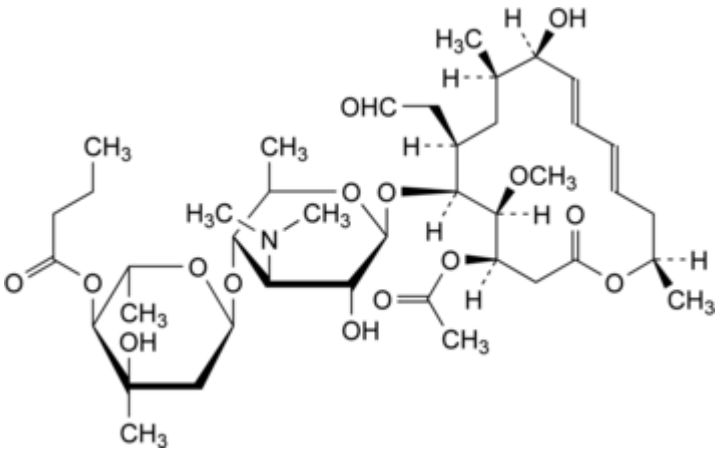
STORAGE

In an airtight container.

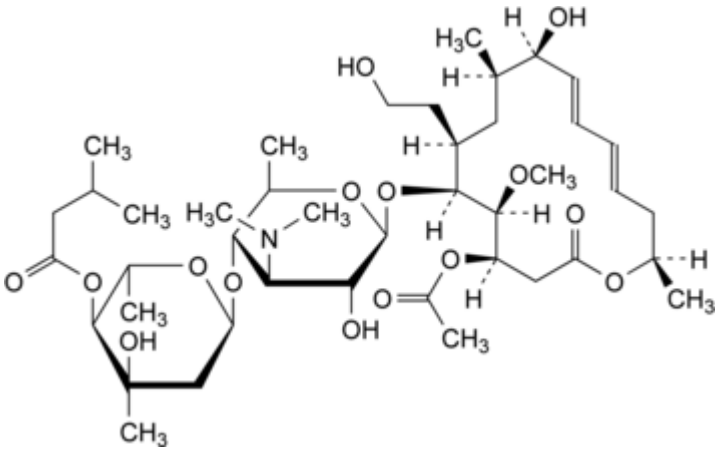
IMPURITIES

Specified impurities *A, B, C, D, E.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *F, G, H, I, J, K.*

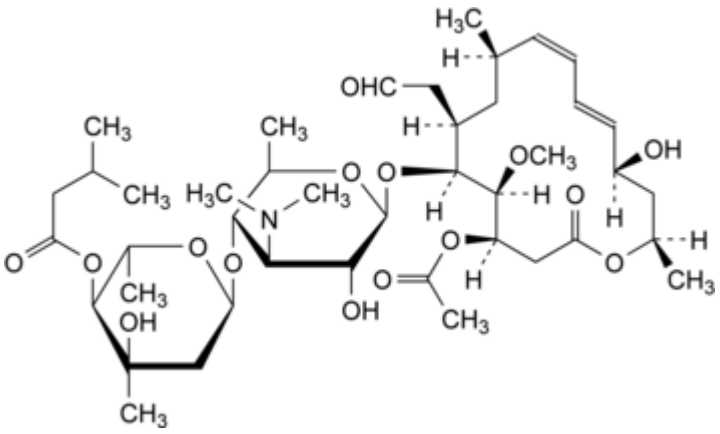


A. (4*R*,5*S*,6*S*,7*R*,9*R*,10*R*,11*E*,13*E*,16*R*)-4-(acetyloxy)-6-[[3,6-dideoxy-4-*O*-(2,6-dideoxy-4-*O*-butanoyl-3-*C*-methyl-α-L-*ribo*-hexopyranosyl)-3-(dimethylamino)-β-D-glucopyranosyl]oxy]-10-hydroxy-5-methoxy-9,16-dimethyl-7-(2-oxoethyl)oxacyclohexadeca-11,13-dien-2-one,

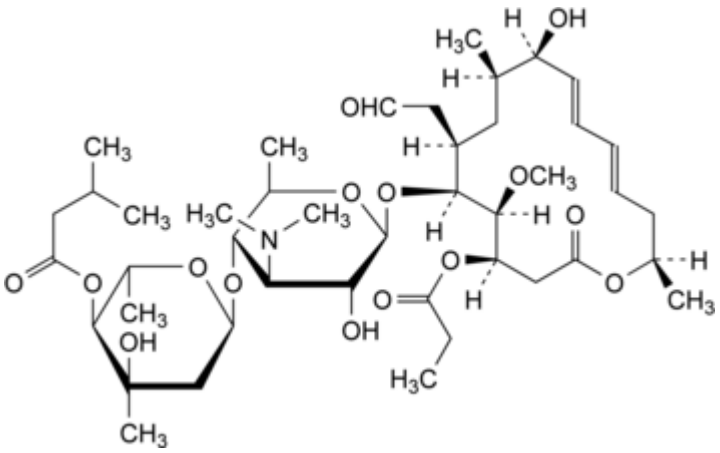


B. (4*R*,5*S*,6*S*,7*R*,9*R*,10*R*,11*E*,13*E*,16*R*)-4-(acetyloxy)-6-[[3,6-dideoxy-4-*O*-[2,6-dideoxy-3-*C*-methyl-4-*O*-(3-methylbutanoyl)-α-L-*ribo*-hexopyranosyl]-3-(dimethylamino)-β-D-glucopyranosyl]oxy]-10-hydroxy-7-(2-hydroxyethyl)-5-methoxy-9,16-dimethyloxacyclohexadeca-11,13-dien-2-one,

C. unknown structure,

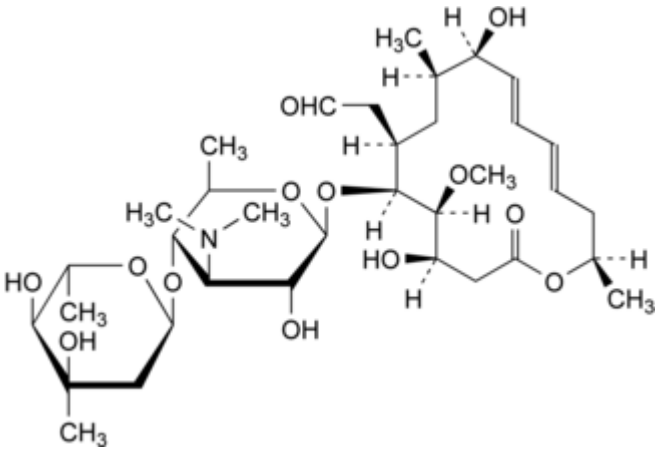


D. (4*R*,5*S*,6*S*,7*R*,9*R*,10*Z*,12*E*,14*R*,16*R*)-4-(acetyloxy)-6-[[3,6-dideoxy-4-*O*-[2,6-dideoxy-3-*C*-methyl-4-*O*-(3-methylbutanoyl)-α-L-*ribo*-hexopyranosyl]-3-(dimethylamino)-β-D-glucopyranosyl]oxy]-14-hydroxy-5-methoxy-9,16-dimethyl-7-(2-oxoethyl)oxacyclohexadeca-10,12-dien-2-one (isojosamycin),

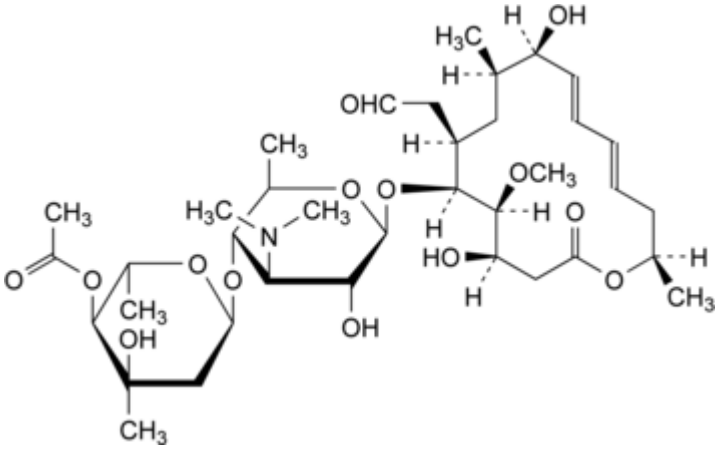


E. (4*R*,5*S*,6*S*,7*R*,9*R*,10*R*,11*E*,13*E*,16*R*)-6-[[3,6-dideoxy-4-*O*-[2,6-dideoxy-3-*C*-methyl-4-*O*-(3-methylbutanoyl)-α-L-*ribo*-hexopyranosyl]-3-(dimethylamino)-β-D-glucopyranosyl]oxy]-10-hydroxy-5-methoxy-9,16-dimethyl-7-(2-oxoethyl)-4-(propanoyloxy)oxacyclohexadeca-11,13-

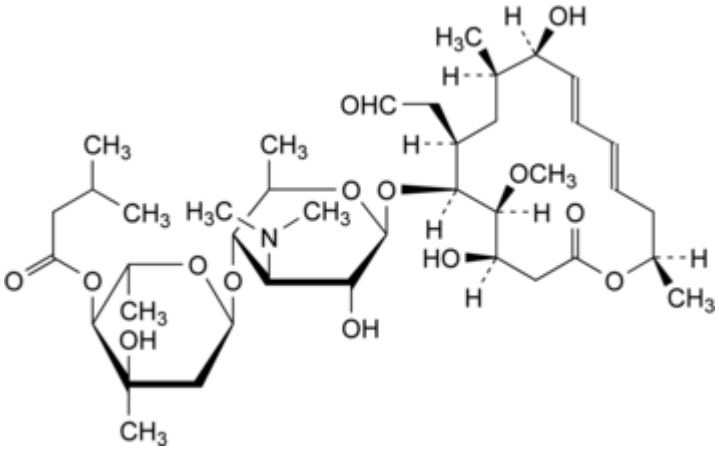
dien-2-one,



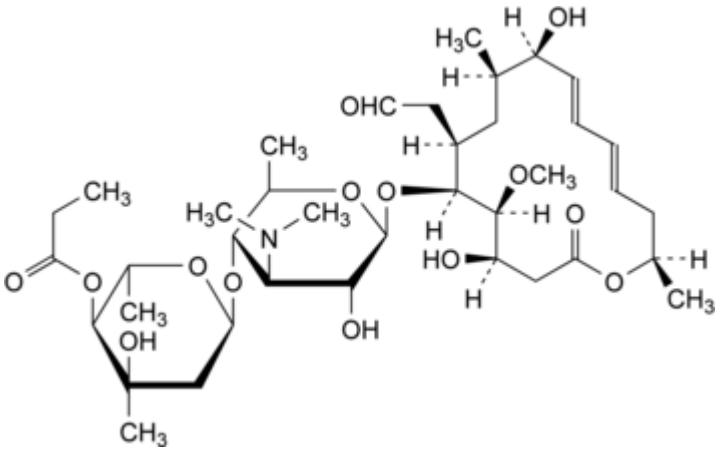
F. (4*R*,5*S*,6*S*,7*R*,9*R*,10*R*,11*E*,13*E*,16*R*)-6-[[3,6-dideoxy-4-*O*-(2,6-dideoxy-3-*C*-methyl-α-L-*ribo*-hexopyranosyl)-3-(dimethylamino)-β-D-glucopyranosyl]oxy]-4,10-dihydroxy-5-methoxy-9,16-dimethyl-7-(2-oxoethyl)oxacyclohexadeca-11,13-dien-2-one,



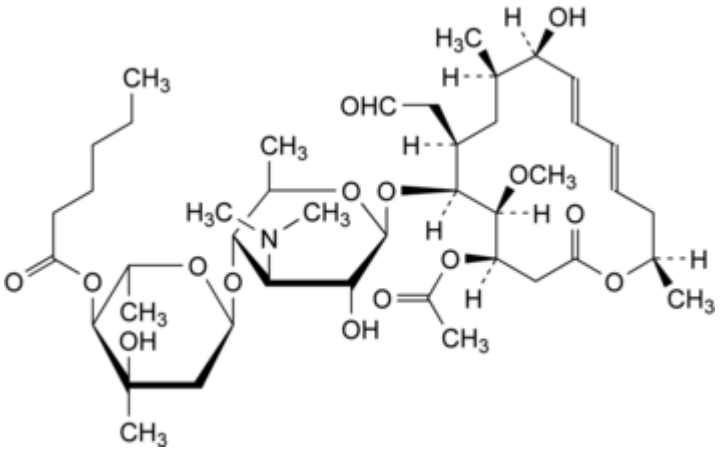
G. (4*R*,5*S*,6*S*,7*R*,9*R*,10*R*,11*E*,13*E*,16*R*)-6-[[4-*O*-(4-*O*-acetyl-2,6-dideoxy-3-*C*-methyl-α-L-*ribo*-hexopyranosyl)-3,6-dideoxy-3-(dimethylamino)-β-D-glucopyranosyl]oxy]-4,10-dihydroxy-5-methoxy-9,16-dimethyl-7-(2-oxoethyl)oxacyclohexadeca-11,13-dien-2-one,



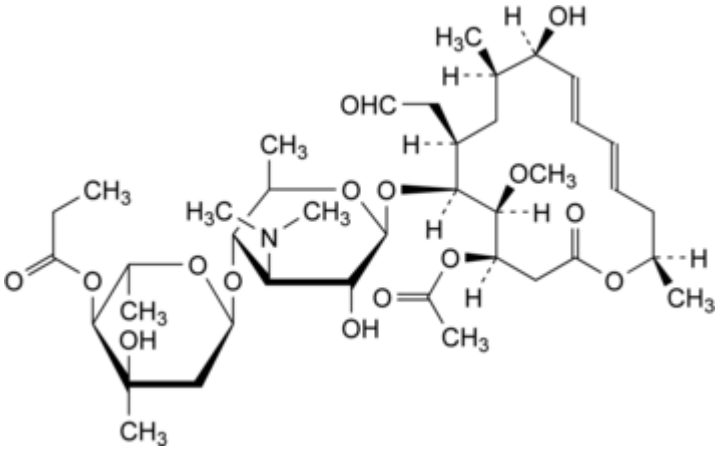
H. (4*R*,5*S*,6*S*,7*R*,9*R*,10*R*,11*E*,13*E*,16*R*)-6-[[3,6-dideoxy-4-*O*-[2,6-dideoxy-3-*C*-methyl-4-*O*-(3-methylbutanoyl)-α-L-*ribo*-hexopyranosyl]-3-(dimethylamino)-β-D-glucopyranosyl]oxy]-4,10-dihydroxy-5-methoxy-9,16-dimethyl-7-(2-oxoethyl)oxacyclohexadeca-11,13-dien-2-one,



I. (4*R*,5*S*,6*S*,7*R*,9*R*,10*R*,11*E*,13*E*,16*R*)-6-[[3,6-dideoxy-4-*O*-(2,6-dideoxy-3-*C*-methyl-4-*O*-propanoyl-α-L-*ribo*-hexopyranosyl)-3-(dimethylamino)-β-D-glucopyranosyl]oxy]-4,10-dihydroxy-5-methoxy-9,16-dimethyl-7-(2-oxoethyl)oxacyclohexadeca-11,13-dien-2-one,



J. (4*R*,5*S*,6*S*,7*R*,9*R*,10*R*,11*E*,13*E*,16*R*)-4-(acetyloxy)-6-[[3,6-dideoxy-4-*O*-(2,6-dideoxy-4-*O*-hexanoyl-3-*C*-methyl-α-L-*ribo*-hexopyranosyl)-3-(dimethylamino)-β-D-glucopyranosyl]oxy]-10-hydroxy-5-methoxy-9,16-dimethyl-7-(2-oxoethyl)oxacyclohexadeca-11,13-dien-2-one,



K. (4*R*,5S,6S,7*R*,9*R*,10*R*,11*E*,13*E*,16*R*)-4-(acetyloxy)-6-[[3,6-dideoxy-4-*O*-(2,6-dideoxy-3-*C*-methyl-4-*O*-propanoyl-α-L-*ribo*-hexopyranosyl)-3-(dimethylamino)-β-D-glucopyranosyl]oxy]-10-hydroxy-5-methoxy-9,16-dimethyl-7-(2-oxoethyl)oxacyclohexadeca-11,13-dien-2-one.

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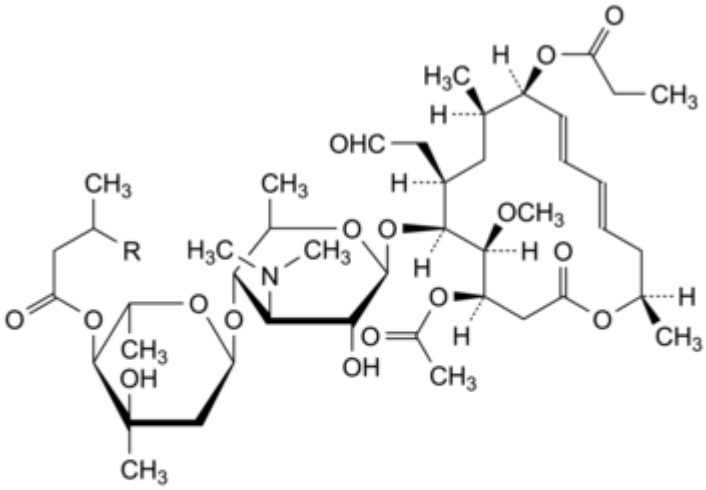
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Josamycin Propionate

General Notices

(Ph. Eur. monograph 1982)



Leucomycin propionate	R	Mol. Formula	M_r
A3	CH_3	$C_{45}H_{73}NO_{16}$	884
A4	H	$C_{44}H_{71}NO_{16}$	870

Action and use

Antibacterial.

Ph Eur

DEFINITION

Propionyl ester of a macrolide antibiotic produced by certain strains of *Streptomyces narbonensis* var. *josamyceticus* var. *nova*, or obtained by any other means. The main component is (4*R*,5*S*,6*S*,7*R*,9*R*,10*R*,11*E*,13*E*,16*R*)-4-(acetyloxy)-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]-5-methoxy-9,16-dimethyl-7-(2-oxoethyl)-10-(propanoyloxy)oxacyclohexadeca-11,13-dien-2-one propionate (leucomycin A3 propionate).

Semi-synthetic product derived from a fermentation product.

Content

— minimum 843 Ph. Eur. U./mg (dried substance).

CHARACTERS

Appearance

White or slightly yellowish, crystalline, slightly hygroscopic powder.

Solubility

Practically insoluble in water, freely soluble in methanol and in methylene chloride, soluble in acetone.

IDENTIFICATION

First identification: A, B.

Second identification: B, C.

Prepare solutions in methanol immediately before use.

A. Dissolve 0.10 g in *methanol R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of the solution to 50.0 mL with *methanol R*. Examined between 220 nm and 350 nm (*2.2.25*), the solution shows an absorption maximum at 231 nm. The specific absorbance at the absorption maximum is 310 to 350.

B. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 10 mg of the substance to be examined in *methanol R* and dilute to 1 mL with the same solvent.

Reference solution (a) Dissolve 10 mg of *josamycin propionate CRS* in *methanol R* and dilute to 1 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of *josamycin CRS* in *methanol R* and dilute to 1 mL with the same solvent.

Reference solution (c) Dissolve 10 mg of *spiramycin CRS* in *methylene chloride R* and dilute to 1 mL with the same solvent.

Reference solution (d) Mix 0.5 mL of reference solution (a) with 0.5 mL of reference solution (b).

Plate *TLC silica gel G plate R*.

Mobile phase *methanol R*, *acetone R*, *ethyl acetate R*, *toluene R*, *hexane R* (8:10:20:25:30 *V/V/V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying At 100 °C for 10 min.

Detection Spray with *dilute sulfuric acid R* and heat at 100 °C for 10 min.

System suitability The chromatogram obtained with reference solution (d) shows 2 clearly separated principal spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a) and its position is different from that of the principal spot in the chromatograms obtained with reference solutions (b) and (c).

C. Dissolve about 10 mg in 5 mL of *hydrochloric acid R1* and allow to stand for 10-20 min. A pink colour develops, turning brown.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution BY_4 (2.2.2, Method II).

Dissolve 1 g in *methanol R* and dilute to 10 mL with the same solvent.

Specific optical rotation (2.2.7)

-65 to -75 (dried substance).

Dissolve 1.000 g in *methanol R* and dilute to 100.0 mL with the same solvent. Allow to stand for 30 min before measuring the angle of rotation.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in *acetonitrile for chromatography R* and dilute to 100.0 mL with the same solvent.

Reference solution (a) Dissolve 50.0 mg of *josamycin propionate CRS* in *acetonitrile for chromatography R* and dilute to 100.0 mL with the same solvent.

Reference solution (b) Dissolve 5 mg of the substance to be examined in 10 mL of *methanol R* and add 40 µL of *dilute phosphoric acid R*. Mix, allow to stand for 5 min and inject.

Reference solution (c) Dilute 2.0 mL of reference solution (a) to 100.0 mL with *acetonitrile for chromatography R*.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase *acetonitrile R*, a 15.4 g/L solution of *ammonium acetate R* previously adjusted to pH 6.0 with *dilute phosphoric acid R* (60:40 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 232 nm.

Injection 20 µL of the test solution and reference solutions (b) and (c).

Run time 3 times the retention time of leucomycin A3 propionate.

Relative retention With reference to leucomycin A3 propionate (retention time = about 18 min): impurity E = about 0.2; impurity A = about 0.3; impurity B = about 0.5; leucomycin A4 propionate = about 0.7; impurity C = about 1.4; impurity D = about 2.0.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the 2 peaks eluting with a relative retention with reference to leucomycin A3 propionate of about 0.5 and 0.7 respectively.

Limits:

— *impurity D*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (c);

— *impurities A, B, C, E*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c);

— *any other impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c);

— *total*: not more than 7 times the area of the principal peak in the chromatogram obtained with reference solution (c);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (c).

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven *in vacuo* at 60 °C for 3 h.

Sulfated ash (2.4.14)

Maximum 0.2 per cent, determined on 1.0 g.

ASSAY

Dissolve 40.0 mg in 20 mL of *methanol R* and dilute to 100.0 mL with *phosphate buffer solution pH 5.6 R*.

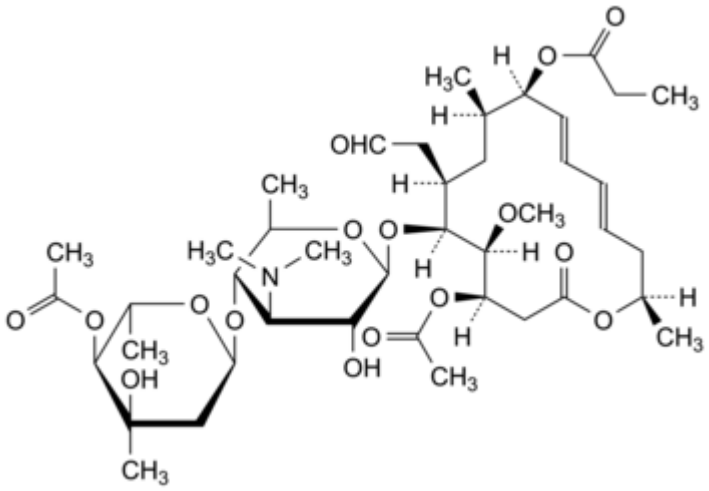
Carry out the microbiological assay of antibiotics (2.7.2). Use *josamycin propionate CRS* as the chemical reference substance.

STORAGE

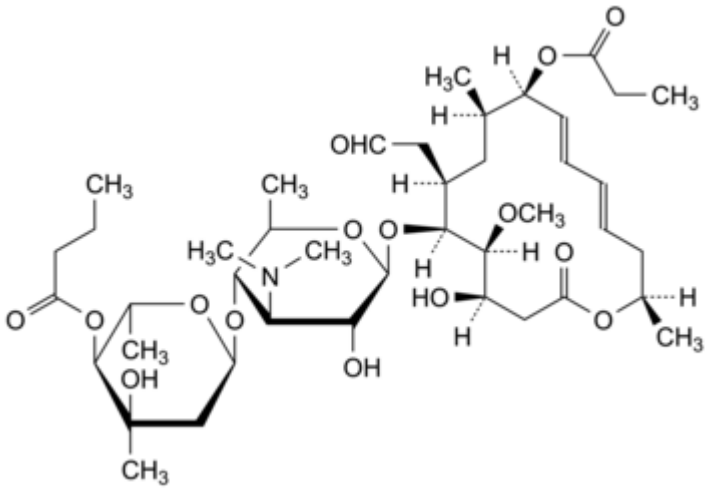
In an airtight container.

IMPURITIES

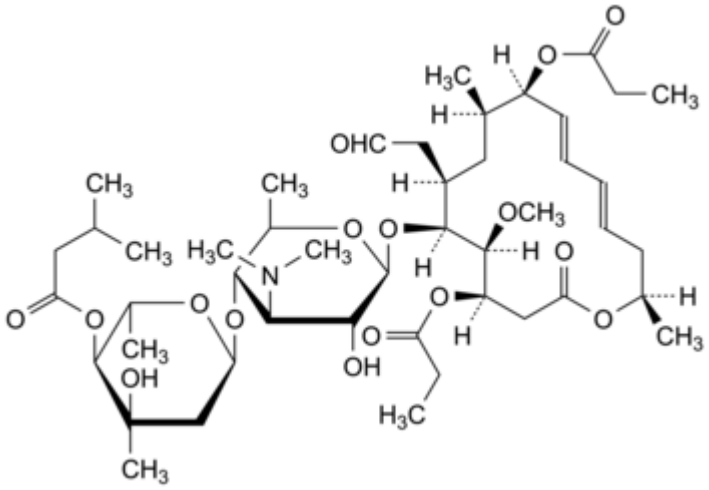
Specified impurities *A, B, C, D, E.*



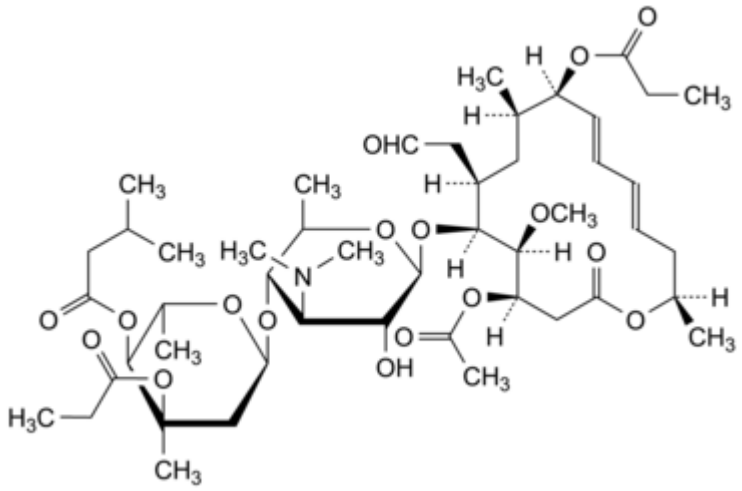
A. leucomycin A8 9-propionate,



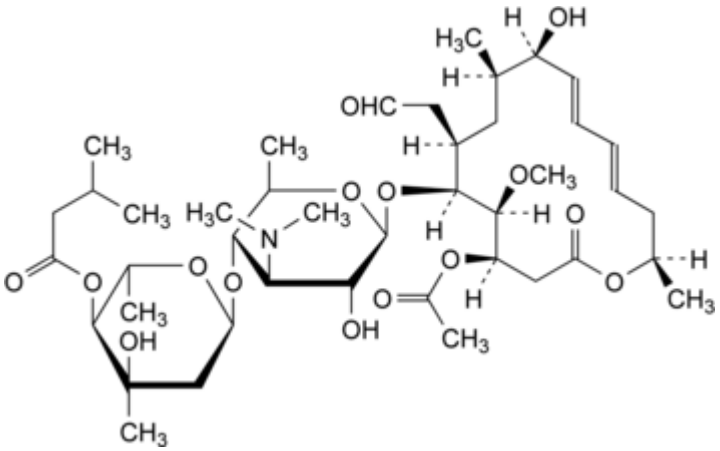
B. leucomycin A5 9-propionate,



C. platenomycin A1 9-propionate,



D. leucomycin A3 3″,9-dipropionate,



E. (4*R*,5*S*,6*S*,7*R*,9*R*,10*R*,11*E*,13*E*,16*R*)-4-(acetyloxy)-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]-10-hydroxy-5-methoxy-9,16-dimethyl-7-(2-oxoethyl)oxacyclohexadeca-11,13-dien-2-one (josamycin).

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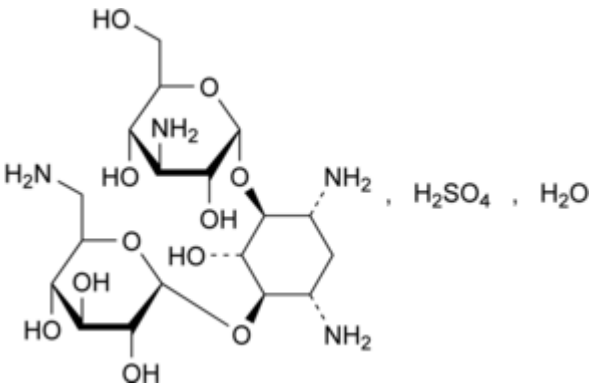
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Kanamycin Sulfate

General Notices

Kanamycin Sulphate

(Kanamycin Monosulfate, Ph. Eur. monograph 0032)



$C_{18}H_{38}N_4O_{15}S,H_2O$ 601 *5965-95-7*

Action and use

Aminoglycoside antibacterial.

Ph Eur

DEFINITION

6-*O*-(3-Amino-3-deoxy-α-D-glucopyranosyl)-4-*O*-(6-amino-6-deoxy-α-D-glucopyranosyl)-2-deoxy-D-streptamine sulfate monohydrate.

Antimicrobial substance produced by the growth of certain strains of *Streptomyces kanamyceticus*.

Content

Minimum 750 IU/mg (dried substance).

PRODUCTION

It is produced by methods of manufacture designed to eliminate or minimise substances lowering blood pressure.

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, practically insoluble in acetone and in ethanol (96 per cent).

IDENTIFICATION

A. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *water R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 10 mg of *kanamycin monosulfate CRS* in *water R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of *kanamycin monosulfate CRS*, 10 mg of *neomycin sulfate CRS* and 10 mg of *streptomycin sulfate for identification CRS* in *water R* and dilute to 10 mL with the same solvent.

Plate Suitable plate coated with a 0.75 mm layer of a mixture prepared as follows: mix 0.3 g of *carbomer R* with 240 mL of *water R* and allow to stand, with moderate shaking, for 1 h; adjust to pH 7 by the gradual addition, with continuous shaking, of *dilute sodium hydroxide solution R* and add 30 g of *silica gel H R*.

Pretreatment Heat the plate at 110 °C for 1 h, allow to cool and use immediately.

Mobile phase 70 g/L solution of *potassium dihydrogen phosphate R*.

Application 10 µL.

Development Over a path of 12 cm.

Drying In a current of warm air.

Detection Spray with a mixture of equal volumes of a 2 g/L solution of *1,3-dihydroxynaphthalene R* in *ethanol (96 per cent) R* and a 460 g/L solution of *sulfuric acid R*. Heat at 150 °C for 5 min to 10 min.

System suitability Reference solution (b):

— the chromatogram shows 3 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

B. Dissolve 0.5 g in 10 mL of *water R*. Add 10 mL of *picric acid solution R*. Initiate crystallisation if necessary by scratching the wall of the tube with a glass rod and allow to stand. Collect the crystals, wash with 20 mL of *water R* and filter. Dry at 100 °C. The crystals melt (2.2.14) at about 235 °C, with decomposition.

C. Dissolve about 50 mg in 2 mL of *water R*. Add 1 mL of a 10 g/L solution of *ninhydrin R* and heat for a few minutes on a water-bath. A violet colour develops.

D. It gives the reactions of sulfates (2.3.1).

TESTS

Solution S

Dissolve 0.20 g in *carbon dioxide-free water R* and dilute to 20.0 mL with the same solvent.

pH (2.2.3)

6.5 to 8.5 for solution S.

Specific optical rotation (2.2.7)

+ 112 to + 123 (dried substance), determined on solution S.

Kanamycin B

Thin-layer chromatography (2.2.27) as described under Identification A with the following modifications.

Test solution Dissolve 0.1 g of the substance to be examined in *water R* and dilute to 20 mL with the same solvent.

Reference solution Dissolve 4 mg of *kanamycin B sulfate CRS* in *water R* and dilute to 20 mL with the same solvent.

Application 4 µL.

Detection Spray with *ninhydrin and stannous chloride reagent R*. Heat at 110 °C for 15 min.

Limit:

— *kanamycin B*: any spot corresponding to kanamycin B in the chromatogram obtained with the test solution is not more intense than the spot in the chromatogram obtained with the reference solution (4.0 per cent).

Loss on drying (2.2.32)

Maximum 1.5 per cent, determined on 1.000 g by drying at 60 °C at a pressure not exceeding 670 Pa for 3 h.

Sulfated ash (2.4.14)

Maximum 0.5 per cent, determined on 1.0 g.

Sulfate

15.0 per cent to 17.0 per cent of sulfate (dried substance).

Dissolve 0.250 g in 100 mL of *water R* and adjust the solution to pH 11 with *concentrated ammonia R*. Add 10.0 mL of *0.1 M barium chloride* and about 0.5 mg of *phthalein purple R*. Titrate with *0.1 M sodium edetate* adding 50 mL of *ethanol (96 per cent) R* when the colour of the solution begins to change and continue the titration until the violet-blue colour disappears.

1 mL of *0.1 M barium chloride* is equivalent to 9.606 mg of SO_4.

Pyrogens (*2.6.8*)

If intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of pyrogens, it complies with the test for pyrogens. Inject per kilogram of the rabbit's mass 1 mL of a 10 mg/mL solution of the substance to be examined in *water for injections R*.

ASSAY

Carry out the microbiological assay of antibiotics (*2.7.2*). Use *kanamycin monosulfate CRS* as the reference substance.

STORAGE

If the substance is sterile, store in a sterile, tamper-evident container.

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Kaolin and Morphine Mixture

General Notices

Kaolin and Morphine Oral Suspension

DEFINITION

Kaolin and Morphine Mixture is an *oral suspension* containing 0.00675% w/v Morphine Hydrochloride, 20% w/v of Light Kaolin or Light Kaolin (Natural) and 5% w/v of Sodium Bicarbonate in a suitable vehicle.

It should be recently prepared unless the kaolin has been sterilised.

The mixture complies with the requirements stated under Oral Liquids and with the following requirements.

Content of sodium bicarbonate, $NaHCO_3$

4.65 to 5.35% w/v.

Content of anhydrous morphine, $C_{17}H_{19}NO_3$

0.0055 to 0.0080% w/v.

IDENTIFICATION

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Centrifuge 10 mL of the preparation, reserving the supernatant liquid. Extract the residue with four 10-mL quantities of a mixture of 38 mL of *acetone* and 2 mL of 5M *ammonia*, centrifuging between each extraction, and evaporate the combined extracts on a water bath to about 5 mL. Mix with the reserved supernatant liquid, add 10 mL of 1M *sulfuric acid*, shake with two 10-mL quantities of *chloroform* and discard the chloroform. Add sufficient 5M *ammonia* to make the aqueous solution alkaline to *litmus paper*, extract with three 10-mL quantities of a mixture of equal volumes of *chloroform* and *ethanol (96%)*, evaporate to dryness and dissolve the residue in 0.5 mL of *ethanol (96%)*.

(2) 0.10% w/v of *morphine hydrochloride*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, heat at 105° to 110° for 30 minutes, allow to cool and spray with *dilute potassium iodobismuthate solution*.

MOBILE PHASE

10 volumes of *diethylamine*, 20 volumes of *ethyl acetate* and 70 volumes of *toluene*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

TESTS

Acid-insoluble matter

13.8 to 18.4% w/w when determined by the following method. To 3 g add 15 mL of *water*, cautiously add sufficient *2M hydrochloric acid* to make the suspension acidic to *litmus paper*, boil for 5 minutes, replacing the water lost by evaporation, cool and filter the supernatant liquid. Boil the residue with 20 mL of *water* and 10 mL of *2M hydrochloric acid*, cool, filter through the same filter and wash the residue with *water* until the washings are free from chloride. Dry and ignite the residue to constant weight at red heat.

ASSAY

For sodium bicarbonate

Boil 20 mL with 40 mL of *water* for 5 minutes, replacing the water lost by evaporation, add 50 mL of *ethanol (96%)* previously neutralised to *methyl red solution* and allow to stand for 1 hour. Filter and wash the residue with 100 mL of a mixture of equal volumes of the neutralised ethanol and *water*. Add 50 mL of *0.5M hydrochloric acid VS* to the combined filtrate and washings, boil, cool and titrate the excess of hydrochloric acid with *0.5M sodium hydroxide VS* using *methyl red solution* as indicator. Each mL of *0.5M hydrochloric acid VS* is equivalent to 42.00 mg of $NaHCO_3$.

For anhydrous morphine

Centrifuge 25 mL, reserving the supernatant liquid, and extract the residue with three 25-mL quantities of *ethanol (96%)*, centrifuging between each extraction and reserving each supernatant liquid. Add 40 mL of *water* and 7 mL of 5M *ammonia* to the combined supernatant liquids and extract the mixture with three 30-mL quantities of *chloroform*. Gently shake each extract with the same 15 mL of a mixture of 2 volumes of *water* and 1 volume of *ethanol (96%)* and discard the aqueous ethanol. Evaporate the combined chloroform solutions just to dryness, warm the residue with 10 mL of 1M *hydrochloric acid*, cool the solution, which may be slightly cloudy, add sufficient *water* to produce 50 mL and filter (Whatman No. 42 paper is suitable). To 20 mL of the filtrate add 8 mL of a freshly prepared 1% w/v solution of *sodium nitrite*, allow to stand in the dark for 15 minutes, add 12 mL of 5M *ammonia* and sufficient *water* to produce 50 mL and measure the *absorbance* of a 4-cm layer at 442 nm without delay, Appendix II B. Use in the reference cell a solution prepared in the same manner but using *water* in place of the sodium nitrite solution. Calculate the content of anhydrous morphine taking 124 as the value of A(1%, 1 cm) at the maximum at 442 nm.

STORAGE

Kaolin and Morphine Mixture should be kept in well-filled glass containers.

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Kaolin Mixture

General Notices

Kaolin Oral Suspension

DEFINITION

Kaolin Mixture is an *oral suspension* containing 20% w/v of Light Kaolin or Light Kaolin (Natural) and 5% w/v each of Light Magnesium Carbonate and Sodium Bicarbonate in a suitable vehicle with a peppermint flavour.

It should be recently prepared unless the kaolin has been sterilised.

The mixture complies with the requirements stated under Oral Liquids and with the following requirements.

Content of magnesium, Mg

1.04 to 1.25% w/w.

Content of sodium bicarbonate, $NaHCO_3$

4.05 to 4.65% w/w.

TESTS

Acid-insoluble matter

13.8 to 18.4% w/w when determined by the following method. Dry and ignite the residue reserved in the Assay for magnesium to constant weight at red heat.

ASSAY

For magnesium

To 3 g add 15 mL of *water*, make acidic to *litmus paper* by the cautious addition of 2M *hydrochloric acid*, boil for 5 minutes, replacing the water lost by evaporation, cool and filter the supernatant liquid. Boil the residue with 20 mL of *water* and 10 mL of 2M *hydrochloric acid*, cool, filter through the same filter and wash the residue with *water* until the washings are free from chloride. Reserve the residue for the test for Acid-insoluble matter. Dilute the combined filtrate and washings to 100 mL with *water*. To 20 mL add 0.1 g of L-*ascorbic acid*, make slightly alkaline to *litmus paper* with 5M *ammonia* and add 10 mL of *triethanolamine*, 10 mL of *ammonia buffer pH 10.9* and 1 mL of a 10% w/v solution of *potassium cyanide*. Titrate with 0.05M *disodium edetate VS*, using *mordant black 11 solution* as indicator, to a full blue colour. Each mL of 0.05M *disodium edetate VS* is equivalent to 1.215 mg of Mg.

For sodium bicarbonate

Boil 10 g with 100 mL of *water* for 5 minutes, filter, boil the residue with 100 mL of *water* for 5 minutes and filter. Combine the filtrates, cool and titrate with *0.5M hydrochloric acid VS* using *methyl orange-xylene cyanol FF solution* as indicator. Add 10 mL of *ammonia buffer pH 10.9* and titrate with 0.05M *disodium edetate VS* using *mordant black 11 solution* as indicator. After subtracting one-fifth of the volume of 0.05M *disodium edetate VS*, each mL of *0.5M hydrochloric acid VS* is equivalent to 42.00 mg of $NaHCO_3$.

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Kaolin Poultice

General Notices

DEFINITION

Heavy Kaolin[1], finely sifted	527 g
Boric Acid, finely sifted	45 g
Methyl Salicylate	2 mL
Thymol	500 mg
Peppermint Oil	0.5 mL
Glycerol	425 g

Extemporaneous preparation

The following directions apply.

Mix the Heavy Kaolin, previously dried at 100°, and the Boric Acid with the Glycerol, heat at 120° for 1 hour, stirring occasionally, and allow to cool. Separately, dissolve the Thymol in the Methyl Salicylate, add to the cooled mixture, add the Peppermint Oil and mix thoroughly.

The heating step may be omitted if some other satisfactory means of mixing the solid ingredients with the Glycerol is used but in this case Heavy Kaolin that has been sterilised is used.

The poultice complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of boric acid, H_3BO_3

4.25 to 4.75% w/w.

ASSAY

Mix 20 g with a solution containing 10 g of D-*mannitol* in 40 mL of *water*, warm and stir until completely dispersed and titrate with *1M sodium hydroxide VS* using *phenolphthalein solution R1* as indicator. Each mL of *1M sodium hydroxide VS* is equivalent to 61.83 mg of H_3BO_3.

STORAGE

Kaolin Poultice should be kept in suitable containers that minimise absorption, diffusion or evaporation of the ingredients.

1 If an appropriate heating step, such as that described under Extemporaneous preparation, is not included in the manufacturing process, Heavy Kaolin that has been sterilised is used.

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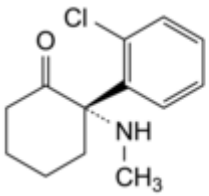
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Ketamine Hydrochloride

General Notices

(Ph. Eur. monograph 1020)



and enantiomer , HCl

$C_{13}H_{17}Cl_2NO$ 274.2 *1867-66-9*

Action and use

Intravenous general anaesthetic

Preparations

Ketamine Injection

Ketamine Nasal Spray

Ketamine Oral Solution

Ph Eur

DEFINITION

(2*RS*)-2-(2-Chlorophenyl)-2-(methylamino)cyclohexanone hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water and in methanol, soluble in ethanol (96 per cent).

mp

About 260 °C, with decomposition.

IDENTIFICATION

A. Optical rotation (see Tests).

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *ketamine hydrochloride CRS*.

C. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S

Dissolve 10.0 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

3.5 to 4.1.

Dilute 10 mL of solution S to 20 mL with *carbon dioxide-free water R*.

Optical rotation (*2.2.7*)

-0.2° to + 0.2°.

Dilute 2.5 mL of solution S to 25.0 mL with *water R*.

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution Dissolve 50 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 5 mg of *ketamine impurity A CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase (using ultrasound if necessary). To 1.0 mL of the solution, add 0.5 mL of the test solution and dilute to 100.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.125 m, Ø = 4.0 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Dissolve 0.95 g of *sodium hexanesulfonate R* in 1 L of a mixture of 25 volumes of *acetonitrile R1* and 75 volumes of *water R* and add 4 mL of *acetic acid R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 20 µL.

Run time 10 times the retention time of ketamine.

Relative retention With reference to ketamine (retention time = about 3 min): impurity A = about 1.6; impurity B = about 3.3; impurity C = about 4.6.

System suitability Reference solution (a):

— *resolution*: minimum 1.5 between the peaks due to ketamine and impurity A.

Limits:

— *impurities A, B, C*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 50 mL of *methanol R* and add 1.0 mL of *0.1 M hydrochloric acid*. Carry out a potentiometric titration (2.2.20), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

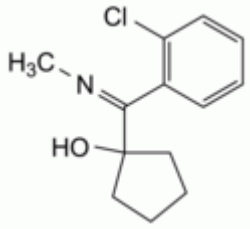
1 mL of *0.1 M sodium hydroxide* is equivalent to 27.42 mg of $C_{13}H_{17}Cl_2NO$.

STORAGE

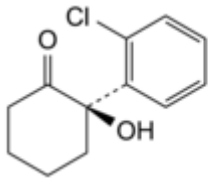
Protected from light.

IMPURITIES

Specified impurities *A, B, C.*

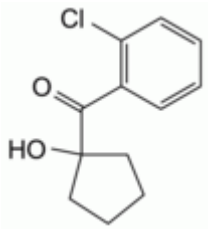


A. 1-(2-chloro-*N*-methylbenzimidoyl)cyclopentanol,



and enantiomer

B. (2*RS*)-2-(2-chlorophenyl)-2-hydroxycyclohexanone,



C. (2-chlorophenyl)(1-hydroxycyclopentyl)methanone.

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Ketamine Injection

General Notices

Action and use

Intravenous general anaesthetic.

DEFINITION

Ketamine Injection is a sterile solution of Ketamine Hydrochloride in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of ketamine, $C_{13}H_{16}ClNO$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Dilute a volume of the injection with a mixture of 1 volume of 1M *sodium hydroxide* and 49 volumes of *methanol* to produce a solution containing the equivalent of 0.07% w/v of ketamine. The *light absorption*, Appendix II B, in the range 230 to 350 nm of this solution exhibits a maximum at 301 nm and shoulders at 274, 268 and 261 nm.

B. Dilute a volume of the injection with *0.1M hydrochloric acid* to produce a solution containing the equivalent of 0.025% w/v of ketamine. The *light absorption*, Appendix II B, in the range 230 to 350 nm of this solution exhibits two maxima at 276 nm and at 269 nm and a shoulder at 260 nm.

TESTS

Acidity

pH, 3.5 to 5.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute the injection, if necessary, to produce a solution containing the equivalent of 0.1% w/v of ketamine.

(2) Dilute 1 volume of solution (1) to 200 volumes.

(3) Dilute 1 volume of solution (2) to 2 volumes.

(4) Add 2 volumes of a 0.05% w/v solution of *ketamine impurity A EPCRS* in the mobile phase to 1 volume of solution (1) and dilute the resulting solution to 100 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.0 mm) and a stainless steel pre-column (4 mm × 4.0 mm), both packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Lichrosorb RP18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 215 nm.

(f) Inject 20 µL of each solution.

(g) For solutions (1), (2) and (3), continue the chromatography for 10 times the retention time of ketamine.

MOBILE PHASE

Dissolve 0.95 g of *sodium hexanesulfonate* in 1 litre of a mixture of 25 volumes of *acetonitrile R1* and 75 volumes of *water*. To the resulting solution add 4 mL of 6M *acetic acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution factor* between the peaks due to ketamine and ketamine impurity A is at least 1.5 and the retention time for ketamine is about 3 to 4.5 minutes. If necessary, adjust the concentrations of water and *acetonitrile* in the mobile phase.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of not more than one such peak is greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.25%);

the sum of the areas of all *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than 0.4 times the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

ASSAY

Dilute a volume of the injection containing the equivalent of 20 mg of ketamine to 100 mL with 0.05M *hydrochloric acid* and mix. Measure the *absorbance* of the resulting solution at the maximum at 269 nm, Appendix II B. Measure the *absorbance* of a 0.023% w/v solution of *ketamine hydrochloride BPCRS* in 0.05M *hydrochloric acid* at the same wavelength. Calculate the content of $C_{13}H_{16}ClNO$, using the declared content of $C_{13}H_{16}ClNO$, in *ketamine hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurity A, listed under Ketamine Hydrochloride.

STORAGE

Ketamine Injection should be protected from light and stored at a temperature not exceeding 30°.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of ketamine.

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Ketamine Nasal Spray

General Notices

NOTE: *This monograph has been developed to cover unlicensed formulations.*

Action and use

Anaesthetic; treatment of chronic pain.

DEFINITION

Ketamine Nasal Spray is an aqueous solution of Ketamine Hydrochloride in a suitable container fitted with an appropriate nasal delivery system.

The nasal spray complies with the requirements stated under Nasal Preparations and with the following requirements. Where appropriate, the nasal spray also complies with the requirements stated under Unlicensed Medicines.

Content of ketamine, $C_{13}H_{16}ClNO$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Dilute a quantity of the nasal spray with a mixture of 1 volume of 1M *sodium hydroxide* and 49 volumes of *methanol* to produce a solution containing the equivalent of 0.1% w/v of ketamine. The *light absorption*, Appendix II B, in the range 230 to 350 nm of this solution exhibits a maximum at 301 nm and shoulders at 274, 268 and 261 nm.

B. Dilute a quantity of the nasal spray with 0.1M *hydrochloric acid* to produce a solution containing the equivalent of 0.025% w/v of ketamine. The *light absorption*, Appendix II B, in the range 230 to 350 nm of this solution exhibits two maxima at 276 nm and at 269 nm and a shoulder at 260 nm.

C. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

D. Complies with the test for Specific optical rotation.

TESTS

Acidity

pH, 3.5 to 5.5, Appendix V L.

Specific optical rotation

Dilute a quantity of the nasal spray with *carbon dioxide-free water* to produce a solution containing the equivalent of 2% w/v of ketamine. The *specific optical rotation* is -0.2 to +0.2, Appendix V F.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute a quantity of the nasal spray, if necessary, to produce a solution containing the equivalent of 0.1% w/v of ketamine.

(2) Dilute 1 volume of solution (1) to 200 volumes.

(3) Dilute 1 volume of solution (2) to 2 volumes.

(4) Add 2 volumes of a 0.05% w/v solution of *ketamine impurity A EPCRS* in *methanol* to 1 volume of solution (1) and dilute the resulting solution to 100 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Kromasil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 215 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 10 times the retention time of ketamine.

When the chromatograms are recorded under the prescribed conditions, the retention time of ketamine is about 5 to 6 minutes and the relative retention of the peak due to impurity A is about 1.6.

MOBILE PHASE

25 volumes of *acetonitrile R1* and 75 volumes of a 0.1% w/v solution of *sodium hexanesulfonate* containing 0.05% w/v of *glacial acetic acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to ketamine and ketamine impurity A is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

not more than one such peak has an area greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.25%);

the sum of the areas of all the *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than 0.4 times the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *water*.

(1) Dilute the nasal spray, if necessary, to produce a solution containing the equivalent of 0.005% w/v of ketamine.

(2) 0.005% w/v of *ketamine hydrochloride BPCRS*.

(3) Mix equal volumes of a 0.0025% w/v solution of *ketamine hydrochloride BPCRS* in *water* and a 0.0025% w/v solution of *ketamine impurity A EPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Kromasil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

35 volumes of *methanol* and 65 volumes of a 0.575% w/v solution of *ammonium dihydrogen orthophosphate* adjusted to pH 3.0 using *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to ketamine and ketamine impurity A is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{13}H_{16}ClNO$ in the nasal spray using the declared content of $C_{13}H_{16}ClNO$ in *ketamine hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurity A listed under Ketamine Hydrochloride.

STORAGE

Ketamine Nasal Spray should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of ketamine.

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Ketamine Oral Solution

General Notices

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Treatment of chronic pain.

DEFINITION

Ketamine Oral Solution is a solution containing Ketamine Hydrochloride in a suitable vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral solution also complies with the requirements stated under Unlicensed Medicines.

Content of ketamine, $C_{13}H_{16}ClNO$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Dilute a quantity of the oral solution with a mixture of 1 volume of 1M *sodium hydroxide* and 49 volumes of *methanol* to produce a solution containing the equivalent of 0.1% w/v of ketamine. The *light absorption*, Appendix II B, in the range 230 to 350 nm of this solution exhibits a maximum at 301 nm and shoulders at 274, 268 and 261 nm.

B. Dilute a quantity of the oral solution with 0.1M *hydrochloric acid* to produce a solution containing the equivalent of 0.025% w/v of ketamine. The *light absorption*, Appendix II B, in the range 230 to 350 nm of this solution exhibits two maxima at 276 nm and at 269 nm and a shoulder at 260 nm.

C. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute a quantity of the oral solution to contain the equivalent of 0.1% w/v of ketamine.

(2) Dilute 1 volume of solution (1) to 200 volumes.

(3) Dilute 1 volume of solution (2) to 2 volumes.

(4) Add 2 volumes of a 0.05% w/v solution of *ketamine impurity A EPCRS* in *methanol* to 1 volume of solution (1) and dilute the resulting solution to 100 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Kromasil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 215 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 10 times the retention time of ketamine.

When the chromatograms are recorded under the prescribed conditions, the retention time of ketamine is about 5 to 6 minutes and the relative retention of the peak due to impurity A is about 1.6.

MOBILE PHASE

25 volumes of *acetonitrile R1* and 75 volumes of a 0.1% w/v solution of *sodium hexanesulfonate* containing 0.05% w/v of *glacial acetic acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to ketamine and ketamine impurity A is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

not more than one such peak has an area greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.25%);

the sum of the areas of all the *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than 0.4 times the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *water*.

(1) Dilute the oral solution to contain the equivalent of 0.005% w/v of ketamine.

(2) 0.005% w/v of *ketamine hydrochloride BPCRS*.

(3) Mix equal volumes of a 0.0025% w/v solution of *ketamine hydrochloride BPCRS* in *water* and a 0.0025% w/v solution of *ketamine impurity A EPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Kromasil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

35 volumes of *methanol* and 65 volumes of a 0.575% w/v solution of *ammonium dihydrogen orthophosphate* adjusted to pH 3.0 using *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to ketamine and ketamine impurity A is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{13}H_{16}ClNO$ in the oral solution using the declared content of $C_{13}H_{16}ClNO$ in *ketamine hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurity A listed under Ketamine Hydrochloride.

STORAGE

Ketamine Oral Solution should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of ketamine.

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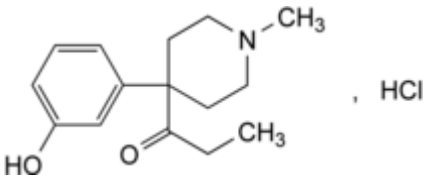
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Ketobemidone Hydrochloride

General Notices

(Ph. Eur. monograph 1746)



$C_{15}H_{22}ClNO_2$ 283.8 *5965-49-1*

Action and use

Opioid receptor agonist; analgesic.

Ph Eur

DEFINITION

1-[4-(3-Hydroxyphenyl)-1-methylpiperidin-4-yl]propan-1-one hydrochloride.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, soluble in ethanol (96 per cent), very slightly soluble in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *Ph. Eur. reference spectrum of ketobemidone hydrochloride*.

B. Solution S (see Tests) gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S

Dissolve 0.250 g in *carbon dioxide-free water R* and dilute to 25.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution B_8 (*2.2.2, Method II*).

pH (*2.2.3*)

4.5 to 5.5 for solution S.

Related substances

Liquid chromatography (*2.2.29*).

Solution A 1.54 g/L solution of *ammonium acetate R* adjusted to pH 8.0 with *dilute ammonia R1*.

Test solution Dissolve 50.0 mg of the substance to be examined in solution A and dilute to 25.0 mL with the same solution.

Reference solution (a) Dissolve 1 mg of *ketobemidone impurity B CRS* and 1 mg of *ketobemidone impurity C CRS* in solution A and dilute to 25 mL with the same solution.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with solution A. Dilute 20.0 mL of this solution to 100.0 mL with solution A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *phenylhexylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase *acetonitrile R*, solution A (20:80 *V/V*).

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 278 nm.

Injection 20 µL.

Run time 4.5 times the retention time of ketobemidone.

Relative retention With reference to ketobemidone (retention time = about 10 min): impurity A = about 0.4; impurity B = about 0.6; impurity C = about 0.7; impurity D = about 3.5.

System suitability Reference solution (a):

— *resolution*: minimum 4.0 between the peaks due to impurity B and impurity C.

Limits:

— *impurities A, B, C, D*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 3.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.7 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (2.5.12)

Maximum 1.0 per cent, determined on 0.50 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

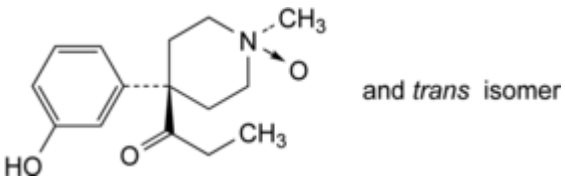
Dissolve 0.200 g in a mixture of 5.0 mL of *0.01 M hydrochloric acid* and 50 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (2.2.20) using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 28.38 mg of $C_{15}H_{22}ClNO_2$.

IMPURITIES

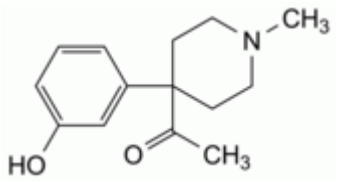
Specified impurities *A, B, C, D.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *E.*

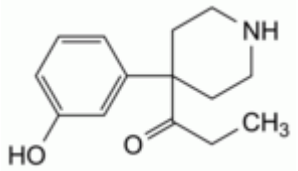


and *trans* isomer

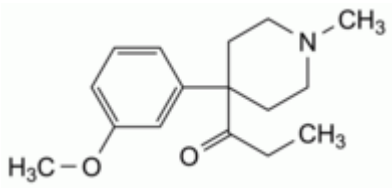
A. 1-[4-(3-hydroxyphenyl)-1-methyl-1-oxidopiperidin-4-yl]propan-1-one (*cis* and *trans* isomers),



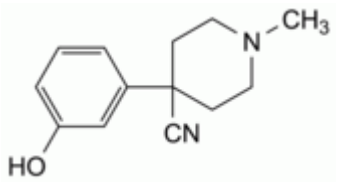
B. 1-[4-(3-hydroxyphenyl)-1-methylpiperidin-4-yl]ethanone,



C. 1-[4-(3-hydroxyphenyl)piperidin-4-yl]propan-1-one,



D. 1-[4-(3-methoxyphenyl)-1-methylpiperidin-4-yl]propan-1-one,



E. 4-(3-hydroxyphenyl)-1-methylpiperidin-4-carbonitrile.

Ph Eur

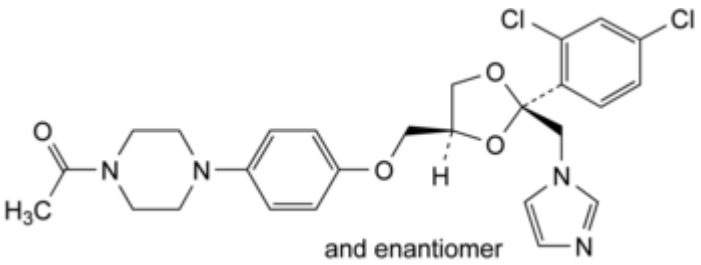
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Ketoconazole

General Notices

(Ph. Eur. monograph 0921)



$C_{26}H_{28}Cl_2N_4O_4$ 531.4 *65277-42-1*

Action and use

Antifungal.

Preparations

Ketoconazole Cream

Ketoconazole Shampoo

Ph Eur

DEFINITION

1-[4-[4-[[(2*RS*,4*SR*)-2-(2,4-Dichlorophenyl)-2-[(1*H*-imidazol-1-yl)methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]piperazin-1-yl]ethan-1-one.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, freely soluble in methylene chloride, soluble in methanol, sparingly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: B.

Second identification: A, C, D.

A. Melting point (2.2.14): 148 °C to 152 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *ketoconazole CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 30 mg of the substance to be examined in the mobile phase and dilute to 5 mL with the mobile phase.

Reference solution (a) Dissolve 30 mg of *ketoconazole CRS* in the mobile phase and dilute to 5 mL with the mobile phase.

Reference solution (b) Dissolve 30 mg of *ketoconazole CRS* and 30 mg of *econazole nitrate CRS* in the mobile phase, then dilute to 5 mL with the mobile phase.

Plate *TLC octadecylsilyl silica gel plate R*.

Mobile phase *ammonium acetate solution R*, *dioxan R*, *methanol R* (20:40:40 *V/V/V*).

Application 5 µL.

Development Over 3/4 of the plate.

Drying In a current of warm air for 15 min.

Detection Expose to iodine vapour until the spots appear and examine in daylight.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

D. To about 30 mg in a porcelain crucible add 0.3 g of *anhydrous sodium carbonate R*. Heat over an open flame for 10 min. Allow to cool. Take up the residue with 5 mL of *dilute nitric acid R* and filter. To 1 mL of the filtrate add 1 mL of *water R*. The solution gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 1.0 g in *methylene chloride R* and dilute to 10.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution BY_4 (2.2.2, *Method II*).

Optical rotation (2.2.7)

-0.10° to + 0.10°, determined on solution S.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.100 g of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve the contents of a vial of *ketoconazole impurity mixture CRS* (impurities C and D) in 1 mL of *methanol R*.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase:

— *mobile phase A*: *acetonitrile for chromatography R*, 3.4 g/L solution of *tetrabutylammonium hydrogen sulfate R* (5:95 *V/V*);

— *mobile phase B*: *acetonitrile for chromatography R*, 3.4 g/L solution of *tetrabutylammonium hydrogen sulfate R* (50:50 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	100 → 0	0 → 100
10 - 15	0	100

Flow rate 2 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 10 µL; inject *methanol R* as a blank.

Identification of impurities Use the chromatogram supplied with *ketoconazole impurity mixture CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities C and D.

Relative retention With reference to ketoconazole (retention time = about 6 min): impurity D = about 0.8; impurity C = about 0.9.

System suitability Reference solution (a):

— *resolution*: minimum 1.5 between the peaks due to impurities D and C.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity D by 1.4;

— for each impurity, use the concentration of ketoconazole in reference solution (b).

Limits:

— *impurity D*: maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 70 mL of a mixture of 1 volume of *anhydrous acetic acid R* and 7 volumes of *methyl ethyl ketone R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 26.57 mg of $C_{26}H_{28}Cl_2N_4O_4$.

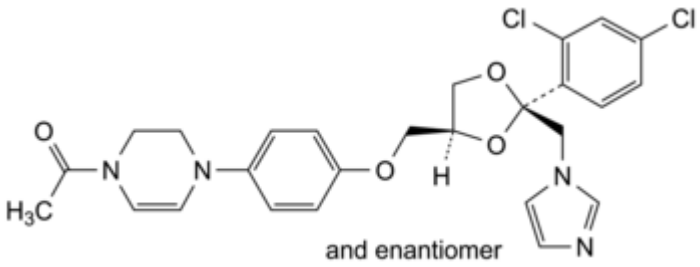
STORAGE

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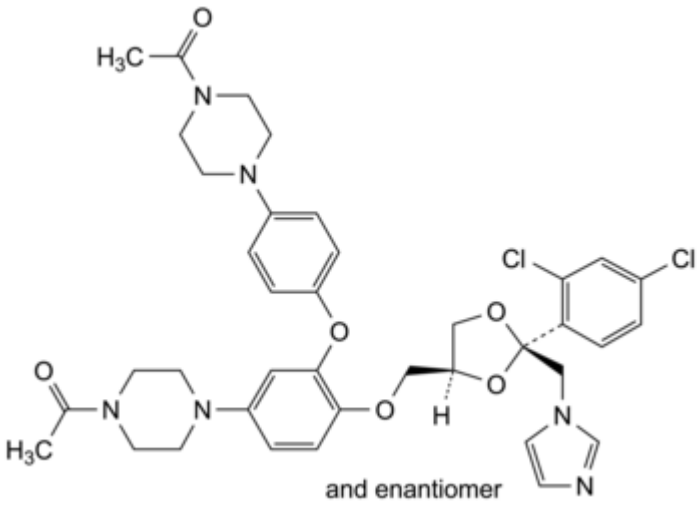
IMPURITIES

Specified impurities D.

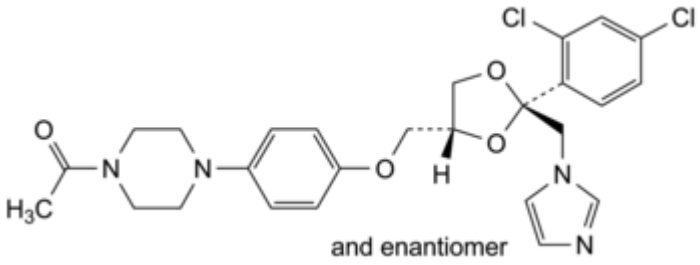
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, E.



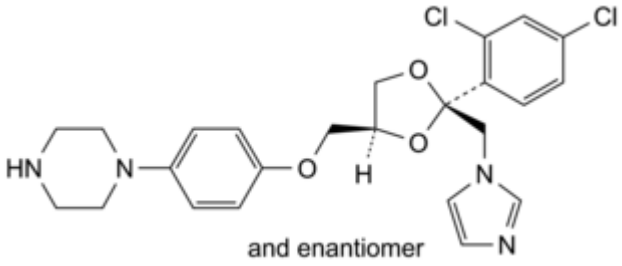
A. 1-[4-[4-[[(2*RS*,4*SR*)-2-(2,4-dichlorophenyl)-2-[(1*H*-imidazol-1-yl)methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1,2,3,4-tetrahydropyrazin-1-yl]ethan-1-one,



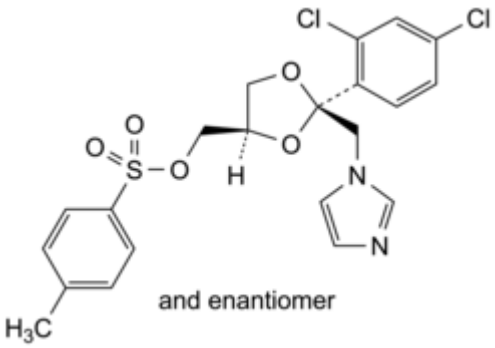
B. 1-[4-[4-[5-(4-acetylpiperazin-1-yl)-2-[[(2*RS*,4*SR*)-2-(2,4-dichlorophenyl)-2-[(1*H*-imidazol-1-yl)methyl]-1,3-dioxolan-4-yl]methoxy]phenoxy]phenyl]piperazin-1-yl]ethan-1-one,



C. 1-[4-[4-[[(2*RS*,4*RS*)-2-(2,4-dichlorophenyl)-2-[(1*H*-imidazol-1-yl)methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]piperazin-1-yl]ethan-1-one,



D. 1-[4-[[(2*RS*,4*SR*)-2-(2,4-dichlorophenyl)-2-[(1*H*-imidazol-1-yl)methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine,



E. [(2*RS*,4*SR*)-2-(2,4-dichlorophenyl)-2-[(1*H*-imidazol-1-yl)methyl]-1,3-dioxolan-4-yl]methyl 4-methylbenzene-1-sulfonate.

Ph Eur

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Ketoconazole Cream

General Notices

Action and use

Antifungal.

DEFINITION

Ketoconazole Cream contains Ketoconazole in a suitable basis.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of ketoconazole, $C_{26}H_{28}Cl_2N_4O_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

In the Assay, record the UV spectrum of the principal peak in the chromatograms obtained with solutions (1) and (2) with a diode array detector in the range 220 to 400 nm.

The UV spectrum of the principal peak in the chromatogram obtained with solution (1) is concordant with that of the peak in the chromatogram obtained with solution (2);

the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in low-actinic glassware. Store the solutions at 4°.

Solution A: 2 volumes of *water* and 98 volumes of *methanol*.

(1) Mix with the aid of ultrasound a quantity of the cream containing 30 mg of Ketoconazole with 50 mL of *methanol*, add 2 mL of *water*, allow to cool and dilute to 100 mL with *methanol*. Cool the solution in an ice-bath for 1 hour and filter.

(2) Dilute 1 volume of solution (1) to 500 volumes with solution A.

(3) 0.03% w/v of *ketoconazole impurity standard BPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer* (5 µm) (Waters XBridge BEH C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use a column temperature of 40°.

(e) Use an autosampler temperature of 4°.

(f) Use a detection wavelength of 230 nm.

(g) Inject 25 µL of each solution.

MOBILE PHASE

Mobile phase A 25 volumes of *acetonitrile* and 75 volumes of 0.05M *ammonium acetate*, adjusted to pH 6.0 with *glacial acetic acid*.

Mobile phase B 20 volumes of 0.05M *ammonium acetate*, adjusted to pH 6.0 with *glacial acetic acid* and 80 volumes of *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	85	15	isocratic
5-10	85→76	15→24	linear gradient
10-20	76→52	24→48	linear gradient
20-21	52→0	48→100	linear gradient
21-22	0	100	isocratic
22-23	0→85	100→15	linear gradient
23-28	85	15	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to ketoconazole (retention time about 17 minutes) are: impurity 2, about 0.35; impurity 1, about 0.40; impurity D, about 0.6.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to impurity 2 and impurity 1 is at least 1.5;

the *signal-to-noise ratio* of the peak due to impurity 2 is at least 40.

LIMITS

Identify any peak in solution (1) corresponding to impurity 2 using the chromatogram obtained with solution (3) and the chromatogram supplied with *ketoconazole impurity standard BPCRS* and multiply the area of this peak by a correction factor of 1.5.

In the chromatogram obtained with solution (1):

the area of any peak due to impurity 1 is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak due to impurity D is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in low-actinic glassware. Store the solutions at 4°.

Solution A: 2 volumes of *water* and 98 volumes of *methanol*.

(1) To a weighed quantity of the cream containing 30 mg of Ketoconazole add 50 mL of *methanol* and shake for 45 minutes, mix with the aid of ultrasound for 10 minutes, add 2 mL of *water,* allow to cool and dilute to 100 mL with *methanol*. Cool the solution at 5° for 1 hour, filter and dilute 1 volume of the resulting solution to 10 volumes with solution A.
(2) 0.003% w/v of *ketoconazole BPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

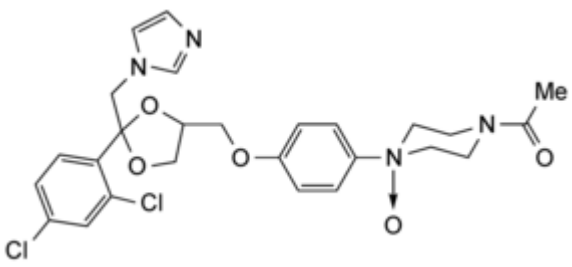
DETERMINATION OF CONTENT

Calculate the content of ketoconazole, $C_{26}H_{28}Cl_2N_4O_4$, in the cream from the chromatograms obtained and using the declared content of $C_{26}H_{28}Cl_2N_4O_4$ in *ketoconazole BPCRS*.

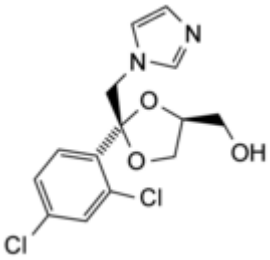
IMPURITIES

The impurities limited by the requirements of this monograph include impurity D listed under Ketoconazole and the following:

1. *rac*-4-acetyl-1-[4-({(2*R*,4*S*)-2-(2,4-dichlorophenyl)-2-[(1*H*-imidazol-1-yl)methyl]-1,3-dioxolan-4-yl}methoxy)phenyl]piperazine N^1-oxide;



2. *rac*-{(2*R*,4*S*)-2-(2,4-dichlorophenyl)-2-[(1*H*-imidazol-1-yl)methyl]-1,3-dioxolan-4-yl}methanol.



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Ketoconazole Shampoo

General Notices

Action and use

Antifungal.

DEFINITION

Ketoconazole Shampoo contains Ketoconazole in a suitable basis.

The shampoo complies with the requirements stated under Liquids for Cutaneous Application and with the following requirements.

Content of ketoconazole, $C_{26}H_{28}Cl_2N_4O_4$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

In the Assay, record the UV spectrum of the principal peak in the chromatograms obtained with solutions (1) and (2) with a diode array detector in the range 220 to 400 nm.

The UV spectrum of the principal peak in the chromatogram obtained with solution (1) is concordant with that of the peak in the chromatogram obtained with solution (2);

the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in low-actinic glassware. Store the solutions at 4°.

Solution A: 15 volumes of mobile phase A and 85 volumes of *methanol*.

(1) Shake a quantity of the shampoo containing 50 mg of Ketoconazole with 50 mL of *methanol*, add 15 mL of mobile phase A, allow to cool and dilute to 100 mL with *methanol*.
(2) Dilute 1 volume of solution (1) to 100 volumes with solution A.
(3) 0.03% w/v of *ketoconazole impurity standard BPCRS* in solution A.
(4) Dilute 1 volume of solution (2) to 10 volumes with solution A.

CHROMATOGRAPHIC CONDITIONS

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 3.0 mm) packed with *end-capped phenylsilyl silica gel for chromatography* (5 µm) (Waters XBridge BEH Phenyl is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 0.6 mL per minute.

(d) Use a column temperature of 45°.

(e) Use an autosampler temperature of 4°.

(f) Use a detection wavelength of 230 nm.

(g) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A Dissolve 1.42 g of *anhydrous disodium hydrogen orthophosphate* and 3.1 g of *anhydrous sodium dihydrogen orthophosphate* in 1000 mL of *water*.

Mobile phase B *acetonitrile*.

Mobile phase C *propan-2-ol R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Mobile phase C (% v/v)	Comment
0-5	70	24	6	isocratic
5-35	70→30	24→64	6	linear gradient
35-40	30	64	6	isocratic
40-45	30→70	64→24	6	linear gradient
45-55	70	24	6	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to ketoconazole (retention time about 17 minutes) are: impurity 2, about 0.5; impurity 1, about 0.6; impurity D, about 0.7; impurity 3, about 0.78.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to impurity 2 and impurity 1 is at least 5.0;

the *signal-to-noise ratio* of the peak due to impurity 2 is at least 40.

LIMITS

Identify any peak in solution (1) corresponding to impurity 2 using the chromatogram obtained with solution (3) and the chromatogram supplied with *ketoconazole impurity standard BPCRS* and multiply the area of this peak by a correction factor of 1.5.

In the chromatogram obtained with solution (1):

the area of any peak due to impurity D is not greater than 0.7 times the area of the principal peak in the chromatogram obtained with solution (2) (0.7%);

the area of any peak due to impurity 2 is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak due to impurity 3 is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the sum of the areas of the *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in low-actinic glassware. Store the solutions at 4°.

Solution A: 15 volumes of mobile phase A and 85 volumes of *methanol*.

(1) Shake a weighed quantity of the shampoo containing 50 mg of Ketoconazole with 50 mL of *methanol*, add 15 mL of mobile phase A, allow to cool and dilute to 100 mL with *methanol*. Dilute 1 volume of the resulting solution to 10 volumes solution A.
(2) Dissolve 50 mg of *ketoconazole BPCRS* in 100 mL of *methanol* and dilute 1 volume of the resulting solution to 10 volumes with solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 3.0 mm) packed with *end-capped phenylsilyl silica gel for chromatography* (5 µm) (Waters XBridge BEH Phenyl is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 0.6 mL per minute.
(d) Use a column temperature of 35°.
(e) Use an autosampler temperature of 4°.
(f) Use a detection wavelength of 230 nm.
(g) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A Dissolve 1.42 g of *anhydrous disodium hydrogen orthophosphate* and 3.1 g of *anhydrous sodium dihydrogen orthophosphate* in 1000 mL of *water*.

Mobile phase B *acetonitrile*.

Mobile phase C *propan-2-ol R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Mobile phase C (% v/v)	Comment
0-3	55	35	10	isocratic
3-13	55→37	35→53	10	linear gradient
13-18	37	53	10	isocratic
18-20	37→55	53→35	10	linear gradient
20-23	55	35	10	re-equilibration

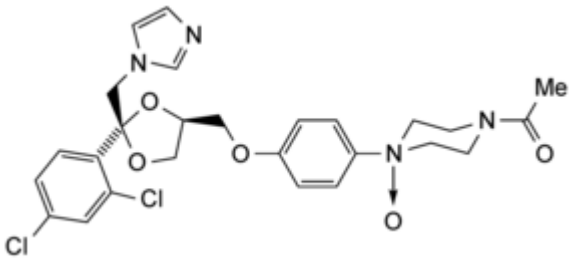
DETERMINATION OF CONTENT

Calculate the content of ketoconazole, $C_{26}H_{28}Cl_2N_4O_4$, in the shampoo from the chromatograms obtained and using the declared content of $C_{26}H_{28}Cl_2N_4O_4$ in *ketoconazole BPCRS*.

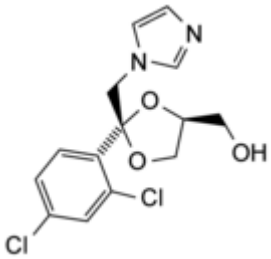
IMPURITIES

The impurities limited by the requirements of this monograph include impurity D listed under Ketoconazole and the following:

1. *rac*-4-acetyl-1-[4-({(2*R*,4*S*)-2-(2,4-dichlorophenyl)-2-[(1*H*-imidazol-1-yl)methyl]-1,3-dioxolan-4-yl}methoxy)phenyl]piperazine N^1-oxide.



2. *rac*-{(2*R*,4*S*)-2-(2,4-dichlorophenyl)-2-[(1*H*-imidazol-1-yl)methyl]-1,3-dioxolan-4-yl}methanol.



3. Unknown structure

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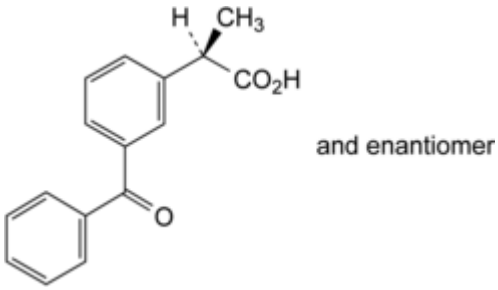
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This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Ketoprofen

General Notices

(Ph. Eur. monograph 0922)



and enantiomer

$C_{16}H_{14}O_3$ 254.3 *22071-15-4*

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

Preparations

Ketoprofen Capsules

Ketoprofen Gel

Ph Eur

DEFINITION

(2*RS*)-2-(3-Benzoylphenyl)propanoic acid.

Content

99.0 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in acetone, in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

First identification: C.

Second identification: A, B, D.

A. Melting point (2.2.14): 94 °C to 97 °C.

B. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 50.0 mg in *ethanol (96 per cent) R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of this solution to 50.0 mL with *ethanol (96 per cent) R*.

Spectral range 230-350 nm.

Absorption maximum At 255 nm.

Specific absorbance at the absorption maximum 615 to 680.

C. Infrared absorption spectrophotometry (2.2.24).

Comparison *ketoprofen CRS*.

D. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *acetone R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 10 mg of *ketoprofen CRS* in *acetone R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of *indometacin CRS* in *acetone R* and dilute to 10 mL with the same solvent. To 1 mL of this solution add 1 mL of reference solution (a).

Plate *TLC silica gel GF_{254} plate R*.

Mobile phase *glacial acetic acid R*, *methylene chloride R*, *acetone R* (1:49:50 *V/V/V*).

Application 10 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated principal spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (2.2.2, Method II).

Dissolve 1.0 g in *acetone R* and dilute to 10 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use*.

Test solution Dissolve 20.0 mg of the substance to be examined in the mobile phase and dilute to 20.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 50.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5.0 mg of *ketoprofen impurity A CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (c) Dissolve 5.0 mg of *ketoprofen impurity C CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (d) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. To 1.0 mL of this solution add 1.0 mL of reference solution (b).

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 2 volumes of freshly prepared *phosphate buffer solution pH 3.5 R*, 43 volumes of *acetonitrile R* and 55 volumes of *water R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 233 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity C.

Run time 7 times the retention time of ketoprofen.

Relative retention With reference to ketoprofen (retention time = about 7 min): impurity C = about 0.3; impurity E = about 0.69; impurity B = about 0.73; impurity D = about 1.35; impurity A = about 1.5; impurity F = about 2.0.

System suitability Reference solution (d):

— *resolution*: minimum 7.0 between the peaks due to ketoprofen and impurity A.

Limits:

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *impurity C*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent);

— *impurities B, D, E, F*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *sum of impurities other than A and C*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying at 60 °C at a pressure not exceeding 0.67 kPa.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

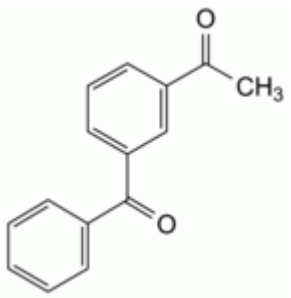
Dissolve 0.200 g in 25 mL of *ethanol (96 per cent) R*. Add 25 mL of *water R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M sodium hydroxide* is equivalent to 25.43 mg of $C_{16}H_{14}O_3$.

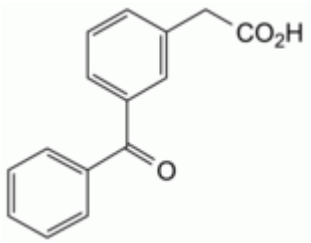
IMPURITIES

Specified impurities *A, B, C, D, E, F*.

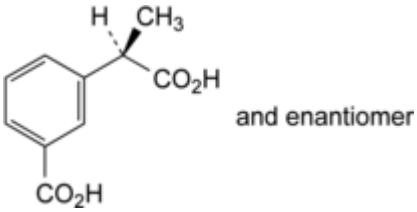
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *G, H, I, J, K, L*.



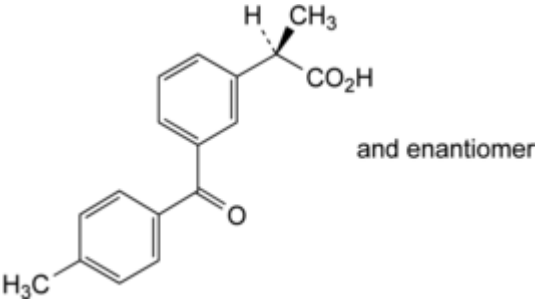
A. 1-(3-benzoylphenyl)ethanone,



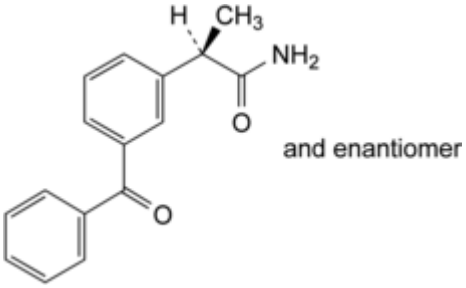
B. (3-benzoylphenyl)acetic acid,



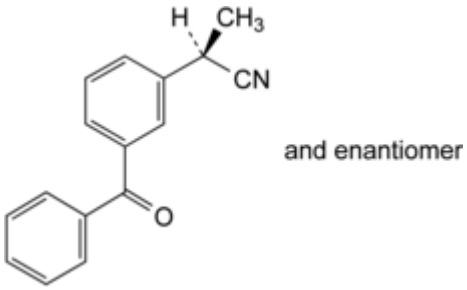
C. 3-[(1*RS*)-1-carboxyethyl]benzoic acid,



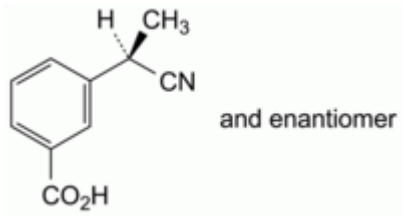
D. (2*RS*)-2-[3-(4-methylbenzoyl)phenyl]propanoic acid,



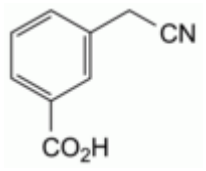
E. (2*RS*)-2-(3-benzoylphenyl)propanamide,



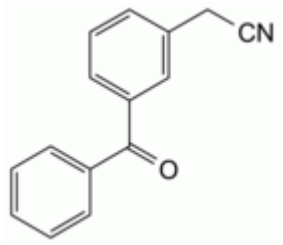
F. (2*RS*)-2-(3-benzoylphenyl)propanenitrile,



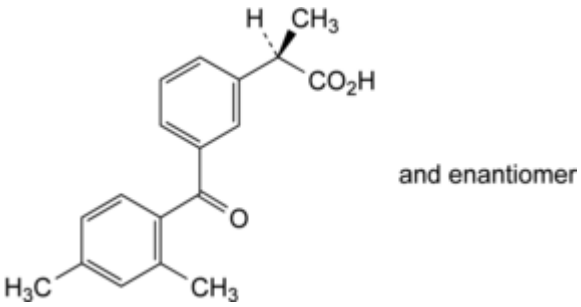
G. 3-[(1*RS*)-1-cyanoethyl]benzoic acid,



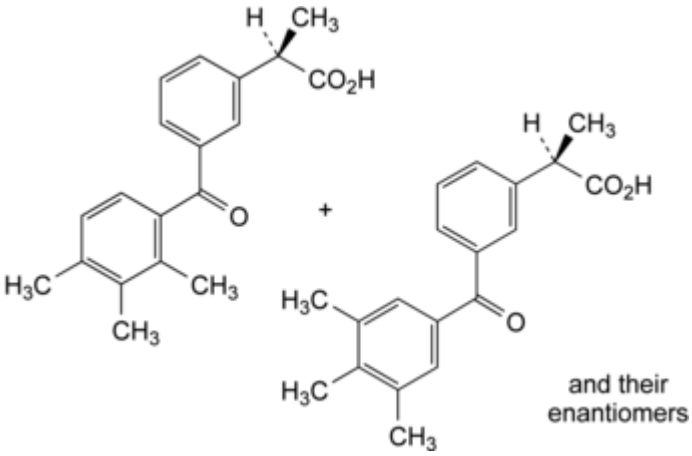
H. 3-(cyanomethyl)benzoic acid,



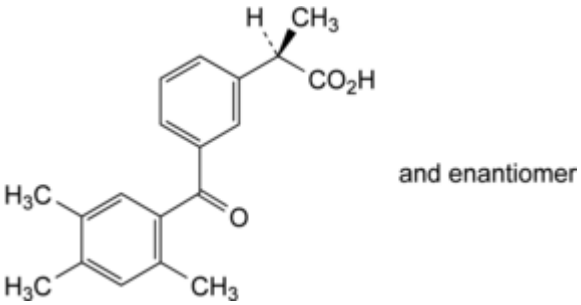
I. (3-benzoylphenyl)ethanenitrile,



J. (2*RS*)-2-[3-(2,4-dimethylbenzoyl)phenyl]propanoic acid,



K. mixture of (2*RS*)-2-[3-(2,3,4-trimethylbenzoyl)phenyl]propanoic acid and (2*RS*)-2-[3-(3,4,5-trimethylbenzoyl)phenyl]propanoic acid,



L. (2*RS*)-2-[3-(2,4,5-trimethylbenzoyl)phenyl]propanoic acid.

Ph Eur

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Ketoprofen Capsules

General Notices

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

DEFINITION

Ketoprofen Capsules contain Ketoprofen.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of ketoprofen, $C_{16}H_{14}O_3$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

Shake a quantity of the contents of the capsules containing 0.5 g of Ketoprofen with 50 mL of *chloroform* for 5 minutes, filter, evaporate to dryness using a rotary evaporator and induce crystallisation by prolonged scratching of the side of the container with a glass rod. The *infrared absorption spectrum* of the crystals, Appendix II A, is concordant with the *reference spectrum* of ketoprofen *(RS 198)*.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of a *phosphate buffer* prepared by dissolving 1.46 g of *potassium dihydrogen orthophosphate* and 20.06 g of *disodium hydrogen orthophosphate* in sufficient *water* to produce 1000 mL, adjusting the pH to 7.5 if necessary with *orthophosphoric acid*, at a temperature of 37 ± 0.5°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium, filter and dilute the filtrate with sufficient of the dissolution medium to give a solution expected to contain about 0.001% w/v of Ketoprofen, at the maximum at 260 nm, Appendix II B, using the dissolution medium in the reference cell

DETERMINATION OF CONTENT

Calculate the total content of ketoprofen, $C_{16}H_{14}O_3$, in the medium taking 662 as the value of A(1%, 1 cm) at the maximum at 260 nm.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following freshly prepared solutions.

Solvent A A mixture of 40 volumes of *acetonitrile* and 60 volumes of *water*.

(1) Shake a quantity of the contents of the capsules containing 0.1 g of Ketoprofen with 100 mL of solvent A, filter and use the filtrate.

(2) Dilute 1 volume of solution (1) with 50 volumes of solvent A. Dilute 1 volume of this solution to 10 volumes with solvent A.

(3) 0.0002% w/v of *ketoprofen impurity C EPCRS* in solvent A.

(4) 0.0003% w/v of *ketoprofen impurity A EPCRS* in solvent A.

(5) Dilute 1 volume of solution (1) to 100 volumes with solvent A. To 1 volume of this solution add 1 volume of solution (4).

(6) Dilute 1 volume of solution (2) to 10 volumes with solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use ambient column temperature

(d) Use a detection wavelength of 233 nm.

(e) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for seven times the retention time of ketoprofen.

When the chromatograms are recorded using the prescribed conditions, the relative retentions with reference to ketoprofen (retention time about 8 minutes) are: impurity A, about 0.3 and impurity C, about 1.6.

MOBILE PHASE

2 volumes of freshly prepared *phosphate buffer pH 3.5*, 43 volumes of *acetonitrile* and 55 volumes of *water*.

When the chromatograms are recorded using the prescribed conditions, the relative retentions with reference to ketoprofen (retention time about 8 minutes) are: Impurity C, about 0.3 and impurity A, about 1.6.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5), the *resolution* between the peaks due to ketoprofen and impurity A is at least 7.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the area of any peak corresponding to impurity A is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (0.3%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* other than those due to the two named impurities is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (6) (0.02%).

ASSAY

Shake a quantity of the mixed contents of 20 capsules containing 50 mg of Ketoprofen for 10 minutes with 300 mL of *methanol (75%)*, mix and dilute to 500 mL with *methanol (75%)*. Allow to stand, dilute 5 mL of the supernatant liquid to 100 mL with *methanol (75%)* and measure the *absorbance* of the resulting solution at the maximum at 258 nm, Appendix II B. Calculate the content of $C_{16}H_{14}O_3$ taking 662 as the value of A(1%, 1 cm) at the maximum at 258 nm.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A and C listed under Ketoprofen.

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Ketoprofen Gel

General Notices

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

DEFINITION

Ketoprofen Gel is a solution of Ketoprofen in a suitable water-miscible basis.

The gel complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of ketoprofen, $C_{16}H_{14}O_3$

92.5 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the gel containing 60 mg of Ketoprofen with 10 mL of *dichloromethane* and filter. Evaporate the filtrate to dryness under nitrogen. Dry the residue at 60° for 1 hour. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of ketoprofen (*RS 484*).

TESTS

Acidity or alkalinity

pH of a 1% w/v dispersion of the gel in *carbon dioxide-free water*, 5.0 to 7.5, Appendix V L.

Ketoprofen ethyl ester

In the Assay, in the chromatogram obtained with solution (1) the area of any peak corresponding to ketoprofen ethyl ester is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (4.0%).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

(1) Dilute a quantity of the gel containing 10 mg of Ketoprofen with sufficient *methanol* to produce a solution containing 0.01% w/v of Ketoprofen.

(2) Dilute 1 volume of solution (1) to 100 volumes with *methanol*.

(3) 0.00002% w/v of *ketoprofen impurity A EPCRS* in the mobile phase.

(4) 0.00002% w/v of *ketoprofen impurity C EPCRS* in the mobile phase.

(5) 0.0005% w/v of *ketoprofen BPCRS* and 0.0001% w/v of *ketoprofen impurity A EPCRS* in *methanol*.

(6) Dilute 1 volume of solution (2) to 10 volumes with methanol.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) with a specific surface area of 350 m^2/g and a pore size of 10 nm (Nucleosil 100 C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 233 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 7 times the retention time of ketoprofen.

MOBILE PHASE

2 volumes of freshly prepared *phosphate buffer solution pH 3.5*, 43 volumes of *acetonitrile* and 55 volumes of *water*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to ketoprofen (retention time about 8 minutes) are: impurity C, about 0.3; impurity E, about 0.7; impurity B, about 0.8; impurity D, about 1.5; impurity A, about 1.6; impurity F, about 2.3.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5), the *resolution* between the peaks due to ketoprofen and impurity A is at least 7.0.

LIMITS

Use the chromatogram obtained with solution (3) to identify the peak due to impurity A; use the chromatogram obtained with solution (4) to identify the peak due to impurity C.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (3) (0.5%);

the area of any peak corresponding to impurity C is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (4) (0.5%);

the area of any peak corresponding to impurity B, D, E or F is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* excluding impurities A and C is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (2.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (6) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

270 mL of *acetonitrile* and 550 mL of a 0.5% w/v solution of *ammonium acetate* (solution A).

(1) Shake a weighed quantity of the gel containing 10 mg of Ketoprofen with 50 mL of *methanol* for 15 minutes, centrifuge the mixture for 5 minutes, and dilute 25 mL of the supernatant liquid with sufficient solution A to produce 100 mL.
(2) Add 19 mL of *methanol* to 5 mL of a 0.1% w/v solution of *ketoprofen BPCRS* in *methanol*, add sufficient solution A to produce 100 mL and mix.
(3) Add 19 mL of *methanol* to 5 mL of a 0.04% w/v solution of *ketoprofen ethyl ester BPCRS* in *methanol*, add sufficient solution A to produce 100 mL and mix.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 254 nm.
(f) Inject 20 µL of each solution.
(g) Allow the chromatography to proceed for 8 times the retention time of ketoprofen.

MOBILE PHASE

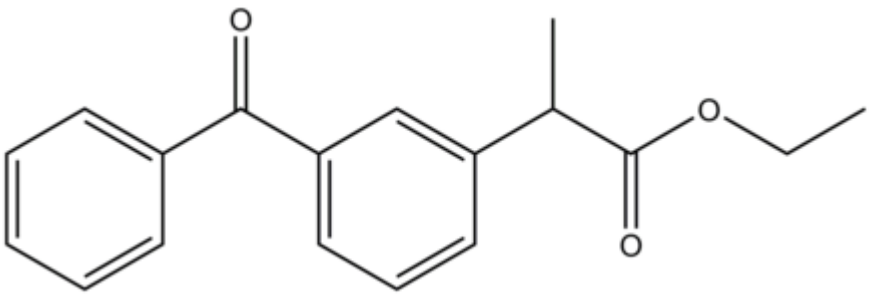
450 volumes of a solution containing 40% v/v of *methanol* and 60% v/v of *acetonitrile* and 550 volumes of a 0.5% w/v solution of *ammonium acetate*, adjusted to pH 5.9 by the addition of 10% w/w *nitric acid*.

DETERMINATION OF CONTENT

Calculate the content of $C_{16}H_{14}O_3$ in the gel using the declared content of $C_{16}H_{14}O_3$ in *ketoprofen BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Ketoprofen and:



1. ethyl 2-(3-benzoylphenyl)propionate (ketoprofen ethyl ester)

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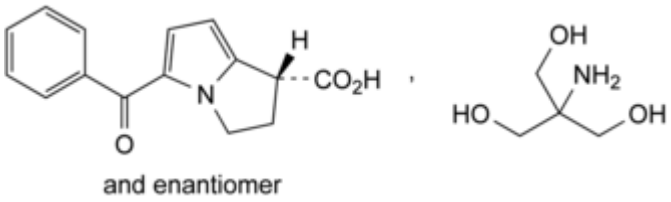
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Ketorolac Trometamol

General Notices

(Ph. Eur. monograph 1755)



$C_{19}H_{24}N_2O_6$ 376.4 *74103-07-4*

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

Ph Eur

DEFINITION

2-Amino-2-(hydroxymethyl)propane-1,3-diol (1*RS*)-5-benzoyl-2,3-dihydro-1*H*-pyrrolizine-1-carboxylate.

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water and in methanol, slightly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *ketorolac trometamol CRS*.

TESTS

Solution S

Dissolve 0.75 g in *carbon dioxide-free water R* and dilute to 25.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*).

pH (*2.2.3*)

5.7 to 6.7.

Dilute 5 mL of solution S to 15 mL with *carbon dioxide-free water R*.

Absorbance (*2.2.25*)

Maximum 0.10, determined at 430 nm for solution S.

Related substances

Liquid chromatography (*2.2.29*). *Protect the solutions from bright light.*

Solvent mixture *tetrahydrofuran R*, *water R* (30:70 *V/V*).

Test solution Dissolve 20 mg of the substance to be examined in the solvent mixture and dilute to 50 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 10.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 100.0 mL with the solvent mixture.

Reference solution (b) Dissolve 2 mg of *ketorolac trometamol for peak identification CRS* (containing impurities A, B, C and D) in 5 mL of the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase Mix 30 volumes of *tetrahydrofuran R* with 70 volumes of a solution prepared as follows: dissolve 5.75 g of *ammonium dihydrogen phosphate R* in 900 mL of *water R*, adjust to pH 3.0 with *phosphoric acid R* and dilute to 1000 mL with *water R*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 313 nm.

Injection 10 µL.

Run time 3 times the retention time of ketorolac.

Identification of impurities Use the chromatogram supplied with *ketorolac trometamol for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C and D.

Relative retention With reference to ketorolac (retention time = about 10 min): impurity C = about 0.5; impurity A = about 0.6; impurity D = about 0.7; impurity B = about 0.9.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurity B and ketorolac.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.67; impurity B = 0.52; impurity C = 2.2;

— *impurities A, B, C, D*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C for 3 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in 60 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 37.64 mg of $C_{19}H_{24}N_2O_6$.

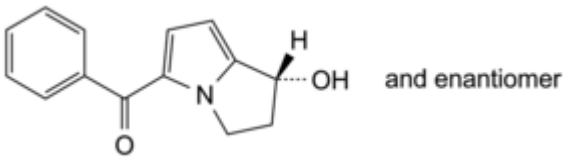
STORAGE

Protected from light.

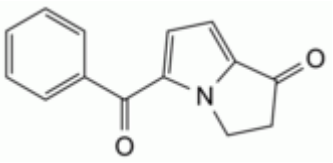
IMPURITIES

Specified impurities *A, B, C, D.*

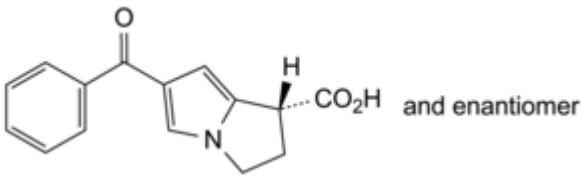
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) E, F, G, H, I, J.



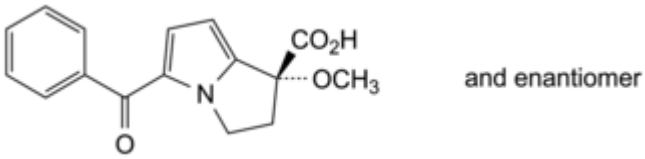
A. (1*RS*)-5-benzoyl-2,3-dihydro-1*H*-pyrrolizin-1-ol,



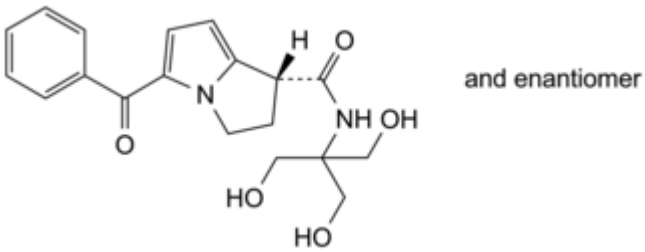
B. 5-benzoyl-2,3-dihydro-1*H*-pyrrolizin-1-one,



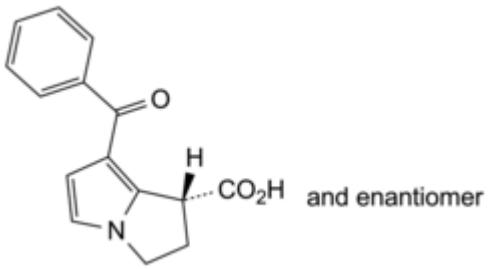
C. (1*RS*)-6-benzoyl-2,3-dihydro-1*H*-pyrrolizine-1-carboxylic acid,



D. (1*RS*)-5-benzoyl-1-methoxy-2,3-dihydro-1*H*-pyrrolizine-1-carboxylic acid,

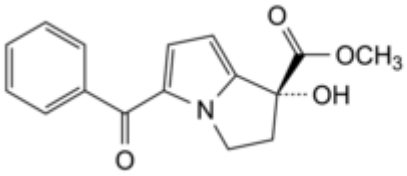


E. (1*RS*)-5-benzoyl-*N*-[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]-2,3-dihydro-1*H*-pyrrolizine-1-carboxamide,



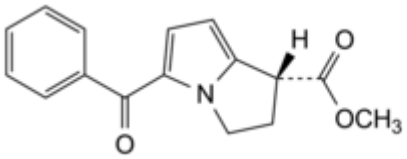
and enantiomer

F. (1*RS*)-7-benzoyl-2,3-dihydro-1*H*-pyrrolizine-1-carboxylic acid,



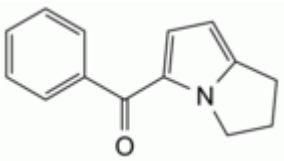
and enantiomer

G. methyl (1*RS*)-5-benzoyl-1-hydroxy2,3-dihydro-1*H*-pyrrolizine-1-carboxylate,

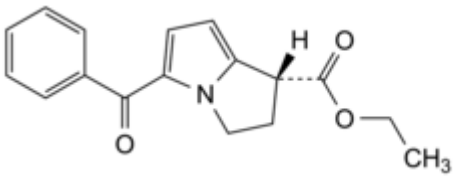


and enantiomer

H. methyl (1*RS*)-5-benzoyl-2,3-dihydro-1*H*-pyrrolizine-1-carboxylate,



I. phenyl(2,3-dihydro-1*H*-pyrrolizin-5-yl)methanone,



and enantiomer

J. ethyl (1*RS*)-5-benzoyl-2,3-dihydro-1*H*-pyrrolizine-1-carboxylate.

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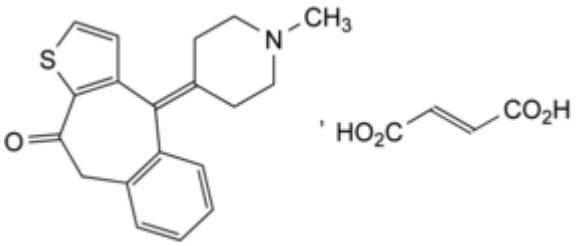
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Ketotifen Fumarate

General Notices

(Ketotifen Hydrogen Fumarate, Ph. Eur. monograph 1592)



$C_{23}H_{23}NO_5S$ 425.5 *34580-14-8*

Action and use

Histamine H_1 receptor antagonist.

Ph Eur

DEFINITION

4-(1-Methylpiperidin-4-ylidene)-4,9-dihydro-10*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-10-one hydrogen (*E*)-butenedioate.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or brownish-yellow, fine, crystalline powder.

Solubility

Sparingly soluble in water, slightly soluble in methanol, practically insoluble in heptane.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *ketotifen hydrogen fumarate CRS*.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_4, BY_4 or B_4 (2.2.2, Method II).

Dissolve 0.2 g in *methanol R* and dilute to 10 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light.*

Solvent mixture *methanol R*, *water R* (50:50 *V/V*).

Test solution Dissolve 30.0 mg of the substance to be examined in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve the contents of a vial of *ketotifen impurity G CRS* in 1.0 mL of a solution prepared as follows: mix 1.0 mL of the test solution with 9.0 mL of the solvent mixture. Sonicate until dissolution of impurity G is complete.

Reference solution (c) Dissolve 5 mg of *ketotifen for peak identification CRS* (containing impurity A) in the solvent mixture and dilute to 5.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.0 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: mix 175 µL of *triethylamine R* and 500 mL of *water R*;

— *mobile phase B*: mix 175 µL of *triethylamine R* and 500 mL of *methanol R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 12	40	60
12 - 20	40 → 10	60 → 90
20 - 25	10	90

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 297 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *ketotifen for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity A; use the chromatogram obtained with reference solution (b) to identify the peak due to impurity G.

Relative retention With reference to ketotifen (retention time = about 11 min): fumaric acid = about 0.1; impurity G = about 0.8; impurity A = about 1.9.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurity G and ketotifen.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity G by 1.4;

— *impurity A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurity G*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent); disregard the peak due to fumaric acid.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

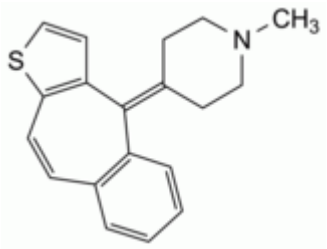
Dissolve 0.350 g in a mixture of 30 mL of *acetic anhydride R* and 30 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 42.55 mg of $C_{23}H_{23}NO_5S$.

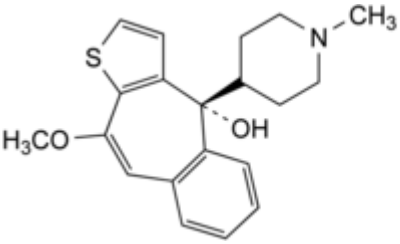
IMPURITIES

Specified impurities *A, G.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D, E, F.*

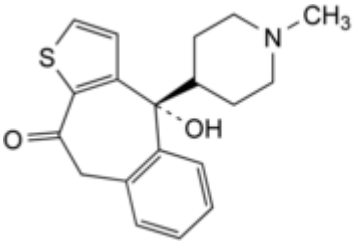


A. 4-(4*H*-benzo[4,5]cycloheptа[1,2-*b*]thiophen-4-ylidene)-1-methylpiperidine,



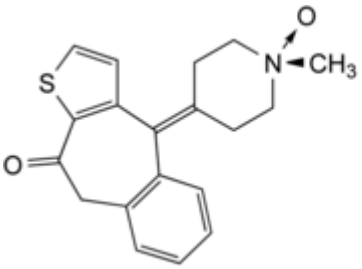
and enantiomer

B. (4*RS*)-10-methoxy-4-(1-methylpiperidin-4-yl)-4*H*-benzo[4,5]cycloheptа[1,2-*b*]thiophen-4-ol,



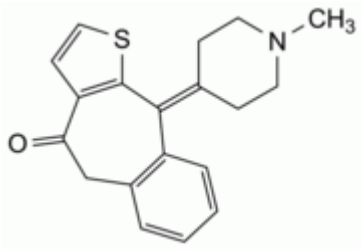
and enantiomer

C. (4*RS*)-4-hydroxy-4-(1-methylpiperidin-4-yl)-4,9-dihydro-10*H*-benzo[4,5]cycloheptа[1,2-*b*]thiophen-10-one,

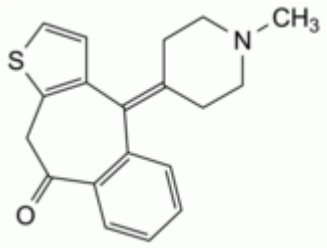


and enantiomer

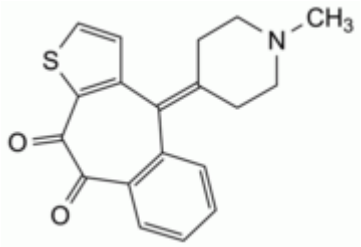
D. 4-[(R_aS_a)-1-methylpiperidin-4-ylidene]-4,9-dihydro-10*H*-benzo[4,5]cycloheptа[1,2-*b*]thiophen-10-one *N*-oxide (ketotifen *N*-oxide),



E. 10-(1-methylpiperidin-4-ylidene)-5,10-dihydro-4*H*-benzo[5,6]cyclohepta[1,2-*b*]thiophen-4-one,



F. 4-(1-methylpiperidin-4-ylidene)-4,10-dihydro-9*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-9-one,



G. 4-(1-methylpiperidin-4-ylidene)-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-9,10-dione.

Ph Eur

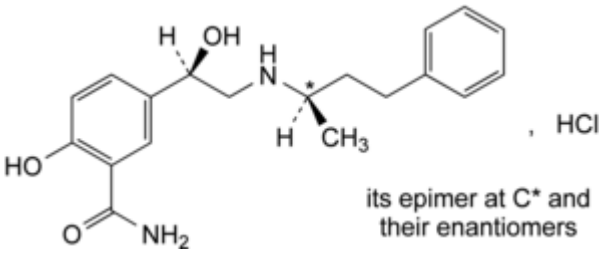
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Labetalol Hydrochloride

General Notices

(Ph. Eur. monograph 0923)



$C_{19}H_{25}ClN_2O_3$ 364.9 *32780-64-6*

Action and use

Alpha-and beta-adrenoceptor antagonist.

Preparations

Labetalol Injection

Labetalol Tablets

Ph Eur

DEFINITION

Mixture of 4 stereoisomers of 2-hydroxy-5-[(1Ξ)-1-hydroxy-2-[[(2Ξ)-4-phenylbutan-2-yl]amino]ethyl]benzamide hydrochloride.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Sparingly soluble in water and in ethanol (96 per cent), practically insoluble in methylene chloride.

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IDENTIFICATION

First identification: A, C, E.

Second identification: A, B, D, E.

A. Optical rotation (2.2.7): -0.05° to + 0.05°, determined on solution S (see Tests).

B. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 25.0 mg in a 10.3 g/L solution of *hydrochloric acid R* and dilute to 250.0 mL with the same solution.

Spectral range 230-350 nm.

Absorption maximum 302 nm.

Specific absorbance at the absorption maximum 83 to 88.

C. Infrared absorption spectrophotometry (2.2.24).

Comparison *labetalol hydrochloride CRS*.

D. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in 1 mL of *ethanol (96 per cent) R*.

Reference solution (a) Dissolve 10 mg of *labetalol hydrochloride CRS* in 1 mL of *ethanol (96 per cent) R*.

Reference solution (b) Dissolve 10 mg of *labetalol hydrochloride CRS* and 10 mg of *propranolol hydrochloride CRS* in *ethanol (96 per cent) R* and dilute to 5 mL with the same solvent.

Plate *TLC octadecylsilyl silica gel F_{254} plate R*.

Mobile phase *perchloric acid R*, *water R*, *methanol R* (0.5:50:80 *V/V/V*).

Application 2 µL.

Development Place the plate in a chromatographic tank immediately after the addition of the mobile phase, close the tank and develop over 3/4 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

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E. It gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 0.50 g in carbon dioxide-free water R and dilute to 50 mL with the same solvent. *Solution S must be freshly prepared.*

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than intensity 6 of the range of reference solutions of the most appropriate colour (2.2.2, Method II).

pH (2.2.3)

4.0 to 5.0 for solution S.

Diastereoisomer ratio

Gas chromatography (2.2.28).

Test solution Dissolve 2.0 mg of the substance to be examined in 1.0 mL of a 12.0 g/L solution of butylboronic acid R in anhydrous pyridine R and allow to stand for 20 min.

Column:

— *material*: glass;

— *size*: *l* = 1.5 m, Ø = 4 mm;

— *stationary phase*: silanised diatomaceous earth for gas chromatography R (125-150 µm) impregnated with 3 per cent *m/m* of phenyl(50)methyl(50)polysiloxane R.

Carrier gas nitrogen for chromatography R.

Flow rate 40 mL/min.

Temperature:

— *column, injection port and detector*: 300 °C.

Detection Flame ionisation.

Injection 2 µL.

System suitability:

— the height of the trough separating the 2 peaks due to the pairs of diastereoisomers is less than 5 per cent of the full scale of the recorder.

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Limit:

— *each pair of diastereoisomers*: for the area of each peak, 45 per cent to 55 per cent of the total area of the 2 peaks.

Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 25.0 mg of the substance to be examined in mobile phase A and dilute to 10.0 mL with mobile phase A.

Test solution (b) Dilute 1.0 mL of test solution (a) to 50.0 mL with mobile phase A.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (b) Dilute 2 mL of test solution (a) to 100 mL with mobile phase A (solution A). Dissolve 5 mg of *labetalol impurity A CRS* in 50 mL of mobile phase B and dilute to 100 mL with solution A.

Reference solution (c) Dissolve 25.0 mg of *labetalol hydrochloride CRS* in mobile phase A and dilute to 10.0 mL with mobile phase A. Dilute 1.0 mL of the solution to 50.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped ethylene-bridged octadecylsilyl silica gel for chromatography (hybrid material) R* (3.5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: *phosphoric acid R*, *water for chromatography R* (0.1:99.9 *V/V*);

— *mobile phase B*: *acetonitrile for chromatography R*, mobile phase A (50:50 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	100	0
5 - 40	100 → 0	0 → 100
40 - 45	0	100

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 20 µL of test solution (a) and reference solutions (a) and (b).

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Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A.

Relative retention With reference to labetalol (retention time = about 22 min): impurity A = about 1.1.

System suitability Reference solution (b):

— *resolution*: minimum 4.5 between the peaks due to labetalol and impurity A.

Calculation of percentage contents:

— for each impurity, use the concentration of labetalol hydrochloride in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.05 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.03 per cent.

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C at a pressure not exceeding 0.7 kPa.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Mobile phase Mobile phase A, mobile phase B (45:55 *V/V*).

Injection Test solution (b) and reference solution (c).

Run time Twice the retention time of labetalol.

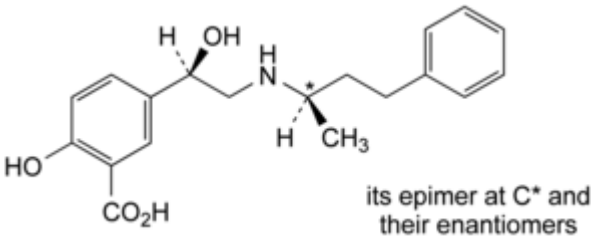
Retention time Labetalol = about 2 min.

Calculate the percentage content of $C_{19}H_{25}ClN_2O_3$ taking into account the assigned content of *labetalol hydrochloride CRS*.

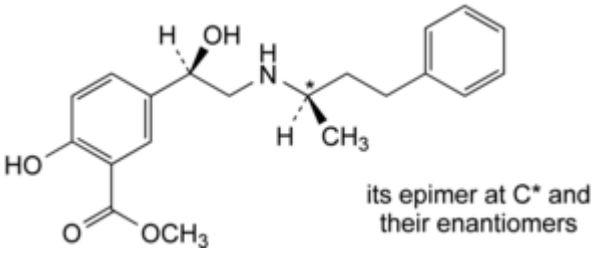
IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, E, F, G.*

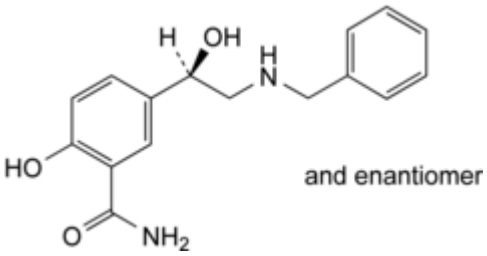
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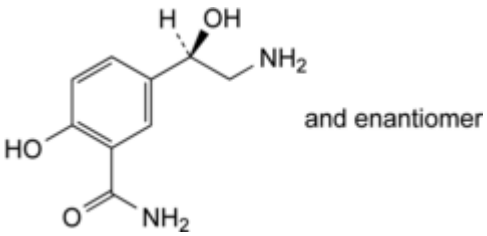
A. mixture of 4 stereoisomers of 2-hydroxy-5-[(1Ξ)-1-hydroxy-2-[[(2Ξ)-4-phenylbutan-2-yl]amino]ethyl]benzoic acid,



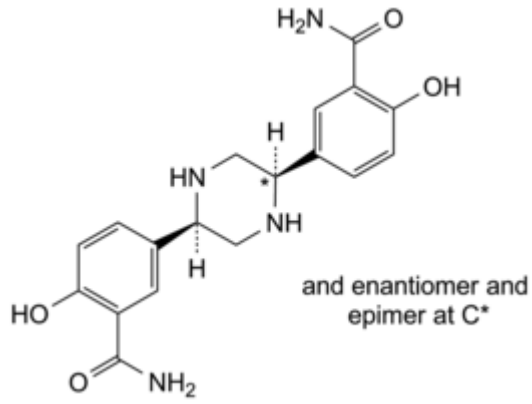
B. mixture of 4 stereoisomers of methyl 2-hydroxy-5-[(1Ξ)-1-hydroxy-2-[[(2Ξ)-4-phenylbutan-2-yl]amino]ethyl]benzoate,



C. 5-[(1*RS*)-2-(benzylamino)-1-hydroxyethyl]-2-hydroxybenzamide,

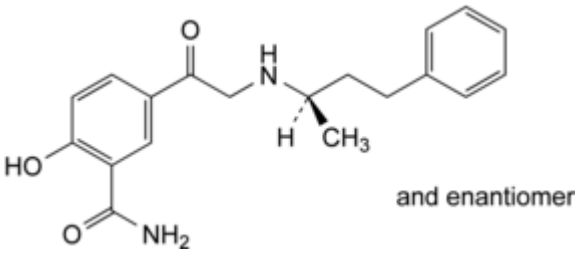


D. 5-[(1*RS*)-2-amino-1-hydroxyethyl]-2-hydroxybenzamide,



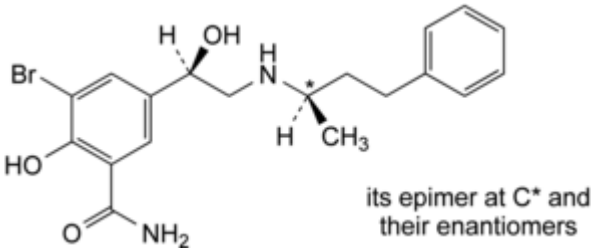
E. mixture of 3 stereoisomers of 5,5′-[(2Ξ,5Ξ)-piperazine-2,5-diyl]bis(2-hydroxybenzamide),

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and enantiomer

F. 2-hydroxy-5-[2-[[(2*RS*)-4-phenylbutan-2-yl]amino]acetyl]benzamide,



its epimer at C* and their enantiomers

G. mixture of 4 stereoisomers of 3-bromo-2-hydroxy-5-[(1Ξ)-1-hydroxy-2-[[(2Ξ)-4-phenylbutan-2-yl]amino]ethyl]benzamide.

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Labetalol Injection

General Notices

Action and use

Alpha- and beta-adrenoceptor antagonist.

DEFINITION

Labetalol Injection is a sterile solution of Labetalol Hydrochloride in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of labetalol hydrochloride, $C_{19}H_{24}N_2O_3,HCl$

90.0 to 110.0% of the stated amount.

CHARACTERISTICS

A colourless or very pale yellow solution.

IDENTIFICATION

A. Mix a volume containing 50 mg of Labetalol Hydrochloride with 50 mL of 0.1M *hydrochloric acid* and heat on a water bath for 30 minutes. Cool, filter, add 10 mL of *ammonia buffer pH 10.0* and extract with three 15-mL quantities of *dichloromethane*. Shake the combined extracts with 5 g of *anhydrous sodium sulfate*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of labetalol *(RS 199)*.

B. The *light absorption*, Appendix II B, in the range 250 to 400 nm, of a 0.004% w/v solution of the residue obtained in test A in 0.1M *sodium hydroxide* exhibits a maximum only at 333 nm.

TESTS

Acidity

pH, 3.5 to 4.5, Appendix V L.

Free carboxylic acid and other related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute a volume of the injection containing 80 mg of Labetalol Hydrochloride to about 50 mL with *ethanol (96%)*, evaporate to dryness using a rotary evaporator and dissolve the residue in 1 mL of *methanol*.

(2) Dilute 1 volume of solution (1) to 200 volumes with *methanol*.

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(3) 0.160% w/v of *5-[1-hydroxy-2-(1-methyl-3-phenylpropylamino)ethyl]salicylic acid hydrochloride BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it in a current of warm air, heat at 105° for 30 minutes, cool and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

5 volumes of 13.5M *ammonia*, 25 volumes of *methanol* and 75 volumes of *dichloromethane*.

LIMITS

In the chromatogram obtained with solution (1):

any spot corresponding to 5-[1-hydroxy-2-(1-methyl-3-phenylpropylamino)ethyl]salicylic acid is not more intense that the spot in the chromatogram obtained with solution (3) (2%);

any other *secondary spot* is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%).

ASSAY

Dilute a volume containing 50 mg of Labetalol Hydrochloride to 100 mL with *water*. To 10 mL of the solution add 10 mL of 0.05M *sulfuric acid* and dilute to 100 mL with *water*. Measure the *absorbance* of the resulting solution at the maximum at 302 nm, Appendix II B. Calculate the content of $C_{19}H_{24}N_2O_3$,HCl in the injection taking 86 as the value of A(1%, 1 cm) at the maximum at 302 nm.

STORAGE

Labetalol Injection should be protected from light.

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Labetalol Tablets

General Notices

Action and use

Alpha- and beta-adrenoceptor antagonist.

DEFINITION

Labetalol Tablets contain Labetalol Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of labetalol hydrochloride, $C_{19}H_{24}N_2O_3$,HCl

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. To a quantity of the powdered tablets containing 50 mg of Labetalol Hydrochloride add 50 mL of 0.1M *hydrochloric acid* and heat on a water bath for 30 minutes. Cool, filter, add 10 mL of *ammonia buffer pH 10.0* and extract with three 15-mL quantities of *dichloromethane*. Shake the combined extracts with 5 g of *anhydrous sodium sulfate*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of labetalol *(RS 199)*.

B. The *light absorption*, Appendix II B, in the range 250 to 400 nm of a 0.004% w/v solution in 0.1M *sodium hydroxide* of the residue obtained in test A exhibits a maximum only at 333 nm.

TESTS

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.5 g of Labetalol Hydrochloride with 10 mL of *methanol*, filter and use the filtrate.

(2) Dilute 1 volume of solution (1) to 100 volumes with *methanol*.

(3) Dilute 1 volume of solution (2) to 2 volumes with *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel GF_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

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(e) After removal of the plate, dry it in a current of warm air, heat at 105° for 30 minutes, cool and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

5 volumes of 13.5M *ammonia*, 25 volumes of *methanol* and 75 volumes of *dichloromethane*.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (1%) and not more than one such spot is more intense than the spot in the chromatogram obtained with solution (3) (0.5%).

ASSAY

Weigh and powder 20 tablets. Shake a quantity of the powdered tablets containing 1 g of Labetalol Hydrochloride with 250 mL of 0.05M *sulfuric acid* for 30 minutes. Dilute the mixture to 500 mL with 0.05M *sulfuric acid*, mix, filter and dilute 10 mL of the filtrate to 250 mL with 0.05M *sulfuric acid*. Measure the *absorbance* of the resulting solution at the maximum at 302 nm, Appendix II B. Calculate the content of $C_{19}H_{24}N_2O_3$,HCl taking 86 as the value of A(1%, 1 cm) at the maximum at 302 nm.

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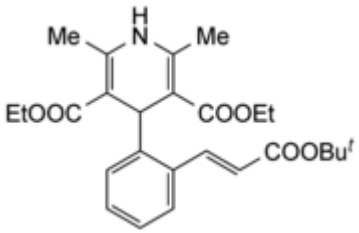
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Lacidipine

General Notices



$C_{26}H_{33}NO_6$ 455.6 *103890-78-4*

Action and use

Calcium channel blocker.

Preparation

Lacidipine Tablets

DEFINITION

Lacidipine is diethyl (*E*)-4-{2-[(*tert*-butoxycarbonyl)vinyl]phenyl}-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate. It contains not less than 97.5% and not more than 102.0% of $C_{26}H_{33}NO_6$, calculated with reference to the anhydrous, propan-2-ol–free substance.

CHARACTERISTICS

A white to pale yellow crystalline powder. It melts at about 178°.

Practically insoluble in *water*; freely soluble in *acetone*; sparingly soluble in *absolute ethanol*.

Carry out all of the following procedures protected from light and prepare solutions immediately before use.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of Lacidipine (*RS 407*).

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Propan-2-ol

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Carry out the method for *gas chromatography*, Appendix III B. Prepare a 0.002% v/v solution of *1,4-dioxan* (internal standard) in *dimethylacetamide* (solution A).

(1) 0.002% v/v solution of *propan-2-ol* in solution A.

(2) 2% w/v of the substance being examined in solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a glass column (60 m × 0.32 mm) bonded with a film (5 µm) of *polymethylsiloxane* (CP-Sil 5CB is suitable).

(b) Use *helium* as the carrier gas at 1.7 mL per minute.

(c) Use a temperature gradient as described below.

(d) Use an injection temperature of 170°.

(e) Use a detector temperature of 250°.

(f) Inject 1 µL of each solution.

Time (Minutes)	Temperature	Comment
0 - 1	60°	isothermal
1 - 18	60°→110°	linear increase 3°/minute
18 – 20	110°→200°	linear increase 50°/minute
20 – 27	200°	isothermal

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (1) shows two clearly separated peaks. The retention time for propan-2-ol is about 6.2 minutes and that for dioxan is about 15 minutes.

LIMITS

In the chromatogram obtained with solution (2):

the percentage content of propan-2-ol is not more than 0.5% w/w.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute 1 volume of a 0.1% w/v solution of the substance being examined in *absolute ethanol* to 5 volumes with the mobile phase.

(2) Dilute 1 volume of solution (1) to 500 volumes with the mobile phase.

(3) Dilute 1 volume of a 0.1% w/v solution of *lacidipine impurity standard BPCRS* in *absolute ethanol* to 5 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm x 4.6 mm) packed with *cyanosilyl silica gel for chromatography* (5 µm) (Spherisorb CN is suitable).

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(b) Use isocratic elution using the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 240 nm.

(f) Inject 20 µL of each solution.

(g) If necessary adjust the composition of the mobile phase so that, in the chromatogram obtained with solution (3), the retention time of the peak due to lacidipine is about 10 minutes.

(h) For solution (1), allow the chromatography to proceed for 2 times the retention time of the principal peak.

MOBILE PHASE

3 volumes of *absolute ethanol* and 97 volumes of n-*hexane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) closely resembles the chromatogram supplied with *lacidipine impurity standard BPCRS*.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak due to lacidipine impurity B is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%, taking into account the correction factor of 0.5);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the total nominal content of impurities is not greater than 0.5%.

Water

Not more than 0.2% w/w, Appendix IX C. Use 0.5 g.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute 5 volumes of a 0.1% w/v solution of the substance being examined in *absolute ethanol* to 100 volumes with the mobile phase.

(2) Dilute 5 volumes of a 0.1% w/v solution of *lacidipine BPCRS* in *absolute ethanol* to 100 volumes with the mobile phase.

(3) Dilute 1 volume of a 0.1% w/v solution of *lacidipine impurity standard BPCRS* in *absolute ethanol* to 5 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Related substances may be used.

SYSTEM SUITABILITY

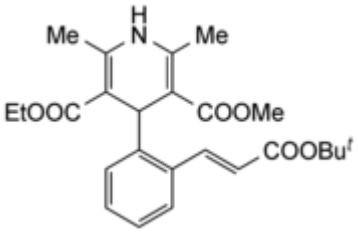
The test is not valid unless the chromatogram obtained with solution (3) closely resembles the corresponding chromatogram supplied with *lacidipine impurity standard BPCRS*.

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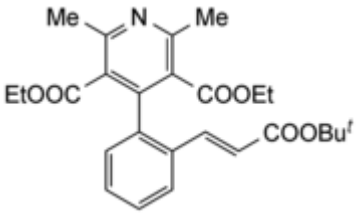
DETERMINATION OF CONTENT

Calculate the content of $C_{26}H_{33}NO_6$ from the chromatograms obtained and using the declared content of $C_{26}H_{33}NO_6$ in *lacidipine BPCRS*.

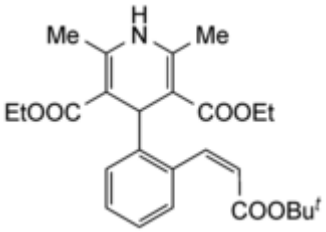
IMPURITIES



A. Ethyl methyl (*E*)-4-{2-[2-(*tert*-butoxycarbonyl)vinyl]phenyl}-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate,



B. Diethyl (*E*)-4-{2-[2-(*tert*-butoxycarbonyl)vinyl]phenyl}-2,6-dimethylpyridine-3,5-dicarboxylate,



C. Diethyl (*Z*)-4-{2-[2-(*tert*-butoxycarbonyl)vinyl]phenyl}-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate.

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Lacidipine Tablets

General Notices

Action and use

Calcium channel blocker.

DEFINITION

Lacidipine Tablets contain Lacidipine. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of lacidipine, $C_{26}H_{33}NO_6$

95.0 to 105.0% of the stated amount.

Carry out all of the following procedures protected from light and prepare solutions immediately before use.

IDENTIFICATION

A. Shake a quantity of whole tablets containing 4 mg of Lacidipine with 50 mL of *absolute ethanol* with the aid of ultrasound for 30 minutes. Dilute to 100 mL with *absolute ethanol* and filter through a 0.45-µm membrane filter (Millipore Millex is suitable). The *light absorption* of the filtrate, Appendix II B, in the range 250 to 400 nm exhibits maxima only at 284 nm and 368 nm.

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use as the medium 500 mL of a solution prepared by mixing 100 mL of *water* with 10 mL of *polysorbate 20*, shaking gently and diluting to 1000 mL with *water* at a temperature of 37°.

PROCEDURE

(1) After 45 minutes, withdraw a sample of 10 mL of the medium and filter immediately through a 0.45-µm membrane filter (Millipore Millex is suitable), having first activated the filter with 3 mL of *methanol* followed by 5 mL of a 1% w/v solution of *polysorbate 20*. Measure

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the *absorbance* of the filtrate in a 2-cm cell, suitably diluted with the dissolution medium if necessary, at the maximum at 284 nm, Appendix II B, using the dissolution medium in the reference cell.

(2) Measure the *absorbance*, in a 2 cm cell, of a solution of *lacidipine BPCRS* prepared by diluting a 0.02% w/v solution in *absolute ethanol* to a suitable volume with the dissolution medium at the maximum at 284 nm, Appendix II B, using the dissolution medium in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of lacidipine, $C_{26}H_{33}NO_6$, in the medium using the declared content of $C_{26}H_{33}NO_6$ in *lacidipine BPCRS*.

Related substances

Carry out method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 20 mg of Lacidipine with 50 mL of *absolute ethanol* with the aid of ultrasound for 15 minutes. Cool, dilute to 100 mL with *absolute ethanol*, filter through a 0.45-µm membrane filter (Millipore Millex is suitable) and dilute 5 volumes of the filtrate to 20 volumes with *hexane*.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase.

(3) Dilute 1 volume of a 0.1% w/v solution of *lacidipine impurity standard BPCRS* in *absolute ethanol* to 5 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm x 4.6 mm) packed with *cyanosilyl silica gel for chromatography* (5 µm) (Spherisorb CN is suitable).

(b) Use isocratic elution using the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use ambient column temperature.

(e) Use a detection wavelength of 240 nm.

(f) Inject 20 µL of each solution.

(g) If necessary adjust the composition of the mobile phase so that, in the chromatogram obtained with solution (3), the retention time of the peak due to lacidipine is about 10 minutes.

(h) For solution (1) allow the chromatography to proceed for 2 times the retention time of the principal peak.

MOBILE PHASE

3 volumes of *absolute ethanol* and 97 volumes of n-*hexane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) closely resembles the chromatogram supplied with *lacidipine impurity standard BPCRS*.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak due to lacidipine impurity B is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (2%, taking into account the correction factor of 0.5);

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the area of any other *secondary peak* is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the total nominal content of impurities is not greater than 2.5%;

disregard any peak with a relative retention time of 1.5 with respect to the peak due to lacidipine impurity B.

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Lacidipine comply with the requirements stated under Tablets using the following method of analysis. Place one tablet in 50 mL of *absolute ethanol*, disperse the tablet completely with the aid of ultrasound for 30 minutes crushing with a glass rod if it does not disintegrate, and mix. Cool and filter through a 0.45-µm membrane filter (Millipore Millex is suitable). If necessary further dilute with *absolute ethanol* to produce a solution containing 0.004% w/v of Lacidipine. Measure the *absorbance* of the resulting solution at the maximum at 368 nm, Appendix II B, using *absolute ethanol* in the reference cell. Calculate the content of $C_{26}H_{33}NO_6$ in each tablet from the *absorbance* obtained from a 0.004% w/v solution of *lacidipine BPCRS* in *absolute ethanol* and using the declared content of $C_{26}H_{33}NO_6$ in *lacidipine BPCRS*.

ASSAY

Carry out method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse with the aid of ultrasound 10 whole tablets in 50 mL of *absolute ethanol* for 10 minutes, cool and filter through a 0.45-µm membrane filter (Millipore Millex is suitable). Dilute a quantity of the filtrate with sufficient mobile phase to produce a solution containing 0.01% w/v of Lacidipine.
(2) Dilute 5 volumes of a 0.04% w/v solution of *lacidipine BPCRS* in *absolute ethanol* to 20 volumes with the mobile phase.
(3) Dilute 1 volume of a 0.1% w/v solution of *lacidipine impurity standard BPCRS* in *absolute ethanol* to 5 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) closely resembles the chromatogram supplied with *lacidipine impurity standard BPCRS*.

DETERMINATION OF CONTENT

Calculate the content of $C_{26}H_{33}NO_6$ in the tablets using the declared content of $C_{26}H_{33}NO_6$ in *lacidipine BPCRS*.

STORAGE

Lacidipine Tablets should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Lacidipine.

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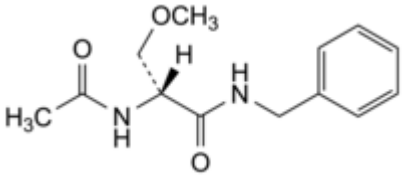
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Lacosamide

General Notices

(Ph. Eur. monograph 2992)



$C_{13}H_{18}N_2O_3$ 250.3 *175481-36-4*

Action and use

Antiepileptic.

Preparations

Lacosamide Infusion

Lacosamide Oral Solution

Lacosamide Tablets

Ph Eur

DEFINITION

(2*R*)-2-Acetamido-*N*-benzyl-3-methoxypropanamide.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white or light yellow powder.

Solubility

Sparingly soluble in water, freely soluble in methanol, practically insoluble in heptane.

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It shows polymorphism (5.9).

IDENTIFICATION

Carry out either tests A, B or tests B, C.

A. Specific optical rotation (2.2.7): + 14 to + 18 (anhydrous substance), measured at 25 °C.

Dissolve 0.100 g in *methanol R* and dilute to 10.0 mL with the same solvent.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *lacosamide CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

C. Enantiomeric purity (see Tests).

TESTS

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, *Method II*).

Dissolve 0.500 g in *water R* and dilute to 50.0 mL with the same solvent.

Enantiomeric purity

Liquid chromatography (2.2.29): use the normalisation procedure.

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 1 mg of *lacosamide impurity A CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 20 mg of the substance to be examined in the mobile phase, add 1.0 mL of reference solution (a) and dilute to 20.0 mL with the mobile phase.

Reference solution (c) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 20.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *amylose derivative of silica gel for chiral separation R* (10 µm).

Mobile phase *water for chromatography R*, *2-propanol R*, *heptane R* (3:100:900 *V/V/V*).

Flow rate 1.0 mL/min.

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Detection Spectrophotometer at 215 nm.

Injection 20 µL of the test solution and reference solutions (b) and (c).

Run time 1.7 times the retention time of lacosamide.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A.

Relative retention With reference to lacosamide (retention time = about 25 min): impurity A = about 0.8.

System suitability Reference solution (b):

— *resolution*: minimum 3.0 between the peaks due to impurity A and lacosamide.

Limit:

— *impurity A*: maximum 0.15 per cent;

— *reporting threshold*: 0.05 per cent (reference solution (c)).

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in 1 mL of *methanol R* and dilute to 10.0 mL with *water R*.

Reference solution (a) Dissolve 50.0 mg of *lacosamide CRS* in 1 mL of *methanol R* and dilute to 10.0 mL with *water R*.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with a mixture of 10 volumes of *methanol R* and 90 volumes of *water R*. Dilute 1.0 mL of this solution to 10.0 mL with the same mixture of solvents.

Reference solution (c) Dissolve 5 mg of *lacosamide for system suitability CRS* (containing impurities B, C, G and I) in 0.1 mL of *methanol R* and dilute to 1.0 mL with *water R*.

Reference solution (d) Dissolve 1 mg of *lacosamide impurity F CRS* in 2 mL of *methanol R* and dilute to 10.0 mL with *water R*. Dilute 1.0 mL of the solution to 10.0 mL with *water R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped extra-dense bonded octylsilyl silica gel for chromatography R* (3.5 µm).

Mobile phase:

— *mobile phase A*: 0.1 per cent *V/V* solution of *trifluoroacetic acid R*;

— *mobile phase B*: *trifluoroacetic acid R*, *acetonitrile R*, *methanol R* (0.3:500:500 *V/V/V*);

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	89	11
2 - 14.2	89 → 69	11 → 31
14.2 - 19.5	69 → 23	31 → 77
19.5 - 20	23 → 0	77 → 100
20 - 21	0	100

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 258 nm.

Injection 20 µL of the test solution and reference solutions (b), (c) and (d).

Identification of impurities Use the chromatogram supplied with *lacosamide for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities B, C, G and I; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity F.

Relative retention With reference to lacosamide (retention time = about 12 min): impurity F = about 0.7; impurity G = about 0.9; impurity B = about 1.2; impurity C = about 1.3; impurity I = about 1.6.

System suitability Reference solution (c):

— *resolution*: minimum 2.0 between the peaks due to impurity G and lacosamide; minimum 4.5 between the peaks due to lacosamide and impurity B.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity G = 0.7; impurity I = 0.7;

— for each impurity, use the concentration of lacosamide in reference solution (b).

Limits:

— *impurities B, C, F, G, I*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Water (*2.5.32*)

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Maximum 0.2 per cent, determined on 0.150 g by direct sample introduction.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection Test solution and reference solution (a).

System suitability Reference solution (a):

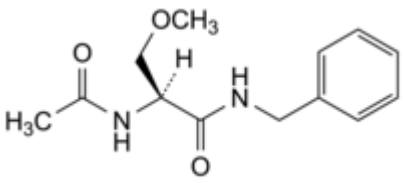
— *symmetry factor*: maximum 2.4 for the peak due to lacosamide.

Calculate the percentage content of $C_{13}H_{18}N_2O_3$ taking into account the assigned content of *lacosamide CRS*.

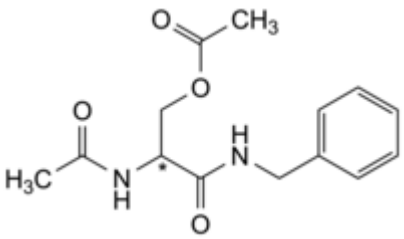
IMPURITIES

Specified impurities *A, B, C, F, G, I.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *D, E, H, J, K.*

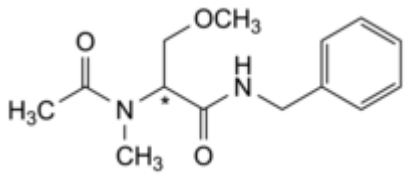


A. (2*S*)-2-acetamido-*N*-benzyl-3-methoxypropanamide,

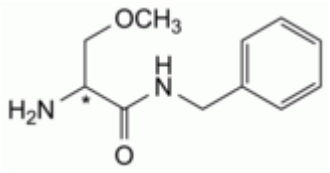


B. (2Ξ)-2-acetamido-3-(benzylamino)-3-oxopropyl acetate,

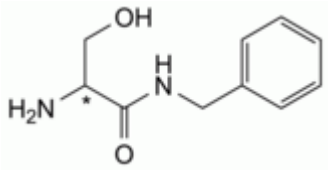
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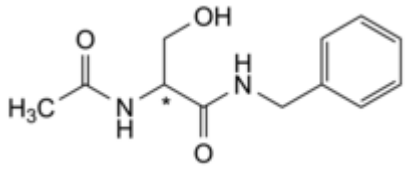
C. (2Ξ)-*N*-benzyl-3-methoxy-2-(*N*-methylacetamido)propanamide,



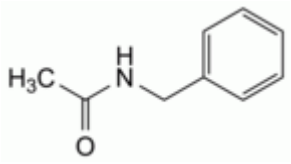
D. (2Ξ)-2-amino-*N*-benzyl-3-methoxypropanamide,



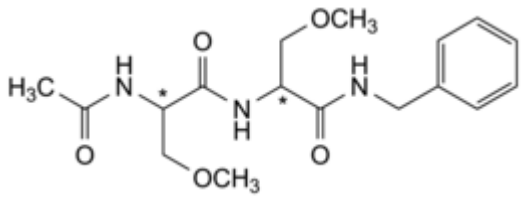
E. (2Ξ)-2-amino-*N*-benzyl-3-hydroxypropanamide,



F. (2Ξ)-2-acetamido-*N*-benzyl-3-hydroxypropanamide,

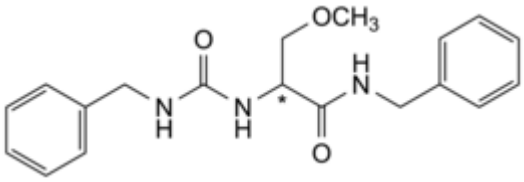


G. *N*-benzylacetamide,

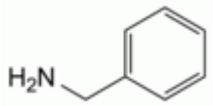


H. (2Ξ)-2-acetamido-*N*-[(2Ξ)-1-(benzylamino)-3-methoxy-1-oxopropan-2-yl]-3-methoxypropanamide,

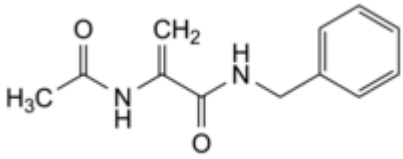
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I. (2Ξ)-*N*-benzyl-2-[(benzylcarbamoyl)amino]-3-methoxypropanamide,



J. phenylmethanamine,



K. 2-acetamido-*N*-benzylprop-2-enamide.

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Lacosamide Infusion

General Notices

(Ph. Eur. monograph 2991)

Action and use

Antiepileptic.

Ph Eur

DEFINITION

Sterile solution for infusion of *Lacosamide (2992)*, for human use.

It complies with the monograph Parenteral preparations (0520) and the following additional requirements.

Content

95.0 per cent to 105.0 per cent of the content of lacosamide ($C_{13}H_{18}N_2O_3$) stated on the label.

IDENTIFICATION

A. Record the UV spectrum of the principal peak in the chromatograms obtained with the solutions used in the assay with a diode array detector in the range of 210-400 nm.

Results The UV spectrum of the principal peak in the chromatogram obtained with the test solution is similar to the UV spectrum of the principal peak in the chromatogram obtained with reference solution (a).

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

TESTS

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture *acetonitrile R*, *water R* (13:87 *V/V*).

Test solution Mix the contents of 10 vials of the preparation to be examined and dilute a suitable volume of the solution with the solvent mixture to obtain a concentration of lacosamide of 1.0 mg/mL.

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Reference solution (a) Dissolve 20.0 mg of *lacosamide CRS* in the solvent mixture and dilute to 20.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 2.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 2 mg of *lacosamide impurity D CRS* and 3 mg of *lacosamide impurity F CRS* in the solvent mixture and dilute to 100 mL with the solvent mixture. Dilute 1 mL of the solution to 10 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped extra-dense bonded octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 35 °C.

Mobile phase *methanesulfonic acid R*, *acetonitrile R1*, *water for chromatography R* (0.75:130:870 *V/V/V*).

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 5 µL of the test solution and reference solutions (b) and (c).

Run time 2.5 times the retention time of lacosamide.

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities D and F.

Relative retention With reference to lacosamide (retention time = about 6 min): impurity D = about 0.4; impurity F = about 0.5.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurities D and F.

Calculation of percentage contents:

— for each impurity, use the concentration of lacosamide in reference solution (b).

Limits:

— *impurity D*: maximum 0.8 per cent;

— *unspecified impurities*: for each impurity, maximum 0.2 per cent;

— *total*: maximum 2.0 per cent;

— *reporting threshold*: 0.1 per cent.

ASSAY

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Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Injection Test solution and reference solution (a).

System suitability Reference solution (a):

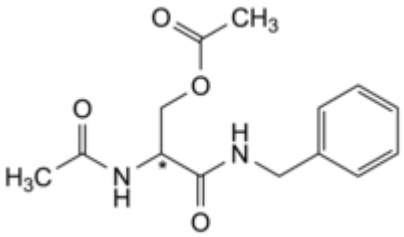
— *repeatability*: maximum relative standard deviation of 1.5 per cent determined on 6 injections.

Calculate the percentage content of lacosamide ($C_{13}H_{18}N_2O_3$) taking into account the assigned content of *lacosamide CRS*.

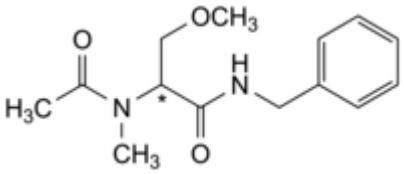
IMPURITIES

Specified impurities *D.*

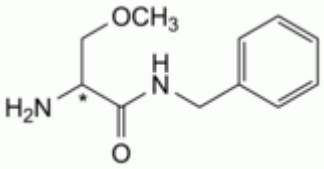
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph)*: B, C, E, F, J, K.*



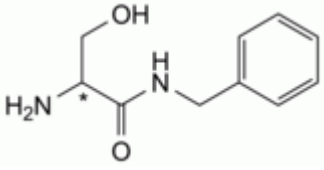
B. (2Ξ)-2-acetamido-3-(benzylamino)-3-oxopropyl acetate,



C. (2Ξ)-*N*-benzyl-3-methoxy-2-(*N*-methylacetamido)propanamide,

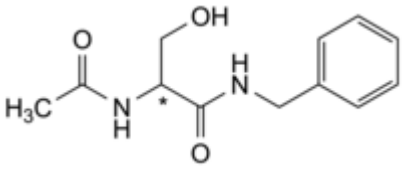


D. (2Ξ)-2-amino-*N*-benzyl-3-methoxypropanamide,

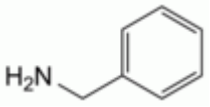


E. (2Ξ)-2-amino-*N*-benzyl-3-hydroxypropanamide,

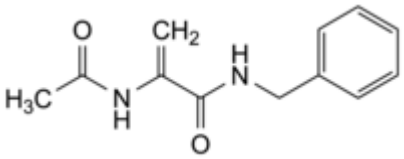
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F. (2Ξ)-2-acetamido-*N*-benzyl-3-hydroxypropanamide,



J. phenylmethanamine,



K. 2-acetamido-*N*-benzylprop-2-enamide.

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Lacosamide Oral Solution

General Notices

(Ph. Eur. monograph 2990)

Action and use

Antiepileptic.

Ph Eur

DEFINITION

Oral solution of *Lacosamide (2992)*, for human use.

It complies with the monograph Liquid preparations for oral use (0672) and the following additional requirements.

Content

95.0 per cent to 105.0 per cent of the content of lacosamide ($C_{13}H_{18}N_2O_3$) stated on the label.

IDENTIFICATION

A. Record the UV spectrum of the principal peak in the chromatograms obtained with the solutions used in the assay, with a diode array detector in the range of 210-400 nm.

Results The UV spectrum of the principal peak in the chromatogram obtained with the test solution is similar to the UV spectrum of the principal peak in the chromatogram obtained with reference solution (a).

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

TESTS

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture *acetonitrile R*, *water R* (13:87 *V/V*).

Test solution Dilute a suitable volume of the preparation to be examined with the solvent mixture to obtain a concentration of lacosamide of 1.0 mg/mL.

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Reference solution (a) Dissolve 20.0 mg of *lacosamide CRS* in the solvent mixture and dilute to 20.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 2.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 2 mg of *lacosamide impurity D CRS* and 3 mg of *lacosamide impurity F CRS* in the solvent mixture and dilute to 100 mL with the solvent mixture. Dilute 1 mL of the solution to 10 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography compatible with 100 per cent aqueous mobile phases R* (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: *trifluoroacetic acid R*, *acetonitrile R1*, *water for chromatography R* (0.56:100:900 *V/V/V*);

— *mobile phase B*: *trifluoroacetic acid R*, *acetonitrile R1* (0.5:1000 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 31	100	0
31 - 33	30	70

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 5 µL of the test solution and reference solutions (b) and (c).

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities D and F; impurities D and F may be inverted in the elution order, but the peak area of each impurity is different, so a clear identification of the impurities is possible.

Relative retention With reference to lacosamide (retention time = about 27 min): impurity D = about 0.4; impurity F = about 0.5 (D and F may be inverted).

System suitability Reference solution (c):

— *resolution*: minimum 3.0 between the peaks due to impurities D and F.

Calculation of percentage contents:

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— for each impurity, use the concentration of lacosamide in reference solution (b).

Limits:

— *impurity D*: maximum 0.6 per cent;

— *unspecified impurities*: for each impurity, maximum 0.2 per cent;

— *total*: maximum 2.0 per cent;

— *reporting threshold*: 0.1 per cent.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Mobile phase:

— *mobile phase A*: 0.05 per cent *V/V* solution of *trifluoroacetic acid R*;

— *mobile phase B*: *trifluoroacetic acid R*, *acetonitrile R1* (0.5:1000 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 9	75	25
9 - 12.5	45	55

Injection 4 µL of the test solution and reference solution (a).

System suitability Reference solution (a):

— *repeatability*: maximum relative standard deviation of 1.5 per cent determined on 6 injections.

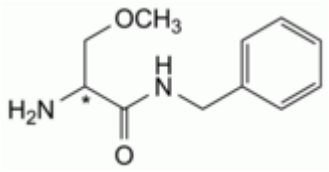
Calculate the percentage content of lacosamide ($C_{13}H_{18}N_2O_3$) taking into account the assigned content of *lacosamide CRS*.

IMPURITIES

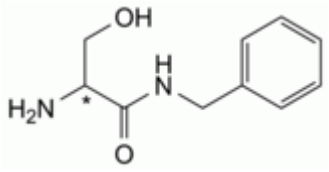
Specified impurities *D.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph)*: E, F, G, J, K.*

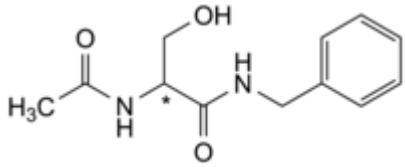
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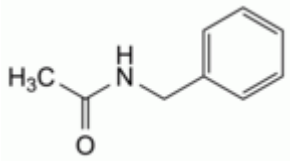
D. (2Ξ)-2-amino-*N*-benzyl-3-methoxypropanamide,



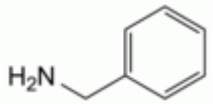
E. (2Ξ)-2-amino-*N*-benzyl-3-hydroxypropanamide,



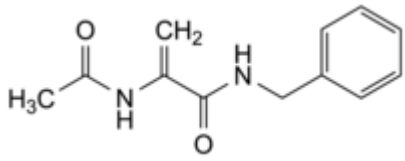
F. (2Ξ)-2-acetamido-*N*-benzyl-3-hydroxypropanamide,



G. *N*-benzylacetamide,



J. phenylmethanamine,



K. 2-acetamido-*N*-benzylprop-2-enamide.

Ph Eur

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Lacosamide Tablets

General Notices

(Ph. Eur. monograph 2989)

Action and use

Antiepileptic.

Ph Eur

DEFINITION

Tablets containing *Lacosamide (2992)*, for human use.

They comply with the monograph Tablets (0478) and the following additional requirements.

Content

95.0 per cent to 105.0 per cent of the content of lacosamide ($C_{13}H_{18}N_2O_3$) stated on the label.

IDENTIFICATION

A. Record the UV spectrum of the principal peak in the chromatograms obtained with the solutions used in the assay, with a diode array detector in the range of 210-400 nm.

Results The UV spectrum of the principal peak in the chromatogram obtained with the test solution is similar to the UV spectrum of the principal peak in the chromatogram obtained with reference solution (a).

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

TESTS

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture *acetonitrile R*, *water R* (13:87 *V/V*).

Test solution To 10 tablets add a suitable volume of the solvent mixture to obtain a concentration of lacosamide of 2-4 mg/mL. Shake vigorously for 30 min, sonicate for 10 min and allow to stand for 30 min. Dilute a suitable volume of the supernatant with the solvent mixture

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to obtain a concentration of lacosamide of 1.0 mg/mL.

Reference solution (a) Dissolve 20.0 mg of *lacosamide CRS* in the solvent mixture and dilute to 20.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 2.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 2 mg of *lacosamide impurity D CRS* and 3 mg of *lacosamide impurity F CRS* in the solvent mixture and dilute to 100 mL with the solvent mixture. Dilute 1 mL of the solution to 10 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped extra-dense bonded octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 35 °C.

Mobile phase *methanesulfonic acid R*, *acetonitrile R1*, *water for chromatography R* (0.75:130:870 *V/V/V*).

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 5 µL of the test solution and reference solutions (b) and (c).

Run time 2.5 times the retention time of lacosamide.

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities D and F.

Relative retention With reference to lacosamide (retention time = about 6 min): impurity D = about 0.4; impurity F = about 0.5.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurities D and F.

Calculation of percentage contents:

— for each impurity, use the concentration of lacosamide in reference solution (b).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.2 per cent;

— *total*: maximum 1.0 per cent;

— *reporting threshold*: 0.1 per cent.

Dissolution[1] (*2.9.3, Apparatus 2*).

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Dissolution medium 10.3 g/L solution of *hydrochloric acid R*. Use 900 mL of the medium.

Rotation speed 50 r/min.

Time 30 min.

Analysis Liquid chromatography (*2.2.29*).

Test solutions Samples withdrawn from the dissolution vessel and filtered.

Reference solution Using sonication, dissolve a suitable quantity of *lacosamide CRS* in a suitable volume of the dissolution medium to obtain a concentration of lacosamide corresponding to the theoretical concentration of lacosamide in the test solution, based on the labelled content of the tablets.

Column:

— *size*: *l* = 0.05 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 35 °C.

Mobile phase *trifluoroacetic acid R*, *acetonitrile R1*, *water for chromatography R* (1:300:700 *V/V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 2 µL.

Run time 2.5 min.

System suitability Reference solution:

— *repeatability*: maximum relative standard deviation of 1.5 per cent determined on 6 injections.

Calculate the amount of dissolved lacosamide ($C_{13}H_{18}N_2O_3$), expressed as a percentage of the content stated on the label, taking into account the assigned content of *lacosamide CRS*.

Acceptance criterion:

— *Q* = 80 per cent after 30 min.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection Test solution and reference solution (a).

System suitability Reference solution (a):

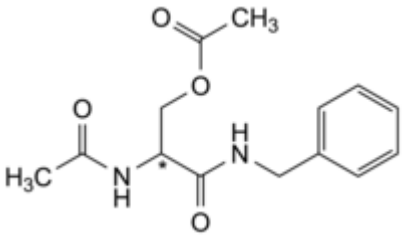
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— *repeatability*: maximum relative standard deviation of 1.5 per cent determined on 6 injections.

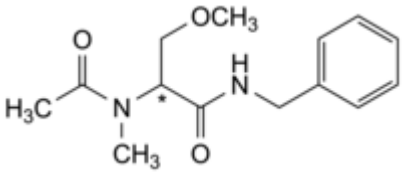
Calculate the percentage content of lacosamide ($C_{13}H_{18}N_2O_3$) taking into account the assigned content of *lacosamide CRS*.

IMPURITIES

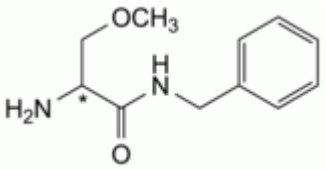
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph)*: B, C, D, E, F, J, K.*



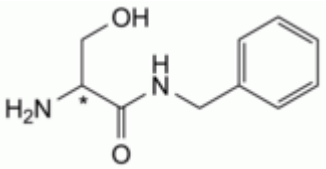
B. (2Ξ)-2-acetamido-3-(benzylamino)-3-oxopropyl acetate,



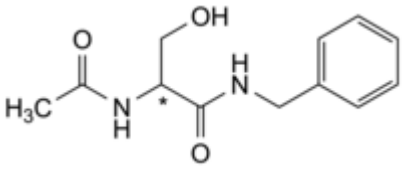
C. (2Ξ)-*N*-benzyl-3-methoxy-2-(*N*-methylacetamido)propanamide,



D. (2Ξ)-2-amino-*N*-benzyl-3-methoxypropanamide,

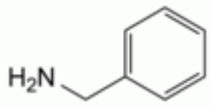


E. (2Ξ)-2-amino-*N*-benzyl-3-hydroxypropanamide,

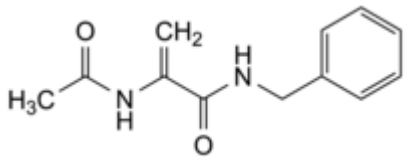


F. (2Ξ)-2-acetamido-*N*-benzyl-3-hydroxypropanamide,

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J. phenylmethanamine,



K. 2-acetamido-*N*-benzylprop-2-enamide.

Ph Eur

1 The test approved in the marketing authorisation is to be used for routine quality control to confirm batch-to-batch consistency. For more information please consult Ph. Eur. *1. General Notices*.

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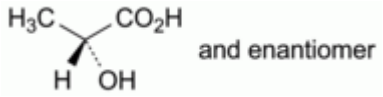
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Lactic Acid

General Notices

(Ph. Eur. monograph 0458)



$C_3H_6O_3$ 90.1

Preparations

Sodium Lactate Infusion

Compound Sodium Lactate Infusion

Lactic Acid Pessaries

Ph Eur

DEFINITION

Mixture of 2-hydroxypropanoic acid, its condensation products, such as lactoyl-lactic acid and polylactic acids, and water. The equilibrium between lactic acid and polylactic acids depends on the concentration and temperature. It is usually the racemate ((*RS*)-lactic acid).

Content

88.0 per cent *m/m* to 92.0 per cent *m/m* of $C_3H_6O_3$.

CHARACTERS

Appearance

Colourless or slightly yellow, syrupy liquid.

Solubility

Miscible with water and with ethanol (96 per cent).

IDENTIFICATION

A. Dissolve 1 g in 10 mL of *water R*. The solution is strongly acidic (2.2.4).

B. Relative density (2.2.5): 1.20 to 1.21.

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C. It gives the reaction of lactates (2.3.1).

TESTS

Solution S

Dissolve 5.0 g in 42 mL of *1 M sodium hydroxide* and dilute to 50 mL with *distilled water R*.

Appearance

The substance to be examined is not more intensely coloured than reference solution Y_6 (2.2.2, *Method II*).

Ether-insoluble substances

Dissolve 1.0 g in 25 mL of *ether R*. The solution is not more opalescent than the solvent used for the test.

Sugars and other reducing substances

To 1 mL of solution S add 1 mL of *1 M hydrochloric acid*, heat to boiling, allow to cool and add 1.5 mL of *1 M sodium hydroxide* and 2 mL of *cupri-tartaric solution R*. Heat to boiling. No red or greenish precipitate is formed.

Methanol (2.4.24)

Maximum 50 ppm, if intended for use in the manufacture of parenteral preparations.

Citric, oxalic and phosphoric acids

To 5 mL of solution S add *dilute ammonia R1* until slightly alkaline (2.2.4). Add 1 mL of *calcium chloride solution R*. Heat on a water-bath for 5 min. Both before and after heating, any opalescence in the solution is not more intense than that in a mixture of 1 mL of *water R* and 5 mL of solution S.

Sulfates (2.4.13)

Maximum 200 ppm.

Dilute 7.5 mL of solution S to 15 mL with *distilled water R*.

Calcium (2.4.3)

Maximum 200 ppm.

Dilute 5 mL of solution S to 15 mL with *distilled water R*.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

Bacterial endotoxins (2.6.14)

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Less than 5 IU/g, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins. Before use, neutralise the test solution to pH 7.0-7.5 with *strong sodium hydroxide solution R* and shake vigorously.

ASSAY

Place 1.000 g in a ground-glass-stoppered flask and add 10 mL of *water R* and 20.0 mL of *1 M sodium hydroxide*. Close the flask and allow to stand for 30 min. Using 0.5 mL of *phenolphthalein solution R* as indicator, titrate with *1 M hydrochloric acid* until the pink colour is discharged.

1 mL of *1 M sodium hydroxide* is equivalent to 90.1 mg of $C_3H_6O_3$.

LABELLING

The label states, where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

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Lactic Acid Pessaries

General Notices

DEFINITION

Lactic Acid Pessaries are moulded pessaries containing Lactic Acid in a suitable basis.

The pessaries comply with the requirements stated under Vaginal Preparations and with the following requirements.

Content of lactic acid, $C_3H_6O_3$

95.0 to 105.0% of the stated amount.

ASSAY

Weigh five pessaries, melt together by warming and allow to cool, stirring continuously. Dissolve a quantity of the mass containing 1 g of Lactic Acid in 50 mL of *water*, add 50 mL of *0.5M sodium hydroxide VS*, boil gently for 5 minutes, cool and titrate the excess of alkali with *0.5M hydrochloric acid VS* using *phenolphthalein solution R1* as indicator. Each mL of *0.5M sodium hydroxide VS* is equivalent to 45.04 mg of $C_3H_6O_3$.

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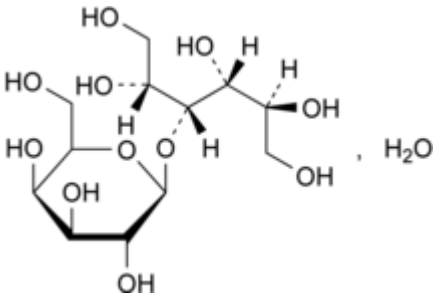
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Lactitol Monohydrate

General Notices

(Ph. Eur. monograph 1337)



$C_{12}H_{24}O_{11},H_2O$ 362.3 *81025-04-9*

Action and use

Osmotic laxative.

Ph Eur

DEFINITION

4-*O*-β-D-Galactopyranosyl-D-glucitol monohydrate.

Content

96.5 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very soluble in water, slightly soluble to very slightly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

First identification: B.

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Second identification: A, C.

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *lactitol monohydrate CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 50 mg of the substance to be examined in *methanol R* and dilute to 20 mL with the same solvent.

Reference solution (a) Dissolve 5 mg of *lactitol monohydrate CRS* in *methanol R* and dilute to 2 mL with the same solvent.

Reference solution (b) Dissolve 2.5 mg of *sorbitol CRS* (impurity E) in 1 mL of reference solution (a) and dilute to 10 mL with *methanol R*.

Plate *TLC silica gel G plate R*.

Mobile phase *water R*, *acetonitrile R* (25:75 *V/V*).

Application 2 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with *4-aminobenzoic acid solution R* and dry in a current of cold air until the acetone is removed; heat at 100 °C for 15 min and allow to cool; spray with a 2 g/L solution of *sodium periodate R* and dry in a current of cold air; heat at 100 °C for 15 min.

System suitability The chromatogram obtained with reference solution (b) shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

TESTS

Solution S

Dissolve 5.000 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution BY_7 (*2.2.2, Method II*).

Acidity or alkalinity

To 10 mL of solution S add 10 mL of *carbon dioxide-free water R*. To 10 mL of this solution add 0.05 mL of *phenolphthalein solution R*. Not more than 0.2 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to pink. To a further 10 mL of the solution add 0.05 mL of *methyl red solution R*. Not more than 0.3 mL of *0.01 M hydrochloric acid* is required to change the colour of the indicator to red.

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Specific optical rotation (*2.2.7*)

+ 13.5 to + 15.5 (anhydrous substance), determined on solution S.

Related substances

Liquid chromatography (*2.2.29*).

Test solution (a) Dissolve 50.0 mg of the substance to be examined in *water R* and dilute to 10.0 mL with the same solvent.

Test solution (b) Dilute 2.0 mL of test solution (a) to 50.0 mL with *water R*.

Reference solution (a) Dissolve 5.0 mg of *lactitol monohydrate CRS* and 5 mg of *glycerol R* in *water R* and dilute to 25.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with *water R*. Dilute 5.0 mL of this solution to 100.0 mL with *water R*.

Reference solution (c) Dilute 2.5 mL of reference solution (a) to 10.0 mL with *water R*.

Column:

— *size*: *l* = 0.30 m, Ø = 7.8 mm;

— *stationary phase*: *strong cation-exchange resin (calcium form) R*;

— *temperature*: 60 °C.

Mobile phase *water for chromatography R*.

Flow rate 0.6 mL/min.

Detection Differential refractometer maintained at a constant temperature (e.g. 35 °C).

Injection 100 µL; inject test solution (a) and reference solutions (b) and (c).

Run time 2.5 times the retention time of lactitol.

Relative retention With reference to lactitol (retention time = about 13 min): impurity A = about 0.7; impurity B = about 0.8; glycerol = about 1.3; impurity C = about 1.5; impurity D = about 1.8; impurity E = about 1.9.

System suitability Reference solution (c):

— *resolution*: minimum 5.0 between the peaks due to lactitol and glycerol.

Limits:

— *impurity B*: not more than the area of the peak due to lactitol in the chromatogram obtained with reference solution (c) (1.0 per cent);

— *total of other impurities*: not more than the area of the peak due to lactitol in the chromatogram obtained with reference solution (c) (1.0 per cent);

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— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Reducing sugars

Maximum 0.2 per cent.

Dissolve 5.0 g in 3 mL of *water R* with gentle heating. Cool and add 20 mL of *cupri-citric solution R* and a few glass beads. Heat so that boiling begins after 4 min and maintain boiling for 3 min. Cool rapidly and add 100 mL of a 2.4 per cent *V/V* solution of *glacial acetic acid R* and 20.0 mL of *0.025 M iodine*. With continuous shaking, add 25 mL of a mixture of 6 volumes of *hydrochloric acid R* and 94 volumes of *water R*. When the precipitate has dissolved, titrate the excess of iodine with *0.05 M sodium thiosulfate* using 1 mL of *starch solution R* added towards the end of the titration, as indicator. Not less than 12.8 mL of *0.05 M sodium thiosulfate* is required.

Water (*2.5.12*)

4.5 per cent to 5.5 per cent, determined on 0.300 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

Microbial contamination

TAMC: acceptance criterion 10^3 CFU/g (*2.6.12*).

TYMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

Absence of *Escherichia coli* (*2.6.13*).

Absence of *Salmonella* (*2.6.13*).

Absence of *Pseudomonas aeruginosa* (*2.6.13*).

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

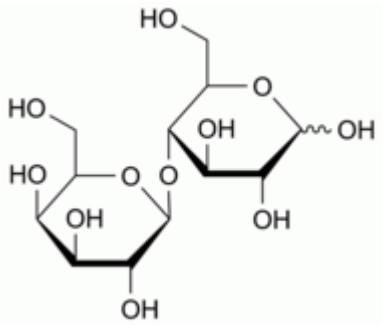
Injection Test solution (b) and reference solution (a).

Calculate the percentage content of $C_{12}H_{24}O_{11}$ taking into account the assigned content of *lactitol monohydrate CRS*.

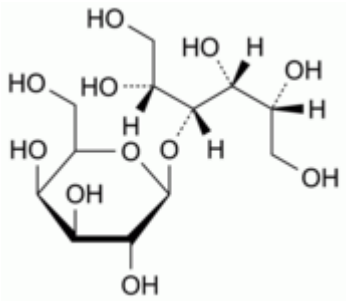
IMPURITIES

Specified impurities *A, B, C, D, E.*

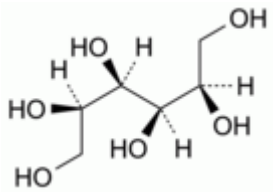
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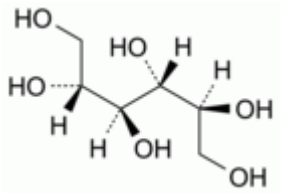
A. 4-*O*-β-D-galactopyranosyl-D-glucopyranose (lactose),



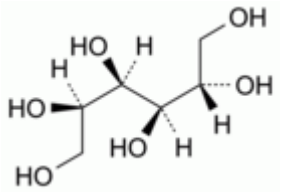
B. 3-*O*-β-D-galactopyranosyl-D-mannitol (lactulitol),



C. D-mannitol,



D. galactitol (dulcitol),



E. D-glucitol (D-sorbitol).

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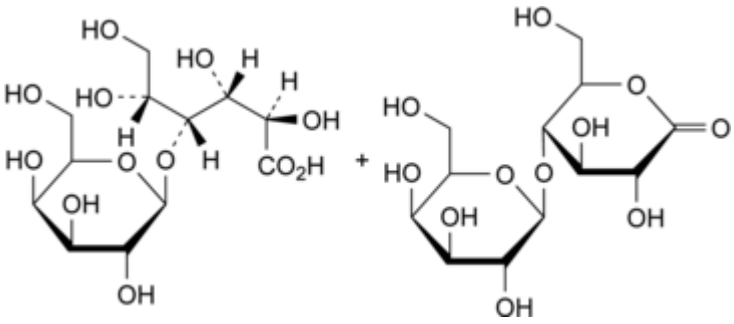
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Lactobionic Acid

General Notices

(Ph. Eur. monograph 1647)



$C_{12}H_{22}O_{12}$ (acid form) 358.3 *96-82-2*

$C_{12}H_{20}O_{11}$ (δ-lactone) 340.3 *5965-65-1*

Ph Eur

DEFINITION

Mixture in variable proportions of 4-*O*-β-D-galactopyranosyl-D-gluconic acid and 4-*O*-β-D-galactopyranosyl-D-glucono-1,5-lactone.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Freely soluble in water, slightly soluble in glacial acetic acid, in anhydrous ethanol and in methanol.

mp

About 125 °C with decomposition.

IDENTIFICATION

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A. Infrared absorption spectrophotometry (2.2.24).

Comparison *lactobionic acid CRS*.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in *water R*, dry at 105 °C and record new spectra using the residues.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *water R* and dilute to 1 mL with the same solvent.

Reference solution Dissolve 10 mg of *lactobionic acid CRS* in *water R* and dilute to 1 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase *concentrated ammonia R1*, *ethyl acetate R*, *water R*, *methanol R* (2:2:2:4 *V/V/V/V*).

Application 5 µL.

Development Over 3/4 of the plate.

Detection Spray 3 times with *ammonium molybdate solution R6* and heat in an oven at 110 °C for 15 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and colour to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_5 (2.2.2, *Method II*).

Dissolve 3.0 g in 25 mL of *water R*.

Specific optical rotation (2.2.7)

+ 23.0 to + 29.0 (anhydrous substance).

Dissolve 1.0 g in 80 mL of *water R* and dilute to 100.0 mL with the same solvent. Allow to stand for 24 h.

Reducing sugars

Maximum 0.2 per cent, calculated as glucose.

Dissolve 5.0 g in 25 mL of *water R* with the aid of gentle heat. Cool and add 20 mL of *cupri-citric solution R* and a few glass beads. Heat so that boiling begins after 4 min and maintain boiling for 3 min. Cool rapidly and add 100 mL of a 2.4 per cent *V/V* solution of *glacial acetic acid R* and 20.0 mL of *0.025 M iodine*. With continuous shaking, add 25 mL of a mixture of 6 volumes of *hydrochloric acid R* and 94 volumes of *water R* and, when the precipitate has dissolved, titrate the excess of iodine with *0.05 M sodium thiosulfate* using 1 mL of *starch solution R*, added towards the end of the titration, as indicator. Not less than 12.8 mL of *0.05 M sodium thiosulfate* is required.

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Water (*2.5.12*)

Maximum 5.0 per cent, determined on 0.50 g.

Use a mixture of 1 volume of *formamide R* and 2 volumes of *methanol R* as solvent.

Total ash (*2.4.16*)

Maximum 0.2 per cent.

ASSAY

Dissolve 0.350 g in 50 mL of *carbon dioxide-free water R*, previously heated to 30 °C. Immediately titrate with *0.1 M sodium hydroxide* and determine the 2 equivalence points potentiometrically (*2.2.20*).

The first equivalence point (V_1) corresponds to the acid form of lactobionic acid and the second equivalence point (V_2 -V_1) corresponds to the δ-lactone form.

1 mL of *0.1 M sodium hydroxide* is equivalent to 35.83 mg of $C_{12}H_{22}O_{12}$.

1 mL of *0.1 M sodium hydroxide* is equivalent to 34.03 mg of $C_{12}H_{20}O_{11}$.

The sum of the 2 results is expressed as a percentage content of lactobionic acid.

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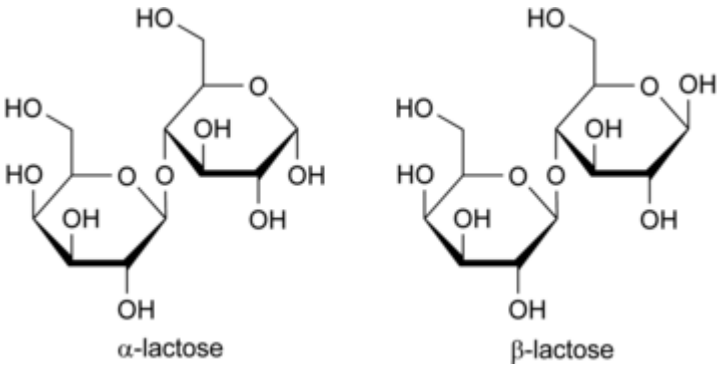
This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Lactose[1]

General Notices

Anhydrous Lactose

(Ph. Eur. monograph 1061)



$C_{12}H_{22}O_{11}$ 342.3 *63-42-3*

Action and use

Excipient.

Ph Eur

DEFINITION

O-β-D-Galactopyranosyl-(1→4)-β-D-glucopyranose or mixture of *O*-β-D-galactopyranosyl-(1→4)-α-D-glucopyranose and *O*-β-D-galactopyranosyl-(1→4)-β-D-glucopyranose.

♦ CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, practically insoluble in ethanol (96 per cent).♦

IDENTIFICATION

IDENTIFICATION

First identification: A, ◊ D.

Second identification: B, C, D.◊

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *anhydrous lactose CRS*.

◊ B. Thin-layer chromatography (2.2.27).

Solvent mixture *water R*, *methanol R* (40:60 *V/V*).

Test solution Dissolve 10 mg of the substance to be examined in the solvent mixture and dilute to 20 mL with the solvent mixture.

Reference solution Dissolve 10 mg of *anhydrous lactose CRS* in the solvent mixture and dilute to 20 mL with the solvent mixture.

Plate *TLC silica gel plate R*.

Mobile phase *water R*, *methanol R*, *glacial acetic acid R*, *methylene chloride R* (10:15:25:50 *V/V/V/V*); measure the volumes accurately, as a slight excess of water produces cloudiness.

Application 2 µL; thoroughly dry the points of application.

Development A Over 3/4 of the plate.

Drying A In a current of warm air.

Development B Immediately, over 3/4 of the plate, after renewing the mobile phase.

Drying B In a current of warm air.

Detection Spray with a solution of 0.5 g of *thymol R* in a mixture of 5 mL of *sulfuric acid R* and 95 mL of *ethanol (96 per cent) R*; heat at 130 °C for 10 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. Dissolve 0.25 g in 5 mL of *water R*. Add 5 mL of *ammonia R* and heat in a water-bath at 80 °C for 10 min. A red colour develops.

D. Water (see Tests).◊

TESTS

Solution S

Dissolve 1.0 g in boiling *water R*, allow to cool and dilute to 10.0 mL with *water R*.

Appearance of solution

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Solution S is clear (2.2.1) and not more intensely coloured than reference solution BY_7 (2.2.2, Method II).

Acidity or alkalinity

Dissolve 6.0 g by heating in 25 mL of *carbon dioxide-free water R*, cool and add 0.3 mL of *phenolphthalein solution R1*. The solution is colourless. Not more than 0.4 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator to pink or red.

Specific optical rotation (2.2.7)

+ 54.4 to + 55.9 (anhydrous substance).

Dissolve 10.0 g in 80 mL of *water R* with heating at 50 °C. Allow to cool and add 0.2 mL of *dilute ammonia R1*. Allow to stand for 30 min and dilute to 100.0 mL with *water R*.

Absorbance: proteins and light-absorbing impurities (2.2.25)

Test solution (a) Solution S.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with *water R*.

Spectral range 400 nm for test solution (a) and 210-300 nm for test solution (b).

Results:

— at 400 nm: maximum 0.04 for test solution (a);

— from 210 nm to 220 nm: maximum 0.25 for test solution (b);

— from 270 nm to 300 nm: maximum 0.07 for test solution (b).

Water (2.5.12)

Maximum 1.0 per cent, determined on 1.00 g, using a mixture of 1 volume of *formamide R* and 2 volumes of *methanol R* as solvent.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

Microbial contamination

TAMC: acceptance criterion 10^2 CFU/g (2.6.12).

Absence of *Escherichia coli* (2.6.13).

◊ FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In

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such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for lactose used as filler/diluent in solid dosage forms (compressed and powder).

Particle-size distribution (2.9.31 or 2.9.38)

Bulk and tapped density (2.9.34)

Determine the bulk density and the tapped density. Calculate the Hausner ratio.

α-Lactose and β-lactose

Gas chromatography (2.2.28).

Silylation reagent dimethyl sulfoxide R, N-trimethylsilylimidazole R, pyridine R (19.5:22:58.5 *V/V/V*).

Test solution Introduce 10 mg of the substance to be examined into a vial with a screw cap and add 4 mL of the silylation reagent. Sonicate for 20 min at room temperature, allow to cool and transfer 400 µL to an injection vial. Add 1 mL of pyridine R, close the vial and mix well.

Reference solution Prepare a mixture of α-lactose monohydrate R and β-lactose R to obtain an anomeric ratio of about 1:1 based on the labelled anomeric contents of the α-lactose monohydrate and the β-lactose. Introduce 10 mg of the mixture into a vial with a screw cap and add 4 mL of the silylation reagent. Sonicate for 20 min at room temperature, allow to cool, and transfer 400 µL to an injection vial. Add 1 mL of pyridine R, close the vial and mix well.

Precolumn:

— *material*: intermediate-polarity deactivated fused silica;

— *size*: *l* = 2 m, Ø = 0.53 mm.

Column:

— *material*: fused silica;

— *size*: *l* = 15 m, Ø = 0.25 mm;

— *stationary phase*: phenyl(5)methyl(95)polysiloxane R (film thickness 0.25 µm).

Carrier gas helium for chromatography R.

Flow rate 2.8 mL/min.

Temperature:

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	Time (min)	Temperature (°C)
Column	0 - 1	80
	1 - 3	80 → 150
	3 - 15.5	150 → 300
	15.5 - 17.5	300
Injection port		275 or use cold on-column injection
Detector		325

Detection Flame ionisation.

Injection 0.5 µL, splitless or by cold on-column injection.

Relative retention With reference to β-lactose (retention time = about 12 min): α-lactose = about 0.9.

System suitability Reference solution:

— *resolution*: minimum 3.0 between the peaks due to α-lactose and β-lactose.

Calculate the percentage content of α-lactose using the following expression:

$$\frac{100S_a}{S_a+S_b}$$

Calculate the percentage content of β-lactose using the following expression:

$$\frac{100S_b}{S_a+S_b}$$

S_a = area of the peak due to α-lactose;

S_b = area of the peak due to β-lactose.

Loss on drying (2.2.32)

Determine on 1.000 g by drying in an oven at 80 °C for 2 h.◊

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[1] This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8. Pharmacopoeial harmonisation*.

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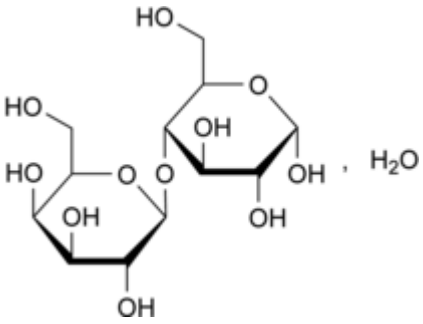
This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Lactose Monohydrate[1]

General Notices

(Ph. Eur. monograph 0187)

NOTE: *The name Lactose was formerly used in the United Kingdom.*



$C_{12}H_{22}O_{11},H_2O$ 360.3

Action and use

Excipient.

Ph Eur

DEFINITION

O-β-D-Galactopyranosyl-(1→4)-α-D-glucopyranose monohydrate.

♦ CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, practically insoluble in ethanol (96 per cent).♦

IDENTIFICATION

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First identification: A, ◊ D.

Second identification: B, C, D.◊

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *lactose monohydrate CRS*.

◊ B. Thin-layer chromatography (2.2.27).

Solvent mixture *water R*, *methanol R* (40:60 *V/V*).

Test solution Dissolve 10 mg of the substance to be examined in the solvent mixture and dilute to 20 mL with the solvent mixture.

Reference solution Dissolve 10 mg of *lactose monohydrate CRS* in the solvent mixture and dilute to 20 mL with the solvent mixture.

Plate *TLC silica gel plate R*.

Mobile phase *water R*, *methanol R*, *glacial acetic acid R*, *methylene chloride R* (10:15:25:50 *V/V/V/V*); measure the volumes accurately, as a slight excess of water produces cloudiness.

Application 2 µL; thoroughly dry the points of application.

Development A Over 3/4 of the plate.

Drying A In a current of warm air.

Development B Immediately, over 3/4 of the plate, after renewing the mobile phase.

Drying B In a current of warm air.

Detection Spray with a solution of 0.5 g of *thymol R* in a mixture of 5 mL of *sulfuric acid R* and 95 mL of *ethanol (96 per cent) R*; heat at 130 °C for 10 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. Dissolve 0.25 g in 5 mL of *water R*. Add 5 mL of *ammonia R* and heat in a water-bath at 80 °C for 10 min. A red colour develops.

D. Water (see Tests).◊

TESTS

Solution S

Dissolve 1.0 g in boiling *water R*, allow to cool and dilute to 10.0 mL with *water R*.

Appearance of solution

Solution S is clear (2.2.1) ◊ and not more intensely coloured than reference solution BY_7 (2.2.2, Method II)◊ .

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Acidity or alkalinity

Dissolve 6.0 g by heating in 25 mL of *carbon dioxide-free water R*, cool and add 0.3 mL of *phenolphthalein solution R1*. The solution is colourless. Not more than 0.4 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator to pink or red.

Specific optical rotation (*2.2.7*)

+ 54.4 to + 55.9 (anhydrous substance).

Dissolve 10.0 g in 80 mL of *water R* with heating at 50 °C. Allow to cool and add 0.2 mL of *dilute ammonia R1*. Allow to stand for 30 min and dilute to 100.0 mL with *water R*.

Absorbance: proteins and light-absorbing impurities (*2.2.25*)

Test solution (a) Solution S.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with *water R*.

Spectral range 400 nm for test solution (a) and 210-300 nm for test solution (b).

Results:

— at 400 nm: maximum 0.04 for test solution (a);

— from 210 nm to 220 nm: maximum 0.25 for test solution (b);

— from 270 nm to 300 nm: maximum 0.07 for test solution (b).

Water (*2.5.12*)

4.5 per cent to 5.5 per cent, determined on 0.50 g, using a mixture of 1 volume of *formamide R* and 2 volumes of *methanol R* as solvent.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

Microbial contamination

TAMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

Absence of *Escherichia coli* (*2.6.13*).

◊ FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process

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and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for lactose monohydrate used as a filler/diluent in solid dosage forms (compressed and powder).

Particle size distribution (*2.9.31* or *2.9.38*)

Bulk and tapped density (*2.9.34*)

Determine the bulk density and the tapped density. Calculate the Hausner ratio.◊

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1 This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8 Pharmacopoeial harmonisation*.

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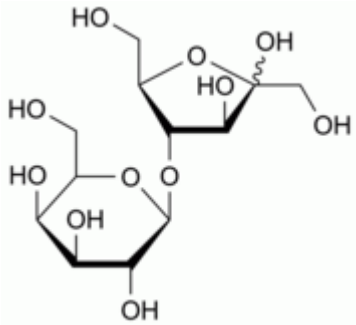
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Lactulose

General Notices

(Ph. Eur. monograph 1230)



$C_{12}H_{22}O_{11}$ 342.3 *4618-18-2*

Action and use

Osmotic laxative.

Preparation

Lactulose Oral Powder

Ph Eur

DEFINITION

4-*O*-β-D-Galactopyranosyl-D-*arabino*-hex-2-ulofuranose.

Content

95.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, sparingly soluble in methanol, practically insoluble in toluene.

mp

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mp

About 168 °C.

IDENTIFICATION

First identification: B, C, D, E.

Second identification: A, C, D, E.

A. Thin-layer chromatography (2.2.27).

Test solution Dissolve 50.0 mg of the substance to be examined in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution Dissolve 50.0 mg of *lactulose CRS* in *water R* and dilute to 10.0 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase *glacial acetic acid R*, 50 g/L solution of *boric acid R*, *methanol R*, *ethyl acetate R* (10:15:20:55 *V/V/V/V*).

Application 2 µL.

Development Over 3/4 of the plate.

Drying At 100-105 °C for 5 min; allow to cool.

Detection Spray with a 1.0 g/L solution of *1,3-dihydroxynaphthalene R* in a mixture of 10 volumes of *sulfuric acid R* and 90 volumes of *methanol R*; heat at 110 °C for 5 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (b).

C. Dissolve 50 mg in 10 mL of *water R*. Add 3 mL of *cupri-tartaric solution R* and heat. A red precipitate is formed.

D. Dissolve 0.125 g in 5 mL of *water R*. Add 5 mL of *ammonia R*. Heat in a water-bath at 80 °C for 10 min. A red colour develops.

E. Specific optical rotation (see Tests).

TESTS

Solution S

Dissolve 3.0 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution BY_5 (2.2.2, *Method II*).

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pH (*2.2.3*)

3.0 to 7.0.

To 10 mL of solution S add 0.1 mL of a saturated solution of *potassium chloride R*.

Specific optical rotation (*2.2.7*)

-50.0 to -46.0 (anhydrous substance).

Dissolve 1.25 g in *water R*, add 0.2 mL of *concentrated ammonia R* and dilute to 25.0 mL with *water R*.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 1.00 g of the substance to be examined in 10 mL of *water R*. Add 12.5 mL of *acetonitrile R* with gentle heating and dilute to 25.0 mL with *water R*.

Reference solution (a) To 3.0 mL of the test solution add 48.5 mL of *acetonitrile R* with gentle heating and dilute to 100.0 mL with *water R*.

Reference solution (b) Dissolve 1.00 g of *lactulose CRS* in 10 mL of *water R*. Add 12.5 mL of *acetonitrile R* with gentle heating and dilute to 25.0 mL with *water R*.

Reference solution (c) Dissolve 10 mg of *lactulose R*, 10 mg of *epilactose R* (impurity A) and 10 mg of *lactose monohydrate R* (impurity C) in 2 mL of *water R*. Add 2.5 mL of *acetonitrile R* with gentle heating and dilute to 5 mL with *water R*.

Reference solution (d) To 5.0 mL of the test solution add 47.5 mL of *acetonitrile R* with gentle heating and dilute to 100.0 mL with *water R*. Dilute 5.0 mL of this solution to 100.0 mL with a mixture of equal volumes of *acetonitrile R* and *water R*.

Column 1:

— *size*: *l* = 0.05 m, Ø = 4.6 mm;

— *stationary phase*: *aminopropylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 38 ± 1 °C.

Column 2:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *aminopropylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 38 ± 1 °C.

Columns 1 and 2 are coupled in series.

Mobile phase Dissolve 0.253 g of *sodium dihydrogen phosphate R* in 200 mL of *water for chromatography R* and dilute to 1000 mL with *acetonitrile R*.

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Flow rate 1.0 mL/min.

Detection Differential refractometer maintained at a constant temperature (e.g. 35 °C).

Injection 20 µL of the test solution and reference solutions (a), (c) and (d).

Run time Twice the retention time of lactulose.

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and C.

Relative retention With reference to lactulose (retention time = about 18 min): impurity A = about 0.9; impurity C = about 1.2.

System suitability Reference solution (c):

— *peak-to-valley ratio*: minimum 5.0, where H_p = height above the baseline of the peak due to impurity A and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to lactulose.

Limits:

— *impurity C*: not more than the area of the peak due to lactulose in the chromatogram obtained with reference solution (a) (3.0 per cent);

— *unspecified impurities*: for each impurity, not more than twice the area of the peak due to lactulose in the chromatogram obtained with reference solution (d) (0.5 per cent);

— *total*: not more than the area of the peak due to lactulose in the chromatogram obtained with reference solution (a) (3.0 per cent);

— *disregard limit*: the area of the peak due to lactulose in the chromatogram obtained with reference solution (d) (0.25 per cent).

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

Methanol

Head-space gas chromatography (*2.2.28*).

Internal standard solution Mix 0.5 mL of *propanol R* and 100.0 mL of *water R*. Dilute 1.0 mL of the solution to 100.0 mL with *water R*. Dilute 5.0 mL of this solution to 50.0 mL with *water R*.

Test solution To 79 mg of the substance to be examined in a 20 mL vial add 1.0 mL of the internal standard solution and 5 µL of a 0.1 per cent *V/V* solution of *methanol R*.

Reference solution To 1.0 mL of the internal standard solution in a 20 mL vial add 5 µL of a 0.1 per cent *V/V* solution of *methanol R*.

Column:

— *size*: *l* = 2 m, Ø = 2 mm;

— *stationary phase*: *ethylvinylbenzene-divinylbenzene copolymer R* (180 µm).

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Carrier gas *helium for chromatography R*.

Flow rate 30 mL/min.

Static head-space conditions that may be used:

— *equilibration temperature*: 60 °C;

— *equilibration time*: 1 h;

— *pressurisation time*: 1 min.

Temperature:

— *column*: 140 °C;

— *injection port*: 200 °C;

— *detector*: 220 °C.

Detection Flame ionisation.

Injection 1 mL of the gaseous phase.

Calculate the content of methanol, taking its density (*2.2.5*) at 20 °C to be 0.79 g/mL.

Limit:

— *methanol*: calculate the ratio (*R*) of the area of the peak due to methanol to the area of the peak due to the internal standard in the chromatogram obtained with the reference solution; calculate the ratio of the area of the peak due to methanol to the area of the peak due to the internal standard in the chromatogram obtained with the test solution: this ratio is not greater than 2*R* (50 ppm).

Boron

Maximum 9 ppm.

Avoid where possible the use of glassware.

Reference solution Dissolve 50.0 mg of *boric acid R* in *water R* and dilute to 100.0 mL with the same solvent. Dilute 5.0 mL of the solution to 100.0 mL with *water R*. *Keep in a well-closed polyethylene container*.

In 4 polyethylene 25 mL flasks, place separately:

— 0.50 g of the substance to be examined dissolved in 2.0 mL of *water R* (solution A);

— 0.50 g of the substance to be examined dissolved in 1.0 mL of the reference solution and 1.0 mL of *water R* (solution B);

— 1.0 mL of the reference solution and 1.0 mL of *water R* (solution C);

— 2.0 mL of *water R* (solution D).

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To each flask add 4.0 mL of *acetate-edetate buffer solution pH 5.5 R*. Mix and add 4.0 mL of freshly prepared *azomethine H solution R*. Mix and allow to stand for 1 h. Measure the absorbance (*2.2.25*) of solutions A, B and C at 420 nm, using solution D as the compensation liquid. The test is not valid unless the absorbance of solution C is at least 0.25. The absorbance of solution B is not less than twice that of solution A.

Water (*2.5.12*)

Maximum 2.5 per cent, determined on 0.500 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

Microbial contamination

TAMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

Absence of *Escherichia coli* (*2.6.13*).

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection Test solution and reference solution (b).

System suitability Reference solution (b):

— *symmetry factor*: 0.6 to 2.0 for the principal peak.

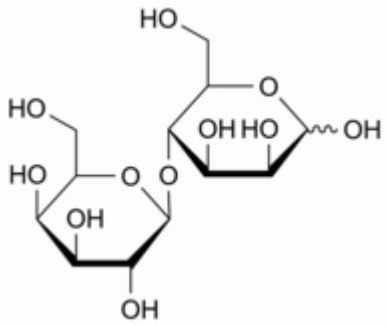
Calculate the percentage content of $C_{12}H_{22}O_{11}$ taking into account the assigned content of *lactulose CRS*.

IMPURITIES

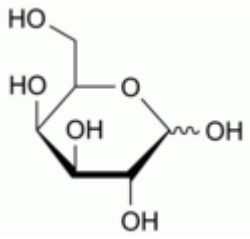
Specified impurities *C.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, D, E.*

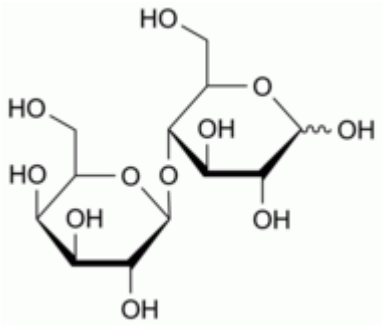
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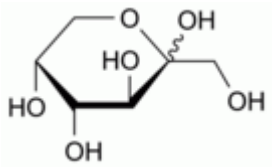
A. 4-*O*-β-D-galactopyranosyl-D-mannopyranose (epilactose),



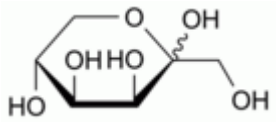
B. D-galactopyranose (galactose),



C. 4-*O*-β-D-galactopyranosyl-D-glucopyranose (lactose),



D. D-*arabino*-hex-2-ulopyranose (fructose),



E. D-*lyxo*-hex-2-ulopyranose (tagatose).

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Lactulose Oral Powder

General Notices

Action and use

Osmotic laxative.

DEFINITION

Lactulose Oral Powder consists of Lactulose with or without lesser amounts of other sugars including lactose and galactose.

The oral powder complies with the requirements stated under Oral Powders and with the following requirements.

Content of lactulose, $C_{12}H_{22}O_{11}$

95.0 to 102.0%.

Dissolve 3 g in carbon dioxide-free water and dilute to 50 mL with the same solvent (solution S).

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel G* as the coating substance and a mixture of 10 volumes of *glacial acetic acid*, 15 volumes of a 5% w/v solution of *boric acid*, 20 volumes of *methanol* and 55 volumes of *ethyl acetate* as the mobile phase. Apply separately to the plate 2 µL of each of the following solutions. For solution (1) dissolve 50 mg of the oral powder in *water* and dilute to 10 mL with the same solvent. For solution (2) dissolve 50 mg of *lactulose BPCRS* in *water* and dilute to 10 mL with the same solvent. After removal of the plate, dry it at 100° to 105° for 5 minutes and allow to cool. Spray the plate with a 0.1% w/v solution of *1,3-dihydroxynaphthalene* in a mixture of 10 volumes of *sulfuric acid* and 90 volumes of *methanol*. Heat the plate at 110° for 5 minutes. The principal spot in the chromatogram obtained with solution (1) is similar in position, colour and size to the principal spot in the chromatogram obtained with solution (2).

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) is similar in position and size to the principal peak in the chromatogram obtained with solution (3).

C. Dissolve 0.05 g in 10 mL of *water*. Add 3 mL of *cupri-tartaric solution* and heat. A red precipitate is formed.

D. Dissolve 0.125 g in 5 mL of *water*. Add 5 mL of *ammonia*. Heat on a water bath at 80° for 10 minutes. A red colour develops.

E. Complies with the test for Specific optical rotation.

TESTS

Clarity and colour of solution

Solution S is *clear*, Appendix IV A, and not more intensely coloured than *reference solution* BY_5, Appendix IV B, Method II.

pH

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To 10 mL of solution S add 0.1 mL of a saturated solution of *potassium chloride*. The pH of the solution is 3.0 to 7.0, Appendix V L.

Specific optical rotation

Dissolve 1.25 g in *water*, add 0.2 mL of 13. 5M *ammonia* and dilute to 25 mL with *water*. The *specific optical rotation* is –46.0° to –50.0°, Appendix V G.

Related substances

In the Assay, in the chromatogram obtained with solution (1), the sum of the areas of any peaks corresponding to the principal peaks in the chromatograms obtained with solutions 5, 6, 7, 8 and 9 respectively (galactose, lactose, epilactose, tagatose and fructose) is not greater than the area of the peak corresponding to lactulose in the chromatogram obtained with solution (2) (3%).

Methanol

Carry out the method for *head-space gas chromatography*, Appendix III B, Method II. Mix 0.5 mL of *propan-1-ol* with 100 mL of *water*. Dilute 1 mL to 100 mL with *water*. Dilute 5 mL to 50 mL with *water* (internal standard solution). For solution (1) add 1 mL of the internal standard solution and 5 µL of a 0.1% v/v solution of *methanol* to 79 mg of the oral powder in a 20 mL vial. For solution (2) add 5 µL of a 0.1% v/v solution of *methanol* to 1 mL of the internal standard solution in a 20 mL vial.

The chromatographic procedure may be carried out using (a) a column (2 m × 2 mm) packed with *ethylvinylbenzene–divinylbenzene co-polymer* (180 µm), (b) *helium for chromatography* as the carrier gas at a flow rate of 30 mL per minute and (c) a flame-ionisation detector, maintaining the temperature of the column at 140°, that of the injection port at 200° and that of the detector at 220°. Maintain each solution at 60° for 1 hour, pressurise for 1 minute and transfer onto the column 1 mL of the gaseous phase.

In the chromatogram obtained with solution (1), the ratio of the area of the methanol peak to that of the internal standard peak is not greater than twice the corresponding ratio for the chromatogram obtained with solution (2) (50 ppm, calculated assuming the density of methanol to be 0.79 g/mL at 20°).

Boron

Avoid where possible the use of glassware. Prepare a reference solution as follows. Dissolve 50 mg of *boric acid* in *water* and dilute to 100 mL with the same solvent. Dilute 5 mL of this solution to 100 mL with *water*. Keep in a well-closed polyethylene container. In four polyethylene 25 mL flasks, place 0.50 g of the oral powder dissolved in 2 mL of *water* (solution A), 0.50 g of the oral powder dissolved in 1 mL of the reference solution and 1 mL of *water* (solution B), 1 mL of the reference solution and 1 mL of *water* (solution C) and 2 mL of *water* (solution D). To each flask, add 4 mL of *acetate-edetate buffer solution pH 5.5*. Mix and add 4 mL of freshly prepared *azomethine H solution*. Mix and allow to stand for 1 hour. Measure the *absorbance*, Appendix II B, of solutions A, B and C at 420 nm, using solution D as the compensation liquid. The test is not valid unless the absorbance of solution C is at least 0.25. The absorbance of solution B is not less than twice that of solution A (9 ppm of boron).

Lead

Complies with the *limit test for lead in sugars*, Appendix VII (0.5 ppm).

Water

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Not more than 2.5%, Appendix IX C, Method I. Use 0.5 g.

Sulfated ash

Not more than 0.1%, Appendix IX A, Method II. Use 1 g.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) dissolve 1 g of the oral powder in 10 mL of *water*, add 12.5 mL of *acetonitrile* with gentle heating and dilute to 25 mL with *water*. For solution (2) add 47.5 mL of *acetonitrile* to 3 mL of solution (1) with gentle heating and dilute to 100 mL with *water*. For solution (3) dissolve 1 g of *lactulose BPCRS* in 10 mL of *water*, add 12.5 mL of *acetonitrile* with gentle heating and dilute to 25 mL with *water*. For solution (4) dissolve 20 mg of *lactulose BPCRS* and 20 mg of *epilactose EPCRS* in 2 mL of *water*, add 2.5 mL of *acetonitrile* with gentle heating and dilute to 5 mL with *water*. For solution (5) dissolve 0.2 g of *galactose* in 20 mL of *water*, add 25 mL of *acetonitrile* with gentle heating and dilute to 50 mL with *water*. For solution (6) dissolve 0.2 g of *lactose* in 20 mL of *water*, add 25 mL of *acetonitrile* with gentle heating and dilute to 50 mL with *water*. For solution (7) dissolve 20 mg of *epilactose EPCRS* in 2 mL of *water*, add 2.5 mL of *acetonitrile* with gentle heating and dilute to 5 mL with *water*. For solution (8) dissolve 0.2 g of *tagatose* in 20 mL of *water*, add 25 mL of *acetonitrile* with gentle heating and dilute to 50 mL with *water*. For solution (9) dissolve 0.2 g of *fructose* in 20 mL of *water*, add 25 mL of *acetonitrile* with gentle heating and dilute to 50 mL with *water*.

The chromatographic procedure may be carried out using (a) a stainless steel column (5 cm × 4.6 mm) followed by a stainless steel column (15 cm × 4.6 mm), both packed with *aminopropylsilyl silica gel for chromatography* (3 µm) and maintained at 37° to 39°, (b) as mobile phase with a flow rate of 1.0 mL per minute a mixture prepared as follows: dissolve 0.253 g of *sodium dihydrogen orthophosphate* in 220 mL of *water* and add 780 mL of *acetonitrile*, and (c) as detector a refractometer maintained at a constant temperature.

When the chromatograms are recorded in the prescribed conditions, the retention time of lactulose is about 18.3 minutes and retention times relative to lactulose are about 0.38 for tagatose, 0.42 for fructose, 0.57 for galactose, 0.90 for epilactose and 1.17 for lactose.

Inject 20 µL of solution (4). The test is not valid unless the *resolution factor* between the peaks corresponding to lactulose and epilactose is at least 1.3. If necessary, adjust the concentration of *acetonitrile* in the mobile phase to between 75.0% and 82.0% v/v to achieve the prescribed resolution.

Inject separately 20 µL of solution (1) and 20 µL of solution (3) and continue the chromatography for 2.5 times the retention time of lactulose. Calculate the percentage content of $C_{12}H_{22}O_{11}$ (lactulose) from the areas of the peaks and from the declared content of $C_{12}H_{22}O_{11}$ in *lactulose BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed in the monograph for Lactulose.

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Lactulose Solution

General Notices

(Liquid Lactulose, Ph. Eur. monograph 0924)

Action and use

Osmotic laxative.

Ph Eur

DEFINITION

Aqueous solution of 4-*O*-β-D-galactopyranosyl-D-*arabino*-hex-2-ulofuranose normally prepared by alkaline isomerisation of lactose. It may contain other sugars including lactose, epilactose, galactose, tagatose and fructose.

Content

Minimum 620 g/L of lactulose ($C_{12}H_{22}O_{11}$; M_r 342.3) and 95.0 per cent to 105.0 per cent of the content of lactulose stated on the label.

It may contain a suitable antimicrobial preservative.

CHARACTERS

Appearance

Clear, viscous liquid, colourless or pale brownish-yellow.

Solubility

Miscible with water. It may be a supersaturated solution or may contain crystals that disappear on heating.

A 10 per cent *V/V* solution is laevorotatory.

IDENTIFICATION

First identification: B, C, D.

Second identification: A, C, D.

A. Thin-layer chromatography (2.2.27).

Test solution Dilute 0.50 g of the substance to be examined in *water R* and dilute to 50.0 mL with the same solvent.

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Reference solution Dissolve 60.0 mg of *lactulose CRS* in *water R* and dilute to 10.0 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase *glacial acetic acid R*, 50 g/L solution of *boric acid R*, *methanol R*, *ethyl acetate R* (10:15:20:55 *V/V/V/V*).

Application 2 µL.

Development Over 3/4 of the plate.

Drying At 100-105 °C for 5 min and allow to cool.

Detection Spray with a 1.0 g/L solution of *1,3-dihydroxynaphthalene R* in a mixture of 10 volumes of *sulfuric acid R* and 90 volumes of *methanol R*; heat at 110 °C for 5 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with reference solution (b).

C. To 0.1 g add 10 mL of *water R* and 3 mL of *cupri-tartaric solution R* and heat. A red precipitate is formed.

D. To 0.25 g add 5 mL of *water R* and 5 mL of *ammonia R*. Heat in a water-bath at 80 °C for 10 min. A red colour develops.

TESTS

Solution S

Mix 10 g with *carbon dioxide-free water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution BY_5 (*2.2.2, Method II*).

pH (*2.2.3*)

3.0 to 7.0.

To 10 mL of solution S add 0.1 mL of a saturated solution of *potassium chloride R*.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Mix 4.00 g of the substance to be examined and 20 mL of *water R*. Add 25.0 mL of *acetonitrile R* with gentle heating and dilute to 50.0 mL with *water R*.

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Reference solution (a) To 5.0 mL of the test solution add 47.5 mL of *acetonitrile R* with gentle heating and dilute to 100.0 mL with *water R*.

Reference solution (b) Dissolve 2.00 g of *lactulose CRS* in 20 mL of *water R*. Add 25.0 mL of *acetonitrile R* with gentle heating and dilute to 50.0 mL with *water R*.

Reference solution (c) Dissolve 65 mg of *fructose CRS* (impurity D) in a mixture of equal volumes of *acetonitrile R* and *water R* and dilute to 100.0 mL with the same mixture of solvents.

Reference solution (d) Dissolve 1 g of *lactulose for peak identification CRS* (containing impurities A, B, C, E, F, G and H) in reference solution (c) and dilute to 25 mL with reference solution (c).

Reference solution (e) Dilute 5.0 mL of reference solution (a) to 100.0 mL with a mixture of equal volumes of *acetonitrile R* and *water R*.

Column 1:

— *size*: *l* = 0.05 m, Ø = 4.6 mm;

— *stationary phase*: *aminopropylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 38 ± 1 °C.

Column 2:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *aminopropylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 38 ± 1 °C.

Columns 1 and 2 are coupled in series.

Mobile phase Dissolve 0.253 g of *sodium dihydrogen phosphate R* in 200 mL of *water for chromatography R* and dilute to 1000 mL with *acetonitrile R*.

Flow rate 1.0 mL/min.

Detection Differential refractometer maintained at a constant temperature (e.g. 35 °C).

Injection 20 µL of the test solution and of reference solutions (a), (d) and (e).

Run time Twice the retention time of lactulose.

Identification of impurities Use the chromatogram supplied with *lactulose for peak identification CRS* and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities A, B, C, D, E, F, G and H.

Relative retention With reference to lactulose (retention time = about 18 min): impurity F = about 0.2; impurity E = about 0.38; impurity D = about 0.42; impurity B = about 0.6; impurity G = about 0.8; impurity A = about 0.9; impurity C = about 1.2; impurity H = about 1.5.

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System suitability Reference solution (d):

— *peak-to-valley ratio*: minimum 5.0, where H_p = height above the baseline of the peak due to impurity A and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to lactulose.

Limits:

— *impurity B*: not more than 3 times the area of the peak due to lactulose in the chromatogram obtained with reference solution (a) (15.0 per cent);

— *impurities A, C*: for each impurity, not more than twice the area of the peak due to lactulose in the chromatogram obtained with reference solution (a) (10.0 per cent);

— *impurities E, F*: for each impurity, not more than 0.8 times the area of the peak due to lactulose in the chromatogram obtained with reference solution (a) (4.0 per cent);

— *impurities G, H*: for each impurity, not more than 0.3 times the area of the peak due to lactulose in the chromatogram obtained with reference solution (a) (1.5 per cent);

— *impurity D*: not more than 0.2 times the area of the peak due to lactulose in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *unspecified impurities*: for each impurity, not more than 0.1 times the area of the peak due to lactulose in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *sum of impurities eluting after impurity H*: not more than 0.26 times the area of the peak due to lactulose in the chromatogram obtained with reference solution (a) (1.3 per cent);

— *total (excluding impurities B and C)*: not more than 2.4 times the area of the peak due to lactulose in the chromatogram obtained with reference solution (a) (12.0 per cent);

— *disregard limit*: not more than the area of the peak due to lactulose in the chromatogram obtained with reference solution (e) (0.25 per cent).

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

Methanol

Head-space gas chromatography (*2.2.28*).

Internal standard solution Mix 0.5 mL of *propanol R* and 100.0 mL of *water R*. Dilute 1.0 mL of the solution to 100.0 mL with *water R*. Dilute 5.0 mL of this solution to 50.0 mL with *water R*.

Test solution To 0.13 g of the substance to be examined in a 20 mL vial add 1.0 mL of the internal standard solution and 5 µL of a 0.1 per cent *V/V* solution of *methanol R*.

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Reference solution To 1.0 mL of the internal standard solution in a 20 mL vial add 5 µL of a 0.1 per cent *V/V* solution of *methanol R*.

Column:

— *size*: *l* = 2 m, Ø = 2 mm;

— *stationary phase*: *ethylvinylbenzene-divinylbenzene copolymer R* (180 µm).

Carrier gas *helium for chromatography R*.

Flow rate 30 mL/min.

Static head-space conditions that may be used:

— *equilibration temperature*: 60 °C;

— *equilibration time*: 1 h;

— *pressurisation time*: 1 min.

Temperature:

— *column*: 140 °C;

— *injection port*: 200 °C;

— *detector*: 220 °C.

Detection Flame ionisation.

Injection 1 mL of the gaseous phase.

Calculate the content of methanol, taking its density (*2.2.5*) at 20 °C to be 0.79 g/mL.

Limit:

— *methanol*: calculate the ratio (*R*) of the area of the peak due to methanol to the area of the peak due to the internal standard in the chromatogram obtained with the reference solution; calculate the ratio of the area of the peak due to methanol to the area of the peak due to the internal standard in the chromatogram obtained with the test solution: this ratio is not greater than 2*R* (30 ppm).

Sulfites

Maximum 30 ppm.

Mix 5.0 g with 40 mL of *water R*, add 2.0 mL of *0.1 M sodium hydroxide* and dilute to 100 mL with *water R*. To 10.0 mL of this solution, add 1.0 mL of *hydrochloric acid R1*, 2.0 mL of *decolorised fuchsin solution R1* and 2.0 mL of a 0.5 per cent *V/V* solution of *formaldehyde R*. Allow to stand for 30 min and measure the absorbance (*2.2.25*) at 583 nm using as the compensation liquid a solution prepared at the same time and in the same manner with 10.0 mL of *water R* instead of the solution of the substance to be examined. The absorbance is not

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greater than that of a reference solution prepared at the same time and in the same manner using 10.0 mL of *sulfite standard solution (1.5 ppm SO_2) R* instead of the solution of the substance to be examined.

Boron

Maximum 5 ppm.

Avoid where possible the use of glassware.

Reference solution Dissolve 56.0 mg of *boric acid R* in *water R* and dilute to 100.0 mL with the same solvent. Dilute 5.0 mL of this solution to 100.0 mL with *water R*. *Keep in a well-closed polyethylene container.*

In 4 polyethylene 25 mL flasks, place separately:

— 1.00 g of the substance to be examined and 1 mL of *water R* (solution A);

— 1.00 g of the substance to be examined and 1 mL of the reference solution (solution B);

— 1 mL of the reference solution and 1 mL of *water R* (solution C);

— 2 mL of *water R* (solution D).

To each flask, add 4.0 mL of *acetate-edetate buffer solution pH 5.5 R*. Mix and add 4.0 mL of freshly prepared *azomethine H solution R*. Mix and allow to stand for 1 h. Measure the absorbance (*2.2.25*) of solutions A, B and C at 420 nm, using solution D as the compensation liquid. The test is not valid unless the absorbance of solution C is at least 0.25. The absorbance of solution B is not less than twice that of solution A.

Sulfated ash (*2.4.14*)

Maximum 0.2 per cent, determined on 1.5 g and calculated with reference to the declared content of lactulose.

Microbial contamination

TAMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

TYMC: acceptance criterion 10^1 CFU/g (*2.6.12*).

Absence of *Escherichia coli* (*2.6.13*).

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection Test solution and reference solution (b).

System suitability Reference solution (b):

— *symmetry factor*: 0.6 to 2.0 for the principal peak.

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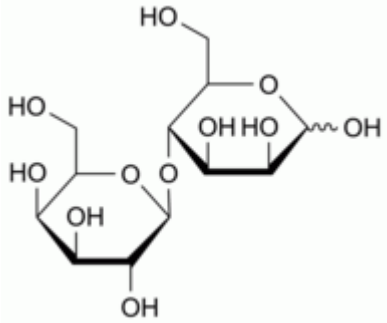
Calculate the percentage content of $C_{12}H_{22}O_{11}$ taking into account the assigned content of *lactulose CRS*.

LABELLING

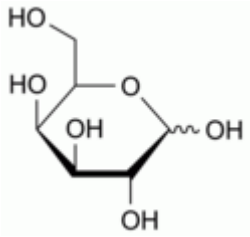
The label states the declared content of lactulose.

IMPURITIES

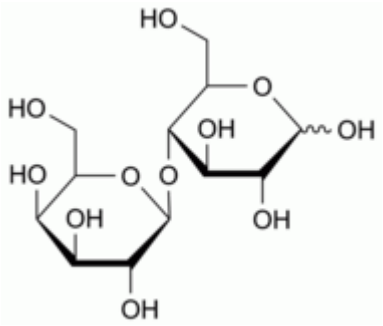
Specified impurities *A, B, C, D, E, F, G, H.*



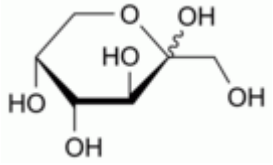
A. 4-*O*-β-D-galactopyranosyl-D-mannopyranose (epilactose),



B. D-galactopyranose (galactose),

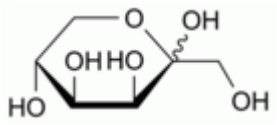


C. 4-*O*-β-D-galactopyranosyl-D-glucopyranose (lactose),

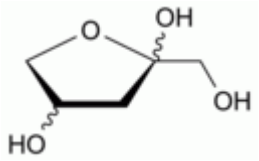


D. D-*arabino*-hex-2-ulopyranose (fructose),

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E. D-*lyxo*-hex-2-ulopyranose (tagatose),



F. (2Ξ,4Ξ)-2-(hydroxymethyl)oxolane-2,4-diol,

G. unknown structure,

H. unknown structure.

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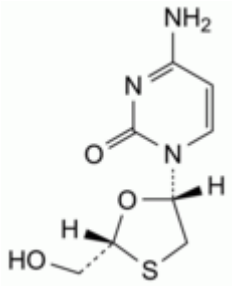
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Lamivudine

General Notices

(Ph. Eur. monograph 2217)



$C_8H_{11}N_3O_3S$ 229.3 *134678-17-4*

Action and use

Nucleoside reverse transcriptase inhibitor; antiviral (HIV).

Preparations

Lamivudine Tablets

Zidovudine and Lamivudine Tablets

Abacavir, Zidovudine and Lamivudine Tablets

Abacavir and Lamivudine Tablets

Ph Eur

DEFINITION

4-Amino-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]pyrimidin-2(1*H*)-one.

Content

97.5 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

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Solubility

Soluble in water, sparingly soluble in methanol, slightly soluble in ethanol (96 per cent).

It shows polymorphism (5.9).

IDENTIFICATION

First identification: B, C.

Second identification: A, B.

A. Specific optical rotation (2.2.7): -99 to -97 (dried substance).
Dissolve 0.250 g in *water R* and dilute to 50.0 mL with the same solvent.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *lamivudine CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

C. Enantiomeric purity (see Tests).

TESTS

Absorbance (2.2.25)

Maximum 0.3 at 440 nm, using a path length of 4 cm.

Dissolve 1.00 g in *water R*, using sonication if necessary, and dilute to 20.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5.0 mg of *salicylic acid R* in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 100.0 mL with the mobile phase.

Reference solution (c) Dissolve 50.0 mg of *lamivudine CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (d) Dissolve 5 mg of *cytosine R* and 5 mg of *uracil R* in the mobile phase and dilute to 100 mL with the mobile phase. Dilute 2 mL of the solution to 10 mL with the mobile phase.

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Reference solution (e) Dissolve 5 mg of *lamivudine for system suitability 1 CRS* (containing impurities A and B) in 2 mL of the mobile phase. Add 1 mL of reference solution (d) and dilute to 10 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 35 °C.

Mobile phase Mix 5 volumes of *methanol R* and 95 volumes of a 1.9 g/L solution of *ammonium acetate R*, previously adjusted to pH 3.8 with *glacial acetic acid R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 277 nm.

Injection 10 µL.

Run time 3 times the retention time of lamivudine.

Identification of impurities Use the chromatograms obtained with reference solutions (b) and (e) to identify the peaks due to impurities A, B, C, E and F.

Relative retention With reference to lamivudine (retention time = about 9 min): impurity E = about 0.28; impurity F = about 0.32; impurity A = about 0.36; impurity B = about 0.91; impurity J = about 1.45; impurity C = about 2.32.

System suitability Reference solution (e):

— *resolution*: minimum 1.5 between the peaks due to impurities F and A; minimum 1.5 between the peaks due to impurity B and lamivudine.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity E = 0.6; impurity F = 2.2; impurity J = 2.2;

— *impurity A*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *impurity B*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurity C*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent);

— *any other impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

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— *total*: not more than 6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.6 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Enantiomeric purity

Liquid chromatography (2.2.29): use the normalisation procedure.

Test solution Dissolve 25.0 mg of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution Dissolve the contents of a vial of *lamivudine for system suitability 2 CRS* (containing impurity D) in 1.0 mL of *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *beta-cyclodextrin derivative of silica gel for chiral separation R* (5 µm);

— *temperature*: maintain at constant temperature between 15 °C and 30 °C; the temperature may be adjusted to optimise the resolution between lamivudine and impurity D; a lower temperature favours improved resolution.

Mobile phase Mix 5 volumes of *methanol R* and 95 volumes of a 7.7 g/L solution of *ammonium acetate R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 270 nm.

Injection 10 µL.

Run time Twice the retention time of lamivudine.

Relative retention With reference to lamivudine (retention time = about 8 min): impurity D = about 1.2; impurity B and enantiomer = about 1.3 and 1.5.

System suitability Reference solution:

— *peak-to-valley-ratio*: minimum 15, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to lamivudine.

Calculate the sum of the percentage contents of all impurity peaks with a relative retention from 1.2 to 1.5. Subtract the percentage content of impurity B as obtained in the test for related substances.

Limit:

— *impurity D*: maximum 0.3 per cent.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

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Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (c).

Calculate the percentage content of $C_8H_{11}N_3O_3S$ using the chromatograms obtained with the test solution and reference solution (c) and the declared content of $C_8H_{11}N_3O_3S$ in *lamivudine CRS*.

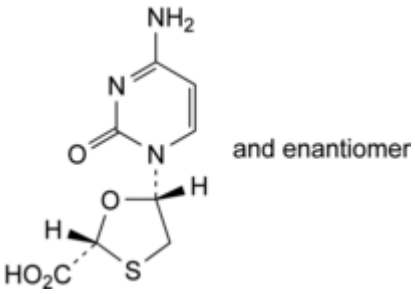
STORAGE

Protected from light.

IMPURITIES

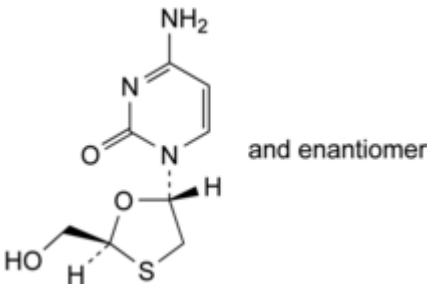
Specified impurities *A, B, C, D.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *E, F, G, H, I, J.*



and enantiomer

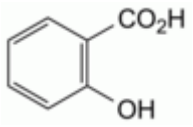
A. (2*RS*,5*SR*)-5-(4-amino-2-oxopyrimidin-1(2*H*)-yl)-1,3-oxathiolane-2-carboxylic acid,



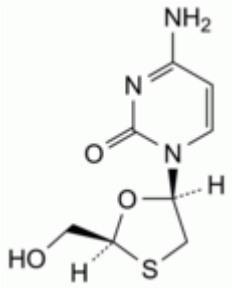
and enantiomer

B. 4-amino-1-[(2*RS*,5*RS*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]pyrimidin-2(1*H*)-one ((±)-*trans*-lamivudine),

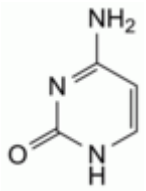
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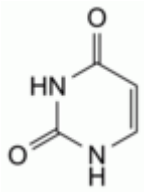
C. 2-hydroxybenzenecarboxylic acid (salicylic acid),



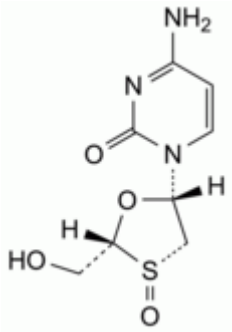
D. 4-amino-1-[(2*S*,5*R*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]pyrimidin-2(1*H*)-one,



E. 4-aminopyrimidin-2(1*H*)-one (cytosine),

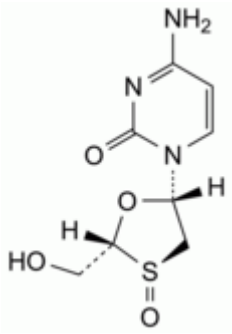


F. pyrimidine-2,4(1*H*,3*H*)-dione (uracil),

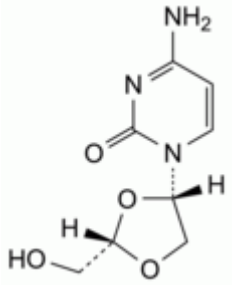


G. 4-amino-1-[(2*R*,3*S*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]pyrimidin-2(1*H*)-one *S*-oxide,

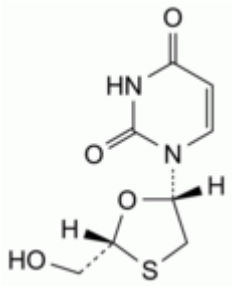
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H. 4-amino-1-[(2*R*,3*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]pyrimidin-2(1*H*)-one *S*-oxide,



I. 4-amino-1-[(2*S*,4*S*)-2-(hydroxymethyl)-1,3-dioxolan-4-yl]pyrimidin-2(1*H*)-one,



J. 1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]pyrimidine-2,4(1*H*,3*H*)-dione.

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Lamivudine Tablets

General Notices

Action and use

Nucleoside reverse transcriptase inhibitor; antiviral (HIV).

DEFINITION

Lamivudine Tablets contain Anhydrous Lamivudine.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of lamivudine, $C_8H_{11}N_3O_3S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

To a quantity of the powdered tablets containing 50 mg of Anhydrous Lamivudine add 20 mL of *methanol*, shake, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of lamivudine (*RS 451*).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2 and rotate the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 280 nm, Appendix II B, using dissolution medium in the reference cell.

(2) Measure the *absorbance* of a suitable solution of *lamivudine BPCRS* using dissolution medium in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of lamivudine, $C_8H_{11}N_3O_3S$, in the medium from the absorbances obtained and using the declared content of $C_8H_{11}N_3O_3S$ in *lamivudine BPCRS*.

LIMITS

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The amount of lamivudine released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.3 g of Anhydrous Lamivudine in 60 mL of *water* with the aid of ultrasound for 30 minutes, dilute to 100 mL and filter. Dilute 1 volume of the filtrate to 10 volumes with the mobile phase.

(2) Dilute 1 volume of solution (1) to 50 volumes with the mobile phase and further dilute 1 volume to 10 volumes with the mobile phase.

(3) Dilute 1 volume of solution (2) to 2 volumes with the mobile phase.

(4) 0.03% w/v of *lamivudine impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil BDS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 277 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

5 volumes of *methanol* and 95 volumes of 0.025M *ammonium acetate*, the pH of the aqueous component having previously been adjusted to 4.0 with *glacial acetic acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4):

the chromatogram closely resembles the reference chromatogram supplied with *lamivudine impurity standard BPCRS*;

the *resolution factor* between the peaks due to lamivudine impurity B and lamivudine is at least 2.0.

LIMITS

Using the chromatogram obtained with solution (4) and the reference chromatogram supplied with *lamivudine impurity standard BPCRS* identify any peaks in solution (1) corresponding to impurity A and impurity B.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to lamivudine impurity A is not greater than 1.5 times the area of the peak due to lamivudine in the chromatogram obtained with solution (2) (0.3%);

the area of any peak corresponding to lamivudine impurity B is not greater than the area of the peak due to lamivudine in the chromatogram obtained with solution (2) (0.2%);

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the area of any other *secondary peak* is not greater than the area of the peak due to lamivudine in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 3 times the area of the peak due to lamivudine in the chromatogram obtained with solution (2) (0.6%).

Disregard any peak with an area less than the area of the peak in the chromatogram obtained with solution (3) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.3 g of Anhydrous Lamivudine in 60 mL of *water* with the aid of ultrasound for 30 minutes, dilute to 100 mL with the mobile phase and filter. Dilute 1 volume of the filtrate to 10 volumes with the mobile phase.
(2) 0.03% w/v of *lamivudine BPCRS* in the mobile phase.
(3) 0.03% w/v of *lamivudine impurity standard BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution factor* between the peaks due to lamivudine impurity B and lamivudine is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_8H_{11}N_3O_3S$ in the tablets using the declared content of $C_8H_{11}N_3O_3S$ in *lamivudine BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, B, C, E, F, G, H, I and J listed under Anhydrous Lamivudine.

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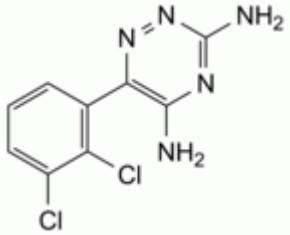
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Lamotrigine

General Notices

(Ph. Eur. monograph 1756)



$C_9H_7Cl_2N_5$ 256.1 *84057-84-1*

Action and use

Antiepileptic.

Preparations

Lamotrigine Dispersible Tablets

Lamotrigine Tablets

Ph Eur

DEFINITION

6-(2,3-Dichlorophenyl)-1,2,4-triazine-3,5-diamine.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Very slightly soluble in water, slightly soluble in anhydrous ethanol.

IDENTIFICATION

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IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison lamotrigine CRS.

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 20 mg of the substance to be examined in 5 mL of methanol R and dilute to 100.0 mL with a 10.3 g/L solution of hydrochloric acid R.

Reference solution (a) Dissolve 5 mg of lamotrigine for system suitability CRS (containing impurity G) in 2.5 mL of methanol R and dilute to 25.0 mL with a 10.3 g/L solution of hydrochloric acid R.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with a 10.3 g/L solution of hydrochloric acid R. Dilute 2.0 mL of this solution to 10.0 mL with a 10.3 g/L solution of hydrochloric acid R.

Reference solution (c) Dissolve 5.0 mg of lamotrigine impurity E CRS in a mixture of 0.25 mL of hydrochloric acid R and 45 mL of methanol R and dilute to 50.0 mL with methanol R. Dilute 5.0 mL of the solution to 100.0 mL with a 10.3 g/L solution of hydrochloric acid R. To 4.0 mL of this solution add 5 mL of methanol R and dilute to 100.0 mL with a 10.3 g/L solution of hydrochloric acid R.

Reference solution (d) Dissolve 10 mg of lamotrigine for peak identification CRS (containing impurities A, E and F) in 2.5 mL of methanol R and dilute to 50.0 mL with a 10.3 g/L solution of hydrochloric acid R.

Blank solution Mix 5 volumes of methanol R and 95 volumes of a 10.3 g/L solution of hydrochloric acid R.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: base-deactivated end-capped octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 35 °C.

Mobile phase:

— *mobile phase A*: mix 1 volume of triethylamine R and 150 volumes of a 2.7 g/L solution of potassium dihydrogen phosphate R; adjust to pH 2.0 with phosphoric acid R;

— *mobile phase B*: acetonitrile R;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 4	85	15

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
4 - 14	85 → 20	15 → 80

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 270 nm.

Injection 10 µL of the test solution, reference solutions (a), (b) and (d) and the blank solution.

Identification of impurities Use the chromatogram supplied with *lamotrigine for peak identification CRS* and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities A, E and F; use the chromatogram supplied with *lamotrigine for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peak due to impurity G.

Relative retention With reference to lamotrigine (retention time = about 7 min): impurity G = about 1.1; impurity A = about 1.3; impurity E = about 1.7; impurity F = about 1.8.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 1.2, where H_p = height above the baseline due to impurity G and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to lamotrigine.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity F by 1.3;

— *impurity F*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *impurities A, G*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent); disregard any peak due to impurity E.

Impurity E

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Mobile phase *acetonitrile for chromatography R*, mobile phase A (35:65 *V/V*).

Detection Spectrophotometer at 210 nm.

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Injection Test solution and reference solutions (d) and (c).

Run time 10 min.

Retention time Impurity E = about 5.5 min; impurity F = about 8.5 min.

System suitability Reference solution (d):

— the chromatogram obtained is similar to the chromatogram supplied with *lamotrigine for peak identification CRS*.

Limit:

— *impurity E*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.1 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 2.000 g by drying in an oven at 105 °C at a pressure not exceeding 0.7 kPa for 3 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 2.0 g.

ASSAY

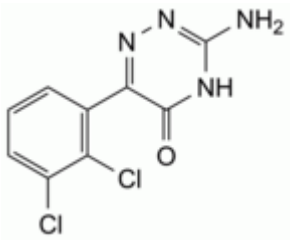
Dissolve 0.200 g in 60 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20). Carry out a blank titration.

1 mL of *0.1 M perchloric acid* is equivalent to 25.61 mg of $C_9H_7Cl_2N_5$.

IMPURITIES

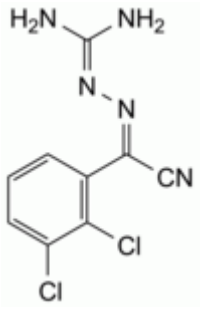
Specified impurities *A, E, F, G.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D.*

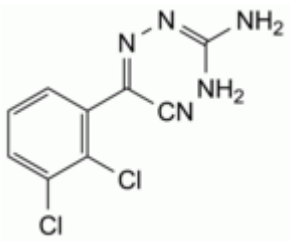


A. 3-amino-6-(2,3-dichlorophenyl)-1,2,4-triazin-5(4*H*)-one,

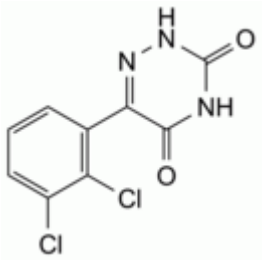
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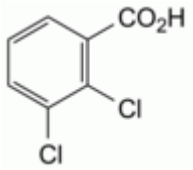
B. (2*E*)-[2-(diaminomethylidene)diazanylidene](2,3-dichlorophenyl)acetonitrile,



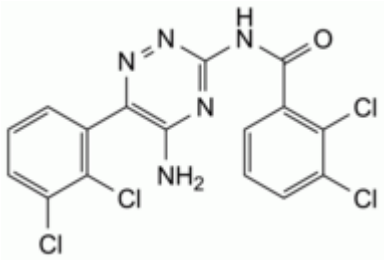
C. (2*Z*)-[2-(diaminomethylidene)diazanylidene](2,3-dichlorophenyl)acetonitrile,



D. 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5(2*H*,4*H*)-dione,

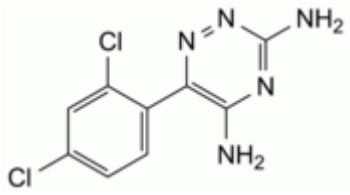


E. 2,3-dichlorobenzoic acid,



F. *N*-[5-amino-6-(2,3-dichlorophenyl)-1,2,4-triazin-3-yl]-2,3-dichlorobenzamide,

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G. 6-(2,4-dichlorophenyl)-1,2,4-triazine-3,5-diamine.

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Lamotrigine Dispersible Tablets

General Notices

Dispersible Lamotrigine Tablets

Lamotrigine Dispersible Tablets from different manufacturers, whilst complying with the requirements of the monograph, may not be interchangeable.

Action and use

Antiepileptic.

DEFINITION

Lamotrigine Dispersible Tablets contain Lamotrigine in a suitable dispersible basis.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of lamotrigine, $C_9H_7Cl_2N_5$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *methanol*.

(1) Shake a quantity of the powdered tablets containing 20 mg of Lamotrigine in 20 mL, dilute to 100 mL, filter and use the filtrate.

(2) 0.02% w/v of *lamotrigine BPCRS*.

(3) 0.02% w/v each of *lamotrigine BPCRS* and *carbamazepine BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air and immediately examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

5 volumes of *concentrated ammonia*, 10 volumes of *methanol* and 85 volumes of *ethyl acetate*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

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The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in thechromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Disintegration

Comply with the requirements for Dispersible Tablets.

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a sample of the medium, filter and dilute 5 mL of the filtrate to 10 mL with 0.3M *sodium hydroxide*. Measure the *absorbance* of the solution at 307 nm, Appendix II B, using 0.1M *sodium hydroxide* in the reference cell. Adjust the concentration with *water* if necessary.

(2) Prepare a suitable solution of *lamotrigine BPCRS* in the dissolution medium, using 0.3M *sodium hydroxide* to produce a solution of the strength expected in solution (1). Measure the *absorbance* of the solution at 307 nm, Appendix II B, using 0.1M *sodium hydroxide* in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of lamotrigine, $C_9H_7Cl_2N_5$, in the medium using the declared content of $C_9H_7Cl_2N_5$ in *lamotrigine BPCRS*.

LIMITS

The amount of lamotrigine released is not less than 80% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 20 mg of Lamotrigine with 40 mL of *water* and add 40 mL of *methanol*. Dilute to 100 mL with *methanol (40%)*, filter and use the filtrate.

(2) Dilute 1 volume of solution (1) to 100 volumes with *methanol (40%)* and dilute 1 volume of the resulting solution to 5 volumes with *methanol (40%)*.

(3) 0.02% w/v of *lamotrigine impurity standard BPCRS*in *methanol (40%)*.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 275 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.5 volumes of *octylamine*, 20 volumes of *glacial acetic acid*, 100 volumes of *acetonitrile*, 100 volumes of *methanol* and 700 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) closely resembles the chromatogram supplied with *lamotrigine impurity standard BPCRS* and the *resolution* between the peaks due to lamotrigine and saccharin sodium is at least 5.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all such peaks is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Lamotrigine comply with the requirement stated under Tablets using the following method of analysis.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake one tablet with 10 mL of *water*, add sufficient *methanol* to produce 25 mL and filter.

(2) 0.008% w/v of *lamotrigine BPCRS* in *methanol (40%)*.

(3) 0.02% w/v of *lamotrigine impurity standard BPCRS* in *methanol (40%)*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

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The test is not valid unless the chromatogram obtained with solution (3) closely resembles the chromatogram supplied with *lamotrigine impurity standard BPCRS* and the *resolution* between the peaks due to lamotrigine and saccharin sodium is at least 5.0.

DETERMINATION OF CONTENT

Calculate the content of $C_9H_7Cl_2N_5$ in each tablet using the declared content of $C_9H_7Cl_2N_5$ in *lamotrigine BPCRS*.

ASSAY

For tablets containing less than 2 mg and/or less than 2% w/w of lamotrigine.

Use the average of the individual results determined in the test for Uniformity of content.

For tablets containing 2 mg or more than 2% w/w of lamotrigine.

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 20 mg of Lamotrigine with 60 mL of *water*, add sufficient *methanol* to produce 100 mL and filter.

(2) 0.02% w/v of *lamotrigine BPCRS* in *methanol (40%)*.

(3) 0.02% w/v of *lamotrigine impurity standard BPCRS* in *methanol (40%)*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) closely resembles the chromatogram supplied with *lamotrigine impurity standard BPCRS* and the *resolution* between the peaks due to lamotrigine and saccharin sodium is at least 5.0.

DETERMINATION OF CONTENT

Calculate the content of $C_9H_7Cl_2N_5$ in the tablets using the declared content of $C_9H_7Cl_2N_5$ in *lamotrigine BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurity A listed under Lamotrigine.

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Lamotrigine Tablets

General Notices

Lamotrigine Tablets from different manufacturers, whilst complying with the requirements of the monograph, may not be interchangeable.

Action and use

Antiepileptic.

DEFINITION

Lamotrigine Tablets contain Lamotrigine.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of lamotrigine, $C_9H_7Cl_2N_5$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *methanol*.

(1) To a quantity of the powdered tablets containing 0.1 g of Lamotrigine add 20 mL of *methanol*, shake well, dilute to 100 mL with *methanol*, filter and use the filtrate.

(2) 0.1% w/v of *lamotrigine BPCRS*.

(3) 0.1% w/v each of *lamotrigine BPCRS* and *carbamazepine BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air and immediately examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

5 volumes of *concentrated ammonia*, 10 volumes of *methanol* and 85 volumes of *ethyl acetate*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

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The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (1) shows a principal peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2 and rotate the paddle at 50 revolutions per minute.
(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a 10 mL sample of the medium and filter. Measure the *absorbance* of the filtrate, Appendix II B, diluted with the dissolution medium if necessary, at the maximum at 267 nm using dissolution medium in the reference cell.
(2) Measure the *absorbance* of a suitable solution of *lamotrigine BPCRS* in the dissolution medium.

DETERMINATION OF CONTENT

Calculate the total content of lamotrigine, $C_9H_7Cl_2N_5$, in the medium from the absorbances obtained and using the declared content of $C_9H_7Cl_2N_5$ in *lamotrigine BPCRS*.

LIMITS

The amount of Lamotrigine released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 20 volumes of *methanol* and 80 volumes of *0.1M hydrochloric acid* (solution A).

(1) Shake a quantity of the powdered tablets containing 0.20 g of Lamotrigine with 20 mL of *methanol*, dilute to 100 mL with 0.1M *hydrochloric acid*, filter and use the filtrate.
(2) Dilute 1 volume of solution (1) to 100 volumes with 0.1M *hydrochloric acid* and dilute 2 volumes of the resulting solution to 10 volumes with solution A.
(3) 0.2% w/v of *lamotrigine impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS1 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2.0 mL per minute.

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(d) Use an ambient column temperature.

(e) Use a detection wavelength of 275 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.5 volumes of *octylamine*, 20 volumes of *glacial acetic acid*, 100 volumes of *acetonitrile*, 100 volumes of *methanol* and 700 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) closely resembles the chromatogram supplied with *lamotrigine impurity standard BPCRS* and the *resolution* between the peaks due to lamotrigine and saccharin sodium is at least 5.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of the peak corresponding to impurity A is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than 0.5 of the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solution A described under Related substances.

(1) Shake a quantity of the powdered tablets containing 0.2 g of Lamotrigine with 20 mL of *methanol*, add sufficient 0.1M *hydrochloric acid* to produce 100 mL and filter. Dilute 1 volume of the filtrate to 10 volumes with solution A.

(2) Shake 50 mg of *lamotrigine BPCRS* with 20 mL of *methanol* and add sufficient 0.1M *hydrochloric acid* to produce 100 mL.Dilute 2 volumes to 5 volumes with solution A.

(3) 0.2% w/v of *lamotrigine impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) closely resembles the chromatogram supplied with *lamotrigine impurity standard BPCRS* and the *resolution* between the peaks due to lamotrigine and saccharin sodium is at least 5.0.

DETERMINATION OF CONTENT

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Calculate the total content of $C_9H_7Cl_2N_5$ in the tablets using the declared content of $C_9H_7Cl_2N_5$ in *lamotrigine BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurity A listed under Lamotrigine.

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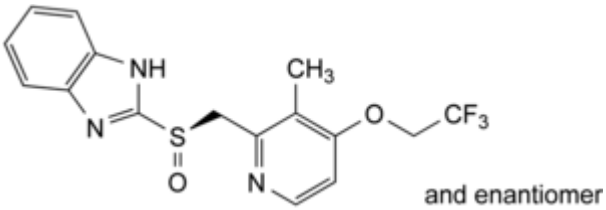
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Lansoprazole

General Notices

(Ph. Eur. monograph 2219)



$C_{16}H_{14}F_3N_3O_2S$ 369.4 *103577-45-3*

Action and use

Proton pump inhibitor; treatment of peptic ulcer disease.

Preparations

Lansoprazole Gastro-resistant Capsules

Lansoprazole Gastro-resistant Tablets

Ph Eur

DEFINITION

2-[(*RS*)-[[3-Methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulfinyl]-1*H*-benzimidazole.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or brownish powder.

Solubility

Practically insoluble in water, soluble in anhydrous ethanol, very slightly soluble in acetonitrile.

It shows polymorphism (*5.9*).

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IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *lansoprazole CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *anhydrous ethanol R*, evaporate to dryness and record new spectra using the residues.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution B_2 or BY_2 (2.2.2, *Method II*).

Dissolve 1.0 g in *dimethylformamide R* and dilute to 20 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use and protect them from light.*

Solvent mixture Mix 1 volume of *triethylamine R* and 60 volumes of *water R* and adjust to pH 10.5 with *phosphoric acid R*; mix this solution with 40 volumes of *acetonitrile R1*.

Test solution Dissolve 10 mg of the substance to be examined in the solvent mixture and dilute to 10 mL with the solvent mixture.

Reference solution (a) Dissolve the contents of a vial of *lansoprazole for peak identification CRS* (containing impurities A and B) in 1.0 mL of the solvent mixture.

Reference solution (b) Dilute 2.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 5 mg of *2-hydroxybenzimidazole R* (impurity D) and 5 mg of *2-mercaptobenzimidazole R* (impurity E) in the solvent mixture and dilute to 100 mL with the solvent mixture. Dilute 1 mL of this solution to 10 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped amidohexadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 1 volume of *triethylamine R* and 60 volumes of *water R* and adjust to pH 6.2 with *phosphoric acid R*; mix this solution with 40 volumes of *acetonitrile R1*.

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 285 nm.

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Injection 10 µL.

Run time 3 times the retention time of lansoprazole.

Identification of impurities Use the chromatogram supplied with *lansoprazole for peak identification CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A and B; use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities D and E.

Relative retention With reference to lansoprazole (retention time = about 7 min): impurity D = about 0.4; impurity A = about 0.5; impurity E = about 0.6; impurity B = about 1.2.

System suitability Reference solution (a):

— *resolution*: minimum 3.0 between the peaks due to lansoprazole and impurity B.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity E by 0.4;

— *impurity B*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.4 per cent);

— *impurities A, D, E*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.6 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (*2.5.32*)

Maximum 0.1 per cent, determined on 0.150-0.200 g using the evaporation technique:

— *temperature*: 50-70 °C;

— *heating time*: 15 min;

— *flow rate*: 150 mL/min.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

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Dissolve 0.300 g in 40 mL of *ethanol (96 per cent) R* and dilute to 50 mL with *water R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M sodium hydroxide* is equivalent to 36.94 mg of $C_{16}H_{14}F_3N_3O_2S$.

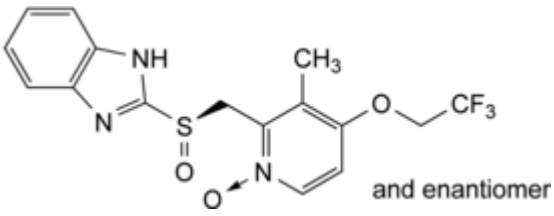
STORAGE

In an airtight container, protected from light.

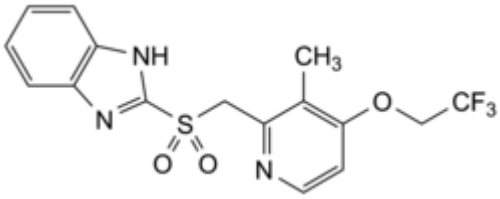
IMPURITIES

Specified impurities *A, B, D, E.*

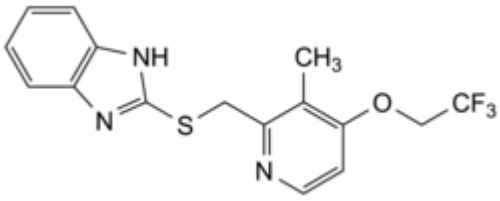
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, F.*



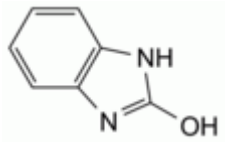
A. 2-[(*RS*)-[[3-methyl-1-oxido-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulfinyl]-1*H*-benzimidazole,



B. 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulfonyl]-1*H*-benzimidazole,

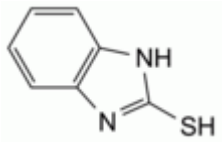


C. 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulfanyl]-1*H*-benzimidazole,

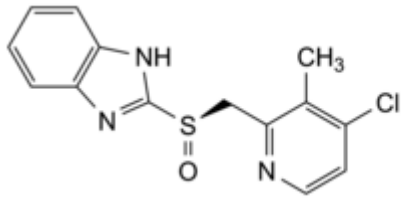


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D. 1*H*-benzimidazol-2-ol,



E. 1*H*-benzimidazole-2-thiol,



and enantiomer

F. 2-[(*RS*)-[(4-chloro-3-methylpyridin-2-yl)methyl]sulfinyl]-1*H*-benzimidazole.

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Lansoprazole Gastro-resistant Capsules

General Notices

Gastro-resistant Lansoprazole Capsules

Action and use

Proton pump inhibitor; treatment of peptic ulcer disease.

DEFINITION

Lansoprazole Gastro-resistant Capsules contain Lansoprazole. They are covered with a gastro-resistant coating or prepared from granules or particles covered with a gastro-resistant coating.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of lansoprazole, $C_{16}H_{14}F_3N_3O_2S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the finely powdered contents of the capsules containing 30 mg of Lansoprazole with 50 mL of *methanol*, filter and dilute 1 volume to 50 volumes. The *light absorption*, Appendix II B, in the range 220 nm to 350 nm exhibits a maximum at 284 nm.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

Mix 11 volumes of 0.25M *trisodium orthophosphate* and 22 volumes of 0.5M *anhydrous disodium hydrogen orthophosphate*, dilute to 100 volumes with *water* and adjust the pH, if necessary, to 11.0 with *orthophosphoric acid* or 10M *sodium hydroxide*, as appropriate (solution A).

Mix 1 volume of 10M *sodium hydroxide* with 99 volumes of *0.05M phosphate buffer solution pH 4.5* (solution B).

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 150 revolutions per minute.

(b) Use as the media the solutions described sequentially below.

First stage (pH 4.5)

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Use as the medium 700 mL of *0.05*M *phosphate buffer solution pH 4.5*. After 45 minutes, withdraw 5 mL of the medium, filter, dilute to 25 mL with solution A and retain the samples for analysis as described below. Proceed immediately to the final stage.

Final stage (pH 6.8)

Within 5 minutes, add 200 mL of solution B at 37° to the vessel. Maintain the rotation speed at 150 revolutions per minute and continue to operate the apparatus for 45 minutes. Withdraw 5 mL of the medium, filter, dilute to 25 mL with solution A and retain the samples for analysis as described below.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Use the sample solutions taken above.

(2) Dissolve a sufficient quantity of *lansoprazole BPCRS* in solution A and dilute with sufficient *water* to produce a final solution of the same concentration as that expected for solution (1).

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the total content of $C_{16}H_{14}F_3N_3O_2S$ in the medium using the declared content of $C_{16}H_{14}F_3N_3O_2S$ in *lansoprazole BPCRS*.

LIMITS

The amount of lansoprazole released after the first stage is not more than 10% of the stated amount. The amount of lansoprazole released after the final stage is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions protected from light.

Mix 1 volume of *triethylamine* with 60 volumes of *water*, adjust the pH to 10.5 using *orthophosphoric acid*, add 40 volumes of *acetonitrile* and mix (solvent A).

(1) Shake a quantity of the finely powdered contents of the capsules containing 50 mg of Lansoprazole with 50 mL of solvent A and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with solvent A and dilute a further 1 volume to 5 volumes with solvent A.

(3) Dilute 1 volume of solution (2) to 4 volumes with solvent A.

(4) 0.1% w/v of *lansoprazole impurity standard BPCRS* in solvent A.

(5) 0.0004% w/v of *2-mercaptobenzimidazole* (impurity E) in solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *amidohexadecylsilyl* *silica gel for chromatography* (5 µm) (Supelcosil LC-ABZ is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use an ambient column temperature.

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(e) Use a detection wavelength of 285 nm.

(f) Inject 10 µL of each solution.

(g) Identify any peaks in the chromatogram obtained with solution (1) corresponding to lansoprazole impurities A and B using solution (3).

MOBILE PHASE

1 volume of *triethylamine*, 60 volumes of *water*, adjusted to pH 6.2 using *orthophosphoric acid* and 40 volumes of *acetonitrile*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to lansoprazole and impurity B is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any peak corresponding to impurity B is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity E is not greater than the area of the principal peak in the chromatogram obtained with solution (5) (0.4%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* is not more than 2.0%.

Disregard any peak with an area less the area of the principal peak in the chromatogram obtained with solution (3) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions and protect from light.

Mix 1 volume of *triethylamine* with 60 volumes of *water*, adjust the pH to 10.5 using *orthophosphoric acid*, add 40 volumes of *acetonitrile* and mix (solvent A).

(1) Add a quantity of the finely powdered mixed contents of 20 capsules containing 20 mg of Lansoprazole to 100 mL of solvent A, shake for 30 minutes and filter.

(2) 0.02% w/v of *lansoprazole BPCRS*.

(3) 0.01% w/v of *lansoprazole impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

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The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to lansoprazole and impurity B is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{16}H_{14}F_3N_3O_2S$ in the capsules using the declared content of $C_{16}H_{14}F_3N_3O_2S$ in *lansoprazole BPCRS*.

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Lansoprazole Gastro-resistant Tablets

General Notices

Gastro-resistant Lansoprazole Tablets

Action and use

Proton pump inhibitor; treatment of peptic ulcer disease.

DEFINITION

Lansoprazole Gastro-resistant Tablets contain Lansoprazole. They are covered with a gastro-resistant coating or prepared from granules or particles covered with a gastro-resistant coating.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of lansoprazole, $C_{16}H_{14}F_3N_3O_2S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A Shake a quantity of the powdered tablets containing 30 mg of Lansoprazole with 50 mL of *methanol*, filter and dilute 1 volume to 50 volumes. The *light absorption*, Appendix II B, in the range 220 nm to 350 nm exhibits a maximum at 285 nm.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

Mix 11 volumes of 0.25M *trisodium orthophosphate* and 22 volumes of 0.5M *anhydrous disodium hydrogen orthophosphate*, dilute to 100 volumes with *water* and adjust the pH, if necessary, to 11.0 with *orthophosphoric acid* or 10M *sodium hydroxide*, as appropriate (solution A).

Mix 1 volume of 10M *sodium hydroxide* with 99 volumes of *0.05M phosphate buffer solution pH 4.5* (solution B).

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 150 revolutions per minute.

(b) Use as the media the solutions described sequentially below.

First stage (pH 4.5)

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Use as the medium 700 mL of *0.05*M *phosphate buffer solution pH 4.5*. After 45 minutes, withdraw 5 mL of the medium, filter, dilute to 25 mL with solution A and retain the samples for analysis as described below. Proceed immediately to the final stage.

Final stage (pH 6.8)

Within 5 minutes, add 200 mL of solution B at 37° to the vessel. Maintain the rotation speed at 150 revolutions per minute and continue to operate the apparatus for 45 minutes. Withdraw 5 mL of the medium, filter, dilute to 25 mL with solution A and retain the samples for analysis as described below.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) The sample solutions taken above.
(2) Dissolve a sufficient quantity of *lansoprazole BPCRS* in solution A and dilute with sufficient *water* to produce a final solution of the same concentration as that expected for solution (1).

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the total content of $C_{16}H_{14}F_3N_3O_2S$, in the medium using the declared content of $C_{16}H_{14}F_3N_3O_2S$ in *lansoprazole BPCRS*.

LIMITS

The amount of lansoprazole released after the first stage is not more than 10% of the stated amount. The amount of lansoprazole released after the final stage is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions protected from light.

Mix 1 volume of *triethylamine* with 60 volumes of *water*, adjust the pH to 10.5 using *orthophosphoric acid*, add 40 volumes of *acetonitrile* and mix (solvent A).

(1) Shake a quantity of the powdered tablets containing 50 mg of Lansoprazole with 50 mL of solvent A and filter.
(2) Dilute 1 volume of solution (1) to 100 volumes with solvent A and dilute a further 1 volume to 5 volumes with solvent A.
(3) Dilute 1 volume of solution (2) to 4 volumes with solvent A.
(4) 0.1% w/v of *lansoprazole impurity standard BPCRS* in solvent A.
(5) 0.0003% w/v of *2-mercaptobenzimidazole* (impurity E) in solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *amidohexadecylsilyl* *silica gel for chromatography* (5 µm) (Supelcosil LC-ABZ is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.2 mL per minute.
(d) Use an ambient column temperature.

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(e) Use a detection wavelength of 285 nm.

(f) Inject 10 µL of each solution.

(g) Identify any peaks in the chromatogram obtained with solution (1) corresponding to lansoprazole impurities A and B using solution (3).

MOBILE PHASE

1 volume of *triethylamine*, 60 volumes of *water*, adjusted to pH 6.2 using *orthophosphoric acid* and mix the solution with 40 volumes of *acetonitrile*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to lansoprazole and impurity B is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any peak corresponding to impurity B is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the area of any peak corresponding to impurity E is not greater than the area of the principal peak in the chromatogram obtained with solution (5) (0.3%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* is not more than 2.0%.

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (3) (0.05%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solvent A, protected from light.

Mix 1 volume of *triethylamine* with 60 volumes of *water*, adjust the pH to 10.5 using *orthophosphoric acid*, add 40 volumes of *acetonitrile* and mix (solvent A).

(1) To a quantity of the powdered tablets containing 50 mg of Lansoprazole add 50 mL of solvent A, shake for 30 minutes and filter. Dilute 1 volume to 5 volumes with solvent A.

(2) 0.02% w/v of *lansoprazole BPCRS*.

(3) 0.01% w/v of *lansoprazole impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

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SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to lansoprazole and impurity B is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of lansoprazole, $C_{16}H_{14}F_3N_3O_2S$, in the tablets using the declared content of $C_{16}H_{14}F_3N_3O_2S$ in *lansoprazole BPCRS*.

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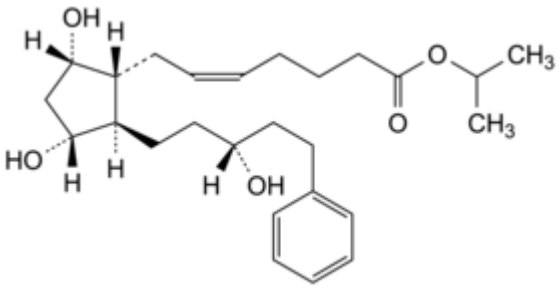
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Latanoprost

General Notices

(Ph. Eur. monograph 2230)



$C_{26}H_{40}O_5$ 432.6 *130209-82-4*

Action and use

Prostaglandin analogue; treatment of intraocular pressure

Ph Eur

DEFINITION

Propan-2-yl (5*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(3*R*)-3-hydroxy-5-phenylpentyl]cyclopentyl]hept-5-enoate.

Content

94.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Clear, colourless or yellow, viscous, oily liquid.

Solubility

Practically insoluble in water, very soluble in acetonitrile, freely soluble in anhydrous ethanol.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of latanoprost*.

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B. Specific optical rotation (see Tests).

TESTS

Specific optical rotation (2.2.7)

+ 32.0 to + 37.0 (anhydrous substance).

Dissolve 0.100 g in *acetonitrile R* and dilute to 10.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light.*

Test solution Dissolve 20.0 mg of the substance to be examined in 2 mL of *anhydrous ethanol R* and dilute to 10.0 mL with *heptane R*.

Reference solution (a) Dissolve the contents of a vial of *latanoprost for system suitability CRS* (containing impurities E and F) in 200 µL of *anhydrous ethanol R* then add 800 µL of *heptane R*.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *heptane R*. Dilute 1.0 mL of this solution to 10.0 mL with *heptane R*.

Reference solution (c) Dissolve 20.0 mg of *latanoprost CRS* in 2 mL of *anhydrous ethanol R* and dilute to 10.0 mL with *heptane R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase *anhydrous ethanol R*, *heptane R* (6:94 *V/V*).

Flow rate 1.3 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 10 µL of the test solution and reference solutions (a) and (b).

Run time Twice the retention time of latanoprost.

Identification of impurities Use the chromatogram supplied with *latanoprost for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities E and F.

Relative retention With reference to latanoprost (retention time = about 16 min): impurity E = about 0.9; impurity F = about 1.1.

System suitability Reference solution (a):

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— *resolution*: minimum 2.0 between the peaks due to latanoprost and impurity F.

Calculation of percentage contents:

— for each impurity, use the concentration of latanoprost in reference solution (b).

Limits:

— *impurity F*: maximum 3.5 per cent;

— *impurity E*: maximum 0.4 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *sum of impurities other than F*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent.

Impurity H

Liquid chromatography (*2.2.29*).

Solvent mixture *acetonitrile R*, *water R* (30:70 *V/V*).

Test solution Dissolve 25.0 mg of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Reference solution (a) Dissolve the contents of a vial of *latanoprost impurity H CRS* in 1.0 mL of the solvent mixture.

Reference solution (b) To 50 µL of the test solution add 450 µL of reference solution (a).

Column:

— *size*: *l* = 0.15 m, Ø = 4 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 60 °C.

Mobile phase:

— *mobile phase A*: *phosphoric acid R*, *acetonitrile R1*, *water for chromatography R* (0.1:30:70 *V/V/V*);

— *mobile phase B*: *phosphoric acid R*, *water for chromatography R*, *acetonitrile R1* (0.1:20:80 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 9	100	0
9 - 10	100 → 0	0 → 100

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
10 - 15	0	100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 200 nm.

Injection 50 µL.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity H.

Relative retention With reference to latanoprost (retention time = about 12 min): impurity H = about 0.7.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to impurity H and latanoprost.

Calculation of percentage content:

— use the concentration of impurity H in reference solution (a).

Limit:

— *impurity H*: maximum 0.15 per cent.

Water (*2.5.32*)

Maximum 0.50 per cent, determined on 0.100 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection Test solution and reference solution (c).

Calculate the percentage content of $C_{26}H_{40}O_5$ taking into account the assigned content of *latanoprost CRS*.

STORAGE

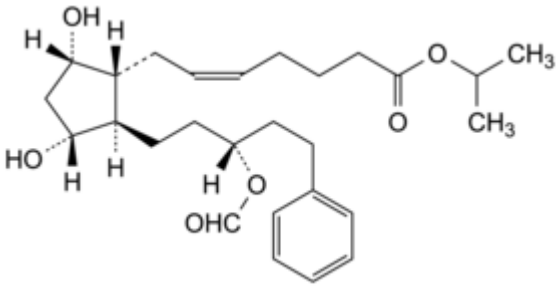
At a temperature of 2 °C to 8 °C.

IMPURITIES

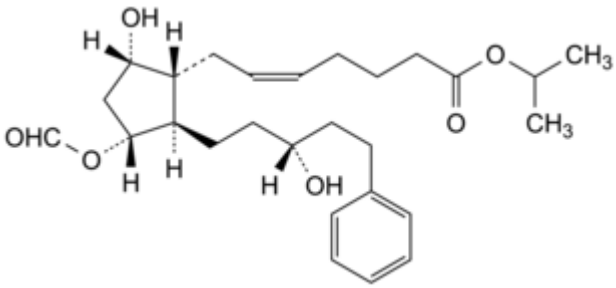
Specified impurities *E, F, H.*

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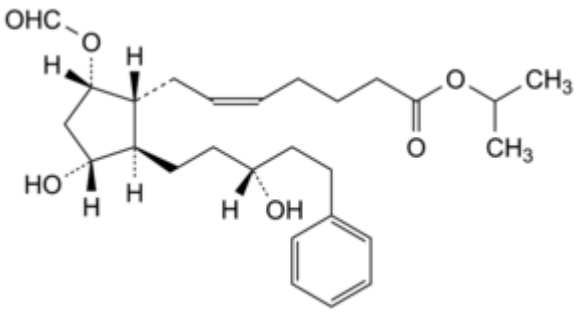
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, G, J.*



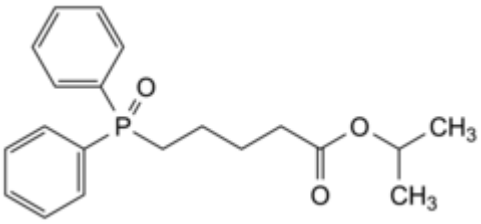
A. propan-2-yl (5*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-2-[(3*R*)-3-(formyloxy)-5-phenylpentyl]-3,5-dihydroxycyclopentyl]hept-5-enoate,



B. propan-2-yl (5*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3-(formyloxy)-5-hydroxy-2-[(3*R*)-3-hydroxy-5-phenylpentyl]cyclopentyl]hept-5-enoate,

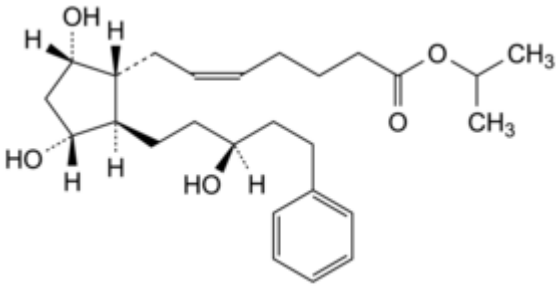


C. propan-2-yl (5*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-5-(formyloxy)-3-hydroxy-2-[(3*R*)-3-hydroxy-5-phenylpentyl]cyclopentyl]hept-5-enoate,

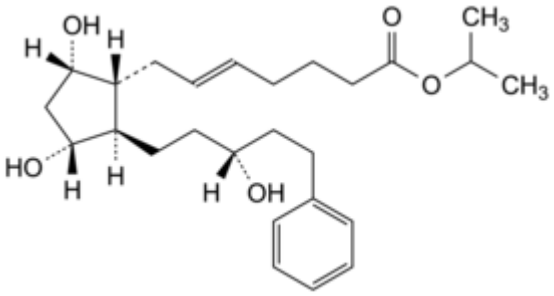


D. propan-2-yl 5-(diphenylphosphoryl)pentanoate,

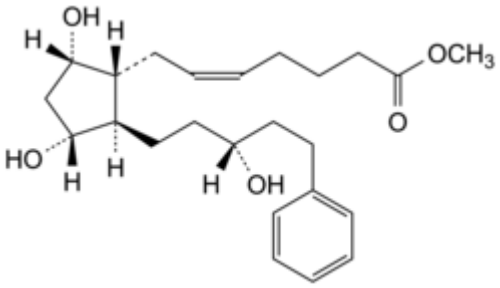
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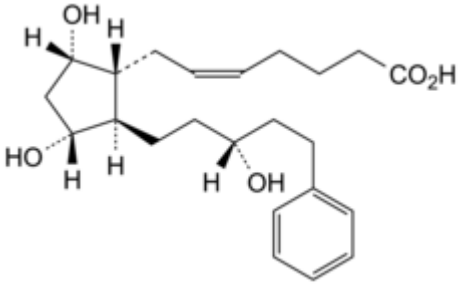
E. propan-2-yl (5*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(3*S*)-3-hydroxy-5-phenylpentyl]cyclopentyl]hept-5-enoate,



F. propan-2-yl (5*E*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(3*R*)-3-hydroxy-5-phenylpentyl]cyclopentyl]hept-5-enoate,

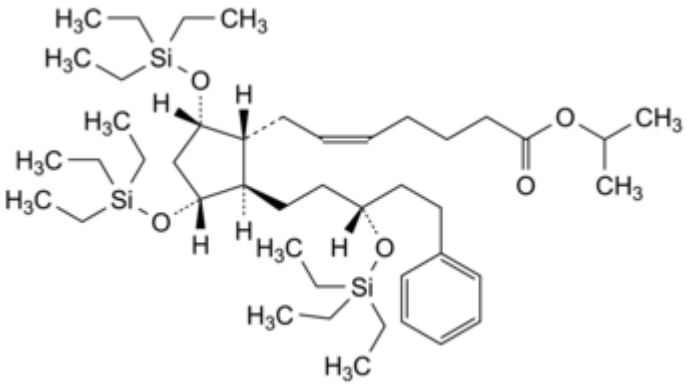


G. methyl (5*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(3*R*)-3-hydroxy-5-phenylpentyl]cyclopentyl]hept-5-enoate,



H. (5*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(3*R*)-3-hydroxy-5-phenylpentyl]cyclopentyl]hept-5-enoic acid,

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J. propan-2-yl (5*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-2-[(3*R*)-5-phenyl-3-[(triethylsilyl)oxy]pentyl]-3,5-bis[(triethylsilyl)oxy]cyclopentyl]hept-5-enoate.

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Lauromacrogol 400

General Notices

(Ph. Eur. monograph 2046)

Action and use

Non-ionic surfactant; sclerosant.

Ph Eur

DEFINITION

Mixture of lauryl alcohol (dodecanol) monoethers of mixed macrogols. It may contain some free macrogols and it contains various amounts of free lauryl alcohol. The number of moles of ethylene oxide reacted per mole of lauryl alcohol is 9. The name of the substance is followed by a number (400) corresponding approximately to the average molecular mass of the macrogol portion.

This monograph applies to lauromacrogol 400 used as active substance.

CHARACTERS

Appearance

White or almost white, unctuous and hygroscopic mass, melting at 24 °C into a colourless or yellowish, viscous liquid.

Solubility

Freely soluble in water, very soluble in acetone and in ethanol (96 per cent).

IDENTIFICATION

A. Hydroxyl value (see Tests).

B. Saponification value (see Tests).

C. Warm the substance to be examined in an incubator at 50 °C for 1 h until fully molten and clear. Transfer 50 mL to a warmed cloud-point tube (flat-bottomed glass tube 30-33.5 mm in internal diameter and 115-125 mm high). Insert the tube into a cooling bath that allows the outer surface of the tube to be in contact with chilled air, contained within a cylindrical metal container (internal diameter 9.5-12.5 mm greater than the external diameter of the sample tube, 115 mm high) that is surrounded by iced water. The base of the glass tube rests on a 6 mm thick cork disc, which prevents direct thermal contact with the cooled metal cylinder. Stir the substance to be examined continuously with a thermometer so that the temperature is constant throughout the substance. Periodically lift the tube out of the cooling bath to check for signs of cloudiness at the bottom of the tube. Examine the tube against a bright light source. When cloudiness is first observed, check more frequently until the substance becomes completely cloudy and the thermometer, suspended in the centre of the substance, is only just visible when viewed horizontally. Record the temperature. It is 20 °C to 25 °C.

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TESTS

Appearance

The molten substance to be examined is clear (2.2.1) and not more intensely coloured than reference solution GY_6 (2.2.2, Method I).

Alkalinity

Dissolve 2.0 g in a hot mixture of 10 mL of carbon dioxide-free water R and 10 mL of ethanol (96 per cent) R. Add 0.1 mL of bromothymol blue solution R1. Not more than 0.5 mL of 0.1 M hydrochloric acid is required to change the colour of the indicator to yellow.

Acid value (2.5.1)

Maximum 1.0, determined on 5.0 g.

Hydroxyl value (2.5.3, Method A)

90 to 105, determined on 2.0 g.

Iodine value (2.5.4, Method A)

Maximum 2.0.

Peroxide value

Maximum 5.0.

Introduce 10.0 g into a 100 mL beaker, dissolve with glacial acetic acid R and dilute to 20 mL with the same solvent. Add 1 mL of saturated potassium iodide solution R, mix and allow to stand for 1 min. Add 50 mL of carbon dioxide-free water R. Titrate with 0.01 M sodium thiosulfate, determining the end-point potentiometrically (2.2.20). Carry out a blank titration.

Determine the peroxide value using the following expression:

$$\frac{\left(n_1 - n_2\right) \times M \times 1000}{m}$$

n_1 = volume of 0.01 M sodium thiosulfate required for the substance to be examined, in millilitres;

n_2 = volume of 0.01 M sodium thiosulfate required for the blank titration, in millilitres;

M = molarity of the sodium thiosulfate solution, in moles per litre;

m = mass of the substance to be examined, in grams.

Saponification value (2.5.6)

Maximum 3.0.

Free lauryl alcohol (dodecanol)

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Gas chromatography (2.2.28).

Test solution Dissolve 0.200 g of the substance to be examined in acetone R and dilute to 10.0 mL with the same solvent.

Reference solution Dissolve 2.00 g of lauryl alcohol R in acetone R and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of the solution to 50.0 mL with acetone R.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.25 mm;

— *stationary phase*: phenyl(5)methyl(95)polysiloxane R (film thickness 0.1 µm).

Carrier gas helium for chromatography R.

Flow rate 1 mL/min.

Split ratio 50:1.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 1	120
	1 - 23	120 → 350
	23 - 33	350
Injection port		300
Detector		350

Detection Flame ionisation.

Injection 1.0 µL.

Retention time Lauryl alcohol = about 5 min.

Limit:

— *free lauryl alcohol*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (2.0 per cent).

Free macrogols

Size-exclusion chromatography (2.2.30).

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Test solution Dissolve 5.0 g of the substance to be examined in the mobile phase and dilute to 250.0 mL with the mobile phase.

Reference solution (a) Dissolve about 0.4 g of *macrogol 1000 R* in the mobile phase and dilute to 250.0 mL with the mobile phase.

Reference solution (b) Dilute 50.0 mL of reference solution (a) to 100.0 mL with the mobile phase.

Precolumns (2):

— *size*: *l* = 0.125 m, Ø = 4 mm;

— *stationary phase*: spherical *octadecylsilyl silica gel for chromatography R* (5 µm) with a pore size of 10 nm.

Column:

— *size*: *l* = 0.30 m, Ø = 7.8 mm;

— *stationary phase*: *hydroxylated polymethacrylate gel R* (6 µm) with a pore size of 12 nm.

Connect both precolumns to the column using a 3-way valve and switch the mobile phase flow according to the following programme:

— 0-114 s: precolumn 1 and column;

— 115 s to the end: precolumn 2 and column;

— 115 s to 8 min: flow back of precolumn 1.

Mobile phase *water R*, *methanol R* (2:8 *V/V*).

Flow rate 1.1 mL/min.

Detection Refractometer.

Injection 20 µL.

Calculate the percentage content of free macrogols using the following expression:

$$\frac{A_1 \times m_2 \times 200}{m_1 \times \left(A_2 + 2A_3\right)}$$

m_1 = mass of the substance to be examined in the test solution, in grams;

m_2 = mass of *macrogol 1000 R* in reference solution (a), in grams;

A_1 = area of the peak due to free macrogols in the chromatogram obtained with the test solution;

A_2 = area of the peak due to macrogol 1000 in the chromatogram obtained with reference solution (a);

A_3 = area of the peak due to macrogol 1000 in the chromatogram obtained with reference solution (b).

Limit:

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— *free macrogols*: maximum 3.0 per cent.

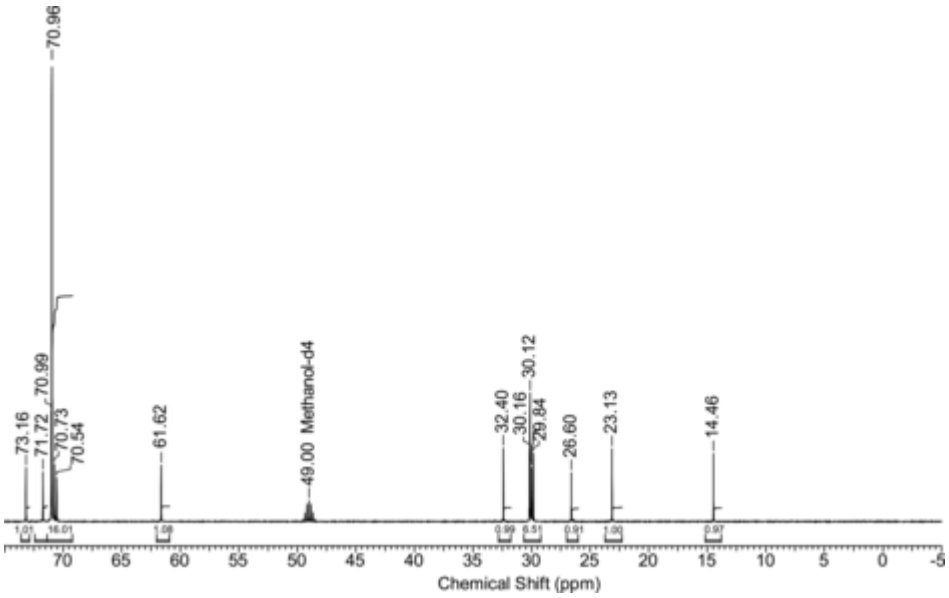


Figure 2046.-1. – *^{13}C NMR spectrum of lauromacrogol 400*

Average chain length of the fatty alcohol and average number of moles of ethylene oxide

Nuclear magnetic resonance spectrometry (2.2.33).

Test solution If the substance is in the solid state at room temperature, heat gently before sampling. Dissolve 0.4 mL of the substance to be examined in 0.3 mL of a mixture of 1 volume of *deuterated methanol R* and 2 volumes of *deuterated chloroform R*, containing 0.1 mol/L of *chromium(III) acetylacetonate R* as a relaxation aid.

Apparatus High resolution FT-NMR spectrometer operating at minimum 300 MHz.

Acquisition of ^{13}C NMR spectra The following parameters may be used:

— *sweep width*: 250 ppm (-15 ppm to 235 ppm);

— *irradiation frequency offset*: 110 ppm;

— *time domain*: 64 K;

— *pulse delay*: 3 s;

— *pulse program*: zgig 30 (inverse gated, 30° excitation pulse);

— *dummy scans*: 4;

— *number of scans*: 2048.

Processing and plotting The following parameters may be used:

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— *size*: 64 K (zero-filling);

— *window multiplication*: exponential;

— *Lorentzian broadening factor*: 1 Hz.

Use the CD_3OD signal for shift referencing. The shift of the central peak of the multiplet is set to 49.0 ppm.

Plot the spectral region δ 0.0-80.0 ppm. Compare the spectrum with the spectrum in Figure 2046.-1. The shift values lie near the values given in Table 2046.-1.

Table 2046.-1. – *Shift values*

Signal	Shift (ppm)	Normalised integrals
CH_3	14.4	0.989
CH_2 (alkyl chain)	23.2	1.000
CH_2 (alkyl chain)	25.5	1.001
CH_2's (alkyl chain)	30	7.410
CH_2 (alkyl chain)	32.5	0.963
CH_2 ($-CH_2-OH$) (end CH_2-group of macrogol)	61.6	1.001
CH_2's (macrogol)	70.7	16.25
CH_2 (R-CH-O-macrogol) (CH_2 in alpha position)	72.6	0.998
CH_2 (macrogol)	73.1	0.929

System suitability:

— *signal-to-noise ratio*: minimum 150, for the smallest relevant peak (CH_2 at 73.1 ppm);

— *peak width at half-height*: maximum 0.05 ppm, for the central $CDCl_3$ signal (at δ 78.6 ppm).

Calculation of the average chain length of the fatty alcohol and the average number of moles of ethylene oxide Define the signal at 23.2 ppm as 1.000 and normalise the integrals of the other signals listed in Table 2046.-1.

The average chain length of the fatty alcohol is calculated using the following expression:

$$\Sigma_{14-33} I_{n,i} + I_{n,72.6}$$

$\Sigma_{14-33} I_{n,i}$ = sum of the normalised integrals of the signals from 14 ppm to 33 ppm;

$I_{n,72.6}$ = normalised integral of the signal at 72.6 ppm.

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The average number of moles of ethylene oxide is calculated using the following expression:

$$0.5 \times \left(I_{n,62} + I_{n,71} + I_{n,73}\right)$$

$I_{n,62}$, $I_{n,71}$, $I_{n,73}$ = normalised integral of the signals at 62 ppm, 71 ppm and 73 ppm respectively.

The sum of the normalised integrals of the signals at 62 ppm, 71 ppm and 73 ppm corresponds to the average number of methylene groups in the macrogol part of lauromacrogol 400.

Limits:

— *average chain length of the fatty alcohol*: 10.0 to 14.0;

— *average number of moles of ethylene oxide*: 7.0 to 11.0.

Ethylene oxide and dioxan (*2.4.25, Method A*)

Maximum 1 ppm of ethylene oxide and maximum 10 ppm of dioxan.

Water (*2.5.12*)

Maximum 2.0 per cent, determined on 0.500 g.

Total ash (*2.4.16*)

Maximum 0.2 per cent, determined on 2.0 g.

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Lauroyl Macrogolglycerides

General Notices

(Ph. Eur. monograph 1231)

Action and use

Excipient.

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DEFINITION

Mixtures of monoesters, diesters and triesters of glycerol and monoesters and diesters of macrogols with a mean relative molecular mass between 300 and 1500.

They are obtained by partial alcoholysis of saturated oils mainly containing triglycerides of lauric (dodecanoic) acid, using macrogol, or by esterification of glycerol and macrogol with saturated fatty acids, or by mixing glycerol esters and condensates of ethylene oxide with the fatty acids of these hydrogenated oils.

CHARACTERS

Appearance

Pale yellow waxy solid.

Solubility

Dispersible in hot water, freely soluble in methylene chloride.

IDENTIFICATION

A. Thin-layer chromatography (2.2.27).

Test solution Dissolve 1.0 g of the substance to be examined in *methylene chloride R* and dilute to 20 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase *hexane R*, *ether R* (30:70 *V/V*).

Application 10 µL.

Development Over a path of 15 cm.

Drying In air.

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Detection Spray with a 0.1 g/L solution of *rhodamine B R* in *ethanol (96 per cent) R* and examine in ultraviolet light at 365 nm.

Results The chromatogram shows a spot due to triglycerides with an R_F value of about 0.9 (R_{st} 1) and spots due to 1,3-diglycerides (R_{st} 0.7), to 1,2-diglycerides (R_{st} 0.6), to monoglycerides (R_{st} 0.1) and to esters of macrogol (R_{st} 0).

B. Hydroxyl value (see Tests).

C. Saponification value (see Tests).

D. Composition of fatty acids (see Tests).

TESTS

Drop point (*2.2.17*)

Introduce into the cup the substance to be examined, which has been melted by heating for 1 h in an oven at 100 ± 2 °C, and allow to stand for 5 h at about 5 °C.

Ethylene oxide units per molecule (nominal value)	Type of macrogol	Drop point
6	300	33 - 38
8	400	36 - 41
12	600	38 - 43
32	1500	42.5 - 47.5

Acid value (*2.5.1*)

Maximum 2.0, determined on 2.0 g.

Hydroxyl value (*2.5.3, Method A*)

Use 1.0 g.

Ethylene oxide units per molecule (nominal value)	Type of macrogol	Hydroxyl value
6	300	65 - 85
8	400	60 - 80
12	600	50 - 70
32	1500	36 - 56

Peroxide value (*2.5.5, Method A*)

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Maximum 6.0, determined on 2.0 g.

Saponification value (*2.5.6*)

Use 2.0 g.

Ethylene oxide units per molecule (nominal value)	Type of macrogol	Saponification value
6	300	190 - 204
8	400	170 - 190
12	600	150 - 170
32	1500	79 - 93

Alkaline impurities

Introduce 5.0 g into a test tube and carefully add a mixture, neutralised if necessary with *0.01 M hydrochloric acid* or with *0.01 M sodium hydroxide*, of 0.05 mL of a 0.4 g/L solution of *bromophenol blue R* in *ethanol (96 per cent) R*, 0.3 mL of *water R* and 10 mL of *ethanol (96 per cent) R*. Shake and allow to stand. Not more than 1.0 mL of *0.01 M hydrochloric acid* is required to change the colour of the upper layer to yellow.

Free glycerol

Maximum 3.0 per cent.

Dissolve 1.20 g in 25.0 mL of *methylene chloride R*. Heat if necessary. After cooling, add 100 mL of *water R*. Shake and add 25.0 mL of *periodic acetic acid solution R*. Shake and allow to stand for 30 min. Add 40 mL of a 75 g/L solution of *potassium iodide R*. Allow to stand for 1 min. Add 1 mL of *starch solution R*. Titrate the iodine with *0.1 M sodium thiosulfate*. Carry out a blank titration.

1 mL of *0.1 M sodium thiosulfate* is equivalent to 2.3 mg of glycerol.

Composition of fatty acids (*2.4.22, Method A*)

Composition of the fatty-acid fraction of the substance:

— *caprylic acid*: maximum 15.0 per cent;

— *capric acid*: maximum 12.0 per cent;

— *lauric acid*: 30.0 per cent to 50.0 per cent;

— *myristic acid*: 5.0 per cent to 25.0 per cent;

— *palmitic acid*: 4.0 per cent to 25.0 per cent;

— *stearic acid*: 5.0 per cent to 35.0 per cent.

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Ethylene oxide and dioxan (2.4.25)

Maximum 1 ppm of ethylene oxide and maximum 10 ppm of dioxan.

Water (2.5.12)

Maximum 1.0 per cent, determined on 1.00 g. Use a mixture of 30 volumes of *anhydrous methanol R* and 70 volumes of *methylene chloride R* as solvent.

Total ash (2.4.16)

Maximum 0.1 per cent.

LABELLING

The label states the type of macrogol used (mean relative molecular mass) or the number of units of ethylene oxide per molecule (nominal value).

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for lauroyl macrogolglycerides used as self-emulsifying agents, solubilisers, modified-release agents and wetting agents for powders and tablets.

Hydroxyl value

(see Tests).

Saponification value

(see Tests).

Composition of fatty acids

(see Tests).

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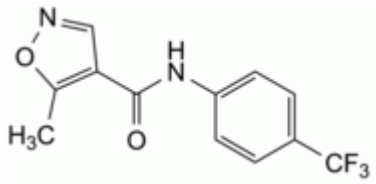
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Leflunomide

General Notices

(Ph. Eur. monograph 2330)



$C_{12}H_9F_3N_2O_2$ 270.2

Action and use

Immunomodulator.

Preparation

Leflunomide Tablets

Ph Eur

DEFINITION

5-Methyl-*N*-[4-(trifluoromethyl)phenyl]isoxazole-4-carboxamide.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, freely soluble in methanol, sparingly soluble in methylene chloride.

It shows polymorphism (*5.9*).

IDENTIFICATION

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Infrared absorption spectrophotometry (2.2.24).

Preparation Heat the substance to be examined and the reference substance at 130 °C for 10 min.

Comparison *leflunomide CRS*.

TESTS

Related substances

Liquid chromatography (2.2.29). *Store all solutions protected from light.*

Test solution (a) Dissolve 25.0 mg of the substance to be examined in 5 mL of *acetonitrile for chromatography R* and dilute to 50.0 mL with the mobile phase.

Test solution (b) Dissolve 0.125 g of the substance to be examined in 5 mL of *acetonitrile for chromatography R* and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dilute 5.0 mL of test solution (a) to 50.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve 12.5 mg of *leflunomide impurity A CRS* in 5 mL of *acetonitrile for chromatography R* and dilute to 100.0 mL with the mobile phase. Dilute 10.0 mL of the solution to 100.0 mL with the mobile phase. Dilute 2.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (c) Dissolve 25.0 mg of *leflunomide CRS* in 5 mL of *acetonitrile for chromatography R* and dilute to 50.0 mL with the mobile phase.

Reference solution (d) Dissolve the contents of 1 vial of *leflunomide for peak identification CRS* (containing impurities B and C) in 2.0 mL of the mobile phase and sonicate for 10 min.

Column:

— *size*: *l* = 0.125 m, Ø = 4.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 5 volumes of *triethylamine R* with 650 volumes of *water for chromatography R*, adjust to pH 3.4 ± 0.1 with *phosphoric acid R* and add 350 volumes of *acetonitrile for chromatography R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 20 µL of test solutions (a) and (b) and reference solutions (a), (b) and (d).

Run time Twice the retention time of leflunomide.

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Identification of impurities Use the chromatogram supplied with *leflunomide for peak identification CRS* and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities B and C.

Relative retention With reference to leflunomide (retention time = about 25 min): impurity B = about 0.2; impurity A = about 0.4; impurity C = about 0.9.

System suitability Reference solution (d):

— *peak-to-valley ratio*: minimum 3, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to leflunomide.

Limits Test solution (a):

— *impurity B*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *sum of impurities C and E*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *sum of impurities other than B*: not more twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Limit Test solution (b):

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.01 per cent).

Loss on drying (2.2.32)

Maximum 0.3 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C for 4 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution (a) and reference solution (c).

Calculate the percentage content of $C_{12}H_9F_3N_2O_2$ from the declared content of *leflunomide CRS*.

STORAGE

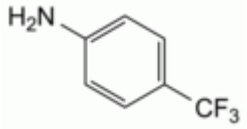
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Protected from light.

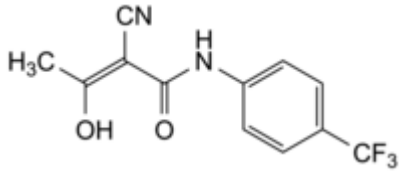
IMPURITIES

Specified impurities *A, B.*

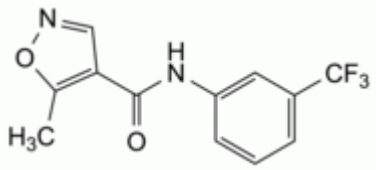
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, D, E, F, G, H.*



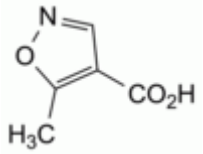
A. 4-(trifluoromethyl)aniline,



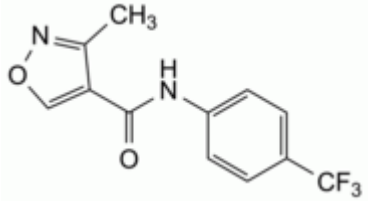
B. (2*Z*)-2-cyano-3-hydroxy-*N*-[4-(trifluoromethyl)phenyl]but-2-enamide (teriflunomide),



C. 5-methyl-*N*-[3-(trifluoromethyl)phenyl]isoxazole-4-carboxamide,

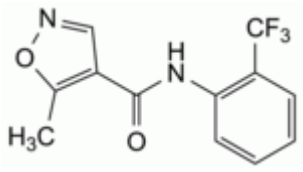


D. 5-methylisoxazole-4-carboxylic acid,

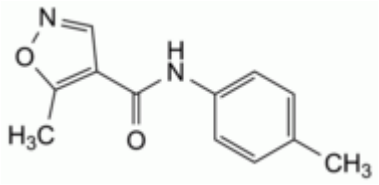


E. 3-methyl-*N*-[4-(trifluoromethyl)phenyl]isoxazole-4-carboxamide,

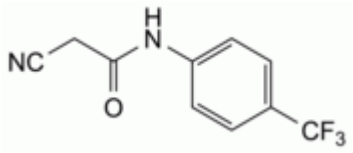
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F. 5-methyl-*N*-[2-(trifluoromethyl)phenyl]isoxazole-4-carboxamide,



G. 5-methyl-*N*-(4-methylphenyl)isoxazole-4-carboxamide,



H. 2-cyano-*N*-[4-(trifluoromethyl)phenyl]acetamide.

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Leflunomide Tablets

General Notices

Action and use

Immunomodulator.

DEFINITION

Leflunomide Tablets contain Leflunomide.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of leflunomide, $C_{12}H_9F_3N_2O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 50 mg of Leflunomide with 20 mL of *methanol* and filter. Dilute 1 volume of the filtrate to 50 volumes with *methanol* and dilute 1 volume of the resulting solution to 5 volumes with *methanol*. The *light absorption*, Appendix II B, of the final solution in the range 220 to 360 nm shows a maximum at about 260 nm.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 100 revolutions per minute.

(b) For tablets containing less than 100 mg of leflunomide, use 1000 mL of *water*, at a temperature of 37°, as the medium.

(c) For tablets containing 100 mg or more of leflunomide, use 1000 mL of 0.6% w/v *polyoxyethylene 23 lauryl ether*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 30 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with *water* if necessary, to produce a solution expected to contain 0.001% w/v of Leflunomide.

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(2) 0.01% w/v of *leflunomide BPCRS* in *acetonitrile*. Dilute 1 volume to 10 volumes with *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Inertsil ODS-3V is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 260 nm.

(f) Inject 40 µL of each solution.

MOBILE PHASE

Equal volumes of *acetonitrile* and *water*.

DETERMINATION OF CONTENT

Calculate the total content of leflunomide, $C_{12}H_9F_3N_2O_2$, in the medium from the chromatograms obtained and using the declared content of $C_{12}H_9F_3N_2O_2$, in *leflunomide BPCRS*.

LIMITS

The amount of leflunomide released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, prepared in the mobile phase.

(1) Shake a quantity of powdered tablets containing 100 mg of Leflunomide with 20 mL of *acetonitrile R1*, add sufficient mobile phase to produce 100 mL and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) 0.1% w/v of *leflunomide for peak identification EPCRS*.

(4) Dissolve 10 mg of *leflunomide impurity A EPCRS* in 5 mL of *acetonitrile R1* and dilute to 100 mL with the mobile phase. Dilute 1 volume of the resulting solution to 100 volumes with the mobile phase and dilute 1 volume of this solution to 10 volumes.

(5) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4 mm) packed with *base-deactivated octadecylsilyl silica gel for chromatography* (5 µm) (Kromasil C18 is suitable is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 210 nm.

(f) Inject 10 µL of each solution.

(g) Allow the chromatography to proceed for twice the retention time of leflunomide.

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MOBILE PHASE

Mix 5 volumes of *triethylamine* with 650 volumes of *water*, adjust to pH 3.4 with *orthophosphoric acid* and add 350 volumes of *acetonitrile R1*.

When the chromatograms are recorded under the prescribed conditions the retention times relative to leflunomide (retention time about 22 minutes) are impurity B, about 0.2; impurity A, about 0.4; impurity C, about 0.9.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the resolution between the peaks due to impurity C and leflunomide is at least 1.5

The test is not valid unless, in the chromatogram obtained with solution (4), the *signal-to-noise ratio* of the peak due to Impurity A is at least 10

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity B is not greater than 3.5 times the area of the principal peak in the chromatogram obtained with solution (2) (3.5%);

the area of any peak corresponding to impurity A is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (0.01%);

the area of any other secondary peak is not greater than twice the area of the principal peak in the chromatogram obtained with solution (5) (0.2%);

the sum of all impurities is not greater 4.0%.

Disregard any peak, with the exception of impurity A, with an area less than half the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, prepared in the mobile phase.

(1) Shake a quantity of powdered tablets containing 100 mg of Leflunomide with 20 mL of *acetonitrile*, add sufficient mobile phase to produce 100 mL and filter. Dilute 1 volume of this solution to 4 volumes with mobile phase.
(2) 0.025% w/v of *leflunomide BPCRS*.
(3) 0.1% w/v of *leflunomide for peak identification EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

When the chromatograms are recorded under the prescribed conditions the retention time of leflunomide is about 8 minutes.

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SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the resolution between the peaks due to impurity C and leflunomide is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{12}H_9F_3N_2O_2$ in the tablets from the chromatograms obtained using the declared content of $C_{12}H_9F_3N_2O_2$ in *leflunomide BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include the impurities listed under *Leflunomide*.

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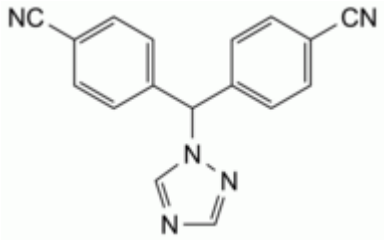
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Letrozole

General Notices

(Ph. Eur. monograph 2334)



$C_{17}H_{11}N_5$ 285.3 *112809-51-5*

Action and use

Aromatase inhibitor; treatment of breast carcinoma.

Preparation

Letrozole Tablets

Ph Eur

DEFINITION

4,4′-[(1*H*-1,2,4-Triazol-1-yl)methylene]dibenzonitrile.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or yellowish, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in methanol.

IDENTIFICATION

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Infrared absorption spectrophotometry (2.2.24).

Comparison *letrozole CRS*.

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 25.0 mg of the substance to be examined in 15 mL of *acetonitrile R* and dilute to 50.0 mL with *water R*.

Test solution (b) To 2.0 mL of test solution (a) add 30 mL of *acetonitrile R* and dilute to 100.0 mL with *water R*.

Reference solution (a) Dilute 2 mL of test solution (a) to 10 mL with a mixture of 30 volumes of *acetonitrile R* and 70 volumes of *water R*. Dissolve the contents of a vial of *letrozole impurity A CRS* in 1 mL of this solution.

Reference solution (b) To 2.0 mL of test solution (a) add 30.0 mL of *acetonitrile R* and dilute to 100.0 mL with *water R*. To 1.0 mL of this solution add 6.0 mL of *acetonitrile R* and dilute to 20.0 mL with *water R*.

Reference solution (c) Dissolve 25.0 mg of *letrozole CRS* in 15 mL of *acetonitrile R* and dilute to 50.0 mL with *water R*. To 2.0 mL of this solution add 30 mL of *acetonitrile R* and dilute to 100.0 mL with *water R*.

Column:

— *size*: *l* = 0.125 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: *water for chromatography R*;

— *mobile phase B*: *acetonitrile for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 4	70	30
4 - 29	70 → 30	30 → 70

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 20 µL of test solution (a) and reference solutions (a) and (b).

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity A.

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Relative retention With reference to letrozole (retention time = about 13 min): impurity A = about 0.6.

System suitability Reference solution (a):

— *resolution*: minimum 5.0 between the peaks due to impurity A and letrozole.

Calculation of percentage contents:

— for each impurity, use the concentration of letrozole in reference solution (b).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

Water (2.5.12)

Maximum 0.3 per cent, determined on 1.00 g. Use a validated pyridine-free iodosulfurous reagent.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Injection Test solution (b) and reference solution (c).

System suitability Reference solution (c):

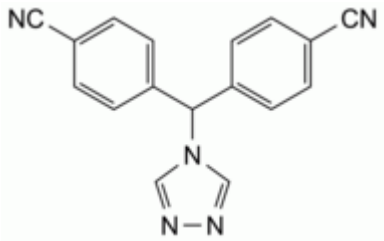
— *symmetry factor*: maximum 1.7 for the peak due to letrozole.

Calculate the percentage content of $C_{17}H_{11}N_5$ from the assigned content of *letrozole CRS*.

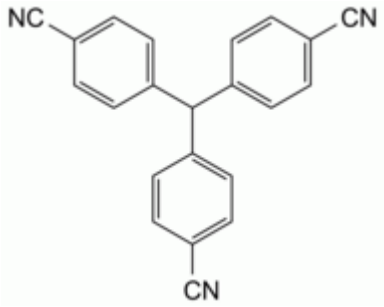
IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B.*

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A. 4,4′-[(4*H*-1,2,4-triazol-4-yl)methylene]dibenzonitrile,



B. 4,4′,4″-methanetriyltribenzonitrile.

Ph Eur

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Letrozole Tablets

General Notices

Action and use

Aromatase inhibitor; treatment of breast carcinoma.

DEFINITION

Letrozole Tablets contain Letrozole.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of letrozole, $C_{17}H_{11}N_5$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Disperse a quantity of whole tablets containing 10 mg of Letrozole with 0.5 mL of *water*. Dilute to 5 mL with *methanol* and mix with the aid of ultrasound. Centrifuge and use the supernatant liquid.

(2) 0.2% w/v of *letrozole BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of *methanol* and 9 volumes of *ethyl acetate*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

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Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 100 revolutions per minute.

(b) Use 500 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 30 minutes, withdraw a sample of the medium and centrifuge. Use the supernatant liquid, diluted with dissolution medium if necessary, to produce a solution expected to contain 0.0005% w/v of Letrozole.

(2) 0.05% w/v of *letrozole BPCRS* in *acetonitrile*. Dilute 1 volume of this solution to 100 volumes with dissolution medium.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil 100-5 C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 230 nm.

(f) Inject 40 µL of each solution.

MOBILE PHASE

48 volumes of *acetonitrile* and 52 volumes of *water*.

DETERMINATION OF CONTENT

Calculate the total content of letrozole, $C_{17}H_{11}N_5$, in the medium from the chromatograms obtained and using the declared content of $C_{17}H_{11}N_5$ in *letrozole BPCRS*.

LIMITS

The amount of letrozole released is not less than 80% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, prepared in a mixture of 3 volumes of *acetonitrile* and 7 volumes of *water* (solution A).

(1) Shake a quantity of whole tablets containing 12.5 mg of Letrozole with 15 mL of solution A and dilute to 25 mL. Centrifuge and use the supernatant liquid.

(2) Dilute 1 volume of solution (1) to 100 volume. Dilute 1 volume of the resulting solution to 10 volumes.

(3) 0.05% w/v of *letrozole EPCRS*.

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CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil 100-5 C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 230 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A *water*.

Mobile phase B *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-4	70	30	isocratic
4-29	70→30	30→70	linear gradient
29-30	30→70	70→30	linear gradient
30-40	70	30	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to letrozole (retention time, about 11 minutes) are: impurity A, about 0.6 and impurity B, about 2.0.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and letrozole is at least 5.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

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Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake 10 whole tablets with 10 mL of *water*, add 30 mL of *acetonitrile* and shake until completely dispersed. Add sufficient *water* to produce 100 mL, mix well and centrifuge. Dilute 1 volume of the supernatant liquid with the mobile phase to produce a solution expected to contain 0.001% w/v of Letrozole.

(2) 0.025% w/v of *letrozole BPCRS* in a mixture of 3 volumes of *acetonitrile* and 7 volumes of *water*. Dilute 1 volume of the resulting solution to 25 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used but with an injection volume of 20 µL.

DETERMINATION OF CONTENT

Calculate the content of letrozole, $C_{17}H_{11}N_5$, in the tablets from the chromatograms obtained and using the declared content of $C_{17}H_{11}N_5$ in *letrozole BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under *Letrozole*.

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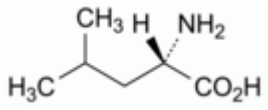
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Leucine

General Notices

(Ph. Eur. monograph 0771)



$C_6H_{13}NO_2$ 131.2 *61-90-5*

Action and use

Amino acid.

Ph Eur

DEFINITION

(2*S*)-2-Amino-4-methylpentanoic acid.

Product of fermentation or of protein hydrolysis.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or shiny flakes.

Solubility

Sparingly soluble in water, practically insoluble in ethanol (96 per cent). It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.

IDENTIFICATION

First identification: A, B.

Second identification: A, C.

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A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24)

Comparison leucine CRS.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in a 10.3 g/L solution of hydrochloric acid R and dilute to 50 mL with the same solution.

Reference solution Dissolve 10 mg of leucine CRS in a 10.3 g/L solution of hydrochloric acid R and dilute to 50 mL with the same solution.

Plate TLC silica gel plate R.

Mobile phase glacial acetic acid R, water R, butanol R (20:20:60 *V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with ninhydrin solution R and heat at 105 °C for 15 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution BY_6 (2.2.2, Method II).

Dissolve 0.5 g in a 103 g/L solution of hydrochloric acid R and dilute to 10 mL with the same solution.

Specific optical rotation (2.2.7)

+ 14.5 to + 16.5 (dried substance).

Dissolve 1.00 g in hydrochloric acid R1 and dilute to 25.0 mL with the same acid.

Ninhydrin-positive substances

Amino acid analysis (2.2.56). For analysis, use Method 1.

The concentrations of the test solutions and the reference solutions may be adapted according to the sensitivity of the equipment used. The concentrations of all solutions are adjusted so that the system suitability requirements described in general chapter 2.2.46 are fulfilled, keeping the ratios of concentrations between all solutions as described.

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Solution A *dilute hydrochloric acid R1* or a sample preparation buffer suitable for the apparatus used.

Test solution (a) Dissolve 30.0 mg of the substance to be examined in solution A and dilute to 50.0 mL with solution A.

Test solution (b) Dilute 1.0 mL of test solution (a) to 25.0 mL with solution A.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with solution A. Dilute 2.0 mL of this solution to 10.0 mL with solution A.

Reference solution (b) Dissolve 30.0 mg of *isoleucine R* (impurity A) in solution A and dilute to 100.0 mL with solution A. Dilute 1.0 mL of the solution to 250.0 mL with solution A. Dilute 1.0 mL of this solution to 10.0 mL with solution A.

Reference solution (c) Dissolve 30.0 mg of *proline R* in solution A and dilute to 100.0 mL with solution A. Dilute 1.0 mL of the solution to 250.0 mL with solution A.

Reference solution (d) Dilute 6.0 mL of *ammonium standard solution (100 ppm NH_4) R* to 50.0 mL with solution A. Dilute 1.0 mL of this solution to 100.0 mL with solution A.

Reference solution (e) Dissolve 30 mg of *isoleucine R* (impurity A) and 30 mg of *leucine R* in solution A and dilute to 50.0 mL with solution A. Dilute 1.0 mL of the solution to 200.0 mL with solution A.

Blank solution Solution A.

Inject suitable, equal amounts of the test solutions, blank solution and reference solutions (a), (b), (c) and (e) into the amino acid analyser. Run a program suitable for the determination of physiological amino acids.

System suitability Reference solution (e):

— *resolution*: minimum 1.5 between the peaks due to impurity A and leucine.

Calculation of percentage contents:

— for impurity A in test solution (b), use the concentration of impurity A in reference solution (b);

— for any ninhydrin-positive substance detected at 570 nm in test solution (a), use the concentration of leucine in reference solution (a);

— for any ninhydrin-positive substance detected at 440 nm in test solution (a), use the concentration of proline in reference solution (c); if a peak is above the reporting threshold at both wavelengths, use the result obtained at 570 nm for quantification.

Limits:

— *impurity A at 570 nm*: maximum 0.8 per cent;

— *any ninhydrin-positive substance*: for each impurity, maximum 0.2 per cent;

— *total*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent.

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The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

Chlorides (2.4.4)

Maximum 200 ppm.

Dissolve 0.25 g in *water R* and dilute to 15 mL with the same solvent.

Sulfates (2.4.13)

Maximum 300 ppm.

Dissolve 0.5 g in 3 mL of *dilute hydrochloric acid R* and dilute to 15 mL with *distilled water R*.

Ammonium

Amino acid analysis (2.2.56) as described in the test for ninhydrin-positive substances with the following modifications.

Injection Test solution (a), reference solution (d) and blank solution.

Limit:

— *ammonium at 570 nm*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.02 per cent), taking into account the peak due to ammonium in the chromatogram obtained with the blank solution.

Iron (2.4.9)

Maximum 10 ppm.

In a separating funnel, dissolve 1.0 g in 10 mL of *dilute hydrochloric acid R*. Shake with 3 quantities, each of 10 mL, of *methyl isobutyl ketone R1*, shaking for 3 min each time. To the combined organic layers add 10 mL of *water R* and shake for 3 min. Use the aqueous layer.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.100 g in 3 mL of *anhydrous formic acid R*. Add 30 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 13.12 mg of $C_6H_{13}NO_2$.

STORAGE

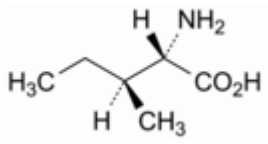
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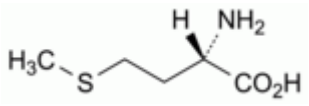
IMPURITIES

Specified impurities A.

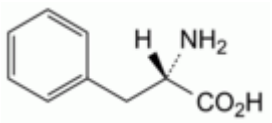
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, C, D, E.



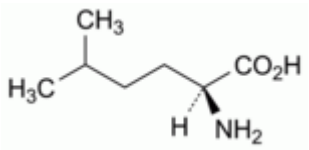
A. (2*S*,3*S*)-2-amino-3-methylpentanoic acid (isoleucine),



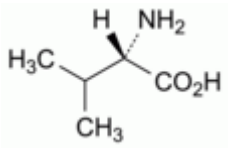
B. (2*S*)-2-amino-4-(methylsulfanyl)butanoic acid (methionine),



C. (2*S*)-2-amino-3-phenylpropanoic acid (phenylalanine),



D. (2*S*)-2-amino-5-methylhexanoic acid (5-methyl-norleucine),



E. (2*S*)-2-amino-3-methylbutanoic acid (valine).

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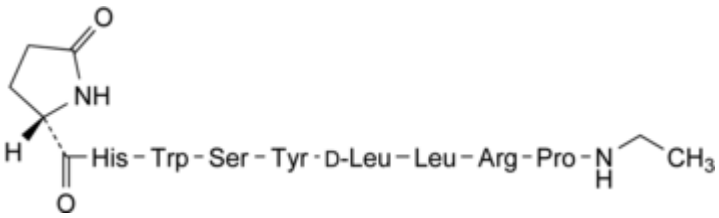
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Leuprorelin

General Notices

(Ph. Eur. Monograph 1442)



$C_{59}H_{84}N_{16}O_{12}$ 1209 *53714-56-0*

Action and use

Gonadotropin releasing hormone (gonadorelin) analogue; treatment of prostate cancer.

Preparation

Leuprorelin Injection

Ph Eur

DEFINITION

5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-*N*-ethyl-L-prolinamide.

Synthetic nonapeptide analogue of the hypothalamic peptide, gonadorelin. It is obtained by chemical synthesis and is available as an acetate.

Content

97.0 per cent to 103.0 per cent (anhydrous and acetic acid-free substance).

CHARACTERS

Appearance

Hygroscopic, white or almost white powder.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

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Preparation Discs of *potassium bromide R*.

Comparison *Ph. Eur. reference spectrum of leuprorelin*.

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with test solution (b) is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (b).

C. Amino acid analysis (*2.2.56*). For hydrolysis use Method 1 and for analysis use Method 1.
Express the content of each amino acid in moles. Calculate the relative proportions of the amino acids taking one seventh of the sum of the number of moles of histidine, glutamic acid, leucine, proline, tyrosine and arginine as equal to 1. The values fall within the following limits: serine present; glutamic acid = 0.85 to 1.1; proline = 0.85 to 1.1; leucine = 1.8 to 2.2; tyrosine = 0.85 to 1.1; histidine = 0.85 to 1.1 and arginine = 0.85 to 1.1. Not more than traces of other amino acids are present, with the exception of tryptophan.

TESTS

Specific optical rotation (*2.2.7*)

-38.0 to -42.0 (anhydrous and acetic acid-free substance).

Dissolve the substance to be examined in a 1 per cent *V/V* solution of *glacial acetic acid R* to obtain a concentration of 10.0 mg/mL.

Related substances

Liquid chromatography (*2.2.29*): use the normalisation procedure.

Test solution (a) Dissolve the substance to be examined in the mobile phase to obtain a concentration of 1.0 mg/mL.

Test solution (b) Dilute 0.5 mL of test solution (a) to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve *leuprorelin CRS* in the mobile phase to obtain a concentration of 1.0 mg/mL.

Reference solution (b) Dilute 0.5 mL of reference solution (a) to 10.0 mL with the mobile phase.

Resolution solution Dilute 5.0 mL of reference solution (a) to 50.0 mL with *water R*. To 5 mL of the solution add 100 µL of *1 M sodium hydroxide* and shake vigorously. Heat in an oven at 100 °C for 60 min, cool immediately and add 50 µL of *dilute phosphoric acid R*. Shake vigorously.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase Dissolve about 15.2 g of *triethylamine R* in 800 mL of *water R*, adjust to pH 3.0 with *phosphoric acid R* and dilute to 1000 mL with *water R*. Add 850 mL of this solution to 150 mL of a mixture of 2 volumes of *propanol R* and 3 volumes of *acetonitrile R*.

Flow rate 1.0-1.5 mL/min.

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Detection Spectrophotometer at 220 nm.

Injection 20 µL of test solution (a) and the resolution solution.

Run time 90 min.

Relative retention With reference to leuprorelin (retention time = 41-49 min): impurity E = about 0.7; impurity F = about 0.7; impurity H = about 0.78; impurity A = about 0.8; impurity B = about 0.9; impurity I = about 0.94; impurity J = about 1.09; impurity C = about 1.2; impurity G = about 1.3; impurity K = about 1.31; impurity D = about 1.5.

System suitability Resolution solution:

— *resolution*: minimum 1.5 between the peaks due to impurity B and leuprorelin.

Limits:

— *impurity D*: maximum 1.0 per cent;

— *impurities A, B, C*: for each impurity, maximum 0.5 per cent;

— *unspecified impurities*: for each impurity, maximum 0.5 per cent;

— *total*: maximum 2.5 per cent;

— *disregard limit*: 0.1 per cent.

Acetic acid (2.5.34)

4.7 per cent to 9.0 per cent.

Test solution Dissolve 10.0 mg of the substance to be examined in a mixture of 5 volumes of mobile phase B and 95 volumes of mobile phase A and dilute to 10.0 mL with the same mixture of mobile phases.

Water (2.5.32)

Maximum 5.0 per cent.

Sulfated ash (2.4.14)

Maximum 0.3 per cent.

Bacterial endotoxins (2.6.14, Method D)

Less than 16.7 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for removal of bacterial endotoxins.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

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Run time 60 min.

Injection 20 µL of test solution (b) and reference solution (b).

Calculate the content of leuprorelin ($C_{59}H_{84}N_{16}O_{12}$) using the areas of the peaks and the declared content of $C_{59}H_{84}N_{16}O_{12}$ in *leuprorelin CRS*.

STORAGE

In an airtight container, protected from light, at a temperature not exceeding 30 °C.

If the substance is sterile, store in a sterile, airtight, tamper-evident container.

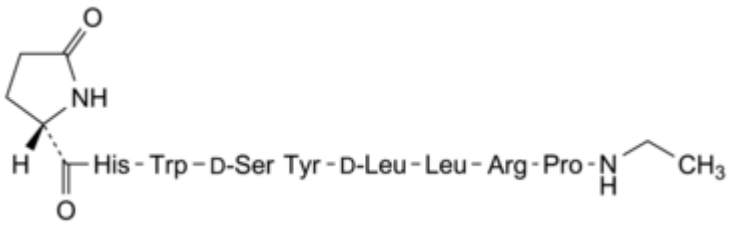
LABELLING

The label states the mass of peptide in the container.

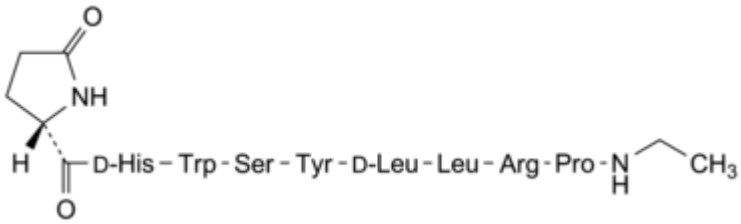
IMPURITIES

Specified impurities *A, B, C, D.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *E, F, G, H, I, J, K.*

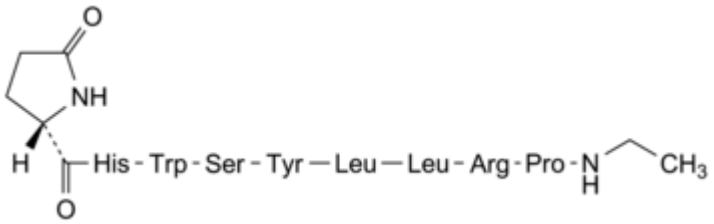


A. [4-D-serine]leuprorelin,

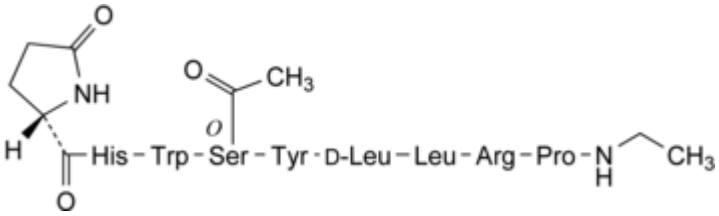


B. [2-D-histidine]leuprorelin,

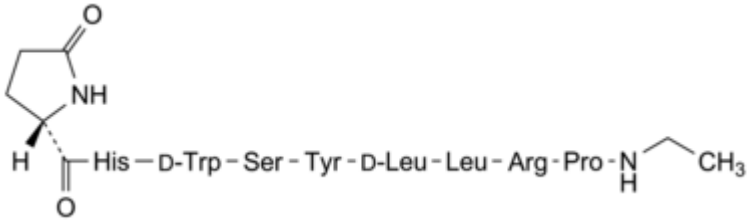
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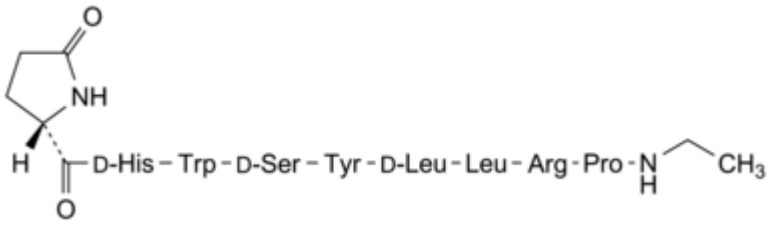
C. [6-L-leucine]leuprorelin,



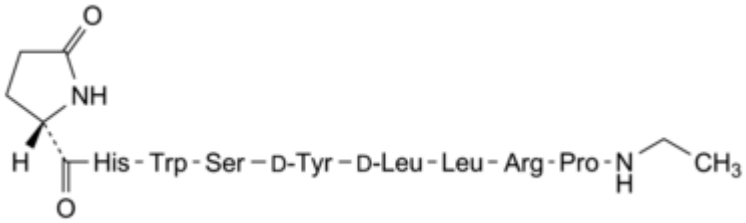
D. [4-(*O*-acetyl-L-serine)]leuprorelin,



E. [3-D-tryptophane]leuprorelin,

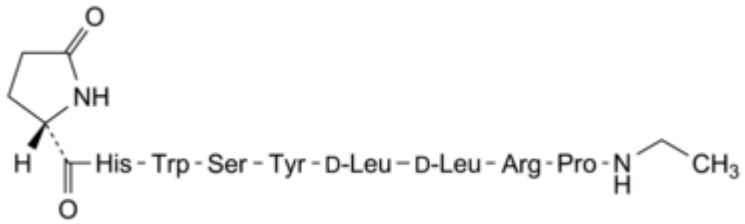


F. [2-D-histidine,4-D-serine]leuprorelin,

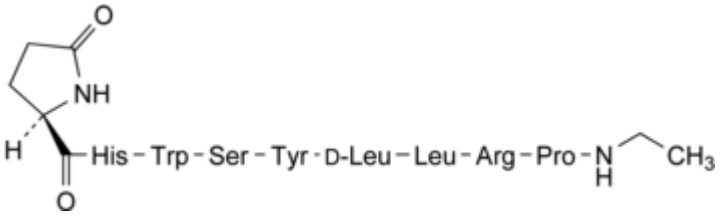


G. [5-D-tyrosine]leuprorelin,

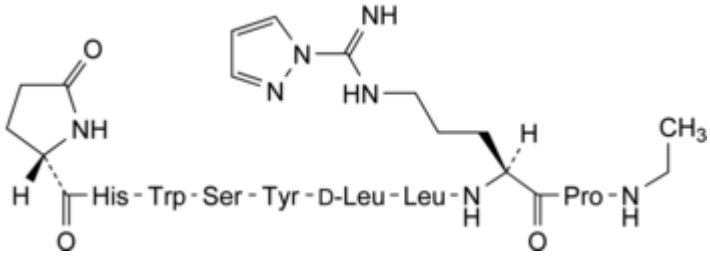
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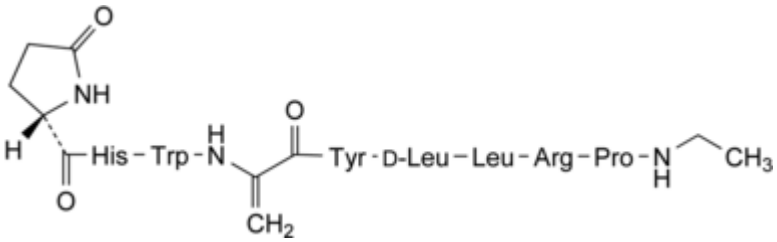
H. [7-D-leucine]leuprorelin,



I. [1-(5-oxo-D-proline)]leuprorelin,



J. [8-[5-*N*-[imino(1*H*-pyrazol-1-yl)methyl]-L-ornithine]]leuprorelin,



K. [4-dehydroalanine]leuprorelin.

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Leuprorelin Injection

General Notices

Action and use

Gonadotropin releasing hormone (gonadorelin) analogue; treatment of prostate cancer.

DEFINITION

Leuprorelin Injection is a sterile suspension of Leuprorelin in a suitable liquid. It is prepared by suspending Leuprorelin for Injection in the requisite amount of the liquid stated on the label immediately before use.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Acidity

pH of the injection when constituted in accordance with the manufacturer's instructions, 5.0 to 7.0, Appendix V L.

STORAGE

Leuprorelin Injection should be used immediately after preparation.

LEUPRORELIN FOR INJECTION

DEFINITION

Leuprorelin for Injection is a sterile powder consisting of Leuprorelin with or without excipients. It is supplied in a sealed container. Leuprorelin for Injection is formulated so that the medicament is released over a period of weeks.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of leuprorelin, $C_{59}H_{84}N_{16}O_{12}$

95.0 to 105.0% of the stated amount of the peptide.

IDENTIFICATION

A. To a quantity of the powder containing the equivalent of 4.5 mg of the peptide in a separating funnel add 15 mL of *dichloromethane* and 35 mL of a 1.15% w/v solution of *ammonium dihydrogen orthophosphate*, previously adjusted to pH 6.0 with *dilute ammonia R1*. Shake for 1 minute and extract the aqueous layer. Dilute the aqueous extract to 50 mL with a 1.15% w/v solution of *ammonium dihydrogen*

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orthophosphate, previously adjusted to pH 6.0 with 6M *ammonia*. The *light absorption* of the resulting solution, Appendix II B, exhibits a maximum between 277 and 282 nm.

B In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions and the *normalisation procedure*.

(1) To a quantity of the powder containing the equivalent of 4.5 mg of the peptide in a separating funnel add 15 mL of *dichloromethane* and 35 mL of a 1.15% w/v solution of *ammonium dihydrogen orthophosphate*, previously adjusted to pH 6.0 with *dilute ammonia R1*. Shake for 1 minute and extract the aqueous layer. Dilute the aqueous extract to 50 mL with a 1.15% w/v solution of *ammonium dihydrogen orthophosphate*, previously adjusted to pH 6.0 with 6M *ammonia*.

(2) 0.1% w/v of *leuprorelin EPCRS* in the mobile phase.

(3) Dilute 5 volumes of solution (2) to 50 volumes with *water*. To 5 mL of the solution add 100 µL of 1M *sodium hydroxide* and shake vigorously. Heat in an oven at 100° for 60 minutes, cool immediately and add 50 µL of 2M *orthophosphoric acid*. Shake vigorously (generation of impurity B).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (3 µm) (Wakosil-II 3C18 HG is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 to 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 20 µL each of solutions (1) and (3).

MOBILE PHASE

150 volumes of a mixture of 2 volumes of *propan-1-ol* and 3 volumes of *acetonitrile* and 850 volumes of the buffer solution prepared as described below.

To prepare the buffer solution, dissolve about 15.2 g of *triethylamine* in 800 mL of *water*, adjust to pH 3.0 with *orthophosphoric acid* and add sufficient *water* to produce 1000 mL.

When the chromatograms are recorded under the prescribed conditions the relative retentions with reference to leuprorelin (retention time = 41 to 49 minutes) are: impurity E = about 0.7; impurity F = about 0.7; impurity H = about 0.78; impurity A = about 0.8; impurity B = about 0.9; impurity I = about 0.94; impurity J = about 1.09; impurity C = about 1.2; impurity G = about 1.3; impurity K = about 1.31; impurity D = about 1.5.

SYSTEM SUITABILITY

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The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks corresponding to impurity B and leuprorelin is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity D is not greater than 1.0%;

the areas of any peaks corresponding to impurities A, B and C are not greater than 0.5%;

the area of any other *secondary peak* is not greater than 0.5%;

the sum of the areas of any *secondary peaks* is not greater than 2.5%.

Disregard any peak with an area less than 0.1%.

Water

Not more than 5.0 % w/w, Appendix IX C, Method III.

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. The endotoxin limit concentration is 11.6 IU per mg of leuprorelin.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve a quantity of the powder containing the equivalent of 9 mg of the peptide in 100 mL of *dimethyl sulfoxide*.

(2) 0.01% w/v of *leuprorelin EPCRS* dissolved in the mobile phase.

(3) 0.1% w/v of *leuprorelin EPCRS* dissolved in the mobile phase.

(4) Dilute 5 volumes of solution (3) to 50 volumes with *water*. To 5 mL of the solution add 100 µL of 1M *sodium hydroxide* and shake vigorously. Heat in an oven at 100° for 60 minutes, cool immediately and add 50 µL of 2M *orthophosphoric acid*. Shake vigorously (generation of impurity B).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (5 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (3 µm) (Wakosil-II 3C18 AR is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.8 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 20 µL of solutions (1), (2) and (4).

MOBILE PHASE

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150 volumes of a mixture of 2 volumes of *propan-1-ol* and 3 volumes of *acetonitrile* and 850 volumes of the buffer solution as described below.

To prepare the buffer solution, add 15.2 g of *triethylamine* to 800 mL of *water*, adjust to pH 3.0 with *orthophosphoric acid* and add sufficient *water* to produce 1000 mL.

When the chromatograms are recorded under the prescribed conditions the relative retention time of impurity B with reference to leuprorelin (retention time is approximately 22 minutes) is approximately 0.9.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution factor* between the peaks corresponding to impurity B and that of leuprorelin is at least 1.2.

DETERMINATION OF CONTENT

Calculate the content of $C_{59}H_{84}N_{16}O_{12}$ using the declared content of $C_{59}H_{84}N_{16}O_{12}$ in *leuprorelin EPCRS*.

STORAGE

The sealed container should be stored at a temperature not exceeding 30°.

LABELLING

The label of the sealed container states the amount of the peptide in milligrams.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Leuprorelin.

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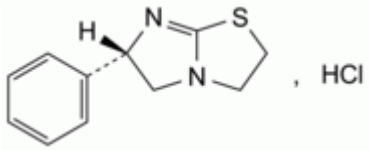
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Levamisole Hydrochloride

General Notices

(Ph. Eur. monograph 0726)



$C_{11}H_{13}ClN_2S$ 240.8 *16595-80-5*

Action and use

Immunostimulant; antihelminthic.

Ph Eur

DEFINITION

(6*S*)-6-Phenyl-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazole hydrochloride.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, soluble in ethanol (96 per cent), slightly soluble in methylene chloride.

IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *levamisole hydrochloride CRS*.

C. It gives reaction (a) of chlorides (*2.3.1*).

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TESTS

Solution S

Dissolve 2.50 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution Y_7 (*2.2.2, Method II*).

pH (*2.2.3*)

3.0 to 4.5 for solution S.

Specific optical rotation (*2.2.7*)

-128 to -121 (dried substance), determined on solution S.

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use, protect from light and keep below 25 °C.*

Test solution Dissolve 0.100 g of the substance to be examined in *methanol R*, add 1.0 mL of *concentrated ammonia R* and dilute to 10.0 mL with *methanol R*.

Reference solution (a) Dissolve 10 mg of *levamisole hydrochloride for system suitability CRS* (containing impurities A, B, C, D and E) in *methanol R*, add 0.1 mL of *concentrated ammonia R* and dilute to 1.0 mL with *methanol R*.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 5.0 mL of this solution to 25.0 mL with *methanol R*.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase:

— *mobile phase A*: dissolve 0.5 g of *ammonium dihydrogen phosphate R* in 90 mL of *water R*, adjust to pH 6.5 with a 40 g/L solution of *sodium hydroxide R* and dilute to 100 mL with *water R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 8	90 → 30	10 → 70

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
8 - 10	30	70

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 215 nm.

Equilibration At least 4 min with the mobile phase at the initial composition.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *levamisole hydrochloride for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, C, D and E.

Relative retention With reference to levamisole (retention time = about 3 min): impurity A = about 0.9; impurity B = about 1.4; impurity C = about 1.5; impurity D = about 1.6; impurity E = about 2.0.

System suitability:

— the chromatogram obtained with reference solution (a) is similar to the chromatogram supplied with *levamisole hydrochloride for system suitability CRS*;

— *symmetry factor*: maximum 3.5 for the principal peak in the chromatogram obtained with reference solution (b).

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 2.0; impurity B = 1.7; impurity C = 2.9; impurity D = 1.3; impurity E = 2.7;

— *impurities A, B, C, D, E*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

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ASSAY

Dissolve 0.200 g in 30 mL of *ethanol (96 per cent) R* and add 5.0 mL of *0.01 M hydrochloric acid*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

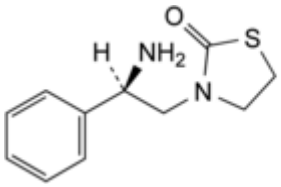
1 mL of *0.1 M sodium hydroxide* is equivalent to 24.08 mg of $C_{11}H_{13}ClN_2S$.

STORAGE

Protected from light.

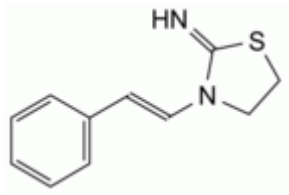
IMPURITIES

Specified impurities *A, B, C, D, E.*

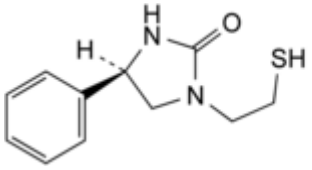


and enantiomer

A. 3-[(2*RS*)-2-amino-2-phenylethyl]thiazolidin-2-one,

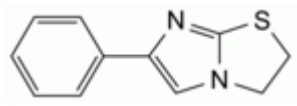


B. 3-[(*E*)-2-phenylethenyl]thiazolidin-2-imine,



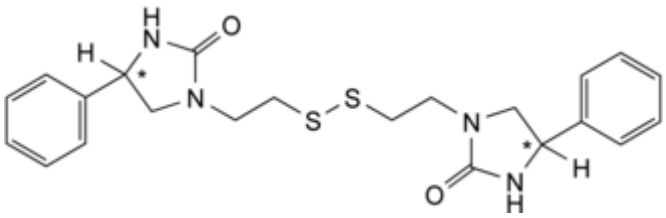
and enantiomer

C. (4*RS*)-4-phenyl-1-(2-sulfanylethyl)imidazolidin-2-one,



D. 6-phenyl-2,3-dihydroimidazo[2,1-*b*]thiazole,

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E. 1,1′-[(disulfane-1,2-diyl)bis(ethylene)]bis[(4*RS*)-4-phenylimidazolidin-2-one].

Ph Eur

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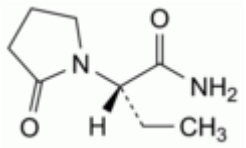
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Levetiracetam

General Notices

(Ph. Eur. monograph 2535)



$C_8H_{14}N_2O_2$ 170.2 *102767-28-2*

Action and use

Antiepileptic.

Ph Eur

DEFINITION

(2*S*)-2-(2-Oxopyrrolidin-1-yl)butanamide.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Very soluble in water, soluble in acetonitrile, practically insoluble in heptane.

IDENTIFICATION

Carry out either tests A, B or tests B, C.

A. Specific optical rotation (2.2.7): -82 to -76.

Dissolve 0.500 g in *water R* and dilute to 25.0 mL with the same solvent.

B. Infrared absorption spectrophotometry (2.2.24).

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Comparison *levetiracetam CRS*.

C. Enantiomeric purity (see Tests).

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

Dissolve 2.0 g in *water R* and dilute to 10.0 mL with the same solvent.

Enantiomeric purity

Liquid chromatography (*2.2.29*): use the normalisation procedure.

Test solution Dissolve 0.200 g of the substance to be examined in *2-propanol R* and dilute to 10.0 mL with the same solvent. Dilute 1.0 mL of the solution to 20.0 mL with the mobile phase.

Reference solution (a) Dissolve 5 mg of the substance to be examined and 5 mg of *levetiracetam impurity D CRS* in the mobile phase and dilute to 5.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *cellulose derivative of silica gel for chiral separation R* (10 µm).

Mobile phase *2-propanol R*, *heptane R* (18:82 *V/V*).

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 205 nm.

Injection 20 µL.

Run time 1.4 times the retention time of levetiracetam.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity D.

Relative retention With reference to levetiracetam (retention time = about 12 min): impurity D = about 0.8.

System suitability Reference solution (a):

— *resolution*: minimum 1.5 between the peaks due to impurity D and levetiracetam;

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— *symmetry factor*: maximum 2.4 for the peak due to levetiracetam.

Limit:

— *impurity D*: maximum 0.8 per cent.

— *reporting threshold*: 0.10 per cent (reference solution (b)).

Impurity G

Liquid chromatography (2.2.29).

Buffer solution Dissolve 1.22 g of *sodium decanesulfonate R* in 850 mL of *water for chromatography R*, add 1.3 mL of *phosphoric acid R*, adjust to pH 3.0 with a 200 g/L solution of *potassium hydroxide R* and dilute to 1000.0 mL with *water for chromatography R*.

Test solution Dissolve 20 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 2.0 mg of *levetiracetam impurity G CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 20.0 mL with the mobile phase.

Reference solution (c) To 1.0 mL of reference solution (a) add 1.0 mL of the test solution and dilute to 20.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 27 °C.

Mobile phase *acetonitrile R1*, buffer solution (15:85 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 200 nm.

Injection 50 µL of the test solution and reference solutions (b) and (c).

Run time 5 times the retention time of levetiracetam.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity G.

Relative retention With reference to levetiracetam (retention time = about 4 min): impurity G = about 3.8.

System suitability Reference solution (c):

— *resolution*: minimum 5.0 between the peaks due to levetiracetam and impurity G.

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Calculation of percentage content:

— for impurity G, use the concentration of impurity G in reference solution (b).

Limit:

— *impurity G*: maximum 0.05 per cent.

Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 50.0 mg of the substance to be examined in mobile phase A and dilute to 10.0 mL with mobile phase A.

Test solution (b) Dilute 1.0 mL of test solution (a) to 50.0 mL with mobile phase A.

Reference solution (a) Dissolve 5 mg of *levetiracetam impurity A CRS* and 5 mg of *levetiracetam impurity E CRS* in mobile phase A, add 1.0 mL of test solution (a) and dilute to 100.0 mL with mobile phase A.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 20.0 mL with mobile phase A.

Reference solution (c) Dissolve 5.0 mg of *levetiracetam impurity C CRS* in mobile phase A and dilute to 100.0 mL with mobile phase A. Dilute 1.0 mL of the solution to 40.0 mL with mobile phase A.

Reference solution (d) Dissolve 50.0 mg of *levetiracetam CRS* in mobile phase A and dilute to 10.0 mL with mobile phase A. Dilute 1.0 mL of the solution to 50.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: *acetonitrile R1*, *phosphate buffer solution pH 5.5 R* (5:95 *V/V*);

— *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	100	0
3 - 20	100 → 71	0 → 29
20 - 25	71	29

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Flow rate 0.9 mL/min.

Detection Spectrophotometer at 205 nm.

Injection 10 µL of test solution (a) and reference solutions (a), (b) and (c).

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A and E; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity C.

Relative retention With reference to levetiracetam (retention time = about 11 min): impurity C = about 0.5; impurity A = about 0.7; impurity E = about 0.9.

System suitability Reference solution (a):

— *resolution*: minimum 3.5 between the peaks due to impurity E and levetiracetam.

Calculation of percentage contents:

— for impurity C, use the concentration of impurity C in reference solution (c);

— for impurities other than C, use the concentration of levetiracetam in reference solution (b).

Limits:

— *impurity A*: maximum 0.3 per cent;

— *impurity C*: maximum 250 ppm;

— *unspecified impurities*: for each impurity, maximum 0.05 per cent;

— *total*: maximum 0.4 per cent;

— *reporting threshold*: 0.03 per cent, except for impurity C.

Water (2.5.32)

Maximum 0.5 per cent, determined on 0.300 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (d).

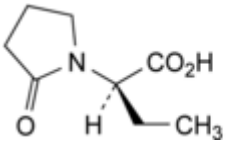
Calculate the percentage content of $C_8H_{14}N_2O_2$ taking into account the assigned content of *levetiracetam CRS*.

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IMPURITIES

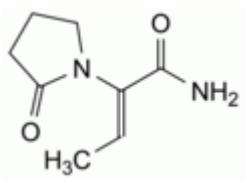
Specified impurities A, C, D, G.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, E.

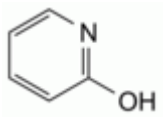


and enantiomer

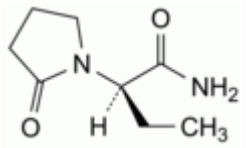
A. (2*RS*)-2-(2-oxopyrrolidin-1-yl)butanoic acid,



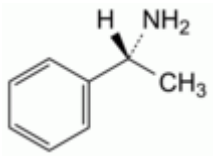
B. (2*Z*)-2-(2-oxopyrrolidin-1-yl)but-2-enamide,



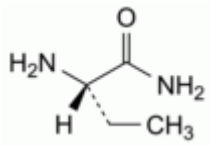
C. pyridin-2-ol,



D. (2*R*)-2-(2-oxopyrrolidin-1-yl)butanamide ((*R*)-etiracetam),



E. (1*R*)-1-phenylethan-1-amine,



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G. (2*S*)-2-aminobutanamide.

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Levobunolol Eye Drops

General Notices

Action and use

Beta-adrenoceptor antagonist.

DEFINITION

Levobunolol Eye Drops are a sterile solution of Levobunolol Hydrochloride in Purified Water.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

Content of levobunolol hydrochloride, $C_{17}H_{25}NO_3$,HCl

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 210 to 350 nm of a solution prepared by diluting the eye drops with *ethanol (96%)* to contain 0.001% w/v of Levobunolol Hydrochloride exhibits two maxima, at 223 nm and at 255 nm and a broad peak at 315 nm.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity

pH, 5.5 to 7.5, Appendix V L.

Related substances

The nominal total amount of related substances determined by tests A and B below is not more than 2.5% of the stated content of Levobunolol Hydrochloride.

A. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a suitable volume of the eye drops with the mobile phase to produce a solution containing 0.10% w/v of Levobunolol Hydrochloride.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase.

(3) 0.0010% w/v of *disodium edetate* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Assay may be used.

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LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%).

Determine the sum of the areas of any *secondary peaks*.

Disregard any peak corresponding to the principal peak in the chromatogram obtained with solution (3).

B. Carry out test A as described above but using a detection wavelength of 400 nm and injecting solution (1).

LIMITS

The area of any peak with a retention time corresponding to that of the principal peak in the chromatogram obtained with solution (2) in test A is not greater than one-fifth of the area of that peak (1%, assuming a response factor of 5).

Calculate the nominal percentage content of this impurity from the area of the peak in the chromatogram obtained with solution (1) taking one-fifth of the area of the peak in the chromatogram obtained with solution (2) in test A to be equivalent to 1%.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a suitable volume of the eye drops with the mobile phase to produce a solution containing 0.005% w/v of Levobunolol Hydrochloride.
(2) 0.005% w/v of *levobunolol hydrochloride BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (30 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (µBondapak C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 254 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

5 volumes of *glacial acetic acid*, 450 volumes of 0.005M *sodium heptanesulfonate* and 550 volumes of *methanol*.

DETERMINATION OF CONTENT

Calculate the content of $C_{17}H_{25}NO_3$,HCl in the eye drops from the declared content of $C_{17}H_{25}NO_3$,HCl in *levobunolol hydrochloride BPCRS*.

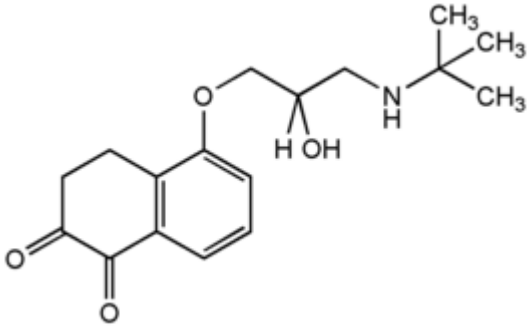
STORAGE

Levobunolol Eye Drops should be protected from light.

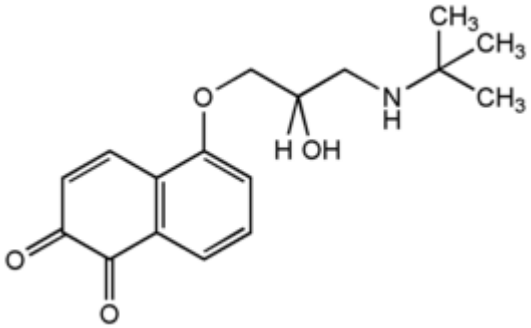
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IMPURITIES

The impurities limited by the requirements of this monograph include:



A. 5-(3-*tert*-butylamino-2-hydroxypropoxy)-3,4-dihydro-1,2-naphthalene dione,



B. 5-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2-naphthoquinone.

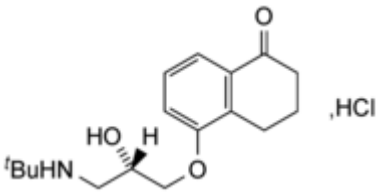
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Levobunolol Hydrochloride

General Notices



$C_{17}H_{25}NO_3$,HCl 327.9 *27912-14-7*

Action and use

Beta-adrenoceptor antagonist.

Preparation

Levobunolol Eye Drops

DEFINITION

Levobunolol Hydrochloride is (*S*)-5-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,3,4-tetrahydronaphthalen-1-one hydrochloride. It contains not less than 98.5% and not more than 101.0% of $C_{17}H_{25}NO_3$,HCl, calculated with reference to the dried substance.

CHARACTERISTICS

A white or pinkish white, crystalline powder.

Freely soluble in *water*; sparingly soluble in *ethanol (96%)*.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of levobunolol hydrochloride *(RS 200)*.

B. Yields the reactions characteristic of *chlorides*, Appendix VI.

TESTS

Acidity

pH of a 5% w/v solution, 4.5 to 6.5, Appendix V L.

Specific optical rotation

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In a 3% w/v solution in *methanol*, –19.0 to –20.0, calculated with reference to the dried substance, Appendix V F.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using solutions in the mobile phase containing (1) 0.10% w/v of the substance being examined, (2) 0.00050% w/v of the substance being examined, (3) 0.0050% w/v of each of *levobunolol hydrochloride BPCRS* and *atenolol*.

The chromatographic procedure described under Assay may be used.

For solution (1) allow the chromatography to proceed for 3 times the retention time of the principal peak. The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 8.

In the chromatogram obtained with solution (1) the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%) and the sum of the areas of any *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1%).

Loss on drying

When dried over *phosphorus pentoxide* at 110° at a pressure not exceeding 2 kPa for 4 hours, loses not more than 0.5% of its weight. Use 1 g.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using solutions in the mobile phase containing (1) 0.01% w/v of the substance being examined, (2) 0.01% w/v of *levobunolol hydrochloride BPCRS* and (3) 0.0050% w/v of each of *levobunolol hydrochloride BPCRS* and *atenolol*.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 3.9 mm) packed with *end-capped octylsilyl silica gel for chromatography* (10 µm) (Lichrosorb RP 8 is suitable), (b) a solution prepared by mixing 53 volumes of 0.005M *sodium heptanesulfonate* in *methanol* with 47 volumes of 0.005M *sodium heptanesulfonate* in *water* containing 1 mL of 0.5M *sulfuric acid* as the mobile phase with a flow rate of 1 mL per minute and (c) a detection wavelength of 223 nm.

The test is not valid unless in the chromatogram obtained with solution (3) the *resolution factor* between the two principal peaks is at least 8.

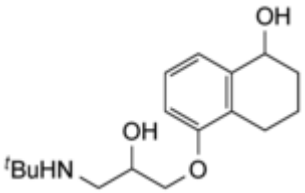
Calculate the content of $C_{17}H_{25}NO_3$,HCl from the declared content of $C_{17}H_{25}NO_3$,HCl in *levobunolol hydrochloride BPCRS*.

STORAGE

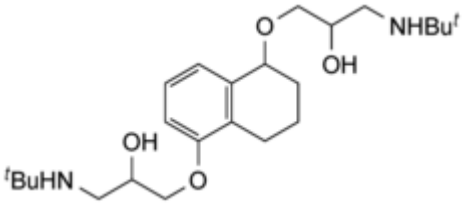
Levobunolol Hydrochloride should be protected from light.

IMPURITIES

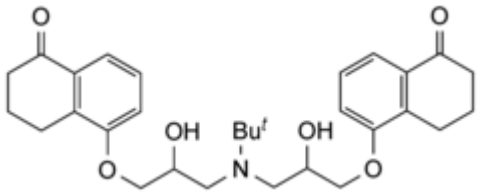
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A. 5-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,3,4-tetrahydro-1-naphthol



B. 1,1′-(1,2,3,4-tetrahydro-1,5-naphthalenedioxy)bis(3-*tert*-butylamino)-2-propanol



C. *meso*-5,5′-[(3,3′-*tert*-butylamino)bis(2-hydroxypropoxy)]bis-3,4-dihydronaphthalen-1(2 *H*)-one

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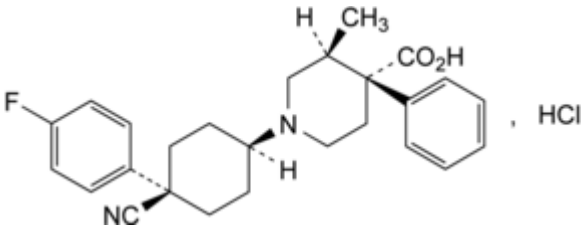
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Levocabastine Hydrochloride

General Notices

(Ph. Eur. monograph 1484)



$C_{26}H_{30}ClFN_2O_2$ 457.0 *79547-78-7*

Action and use

Histamine H_1 receptor antagonist; antihistamine.

Ph Eur

DEFINITION

(3*S*,4*R*)-1-[*cis*-4-Cyano-4-(4-fluorophenyl)cyclohexyl]-3-methyl-4-phenylpiperidine-4-carboxylic acid hydrochloride.

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, sparingly soluble in methanol, slightly soluble in ethanol (96 per cent) and in a 2 g/L solution of sodium hydroxide.

IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *levocabastine hydrochloride CRS*.

C. Dissolve 50 mg in a mixture of 0.4 mL of *ammonia R* and 2 mL of *water R*. Mix, allow to stand for 5 min and filter. Acidify the filtrate with *dilute nitric acid R*. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S

Dissolve 0.250 g in *methanol R* and dilute to 25.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution Y_7 (*2.2.2, Method II*).

Specific optical rotation (*2.2.7*)

-106 to -102 (dried substance), determined on solution S.

Related substances

Liquid chromatography (*2.2.29*). *Carry out the test protected from light*.

Test solution Dissolve 50 mg of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve the contents of a vial of *levocabastine for system suitability 1 CRS* (containing impurities A, B, E, J and K) in 1 mL of *methanol R*.

Reference solution (b) Dilute 1.0 mL of the test solution to 20.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Column:

— *size*: *l* = 0.10 m, Ø = 2.1 mm;

— *stationary phase*: *end-capped ethylene-bridged phenylsilyl silica gel for chromatography (hybrid material) R* (1.7 µm);

— *temperature*: 60 °C.

Mobile phase:

— *mobile phase A*: 17 g/L solution of *tetrabutylammonium hydrogen sulfate R*;

— *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 0.5	95	5

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0.0 - 3.5	95 → 90	5 → 10
3.5 - 6.0	90 → 85	10 → 15
6.0 - 11.0	85 → 70	15 → 30
11.0 - 14.5	70 → 20	30 → 80
14.5 - 15.5	20	80

Flow rate 0.45 mL/min.

Detection Spectrophotometer at 214 nm.

Injection 2.0 µL.

Identification of impurities Use the chromatogram supplied with *levocabastine for system suitability 1 CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, E, J and K.

Relative retention With reference to levocabastine (retention time = about 6.5 min): impurity A = about 0.85; impurity J = about 0.86; impurity B = about 0.90; impurity E = about 0.94; impurity K = about 1.07.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 2.9, where H_p = height above the baseline of the peak due to impurity K and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to levocabastine; minimum 5.0, where H_p = height above the baseline of the peak due to impurity J and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity A.

Calculation of percentage contents:

— for each impurity, use the concentration of levocabastine hydrochloride in reference solution (b).

Limits:

— *impurity E*: maximum 0.4 per cent;

— *impurity A*: maximum 0.2 per cent;

— *impurity B*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.6 per cent;

— *reporting threshold*: 0.05 per cent.

Impurity C

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Liquid chromatography (2.2.29). *Carry out the test protected from light.*

Test solution Dissolve 50 mg of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve the contents of a vial of *levocabastine for system suitability 2 CRS* (containing impurity C) in 1 mL of *methanol R*.

Reference solution (b) Dilute 1.0 mL of the test solution to 20.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Column:

— *size*: *l* = 0.15 m, Ø = 2.1 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography compatible with 100 per cent aqueous mobile phases R* (1.8 µm);

— *temperature*: 35 °C.

Mobile phase:

— *mobile phase A*: 17 g/L solution of *tetrabutylammonium hydrogen sulfate R*;

— *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 0.5	90	10
0.5 - 15.5	90 → 80	10 → 20
15.5 - 20.5	80 → 50	20 → 50

Flow rate 0.30 mL/min.

Detection Spectrophotometer at 214 nm.

Injection 2.0 µL.

Identification of impurities Use the chromatogram supplied with *levocabastine for system suitability 2 CRS* and the chromatogram obtained with reference solution (a) to identify the peak due to impurity C.

Relative retention With reference to levocabastine (retention time = about 16 min): impurity C = about 0.98.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 10.0, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to levocabastine.

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Calculation of percentage content:

— for impurity C, use the concentration of levocabastine hydrochloride in reference solution (b).

Limit:

— *impurity C*: maximum 0.3 per cent.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Dissolve 0.175 g in 50 mL of *ethanol (96 per cent) R*, previously neutralised to *phenol red solution R*, and add 5.0 mL of *water R*. Carry out a potentiometric titration (2.2.20), using *0.1 M sodium hydroxide*. Read the volume at the 2nd point of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 22.85 mg of $C_{26}H_{30}ClFN_2O_2$.

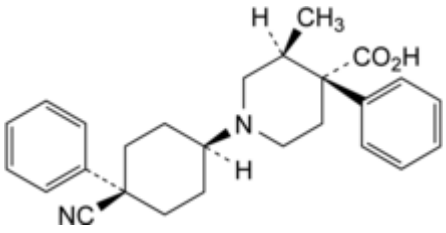
STORAGE

Protected from light.

IMPURITIES

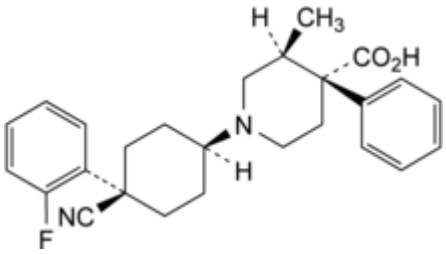
Specified impurities A, B, C, E.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) D, F, G, H, I, J, K, L.

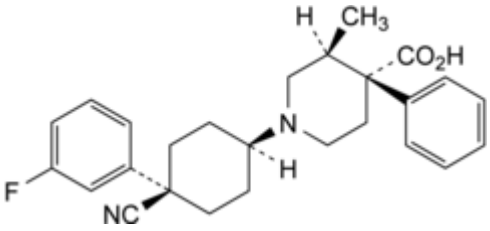


A. (3*S*,4*R*)-1-(*cis*-4-cyano-4-phenylcyclohexyl)-3-methyl-4-phenylpiperidine-4-carboxylic acid,

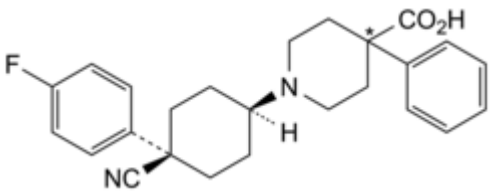
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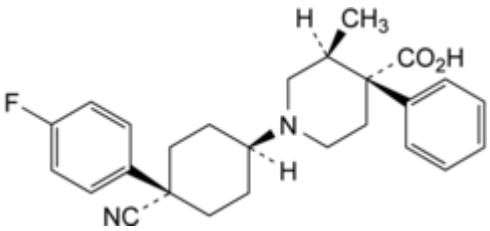
B. (3*S*,4*R*)-1-[*cis*-4-cyano-4-(2-fluorophenyl)cyclohexyl]-3-methyl-4-phenylpiperidine-4-carboxylic acid,



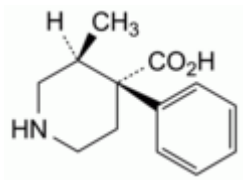
C. (3*S*,4*R*)-1-[*cis*-4-cyano-4-(3-fluorophenyl)cyclohexyl]-3-methyl-4-phenylpiperidine-4-carboxylic acid,



D. 1-[*cis*-4-cyano-4-(4-fluorophenyl)cyclohexyl]-4-phenylpiperidine-4-carboxylic acid,

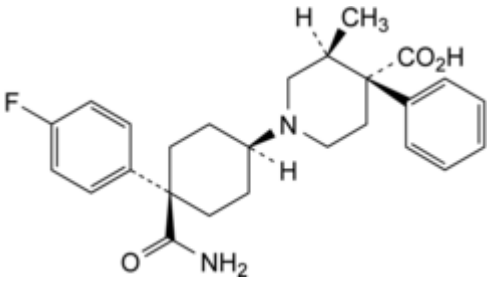


E. (3*S*,4*R*)-1-[*trans*-4-cyano-4-(4-fluorophenyl)cyclohexyl]-3-methyl-4-phenylpiperidine-4-carboxylic acid,

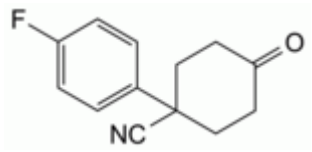


F. (3*S*,4*R*)-3-methyl-4-phenylpiperidine-4-carboxylic acid,

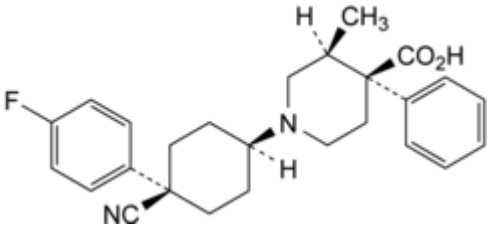
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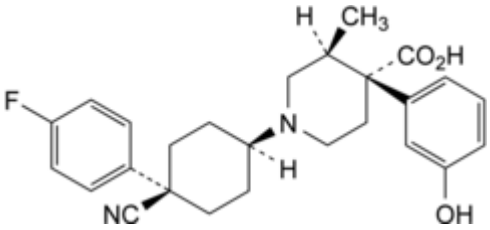
G. (3*S*,4*R*)-1-[*cis*-4-carbamoyl-4-(4-fluorophenyl)cyclohexyl]-3-methyl-4-phenylpiperidine-4-carboxylic acid,



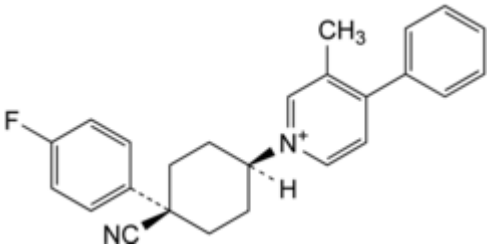
H. 1-(4-fluorophenyl)-4-oxocyclohexanecarbonitrile,



I. (3*S*,4*S*)-1-[*cis*-4-cyano-4-(4-fluorophenyl)cyclohexyl]-3-methyl-4-phenylpiperidine-4-carboxylic acid,

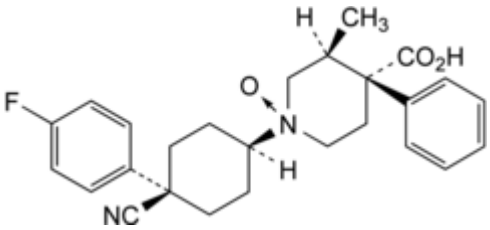


J. (3*S*,4*R*)-1-[*cis*-4-cyano-4-(4-fluorophenyl)cyclohexyl]-4-(3-hydroxyphenyl)-3-methylpiperidine-4-carboxylic acid,



K. 1-[*cis*-4-cyano-4-(4-fluorophenyl)cyclohexyl]-3-methyl-4-phenylpyridinium,

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L. (3*S*,4*R*)-1-[*cis*-4-cyano-4-(4-fluorophenyl)cyclohexyl]-3-methyl-4-phenylpiperidine-4-carboxylic acid 1-oxide.

Ph Eur

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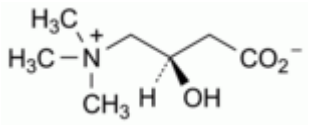
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This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Levocarnitine

General Notices

(Ph. Eur. monograph 1339)



$C_7H_{15}NO_3$ 161.2 *541-15-1*

Action and use

Carnitine substitute.

Ph Eur

DEFINITION

(3*R*)-3-Hydroxy-4-(trimethylazaniumyl)butanoate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals, hygroscopic.

Solubility

Freely soluble in water, soluble in warm ethanol (96 per cent), practically insoluble in acetone.

IDENTIFICATION

First identification: A, B.

Second identification: A, C.

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A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Preparation Discs, prepared using substance previously dried *in vacuo* at 50 °C for 5 h.

Comparison *levocarnitine CRS*.

C. To 1 mL of solution S (see Tests) add 9 mL of *water R*, 10 mL of *dilute sulfuric acid R* and 30 mL of *ammonium reineckate solution R*. A pink precipitate is formed. Allow to stand for 30 min. Filter and wash with *water R*, with *ethanol (96 per cent) R* and then with *acetone R* and dry at 80 °C. The precipitate melts (2.2.14) at 147 °C to 150 °C.

TESTS

Solution S

Dissolve 5.00 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 50.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, *Method II*).

pH (2.2.3)

6.5 to 8.5.

Dilute 10 mL of solution S to 20 mL with *carbon dioxide-free water R*.

Specific optical rotation (2.2.7)

-32.0 to -29.0 (anhydrous substance), determined on solution S at 25 °C.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.100 g of the substance to be examined in the mobile phase and dilute to 20.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 12.5 mg of *levocarnitine impurity A CRS* in *water R* and dilute to 50.0 mL with the same solvent. Dilute 2.0 mL of the solution to 20.0 mL with the mobile phase.

Reference solution (c) Dissolve 50 mg of the substance to be examined in 10 mL of reference solution (b).

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

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— *stationary phase*: *zwitterion-bonded silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase Mix 25 volumes of a 0.77 g/L solution of *ammonium acetate R* in *water for chromatography R* previously adjusted to pH 5 with *acetic acid R* with 75 volumes of *acetonitrile R1*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 205 nm.

Injection 20 µL.

Run time 2.5 times the retention time of levocarnitine.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A.

Relative retention With reference to levocarnitine (retention time = about 8 min): impurity A = about 1.2.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to levocarnitine and impurity A.

Calculation of percentage contents:

— for impurity A, use the concentration of impurity A in reference solution (b);

— for impurities other than A, use the concentration of levocarnitine in reference solution (a).

Limits:

— *impurity A*: maximum 0.3 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total (excluding impurity A)*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Chlorides (2.4.4)

Maximum 200 ppm.

Dilute 2.5 mL of solution S to 15 mL with *water R*.

Sulfates (2.4.13)

Maximum 300 ppm.

Dilute 5 mL of solution S to 15 mL with *distilled water R*.

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Water (*2.5.12*)

Maximum 1.0 per cent, determined on 2.00 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.125 g in a mixture of 3 volumes of *formic acid R* and 50 volumes of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 16.12 mg of $C_7H_{15}NO_3$.

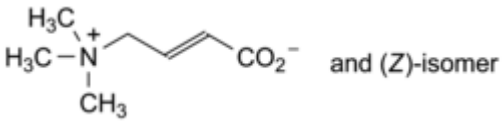
STORAGE

In an airtight container.

IMPURITIES

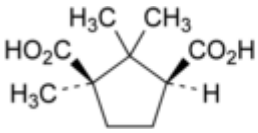
Specified impurities *A*.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D*.



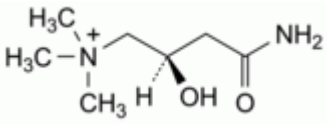
and (*Z*)-isomer

A. (2*EZ*)-4-(trimethylazaniumyl)but-2-enoate,



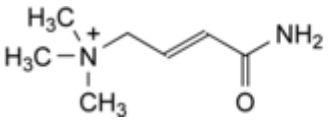
and enantiomer

B. (1*RS*,3*SR*)-1,2,2-trimethylcyclopentane-1,3-dicarboxylic acid (camphoric acid),



C. (2*R*)-4-amino-2-hydroxy-*N,N,N*-trimethyl-4-oxobutan-1-aminium (carnitinamide),

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 and (*Z*)-isomer

D. (2*EZ*)-4-amino-*N,N,N*-trimethyl-4-oxobut-2-en-1-aminium.

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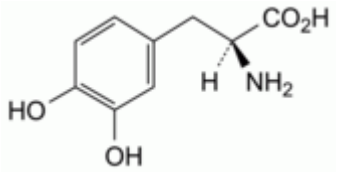
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Levodopa

General Notices

(Ph. Eur. monograph 0038)



$C_9H_{11}NO_4$ 197.2 *59-92-7*

Action and use

Dopamine precursor; treatment of Parkinson's disease.

Preparations

Co-beneldopa Capsules

Co-beneldopa Dispersible Tablets

Co-beneldopa Prolonged-release Capsules

Co-careldopa Tablets

When L-dopa is prescribed or demanded, Levodopa shall be dispensed or supplied.

Ph Eur

DEFINITION

(2*S*)-2-Amino-3-(3,4-dihydroxyphenyl)propanoic acid.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

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Solubility

Slightly soluble in water, practically insoluble in ethanol (96 per cent). It is freely soluble in *1 M hydrochloric acid* and sparingly soluble in *0.1 M hydrochloric acid*.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *levodopa CRS*.

TESTS

Appearance of solution

The solution is not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

Dissolve 1.0 g in a 103 g/L solution of *hydrochloric acid R* and dilute to 25 mL with the same solution.

pH (*2.2.3*)

4.5 to 7.0.

Shake 0.10 g with 10 mL of *carbon dioxide-free water R* for 15 min.

Related substances

Liquid chromatography (*2.2.29*). *Use freshly prepared solutions.*

Solution A 10.3 g/L solution of *hydrochloric acid R*.

Test solution Dissolve 0.100 g of the substance to be examined in solution A and dilute to 25 mL with solution A.

Reference solution (a) Dilute 1.0 mL of the test solution to 50.0 mL with solution A. Dilute 5.0 mL of this solution to 100.0 mL with solution A.

Reference solution (b) Dissolve 8 mg of *tyrosine R* (impurity B) and 4 mg of *3-methoxy-L-tyrosine R* (L-isomer of impurity C) in 2 mL of the test solution and dilute to 50 mL with solution A. Dilute 5 mL of this solution to 100 mL with solution A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: spherical *di-isobutyloctadecylsilyl silica gel for chromatography R* (5 µm) with a pore size of 8 nm.

Mobile phase:

— *mobile phase A*: 0.1 M phosphate buffer solution pH 3.0 R;

— *mobile phase B*: *methanol R*, 0.1 M phosphate buffer solution pH 3.0 R (18:85 *V/V*);

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 18	90	10
18 - 22	90 → 0	10 → 100
22 - 35	0	100

Flow rate 1 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B and C.

Relative retention With reference to levodopa (retention time = about 6 min): impurity A = about 0.7; impurity B = about 2; impurity C = about 3.5.

System suitability Reference solution (b):

— *resolution*: minimum 10 between the peaks due to levodopa and impurity B.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity B by 2.2;

— *impurity B*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *impurity C*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent);

— *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.03 per cent).

Enantiomeric purity

Liquid chromatography (2.2.29). *Use freshly prepared solutions*.

Test solution Dissolve 25 mg of the substance to be examined in the mobile phase and dilute to 25 mL with the mobile phase.

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Reference solution (a) Dilute 5.0 mL of the test solution to 20.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (b) Dissolve 10 mg of *D-dopa R* (impurity D) in 10 mL of the test solution. Dilute 1 mL of this solution to 100 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

— *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Dissolve separately 200 mg of *copper acetate R* and 387 mg of *N,N-dimethyl-L-phenylalanine R* in 250 mL of *water R*; mix the 2 solutions and adjust immediately to pH 4.0 with *acetic acid R*; add 50 mL of *methanol R* and dilute to 1000 mL with *water R*; mix and filter.

Flow rate 1 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 20 µL.

Run time Twice the retention time of levodopa.

Relative retention With reference to levodopa (retention time = about 7 min): impurity D = about 0.4.

System suitability Reference solution (b):

— *resolution*: minimum 5 between the peaks due to impurity D and levodopa.

Limit:

— *impurity D*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent).

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 0.500 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.150 g, heating if necessary, in 5 mL of *anhydrous formic acid R*. Add 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 19.72 mg of $C_9H_{11}NO_4$.

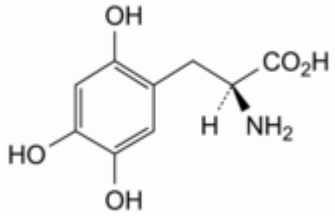
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STORAGE

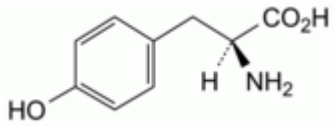
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IMPURITIES

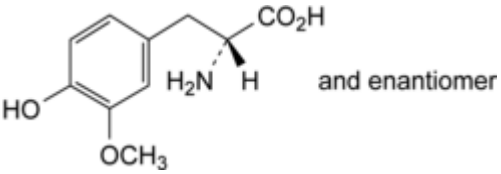
Specified impurities *A, B, C, D.*



A. (2*S*)-2-amino-3-(2,4,5-trihydroxyphenyl)propanoic acid,

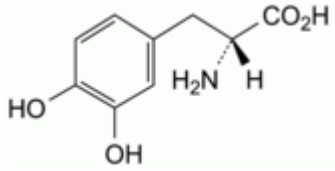


B. (2*S*)-2-amino-3-(4-hydroxyphenyl)propanoic acid (tyrosine),



and enantiomer

C. (2*RS*)-2-amino-3-(4-hydroxy-3-methoxyphenyl)propanoic acid (3-methoxy-DL-tyrosine),



D. (2*R*)-2-amino-3-(3,4-dihydroxyphenyl)propanoic acid (D-dopa).

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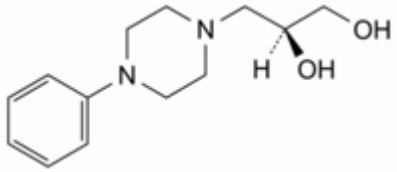
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Levodropropizine

General Notices

(Ph. Eur. monograph 1535)



$C_{13}H_{20}N_2O_2$ 236.3 *99291-25-5*

Action and use

Cough suppressant.

Ph Eur

DEFINITION

(2*S*)-3-(4-Phenylpiperazin-1-yl)propane-1,2-diol.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Slightly soluble in water, freely soluble in dilute acetic acid and in methanol, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

Carry out either tests A, B or tests B, C.

A. Specific optical rotation (2.2.7): -33.5 to -30.0 (dried substance).

Dissolve 1.50 g in a 21 g/L solution of *hydrochloric acid R* and dilute to 50.0 mL with the same acid.

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B. Infrared absorption spectrophotometry (2.2.24).

Comparison levodropropizine CRS.

C. Enantiomeric purity (see Tests).

TESTS

pH (2.2.3)

9.2 to 10.2.

Suspend 2.5 g in carbon dioxide-free water R, heat to dissolve, cool to room temperature and dilute to 100 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 25.0 mg of levodropropizine impurity B CRS in methanol R and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (b) Mix 1 mL of the test solution with 1 mL of reference solution (a).

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: end-capped extra-dense bonded octadecylsilyl silica gel for chromatography R (5 µm).

Mobile phase Mix 12 volumes of methanol R and 88 volumes of a 6.81 g/L solution of potassium dihydrogen phosphate R previously adjusted to pH 3.0 with phosphoric acid R.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

Run time Twice the retention time of levodropropizine.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity B.

Relative retention With reference to levodropropizine (retention time = about 7 min): impurity B = about 1.2.

System suitability Reference solution (b):

— resolution: minimum 2.0 between the peaks due to levodropropizine and impurity B.

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Limits:

— *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than 0.2 times the area of the peak due to impurity B in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 1.2 times the area of the peak due to impurity B in the chromatogram obtained with reference solution (a) (0.6 per cent);

— *disregard limit*: 0.1 times the area of the peak due to impurity B in the chromatogram obtained with reference solution (a) (0.05 per cent).

Impurity C

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use. Use vials sealed with a crimp-top to prevent evaporation of the solvent.*

Test solution Dissolve 50 mg of *sodium diethyldithiocarbamate R* and 1.0 g of the substance to be examined in *methanol R* and dilute to 5.0 mL with the same solvent. Heat at 60 °C for 20 min and then cool to room temperature. Add 5 mL of *water R* and 0.5 mL of *phosphoric acid R*. Extract with 5 mL of *methylene chloride R*.

Reference solution (a) Dissolve 0.100 g of *levodropropizine impurity C CRS* in *methanol R* and dilute to 50.0 mL with the same solvent. Dilute 1.0 mL of the solution to 20.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 100.0 mL with *methanol R*.

Reference solution (b) Dissolve 50 mg of *sodium diethyldithiocarbamate R* in reference solution (a) and dilute to 5.0 mL with reference solution (a). Heat at 60 °C for 20 min and then cool to room temperature. Add 5 mL of *water R* and 0.5 mL of *phosphoric acid R*. Extract with 5 mL of *methylene chloride R*.

Reference solution (c) Dissolve 50 mg of *sodium diethyldithiocarbamate R* and 1.0 g of the substance to be examined in reference solution (a) and dilute to 5.0 mL with reference solution (a). Heat at 60 °C for 20 min and then cool to room temperature. Add 5 mL of *water R* and 0.5 mL of *phosphoric acid R*. Extract with 5 mL of *methylene chloride R*.

Blank solution Dissolve 50 mg of *sodium diethyldithiocarbamate R* in *methanol R* and dilute to 5.0 mL with the same solvent. Heat at 60 °C for 20 min and then cool to room temperature. Add 5 mL of *water R* and 0.5 mL of *phosphoric acid R*. Extract with 5 mL of *methylene chloride R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *aminopropylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *methanol R*, *tetrahydrofuran R*, *heptane R* (15:15:70 *V/V/V*).

Flow rate 1 mL/min.

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Detection Spectrophotometer at 278 nm.

Injection 20 µL of the blank solution, the test solution and reference solutions (b) and (c).

Run time 3 times the retention time of impurity C.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity C.

Retention time Impurity C = about 8 min.

System suitability Reference solution (b):

— *signal-to-noise ratio*: minimum 50 for the peak due to impurity C.

Calculate the content of impurity C in parts per million using the following expression:

$$\frac{A}{B}$$

A	=	area of the peak due to impurity C in the chromatogram obtained with the test solution;
B	=	area of the peak due to impurity C in the chromatogram obtained with reference solution (c).

Limit:

— *impurity C*: maximum 5 ppm.

Enantiomeric purity

Liquid chromatography (*2.2.29*).

Solvent mixture *anhydrous ethanol R*, *hexane R* (40:60 *V/V*).

Test solution Dissolve 10.0 mg of the substance to be examined in 10.0 mL of the solvent mixture. Dilute 1.0 mL of this solution to 50.0 mL with the solvent mixture.

Reference solution (a) Dissolve 10 mg of *levodropropizine CRS* in 10.0 mL of the solvent mixture. Dilute 1.0 mL of this solution to 50.0 mL with the solvent mixture.

Reference solution (b) Dissolve 10.0 mg of *levodropropizine impurity A CRS* in 10 mL of the solvent mixture. Dilute 1 mL of this solution to 50 mL with the solvent mixture.

Reference solution (c) Dilute 1.0 mL of reference solution (b) to 50.0 mL with the solvent mixture.

Reference solution (d) Dilute 0.5 mL of reference solution (b) to 25 mL with reference solution (a).

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *cellulose derivative of silica gel for chiral separation R* (10 µm).

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Mobile phase *diethylamine R*, *anhydrous ethanol R*, *hexane R* (0.2:5:95 *V/V/V*).

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL of the test solution and reference solutions (a), (c) and (d).

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peak due to impurity A.

Relative retention With reference to levodropropizine (retention time = about 28 min): impurity A = about 0.9.

System suitability:

— *retention times*: the retention times of the principal peaks in the chromatograms obtained with the test solution and reference solution (a) are similar;

— *resolution*: minimum 1.3 between the peaks due to impurity A and levodropropizine in the chromatogram obtained with reference solution (d).

Limit:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (2 per cent).

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 0.500 g by drying *in vacuo* at 60 °C at a pressure of 0.15-0.25 kPa for 4 h.

Sulfated ash (2.4.14)

Maximum 0.2 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.100 g in 50 mL of *anhydrous acetic acid R*. Carry out a potentiometric titration (2.2.20), using *0.1 M perchloric acid*. Read the volume added at the 2nd point of inflexion.

1 mL of *0.1 M perchloric acid* is equivalent to 11.82 mg of $C_{13}H_{20}N_2O_2$.

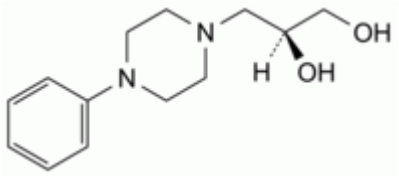
STORAGE

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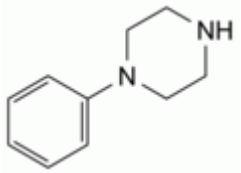
IMPURITIES

Specified impurities *A, B, C.*

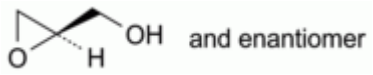
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A. (2*R*)-3-(4-phenylpiperazin-1-yl)propane-1,2-diol (dextrodropropizine),



B. 1-phenylpiperazine,



C. [(2*RS*)-oxiran-2-yl]methanol (glycidol).

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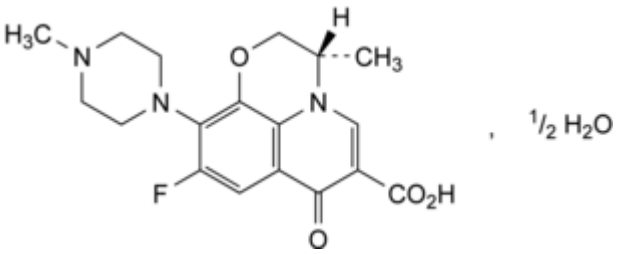
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Levofloxacin Hemihydrate

General Notices

(Ph. Eur. monograph 2598)



$C_{18}H_{20}FN_3O_4,½H_2O$ 370.4 *138199-71-0*

Action and use

Fluoroquinolone antibacterial.

Ph Eur

DEFINITION

(3*S*)-9-Fluoro-3-methyl-10-(4-methylpiperazin-1-yl)-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylic acid hemihydrate.

Content

98.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Light yellowish-white or light yellow, crystalline powder.

Solubility

Sparingly soluble in water, freely soluble in acetic acid, sparingly soluble in methanol, slightly soluble in anhydrous ethanol.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *levofloxacin hemihydrate CRS*.

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B. Examine the chromatograms obtained in the test for related substances.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with reference solution (b).

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution GY_3 (2.2.2, Method II).

Dissolve 0.100 g in *water R* and dilute to 10 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Buffer solution Solution containing 1.25 g/L of *copper sulfate pentahydrate R*, 1.3 g/L of *isoleucine R* and 8.5 g/L of *ammonium acetate R* in *water for chromatography R*.

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve the contents of a vial of *levofloxacin for system suitability CRS* (containing impurities A, B and G) in 1 mL of the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 45 °C.

Mobile phase *methanol R*, buffer solution (30:70 *V/V*).

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 360 nm.

Injection 25 µL.

Run time 3 times the retention time of levofloxacin.

Identification of impurities Use the chromatogram supplied with *levofloxacin for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B and G.

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Relative retention With reference to levofloxacin (retention time = about 20 min): impurity B = about 0.50; impurity G = about 0.56; impurity A = about 1.22.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurities B and G.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity B by 1.3;

— for each impurity, use the concentration of levofloxacin hemihydrate in reference solution (a).

Limits:

— *impurity A*: maximum 0.5 per cent;

— *impurity B*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.6 per cent;

— *reporting threshold*: 0.05 per cent.

Impurity F

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 5.0 mg of *levofloxacin impurity F CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 25.0 mL with the mobile phase.

Reference solution (c) Dilute 4 mL of reference solution (a) to 10 mL with the mobile phase. Dilute 1 mL of this solution to 10 mL with the test solution.

Mobile phase *methanol R*, buffer solution (50:50 *V/V*).

Detection Spectrophotometer at 320 nm.

Injection Test solution and reference solutions (b) and (c).

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity F.

Relative retention With reference to levofloxacin (retention time = about 6 min): impurity F = about 1.8.

System suitability Reference solution (c):

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— *resolution*: minimum 5.0 between the peaks due to levofloxacin and impurity F.

Calculation of percentage content:

— for impurity F, use the concentration of impurity F in reference solution (b).

Limit:

— *impurity F*: maximum 0.2 per cent.

Water (2.5.12)

2.0 per cent to 3.0 per cent, determined on 0.500 g using a mixture of equal volumes of *formamide R* and *methanol R* as solvent.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Dissolve 0.300 g in 100 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 36.14 mg of $C_{18}H_{20}FN_3O_4$.

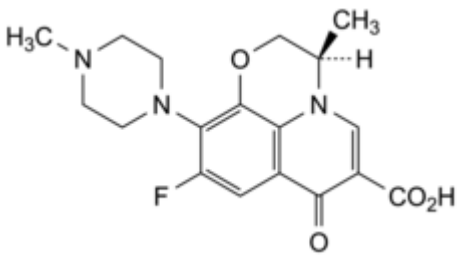
STORAGE

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IMPURITIES

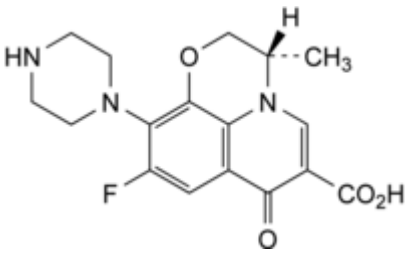
Specified impurities *A, B, F.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, D, E, G, H, I.*

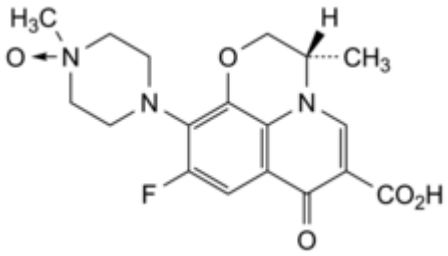


A. (3*R*)-9-fluoro-3-methyl-10-(4-methylpiperazin-1-yl)-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylic acid (enantiomer of levofloxacin),

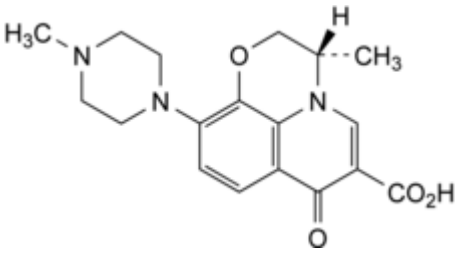
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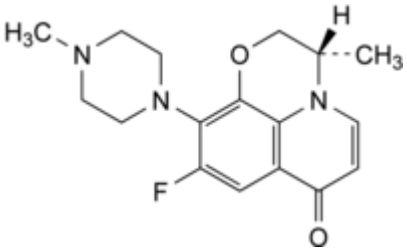
B. (3*S*)-9-fluoro-3-methyl-7-oxo-10-(piperazin-1-yl)-2,3-dihydro-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylic acid,



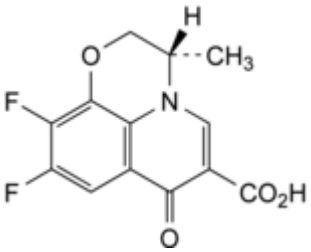
C. 4-[(3*S*)-6-carboxy-9-fluoro-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazin-10-yl]-1-methylpiperazine 1-oxide,



D. (3*S*)-3-methyl-10-(4-methylpiperazin-1-yl)-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylic acid,

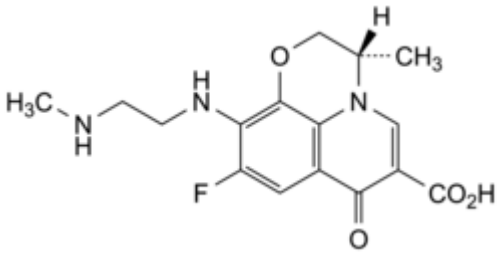


E. (3*S*)-9-fluoro-3-methyl-10-(4-methylpiperazin-1-yl)-2,3-dihydro-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazin-7-one,

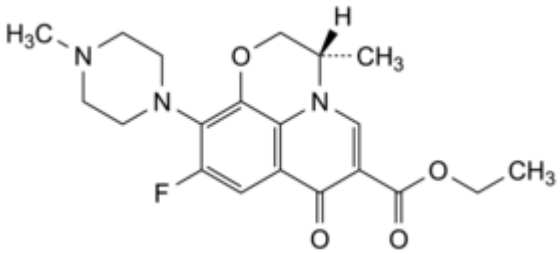


F. (3*S*)-9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylic acid,

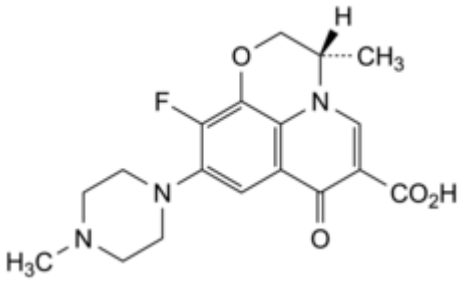
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G. (3*S*)-9-fluoro-3-methyl-10-[[2-(methylamino)ethyl]amino]-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylic acid,



H. ethyl (3*S*)-9-fluoro-3-methyl-10-(4-methylpiperazin-1-yl)-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylate,



I. (3*S*)-10-fluoro-3-methyl-9-(4-methylpiperazin-1-yl)-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylic acid.

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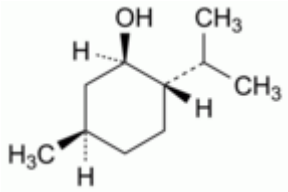
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Levomenthol

General Notices

(Ph. Eur. monograph 0619)



$C_{10}H_{20}O$ 156.3 *2216-51-5*

Action and use

Decongestant.

Preparations

Levomenthol Cream

Menthol and Benzoin Inhalation

Ph Eur

DEFINITION

(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methylethyl)cyclohexanol.

CHARACTERS

Appearance

Prismatic or acicular, colourless, shiny crystals.

Solubility

Practically insoluble in water, very soluble in ethanol (96 per cent) and in light petroleum, freely soluble in fatty oils and in liquid paraffin, very slightly soluble in glycerol.

mp

About 43 °C.

IDENTIFICATION

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IDENTIFICATION

First identification: A, C.

Second identification: B, D.

A. Specific optical rotation (see Tests).

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 25 mg of the substance to be examined in *methanol R* and dilute to 5 mL with the same solvent.

Reference solution Dissolve 25 mg of *menthol CRS* in *methanol R* and dilute to 5 mL with the same solvent.

Plate *TLC silica gel G plate R*.

Mobile phase *ethyl acetate R*, *toluene R* (5:95 *V/V*).

Application 2 µL.

Development Over a path of 15 cm.

Drying In air, until the solvents have evaporated.

Detection Spray with *anisaldehyde solution R* and heat at 100-105 °C for 5-10 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. Examine the chromatograms obtained in the test for related substances.

Results The principal peak in the chromatogram obtained with test solution (b) is similar in position and approximate dimensions to the principal peak in the chromatogram obtained with reference solution (c).

D. Dissolve 0.20 g in 0.5 mL of *anhydrous pyridine R*. Add 3 mL of a 150 g/L solution of *dinitrobenzoyl chloride R* in *anhydrous pyridine R*. Heat on a water-bath for 10 min. Add 7.0 mL of *water R* in small quantities with stirring and allow to stand in iced water for 30 min. A precipitate is formed. Allow to stand and decant the supernatant. Wash the precipitate with 2 quantities, each of 5 mL, of iced *water R*, recrystallise from 10 mL of *acetone R*, wash with iced *acetone R* and dry at 75 °C at a pressure not exceeding 2.7 kPa for 30 min. The crystals melt (2.2.14) at 154 °C to 157 °C.

TESTS

Solution S

Dissolve 2.50 g in 10 mL of *ethanol (96 per cent) R* and dilute to 25.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, *Method II*).

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Acidity or alkalinity

Dissolve 1.0 g in *ethanol (96 per cent) R* and dilute to 10 mL with the same solvent. Add 0.1 mL of *phenolphthalein solution R*. The solution is colourless. Not more than 0.5 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to pink.

Specific optical rotation (*2.2.7*)

-48 to -51, determined on solution S.

Related substances

Gas chromatography (*2.2.28*).

Test solution (a) Dissolve 0.20 g of the substance to be examined in *methylene chloride R* and dilute to 50.0 mL with the same solvent.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with *methylene chloride R*.

Reference solution (a) Dissolve 40.0 mg of the substance to be examined and 40.0 mg of *isomenthol R* in *methylene chloride R* and dilute to 100.0 mL with the same solvent.

Reference solution (b) Dilute 0.10 mL of test solution (a) to 100.0 mL with *methylene chloride R*.

Reference solution (c) Dissolve 40.0 mg of *menthol CRS* in *methylene chloride R* and dilute to 100.0 mL with the same solvent.

Column:

— *material*: glass;

— *size*: *l* = 2.0 m, Ø = 2 mm;

— *stationary phase*: diatomaceous earth for gas chromatography R impregnated with 15 per cent *m/m* of *macrogol 1500 R*.

Carrier gas *nitrogen for chromatography R*.

Flow rate 30 mL/min.

Temperature:

— *column*: 120 °C;

— *injection port*: 150 °C;

— *detector*: 200 °C.

Detection Flame ionisation.

Injection 1 µL.

Run time Twice the retention time of menthol.

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System suitability:

— *resolution*: minimum 1.4 between the peaks due to menthol and isomenthol in the chromatogram obtained with reference solution (a);

— *signal-to-noise ratio*: minimum 5 for the principal peak in the chromatogram obtained with reference solution (b).

Limits Test solution (a):

— *total*: not more than 1 per cent of the area of the principal peak;

— *disregard limit*: 0.05 per cent of the area of the principal peak.

Residue on evaporation

Maximum 0.05 per cent.

Evaporate 2.00 g on a water-bath and heat in an oven at 100-105 °C for 1 h. The residue weighs not more than 1.0 mg.

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Levomenthol Cream

General Notices

Menthol in Aqueous Cream

NOTE: This monograph has been developed to cover unlicensed formulations.

DEFINITION

Levomenthol Cream contains Levomenthol in Aqueous Cream.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements. Where appropriate, the cream also complies with the requirements stated under Unlicensed Medicines.

Content of levomenthol, $C_{10}H_{20}O$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

In the Assay, the chromatogram obtained with solution (2) shows a peak with the same retention time as the peak due to levomenthol in the chromatogram obtained with solution (3).

ASSAY

Carry out the method for *gas chromatography*, Appendix III B, using the following freshly prepared solutions.

(1) 0.1% w/v of *camphor* (internal standard) in *industrial methylated spirit (95%)*.

(2) Disperse a quantity of the well-mixed cream containing 50 mg of Levomenthol in 20 mL of *industrial methylated spirit (95%)* and mix with the aid of ultrasound for 15 minutes. Transfer the liquid contents to a 50 mL graduated flask, rinse the original flask with two 10-mL quantities of *industrial methylated spirit (95%)*, transfer the washings to the graduated flask and add sufficient *industrial methylated spirit (95%)* to produce 50 mL; mix well and filter (Whatman No. 1 paper is suitable) discarding the first 5 mL of filtrate. Add 10 mL of solution (1) to 10 mL of the filtrate and add sufficient *industrial methylated spirit (95%)* to produce 25 mL; mix well.

(3) Mix 5 mL of a 0.2% w/v solution of *levomenthol BPCRS* in *industrial methylated spirit (95%)* with 10 mL of solution (1) and dilute to 25 mL with *industrial methylated spirit (95%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a fused silica column (10 m × 0.53 mm) bonded with a 0.25-µm layer of dimethylpolysiloxane.

(b) Use *helium* as the carrier gas.

(c) Use the gradient conditions described below.

(d) Use an inlet temperature of 250°.

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(e) Use a flame ionisation detector at a temperature of 250°.

(f) Inject 1 µL of each solution.

Time (Minutes)	Temperature	Comment
0 → 1	90°	isothermal
1 → 5	90° → 230°	linear gradient
5 → 9	230°	isothermal

When the chromatograms are recorded under the prescribed conditions the retention times are: levomenthol, about 2.1 minutes; camphor, about 2 minutes.

DETERMINATION OF CONTENT

Calculate the content of $C_{10}H_{20}O$ in the cream using the declared content of $C_{10}H_{20}O$ in *levomenthol BPCRS*.

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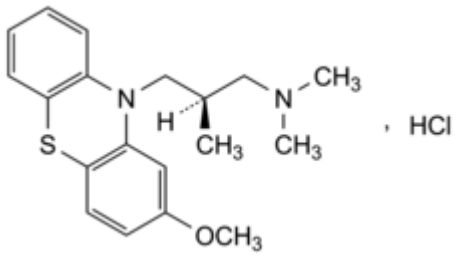
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This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Levomepromazine Hydrochloride

General Notices

(Ph. Eur. monograph 0505)



$C_{19}H_{25}ClN_2OS$ 364.9 *1236-99-3*

Action and use

Dopamine receptor antagonist; neuroleptic.

Preparation

Levomepromazine Injection

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DEFINITION

(2*R*)-3-(2-Methoxy-10*H*-phenothiazin-10-yl)-*N*,*N*,2-trimethylpropan-1-amine hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or very slightly yellow, crystalline powder, slightly hygroscopic.

Solubility

Freely soluble in water and in ethanol (96 per cent), practically insoluble in heptane.

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It deteriorates when exposed to air and light.

It shows polymorphism (5.9). It may exist in 2 forms, one melting at about 142 °C and the other at about 162 °C.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *levomepromazine hydrochloride CRS*.

B. Specific optical rotation (see Tests).

C. Dissolve 20 mg in 2 mL of *methanol R*. The solution gives reaction (a) of chlorides (2.3.1); use *methanol R* instead of *water R* to wash and suspend the precipitate.

TESTS

pH (2.2.3)

4.0 to 5.5.

Dissolve 0.3 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Specific optical rotation (2.2.7)

+ 9.5 to + 11.5 (dried substance).

Dissolve 2.50 g in *water R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use and carry out the test protected from light.*

Solvent mixture *acetonitrile R*, *water R* (50:50 *V/V*).

Buffer solution Dissolve 6.16 g of *ammonium acetate R* in about 900 mL of *water for chromatography R*, adjust to pH 6.0 with *dilute acetic acid R* and dilute to 1000 mL with *water for chromatography R*.

Test solution Dissolve 30.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 2.5 mg of *levomepromazine for system suitability CRS* (containing impurities B, D and E) in 5 mL of the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

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— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: *tetrahydrofuran R*, *acetonitrile R*, *methanol R*, buffer solution (1:10:10:79 *V/V/V/V*);

— *mobile phase B*: *tetrahydrofuran R*, buffer solution, *acetonitrile R*, *methanol R* (1:10:44.5:44.5 *V/V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	65	35
2 - 20	65 → 40	35 → 60
20 - 28	40 → 0	60 → 100
28 - 55	0	100

Flow rate 1.1 mL/min.

Autosampler Set at 4 °C.

Injection 10 µL.

Detection Spectrophotometer at 253 nm.

Identification of impurities Use the chromatogram supplied with *levomepromazine for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B, D and E.

Relative retention With reference to levomepromazine (retention time = about 14 min): impurity B = about 0.3; impurity D = about 2.30; impurity E = about 2.33.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 10.0, where H_p = height above the baseline of the peak due to impurity E and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity D.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity E by 1.5;

— for each impurity, use the concentration of levomepromazine hydrochloride in reference solution (a).

Limits:

— *impurities B, D and E*: for each impurity, maximum 0.15 per cent;

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— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in 5 mL of *water R* and add 50 mL of *2-propanol R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M sodium hydroxide* is equivalent to 36.49 mg of $C_{19}H_{25}ClN_2OS$.

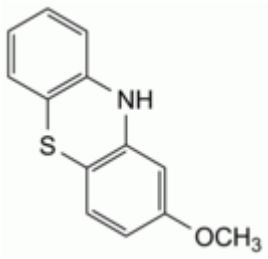
STORAGE

In an airtight container, protected from light.

IMPURITIES

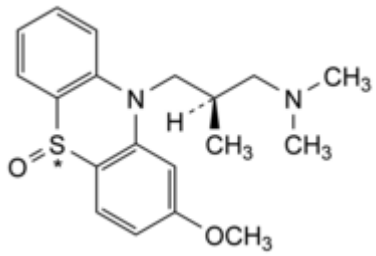
Specified impurities *B, D, E.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, C.*

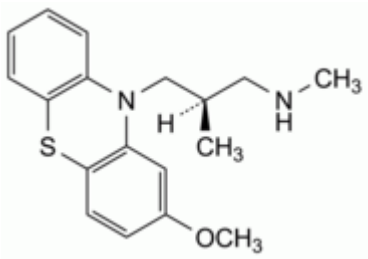


A. 2-methoxy-10*H*-phenothiazine,

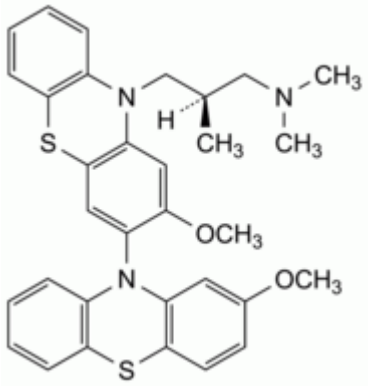
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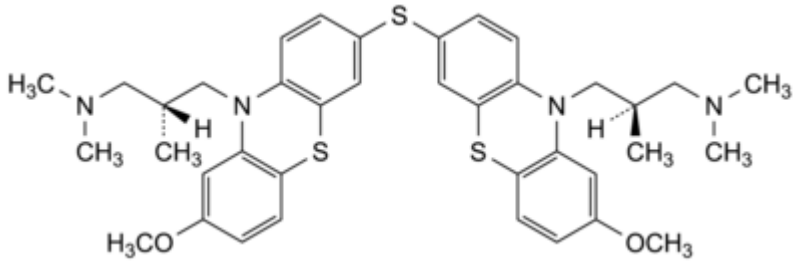
B. (5Ξ-10-[(2*R*)-3-(dimethylamino)-2-methylpropyl]-2-methoxy-5λ^4-phenothiazin-5(10*H*)-one,



C. (2*R*)-3-(2-methoxy-10*H*-phenothiazin-10-yl)-*N*,2-dimethylpropan-1-amine,



D. (2*R*)-3-(2,2′-dimethoxy-10*H*,10′*H*-[3,10′-biphenothiazin]-10-yl)-*N*,*N*,2-trimethylpropan-1-amine,



E. (2*R*,2′*R*)-3,3′-[sulfanediylbis[(8-methoxy-10*H*-phenothiazine-3,10-diyl)]]bis(*N*,*N*,2-trimethylpropan-1-amine).

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Levomepromazine Injection

General Notices

Action and use

Dopamine receptor antagonist; neuroleptic.

DEFINITION

Levomepromazine Injection is a solution of Levomepromazine Hydrochloride in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of levomepromazine hydrochloride, $C_{19}H_{24}N_2OS,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

To a volume of the injection containing 50 mg of Levomepromazine Hydrochloride add 2 mL of 1M *sodium hydroxide*, shake, extract with 15 mL of *ether* and allow to separate. Wash the ethereal layer with 5 mL of *water*, filter through phase-separating paper (Whatman 1 PS is suitable) containing *anhydrous sodium sulfate*, evaporate the ether to dryness and dry the residue at 100° for 3 hours. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of levomepromazine (*RS 404*).

TESTS

Acidity

pH, 4.0 to 5.0, Appendix V L.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions protected from light.

(1) Dilute a volume of the injection, if necessary, with sufficient of a mixture of 95 volumes of *methanol* and 5 volumes of *diethylamine* to produce a solution containing 0.5% w/v of Levomepromazine Hydrochloride.
(2) Dilute 1 volume of solution (1) to 100 volumes with a mixture of 95 volumes of *methanol* and 5 volumes of *diethylamine* and further dilute 1 volume to 2 volumes with the same solvent mixture.
(3) 0.005% w/v of *levomepromazine sulfoxide BPCRS* in a mixture of 95 volumes of *methanol* and 5 volumes of *diethylamine*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *TLC silica gel GF_{254} plate*.

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(b) Use the mobile phase, maintained at 35°, as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

5 volumes of *diethylamine*, 10 volumes of *acetone* and 85 volumes of *toluene*.

LIMITS

In the chromatogram obtained with solution (1):

any spot corresponding to levomepromazine sulfoxide is not more intense than the spot in the chromatogram obtained with solution (3) (1%);

any other *secondary spot* is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%). Disregard any spot remaining on the line of application.

ASSAY

Carry out the following procedure protected from light. Dilute a volume of the injection containing 0.1 g of Levomepromazine Hydrochloride to 100 mL with *water* and dilute 1 volume of this solution to 25 volumes with *water*. Immediately measure the *absorbance* of the solution at the maximum at 302 nm, Appendix II B, using *water* in the reference cell. Measure the absorbance of a 0.004% w/v solution of *levomepromazine maleate BPCRS* in *water* and calculate the content of $C_{19}H_{24}N_2OS,HCl$ from the absorbances obtained using the declared content of $C_{19}H_{24}N_2OS,C_4H_4O_4$ in *levomepromazine maleate BPCRS*. Each mg of $C_{19}H_{24}N_2OS,C_4H_4O_4$ is equivalent to 0.8207 mg of $C_{19}H_{24}N_2OS,HCl$.

STORAGE

Levomepromazine Injection should be protected from light.

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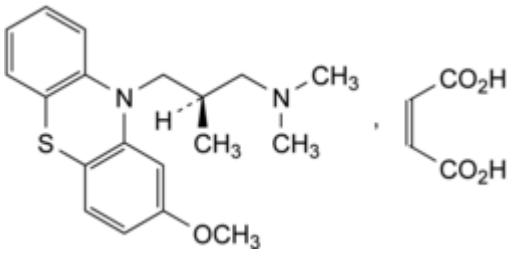
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This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Levomepromazine Maleate

General Notices

(Ph. Eur. monograph 0925)



$C_{23}H_{28}N_2O_5S$ 444.5 *7104-38-3*

Action and use

Dopamine receptor antagonist; neuroleptic.

Preparation

Levomepromazine Tablets

Ph Eur

DEFINITION

(2*R*)-3-(2-Methoxy-10*H*-phenothiazin-10-yl)-*N*,*N*,2-trimethylpropan-1-amine (2*Z*)-but-2-enedioate.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or slightly yellowish, crystalline powder.

Solubility

Slightly soluble in water and in ethanol (96 per cent), sparingly soluble in methylene chloride.

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It deteriorates when exposed to air and light.

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About 186 °C, with decomposition.

IDENTIFICATION

First identification: A, B.

Second identification: C, D.

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *levomepromazine maleate CRS*.

C. Identification of phenothiazines by thin-layer chromatography (2.3.3): use *levomepromazine maleate CRS* to prepare the reference solution.

D. Thin-layer chromatography (2.2.27).

Solvent mixture *water R*, *acetone R* (10:90 *V/V*).

Test solution Dissolve 0.20 g of the substance to be examined in the solvent mixture and dilute to 10 mL with the solvent mixture.

Reference solution Dissolve 50 mg of *maleic acid CRS* in the solvent mixture and dilute to 10 mL with the solvent mixture.

Plate *TLC silica gel F_{254} plate R* .

Mobile phase *water R*, *formic acid R*, *di-isopropyl ether R* (3:7:90 *V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying At 120 °C for 10 min.

Detection Examine in ultraviolet light at 254 nm.

Retardation factors Levomepromazine = 0; maleic acid = about 0.1.

Results The chromatogram obtained with the test solution shows a zone at the point of application and another zone similar in position and size to the principal zone in the chromatogram obtained with the reference solution.

TESTS

pH (2.2.3)

3.5 to 5.5.

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Carry out the test protected from bright light.

Suspend 0.50 g in 25 mL of *carbon dioxide-free water R*. Shake and allow the solids to settle. Use the supernatant.

Specific optical rotation (2.2.7)

-8.5 to -7.0 (dried substance).

Dissolve 1.25 g in *dimethylformamide R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use and carry out the test protected from light.*

Solvent mixture *acetonitrile R*, *water R* (50:50 *V/V*).

Buffer solution Dissolve 6.16 g of *ammonium acetate R* in about 900 mL of *water for chromatography R*, adjust to pH 6.0 with *dilute acetic acid R* and dilute to 1000 mL with *water for chromatography R*.

Test solution Dissolve 35.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 2.5 mg of *levomepromazine for system suitability CRS* (containing impurities B, D and E) in 5 mL of the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: *tetrahydrofuran R*, *acetonitrile R*, *methanol R*, buffer solution (1:10:10:79 *V/V/V/V*);

— *mobile phase B*: *tetrahydrofuran R*, buffer solution, *acetonitrile R*, *methanol R* (1:10:44.5:44.5 *V/V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	65	35
2 - 20	65 → 40	35 → 60
20 - 28	40 → 0	60 → 100

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
28 - 55	0	100

Flow rate 1.1 mL/min.

Autosampler Set at 4 °C.

Injection 10 µL.

Detection Spectrophotometer at 253 nm.

Identification of impurities Use the chromatogram supplied with *levomepromazine for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B, D and E.

Relative retention With reference to levomepromazine (retention time = about 14 min): maleic acid = about 0.1; impurity B = about 0.3; impurity D = about 2.30; impurity E = about 2.33.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 10.0, where H_p = height above the baseline of the peak due to impurity E and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity D.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity D = 0.7; impurity E = 1.4;

— for each impurity, use the concentration of levomepromazine maleate in reference solution (a).

Limits:

— *impurities B, D and E*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent; disregard the peak due to maleic acid.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

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ASSAY

Dissolve 0.350 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 44.45 mg of $C_{23}H_{28}N_2O_5S$.

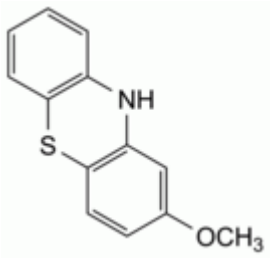
STORAGE

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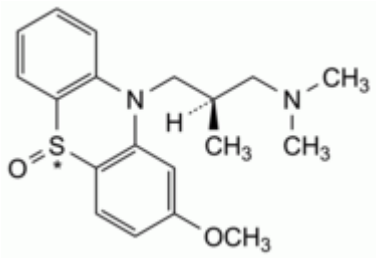
IMPURITIES

Specified impurities *B, D, E.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, C.*

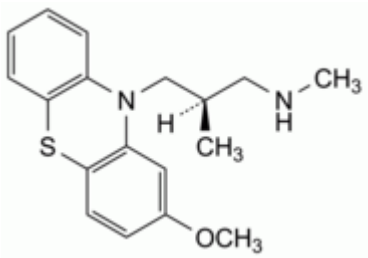


A. 2-methoxy-10*H*-phenothiazine,

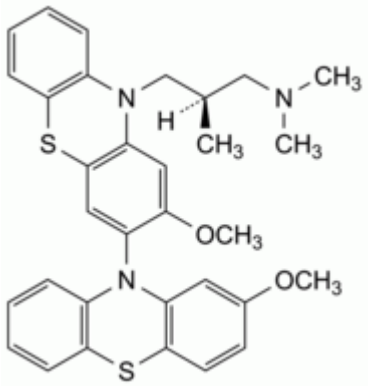


B. (5Ξ)-10-[(2*R*)-3-(dimethylamino)-2-methylpropyl]-2-methoxy-5λ^4-phenothiazin-5(10*H*)-one,

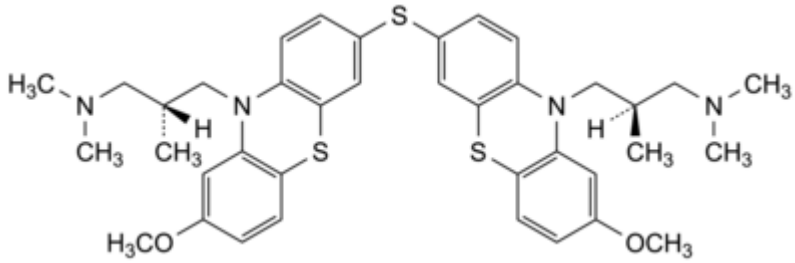
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C. (2*R*)-3-(2-methoxy-10*H*-phenothiazin-10-yl)-*N*,2-dimethylpropan-1-amine,



D. (2*R*)-3-(2,2′-dimethoxy-10*H*,10′*H*-[3,10′-biphenothiazin]-10-yl)-*N*,*N*,2-trimethylpropan-1-amine,



E. (2*R*,2′*R*)-3,3′-[sulfanediylbis[(8-methoxy-10*H*-phenothiazine-3,10-diyl)]]bis(*N*,*N*,2-trimethylpropan-1-amine).

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Levomepromazine Tablets

General Notices

Action and use

Dopamine receptor antagonist; neuroleptic.

DEFINITION

Levomepromazine Tablets contain Levomepromazine Maleate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of levomepromazine maleate, $C_{19}H_{24}N_2OS,C_4H_4O_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. To a quantity of the powdered tablets containing 50 mg of Levomepromazine Maleate add 10 mL of *water* and 2 mL of 1M *sodium hydroxide*, shake, extract with 15 mL of *ether* and allow to separate. Wash the ethereal layer with 5 mL of *water*, filter through phase-separating paper (Whatman 1 PS is suitable) containing *anhydrous sodium sulfate*, evaporate the ether to dryness and dry the residue at 100° for 3 hours. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of levomepromazine (*RS 404*).

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Mix a quantity of the powdered tablets containing 0.2 g of Levomepromazine Maleate with 10 mL of a mixture of 1 volume of *water* and 9 volumes of *acetone*, shake with the aid of ultrasound for 5 minutes, allow to stand and use the clear supernatant liquid.

(2) 0.6% w/v of *maleic acid* in *anhydrous formic acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *TLC silica gel* F_{254} (Macherey-Nagel plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry at 120° for 10 minutes and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

3 volumes of *water*, 7 volumes of *anhydrous formic acid* and 90 volumes of *di-isopropyl ether*.

CONFIRMATION

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The chromatogram obtained with solution (1) shows a spot remaining on the line of application and a spot which is similar in position to the principal spot in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 500 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 30 minutes withdraw a 10 mL sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 311 nm, Appendix II B using 0.1M *hydrochloric acid* in the reference cell.

(2) Measure the *absorbance* of a suitable solution of *levomepromazine maleate BPCRS* at the maximum at 311 nm, Appendix II B, using 0.1M *hydrochloric acid* in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of levomepromazine maleate, $C_{19}H_{24}N_2OS,C_4H_4O_4$, in the medium from the absorbances obtained and using the declared content of $C_{19}H_{24}N_2OS,C_4H_4O_4$ in *levomepromazine maleate BPCRS*. The amount of levomepromazine maleate released is not less than 60% of the stated amount.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, protected from light using the following solutions.

(1) Mix a quantity of the powdered tablets containing 0.1 g of Levomepromazine Maleate with 10 mL of a mixture of 1 volume of 18M *ammonia* and 99 volumes of *methanol*, shake with the aid of ultrasound for 5 minutes, mix, filter (Whatman No. 40 paper is suitable), discarding the first portion of filtrate, and use the filtrate.

(2) Dilute 1 volume of solution (1) to 200 volumes with the same solvent.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *TLC silica gel* GF_{254}.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

5 volumes of *diethylamine*, 10 volumes of *acetone* and 85 volumes of *toluene*.

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LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%).

ASSAY

Carry out the following procedure protected from light. Weigh and powder 20 tablets. To a quantity of the powdered tablets containing 50 mg of Levomepromazine Maleate add 15 mL of 0.2M *methanolic ammonia*, stir for 2 minutes, filter and collect the filtrate. Repeat the extraction with a further 3 successive 15-mL quantities of 0.2M *methanolic ammonia*, grinding the residue with a glass rod before extraction. Dilute the combined filtrates to 100 mL with 0.2M *methanolic ammonia*, mix and dilute 10 volumes of the solution to 100 volumes with *methanol* and further dilute 10 volumes of this solution to 100 volumes with the same solvent. Measure the *absorbance* of this solution at the maximum at 254 nm, Appendix II B, using *methanol* in the reference cell. Measure the *absorbance* of a 0.0005% w/v solution of *levomepromazine maleate BPCRS* in 0.002M *methanolic ammonia* at the same wavelength using *methanol* in the reference cell and calculate the content of $C_{19}H_{24}N_2OS,C_4H_4O_4$ in the tablets using the declared content of $C_{19}H_{24}N_2OS,C_4H_4O_4$ in *levomepromazine maleate BPCRS*.

STORAGE

Levomepromazine Tablets should be protected from light.

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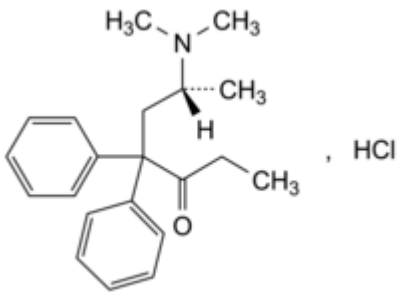
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Levomethadone Hydrochloride

General Notices

(Ph. Eur. monograph 1787)



$C_{21}H_{28}ClNO$ 345.9 *5967-73-7*

Action and use

Opioid analgesic.

Ph Eur

DEFINITION

(6*R*)-6-(Dimethylamino)-4,4-diphenylheptan-3-one hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Soluble in water, freely soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, C, D.

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Second identification: A, B, D.

A. Specific optical rotation (see Tests).

B. Melting point (2.2.14): 239 °C to 242 °C.

C. Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of methadone hydrochloride*.

D. Dilute 1 mL of solution S (see Tests) to 5 mL with *water R* and add 1 mL of *dilute ammonia R1*. Mix, allow to stand for 5 min and filter. The filtrate gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 2.50 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, *Method II*).

Acidity or alkalinity

Dilute 10 mL of solution S to 25 mL with *carbon dioxide-free water R*. To 10 mL of the solution add 0.2 mL of *methyl red solution R* and 0.2 mL of *0.01 M sodium hydroxide*. The solution is yellow. Add 0.4 mL of *0.01 M hydrochloric acid*. The solution is red.

Specific optical rotation (2.2.7)

-125 to -135 (dried substance), determined on solution S.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 50.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 12.0 mg of *imipramine hydrochloride CRS* in the mobile phase and dilute to 10 mL with the mobile phase. To 1 mL of the solution add 5 mL of the test solution and dilute to 10 mL with the mobile phase.

Column:

— *size*: *l* = 0.125 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 25 °C.

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Mobile phase Mix 35 volumes of *acetonitrile R* and 65 volumes of an 11.5 g/L solution of *phosphoric acid R* adjusted to pH 3.6 with *tetraethylammonium hydroxide solution R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Equilibration About 30 min.

Injection 10 µL.

Run time 7 times the retention time of levomethadone.

Retention time Levomethadone = about 5 min.

System suitability Reference solution (b):

— *resolution*: minimum 2.5 between the peaks due to imipramine and levomethadone.

Limits:

— *any impurity*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *total*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Dextromethadone

Liquid chromatography (*2.2.29*).

Test solution Dissolve 40.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution Dilute 1.0 mL of the test solution to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 20.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *2-hydroxypropylbetadex for chromatography R* (5 µm);

— *temperature*: 10 °C.

Mobile phase Mix 1 volume of *triethylamine R* adjusted to pH 4.0 with *phosphoric acid R*, 15 volumes of *acetonitrile R* and 85 volumes of a 13.6 g/L solution of *potassium dihydrogen phosphate R*.

Flow rate 0.7 mL/min.

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Detection Spectrophotometer at 210 nm.

Equilibration About 30 min.

Injection 10 µL.

Relative retention With reference to levomethadone: dextromethadone = about 1.4.

System suitability Test solution:

— *number of theoretical plates*: minimum 2000, calculated for the peak due to levomethadone;

— *tailing factor*: maximum 3 for the peak due to levomethadone.

Limit:

— *dextromethadone*: not more than the area of the principal peak in the chromatogram obtained with the reference solution (0.5 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in a mixture of 40 mL of *water R* and 5 mL of *acetic acid R*. Titrate with *0.1 M silver nitrate*. Determine the end-point potentiometrically (2.2.20), using a silver electrode.

1 mL of *0.1 M silver nitrate* is equivalent to 34.59 mg of $C_{21}H_{28}ClNO$.

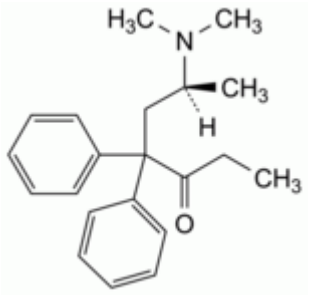
STORAGE

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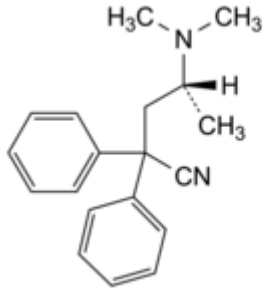
IMPURITIES

Specified impurities *A, B, C, D, E, F.*

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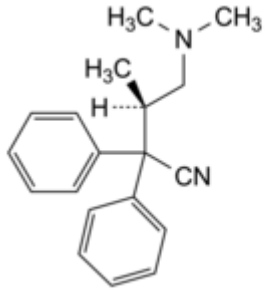


A. (6*S*)-6-(dimethylamino)-4,4-diphenylheptan-3-one,



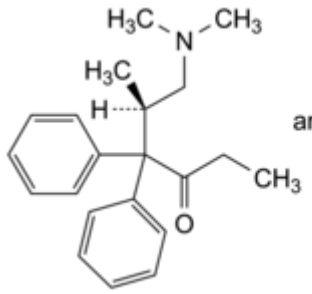
and enantiomer

B. (4*RS*)-4-(dimethylamino)-2,2-diphenylpentanenitrile,



and enantiomer

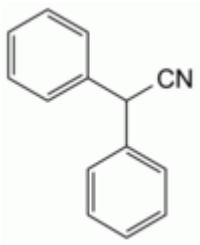
C. (3*RS*)-4-(dimethylamino)-3-methyl-2,2-diphenylbutanenitrile,



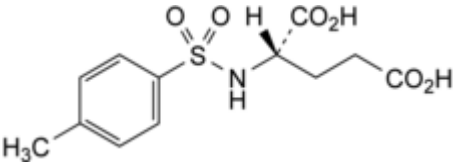
and enantiomer

D. (5*RS*)-6-(dimethylamino)-5-methyl-4,4-diphenylhexan-3-one,

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E. diphenylacetonitrile,



F. (2*S*)-2-[[(4-methylphenyl)sulfonyl]amino]pentanedioic acid (*N*-*p*-tosyl-L-glutamic acid).

Ph Eur

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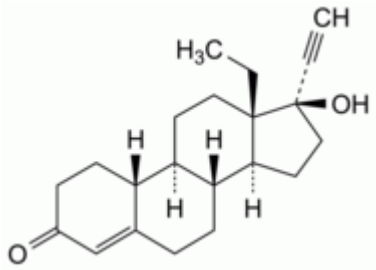
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Levonorgestrel

General Notices

(Ph. Eur. monograph 0926)



$C_{21}H_{28}O_2$ 312.5 *797-63-7*

Action and use

Progestogen.

Preparations

Levonorgestrel Tablets

Levonorgestrel and Ethinylestradiol Tablets

Ph Eur

DEFINITION

13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, sparingly soluble in methylene chloride, slightly soluble in ethanol (96 per cent).

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IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison levonorgestrel CRS.

TESTS

Specific optical rotation (2.2.7)

-35 to -30.

Dissolve 0.200 g in methylene chloride R and dilute to 20.0 mL with the same solvent.

Related substances

A. Impurities A, B, H, K, M, O, S, U. Liquid chromatography (2.2.29).

Solvent mixture water R, acetonitrile R (30:70 *V/V*).

Test solution Dissolve 10.0 mg of the substance to be examined in 7 mL of acetonitrile R using sonication and dilute to 10.0 mL with water R.

Reference solution (a) Dissolve 5 mg of levonorgestrel for system suitability 1 CRS (containing impurities A, H, K, M, O and S) in 3.5 mL of acetonitrile R using sonication and dilute to 5 mL with water R.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 5.0 mg of levonorgestrel impurity B CRS in 35 mL of acetonitrile R and dilute to 50.0 mL with water R. Dilute 1.0 mL of the solution to 100.0 mL with the solvent mixture.

Reference solution (d) Dissolve 5.0 mg of norethisterone CRS (impurity U) in 35 mL of acetonitrile R and dilute to 50.0 mL with water R. Dilute 1.0 mL of the solution to 100.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octylsilyl silica gel for chromatography with embedded polar groups R (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: acetonitrile R1, water for chromatography R (40:60 *V/V*);

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— *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 50	100 → 20	0 → 80

Flow rate 0.7 mL/min.

Detection Spectrophotometer at 215 nm and, for impurity O, at 200 nm.

Injection 50 µL.

Identification of impurities Use the chromatograms supplied with *levonorgestrel for system suitability 1 CRS* and the chromatograms obtained with reference solution (a) at 215 nm to identify the peaks due to impurities A, H, K, M and S, and at 200 nm to identify the peak due to impurity O; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity B; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity U.

Relative retention With reference to levonorgestrel (retention time = about 20 min): impurity H = about 0.5; impurity U = about 0.8; impurity K = about 0.85; impurity A = about 0.91; impurity M = about 0.95; impurity O = about 1.16; impurity B = about 1.26; impurity S = about 1.9.

System suitability:

— *signal-to-noise ratio*: minimum 60 for the principal peak in the chromatogram obtained with reference solution (b);

— *peak-to-valley ratio*: minimum 3.0, where H_p = height above the baseline of the peak due to impurity M and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity A in the chromatogram obtained with reference solution (a).

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.4; impurity M = 3.1; impurity O = 2.6;

— for impurity B, use the concentration of impurity B in reference solution (c);

— for impurity U, use the concentration of impurity U in reference solution (d);

— for impurities other than B and U, use the concentration of levonorgestrel in reference solution (b).

Limits:

— *impurities A, B, K*: for each impurity, maximum 0.3 per cent;

— *impurity O at 200 nm*: maximum 0.3 per cent;

— *impurities M, S, U*: for each impurity, maximum 0.2 per cent;

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— *impurity H*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *sum of impurities other than O*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent.

B. Impurities V and W. Liquid chromatography (2.2.29).

Solvent mixture water R, acetonitrile R (30:70 *V/V*).

Test solution Dissolve 10.0 mg of the substance to be examined in 7 mL of acetonitrile R using sonication and dilute to 10.0 mL with water R.

Reference solution (a) Dissolve 5 mg of levonorgestrel for system suitability 2 CRS (containing impurities V and W) in 3.5 mL of acetonitrile R using sonication and dilute to 5 mL with water R.

Reference solution (b) Dissolve 5.0 mg of ethinylestradiol CRS in 35 mL of acetonitrile R using sonication and dilute to 50.0 mL with water R. Dilute 3.0 mL of the solution to 100.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography compatible with 100 per cent aqueous mobile phases R (3 µm).

Mobile phase:

— *mobile phase A*: acetonitrile R1, water for chromatography R (40:60 *V/V*);

— *mobile phase B*: water for chromatography R, acetonitrile R1 (10:90 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 1	92	8
1 - 3	92 → 82	8 → 18
3 - 6	82	18
6 - 16	82 → 60	18 → 40
16 - 21	60 → 0	40 → 100
21 - 32	0	100

Flow rate 1 mL/min.

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Detection Spectrophotometer at 200 nm.

Injection 50 µL.

Identification of impurities Use the chromatogram supplied with *levonorgestrel for system suitability 2 CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities V and W.

Relative retention With reference to levonorgestrel (retention time = about 12 min): impurity W = about 0.9; impurity V = about 1.9.

System suitability Reference solution (a):

— *resolution*: minimum 2.8 between the peaks due to impurity W and levonorgestrel.

Calculation of percentage contents:

— for each impurity, use the concentration of ethinylestradiol in reference solution (b).

Limits:

— *impurity W*: maximum 0.3 per cent;

— *impurity V*: maximum 0.15 per cent.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 45 mL of *tetrahydrofuran R*. Add 10 mL of a 100 g/L solution of *silver nitrate R*. After 1 min, titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (2.2.20). Carry out a blank titration.

1 mL of *0.1 M sodium hydroxide* is equivalent to 31.25 mg of $C_{21}H_{28}O_2$.

STORAGE

Protected from light.

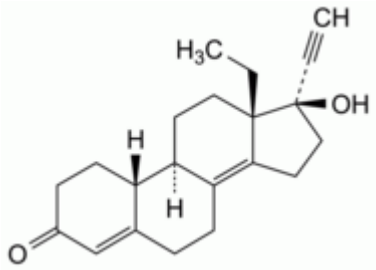
IMPURITIES

Specified impurities *A, B, H, K, M, O, S, U, V, W.*

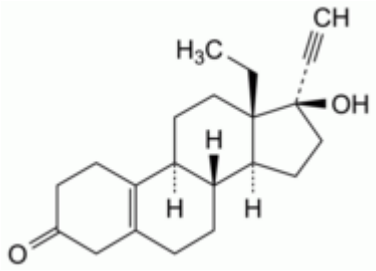
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph

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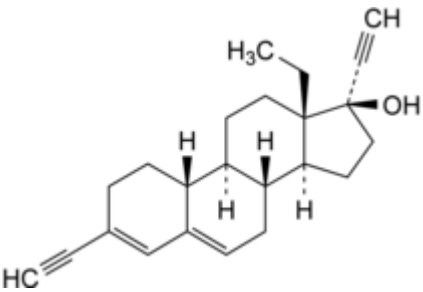
Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, D, G, I, J, L, N, P, Q, R, T.*



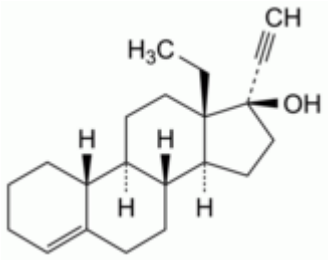
A. 13-ethyl-17-hydroxy-18,19-dinor-17α-pregna-4,8(14)-dien-20-yn-3-one,



B. 13-ethyl-17-hydroxy-18,19-dinor-17α-pregn-5(10)-en-20-yn-3-one,

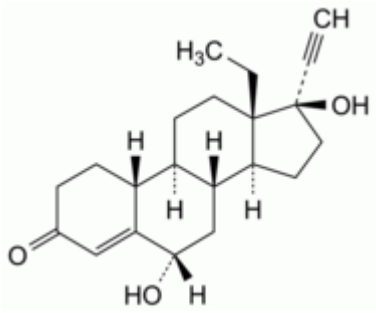


C. 13-ethyl-3-ethynyl-18,19-dinor-17α-pregna-3,5-dien-20-yn-17-ol,

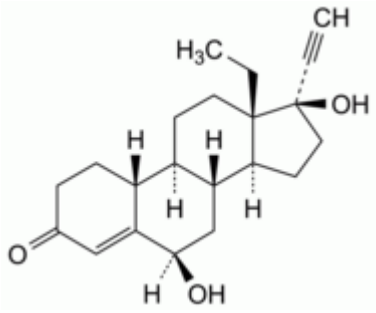


D. 13-ethyl-18,19-dinor-17α-pregn-4-en-20-yn-17-ol (3-deoxolevonorgestrel),

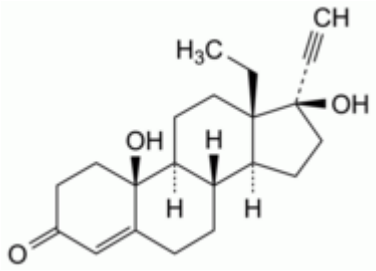
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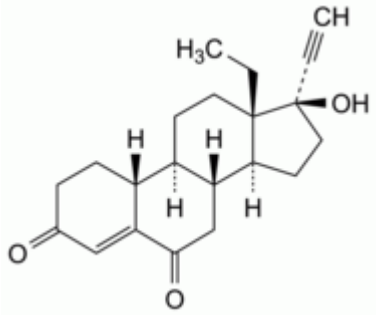
G. 13-ethyl-6α,17-dihydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one (6α-hydroxylevonorgestrel),



H. 13-ethyl-6β,17-dihydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one (6β-hydroxylevonorgestrel),

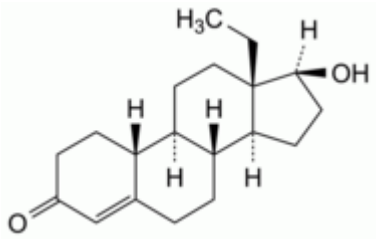


I. 13-ethyl-10,17-dihydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one (10-hydroxylevonorgestrel),

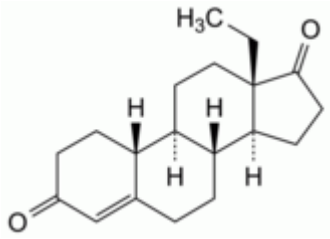


J. 13-ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yne-3,6-dione (6-oxolevonorgestrel),

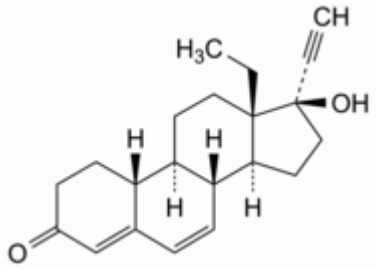
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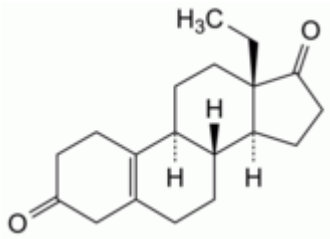
K. 13-ethyl-17β-hydroxygon-4-en-3-one (18-methylnandrolone),



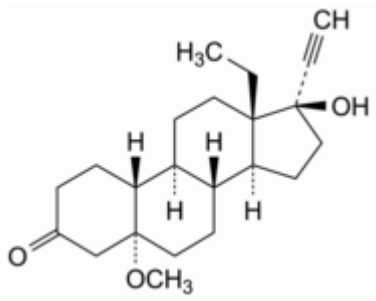
L. 13-ethylgon-4-ene-3,17-dione (levodione),



M. 13-ethyl-17-hydroxy-18,19-dinor-17α-pregna-4,6-dien-20-yn-3-one (Δ6-levonorgestrel),

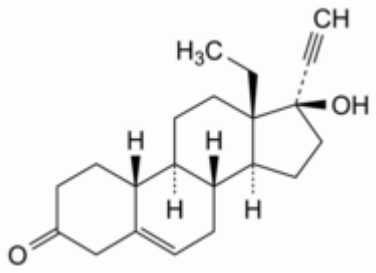


N. 13-ethylgon-5(10)-ene-3,17-dione (Δ5(10)-levodione),

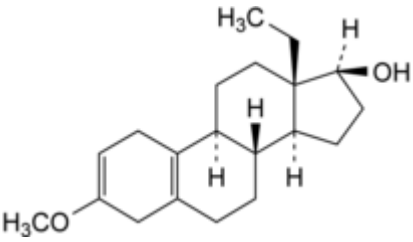


O. 13-ethyl-17-hydroxy-5α-methoxy-18,19-dinor-17α-pregn-20-yn-3-one (4,5-dihydro-5α-methoxylevonorgestrel),

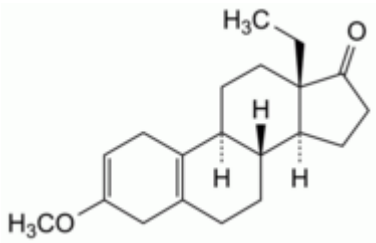
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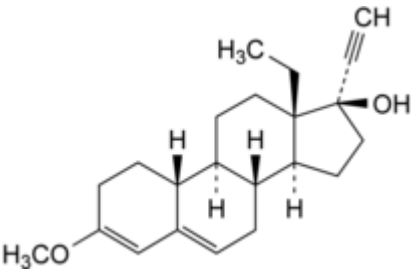
P. 13-ethyl-17-hydroxy-18,19-dinor-17α-pregn-5-en-20-yn-3-one (Δ5-levonorgestrel),



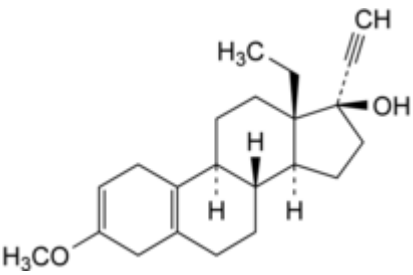
Q. 13-ethyl-3-methoxygona-2,5(10)-dien-17β-ol,



R. 13-ethyl-3-methoxygona-2,5(10)-dien-17-one,

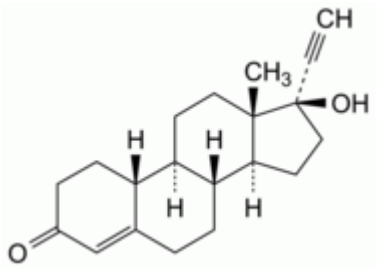


S. 13-ethyl-3-methoxy-18,19-dinor-17α-pregna-3,5-dien-20-yn-17-ol,

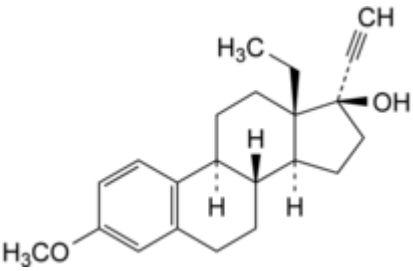


T. 13-ethyl-3-methoxy-18,19-dinor-17α-pregna-2,5(10)-dien-20-yn-17-ol,

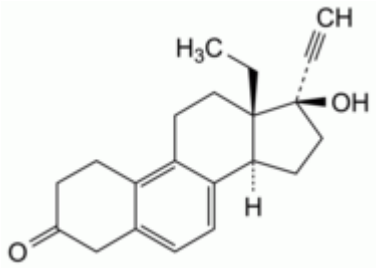
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U. 17-hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one (norethisterone),



V. 13-ethyl-3-methoxy-18,19-dinor-17α-pregna-1,3,5(10)-trien-20-yn-17-ol,



W. 13-ethyl-17-hydroxy-18,19-dinor-17α-pregna-5,7,9-trien-20-yn-3-one.

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Levonorgestrel and Ethinylestradiol Tablets

General Notices

Action and use

Progestogen.

DEFINITION

Levonorgestrel and Ethinylestradiol Tablets contain Levonorgestrel and Ethinylestradiol.

The tablets comply with the requirements stated under Tablets and with the following requirements. For Levonorgestrel and Ethinylestradiol Tablets presented in 21-day or 28-day calendar packs, apply the requirements separately to tablets of each combination of different proportions, by weight, of the active ingredients. Where applicable, disregard any tablets that contain no active ingredient (placebo tablets).

Content of levonorgestrel, $C_{21}H_{28}O_2$

90.0 to 110.0% of the stated amount.

Content of ethinylestradiol, $C_{20}H_{24}O_2$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Extract 15 powdered tablets with 30 mL of *acetone*, filter, evaporate to dryness and dissolve the residue in 1 mL of *chloroform*.

(2) 0.075% w/v of *levonorgestrel BPCRS* in *chloroform*.

(3) 0.045% w/v of *ethinylestradiol BPCRS* in *chloroform*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* GF_{254}.

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm. Develop the chromatograms twice, drying the plates between developments.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

(f) Spray the plate with a 2% w/v solution of *toluene*-p-*sulfonic acid* in *water* and heat at 105° for 10 minutes and examine under *ultraviolet light (365 nm)*.

MOBILE PHASE

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1 volume of *methanol* and 99 volumes of *chloroform*.

CONFIRMATION

By the first method of visualisation:

one of the principal spots in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2) and the other principal spot corresponds to that in the chromatogram obtained with solution (3).

By the second method of visualisation:

the spots corresponding to levonorgestrel and ethinylestradiol appear as blue spots.

Uniformity of content

Prepare the following stock solutions using a mixture of 40 volumes of *water* and 60 volumes of *acetonitrile*.

Solution A 0.0625% w/v of *levonorgestrel* BPCRS.

Solution B 0.025% of *ethinylestradiol* BPCRS.

Solution C 0.020% w/v of *2-hydroxybiphenyl* (internal standard).

Solution D Dilute 1 mL of solution C to 20 mL with the solvent mixture.

Tablets containing less than 2 mg and/or less than 2% w/w of Levonorgestrel or less than 2 mg and/or less than 2% w/w of Ethinylestradiol comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 4 mL of solution D to one tablet, heat at 60° in an ultrasonic bath for 25 minutes, shake and repeat the ultrasound treatment. Cool, centrifuge and use the clear supernatant liquid.

(2) Mix the volumes of solutions A and B specified in the table with 5 mL of solution C and dilute to 100 mL with a mixture of 40 volumes of *water* and 60 volumes of *acetonitrile*.

Content of		Volume of	
Levonorgestrel µg	Ethinyloestradiol µg	Solution A ml	Solution B ml
250	50	10.0	5.0
250	30	10.0	3.0
150	30	6.0	3.0
125	30	5.0	3.0
75	40	3.0	4.0
50	30	2.0	3.0

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

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(e) Use a detection wavelength of 215 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

49 volumes of *acetonitrile* and 51 volumes of *water*.

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{28}O_2$ and of $C_{20}H_{24}O_2$ in each tablet using the declared content of $C_{21}H_{28}O_2$ in *levonorgestrel BPCRS* and the declared content of $C_{20}H_{24}O_2$ in *ethinylestradiol BPCRS*.

ASSAY

For both levonorgestrel and ethinylestradiol use the average of the individual results determined in the test for Uniformity of content.

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Levonorgestrel Tablets

General Notices

Action and use

Progestogen.

DEFINITION

Levonorgestrel Tablets contain Levonorgestrel.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of levonorgestrel, $C_{21}H_{28}O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *methanol (80%)*.

(1) To a quantity of the powdered tablets containing 0.15 mg of Levonorgestrel add 25 mL of *methanol (80%)*, heat in a water bath at 60° for 10 minutes, allow to cool and filter through a 0.45-µm filter.

(2) 0.0006% w/v of *levonorgestrel BPCRS*.

(3) 0.0012% w/v of *norgestrel BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 242 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

50 volumes of *methanol* and 50 volumes of a 1% w/v solution of *gamma-cyclodextrin*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to dextronorgestrel and levonorgestrel and is at least 1.0.

CONFIRMATION

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The principal peak in the chromatogram obtained with solution (1) has the same retention time as the peak due to levonorgestrel in the chromatogram obtained with solution (2).

B. In the test for Uniformity of content, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

For tablets containing less than 100 µg of levonorgestrel

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 75 revolutions per minute.
(b) Use 500 mL of 0.01M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 30 minutes withdraw a sample of the medium and filter. Dilute the filtrate, with 0.01M *hydrochloric acid* if necessary, to produce a solution expected to contain 0.000006% w/v of Levonorgestrel.
(2) 0.000006% w/v of *levonorgestrel BPCRS* in dissolution medium.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 2 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.3 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 220 nm.
(f) Inject 500 µL of each solution.

MOBILE PHASE

50 volumes of *acetonitrile* and 50 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *column efficiency,* determined on the peak due to levonorgestrel is at least 5000 theoretical plates per metre.

DETERMINATION OF CONTENT

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Calculate the total content of $C_{21}H_{28}O_2$ in the medium from the chromatograms obtained and using the declared content of $C_{21}H_{28}O_2$ in *levonorgestrel BPCRS*.

LIMITS

The amount of levonorgestrel released is not less than 75% (Q) of the stated amount.

For tablets containing 100 µg or more of levonorgestrel

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 75 revolutions per minute.

(b) Use 500 mL of a 0.1% w/v solution of *sodium dodecylsulfate* in *0.1M hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 30 minutes withdraw a sample of the medium and filter. Dilute the filtrate, with a 0.1% w/v solution of *sodium dodecylsulfate* in *0.1M hydrochloric acid* if necessary, to produce a solution expected to contain 0.00015% w/v of Levonorgestrel.

(2) 0.00015% w/v of *levonorgestrel BPCRS* in dissolution medium.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution (For tablets containing less than 100 µg of levonorgestrel) may be used with an injection volume of 25 µL.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *column efficiency,* determined on the peak due to levonorgestrel is at least 5000 theoretical plates per metre.

DETERMINATION OF CONTENT

Calculate the total content of $C_{21}H_{28}O_2$ in the medium from the chromatograms obtained and using the declared content of $C_{21}H_{28}O_2$ in *levonorgestrel BPCRS*.

LIMITS

The amount of levonorgestrel released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *methanol (50%)*.

(1) Add 5 mL of *methanol (50%)* to a quantity of the powdered tablets containing 0.18 mg of Levonorgestrel, mix with the aid of ultrasound for 30 minutes, stir vigorously for 15 minutes, centrifuge and use the supernatant liquid.

(2) Dilute 1 volume of solution (1) to 100 volumes.

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(3) 0.004% w/v each of *ethinylestradiol BPCRS* and *levonorgestrel BPCRS*.

(4) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 220 nm.

(f) Inject 200 µL of each solution.

(g) Allow the chromatography to proceed for twice the retention time of levonorgestrel.

MOBILE PHASE

100 volumes of *methanol*, 240 volumes of *acetonitrile* and 500 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to ethinylestradiol and levonorgestrel is at least 12.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the sum of the areas of any such peaks is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Levonorgestrel comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To 1 tablet add 5 mL of the mobile phase, disperse with the aid of ultrasound for 45 minutes, shaking every 15 minutes, centrifuge and dilute the clear supernatant liquid with the mobile phase, if necessary, to produce a solution expected to contain 0.0006% w/v of levonorgestrel.

(2) 0.0006% w/v of *levonorgestrel BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution (For tablets containing less than 100 µg of levonorgestrel) may be used with an injection volume of 25 µL.

MOBILE PHASE

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50 volumes of *acetonitrile* and 50 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *column efficiency,* determined on the peak due to levonorgestrel is at least 5000 theoretical plates per metre.

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{28}O_2$ in each tablet using the declared content of $C_{21}H_{28}O_2$ in *levonorgestrel BPCRS*.

ASSAY

Use the average of the individual results determined in the test for Uniformity of content.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Levonorgestrel.

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Levothyroxine Oral Solution

General Notices

Action and use

Thyroid hormone replacement.

DEFINITION

Levothyroxine Oral Solution is a solution of Levothyroxine Sodium in a suitable aqueous vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of anhydrous levothyroxine sodium, $C_{15}H_{10}I_4NNaO_4$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

In the Assay, record the UV spectrum of the principal peak in the chromatograms obtained with solutions (1) and (2) with a diode array detector in the range of 210 to 400 nm.

The UV spectrum of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2);

the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in the mobile phase and protected from light.

(1) Dilute, if necessary, a weighed quantity of the oral solution with sufficient mobile phase to produce a solution containing the equivalent of 0.0005% w/v of anhydrous levothyroxine sodium.
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) 0.000015% w/v of *liothyronine sodium EPCRS*.
(4) 0.0005% w/v of *levothyroxine sodium EPCRS* and 0.0005% w/v of *liothyronine sodium EPCRS*.
(5) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *cyanosilyl silica gel for chromatography* (5 µm) (Microsorb CN is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 225 nm.

(f) Inject 100 µL of each solution.

(g) Allow the chromatography to proceed for 5 times the retention time of levothyroxine.

MOBILE PHASE

5 volumes of *orthophosphoric acid*, 300 volumes of *acetonitrile* and 700 volumes of *water*.

When the chromatograms are recorded under the prescribed conditions, the relative retention with reference to levothyroxine (retention time about 6 minutes) for liothyronine is about 2.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to levothyroxine and liothyronine is at least 4.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to liothyronine (impurity A) is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (3.0%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the sum of the areas of all *secondary peaks*, other than the peak due to liothyronine, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D using the following solutions prepared in solution A and protected from light.

Solution A Equal volumes of *methanol* and 0.1M *sodium hydroxide*.

(1) Dilute, if necessary, a weighed quantity of the oral solution with sufficient solution A to produce a solution containing the equivalent of 0.0005% w/v of anhydrous levothyroxine sodium.

(2) 0.00056% w/v of *levothyroxine sodium EPCRS*.

(3) 0.0005% w/v of *liothyronine sodium EPCRS* and 0.0005% w/v of *levothyroxine sodium EPCRS*.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *cyanosilyl silica gel for chromatography* (5 µm) (Spherisorb S5 CN is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 225 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

5 volumes of *orthophosphoric acid*, 300 volumes of *acetonitrile* and 700 volumes of *water*.

When the chromatograms are recorded under the prescribed conditions, the retention time of levothyroxine is about 4 minutes.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to liothyronine and levothyroxine is at least 4.0.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_{15}H_{10}I_4NNaO_4$, weight in volume, using the declared content of $C_{15}H_{10}I_4NNaO_4$ in *levothyroxine sodium EPCRS*.

STORAGE

Levothyroxine Oral Solution should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of anhydrous levothyroxine sodium.

IMPURITIES

The impurities limited by the requirements of this monograph include impurity A listed under Levothyroxine Sodium.

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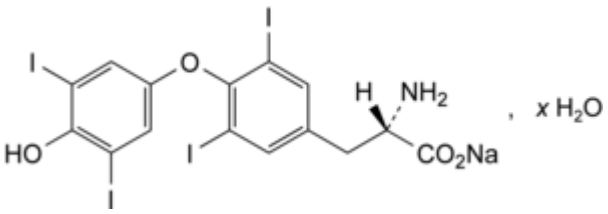
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Levothyroxine Sodium

General Notices

(Ph. Eur. Monograph 0401)



$C_{15}H_{10}I_4NNaO_4,xH_2O$ ($x \approx 5$) 799 (anhydrous substance) *25416-65-3*

Action and use

Thyroid hormone replacement.

Preparations

Levothyroxine Oral Solution

Levothyroxine Tablets

Ph Eur

DEFINITION

Sodium (2*S*)-2-amino-3-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl]propanoate.

Content

97.0 per cent to 102.0 per cent (anhydrous substance).

It contains a variable quantity of water.

CHARACTERS

Appearance

Almost white or slightly brownish-yellow, fine, slightly hygroscopic, crystalline powder.

Solubility

Very slightly soluble in water, slightly soluble in ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides.

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IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *levothyroxine sodium CRS*.

B. To 200 mg add 2 mL of *dilute sulfuric acid R*. Heat on a water-bath and then carefully over a naked flame, increasing the temperature gradually up to 600 ± 50 °C. Continue the ignition until most of the black particles have disappeared. Dissolve the residue in 2 mL of *water R*. The solution gives reaction (a) of sodium (2.3.1).

TESTS

Solution S

Dissolve 0.500 g in 23 mL of a gently boiling mixture of 1 volume of *1 M hydrochloric acid* and 4 volumes of *ethanol (96 per cent) R*. Cool and dilute to 25.0 mL with the same mixture of solvents.

Appearance of solution

Freshly prepared solution S is not more intensely coloured than reference solution BY_3 (2.2.2, *Method II*).

Specific optical rotation (2.2.7)

+ 16 to + 20 (anhydrous substance), determined on freshly prepared solution S.

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light.*

Solvent mixture Mobile phase A, *ethanol (96 per cent) R* (1:2 *V*/*V*).

Test solution Dissolve 25.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Dilute 10.0 mL of the solution to 25.0 mL with the solvent mixture.

Reference solution (a) Dissolve 2.5 mg of *levothyroxine sodium CRS* and 2.5 mg of *liothyronine sodium CRS* (impurity A) in the solvent mixture and dilute to 25.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 50.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 25.0 mg of *levothyroxine sodium CRS* in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Dilute 10.0 mL of the solution to 25.0 mL with the solvent mixture.

Reference solution (d) Dissolve 2.0 mg of *levothyroxine for peak identification CRS* (containing impurities F and G) in 10.0 mL of the solvent mixture and sonicate for 10 min.

Column:

— *size*: *l* = 0.15 m, Ø = 4.0 mm;

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— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase:

— *mobile phase A*: dissolve 1.97 g of *phosphoric acid R* in *water R* and dilute to 2 L with the same solvent;

— *mobile phase B*: dissolve 1.97 g of *phosphoric acid R* in *acetonitrile R1* and dilute to 2 L with the same solvent;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	70	30
10 - 40	70 → 20	30 → 80
40 - 50	20	80

Flow rate 1 mL/min.

Detection Spectrophotometer at 225 nm.

Injection 25 µL of the test solution and reference solutions (a), (b) and (d).

Identification of impurities Use the chromatogram supplied with *levothyroxine for peak identification CRS* and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities F and G.

Relative retention With reference to levothyroxine (retention time = about 11 min): impurity A = about 0.5; impurity F = about 2.0; impurity G = about 2.4.

System suitability Reference solution (a):

— *resolution*: minimum 5.0 between the peaks due to impurity A and levothyroxine.

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *impurity F*: not more than 5 times the area of the peak due to levothyroxine in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *impurity G*: not more than 3 times the area of the peak due to levothyroxine in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *unspecified impurities*: for each impurity, not more than twice the area of the peak due to levothyroxine in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *total*: maximum 2.0 per cent;

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— *disregard limit*: 0.5 times the area of the peak due to levothyroxine in the chromatogram obtained with reference solution (b) (0.05 per cent).

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

Water (*2.5.32*)

6.0 per cent to 12.0 per cent, determined on 0.100 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (c).

Calculate the percentage content of $C_{15}H_{10}I_4NNaO_4$ taking into account the assigned content of *levothyroxine sodium CRS*.

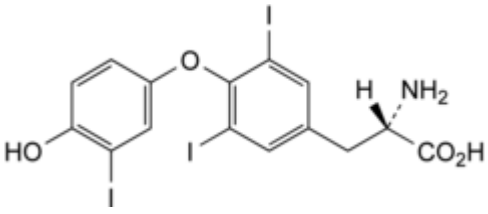
STORAGE

In an airtight container, protected from light, at a temperature of 2 °C to 8 °C.

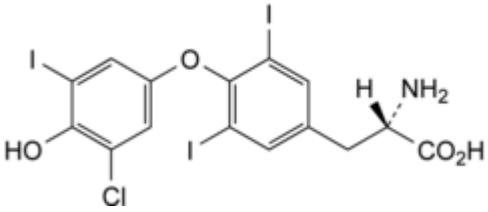
IMPURITIES

Specified impurities *A, F, G.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D, E, H, I, J, K.*

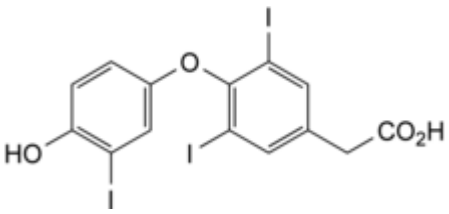


A. (2*S*)-2-amino-3-[4-(4-hydroxy-3-iodophenoxy)-3,5-diiodophenyl]propanoic acid (liothyronine),

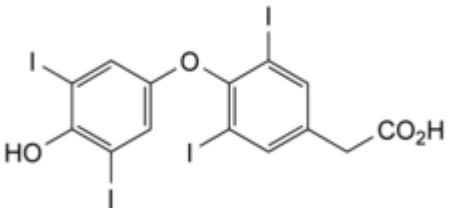


B. (2*S*)-2-amino-3-[4-(3-chloro-4-hydroxy-5-iodophenoxy)-3,5-diiodophenyl]propanoic acid,

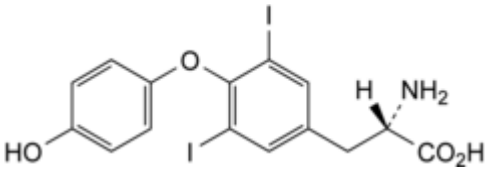
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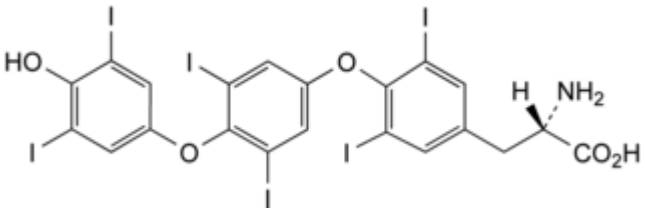
C. [4-(4-hydroxy-3-iodophenoxy)-3,5-diiodophenyl]acetic acid (triiodothyroacetic acid),



D. [4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl]acetic acid (tetraiodothyroacetic acid),

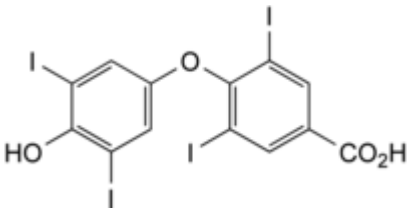


E. (2*S*)-2-amino-3-[4-(4-hydroxyphenoxy)-3,5-diiodophenyl]propanoic acid (diiodothyronine),

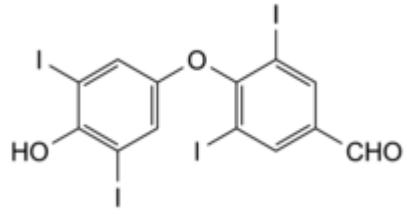


F. (2*S*)-2-amino-3-[4-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenoxy]-3,5-diiodophenyl]propanoic acid,

G. unknown structure,

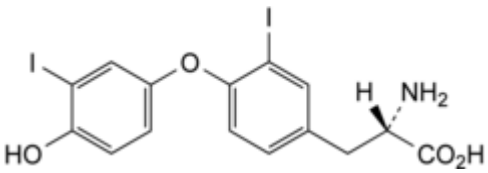


H. 4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodobenzoic acid,

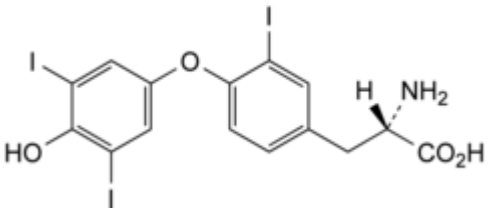


I. 4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodobenzaldehyde,

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J. (2*S*)-2-amino-3-[4-(4-hydroxy-3-iodophenoxy)-3-iodophenyl]propanoic acid,



K. (2*S*)-2-amino-3-[4-(4-hydroxy-3,5-diiodophenoxy)-3-iodophenyl]propanoic acid.

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Levothyroxine Tablets

General Notices

Action and use

Thyroid hormone replacement.

DEFINITION

Levothyroxine Tablets contain Levothyroxine Sodium.

The tablets comply with the requirements stated under Tablets and with the following requirements.

PRODUCTION

Levothyroxine Sodium used in the formulation of Levothyroxine Tablets exists primarily in its most stable form, a crystalline pentahydrate.

Care should be taken during manufacture to avoid exposure to higher temperatures (> 50°) or very low humidities.

Content of anhydrous levothyroxine sodium, $C_{15}H_{10}I_4NNaO_4$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

In the Assay, record the UV spectrum of the principal peak in the chromatograms obtained with solutions (1) and (2) with a diode array detector in the range of 210 to 400 nm.

The UV spectrum of the principal peak in the chromatogram obtained with solution (1) is concordant with that of the peak in the chromatogram obtained with solution (2);

the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

Plastic containers must not be used to prepare and store solutions.

TEST CONDITIONS

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(a) Use Apparatus 2, rotating the paddle at 100 revolutions per minute.

(b) Use 500 mL of *water*, at a temperature of 37°, as the medium.

(c) For tablets containing the equivalent of 25 µg or less of anhydrous levothyroxine sodium, place two tablets in the dissolution vessel; for tablets containing more than the equivalent of 25 µg of anhydrous levothyroxine sodium, place one tablet in the dissolution vessel.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a 5 -mL sample of the medium and centrifuge, dilute with sufficient of the dissolution medium, if necessary, to produce a solution expected to contain 0.00001% w/v of anhydrous levothyroxine sodium. To a 5 -mL aliquot add 200 µL of 0.1M *sodium hydroxide* and 125 µL of a 2% v/v solution of *diethylamine*.

(2) To 5 mL of 0.00001% w/v *levothyroxine sodium EPCRS* in 0.001M *sodium hydroxide* add 200 µL of 0.1M *sodium hydroxide* and 125 µL of a 2% v/v solution of *diethylamine* and mix.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *cyanosilyl silica gel for chromatography* (5 µm) (Spherisorb S5 CN is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 225 nm.

(f) Inject 150 µL of each solution.

MOBILE PHASE

5 volumes of *orthophosphoric acid*, 300 volumes of *acetonitrile R1* and 700 volumes of *water*.

DETERMINATION OF CONTENT

Calculate the total content of anhydrous levothyroxine sodium, $C_{15}H_{10}I_4NNaO_4$, in the medium from the chromatograms obtained and using the declared content of $C_{15}H_{10}I_4NNaO_4$ in *levothyroxine sodium EPCRS*.

LIMITS

The amount of anhydrous levothyroxine sodium released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, prepared in solution A, protected from light.

Solution A Equal volumes of *methanol* and 0.1M *sodium hydroxide*.

(1) Shake a quantity of powdered tablets containing the equivalent of 0.25 mg of anhydrous levothyroxine sodium with 2.5 mL of 0.1M *sodium hydroxide*. Dilute to 5 mL with *methanol*, shake and mix with the aid of ultrasound. Centrifuge and filter the supernatant liquid through a 0.7-µm glass microfibre filter (Whatman GMF is suitable).

(2) Dilute 1 volume of solution (1) to 50 volumes.

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(3) 0.0005% w/v of *levothyroxine sodium impurity BPCRS*.

(4) Dilute 1 volume of solution (2) to 20 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.0 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3.5 µm) (Waters Sunfire C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 0.6 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 225 nm.

(f) Inject 6 µL of each solution.

MOBILE PHASE

Mobile phase A 200 volumes of 0.098% w/v of *orthophosphoric acid* in *acetonitrile* and 800 volumes of 0.098% w/v of *orthophosphoric acid* in *water*.

Mobile phase B 180 volumes of 0.098% w/v of *orthophosphoric acid* in *water* and 820 volumes of 0.098% w/v of *orthophosphoric acid* in *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	100→89	0→11	linear gradient
2-17	89→72	11→28	linear gradient
17-45	72→0	28→100	linear gradient
45-50	0	100	isocratic
50-52	0→100	100→0	linear gradient
52-60	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to levothyroxine (retention time about 14 minutes) are: impurity A, about 0.7; impurity 1, about 0.8 and impurity D, about 2.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between impurity A and levothyroxine is at least 10.0;

the *signal-to-noise ratio* of the principal peak in the chromatogram obtained with solution (4) is at least 20.

LIMITS

Identify any peak corresponding to impurity 1 in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (3), and multiply the area of this peak by a correction factor of 1.8.

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In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity 1 is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (8%);

the area of any other *secondary peak* is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the sum of the areas of any *secondary peaks*, excluding impurity 1, is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (5%);

the sum of the areas of all *secondary peaks*, is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (10%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Levothyroxine Sodium comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in solution A, unless otherwise stated, protected from light.

Solution A Equal volumes of *methanol* and 0.1M *sodium hydroxide*.

(1) Add sufficient 0.05M *sodium hydroxide* to one tablet to produce a solution containing the equivalent of about 6 µg per mL of anhydrous levothyroxine sodium, mix with the aid of ultrasound until the tablet is fully dispersed, cool and shake for 2 minutes. Add sufficient 0.05M *sodium hydroxide* to produce a solution containing the equivalent of 0.0005% w/v of anhydrous levothyroxine sodium, filter through glass microfibre filter (Whatman GF/C is suitable) and use the filtrate.

(2) 0.00055% w/v of *levothyroxine sodium EPCRS* in 0.05M *sodium hydroxide*.

(3) 0.0005% w/v of *liothyronine sodium EPCRS* and 0.0005% w/v of *levothyroxine sodium EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *cyanosilyl silica gel for chromatography* (5 µm) (Nucleosil 5 CN is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 225 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

5 volumes of *orthophosphoric acid*, 300 volumes of *acetonitrile* and 700 volumes of *water*.

SYSTEM SUITABILITY

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The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to liothyronine and levothyroxine is at least 4.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{15}H_{10}I_4NNaO_4$ in each tablet using the declared content of $C_{15}H_{10}I_4NNaO_4$ in *levothyroxine sodium EPCRS*.

ASSAY

Use the average of the individual results determined in the test for Uniformity of content.

STORAGE

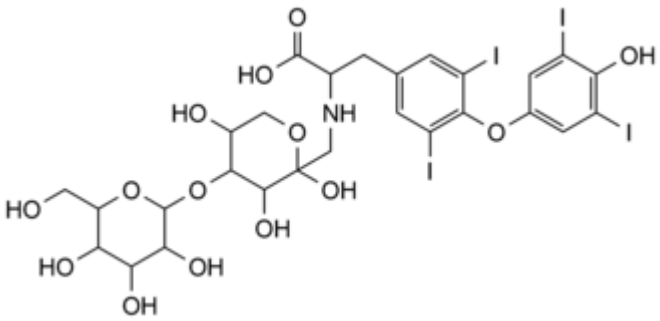
Levothyroxine Tablets should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of anhydrous levothyroxine sodium.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, D, F and G listed under Levothyroxine Sodium and:



1. 3-(4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl)-2-(((4,5,6-trihydroxy-3-((3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)tetrahydro-2*H*-pyran-2-yl)methyl)amino)propanoic acid (levothyroxine-lactose maillard impurity).

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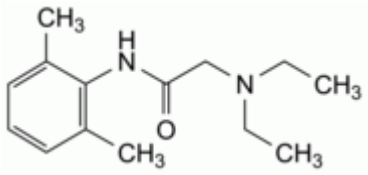
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Lidocaine

General Notices

(Ph. Eur. Monograph 0727)



$C_{14}H_{22}N_2O$ 234.3 *137-58-6*

Action and use

Local anaesthetic; Class I antiarrhythmic.

Preparation

Lidocaine Ointment

Ph Eur

DEFINITION

2-(Diethylamino)-*N*-(2,6-dimethylphenyl)acetamide.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, very soluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

First identification: A.

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Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *lidocaine CRS*.

B. Melting point (2.2.14): 66 °C to 70 °C, determined without previous drying.

C. To about 5 mg add 0.5 mL of *fuming nitric acid R*. Evaporate to dryness on a water-bath, cool, and dissolve the residue in 5 mL of *acetone R*. Add 0.2 mL of *alcoholic potassium hydroxide solution R*. A green colour develops.

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 50.0 mg of *2,6-dimethylaniline R* (impurity A) in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 10.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve 5.0 mg of *2-chloro-N-(2,6-dimethylphenyl)acetamide R* (impurity H) in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (c) Dilute 1.0 mL of the test solution to 10.0 mL with the mobile phase.

Reference solution (d) Mix 1.0 mL of reference solution (a), 1.0 mL of reference solution (b) and 1.0 mL of reference solution (c), then dilute to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

— *stationary phase*: *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer R* (5 µm);

— *temperature*: 30 °C.

Mobile phase Mix 30 volumes of *acetonitrile for chromatography R* and 70 volumes of a 4.85 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 8.0 with *strong sodium hydroxide solution R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 20 µL.

Run time 3.5 times the retention time of lidocaine.

Relative retention With reference to lidocaine (retention time = about 17 min): impurity H = about 0.37; impurity A = about 0.40.

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System suitability Reference solution (d):

— *resolution*: minimum 1.5 between the peaks due to impurities H and A.

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.01 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the peak due to lidocaine in the chromatogram obtained with reference solution (d) (0.10 per cent);

— *total*: not more than 5 times the area of the peak due to lidocaine in the chromatogram obtained with reference solution (d) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the peak due to lidocaine in the chromatogram obtained with reference solution (d) (0.05 per cent).

Chlorides (2.4.4)

Maximum 35 ppm.

Dissolve 1.4 g in a mixture of 3 mL of *dilute nitric acid R* and 12 mL of *water R*.

Sulfates (2.4.13)

Maximum 0.1 per cent.

Dissolve 0.2 g in 5 mL of *ethanol (96 per cent) R* and dilute to 20 mL with *distilled water R*.

Water (2.5.12)

Maximum 1.0 per cent, determined on 1.00 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

To 0.200 g add 50 mL of *anhydrous acetic acid R* and stir until dissolution is complete. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

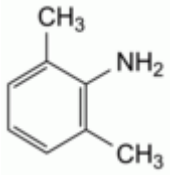
1 mL of *0.1 M perchloric acid* is equivalent to 23.43 mg of $C_{14}H_{22}N_2O$.

IMPURITIES

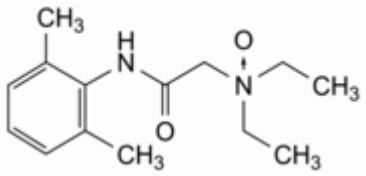
Specified impurities *A.*

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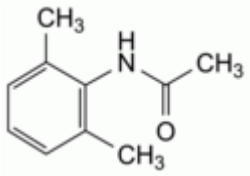
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D, E, F, G, H, I, J.*



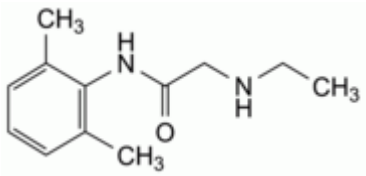
A. 2,6-dimethylaniline,



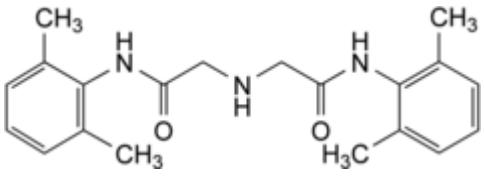
B. 2-(diethylazinoyl)-*N*-(2,6-dimethylphenyl)acetamide (lidocaine *N*-oxide),



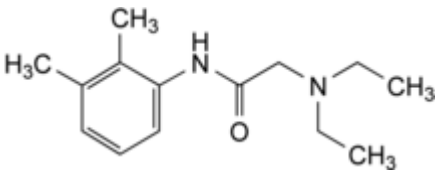
C. *N*-(2,6-dimethylphenyl)acetamide,



D. *N*-(2,6-dimethylphenyl)-2-(ethylamino)acetamide,

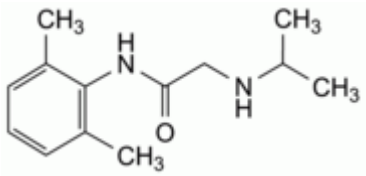


E. 2,2′-iminobis(*N*-(2,6-dimethylphenyl)acetamide),

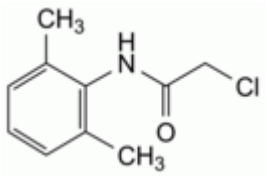


F. 2-(diethylamino)-*N*-(2,3-dimethylphenyl)acetamide,

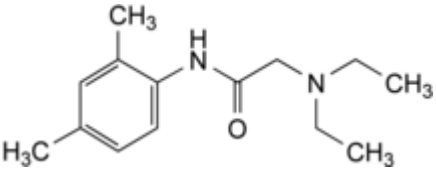
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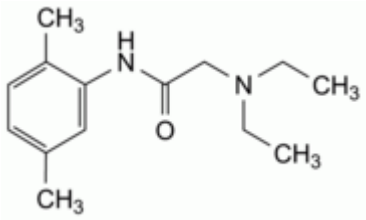
G. *N*-(2,6-dimethylphenyl)-2-((1-methylethyl)amino) acetamide,



H. 2-chloro-*N*-(2,6-dimethylphenyl)acetamide,



I. 2-(diethylamino)-*N*-(2,4-dimethylphenyl)acetamide,



J. 2-(diethylamino)-*N*-(2,5-dimethylphenyl)acetamide.

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Lidocaine and Adrenaline Injection / Lidocaine and Epinephrine Injection

General Notices

Action and use

Local anaesthetic + class I antiarrhythmic; adrenoceptor agonist.

DEFINITION

Lidocaine and Adrenaline Injection is a sterile solution of Lidocaine Hydrochloride Monohydrate and Adrenaline Acid Tartrate in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of lidocaine hydrochloride monohydrate, $C_{14}H_{22}N_2O,HCl,H_2O$

95.0 to 105.0% of the stated amount.

Content of adrenaline, $C_9H_{13}NO_3$

87.5 to 112.5% of the stated amount.

CHARACTERISTICS

A colourless solution.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *water*.

(1) Dilute a quantity of the injection, if necessary, to produce a solution containing 0.2% w/v of Lidocaine Hydrochloride Monohydrate.

(2) 0.2% w/v of *lidocaine hydrochloride BPCRS*.

(3) 0.2% w/v of each of *lidocaine hydrochloride BPCRS* and *bupivacaine hydrochloride BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a silica gel precoated plate (Merck silica gel 60G plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it in a current of cold air, heat at 110° for 1 hour, place the hot plate in a tank of chlorine gas prepared by the addition of *hydrochloric acid* to a 5% w/v solution of *potassium permanganate* contained in a beaker placed in the tank and allow to

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stand for 2 minutes. Dry the plate in a current of cold air until an area of the plate below the line of application gives at most a very faint blue colour with a 0.5% w/v solution of *potassium iodide* in *starch mucilage*; avoid prolonged exposure to cold air. Spray the plate with a 0.5% w/v solution of *potassium iodide* in *starch mucilage*.

MOBILE PHASE

5 volumes of *methanol* and 95 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated principal spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the Assay for adrenaline, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

Acidity

pH, 3.0 to 4.5, Appendix V L.

ASSAY

For lidocaine hydrochloride monohydrate

Make a quantity containing 0.1 g of Lidocaine Hydrochloride Monohydrate alkaline with 2M *sodium hydroxide* and extract with three 20-mL quantities of *chloroform*, washing each extract with the same 10 mL of *water*. Filter the washed extracts through a filter paper moistened with *chloroform* and wash the filter with 10 mL of *chloroform*. Add the washings to the filtrate and carry out Method I for *non-aqueous titration*, Appendix VIII A, using *0.02M perchloric acid VS* as titrant and *crystal violet solution* as indicator. Each mL of *0.02M perchloric acid VS* is equivalent to 5.776 mg of $C_{14}H_{22}N_2O,HCl,H_2O$.

For adrenaline

Prepare a solution by adding 8.0 g of *tetramethylammonium hydrogen sulfate*, 2.2 g of *sodium heptanesulfonate* and 2 mL of 0.1M *disodium edetate* to a mixture of 900 mL of *water* and 100 mL of *methanol*, adjust the pH to 3.5 using 1M *sodium hydroxide* and filter through glass microfibre paper under reduced pressure (solution A).

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute the injection with solution A, if necessary, to contain 0.0005% w/v of adrenaline and dilute 5 mL of the resulting solution to 10 mL with solution A.
(2) Dilute 5 mL of a 0.001% w/v solution of *adrenaline acid tartrate BPCRS* to 10 mL with solution A.
(3) Mix 5 mL of solution (2) with 5 mL of a 0.001% w/v solution of *noradrenaline acid tartrate* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 205 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

A solution prepared by adding 4.0 g of *tetramethylammonium hydrogen sulfate*, 1.1 g of *sodium heptanesulfonate* and 2 mL of 0.1M *disodium edetate* to a mixture of 950 mL of *water* and 50 mL of *methanol* and adjusting the pH to 3.5 with 1M *sodium hydroxide*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_9H_{13}NO_3$ in the injection using the declared content of $C_9H_{13}NO_3$ in *adrenaline acid tartrate BPCRS*.

STORAGE

Lidocaine and Adrenaline Injection should be protected from light.

LABELLING

The quantity of Adrenaline Acid Tartrate is stated in terms of the equivalent amount of adrenaline (epinephrine).

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Lidocaine and Chlorhexidine Gel

General Notices

Action and use

Local anaesthetic; class I antiarrhythmic and antiseptic.

DEFINITION

Lidocaine and Chlorhexidine Gel is a sterile solution of Lidocaine Hydrochloride Monohydrate containing 0.25% v/v of Chlorhexidine Gluconate Solution in a suitable water-miscible basis.

The gel complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of anhydrous lidocaine hydrochloride, $C_{14}H_{22}N_2O,HCl$

95.0 to 105.0% of the stated amount.

Content of chlorhexidine gluconate solution

0.225 to 0.275% v/v.

IDENTIFICATION

To a quantity of the gel containing the equivalent of 80 mg of anhydrous lidocaine hydrochloride add 4 mL of *hydrochloric acid* and heat on a water bath for 10 minutes. Allow to cool, transfer to a separating funnel with the aid of 20 mL of *water*, add 5M *sodium hydroxide* until precipitation is complete and extract with two 20-mL quantities of *chloroform*. Filter the chloroform extracts through *anhydrous sodium sulfate* and evaporate the filtrate to dryness on a water bath using a current of nitrogen. The residue complies with tests A, B and C.

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of lidocaine *(RS 202)*.

B. Dissolve 20 mg in 1 mL of *ethanol (96%)*, add 0.5 mL of a 10% w/v solution of *cobalt(II) chloride* and 0.5 mL of 5M *sodium hydroxide* and shake for 2 minutes. A bluish-green precipitate is produced.

C. Dissolve 40 mg in 5 mL of a 1% w/v solution of *cetrimide* and add 1 mL of 5M *sodium hydroxide* and 1 mL of *bromine water*. An orange colour is produced.

D. In the Assay for chlorhexidine gluconate solution, the chromatogram obtained with solution (2) shows a peak with the same retention time as the peak due to chlorhexidine acetate in the chromatogram obtained with solution (1).

TESTS

Aromatic amines

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Not more than 8 ppm of 2,6-dimethylaniline and not more than 1.5 ppm of 4-chloroaniline when determined in the following manner. Carry out the method for *gas chromatography*, Appendix III B, using the following solutions.

(1) Shake 0.2 g of the gel with 20 mL of a mixture of 20 volumes of *ether* and 80 volumes of *hexane* and 5 mL of a buffer solution prepared by adjusting the pH of 0.1M *sodium citrate* to 5.0 with 0.2M *sodium hydroxide*, allow to separate and discard the aqueous layer. Shake the organic layer with *anhydrous sodium sulfate* and filter through silica-treated filter paper (Whatman 1PS is suitable), add 100 µL of *heptafluorobutyric anhydride* and shake for 30 seconds. Allow the solution to stand for 2 minutes, add 5 mL of 0.6M *sodium hydrogen carbonate solution*, shake, allow to separate and use the upper layer

(2) Dissolve 80 mg of *2,6-dimethylaniline* in 1 mL of 1M *hydrochloric acid* with the aid of ultrasound, add sufficient *water* to produce 100 mL, dilute 1 volume of this solution to 50 volumes with 0.01M *hydrochloric acid* and further dilute 1 volume to 20 volumes with the same solvent. Shake 2 mL of this solution with 20 mL of a mixture of 20 volumes of *ether* and 80 volumes of *hexane* and 5 mL of 0.6M *sodium hydrogen carbonate solution* and continue in the same manner as for solution (1) beginning at the words 'allow to separate …'.

(3) Dissolve 30 mg of *4-chloroaniline* in 1 mL of 1M *hydrochloric acid* with the aid of ultrasound, add sufficient *water* to produce 200 mL and dilute 1 volume to 50 volumes with the same solvent; further dilute 1 volume to 20 volumes with the same solvent. Shake 2 mL of this solution with 20 mL of a mixture of 20 volumes of *ether* and 80 volumes of *hexane* and 5 mL of 0.6M *sodium hydrogen carbonate solution* and continue in the same manner as for solution (1) beginning at the words 'allow to separate …'.

CHROMATOGRAPHIC CONDITIONS

(a) Use a glass column (1.5 m × 4 mm) packed with *acid-washed, silanised diatomaceous support* (100 to 120 mesh) coated with 15% w/w of cyanopropylmethylphenyl methyl silicone fluid (OV-225 is suitable).

(b) Use *nitrogen* as the carrier gas at a flow rate of 50 mL per minute.

(c) Use isothermal conditions maintained at 190°.

(d) Use an inlet temperature of 200°.

(e) Use an electron capture detector at a temperature of 270°.

(f) Inject 1 µL of each solution.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to 2,6-dimethylaniline is not greater than the area of the principal peak in the chromatogram obtained with solution (2);

the area of any peak corresponding to 4-chloroaniline is not greater than the area of the principal peak in the chromatogram obtained with solution (3).

Sterility

Complies with the *test for sterility*, Appendix XVI A.

ASSAY

For anhydrous lidocaine hydrochloride

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Disperse a quantity containing the equivalent of 10 mg of anhydrous lidocaine hydrochloride in 20 mL of *water*. Add 5 mL of *acetate buffer pH 2.8*, 120 mL of *chloroform* and 5 mL of *dimethyl yellow and oracet blue 2R solution* and titrate with 0.005M *dioctyl sodium sulfosuccinate VS*, swirling vigorously. Near the end point add the titrant dropwise and, after each addition, swirl vigorously, allow to separate and swirl gently for 5 seconds. The end point is indicated when the colour of the chloroform layer changes from green to pinkish-grey. Repeat the operation without the preparation being examined. The difference between the titrations represents the amount of dioctyl sodium sulfosuccinate required. Each mL of 0.005M *dioctyl sodium sulfosuccinate VS* is equivalent to 1.354 mg of $C_{14}H_{22}N_2O$,HCl. Determine the *weight per mL* of the gel, Appendix V G, and calculate the percentage of $C_{14}H_{22}N_2O$,HCl, weight in volume.

For chlorhexidine gluconate solution

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 5 mL of a 0.080% w/v solution of *diphenylamine* (internal standard) in the mobile phase to 5 mL of a 0.070% w/v solution of *chlorhexidine acetate BPCRS* in the mobile phase and dilute to 100 mL with the mobile phase.

(2) Mix 10 g of the gel with sufficient of the mobile phase to produce 100 mL.

(3) Prepare solution (3) in the same manner as solution (2) but adding 5 mL of the internal standard solution before diluting to 100 mL.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.01M *sodium octanesulfonate* in *methanol (73%)* adjusted to pH 3.0 with *glacial acetic acid*

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{30}Cl_2N_{10},2C_6H_{12}O_7$ from the declared content of $C_{22}H_{30}Cl_2N_{10}$ in *chlorhexidine acetate BPCRS*. Each mg of $C_{22}H_{30}Cl_2N_{10}$ is equivalent to 1.776 mg of $C_{22}H_{30}Cl_2N_{10},2C_6H_{12}O_7$. Determine the *weight per mL* of the gel, Appendix V G, and express the result as the percentage volume in volume of Chlorhexidine Gluconate Solution, which contains 20% w/v of $C_{22}H_{30}Cl_2N_{10},2C_6H_{12}O_7$.

LABELLING

The quantity of Lidocaine Hydrochloride is stated in terms of the equivalent amount of anhydrous lidocaine hydrochloride.

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Lidocaine Gel

General Notices

Action and use

Local anaesthetic; Class I antiarrhythmic.

DEFINITION

Lidocaine Gel is a sterile solution of Lidocaine Hydrochloride Monohydrate in a suitable water-miscible basis.

The gel complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of anhydrous lidocaine hydrochloride, $C_{14}H_{22}N_2O,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

To a quantity of the gel containing the equivalent of 80 mg of anhydrous lidocaine hydrochloride add 4 mL of *hydrochloric acid* and heat on a water bath for 10 minutes. Allow to cool, transfer to a separating funnel with the aid of 20 mL of *water*, add 5M *sodium hydroxide* until precipitation is complete and extract with two 20-mL quantities of *chloroform*. Filter the chloroform extracts through *anhydrous sodium sulfate* and evaporate the filtrate to dryness on a water bath using a current of nitrogen. The residue complies with the following tests.

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of lidocaine *(RS 202)*.

B. Dissolve 20 mg in 1 mL of *ethanol (96%)*, add 0.5 mL of a 10% w/v solution of *cobalt(II) chloride* and 0.5 mL of 5M *sodium hydroxide* and shake for 2 minutes. A bluish-green precipitate is produced.

C. Dissolve 40 mg in 5 mL of a 1% w/v solution of *cetrimide* and add 1 mL of 5M *sodium hydroxide* and 1 mL of *bromine water*. A yellow colour is produced.

TESTS

2,6-Dimethylaniline

Mix a quantity of the gel containing the equivalent of 15 mg of anhydrous lidocaine hydrochloride with sufficient *water* to produce 3 mL using a rotary vortex mixer. To 2 mL of the resulting solution add 1 mL of a freshly prepared 1% w/v solution of *4-dimethyl-aminobenzaldehyde* in *methanol*, mix thoroughly using a rotary vortex mixer, add 2 mL of *glacial acetic acid* and allow to stand for 10 minutes. The yellow colour produced is not more intense than that obtained using a mixture of 2 mL of a solution of *2,6-dimethylaniline* in *methanol* containing 2 µg per mL in place of the solution of the gel.

Sterility

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Complies with the *test for sterility*, Appendix XVI A.

ASSAY

Disperse a quantity containing the equivalent of 10 mg of anhydrous lidocaine hydrochloride in 20 mL of *water*. Add 5 mL of *acetate buffer pH 2.8*, 120 mL of *chloroform* and 5 mL of *dimethyl yellow and oracet blue 2R solution* and titrate with 0.005M *dioctyl sodium sulfosuccinate VS*, swirling vigorously. Near the end point add the titrant dropwise and, after each addition, swirl vigorously, allow to separate and swirl gently for 5 seconds. The end point is indicated when the colour of the chloroform layer changes from green to pinkish-grey. Repeat the operation without the preparation being examined. The difference between the titrations represents the amount of dioctyl sodium sulfosuccinate required. Each mL of 0.005M *dioctyl sodium sulfosuccinate VS* is equivalent to 1.354 mg of $C_{14}H_{22}N_2O$,HCl. Determine the *weight per mL* of the gel, Appendix V G, and calculate the percentage of $C_{14}H_{22}N_2O$,HCl, weight in volume.

STORAGE

Lidocaine Gel should be stored in accordance with the manufacturer's instructions.

LABELLING

The quantity of active ingredent is stated in terms of the equivalent amount of anhydrous lidocaine hydrochloride.

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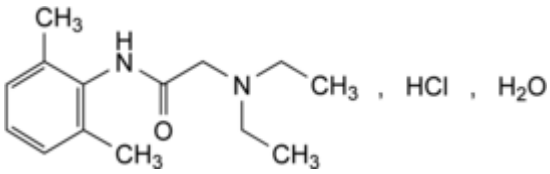
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Lidocaine Hydrochloride Monohydrate

General Notices

Lidocaine Hydrochloride

(Ph. Eur. monograph 0227)



$C_{14}H_{23}ClN_2O,H_2O$ 288.8 *6108-05-0*

Action and use

Local anaesthetic; Class I antiarrhythmic.

Preparations

Lidocaine Gel

Lidocaine and Chlorhexidine Gel

Lidocaine Injection

Lidocaine and Adrenaline Injection/Lidocaine and Epinephrine Injection

Lidocaine Intraocular Injection

Lidocaine Sterile Solution

Ph Eur

DEFINITION

2-(Diethylamino)-*N*-(2,6-dimethylphenyl)acetamide hydrochloride monohydrate.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very soluble in water, freely soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

A. Melting point (*2.2.14*): 74 °C to 79 °C, determined without previous drying.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *lidocaine hydrochloride CRS*.

C. To about 5 mg add 0.5 mL of *fuming nitric acid R*. Evaporate to dryness on a water-bath, cool and dissolve the residue in 5 mL of *acetone R*. Add 0.2 mL of *alcoholic potassium hydroxide solution R*. A green colour is produced.

D. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

4.0 to 5.5.

Dilute 1 mL of solution S to 10 mL with *carbon dioxide-free water R*.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 50.0 mg of *2,6-dimethylaniline R* (impurity A) in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 10.0 mL of the solution to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of *2-chloro-N-(2,6-dimethylphenyl)acetamide R* (impurity H) in the mobile phase and dilute to 10.0 mL with the mobile phase.

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Reference solution (c) Dilute 1.0 mL of the test solution to 10.0 mL with the mobile phase.

Reference solution (d) Mix 1.0 mL of reference solution (a), 1.0 mL of reference solution (b) and 1.0 mL of reference solution (c), and dilute to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

— *stationary phase*: *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer R* (5 µm);

— *temperature*: 30 °C.

Mobile phase Mix 30 volumes of *acetonitrile for chromatography R* and 70 volumes of a 4.85 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 8.0 with *strong sodium hydroxide solution R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 20 µL of the test solution and reference solutions (a), (b) and (d).

Run time 3.5 times the retention time of lidocaine.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity A; use the chromatogram obtained with reference solution (b) to identify the peak due to impurity H.

Relative retention With reference to lidocaine (retention time = about 17 min): impurity H = about 0.37; impurity A = about 0.40.

System suitability Reference solution (d):

— *resolution*: minimum 1.5 between the peaks due to impurities H and A.

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.01 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the peak due to lidocaine in the chromatogram obtained with reference solution (d) (0.10 per cent);

— *total*: not more than 5 times the area of the peak due to lidocaine in the chromatogram obtained with reference solution (d) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the peak due to lidocaine in the chromatogram obtained with reference solution (d) (0.05 per cent); do not disregard the peak due to impurity A .

Water (*2.5.12*)

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5.5 per cent to 7.0 per cent, determined on 0.25 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.220 g in 50 mL of *ethanol (96 per cent) R* and add 5.0 mL of *0.01 M hydrochloric acid*. Carry out a potentiometric titration (2.2.20), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 27.08 mg of $C_{14}H_{23}ClN_2O$.

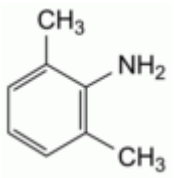
STORAGE

Protected from light.

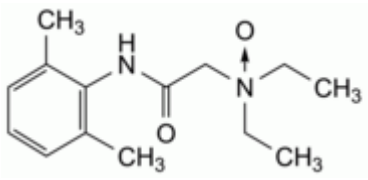
IMPURITIES

Specified impurities A.

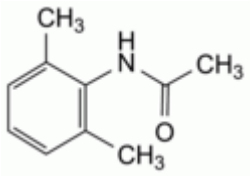
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, C, D, E, F, G, H, I, J, K.



A. 2,6-dimethylaniline,

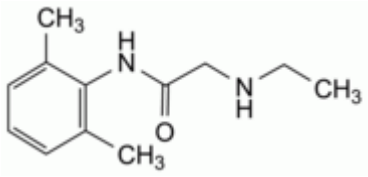


B. 2-(diethylazinoyl)-*N*-(2,6-dimethylphenyl)acetamide (lidocaine N^2-oxide),

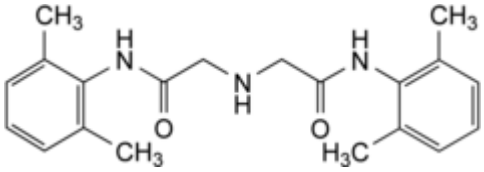


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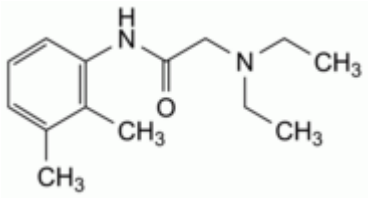
C. *N*-(2,6-dimethylphenyl)acetamide,



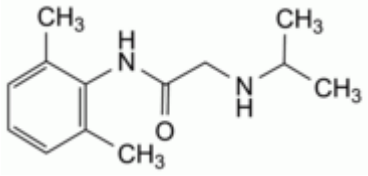
D. *N*-(2,6-dimethylphenyl)-2-(ethylamino)acetamide,



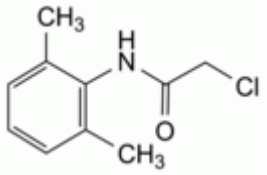
E. 2-2′-(azanediyl)bis[*N*-(2,6-dimethylphenyl)acetamide],



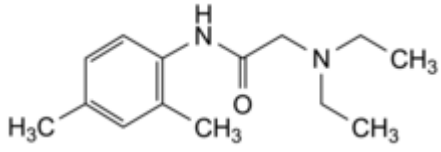
F. 2-(diethylamino)-*N*-(2,3-dimethylphenyl)acetamide,



G. *N*-(2,6-dimethylphenyl)-2-[(1-methylethyl)amino]acetamide,

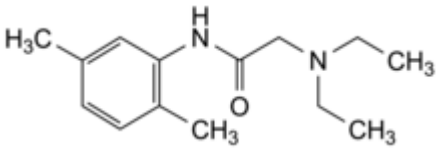


H. 2-chloro-*N*-(2,6-dimethylphenyl)acetamide,

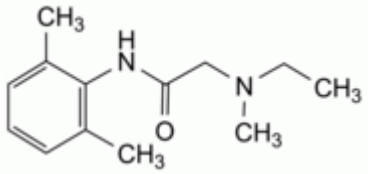


I. 2-(diethylamino)-*N*-(2,4-dimethylphenyl)acetamide,

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J. 2-(diethylamino)-*N*-(2,5-dimethylphenyl)acetamide,



K. *N*-(2,6-dimethylphenyl)-2-(ethylmethylamino)acetamide.

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Lidocaine Injection

General Notices

Action and use

Local anaesthetic; Class I antiarrhythmic.

DEFINITION

Lidocaine Injection is a sterile solution of Lidocaine Hydrochloride Monohydrate in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of lidocaine hydrochloride monohydrate, $C_{14}H_{22}N_2O,HCl,H_2O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Make a volume containing 0.1 g of Lidocaine Hydrochloride Monohydrate alkaline with 5M *sodium hydroxide*, filter, wash the residue with *water*, dissolve it in 1 mL of *ethanol (96%)*, add 0.5 mL of a 10% w/v solution of *cobalt(II) chloride* and shake for 2 minutes. A bluish-green precipitate is produced.

B. To a volume containing 0.1 g of Lidocaine Hydrochloride add 10 mL of *picric acid solution R1*. The *melting point* of the precipitate, after washing with *water* and drying at 105°, is about 229°, Appendix V A.

C. Yields the reactions characteristic of *chlorides*, Appendix VI.

2,6-Dimethylaniline

To a volume of the injection containing 25 mg of Lidocaine Hydrochloride Monohydrate add *water* if necessary to produce 10 mL, add 2M *sodium hydroxide* until the solution is just alkaline and extract with three 5 mL quantities of *chloroform*. Dry the combined chloroform extracts over *anhydrous sodium sulfate*, filter, wash with a further 5 mL of *chloroform* and evaporate the filtrate to dryness at a pressure of 2 kPa. Dissolve the residue in 2 mL of *methanol*, add 1 mL of a 1% w/v solution of *4-dimethylaminobenzaldehyde* in *methanol* and 2 mL of *glacial acetic acid* and allow to stand at room temperature for 10 minutes. Any yellow colour produced is not more intense than the colour obtained by repeating the operation using 10 mL of a solution of *2,6-dimethylaniline* in *water* containing 1 µg per mL in place of the injection (400 ppm).

ASSAY

Make a quantity containing 0.1 g of Lidocaine Hydrochloride Monohydrate alkaline with 2M *sodium hydroxide* and extract with three 20 mL quantities of *chloroform*, washing each extract with the same 10 mL of *water*. Filter the washed extracts through a filter paper moistened with *chloroform* and wash the filter with 10 mL of *chloroform*. Add the washings to the filtrate and carry out Method I for *non-aqueous*

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titration, Appendix VIII A, using *0.02M perchloric acid VS* as titrant and *crystal violet solution* as indicator. Each mL of *0.02M perchloric acid VS* is equivalent to 5.776 mg of $C_{14}H_{22}N_2O,HCl,H_2O$.

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Lidocaine Intraocular Injection

General Notices

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Intraocular anaesthetic.

DEFINITION

Lidocaine Intraocular Injection is a sterile, isotonic solution of Lidocaine Hydrochloride Monohydrate in a suitable diluent. It is supplied as a ready-to-use solution.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements. Where appropriate, the injection also complies with the requirements stated under Unlicensed Medicines.

Content of lidocaine hydrochloride monohydrate, $C_{14}H_{22}N_2O,HCl,H_2O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Make a volume of the injection containing 10 mg of Lidocaine Hydrochloride Monohydrate alkaline with 5M *sodium hydroxide*; filter, wash the residue with *water*, dissolve it in 1 mL of *ethanol (96%)*, add 0.5 mL of a 10% w/v solution of *cobalt(II) chloride* and shake for 2 minutes. A bluish-green precipitate is produced.

B. To a volume of the injection containing 10 mg of Lidocaine Hydrochloride Monohydrate add 10 mL of *picric acid solution R1*. The *melting point* of the precipitate, after washing with *water* and drying at 105°, is about 229°, Appendix V A.

TESTS

Acidity or alkalinity

pH, 6.0 to 7.0, Appendix V L.

Osmolality

The osmolality of the injection is 270 to 330 mosmol/kg, Appendix V N.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a buffer prepared by dissolving 2.72 g of *potassium dihydrogen orthophosphate* and 1.01 g of *sodium heptanesulfonate* in 1000 mL of *water* and adjusting the pH to 3.0 with

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orthophosphoric acid (solution A).

(1) Dilute a volume of the injection to contain 0.2% w/v of Lidocaine Hydrochloride Monohydrate.

(2) 0.0004% w/v of *2,6-dimethylaniline*.

(3) Dilute 1 volume of solution (1) to 100 volumes and further dilute 1 volume to 5 volumes.

(4) Mix 1 volume of a 0.2% w/v solution of *lidocaine hydrochloride BPCRS* with 5 volumes of solution (2) and dilute to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Luna C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 263 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

30 volumes of *acetonitrile* and 70 volumes of solution A.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (4) shows a peak due to lidocaine (retention time about 6 minutes) and a peak due to 2,6-dimethylaniline with a retention relative to lidocaine of about 2.35.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to 2,6-dimethylaniline is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 10 times the area of the principal peak in the chromatogram obtained with solution (3) (2.0%).

Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (3) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solution A described under Related substances.

(1) Dilute a volume of the injection to contain 0.2% w/v of Lidocaine Hydrochloride Monohydrate.

(2) 0.2% w/v of *lidocaine hydrochloride BPCRS*.

CHROMATOGRAPHIC CONDITIONS

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The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *column efficiency*, determined on the peak due to lidocaine is at least 2000 *theoretical plates*.

DETERMINATION OF CONTENT

Calculate the content of $C_{14}H_{22}N_2O,HCl,H_2O$ in the injection using the declared content of $C_{14}H_{22}N_2O,HCl,H_2O$ in *lidocaine hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include 2,6-dimethylaniline.

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Lidocaine Ointment

General Notices

Action and use

Local anaesthetic; Class I antiarrhythmic.

DEFINITION

Lidocaine Ointment contains Lidocaine in a suitable hydrophilic basis.

The ointment complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of lidocaine, $C_{14}H_{22}N_2O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Warm a quantity of the ointment containing about 25 mg of Lidocaine until the basis has melted, add 1 mL of *saturated sodium chloride solution* and 0.2 mL of 1M *sodium hydroxide* and cool. Add 5 mL of *ether*, shake vigorously for 1 minute and allow the layers to separate. Filter the ether layer through *anhydrous sodium sulfate* and evaporate the *ether* to dryness. Dissolve the residue in the minimum volume of *chloroform IR*, apply the solution directly to a *sodium chloride* disc and allow the solvent to evaporate. The *infrared absorption spectrum* of the resulting thin film, Appendix II A, is concordant with the *reference spectrum* of lidocaine *(RS 405)*.

2,6-Dimethylaniline

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve a quantity of the ointment containing 50 mg of Lidocaine in the mobile phase, dilute to 50 mL with the mobile phase and dilute 1 volume of this solution to 10 volumes with the mobile phase.
(2) Dilute a 0.1% w/v solution of *2,6-dimethylaniline* in *methanol* with the mobile phase to produce a solution containing 0.04 µg per mL of 2,6-dimethylaniline.
(3) Mix equal volumes of a 0.01% w/v solution of *lidocaine BPCRS* in the mobile phase with a 0.005% w/v solution of *2,6-dimethylaniline* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Apex ODS 2 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 0.8 mL per minute.

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(d) Use an ambient column temperature.

(e) Use a detection wavelength of 230 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

35 volumes of a phosphate buffer pH 8.0 prepared by adding a 0.408% w/v solution of *potassium dihydrogen orthophosphate* to a suitable volume of a 0.685% w/v solution of *dipotassium hydrogen orthophosphate* until pH 8.0 is attained and 65 volumes of *methanol*.

The chromatogram obtained with solution (3) shows a peak due to lidocaine and a peak due to 2,6-dimethylaniline with a retention time relative to lidocaine of about 0.5.

LIMITS

In the chromatogram obtained with solution (1), the area of any peak corresponding to 2,6-dimethylaniline is not greater than the area of the peak in the chromatogram obtained with solution (2) (400 ppm).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve a quantity of the ointment containing 50 mg of Lidocaine in the mobile phase, dilute to 50 mL with the mobile phase and dilute 1 volume of this solution to 10 volumes with the mobile phase.

(2) 0.010% w/v of *lidocaine BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under 2,6-Dimethylaniline may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{14}H_{22}N_2O$ in the ointment using the declared content of $C_{14}H_{22}N_2O$ in *lidocaine BPCRS*.

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Light Kaolin

General Notices

Action and use

Antidiarrhoeal.

Preparations

Kaolin Mixture

Kaolin and Morphine Mixture

When Kaolin or Light Kaolin is prescribed or demanded, Light Kaolin shall be dispensed or supplied unless it is ascertained that Light Kaolin (Natural) is required.

DEFINITION

Light Kaolin is a native hydrated aluminium silicate, freed from most of its impurities by elutriation and dried. It contains a suitable dispersing agent.

CHARACTERISTICS

A light, white powder free from gritty particles; odourless or almost odourless; unctuous.

Practically insoluble in *water* and in mineral acids.

IDENTIFICATION

A. To 0.5 g in a metal crucible add 1 g of *potassium nitrate* and 3 g of *sodium carbonate* and heat until the mixture melts. Allow to cool. To the residue add 20 mL of boiling *water*, mix and filter. Wash the residue with 50 mL of *water*, add to the residue 1 mL of *hydrochloric acid* and 5 mL of *water*, mix and filter. To the filtrate add 1 mL of *strong sodium hydroxide solution*, filter and add to the filtrate 3 mL of *ammonium chloride solution*. A gelatinous white precipitate is produced.

B. 0.25 g yields the reaction characteristic of *silicates*, Appendix VI.

C. Triturate 2 g with 2 mL of *water*. The resulting mixture flows.

TESTS

Coarse particles

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Transfer 5 g to a stoppered cylinder (about 16 cm × 35 mm), add 60 mL of a 1% w/v solution of *sodium pyrophosphate*, shake thoroughly and allow to stand for 5 minutes. Using a pipette, withdraw 50 mL from a point about 5 cm below the surface of the liquid. To the remaining liquid add 50 mL of *water*, shake, allow to stand for 5 minutes and withdraw 50 mL in the same manner as before. Repeat the operation until a total of 400 mL of suspension has been withdrawn under the prescribed conditions. Transfer the remainder to an evaporating dish and evaporate to dryness on a water bath. The residue, after drying at 105°, weighs not more than 25 mg.

Fine particles

Disperse 5 g in 250 mL of *water* by shaking vigorously for 2 minutes in a stoppered flask, pour immediately into a glass cylinder 5 cm in diameter and transfer 20 mL to a glass dish using a pipette. Evaporate to dryness and dry to constant weight at 105°. Allow the remainder of the suspension to stand for 4 hours at 20° and withdraw a second 20 mL portion using a pipette with its tip exactly 5 cm below the surface and without disturbing the sediment. Transfer the second portion to a glass dish, evaporate to dryness and dry to constant weight at 105°. The weight of the residue from the second portion is not less than 70% of the weight of the residue from the first portion.

Arsenic

0.50 g dispersed in 25 mL of *water* complies with the *limit test for arsenic*, Appendix VII (2 ppm).

Chloride

Boil 1.0 g with 80 mL of *water* and 20 mL of 2M *nitric acid* under a reflux condenser for 5 minutes, cool and filter. 15 mL of the filtrate complies with the *limit test for chlorides*, Appendix VII (330 ppm).

Loss on drying

When dried to constant weight at 105°, loses not more than 1.5% of its weight. Use 1 g.

Loss on ignition

When ignited at 600°, loses not more than 15.0% of its weight. Use 1 g.

Soluble matter

Boil 2 g with 100 mL of 0.2M *hydrochloric acid* under a reflux condenser for 5 minutes, cool, filter and evaporate 50 mL of the filtrate to dryness. The residue, after ignition at about 600° for 30 minutes, weighs not more than 10 mg.

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Light Kaolin (Natural)

General Notices

Action and use

Antidiarrhoeal.

Preparations

Kaolin Mixture

Kaolin and Morphine Mixture

When Kaolin or Light Kaolin is prescribed or demanded, Light Kaolin shall be dispensed or supplied unless it is ascertained that Light Kaolin (Natural) is required.

DEFINITION

Light Kaolin (Natural) is a native hydrated aluminium silicate, freed from most of its impurities by elutriation and dried. It does not contain a dispersing agent.

CHARACTERISTICS

A light, white powder free from gritty particles; odourless or almost odourless; unctuous.

Practically insoluble in *water* and in mineral acids.

IDENTIFICATION

A. To 0.5 g in a metal crucible add 1 g of *potassium nitrate* and 3 g of *sodium carbonate* and heat until the mixture melts. Allow to cool. To the residue add 20 mL of boiling *water*, mix and filter. Wash the residue with 50 mL of *water*, add to the residue 1 mL of *hydrochloric acid* and 5 mL of *water*, mix and filter. To the filtrate add 1 mL of *strong sodium hydroxide solution*, filter and add to the filtrate 3 mL of *ammonium chloride solution*. A gelatinous white precipitate is produced.

B. 0.25 g yields the reaction characteristic of *silicates*, Appendix VI.

C. Triturate 2 g with 2 mL of *water*. The resulting mixture does not flow.

TESTS

Coarse particles

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Transfer 5 g to a stoppered cylinder (about 16 cm × 35 mm), add 60 mL of a 1% w/v solution of *sodium pyrophosphate*, shake thoroughly and allow to stand for 5 minutes. Using a pipette, withdraw 50 mL from a point about 5 cm below the surface of the liquid. To the remaining liquid add 50 mL of *water*, shake, allow to stand for 5 minutes and withdraw 50 mL in the same manner as before. Repeat the operation until a total of 400 mL of suspension has been withdrawn under the prescribed conditions. Transfer the remainder to an evaporating dish and evaporate to dryness on a water bath. The residue, after drying at 105°, weighs not more than 25 mg.

Fine particles

Disperse 5 g in 250 mL of *water* containing 50 mg of *sodium pyrophosphate* by shaking vigorously for 2 minutes in a stoppered flask, pour immediately into a glass cylinder 5 cm in diameter and transfer 20 mL to a glass dish using a pipette. Evaporate to dryness and dry to constant weight at 105°. Allow the remainder of the suspension to stand for 4 hours at 20° and withdraw a second 20 mL portion using a pipette with its tip exactly 5 cm below the surface and without disturbing the sediment. Transfer the second portion to a glass dish, evaporate to dryness and dry to constant weight at 105°. The weight of the residue from the second portion is not less than 70% of the weight of the residue from the first portion.

Arsenic

0.50 g dispersed in 25 mL of *water* complies with the *limit test for arsenic*, Appendix VII (2 ppm).

Chloride

Boil 1.0 g with 80 mL of *water* and 20 mL of 2M *nitric acid* under a reflux condenser for 5 minutes, cool and filter. 15 mL of the filtrate complies with the *limit test for chlorides*, Appendix VII (330 ppm).

Loss on drying

When dried to constant weight at 105°, loses not more than 1.5% of its weight. Use 1 g.

Loss on ignition

When ignited at 600°, loses not more than 15.0% of its weight. Use 1 g.

Soluble matter

Boil 2 g with 100 mL of 0.2M *hydrochloric acid* under a reflux condenser for 5 minutes, cool, filter and evaporate 50 mL of the filtrate to dryness. The residue, after ignition at about 600° for 30 minutes, weighs not more than 10 mg.

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Light Liquid Paraffin

General Notices

(Ph. Eur. monograph 0240)

Preparation

Light Liquid Paraffin Eye Drops

Ph Eur

DEFINITION

Purified mixture of liquid saturated hydrocarbons obtained from petroleum.

CHARACTERS

Appearance

Colourless, transparent, oily liquid, free from fluorescence in daylight.

Solubility

Practically insoluble in water, slightly soluble in ethanol (96 per cent), miscible with hydrocarbons.

IDENTIFICATION

First identification: A, C.

Second identification: B, C.

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *Ph. Eur. reference spectrum of liquid paraffin*.

B. In a test tube cautiously boil 1 mL with 1 mL of *0.1 M sodium hydroxide*, with continuous shaking, for about 30 s. On cooling to room temperature, 2 phases separate. To the aqueous phase add 0.1 mL of *phenolphthalein solution R*. The solution becomes red.

C. Viscosity (see Tests).

TESTS

Acidity or alkalinity

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To 10 mL add 20 mL of boiling *water R* and shake vigorously for 1 min. Separate the aqueous layer and filter. To 10 mL of the filtrate, add 0.1 mL of *phenolphthalein solution R*. The solution is colourless. Not more than 0.1 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator to pink.

Relative density (*2.2.5*)

0.810 to 0.875.

Viscosity (*2.2.9*)

25 mPa·s to 80 mPa·s.

Polycyclic aromatic hydrocarbons

Use reagents for ultraviolet spectrophotometry.

Introduce 25.0 mL into a 125 mL separating funnel with unlubricated ground-glass parts (stopper, stopcock). Add 25 mL of *hexane R* which has been previously shaken twice with one-fifth its volume of *dimethyl sulfoxide R*. Mix and add 5.0 mL of *dimethyl sulfoxide R*. Shake vigorously for 1 min and allow to stand until 2 clear layers are formed. Transfer the lower layer to a 2nd separating funnel, add 2 mL of *hexane R* and shake the mixture vigorously. Allow to stand until 2 clear layers are formed. Separate the lower layer and measure its absorbance (*2.2.25*) between 260 nm and 420 nm, using as the compensation liquid the clear lower layer obtained by vigorously shaking 5.0 mL of *dimethyl sulfoxide R* with 25 mL of *hexane R* for 1 min. Prepare a 7.0 mg/L reference solution of *naphthalene R* in *trimethylpentane R* and measure the absorbance of the solution at the absorption maximum at 275 nm, using *trimethylpentane R* as the compensation liquid. At no wavelength between 260 nm and 420 nm does the absorbance of the test solution exceed one-third that of the reference solution at 275 nm.

Readily carbonisable substances

Use a ground-glass-stoppered tube about 125 mm long and 18 mm in internal diameter, graduated at 5 mL and 10 mL; wash with hot *water R* (temperature at least 60 °C), *acetone R*, *heptane R* and finally with *acetone R*, dry at 100-110 °C. Cool in a desiccator. Introduce 5 mL of the substance to be examined and add 5 mL of *nitrogen-free sulfuric acid R1*. Insert the stopper and shake as vigorously as possible, in the longitudinal direction of the tube, for 5 s. Loosen the stopper, immediately place the tube in a water-bath, avoiding contact of the tube with the bottom or side of the bath, and heat for 10 min. After 2 min, 4 min, 6 min and 8 min, remove the tube from the bath and shake as vigorously as possible, in the longitudinal direction of the tube for 5 s. At the end of 10 min of heating, remove the tube from the water-bath and allow to stand for 10 min. Centrifuge at 2000 *g* for 5 min. The lower layer is not more intensely coloured (*2.2.2, Method I*) than a mixture of 0.5 mL of blue primary solution, 1.5 mL of red primary solution, 3.0 mL of yellow primary solution and 2 mL of a 10 g/L solution of *hydrochloric acid R*.

Solid paraffins

Dry a suitable quantity of the substance to be examined by heating at 100 °C for 2 h and cool in a desiccator over *sulfuric acid R*. Place in a glass tube with an internal diameter of about 25 mm, close the tube and immerse in a bath of iced water. After 4 h, the liquid is sufficiently clear for a black line, 0.5 mm wide, to be easily seen against a white background held vertically behind the tube.

STORAGE

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Protected from light.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristic may be relevant for light liquid paraffin used as emollient in ointments, as vehicle in eye preparations or as lubricant in tablets and capsules.

Viscosity

(see Tests).

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Light Liquid Paraffin Eye Drops

General Notices

DEFINITION

Light Liquid Paraffin Eye Drops are Light Liquid Paraffin in a suitable container.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

TESTS

Acidity or alkalinity

To 10 mL add 20 mL of boiling *water* and shake vigorously for 1 minute. Separate the aqueous layer and filter. To 10 mL of the filtrate, add 0.1 mL of *phenolphthalein solution*. The solution is colourless. Not more than 0.1 mL of *0.1M sodium hydroxide VS* is required to change the colour to pink.

Relative density

0.810 to 0.875, Appendix V G.

Viscosity

25 mPa.s to 80 mPa.s, Appendix V H, Method II.

Solid paraffins

Dry a suitable quantity of the eye drops by heating at 100° for 2 hours and cool in a desiccator over *sulfuric acid*. Place in a glass tube with an internal diameter of about 25 mm, close the tube and immerse in a bath of iced water. After 4 hours, the liquid is sufficiently clear for a black line, 0.5 mm wide, to be easily seen against a white background held vertically behind the tube.

STORAGE

Light Liquid Paraffin Eye Drops should be protected from light.

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Light Magnesium Carbonate

General Notices

(Ph. Eur. monograph 0042)

Action and use

Antacid; osmotic laxative.

Preparations

Aromatic Magnesium Carbonate Mixture

Kaolin Mixture

Magnesium Sulfate Mixture

Magnesium Trisilicate Mixture

Ph Eur

DEFINITION

Hydrated basic magnesium carbonate.

Content

40.0 per cent to 45.0 per cent, calculated as MgO (M_r 40.30).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water. It dissolves in dilute acids with effervescence.

IDENTIFICATION

A. Bulk density (*2.9.34*): maximum 0.15 g/mL.

B. It gives the reaction of carbonates (*2.3.1*).

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C. Dissolve about 15 mg in 2 mL of *dilute nitric acid R* and neutralise with *dilute sodium hydroxide solution R*. The solution gives the reaction of magnesium (*2.3.1*).

TESTS

Solution S

Dissolve 5.0 g in 100 mL of *dilute acetic acid R*. When the effervescence has ceased, boil for 2 min, allow to cool and dilute to 100 mL with *dilute acetic acid R*. Filter, if necessary, through a previously ignited and tared porcelain or silica filter crucible of suitable porosity to give a clear filtrate. Keep the residue for the test for substances insoluble in acetic acid.

Appearance of solution

Solution S is not more intensely coloured than reference solution B_4 (*2.2.2, Method II*).

Soluble substances

Maximum 1.0 per cent.

Mix 2.00 g with 100 mL of *water R* and boil for 5 min. Filter whilst hot through a sintered-glass filter (40) (*2.1.2*), allow to cool and dilute to 100 mL with *water R*. Evaporate 50 mL of the filtrate to dryness and dry at 100-105 °C. The residue weighs a maximum of 10 mg.

Substances insoluble in acetic acid

Maximum 0.05 per cent.

Any residue obtained during the preparation of solution S, washed, dried and ignited at 600 ± 50 °C, weighs a maximum of 2.5 mg.

Chlorides (*2.4.4*)

Maximum 700 ppm.

Dilute 1.5 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 0.3 per cent.

Dilute 1 mL of solution S to 15 mL with *distilled water R*.

Elemental impurities

Any method that fulfils the requirements of general chapter *2.4.20*. *Determination of elemental impurities* may be used.

Element	Maximum content (ppm)
Arsenic	1
Cobalt	1

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Element	Maximum content (ppm)
Nickel	50
Vanadium	5

Calcium (*2.4.3*)

Maximum 0.75 per cent.

Dilute 2.6 mL of solution S to 150 mL with *distilled water R*. 15 mL of the solution complies with the test.

Iron (*2.4.9*)

Maximum 400 ppm.

Dissolve 0.1 g in 3 mL of *dilute hydrochloric acid R* and dilute to 10 mL with *water R*. Dilute 2.5 mL of this solution to 10 mL with *water R*.

ASSAY

Dissolve 0.150 g in a mixture of 2 mL of *dilute hydrochloric acid R* and 20 mL of *water R*. Carry out the complexometric titration of magnesium (*2.5.11*).

1 mL of *0.1 M sodium edetate* is equivalent to 4.030 mg of MgO.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for light magnesium carbonate used as filler in oral solid dosage forms.

Particle-size distribution (*2.9.31* or *2.9.38*)

Bulk and tapped density (*2.9.34*)

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Light Magnesium Oxide

General Notices

Light Magnesia

(Ph. Eur. monograph 0040)

MgO 40.30 *1309-48-4*

Action and use

Antacid; osmotic laxative.

Preparation

Compound Sodium Picosulfate Powder for Oral Solution

Ph Eur

DEFINITION

Content

98.0 per cent to 100.5 per cent of MgO (ignited substance).

CHARACTERS

Appearance

Fine, white or almost white, amorphous powder.

Solubility

Practically insoluble in water. It dissolves in dilute acids with at most slight effervescence.

IDENTIFICATION

A. Bulk density (*2.9.34*): maximum 0.15 g/mL.

B. Dissolve about 15 mg in 2 mL of *dilute nitric acid R* and neutralise with *dilute sodium hydroxide solution R*. The solution gives the reaction of magnesium (*2.3.1*).

C. Loss on ignition (see Tests).

TESTS

Solution S

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Solution S

Dissolve 5.0 g in a mixture of 30 mL of *distilled water R* and 70 mL of *acetic acid R*, boil for 2 min, allow to cool and dilute to 100 mL with *dilute acetic acid R*. Filter, if necessary, through a previously ignited and tared porcelain or silica filter crucible of a suitable porosity to give a clear filtrate. Keep the residue for the test for substances insoluble in acetic acid.

Appearance of solution

Solution S is not more intensely coloured than reference solution B_2 (*2.2.2, Method II*).

Soluble substances

Maximum 2.0 per cent.

To 2.00 g add 100 mL of *water R* and boil for 5 min. Filter whilst hot through a sintered-glass filter (40) (*2.1.2*), allow to cool and dilute to 100 mL with *water R*. Evaporate 50 mL of the filtrate to dryness and dry at 100-105 °C. The residue weighs a maximum of 20 mg.

Substances insoluble in acetic acid

Maximum 0.1 per cent.

Any residue obtained during the preparation of solution S, washed, dried, and ignited at 600 ± 50 °C, weighs a maximum of 5 mg.

Chlorides (*2.4.4*)

Maximum 0.15 per cent.

Dilute 0.7 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 1.0 per cent.

Dilute 0.3 mL of solution S to 15 mL with *distilled water R*.

Calcium (*2.4.3*)

Maximum 1.5 per cent.

Dilute 1.3 mL of solution S to 150 mL with *distilled water R*. 15 mL of this solution complies with the test.

Iron (*2.4.9*)

Maximum 0.1 per cent.

Dissolve 50 mg in 5 mL of *dilute hydrochloric acid R* and dilute to 10 mL with *water R*. Dilute 2 mL of this solution to 10 mL with *water R*.

Loss on ignition

Maximum 8.0 per cent, determined on 1.00 g at 900 ± 25 °C.

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ASSAY

Dissolve 0.320 g in 20 mL of *dilute hydrochloric acid R* and dilute to 100.0 mL with *water R*. Using 20.0 mL of this solution, carry out the complexometric titration of magnesium (2.5.11).

1 mL of *0.1 M sodium edetate* is equivalent to 4.030 mg of MgO.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for light magnesium oxide used as filler in oral solid dosage forms.

Particle-size distribution (2.9.31 or 2.9.38)

Bulk and tapped density (2.9.34)

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Lincomycin Capsules

General Notices

Action and use

Lincosamide antibacterial.

DEFINITION

Lincomycin Capsules contain Lincomycin Hydrochloride.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of lincomycin, $C_{18}H_{34}N_2O_6S$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Extract a quantity of the capsules contents containing the equivalent of 0.2 g of lincomycin with 5 mL of a mixture of 4 volumes of *chloroform* and 1 volume of *methanol*, filter and evaporate the filtrate. Dissolve the oily residue in 1 mL of *water*, add *acetone* until precipitation begins and add a further 20 mL of *acetone*. Filter the precipitate, wash with two 10-mL quantities of *acetone*, dissolve the residue in a little of the chloroform–methanol mixture, evaporate to dryness and dry at 60° at a pressure not exceeding 2 kPa for 4 hours. The *infrared absorption spectrum* of the dried precipitate, Appendix II A, is concordant with the *reference spectrum* of lincomycin hydrochloride *(RS 203)*.

B. In the Assay, the chromatogram obtained with solution (2) shows a peak with the same retention time as the peak due to the trimethylsilyl derivative of lincomycin in the chromatogram obtained with solution (1).

TESTS

Lincomycin B

Examine solution (3) as described under the Assay but increasing the sensitivity by 8 to 10 times while recording the peak derived from lincomycin B, which is eluted immediately before that derived from lincomycin.

LIMITS

The area of the peak derived from lincomycin B, when corrected for the sensitivity factor, is not more than 5% of the area of the peak derived from lincomycin.

Water

The contents of the capsules contain not more than 7.0% w/w of water, Appendix IX C. Use 0.3 g.

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ASSAY

Carry out the method for *gas chromatography*, Appendix III B, using the following solutions.

(1) Add 10 mL of a 0.8% w/w solution of *dotriacontane* (internal standard) in *chloroform* to 0.1 g of *lincomycin hydrochloride BPCRS*, dilute to 100 mL with a 2% w/v solution of *imidazole* in *chloroform* and shake to dissolve. Place 4 mL of the resulting solution in a 15-mL ground-glass-stoppered centrifuge tube, add 1 mL of a mixture of 99 volumes of N,O-*bis(trimethylsilyl)acetamide* and 1 volume of *trimethylchlorosilane* and swirl gently. Loosen the glass stopper and heat at 65° for 30 minutes.

(2) Prepare in the same manner as solution (1) but omitting the internal standard and using a quantity of the mixed contents of 20 capsules containing the equivalent of 90 mg of lincomycin in place of the *lincomycin hydrochloride BPCRS*.

(3) Prepare in the same manner as solution (1) but using a quantity of the mixed contents of 20 capsules containing the equivalent of 90 mg of lincomycin in place of the *lincomycin hydrochloride BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a glass column (1.5 m × 3 mm) packed with *acid-washed silanised diatomaceous support* impregnated with 3% w/w of phenyl methyl silicone fluid (50% phenyl) (OV-17 is suitable) and maintained at 260°.

(b) Use *helium* as the carrier gas at a flow rate of about 45 mL per minute.

(c) Use an inlet temperature of 260° to 290°.

(d) Use a flame ionisation detector at a temperature of 260° to 290°.

(e) Inject 1 µL of each solution.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{34}N_2O_6S$ in the capsules using the declared content of $C_{18}H_{34}N_2O_6S$ in *lincomycin hydrochloride BPCRS*.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of lincomycin.

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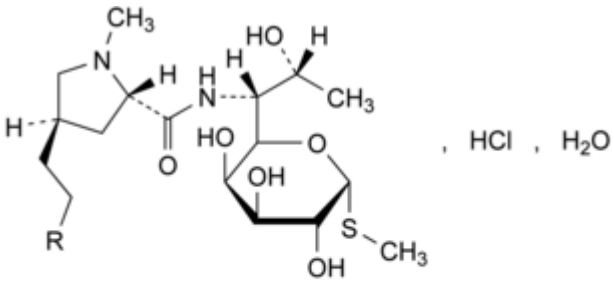
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Lincomycin Hydrochloride

General Notices

(Ph. Eur. monograph 0583)



Compound	R	Molecular formula	M_r
Lincomycin	CH_3	$C_{18}H_{35}ClN_2O_6S,H_2O$	461.0
Lincomycin B	H	$C_{17}H_{33}ClN_2O_6S,H_2O$	447.0

Lincomycin hydrochloride monohydrate *7179-49-9*

Action and use

Antibacterial.

Preparations

Lincomycin Capsules

Lincomycin Injection

Ph Eur

DEFINITION

Mixture of antibiotics produced by *Streptomyces lincolnensis* var. *lincolnensis* or obtained by any other means, the main component being methyl 6,8-dideoxy-6-[[[(2*S*,4*R*)-1-methyl-4-propylpyrrolidin-2-yl]carbonyl]amino]-1-thio-D-*erythro*-α-D-*galacto*-octopyranoside (lincomycin) hydrochloride monohydrate.

Content

— *sum of the contents of lincomycin hydrochloride and lincomycin B hydrochloride*: 96.0 per cent to 102.0 per cent (anhydrous substance);

— *lincomycin B hydrochloride*: maximum 5.0 per cent (anhydrous substance).

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CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very soluble in water, slightly soluble in ethanol (96 per cent), very slightly soluble in acetone.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *lincomycin hydrochloride CRS*.

B. Dissolve 0.1 g in *water R* and dilute to 10 mL with the same solvent. The solution gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S

Dissolve 2.0 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

pH (*2.2.3*)

3.5 to 5.5 for solution S.

Specific optical rotation (*2.2.7*)

+ 135 to + 150 (anhydrous substance).

Dissolve 1.000 g in *water R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 25.0 mg of *lincomycin hydrochloride CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of *lincomycin hydrochloride for system suitability CRS* (containing impurities A, B and C) in 2 mL of the mobile phase.

Reference solution (c) Dilute 2.0 mL of reference solution (a) to 100.0 mL with the mobile phase.

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Reference solution (d) Dilute 1.0 mL of reference solution (c) to 20.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 50 °C.

Buffer solution pH 6.1 Dissolve 34 g of *phosphoric acid R* in 900 mL of *water for chromatography R*, adjust to pH 6.1 with *concentrated ammonia R* and dilute to 1000 mL with *water for chromatography R*.

Mobile phase *methanol R*, *acetonitrile R1*, buffer solution pH 6.1 (8:17:75 *V/V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 20 µL of the test solution and reference solutions (b), (c) and (d).

Run time 5.5 times the retention time of lincomycin.

Relative retention With reference to lincomycin (retention time = about 10 min): impurity C = about 0.4; lincomycin B = about 0.5; impurity A = about 0.7; impurity B = about 1.2 and 1.3.

System suitability Reference solution (b):

— *resolution*: minimum 1.8 between the peak due to lincomycin and the 1st peak due to impurity B.

Limits:

— *impurity A*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (d) (0.5 per cent);

— *sum of the areas of the peaks due to impurity B*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (d) (0.5 per cent);

— *impurity C*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (d) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (d) (0.10 per cent);

— *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (2.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (d) (0.05 per cent).

Water (*2.5.12*)

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3.1 per cent to 4.6 per cent, determined on 0.500 g.

Sulfated ash (2.4.14)

Maximum 0.5 per cent, determined on 1.0 g.

Bacterial endotoxins (2.6.14)

Less than 0.50 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution and reference solutions (a) and (c).

Calculate the percentage content of $C_{18}H_{35}ClN_2O_6S$ (lincomycin) and $C_{17}H_{33}ClN_2O_6S$ (lincomycin B) taking into account the assigned content of $C_{18}H_{35}ClN_2O_6S$ in *lincomycin hydrochloride CRS*. Determine the content of lincomycin by comparing with the area of the peak due to lincomycin in the chromatogram obtained with reference solution (a). Determine the content of lincomycin B by comparing with the area of the peak due to lincomycin in the chromatogram obtained with reference solution (c).

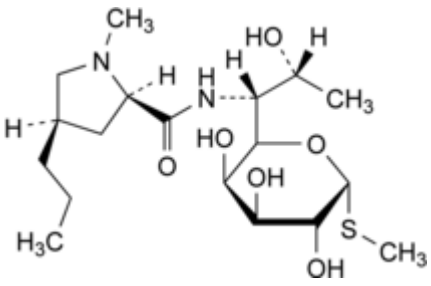
STORAGE

At a temperature not exceeding 30 °C. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

IMPURITIES

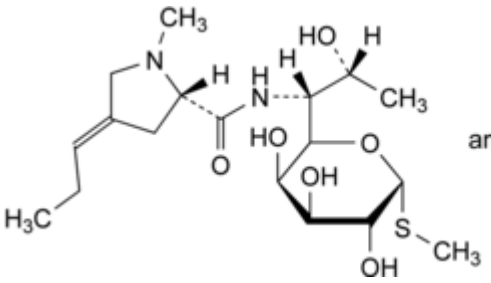
Specified impurities *A, B, C.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *D, E, F.*

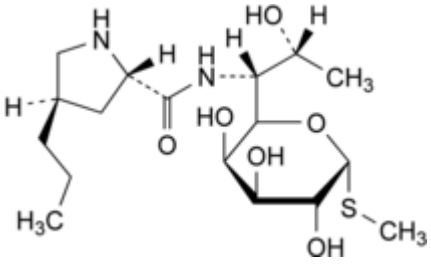


A. methyl 6,8-dideoxy-6-[[[(2*R*,4*R*)-1-methyl-4-propylpyrrolidin-2-yl]carbonyl]amino]-1-thio-D-*erythro*-α-D-*galacto*-octopyranoside (α-amide epimer),

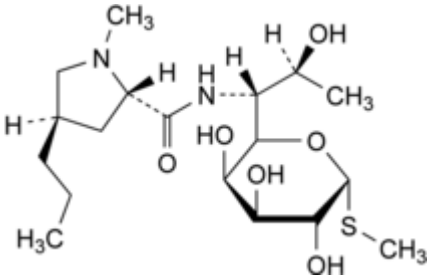
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and (*Z*)-isomer

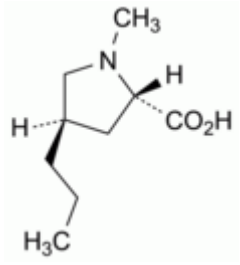
B. methyl 6,8-dideoxy-6-[[[(2*S*,4*EZ*)-1-methyl-4-propylidenepyrrolidin-2-yl]carbonyl]amino]-1-thio-D-*erythro*-α-D-*galacto*-octopyranoside (propylidene analogues),



C. methyl 6,8-dideoxy-6-[[[(2*S*,4*R*)-4-propylpyrrolidin-2-yl]carbonyl]amino]-1-thio-D-*erythro*-α-D-*galacto*-octopyranoside (*N*-desmethyl lincomycin),

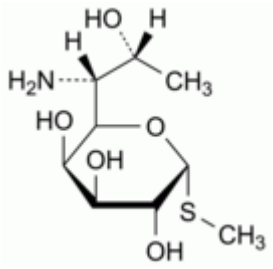


D. methyl 6,8-dideoxy-6-[[[(2*S*,4*R*)-1-methyl-4-propylpyrrolidin-2-yl]carbonyl]amino]-1-thio-L-*threo*-α-D-*galacto*-octopyranoside (7-*epi*-lincomycin),



E. (2*S*,4*R*)-1-methyl-4-propylpyrrolidine-2-carboxylic acid (4-propyl hygric acid),

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F. methyl 6-amino-6,8-dideoxy-1-thio-D-*erythro*-α-D-*galacto*-octopyranoside (methyl-1-thiolincosaminide).

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Lincomycin Injection

General Notices

Action and use

Lincosamide antibacterial.

DEFINITION

Lincomycin Injection is a sterile solution of Lincomycin Hydrochloride in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of lincomycin, $C_{18}H_{34}N_2O_6S$

92.5 to 107.5% of the stated amount.

CHARACTERISTICS

A colourless or almost colourless solution.

IDENTIFICATION

A. Add *acetone* to a volume of the injection containing the equivalent of 0.2 g of lincomycin until precipitation begins and add a further 20 mL of *acetone*. Filter the precipitate, wash with two 10-mL quantities of *acetone*, dissolve the residue in the minimum of a mixture of 4 volumes of *chloroform* and 1 volume of *methanol*, evaporate to dryness and dry at 60° at a pressure not exceeding 2 kPa for 4 hours. The *infrared absorption spectrum* of the dried precipitate, Appendix II A, is concordant with the *reference spectrum* of lincomycin hydrochloride *(RS 203)*.

B. In the Assay, the chromatogram obtained with solution (2) shows a peak with the same retention time as the peak due to the trimethylsilyl derivative of lincomycin in the chromatogram obtained with solution (1).

TESTS

Acidity

pH, 3.0 to 5.5, Appendix V L.

Lincomycin B

Examine solution (3) as described under the Assay but increase the sensitivity by 8 to 10 times while recording the peak derived from lincomycin B, which is eluted immediately before that derived from lincomycin.

LIMITS

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The area of the peak derived from lincomycin B, when corrected for the sensitivity factor, is not more than 5% of the area of the peak derived from lincomycin.

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. Dilute the injection if necessary with *water BET* to give a solution containing the equivalent of 10 mg of lincomycin per mL (solution A). The endotoxin limit concentration of solution A is 5.0 IU per mL.

ASSAY

Carry out the method for *gas chromatography*, Appendix III B, using the following solutions.

(1) Add 10 mL of a 0.8% w/w solution of *dotriacontane* (internal standard) in *chloroform* to 0.1 g of *lincomycin hydrochloride BPCRS*, dilute to 100 mL with a 2% w/v solution of *imidazole* in *chloroform* and shake to dissolve. Place 4 mL of the resulting solution in a 15-mL ground-glass-stoppered centrifuge tube, add 1 mL of a mixture of 99 volumes of N,O-*bis(trimethylsilyl)acetamide* and 1 volume of *trimethylchlorosilane* and swirl gently. Loosen the glass stopper and heat at 65° for 30 minutes.

(2) Prepare in the same manner as solution (1) but omitting the internal standard and using the residue obtained by evaporating to dryness 1 mL of a solution prepared by diluting a volume of the injection containing the equivalent of 0.9 g of lincomycin to 10 mL with *methanol* in place of the *lincomycin hydrochloride BPCRS*.

(3) Prepare in the same manner as solution (1) but using the residue obtained by evaporating to dryness 1 mL of a solution prepared by diluting a volume of the injection containing the equivalent of 0.9 g of lincomycin to 10 mL with *methanol* in place of the *lincomycin hydrochloride BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a glass column (1.5 m × 3 mm) packed with *acid-washed silanised diatomaceous support* impregnated with 3% w/w of phenyl methyl silicone fluid (50% phenyl) (OV-17 is suitable) and maintained at 260°.

(b) Use *helium* as the carrier gas at a flow rate of about 45 mL per minute.

(c) Use an inlet temperature of 260° to 290°.

(d) Use a flame ionisation detector at a temperature of 260° to 290°.

(e) Inject 1 µL of each solution.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{34}N_2O_6S$ in the injection using the declared content of $C_{18}H_{34}N_2O_6S$ in *lincomycin hydrochloride BPCRS*.

STORAGE

Lincomycin Injection should be protected from light and stored at a temperature not exceeding 30°.

LABELLING

The strength is stated as the equivalent amount of lincomycin in a suitable dose-volume.

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Linoleoyl Macrogolglycerides

General Notices

(Ph. Eur. monograph 1232)

Action and use

Excipient.

Ph Eur

DEFINITION

Mixtures of monoesters, diesters and triesters of glycerol and monoesters and diesters of macrogols.

They are obtained by partial alcoholysis of an unsaturated oil mainly containing triglycerides of linoleic ((9*Z*,12*Z*)-octadeca-9,12-dienoic) acid, using macrogol with a mean relative molecular mass between 300 and 400, or by esterification of glycerol and macrogol with unsaturated fatty acids, or by mixing glycerol esters and condensates of ethylene oxide with the fatty acids of this unsaturated oil.

CHARACTERS

Appearance

Amber, oily liquid which may give rise to a deposit after prolonged periods at 20 °C.

Solubility

Practically insoluble but dispersible in water, freely soluble in methylene chloride.

Relative density

About 0.95 at 20 °C.

Refractive index

About 1.47 at 20 °C.

Viscosity

About 35 mPa·s at 40 °C.

IDENTIFICATION

A. Thin-layer chromatography (*2.2.27*).

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Test solution Dissolve 1.0 g of the substance to be examined in *methylene chloride R* and dilute to 20 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase *hexane R*, *ether R* (30:70 *V/V*).

Application 10 µL.

Development Over a path of 15 cm.

Drying In air.

Detection Spray with a 0.1 g/L solution of *rhodamine B R* in *ethanol (96 per cent) R* and examine in ultraviolet light at 365 nm.

Results The chromatogram shows a spot due to triglycerides with an R_F value of about 0.9 (R_{st} 1) and spots due to 1,3-diglycerides (R_{st} 0.7), to 1,2-diglycerides (R_{st} 0.6), to monoglycerides (R_{st} 0.1) and to esters of macrogol (R_{st} 0).

B. Hydroxyl value (see Tests).

C. Saponification value (see Tests).

D. Composition of fatty acids (see Tests).

TESTS

Acid value (*2.5.1*)

Maximum 2.0, determined on 2.0 g.

Hydroxyl value (*2.5.3, Method A*)

45 to 65, determined on 1.0 g.

Iodine value (*2.5.4, Method A*)

90 to 110.

Peroxide value (*2.5.5, Method A*)

Maximum 12.0, determined on 2.0 g.

Saponification value (*2.5.6*)

150 to 170, determined on 2.0 g.

Alkaline impurities

Introduce 5.0 g into a test tube and carefully add a mixture, neutralised if necessary with *0.01 M hydrochloric acid* or with *0.01 M sodium hydroxide*, of 0.05 mL of a 0.4 g/L solution of *bromophenol blue R* in *ethanol (96 per cent) R*, 0.3 mL of *water R* and 10 mL of *ethanol*

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(96 per cent) R. Shake and allow to stand. Not more than 1.0 mL of *0.01 M hydrochloric acid* is required to change the colour of the upper layer to yellow.

Free glycerol

Maximum 3.0 per cent.

Dissolve 1.20 g in 25.0 mL of *methylene chloride R*. Heat if necessary. After cooling, add 100 mL of *water R*. Shake and add 25.0 mL of *periodic acetic acid solution R*. Shake and allow to stand for 30 min. Add 40 mL of a 75 g/L solution of *potassium iodide R*. Allow to stand for 1 min. Add 1 mL of *starch solution R*. Titrate the iodine with *0.1 M sodium thiosulfate*. Carry out a blank titration.

1 mL of *0.1 M sodium thiosulfate* is equivalent to 2.3 mg of glycerol.

Composition of fatty acids (*2.4.22, Method A*)

Composition of the fatty-acid fraction of the substance:

— *palmitic acid*: 4.0 per cent to 20.0 per cent;

— *stearic acid*: maximum 6.0 per cent;

— *oleic acid*: 20.0 per cent to 35.0 per cent;

— *linoleic acid*: 50.0 per cent to 65.0 per cent;

— *linolenic acid*: maximum 2.0 per cent;

— *arachidic acid*: maximum 1.0 per cent;

— *eicosenoic acid*: maximum 1.0 per cent.

Ethylene oxide and dioxan (*2.4.25*)

Maximum 1 ppm of ethylene oxide and maximum 10 ppm of dioxan.

Water (*2.5.12*)

Maximum 1.0 per cent, determined on 1.00 g. Use a mixture of 30 volumes of *anhydrous methanol R* and 70 volumes of *methylene chloride R* as solvent.

Total ash (*2.4.16*)

Maximum 0.1 per cent.

STORAGE

Protected from light.

LABELLING

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The label states the type of macrogol used (mean relative molecular mass) or the number of units of ethylene oxide per molecule (nominal value).

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for linoleoyl macrogolglycerides used as self-emulsifying agents and solubilisers.

Hydroxyl value

(see Tests).

Saponification value

(see Tests).

Composition of fatty acids

(see Tests).

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Liothyronine for Injection

General Notices

Action and use

Thyroid hormone replacement.

DEFINITION

Liothyronine for Injection is a sterile material consisting of Liothyronine Sodium with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of liothyronine sodium, $C_{15}H_{11}I_3NNaO_4$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

In the Assay, record the UV spectrum of the principal peak in the chromatograms obtained with solutions (1) and (2) with a diode array detector in the range of 210 to 400 nm.

The UV spectrum of the principal peak in the chromatogram obtained with solution (1) is concordant with that of the peak in the chromatogram obtained with solution (2);

the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Clarity and colour of solution

Dissolve the contents of a sealed container in *water for injections* and dilute to produce a final solution containing 0.002% w/v of Liothyronine Sodium. The solution is *clear*, Appendix IV A, and *colourless*, Appendix IV B.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in the mobile phase. Carry out the test protected from light.

(1) Dissolve the mixed contents of sealed containers containing 0.025 mg of Liothyronine Sodium with 4 mL and dilute to produce 5 mL.

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(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) 0.00025% w/v of *liothyronine sodium EPCRS* and 0.00005% w/v of *levothyroxine sodium EPCRS* (impurity A).

(4) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped extra-dense bonded cyanosilyl silica gel for chromatography* (5 µm) (Zorbax Eclipse XDB-CN is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 60°.

(e) Use a detection wavelength of 225 nm.

(f) Inject 50 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for 10 times the retention time of liothyronine.

MOBILE PHASE

5 volumes of *orthophosphoric acid*, 300 volumes of *acetonitrile* and 700 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to liothyronine and impurity A is at least 4.0.

CALCULATION OF IMPURITIES

For impurity A, use the concentration of impurity A in solution (3).

For each unspecified impurity, use the concentration of liothyronine in solution (2).

For the reporting threshold, use the concentration of liothyronine in solution (4).

For peak identification, use solution (3).

Liothyronine retention time: about 4 minutes.

Relative retention: impurity B, about 0.5; impurity E, about 0.7; impurity A, about 1.4; impurity C, about 5.0 and impurity D, about 5.7.

LIMITS

— impurity A, not more than 1.0%;

— unspecified impurities: for each impurity, not more than 1.0%;

— total impurities: not more than 3.0%;

— reporting threshold: 0.1%.

Uniformity of content

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Sealed containers containing the equivalent of 2 mg or less of Liothyronine Sodium comply with the requirements stated under *Parenteral Preparations*, *Powders for Injections or Infusions*. Use the individual results obtained in the Assay.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, prepared in the mobile phase. Carry out the test protected from light.

(1) Dissolve the contents of a sealed container to produce a solution containing 0.0005% w/v of Liothyronine Sodium.

(2) 0.0005% w/v of *liothyronine sodium EPCRS*.

(3) 0.0005% w/v of *liothyronine sodium EPCRS* and 0.0005% w/v of *levothyroxine sodium EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to liothyronine and impurity A is at least 4.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{15}H_{11}I_3NNaO_4$ in the sealed containers using the chromatograms obtained and the declared content of $C_{15}H_{11}I_3NNaO_4$ in *liothyronine sodium EPCRS*.

STORAGE

Liothyronine for Injection should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Liothyronine Sodium.

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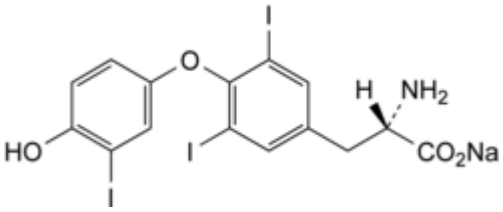
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Liothyronine Sodium

General Notices

(Ph. Eur. monograph 0728)



$C_{15}H_{11}I_3NNaO_4$ 673 *55-06-1*

Action and use

Thyroid hormone replacement.

Preparations

Liothyronine for Injection

Liothyronine Tablets

Ph Eur

DEFINITION

Sodium (2*S*)-2-amino-3-[4-(4-hydroxy-3-iodophenoxy)-3,5-diiodophenyl]propanoate.

Content

95.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or slightly coloured, hygroscopic powder.

Solubility

Practically insoluble in water, slightly soluble in ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides.

IDENTIFICATION

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First identification: A, C, E.

Second identification: A, B, D, E.

A. Specific optical rotation (see Tests).

B. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 10.0 mg in *0.1 M sodium hydroxide* and dilute to 100.0 mL with the same solvent.

Spectral range 230-350 nm.

Absorption maximum At 319 nm.

Specific absorbance at the absorption maximum 63 to 69 (dried substance).

C. Infrared absorption spectrophotometry (2.2.24).

Comparison *liothyronine sodium CRS*.

D. To about 50 mg in a porcelain dish add a few drops of *sulfuric acid R* and heat. Violet vapour is evolved.

E. To 200 mg add 2 mL of *dilute sulfuric acid R*. Heat on a water-bath and then carefully over a naked flame, increasing the temperature gradually up to about 600 °C. Continue the ignition until most of the particles have disappeared. Dissolve the residue in 2 mL of *water R*. The solution gives reaction (a) of sodium (2.3.1).

TESTS

Specific optical rotation (2.2.7)

+ 18.0 to + 22.0 (dried substance).

Dissolve 0.200 g in a mixture of 1 volume of *1 M hydrochloric acid* and 4 volumes of *ethanol (96 per cent) R* and dilute to 20.0 mL with the same mixture of solvents.

Related substances

Liquid chromatography (2.2.29). *Protect the solutions from light throughout the test.*

Solution A Mix 10 volumes of mobile phase A with 90 volumes of *methanol R*.

Solution B Mix 30 volumes of mobile phase B and 70 volumes of mobile phase A. Mix equal volumes of this solution with solution A.

Test solution Dissolve 20.0 mg of the substance to be examined in 20 mL of solution A. Dilute 4.0 mL of this solution to 20.0 mL with solution B.

Reference solution (a) Dissolve 2.5 mg of *levothyroxine sodium CRS* (impurity A) and 2.5 mg of *liothyronine sodium CRS* in solution A and dilute to 25 mL with the same solution. Dilute 1.0 mL of this solution to 50.0 mL with solution B.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 10.0 mL with solution B.

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Reference solution (c) Dissolve the contents of a vial of *liothyronine for peak identification CRS* (containing impurities A, B, C, D and E) in solution B and dilute to 1.0 mL with the same solution.

Reference solution (d) Dissolve 20.0 mg of *liothyronine sodium CRS* in 20 mL of solution A. Dilute 4.0 mL of this solution to 20.0 mL with solution B.

Blank solution Solution B.

Column:

— *size*: *l* = 0.15 m, Ø = 4.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase:

— *mobile phase A*: dissolve 9.7 g of *sulfamic acid R* in *water R* and dilute to 2000 mL with the same solvent; add 1.5 g of *sodium hydroxide R* and adjust to pH 2.0 with *2 M sodium hydroxide*;

— *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	75	25
3 - 4	75 → 70	25 → 30
4 - 14	70	30
14 - 44	70 → 20	30 → 80
44 - 54	20	80

Flow rate 1 mL/min.

Detection Spectrophotometer at 225 nm.

Injection 25 µL of the test solution and reference solutions (a), (b) and (c).

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B, C, D and E.

— *relative retention* with reference to liothyronine (retention time = about 14 min): impurity B = about 0.2; impurity E = about 0.5; impurity A = about 1.4; impurity C = about 2; impurity D = about 2.4.

System suitability:

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— *resolution*: minimum 5.0 between the peaks due to impurity A and liothyronine in the chromatogram obtained with reference solution (a).

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *impurity E*: not more than 5 times the area of the peak due to liothyronine in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *impurities B, C*: for each impurity, not more than 3 times the area of the peak due to liothyronine in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *impurity D*: not more than twice the area of the peak due to liothyronine in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the peak due to liothyronine in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than twice the area of the peak due to liothyronine in the chromatogram obtained with reference solution (a) (2.0 per cent);

— *disregard limit*: 0.5 times the area of the peak due to liothyronine in the chromatogram obtained with reference solution (b) (0.05 per cent).

Chlorides

Maximum 2.0 per cent, expressed as NaCl (dried substance).

Dissolve 0.500 g in a 2 g/L solution of *sodium hydroxide R* and dilute to 100 mL with the same solvent. Add 15 mL of *dilute nitric acid R* and titrate with *0.05 M silver nitrate*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.05 M silver nitrate* is equivalent to 2.93 mg of NaCl.

Loss on drying (*2.2.32*)

Maximum 4.0 per cent, determined on 0.500 g by drying *in vacuo* at 60 °C.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection Test solution and reference solution (d).

Calculate the percentage content of $C_{15}H_{11}I_3NNaO_4$ from the declared content of *liothyronine sodium CRS*.

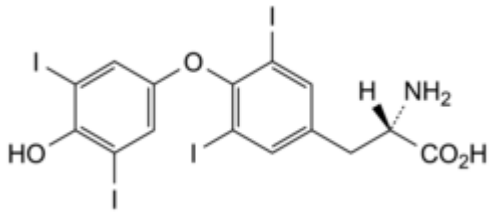
STORAGE

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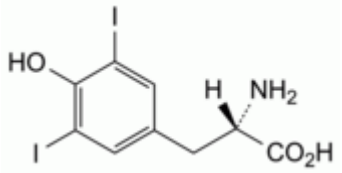
In an airtight container, protected from light, at a temperature between 2 °C and 8 °C.

IMPURITIES

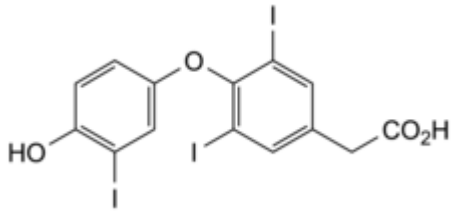
Specified impurities *A, B, C, D, E.*



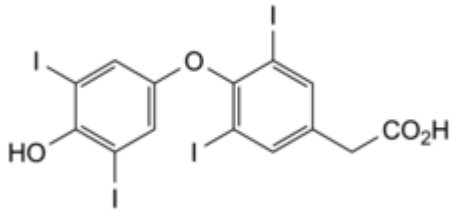
A. (2*S*)-2-amino-3-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl)propanoic acid (levothyroxine),



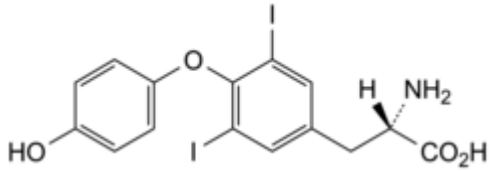
B. (2*S*)-2-amino-3-(4-hydroxy-3,5-diiodophenyl)propanoic acid (diiodotyrosine),



C. [4-(4-hydroxy-3-iodophenoxy)-3,5-diiodophenyl]acetic acid (triiodothyroacetic acid),



D. [4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl]acetic acid (tetraiodothyroacetic acid),



E. (2*S*)-2-amino-3-[4-(4-hydroxyphenoxy)-3,5-diiodophenyl]propanoic acid (diiodothyronine).

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Liothyronine Tablets

General Notices

Action and use

Thyroid hormone replacement.

DEFINITION

Liothyronine Tablets contain Liothyronine Sodium.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of liothyronine sodium, $C_{15}H_{11}I_3NNaO_4$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

In the test for Uniformity of content, record the UV spectrum of the principal peak in the chromatograms obtained with solutions (1) and (2) with a diode array detector in the range of 210 to 400 nm.

The UV spectrum of the principal peak in the chromatogram obtained with solution (1) is concordant with that of the peak in the chromatogram obtained with solution (2);

the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

Plastic containers must not be used to prepare and store solutions.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 100 revolutions per minute.

(b) Use 500 mL of *water*, at a temperature of 37°, as the medium.

(c) Place a number of tablets containing 40 µg of Liothyronine Sodium in the dissolution vessel.

PROCEDURE

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Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

(1) After 45 minutes withdraw a sample of the medium and filter (a GMF filter is suitable), discarding the first 6 mL of the filtrate. To 10 volumes of the resulting solution, add 0.25 volume of a 2% v/v solution of *diethylamine* and 0.4 volume of 0.1M *sodium hydroxide*.

(2) 0.004% w/v of *liothyronine sodium EPCRS* in 0.001M *sodium hydroxide*. Dilute with *water* to produce a solution containing 0.000008% w/v of *liothyronine sodium EPCRS*. To 10 volumes of the resulting solution, add 0.25 volume of a 2% v/v solution of *diethylamine* and 0.4 volume of 0.1M *sodium hydroxide*.

(3) 0.004% w/v of *liothyronine sodium EPCRS* in 0.001M *sodium hydroxide* and 0.004% w/v of *levothyroxine sodium EPCRS* in *water*. Dilute with *water* to produce a solution containing 0.000008% w/v of *liothyronine sodium EPCRS*. To 10 volumes of the resulting solution, add 0.25 volume of a 2% v/v solution of *diethylamine* and 0.4 volume of 0.1M *sodium hydroxide*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *cyanosilyl silica gel for chromatography* (5 µm) (Spherisorb CN is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 225 nm.

(f) Inject 200 µL of each solution.

MOBILE PHASE

5 volumes of *orthophosphoric acid*, 100 volumes of *acetonitrile R1* and 900 volumes of *water*.

When the chromatograms are recorded under the prescribed conditions, the retention time of liothyronine is about 6 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to liothyronine and levothyroxine is at least 1.5.

DETERMINATION OF CONTENT

Calculate the total content of liothyronine sodium, $C_{15}H_{11}I_3NNaO_4$, in the medium from the chromatograms obtained and using the declared content of $C_{15}H_{11}I_3NNaO_4$ in *liothyronine sodium EPCRS*.

LIMITS

The amount of liothyronine sodium released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in solution A. Prepare the solutions immediately before use and protect from light.

Solution A 25 volumes of *methanol* and 75 volumes of 0.1M *sodium hydroxide*.

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(1) To a quantity of powdered tablets containing 0.25 mg of Liothyronine Sodium add 20 mL of solution A. Shake for about 45 minutes and then mix with the aid of ultrasound. Dilute to 25 mL, centrifuge and use the supernatant liquid.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) 0.0002% w/v of *liothyronine sodium impurity BPCRS*.

(4) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Phenomenex Gemini NX C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 45°.

(e) Use a detection wavelength of 225 nm.

(f) Inject 200 µL of each solution.

MOBILE PHASE

Mobile phase A 0.136% w/v of *potassium dihydrogen orthophosphate* in *water*, adjusted to pH 2.2 with *orthophosphoric acid*.

Mobile phase B 100 volumes of mobile phase A, 400 volumes of *methanol* and 500 volumes of *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	70	30	isocratic
5-30	70→35	30→65	linear gradient
30-42	35→25	65→75	linear gradient
42-47	25→5	75→95	linear gradient
47-52	5	95	isocratic
52-53	5→70	95→30	linear gradient
53-62	70	30	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to liothyronine (retention time about 21 minutes) are: impurity E, about 0.6; impurity 1, about 0.9; impurity A, about 1.2; impurity C, about 1.7 and impurity D, about 1.9.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between liothyronine and impurity A is at least 10.0;

the *signal-to-noise ratio* of the principal peak in the chromatogram obtained with solution (4) is at least 25.

LIMITS

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Identify any peak corresponding to impurity 1 in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (3), and multiply the area of this peak by a correction factor of 2.2.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity 1 is not greater than 6 times the area of the principal peak in the chromatogram obtained with solution (2) (6%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the sum of the areas of any *secondary peaks*, excluding impurity 1, is not greater than 3.5 times the area of the principal peak in the chromatogram obtained with solution (2) (3.5%);

the sum of the areas of all *secondary peaks*, is not greater than 8 times the area of the principal peak in the chromatogram obtained with solution (2) (8%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Liothyronine Sodium comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 0.05M *sodium hydroxide*. Carry out the test protected from light.

(1) To one tablet, add 1 mL of 0.05M *sodium hydroxide* and mix with the aid of ultrasound until the tablet is fully dispersed, cool and shake for 2 minutes. Add sufficient 0.05M *sodium hydroxide* to produce a solution containing 0.0005% w/v of Liothyronine Sodium, filter through a glass microfibre filter paper (Whatman GF/C is suitable) and use the filtrate.
(2) 0.00055% w/v of *liothyronine sodium EPCRS*.
(3) 0.0005% w/v of *liothyronine sodium EPCRS* and 0.0005% w/v of *levothyroxine sodium EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *cyanosilyl silica gel for chromatography* (5 µm) (Nucleosil 5 CN is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 225 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

5 volumes of *orthophosphoric acid*, 300 volumes of *acetonitrile R1* and 700 volumes of *water*.

When the chromatograms are recorded under the prescribed conditions, the retention time of liothyronine is about 7 minutes.

SYSTEM SUITABILITY

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The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to liothyronine and levothyroxine is at least 4.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{15}H_{11}I_3NNaO_4$ in each tablet using the declared content of $C_{15}H_{11}I_3NNaO_4$ in *liothyronine sodium EPCRS*.

ASSAY

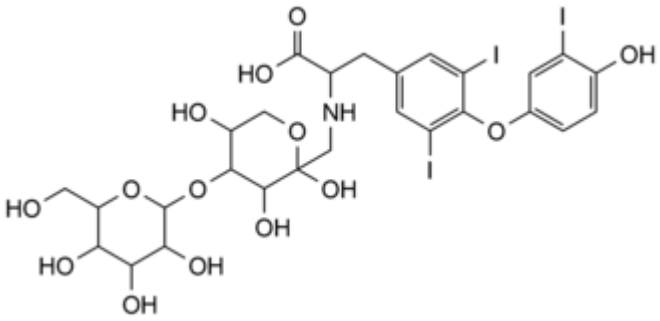
Use the average of the individual results determined in the test for Uniformity of content.

STORAGE

Liothyronine Tablets should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Liothyronine Sodium and:



1. 3-(4-(4-hydroxy-3-iodophenoxy)-3,5-diiodophenyl)-2-(((4,5,6-trihydroxy-3-((3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)tetrahydro-2*H*-pyran-2-yl)methyl)amino)propanoic acid (Liothyronine-lactose maillard impurity).

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Liquefied Phenol

General Notices

Action and use

Antiseptic; antimicrobial preservative; antipruritic.

When Phenol is to be mixed with collodion, fixed oils or paraffins, melted Phenol should be used and not Liquefied Phenol.

DEFINITION

Liquefied Phenol contains not less than 77.0% and not more than 81.5% w/w of Phenol in Purified Water. It is prepared by adding Purified Water to melted Phenol.

CHARACTERISTICS

A colourless or faintly coloured liquid; caustic.

Soluble in *water*; miscible with *ethanol (96%)*, with *ether* and with *glycerol*.

IDENTIFICATION

A. Dissolve 0.6 g in 2 mL of 13.5M *ammonia* and dilute to 100 mL with *water*. To 2 mL of the resulting solution add 0.05 mL of *sodium hypochlorite solution*. A blue colour is produced which becomes progressively more intense.

B. Dilute 1 mL of a 15% w/v solution to 10 mL and add 0.1 mL of *iron(III) chloride solution R1*. A violet colour is produced which is discharged on the addition of *propan-2-ol*.

C. To 1 mL of a 15% w/v solution add 10 mL of *water* and 1 mL of *bromine water*. A white or yellowish white precipitate is produced.

TESTS

Acidity

To 2 mL of a 15% w/v solution add 0.05 mL of *methyl orange solution*. The solution is yellow.

Clarity and colour of solution

A solution of 1.0 mL in 14 mL of *water*, at 20°, is *clear*, Appendix IV A, and not more intensely coloured than *reference solution* R_7 or B_7, Appendix IV B, Method II.

Weight per mL

1.055 to 1.060 g, Appendix V G.

Non-volatile matter

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Non-volatile matter

When heated on a water bath and dried at 105°, leaves not more than 0.05% w/v of residue.

ASSAY

Dissolve 2.5 g in sufficient *water* to produce 1000 mL, transfer 25 mL to a 500 mL glass-stoppered flask and add 50 mL of *0.05M bromine VS* and 5 mL of *hydrochloric acid*, stopper, swirl occasionally over a period of 30 minutes and allow to stand for 15 minutes. Add 5 mL of a 20% w/v solution of *potassium iodide* taking care to avoid loss of bromine, shake thoroughly and titrate with 0.1M *sodium thiosulfate VS* until only a faint yellow colour remains. Add 0.1 mL of *starch mucilage* and 10 mL of *chloroform* and complete the titration with vigorous shaking. Repeat the operation without the material being examined. The difference between the titrations represents the amount of bromine required. Each mL of *0.05M bromine VS* is equivalent to 1.569 mg of C_6H_6O.

STORAGE

Liquefied Phenol should be protected from light. Liquefied Phenol may congeal or deposit crystals if stored at a temperature below 4°. It should be completely melted before use.

LABELLING

The label states ‘contains 80% phenol’.

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Liquid Glucose

General Notices

(Ph. Eur. monograph 1330)

Action and use

Excipient.

Ph Eur

DEFINITION

Aqueous solution containing a mixture of glucose, oligosaccharides and polysaccharides obtained by hydrolysis of starch.

It contains a minimum of 70.0 per cent dry matter.

The degree of hydrolysis, expressed as dextrose equivalent (DE), is not less than 20 (nominal value).

CHARACTERS

Appearance

Clear, colourless or brown, viscous liquid.

Solubility

Miscible with water.

It may partly or totally solidify at room temperature and liquefies again when heated to 50 °C.

IDENTIFICATION

A. Dissolve 0.1 g in 2.5 mL of *water R* and heat with 2.5 mL of *cupri-tartaric solution R*. A red precipitate is formed.

B. Dip, for 1 s, a suitable stick with a reactive pad containing glucose-oxidase, peroxidase and a hydrogen-donating substance, such as tetramethylbenzidine, in a 5 g/L solution of the substance to be examined. Observe the colour of the reactive pad; within 60 s the colour changes from yellow to green or blue.

C. It is a clear, colourless or brown, viscous liquid, miscible with water. The substance may partly or totally solidify at room temperature and liquefies again when heated to 50 °C.

D. Dextrose equivalent (see Tests).

TESTS

Solution S

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Dissolve 25.0 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

pH (*2.2.3*)

4.0 to 6.0.

Mix 1 mL of a 223.6 g/L solution of *potassium chloride R* and 30 mL of solution S.

Sulfur dioxide (*2.5.29*)

Maximum 20 ppm; maximum 400 ppm if intended for the production of lozenges or pastilles obtained by high boiling techniques, provided that the final product contains maximum 50 ppm of sulfur dioxide.

Loss on drying (*2.2.32*)

Maximum 30.0 per cent, determined on 1.000 g. Triturate the sample with 3.000 g of *kieselguhr G R*, previously dried at 80 °C under high vacuum for 2 h, and dry at 80 °C under high vacuum for 2 h.

Sulfated ash (*2.4.14*)

Maximum 0.5 per cent, determined on 1.0 g.

Dextrose equivalent

(DE): within 10 per cent of the nominal value.

Weigh an amount of the substance to be examined equivalent to 2.85-3.15 g of reducing carbohydrates, calculated as dextrose equivalent, into a 500 mL volumetric flask. Dissolve in *water R* and dilute to 500.0 mL with the same solvent. Transfer the solution to a 50 mL burette.

Pipette 25.0 mL of *cupri-tartaric solution R* into a 250 mL flask and add 18.5 mL of the test solution from the burette, mix and add a few glass beads. Place the flask on a hot plate, previously adjusted so that the solution begins to boil after 2 min ± 15 s. Allow to boil for exactly 120 s, add 1 mL of a 1 g/L solution of *methylene blue R* and titrate with the test solution (V_1) until the blue colour disappears. Maintain the solution at boiling throughout the titration.

Standardise the cupri-tartaric solution using a 6.00 g/L solution of *glucose R* (V_0).

Calculate the dextrose equivalent using the following expression:

$$\frac{300 \times V_0 \times 100}{V_1 \times M \times D}$$

V_0	=	total volume of glucose standard solution, in millilitres,
V_1	=	total volume of test solution, in millilitres,
M	=	mass of the sample, in grams,
D	=	percentage content of dry matter in the substance.

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LABELLING

The label states the dextrose equivalent (DE) (= nominal value).

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Liquid Maltitol

General Notices

(Ph. Eur. monograph 1236)

Action and use

Excipient.

Ph Eur

DEFINITION

Aqueous solution of a hydrogenated, partly hydrolysed starch, composed of a mixture of mainly 4-*O*-α-D-glucopyranosyl-D-glucitol (D-maltitol) with D-glucitol (D-sorbitol) and hydrogenated oligo- and polysaccharides.

Content

— *D-maltitol* ($C_{12}H_{24}O_{11}$): minimum 50.0 per cent *m/m* (anhydrous substance) and 95.0 per cent to 105.0 per cent of the content stated on the label;

— *D-sorbitol* ($C_6H_{14}O_6$): maximum 8.0 per cent *m/m* (anhydrous substance);

— *anhydrous substance*: 68.0 per cent *m/m* to 85.0 per cent *m/m*.

CHARACTERS

Appearance

Clear, colourless, syrupy liquid.

Solubility

Miscible with water and with glycerol.

IDENTIFICATION

First identification: A.

Second identification: B, C.

A. Examine the chromatograms obtained in the assay.

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Results The principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with reference solution (a).

B. Thin-layer chromatography (2.2.27).

Test solution Dilute 0.35 g of the substance to be examined to 100 mL with *water R*.

Reference solution (a) Dissolve 20 mg of *maltitol CRS* in *water R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 20 mg of *maltitol CRS* and 20 mg of *sorbitol CRS* in *water R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel G plate R*.

Mobile phase *water R*, *ethyl acetate R*, *propanol R* (10:20:70 *V/V/V*).

Application 2 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Spray with *4-aminobenzoic acid solution R*. Dry in a current of cold air until the acetone is removed. Heat at 100-105 °C for 15 min. Allow to cool and spray with a 2 g/L solution of *sodium periodate R*. Dry in a current of cold air. Heat at 100 °C for 15 min.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and colour to the principal spot in the chromatogram obtained with reference solution (a).

C. To 3 mL of a freshly prepared 100 g/L solution of *pyrocatechol R*, add 6 mL of *sulfuric acid R* while cooling in iced water. To 3 mL of the cooled mixture, add 0.3 mL of solution S (see Tests). Heat gently over a naked-flame for about 30 s. A pink colour develops.

TESTS

Solution S

Dilute 7.0 g to 50 mL with *water R*.

Appearance of solution

Solution S is clear (2.2.1) and colourless (*2.2.2, Method II*).

Conductivity (2.2.38)

Maximum 10 µS·cm^{-1}, measured on undiluted liquid maltitol while gently stirring with a magnetic stirrer.

Reducing sugars

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Maximum 0.2 per cent, calculated as glucose equivalent.

To 5.0 g add 6 mL of *water R*, 20 mL of *cupri-citric solution R* and a few glass beads. Heat so that boiling begins after 4 min and maintain boiling for 3 min. Cool rapidly and add 100 mL of a 2.4 per cent *V/V* solution of *glacial acetic acid R* and 20.0 mL of *0.025 M iodine*. With continuous shaking, add 25 mL of a mixture of 6 volumes of *hydrochloric acid R* and 94 volumes of *water R* and, when the precipitate has dissolved, titrate the excess of iodine with *0.05 M sodium thiosulfate* using 1 mL of *starch solution R*, added towards the end of the titration, as indicator. Not less than 12.8 mL of *0.05 M sodium thiosulfate* is required.

Water (*2.5.12*)

15.0 per cent *m/m* to 32.0 per cent *m/m*, determined on 0.100 g. Use as solvent a mixture of equal volumes of *anhydrous methanol R* and *formamide R1*. Carry out the titration at about 50 °C.

ASSAY

Liquid chromatography (*2.2.29*).

Test solution Mix 1.00 g of the solution to be examined with 20 mL of *water R* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dissolve 50.0 mg of *maltitol CRS* in 2 mL of *water R* and dilute to 5.0 mL with the same solvent.

Reference solution (b) Dissolve 8.0 mg of *sorbitol CRS* in 2 mL of *water R* and dilute to 5.0 mL with the same solvent.

Reference solution (c) Dissolve 50 mg of *maltitol R* and 50 mg of *sorbitol R* in 2 mL of *water R* and dilute to 5 mL with the same solvent.

Column:

— *size*: *l* = 0.3 m, Ø = 7.8 mm;

— *stationary phase*: *strong cation-exchange resin (calcium form) R* (9 µm);

— *temperature*: 85 ± 2 °C.

Mobile phase Degassed *water for chromatography R*.

Flow rate 0.5 mL/min.

Detection Differential refractometer maintained at a constant temperature (e.g. 35 °C).

Injection 20 µL.

Run time 3 times the retention time of maltitol.

Relative retention With reference to maltitol (retention time = about 16 min): sorbitol = about 1.8.

System suitability Reference solution (c):

— *resolution*: minimum 2.0 between the peaks due to maltitol and sorbitol.

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Calculate the percentage contents of D-maltitol ($C_{12}H_{24}O_{11}$) and D-sorbitol ($C_6H_{14}O_6$) taking into account the assigned contents of *maltitol CRS* and *sorbitol CRS*.

LABELLING

The label states the content of D-maltitol.

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Liquid Paraffin

General Notices

(Ph. Eur. monograph 0239)

Action and use

Faecal softener.

Preparations

Liquid Paraffin Oral Emulsion

Liquid Paraffin and Magnesium Hydroxide Oral Emulsion

Ph Eur

DEFINITION

Purified mixture of liquid saturated hydrocarbons obtained from petroleum.

CHARACTERS

Appearance

Colourless, transparent, oily liquid, free from fluorescence in daylight.

Solubility

Practically insoluble in water, slightly soluble in ethanol (96 per cent), miscible with hydrocarbons.

IDENTIFICATION

First identification: A, C.

Second identification: B, C.

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *Ph. Eur. reference spectrum of liquid paraffin*.

B. In a test tube cautiously boil 1 mL with 1 mL of *0.1 M sodium hydroxide*, with continuous shaking, for about 30 s. On cooling to room temperature, 2 phases separate. To the aqueous phase add 0.1 mL of *phenolphthalein solution R*. The solution becomes red.

C. Viscosity (see Tests).

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TESTS

Acidity or alkalinity

To 10 mL add 20 mL of boiling *water R* and shake vigorously for 1 min. Separate the aqueous layer and filter. To 10 mL of the filtrate, add 0.1 mL of *phenolphthalein solution R*. The solution is colourless. Not more than 0.1 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator to pink.

Relative density (*2.2.5*)

0.827 to 0.890.

Viscosity (*2.2.9*)

110 mPa·s to 230 mPa·s.

Polycyclic aromatic hydrocarbons

Use reagents for ultraviolet spectrophotometry.

Introduce 25.0 mL into a 125 mL separating funnel with unlubricated ground-glass parts (stopper, stopcock). Add 25 mL of *hexane R* which has been previously shaken twice with one-fifth its volume of *dimethyl sulfoxide R*. Mix and add 5.0 mL of *dimethyl sulfoxide R*. Shake vigorously for 1 min and allow to stand until 2 clear layers are formed. Transfer the lower layer to a 2^d separating funnel, add 2 mL of *hexane R* and shake the mixture vigorously. Allow to stand until 2 clear layers are formed. Separate the lower layer and measure its absorbance (*2.2.25*) between 260 nm and 420 nm, using as the compensation liquid the clear lower layer obtained by vigorously shaking 5.0 mL of *dimethyl sulfoxide R* with 25 mL of *hexane R* for 1 min. Prepare a 7.0 mg/L reference solution of *naphthalene R* in *trimethylpentane R* and measure the absorbance of the solution at the absorption maximum at 275 nm, using *trimethylpentane R* as the compensation liquid. At no wavelength between 260 nm and 420 nm does the absorbance of the test solution exceed one-third that of the reference solution at 275 nm.

Readily carbonisable substances

Use a ground-glass-stoppered tube about 125 mm long and 18 mm in internal diameter, graduated at 5 mL and 10 mL; wash with hot *water R* (temperature at least 60 °C), *acetone R*, *heptane R* and finally with *acetone R*, dry at 100-110 °C. Cool in a desiccator. Introduce 5 mL of the substance to be examined and add 5 mL of *nitrogen-free sulfuric acid R1*. Insert the stopper and shake as vigorously as possible, in the longitudinal direction of the tube, for 5 s. Loosen the stopper, immediately place the tube in a water-bath, avoiding contact of the tube with the bottom or side of the bath, and heat for 10 min. After 2 min, 4 min, 6 min and 8 min, remove the tube from the bath and shake as vigorously as possible, in the longitudinal direction of the tube for 5 s. At the end of 10 min of heating, remove the tube from the water-bath and allow to stand for 10 min. Centrifuge at 2000 *g* for 5 min. The lower layer is not more intensely coloured (*2.2.2, Method I*) than a mixture of 0.5 mL of blue primary solution, 1.5 mL of red primary solution, 3.0 mL of yellow primary solution and 2 mL of a 10 g/L solution of *hydrochloric acid R*.

Solid paraffins

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Dry a suitable quantity of the substance to be examined by heating at 100 °C for 2 h and cool in a desiccator over *sulfuric acid R*. Place in a glass tube with an internal diameter of about 25 mm, close the tube and immerse in a bath of iced water. After 4 h, the liquid is sufficiently clear for a black line, 0.5 mm wide, to be easily seen against a white background held vertically behind the tube.

STORAGE

Protected from light.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristic may be relevant for liquid paraffin used as emollient in ointments or as lubricant in tablets and capsules.

Viscosity

(see Tests).

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Liquid Paraffin and Magnesium Hydroxide Oral Emulsion

General Notices

DEFINITION

Liquid Paraffin and Magnesium Hydroxide Oral Emulsion is a 25% v/v dispersion of Liquid Paraffin in an aqueous suspension containing 6% w/w of hydrated magnesium oxide prepared from a suitable grade of Light Magnesium Oxide.

The oral emulsion complies with the requirements stated under Oral Liquids and with the following requirements.

Content of magnesium hydroxide, $Mg(OH)_2$

5.1 to 7.0% w/w.

Content of liquid paraffin

19.7 to 24.0% w/w.

ASSAY

For magnesium hydroxide

Dilute 4 g with 50 mL of *water*, shake with 25 mL of *0.5M hydrochloric acid VS* and titrate with *0.5M sodium hydroxide VS* using *methyl orange solution* as indicator. Each mL of *0.5M hydrochloric acid VS* is equivalent to 14.58 mg of $Mg(OH)_2$.

For liquid paraffin

Extract the neutralised liquid obtained in the Assay for magnesium hydroxide with three 25 mL quantities of a mixture of equal volumes of *petroleum spirit* (*boiling range, 40° to 60°*) and *ether*, wash the combined extracts with two 10-mL quantities of *water*, discard the washings, evaporate the solvent, add 5 mL of *acetone* and again evaporate. Repeat the addition and evaporation of *acetone* until the residue is free from water, dry at 105° for 15 minutes and weigh.

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Liquid Paraffin Oral Emulsion

General Notices

Liquid Paraffin Emulsion

DEFINITION

Liquid Paraffin Oral Emulsion contains Liquid Paraffin in a suitable vehicle.

The oral emulsion complies with the requirements stated under Oral Liquids and with the following requirements.

Content of liquid paraffin

44.0 to 49.0% w/w.

ASSAY

To 5 g add 10 mL of *water*, extract with two 40-mL quantities of a mixture of 2 volumes of *ethanol* (*96%*), 3 volumes of *petroleum spirit* (*boiling range, 40° to 60°*) and 3 volumes of *ether* and then with 30 mL of a mixture of equal volumes of *petroleum spirit* (*boiling range, 40° to 60°*) and *ether*. Wash the combined extracts with 15 mL of 0.5M *sodium hydroxide* and then with 15 mL of *water*, evaporate the solvent, add 5 mL of *acetone* and evaporate again. Repeat the addition and evaporation of *acetone* until the residue is free from water, dry at 105° for 15 minutes and weigh.

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Liquid Sorbitol (Crystallising)

General Notices

Sorbitol Solution (70 per cent) (Crystallising)

(Ph. Eur. monograph 0436)

Action and use

Excipient.

Ph Eur

DEFINITION

Aqueous solution of a hydrogenated, partly hydrolysed starch.

Content

— anhydrous substance: 68.0 per cent *m/m* to 72.0 per cent *m/m*,

— D-glucitol (D-sorbitol, $C_6H_{14}O_6$): 92.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Clear, colourless, syrupy liquid, miscible with water.

IDENTIFICATION

A. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with reference solution (a).

B. To 7.0 g add 40 mL of *water R* and 6.4 g of *disodium tetraborate R*, allow to stand for 1 h, shaking occasionally, and dilute to 50.0 mL with *water R*. Filter if necessary. The angle of rotation (2.2.7) is 0° to + 1.5°.

C. It is a clear, syrupy liquid at a temperature of 25 °C.

TESTS

Appearance of solution

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The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Dilute 7.0 g to 50 mL with *water R*.

Conductivity (*2.2.38*)

Maximum 10 µS·cm^{-1} measured on the undiluted liquid sorbitol (crystallising) while gently stirring with a magnetic stirrer.

Reducing sugars

Maximum 0.2 per cent calculated as glucose equivalent.

To 5.0 g add 6 mL of *water R*, 20 mL of *cupri-citric solution R* and a few glass beads. Heat so that boiling begins after 4 min and maintain boiling for 3 min. Cool rapidly and add 100 mL of a 2.4 per cent *V/V* solution of *glacial acetic acid R* and 20.0 mL of *0.025 M iodine*. With continuous shaking, add 25 mL of a mixture of 6 volumes of *hydrochloric acid R* and 94 volumes of *water R* and, when the precipitate has dissolved, titrate the excess of iodine with *0.05 M sodium thiosulfate* using 1 mL of *starch solution R*, added towards the end of the titration, as indicator. Not less than 12.8 mL of *0.05 M sodium thiosulfate* is required.

Water (*2.5.12*)

28.0 per cent to 32.0 per cent *m/m*, determined on 0.100 g.

ASSAY

Liquid chromatography (*2.2.29*).

Test solution Mix 1.00 g of the substance to be examined with 20 mL of *water R* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dissolve 65.0 mg of *sorbitol CRS* in 2 mL of *water R* and dilute to 5.0 mL with the same solvent.

Reference solution (b) Dissolve 65 mg of *mannitol R* and 65 mg of *sorbitol R* in 2 mL of *water R* and dilute to 5 mL with the same solvent.

Column:

— *size*: *l* = 0.3 m, Ø = 7.8 mm,

— *stationary phase*: *strong cation-exchange resin (calcium form) R* (9 µm),

— *temperature*: 85 ± 1 °C.

Mobile phase Degassed *water for chromatography R*.

Flow rate 0.5 mL/min.

Detection Differential refractometer maintained at a constant temperature (e.g. 35 °C).

Injection 20 µL.

Run time Twice the retention time of sorbitol.

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Relative retention With reference to sorbitol (retention time = about 27 min): mannitol = about 0.8.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to mannitol and to sorbitol.

Calculate the percentage content of $C_6H_{14}O_6$ taking into account the assigned content of *sorbitol CRS*.

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Liquid Sorbitol (Non-crystallising)

General Notices

Sorbitol Solution (70 per cent) (Non-crystallising)

(Ph. Eur. monograph 0437)

Action and use

Excipient.

Ph Eur

DEFINITION

Aqueous solution of a hydrogenated, partly hydrolysed starch.

Content

— anhydrous substance: 68.0 per cent *m/m* to 72.0 per cent *m/m*,

— D-glucitol (D-sorbitol, $C_6H_{14}O_6$): 72.0 per cent to 92.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Clear, colourless, syrupy liquid, miscible with water.

IDENTIFICATION

A. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with reference solution (a).

B. To 7.0 g add 40 mL of *water R* and 6.4 g of *disodium tetraborate R*. Allow to stand for 1 h, shaking occasionally, and dilute to 50.0 mL with *water R*. Filter if necessary. The angle of rotation (2.2.7) is + 1.5° to + 3.5°.

C. It is a clear, syrupy liquid at 25 °C.

TESTS

Appearance of solution

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The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Dilute 7.0 g to 50 mL with *water R*.

Conductivity (*2.2.38*)

Maximum 10 $\mu S \cdot cm^{-1}$ measured on the undiluted liquid sorbitol (non crystallising) while gently stirring with a magnetic stirrer.

Reducing sugars

Maximum 0.2 per cent calculated as glucose equivalent.

To 5.0 g add 6 mL of *water R*, 20 mL of *cupri-citric solution R* and a few glass beads. Heat so that boiling begins after 4 min and maintain boiling for 3 min. Cool rapidly and add 100 mL of a 2.4 per cent *V/V* solution of *glacial acetic acid R* and 20.0 mL of *0.025 M iodine*. With continuous shaking, add 25 mL of a mixture of 6 volumes of *hydrochloric acid R* and 94 volumes of *water R* and, when the precipitate has dissolved, titrate the excess of iodine with *0.05 M sodium thiosulfate* using 1 mL of *starch solution R*, added towards the end of the titration, as indicator. Not less than 12.8 mL of *0.05 M sodium thiosulfate* is required.

Reducing sugars after hydrolysis

Maximum 9.3 per cent calculated as glucose equivalent.

To 6.0 g add 35 mL of *water R*, 40 mL of *1 M hydrochloric acid* and a few glass beads. Boil under a reflux condenser for 4 h. Cool and neutralise with *dilute sodium hydroxide solution R* using 0.2 mL of *bromothymol blue solution R1* as indicator. Cool and dilute to 100.0 mL with *water R*. To 3.0 mL of the solution add 5 mL of *water R*, 20 mL of *cupri-citric solution R* and a few glass beads. Heat so that boiling begins after 4 min and maintain boiling for 3 min. Cool rapidly and add 100 mL of a 2.4 per cent *V/V* solution of *glacial acetic acid R* and 20.0 mL of *0.025 M iodine*. With continuous shaking, add 25 mL of a mixture of 6 volumes of *hydrochloric acid R* and 94 volumes of *water R*. When the precipitate has dissolved, titrate the excess of iodine with *0.05 M sodium thiosulfate* using 1 mL of *starch solution R*, added towards the end of the titration, as indicator. Not less than 8.0 mL of *0.05 M sodium thiosulfate* is required.

Water (*2.5.12*)

28.0 per cent to 32.0 per cent *m/m*, determined on 0.100 g.

ASSAY

Liquid chromatography (*2.2.29*).

Test solution Mix 1.00 g of the substance to be examined with 20 mL of *water R* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dissolve 55.0 mg of *sorbitol CRS* in 2 mL of *water R* and dilute to 5.0 mL with the same solvent.

Reference solution (b) Dissolve 55 mg of *mannitol R* and 55 mg of *sorbitol R* in 2 mL of *water R* and dilute to 5 mL with the same solvent.

Column:

— *size*: *l* = 0.3 m, Ø = 7.8 mm,

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— *stationary phase*: *strong cation-exchange resin (calcium form) R* (9 µm),

— *temperature*: 85 ± 1 °C.

Mobile phase Degassed *water for chromatography R*.

Flow rate 0.5 mL/min.

Detection Differential refractometer maintained at a constant temperature (e.g. 35 °C).

Injection 20 µL.

Run time Twice the retention time of sorbitol.

Relative retention With reference to sorbitol (retention time = about 27 min): mannitol = about 0.8.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to mannitol and to sorbitol.

Calculate the percentage content of $C_6H_{14}O_6$ taking into account the assigned content of *sorbitol CRS*.

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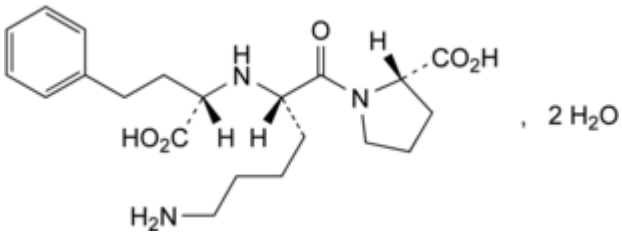
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Lisinopril Dihydrate

General Notices

(Ph. Eur. monograph 1120)



$C_{21}H_{31}N_3O_5,2H_2O$ 441.5 *83915-83-7*

Action and use

Angiotensin converting enzyme inhibitor.

Preparations

Lisinopril Oral Solution

Lisinopril Tablets

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DEFINITION

(2*S*)-1-[(2*S*)-6-Amino-2-[[(1*S*)-1-carboxy-3-phenylpropyl]amino]hexanoyl]pyrrolidine-2-carboxylic acid dihydrate.

Content

98.5 per cent to 101.5 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Soluble in water, practically insoluble in anhydrous ethanol and in heptane.

IDENTIFICATION

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IDENTIFICATION

A. Specific optical rotation (2.2.7): -47 to -43 (anhydrous substance).

Dissolve 0.5 g in *zinc acetate solution R* and dilute to 50.0 mL with the same solvent.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *lisinopril dihydrate CRS*.

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in mobile phase A and dilute to 10.0 mL with mobile phase A.

Reference solution (a) Dissolve 5 mg of *lisinopril for system suitability A CRS* (containing impurities A and E) in mobile phase A and dilute to 1 mL with mobile phase A.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (c) Dissolve the contents of a vial of *lisinopril impurity F CRS* in 1 mL of mobile phase A.

Reference solution (d) Dissolve 5 mg of *lisinopril for peak identification CRS* (containing impurity G) in mobile phase A and dilute to 1 mL with mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 50 °C.

Mobile phase:

— *mobile phase A*: mix 3 volumes of *acetonitrile R1* and 97 volumes of a 3.12 g/L solution of *sodium dihydrogen phosphate R* previously adjusted to pH 3.8 with *dilute phosphoric acid R*;

— *mobile phase B*: mix 20.5 volumes of *acetonitrile R1* and 79.5 volumes of a 3.12 g/L solution of *sodium dihydrogen phosphate R* previously adjusted to pH 3.5 with *dilute phosphoric acid R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	100	0
2 - 37	100 → 0	0 → 100

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
37 - 62	0	100

Flow rate 1.6 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 50 µL.

Identification of impurities Use the chromatogram supplied with *lisinopril for system suitability A CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A and E; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity F; use the chromatogram supplied with *lisinopril for peak identification CRS* and the chromatogram obtained with reference solution (d) to identify the peak due to impurity G.

Relative retention With reference to lisinopril (retention time = about 14 min): impurity A = about 0.7; impurity E = about 1.2; impurity F = about 1.9; impurity G = about 2.9.

System suitability:

— *resolution*: minimum 1.5 between the peaks due to lisinopril and impurity E in the chromatogram obtained with reference solution (a);

— *signal-to-noise ratio*: minimum 45 for the principal peak in the chromatogram obtained with reference solution (b).

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity F by 2.1;

— for each impurity, use the concentration of lisinopril dihydrate in reference solution (b).

Limits:

— *impurities A, E, F*: for each impurity, maximum 0.2 per cent;

— *impurity G*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent; disregard any peak with a retention time less than 3 min.

Water (*2.5.12*)

8.0 per cent to 9.5 per cent, determined on 0.200 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

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ASSAY

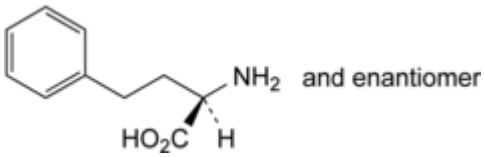
Dissolve 0.350 g in 50 mL of *water R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*) at the 1st point of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 40.55 mg of $C_{21}H_{31}N_3O_5$.

IMPURITIES

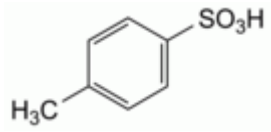
Specified impurities *A, E, F, G.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D, H, I, J.*

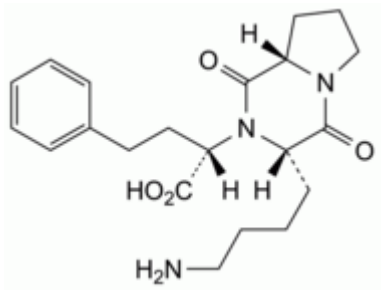


and enantiomer

A. (2*RS*)-2-amino-4-phenylbutanoic acid,

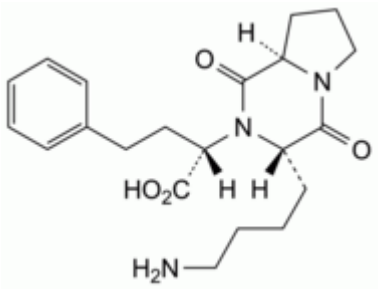


B. 4-methylbenzenesulfonic acid,

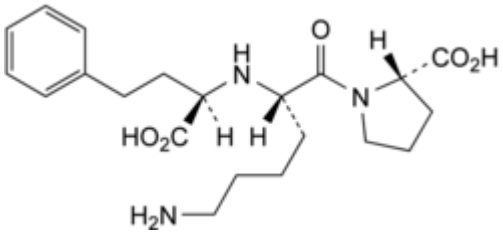


C. (2*S*)-2-[(3*S*,8a*S*)-3-(4-aminobutyl)-1,4-dioxohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-4-phenylbutanoic acid (*S*,*S*,*S*-diketopiperazine),

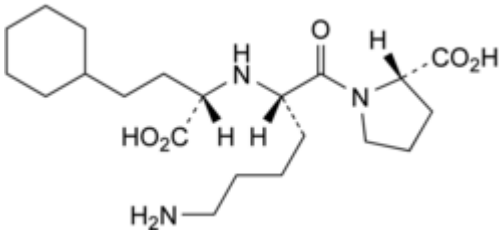
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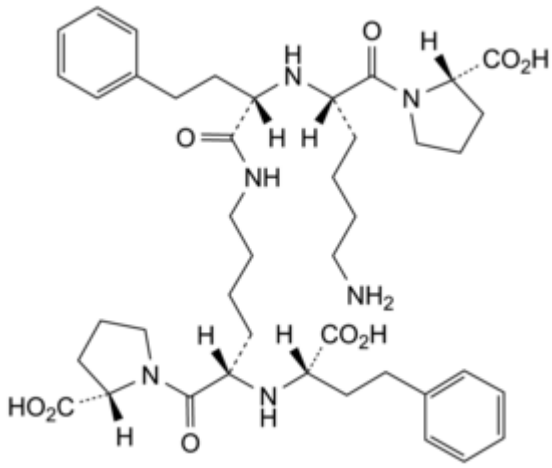
D. (2*S*)-2-[(3*S*,8a*R*)-3-(4-aminobutyl)-1,4-dioxohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-4-phenylbutanoic acid (*R*,*S*,*S*-diketopiperazine),



E. (2*S*)-1-[(2*S*)-6-amino-2-[[(1*R*)-1-carboxy-3-phenylpropyl]amino]hexanoyl]pyrrolidine-2-carboxylic acid (lisinopril *R*,*S*,*S*-isomer),

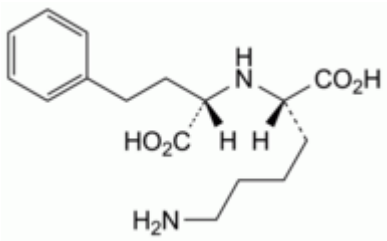


F. (2*S*)-1-[(2*S*)-6-amino-2-[[(1*S*)-1-carboxy-3-cyclohexylpropyl]amino]hexanoyl]pyrrolidine-2-carboxylic acid (cyclohexyl analogue),

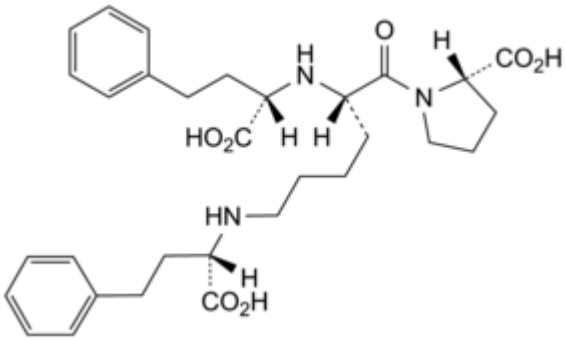


G. (2*S*)-1-[(2*S*)-6-amino-2-[[(2*S*)-1-[[(5*S*)-5-[[(1*S*)-1-carboxy-3-phenylpropyl]amino]-6-[(2*S*)-2-carboxypyrrolidin-1-yl]-6-oxohexyl]amino]-1-oxo-4-phenylbutan-2-yl]amino]hexanoyl]pyrrolidine-2-carboxylic acid (lisinopril dimer),

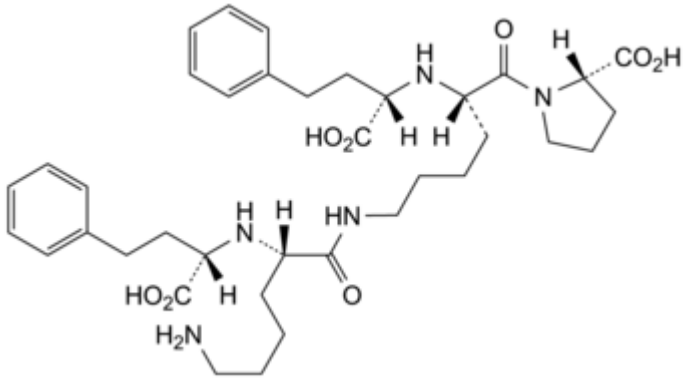
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H. (2*S*)-6-amino-2-[[(1*S*)-1-carboxy-3-phenylpropyl]amino]hexanoic acid,



I. (2*S*)-1-[(2*S*)-2,6-bis[[(1*S*)-1-carboxy-3-phenylpropyl]amino]hexanoyl]pyrrolidine-2-carboxylic acid,



J. (2*S*)-1-[(2*S*)-6-[(2*S*)-6-amino-2-[[(1*S*)-1-carboxy-3-phenylpropyl]amino]hexanamido]-2-[[(1*S*)-1-carboxy-3-phenylpropyl]amino]hexanoyl]pyrrolidine-2-carboxylic acid.

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Lisinopril Oral Solution

General Notices

Action and use

Angiotensin converting enzyme inhibitor.

DEFINITION

Lisinopril Oral Solution is a solution of Lisinopril Dihydrate in a suitable aqueous vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of anhydrous lisinopril, $C_{21}H_{31}N_3O_5$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a volume of the oral solution with sufficient of a mixture of 20 volumes of *water* and 80 volumes of *methanol* to produce a solution containing the equivalent of 0.05% w/v of anhydrous lisinopril.

(2) 0.055% w/v of *lisinopril dihydrate BPCRS* in a mixture of 20 volumes of *water* and 80 volumes of *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.

(b) Pre-wash the plate with *methanol* and allow to dry in air before use.

(c) Use the mobile phase as described below.

(d) Apply 20 µL of each solution.

(e) Develop the plate to 15 cm.

(f) After removal of the plate, dry in air, spray with a 0.2% w/v solution of *ninhydrin* in *absolute ethanol*, heat at 105° for 10 minutes and examine in daylight.

MOBILE PHASE

Equal volumes of *glacial acetic acid*, *butan-1-ol*, *ethyl acetate* and *water*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

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B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is the same as that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a volume of the oral solution containing the equivalent of 5 mg of anhydrous lisinopril to 20 mL with mobile phase A.

(2) Dilute 1 volume of solution (1) to 200 volumes with mobile phase A.

(3) Dilute 1 volume of solution (2) to 5 volumes with mobile phase A.

(4) Heat 20 mg of *lisinopril dihydrate BPCRS* at 175° under nitrogen for 4 hours. Allow to cool and dissolve the residue in 10 mL of mobile phase A (generation of lisinopril diketopiperazine).

(5) Boil 20 mL of a 0.1% w/v solution of *lisinopril dihydrate BPCRS* in *water* under a reflux condenser for 2 hours. Allow to cool to room temperature, dilute 5 mL of the resulting solution to 20 mL with mobile phase A and mix thoroughly.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography compatible with 100 per cent aqueous mobile phases* (4 µm) (Phenomenex Synergi Hydro-RP is suitable) fitted with a guard column (4 mm × 3 mm) packed with the same material.

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 210 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 25 volumes of *methanol* and 75 volumes of a solution prepared by dissolving 13.7 g of *sodium dihydrogen orthophosphate*, 2.1 g of *disodium hydrogen orthophosphate dihydrate* and 6.8 g of *tetrabutylammonium hydrogen sulfate* in 2000 mL of *water* and adjusting the pH to 5.7 with either 5M *sodium hydroxide* or *orthophosphoric acid*.

Mobile phase B *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-30	100	0	isocratic
30-31	100→50	0→50	linear gradient
31-39	50	50	isocratic
39-40	50→100	50→0	linear gradient
40-60	100	0	re-equilibration

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When the chromatograms are recorded under the prescribed conditions, the relative retention with reference to lisinopril (retention time about 8 minutes) is: lisinopril diketopiperazine, about 2.6.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3), the *signal-to-noise ratio* of the peak due to lisinopril is at least 15;

in the chromatogram obtained with solution (5), a peak on the tail of the lisinopril peak is visible.

LIMITS

Identify any peak corresponding to lisinopril diketopiperazine in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (4), and multiply the area of this peak by a correction factor of 1.4.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to lisinopril diketopiperazine is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%);

the area of any other *secondary peak* is not greater than 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the sum of the areas of any such peaks is not greater than 1.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.6%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a weighed quantity of the oral solution containing the equivalent of 5 mg of anhydrous lisinopril to 20 mL with mobile phase A.
(2) 0.027% w/v of *lisinopril dihydrate BPCRS* in mobile phase A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used but using isocratic elution and mobile phase A.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_{21}H_{31}N_3O_5$, weight in volume, using the declared content of $C_{21}H_{31}N_3O_5$ in *lisinopril dihydrate BPCRS*.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of anhydrous lisinopril.

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Lisinopril Tablets

General Notices

Action and use

Angiotensin converting enzyme inhibitor.

DEFINITION

Lisinopril Tablets contain Lisinopril Dihydrate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of anhydrous lisinopril, $C_{21}H_{31}N_3O_5$

92.5 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing the equivalent of 10 mg of anhydrous lisinopril with 2 mL of *water* and add 8 mL of *methanol*.

(2) 0.11% w/v of *lisinopril dihydrate BPCRS* in a mixture of 20 volumes of *water* and 80 volumes of *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* GF_{254}.

(b) Pre-wash the plate with *methanol* and allow to dry in air before use.

(c) Use the mobile phase as described below.

(d) Apply 20 µL of each solution.

(e) Develop the plate to 15 cm.

(f) After removal of the plate, dry in air, spray with a 0.2% w/v solution of *ninhydrin* in *absolute ethanol*, heat at 105° for 10 minutes and examine in daylight.

MOBILE PHASE

Equal volumes of *glacial acetic acid*, *butan-1-ol*, *ethyl acetate* and *water*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

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B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the peak due to lisinopril in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 30 minutes withdraw a 10 mL sample of the medium and filter. Use the filtered medium, suitably diluted with 0.1M *hydrochloric acid*, if necessary.

(2) Dissolve a quantity of *lisinopril dihydrate BPCRS* in sufficient of the dissolution medium to produce a solution of the same concentration as that expected for solution (1).

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the total content of lisinopril, $C_{21}H_{31}N_3O_5$, in the medium from the chromatograms obtained and using the declared content of $C_{21}H_{31}N_3O_5$, in *lisinopril dihydrate BPCRS*.

LIMITS

The amount of anhydrous lisinopril released is not less than 80% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in a mixture of 1 volume of *methanol* and 4 volumes of *water*.

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing the equivalent of 20 mg of anhydrous lisinopril in 80 mL for 5 minutes. Dilute to 100 mL, mix with the aid of ultrasound for a further 10 minutes ensuring that the temperature of the solution does not exceed room temperature, and filter through a 0.45-µm membrane filter.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) Dilute 1 volume of solution (2) to 10 volumes.

(4) Heat 20 mg of *lisinopril dihydrate BPCRS* at 175° under nitrogen for 4 hours. Allow to cool and dissolve the residue in 10 mL (generation of lisinopril diketopiperazine).

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (10 µm) (Lichrosorb RP-8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 215 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

200 volumes of *acetonitrile R1* and 800 volumes of solution A.

Solution A 0.125% w/v of *sodium hexanesulfonate* in solution B.

Solution B 0.408% w/v of *anhydrous potassium dihydrogen orthophosphate* adjusted to pH 2.0 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions, the relative retention with reference to lisinopril (retention time about 6 minutes) is: lisinopril diketopiperazine, about 1.9.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (4), the *resolution* between the peaks due to lisinopril and lisinopril diketopiperazine is at least 5.0;

in the chromatogram obtained with solution (3), the *signal to noise ratio* of the peak due to lisinopril is at least 13.

LIMITS

Identify any peak corresponding to lisinopril diketopiperazine in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (4), and multiply the area of this peak by a correction factor of 1.3.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to lisinopril diketopiperazine is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%);

the area of any other *secondary peak* is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the sum of the areas of any other *secondary peaks* is not greater than 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.6%);

the sum of the content of lisinopril diketopiperazine and the nominal total content of any other impurities is not more than 2%.

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

ASSAY

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Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in a mixture of 1 volume of *methanol* and 4 volumes of *water*.

(1) Mix with the aid of ultrasound 10 whole tablets for 5 minutes, dilute to a suitable volume and further mix with the aid of ultrasound again for about 10 minutes ensuring that the temperature of the solution does not exceed room temperature, and filter through a 0.45-µm membrane filter. Dilute a volume of the filtrate to produce a solution containing the equivalent of 0.02% w/v of anhydrous lisinopril.

(2) 0.022% w/v of *lisinopril dihydrate BPCRS*.

(3) Heat 20 mg of *lisinopril dihydrate BPCRS* at 175° under nitrogen for 4 hours. Allow to cool and dissolve the residue in 10 mL (generation of lisinopril diketopiperazine).

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to lisinopril and lisinopril diketopiperazine is at least 5.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{31}N_3O_5$ in the tablets using the declared content of $C_{21}H_{31}N_3O_5$ in *lisinopril dihydrate BPCRS*.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of anhydrous lisinopril.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities C and D listed under *Lisinopril Dihydrate*.

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Lithium Carbonate

General Notices

(Ph. Eur. monograph 0228)

Li_2CO_3 73.9 *554-13-2*

Action and use

Prophylaxis of affective disorders.

Preparations

Lithium Carbonate Tablets

Lithium Carbonate Prolonged-release Tablets

Ph Eur

DEFINITION

Content

98.5 per cent to 100.5 per cent.

CHARACTERS

Appearance

White or almost white powder.

Solubility

Slightly soluble in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. When moistened with *hydrochloric acid R*, it gives a red colour to a non-luminous flame.

B. Dissolve 0.2 g in 1 mL of *hydrochloric acid R*. Evaporate to dryness on a water-bath. The residue dissolves in 3 mL of *ethanol (96 per cent) R*.

C. It gives the reaction of carbonates (*2.3.1*).

TESTS

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Solution S

Suspend 10.0 g in 30 mL of *distilled water R* and dissolve by the addition of 22 mL of *nitric acid R*. Add *dilute sodium hydroxide solution R* until the solution is neutral and dilute to 100 mL with *distilled water R*.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Chlorides (*2.4.4*)

Maximum 200 ppm.

Dilute 2.5 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 200 ppm.

Disperse 1.25 g in 5 mL of *distilled water R* and dissolve by adding 5 mL of *hydrochloric acid R1*. Boil for 2 min. Cool and add *dilute sodium hydroxide solution R* until neutral. Dilute to 25 mL with *distilled water R*.

Arsenic (*2.4.2, Method A*)

Maximum 2 ppm, determined on 0.5 g.

Calcium (*2.4.3*)

Maximum 200 ppm.

Dilute 5 mL of solution S to 15 mL with *distilled water R*.

Iron (*2.4.9*)

Maximum 20 ppm.

Dilute 5 mL of solution S to 10 mL with *water R*.

Magnesium (*2.4.6*)

Maximum 150 ppm.

Dilute 1 mL of solution S to 10 mL with *water R*. Dilute 6.7 mL of this solution to 10 mL with *water R*.

Potassium

Maximum 300 ppm.

Atomic emission spectrometry (*2.2.22, Method I*).

Test solution Dissolve 1.0 g in 10 mL of *hydrochloric acid R1* and dilute to 50.0 mL with *water R*.

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Reference solutions Prepare the reference solutions using a solution of *potassium chloride R* containing 500 µg of K per millilitre, diluted as necessary with *water R*.

Wavelength 766.5 nm.

Sodium

Maximum 300 ppm.

Atomic emission spectrometry (*2.2.22, Method I*).

Test solution Dissolve 1.0 g in 10 mL of *hydrochloric acid R1* and dilute to 50.0 mL with *water R*.

Reference solutions Prepare the reference solutions using a solution of *sodium chloride R* containing 500 µg of Na per millilitre, diluted as necessary with *water R*.

Wavelength 589 nm.

ASSAY

Dissolve 0.250 g in 50 mL of *carbon dioxide-free water R*. Titrate with *1 M hydrochloric acid*, determining the end-point potentiometrically (*2.2.20*). Read the volume added at the 2nd point of inflection.

1 mL of *1 M hydrochloric acid* is equivalent to 36.95 mg of Li_2CO_3.

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Lithium Carbonate Prolonged-release Tablets

General Notices

Prolonged-release Lithium Carbonate Tablets

Lithium Carbonate Prolonged-release Tablets from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

DEFINITION

Lithium Carbonate Prolonged-release Tablets contain Lithium Carbonate and are formulated so as to release the medicament over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of lithium carbonate. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of lithium carbonate, Li_2CO_3

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A small quantity of the powdered tablets, when moistened with *hydrochloric acid* and introduced on a platinum wire into a flame, imparts a carmine red colour to the flame.

ASSAY

Weigh and powder 20 tablets. Add a quantity of the powder containing 1 g of Lithium Carbonate to 100 mL of *water*, add 50 mL of *1M hydrochloric acid VS* and boil for 1 minute to remove the carbon dioxide. Cool and titrate the excess of acid with *1M sodium hydroxide VS* using *methyl orange solution* as indicator. Each mL of *1M hydrochloric acid VS* is equivalent to 36.95 mg of Li_2CO_3.

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Lithium Carbonate Tablets

General Notices

DEFINITION

Lithium Carbonate Tablets contain Lithium Carbonate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of lithium carbonate, Li_2CO_3

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A small quantity of the powdered tablets, when moistened with *hydrochloric acid* and introduced on a platinum wire into a flame, imparts a carmine red colour to the flame.

ASSAY

Weigh and powder 20 tablets. Add a quantity of the powder containing 1 g of Lithium Carbonate to 100 mL of *water*, add 50 mL of *1M hydrochloric acid VS* and boil for 1 minute to remove the carbon dioxide. Cool and titrate the excess of acid with *1M sodium hydroxide VS* using *methyl orange solution* as indicator. Each mL of *1M hydrochloric acid VS* is equivalent to 36.95 mg of Li_2CO_3.

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Lithium Citrate

General Notices

(Ph. Eur. monograph 0621)

$C_6H_5Li_3O_7,4H_2O$ 282.0

Action and use

Prophylaxis of affective disorders.

Preparation

Lithium Citrate Oral Solution

Ph Eur

DEFINITION

Trilithium 2-hydroxypropane-1,2,3-tricarboxylate tetrahydrate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, fine crystalline powder.

Solubility

Freely soluble in water, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. When moistened with *hydrochloric acid R*, it gives a red colour to a non-luminous flame.

B. Dilute 3 mL of solution S (see Tests) to 10 mL with *water R*. Add 3 mL of *potassium ferriperiodate solution R*. A white or yellowish-white precipitate is formed.

C. To 1 mL of solution S add 4 mL of *water R*. The solution gives the reaction of citrates (*2.3.1*).

TESTS

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Solution S

Dissolve 10.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

To 10 mL of solution S add 0.1 mL of *phenolphthalein solution R*. Not more than 0.2 mL of *0.1 M hydrochloric acid* or *0.1 M sodium hydroxide* is required to change the colour of the indicator.

Readily carbonisable substances

To 0.20 g of the powdered substance to be examined add 10 mL of *sulfuric acid R* and heat in a water-bath at 90 ± 1 °C for 60 min. Cool rapidly. The solution is not more intensely coloured than reference solution Y_2 or GY_2 (*2.2.2, Method II*).

Chlorides (*2.4.4*)

Maximum 100 ppm.

Dilute 5 mL of solution S to 15 mL with *water R*.

Oxalates

Maximum 300 ppm, calculated as anhydrous oxalate ion.

Dissolve 0.50 g in 4 mL of *water R*, add 3 mL of *hydrochloric acid R* and 1 g of *zinc R* in granules and heat on a water-bath for 1 min. Allow to stand for 2 min, decant the liquid into a test-tube containing 0.25 mL of a 10 g/L solution of *phenylhydrazine hydrochloride R* and heat to boiling. Cool rapidly, transfer to a graduated cylinder and add an equal volume of *hydrochloric acid R* and 0.25 mL of *potassium ferricyanide solution R*. Shake and allow to stand for 30 min. Any pink colour in the solution is not more intense than that in a standard prepared at the same time and in the same manner using 4 mL of a 0.05 g/L solution of *oxalic acid R*.

Sulfates (*2.4.13*)

Maximum 500 ppm.

To 3 mL of solution S add 2 mL of *hydrochloric acid R1* and dilute to 17 mL with *distilled water R*. Prepare the reference solution using 15 mL of a mixture of 2 mL of *hydrochloric acid R1* and 15 mL of *sulfate standard solution (10 ppm SO_4) R* and compare the opalescence after 15 min.

Water (*2.5.12*)

24.0 per cent to 27.0 per cent, determined on 0.100 g. After adding the substance to be examined, stir for 15 min before titrating. Carry out a blank titration.

ASSAY

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Dissolve 80.0 mg in 50 mL of *anhydrous acetic acid R*, heating to about 50 °C. Allow to cool. Titrate with *0.1 M perchloric acid*, using 0.25 mL of *naphtholbenzein solution R* as indicator, until the colour changes from yellow to green.

1 mL of *0.1 M perchloric acid* is equivalent to 7.00 mg of $C_6H_5Li_3O_7$.

STORAGE

In an airtight container.

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Lithium Citrate Oral Solution

General Notices

DEFINITION

Lithium Citrate Oral Solution is a solution of Lithium Citrate in a suitable flavoured vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of lithium citrate, $C_6H_5Li_3O_7,4H_2O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. The oral solution, when diluted with an equal volume of *3M hydrochloric acid* and introduced on a platinum wire into a flame, imparts a carmine red colour to the flame.

B. Boil 5 mL of the oral solution with 5 mL of *mercury(II) sulfate solution* and add a few drops of *dilute potassium permanganate solution*. The solution is decolorised and an off-white precipitate is produced.

TESTS

Acidity

pH, 4.0 to 5.5, Appendix V L.

ASSAY

Dilute a weighed quantity of the oral solution containing 0.4 g of Lithium Citrate to 1000 mL with *water* and add 0.05 mL of *polysorbate 80*. Determine the content of lithium by Method I for *atomic emission spectrophotometry*, Appendix II D, measuring at 671 nm and using *lithium standard solution (100 ppm Li),* suitably diluted with *water* and 0.05 mL of *polysorbate 80*, to prepare the standard solutions. Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of lithium citrate, weight in volume, taking each mg of Li to be equivalent to 13.54 mg of $C_6H_5Li_3O_7,4H_2O$.

STORAGE

Lithium Citrate Oral Solution should be protected from light and stored at a temperature not exceeding 30°.

LABELLING

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The quantity of the active ingredient in a suitable dose-volume is stated (1) as the amount of Lithium Citrate; (2) as the concentration of lithium ions in millimoles; (3) in terms of the equivalent amount of Lithium Carbonate.

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Live Biotherapeutic Products for Human Use

General Notices

(Ph. Eur. monograph 3053)

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DEFINITION

Live biotherapeutic products (LBP) are medicinal products containing live micro-organisms (bacteria or yeasts) for human use.

LBP are administered orally or vaginally and are available in different pharmaceutical forms.

LBP may contain one or multiple microbial strains from the same or different species of micro-organisms. The quantity of living bacteria or yeasts is determined by counting viable and culturable micro-organisms of the intended strain(s).

Faecal microbiota transplantation (FMT) and products intended as gene therapy agents are excluded from this monograph.

PRODUCTION

GENERAL PROVISIONS

The production method for a given product must have been shown to yield consistently an LBP comparable with the batch(es) of proven clinical efficacy and safety in man. Suitable in-process controls ensure that the production process is under control and consistently produces LBP of defined quality.

LBP are produced using a seed-lot system. The methods of preparation are designed to maintain the viability of the micro-organisms. Stabilisers and other excipients of controlled microbiological quality may be added.

Where LBP are produced using substances of human or animal origin, the requirements of general chapter *5.1.7. Viral safety* apply. The production process is optimised to consistently minimise or remove adventitious agents and toxic or other impurities.

In the production of a final lot of LBP, the number of subcultures of a bacterium or yeast, from the master seed lot, shall not exceed that used for production of the LBP shown to be satisfactory in clinical trials with respect to quality, safety and efficacy.

Consistency of production is important to ensure the quality of LBP. Limits for process parameters and for tests carried out during production and on the final lot may be in the form of maximum values, minimum values, or tolerances around a given value. Limits are based on the results found for batches tested clinically and those used to demonstrate consistency of production. These limits may subsequently be refined on a statistical basis in the light of production data.

CHARACTERISATION OF THE MICRO-ORGANISM(S)

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The characterisation of the micro-organism(s) is carried out at the strain level. The strain used for master seed lots is identified by historical records that include information on its origin, subsequent manipulation and the tests used to characterise the strain. Characterisation includes determination of the phenotype and genotype of the strain, using methods such as macroscopic and microscopic methods, biochemical tests, molecular genetic tests, sequencing or mass spectrometry. The strain must be phenotypically and genotypically stable. Antimicrobial resistance is determined and any resistance transferable from the micro-organism to the relevant microbiota is investigated and excluded. The presence of virulence factors must be investigated and evaluated with respect to safety.

For products to be administered orally, survivability of the micro-organism(s) in the human gut is demonstrated by *in vitro* gastric acid and bile resistance testing.

SEED-LOT SYSTEM

A seed-lot system is used. Suitable measures are taken to ensure that adventitious agents and toxic or other impurities are not present in master or working seed-lots. When a master seed-lot is replaced, the new master seed-lot must be fully characterised and the critical steps in the production process revalidated to the extent required to demonstrate that no adverse change has occurred in the quality, safety and efficacy of the product.

CULTURE MEDIA

Culture media are sterile and, as far as possible, free from ingredients known to cause toxic, allergic or other undesirable reactions in humans; if inclusion of such ingredients is necessary, it is demonstrated that the residual amount in the final lot does not adversely affect product safety.

GROWTH AND HARVESTING

Each strain is cultured and the culture is examined for purity by suitable tests. These tests may include inoculation into suitable media, examination of colony morphology and microscopic examination. The culture is harvested under defined conditions and may be stored under appropriate conditions.

INTERMEDIATE PRODUCTS

When intermediate products are stored, a storage period justified by stability data is established for each intermediate.

Test for microbial contamination

Each intermediate is shown to comply with defined in-process limits using a suitable method.

FINAL BULK

The final bulk may contain a single strain or a mixture of 2 or more strains. Stabilisers and other excipients may be added depending on the dosage form.

FINAL LOT

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When the final lot is an aqueous suspension, it is distributed into sterile, tamper-evident containers (3.2).

The final lot complies with the requirements under Identification, Tests and Assay. Certain tests prescribed for the final lot may be carried out on the final bulk, provided it has been demonstrated that subsequent manufacturing operations do not affect compliance.

IDENTIFICATION

Each micro-organism is identified by a suitable method.

TESTS

Appearance

It complies with the established specification.

Microbial contamination

Microbiological examination of LBP is performed according to the methods given in general chapters 2.6.36 and 2.6.38.

When an acceptance criterion for microbial contamination is prescribed it is interpreted as follows:

— 10^1 CFU: maximum acceptable count = 20;

— 10^2 CFU: maximum acceptable count = 200;

— 10^3 CFU: maximum acceptable count = 2000.

Acceptance criteria based upon the aerobic microbial contamination count (AMCC) and the combined yeasts/ moulds contamination count (YMCC) are given in Table 3053.-1.

Table 3053.-1. – *Acceptance criteria for microbiological quality of LBP*

Route of administration	AMCC* (CFU/g or CFU/mL)	YMCC** (CFU/g or CFU/mL)	Specified micro-organisms***
Non-aqueous preparations for oral use	10^3	10^2	Absence of *Escherichia coli***** (1 g or 1 mL)
Aqueous preparations for oral use	10^2	10^1	Absence of *Escherichia coli***** (1 g or 1 mL)
Vaginal use	10^2	10^1	Absence of *Pseudomonas aeruginosa* (1 g or 1 mL) Absence of *Staphylococcus aureus* (1 g or 1 mL) Absence of *Candida albicans* (1 g or 1 mL)

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Route of administration	AMCC* (CFU/g or CFU/mL)	YMCC** (CFU/g or CFU/mL)	Specified micro-organisms***
* If it is not possible to determine the AMCC due to the absence of a suitable method for the LBP, then test for the absence of the following specified micro-organisms using the methods in general chapter 2.6.38: bile-tolerant Gram-negative bacteria(1) (1 g or 1 mL), *P. aeruginosa* (1 g or 1 mL), *S. aureus* (1 g or 1 mL), *Salmonella* spp. (10 g or 10 mL). Tests for other pathogens may be carried out based on a risk assessment (e.g. specific environmental contaminants). (1) If the LBP consists of *E. coli*, test for the absence of Enterobacteriaceae and other Gram-negative bacteria using suitable culture media instead of testing for the absence of bile-tolerant Gram-negative bacteria. ** If it is not possible to determine the YMCC due to the absence of a suitable method for the LBP, then test for the absence of *C. albicans* and test for pathogenic moulds based on a risk assessment. *** If the LBP consists of *Bacillus* spp. spores, test for the absence of *Bacillus cereus* in addition to the tests described in the table. **** If the LBP consists of *E. coli*, the test for *E. coli* should be replaced by another test for the absence of faecal contaminants by testing for *Enterococcus faecalis* and *Enterococcus faecium* as indicators. A search for other pathogens may be carried out based on a risk assessment (e.g. pathogenic *E. coli*).			

In addition to the micro-organisms listed in Table 3053.-1, tests for other pathogens may be carried out based on a risk assessment (e.g. specific environmental contaminants, anaerobic contaminants (e.g. Clostridia)).

The significance of other micro-organisms recovered is evaluated in terms of:

— intended recipient: risk may differ for neonates, infants, the debilitated;

— use of immunosuppressive agents, corticosteroids;

— presence of disease, wounds, organ damage.

pH (2.2.3)

It complies with the limit approved for the particular product.

Water (2.5.12), Loss on drying (2.2.32) or Water activity (2.9.39)

It complies with the limit approved for the particular product.

ASSAY

Number of live micro-organisms

The number of micro-organisms, expressed in CFU, is determined by a suitable microbial enumeration test, for example by the pour-plate method or surface-spread method.

The potency of each strain is expressed in CFU/g, CFU/mL, or CFU/unit; it is not less than the stated value or it is within the stated range.

The potency may be expressed in number of viable cells/mL based on viable-cell assay, in agreement with the competent authority.

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STORAGE

Liquid LBP are not to be frozen.

LABELLING

The label states:

— the name of the strain(s);

— the route of administration;

— the storage conditions;

— the expiry date;

— the potency of each strain expressed in CFU/mL, CFU/g, CFU/unit or viable cells/mL;

— the name of any stabilisers and other excipients;

— where applicable, for freeze-dried preparations to be reconstituted before use:

— the name, composition and volume of the reconstituting liquid to be added;

— the storage conditions and the period of time within which the LBP is to be used after reconstitution.

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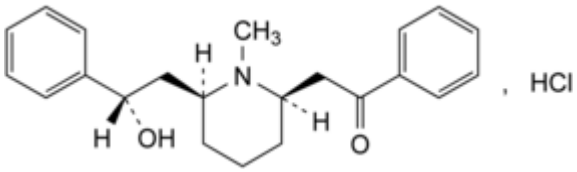
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Lobeline Hydrochloride

General Notices

(Ph. Eur. monograph 1988)



$C_{22}H_{28}ClNO_2$ 373.9 *134-63-4*

Action and use

Respiratory stimulant.

Ph Eur

DEFINITION

2-[(2*R*,6*S*)-6-[(2*S*)-2-Hydroxy-2-phenylethyl]-1-methylpiperidin-2-yl]-1-phenylethanone hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, microcrystalline powder.

Solubility

Sparingly soluble in water, freely soluble in ethanol (96 per cent), soluble in methylene chloride.

IDENTIFICATION

First identification: A, B.

Second identification: B, C.

A. Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *lobeline hydrochloride CRS*.

B. Solution S (see Tests) gives reaction (a) of chlorides (*2.3.1*).

C. Examine the chromatograms obtained in the test for foreign alkaloids.

Results The principal spot in the chromatogram obtained with test solution (b) is similar in position and size to the principal spot in the chromatogram obtained with reference solution (b).

TESTS

Solution S

Dissolve 0.250 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 25.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

4.6 to 6.4 for solution S.

Specific optical rotation (*2.2.7*)

-55 to -59 (dried substance), determined on solution S.

Foreign alkaloids

Thin-layer chromatography (*2.2.27*).

Test solution (a) Dissolve 0.10 g of the substance to be examined in *methanol R* and dilute to 5.0 mL with the same solvent.

Test solution (b) Dilute 1 mL of test solution (a) to 10 mL with *methanol R*.

Reference solution (a) Dilute 0.1 mL of test solution (a) to 10 mL with *methanol R*.

Reference solution (b) Dissolve 10 mg of *lobeline hydrochloride CRS* in *methanol R* and dilute to 5 mL with the same solvent.

Plate *TLC silica gel GF_{254} plate R*.

Mobile phase *diethylamine R*, *cyclohexane R* (10:90 *V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying At 120 °C.

Detection Examine in ultraviolet light at 254 nm.

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Limits In the chromatogram obtained with test solution (a):

— *any impurity*: any spot, apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (a) (1 per cent).

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 10.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of *phenytoin CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase. To 1 mL of the solution add 0.1 mL of the test solution and dilute to 25 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm,

— *stationary phase*: spherical *end-capped octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Dissolve 1.0 g of *sodium methanesulfonate R* and 2.50 g of *disodium hydrogen phosphate dihydrate R* in a mixture of 3 volumes of a 6.7 per cent *V/V* solution of *phosphoric acid R*, 29 volumes of *acetonitrile R* and 70 volumes of *water R* and dilute to 1000 mL with the same mixture of solvents.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 10 µL.

Run time 2 times the retention time of lobeline which is about 17 min.

System suitability Reference solution (b):

— *resolution*: minimum 4.0 between the peaks due to phenytoin and to lobeline.

Limits:

— *any impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent),

— *total*: maximum of 2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent),

— *disregard level*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Sulfates (2.4.13)

Maximum 0.1 per cent, determined on solution S.

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Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g *in vacuo*.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on the residue obtained in the test for loss on drying.

ASSAY

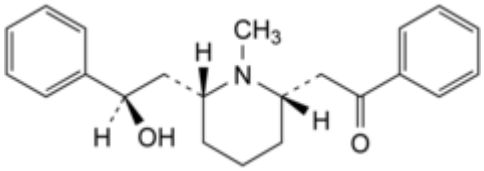
Dissolve 0.300 g in 50 mL of *ethanol (96 per cent) R*. Add 5 mL of *0.01 M hydrochloric acid*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 37.39 mg of $C_{22}H_{28}ClNO_2$.

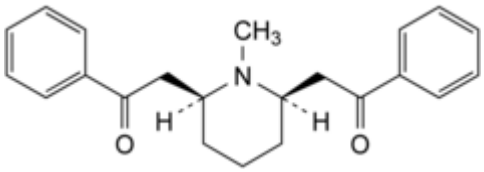
STORAGE

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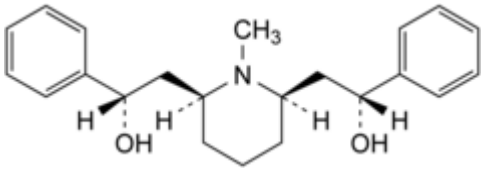
IMPURITIES



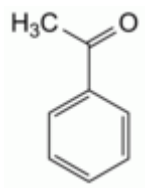
A. 2-[(2*S*,6*R*)-6-[(2*R*)-2-hydroxy-2-phenylethyl]-1-methylpiperidin-2-yl]-1-phenylethanone ((+)-lobeline),



B. 2,2′-[(2*R*,6*S*)-1-methylpiperidine-2,6-diyl]bis(1-phenylethanone) (lobelanine),



C. *meso*-(1*R*,1′*S*)-2,2′-[(2*R*,6*S*)-1-methylpiperidine-2,6-diyl]bis(1-phenylethanol) (lobelanidine),



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D. acetophenone.

Ph Eur

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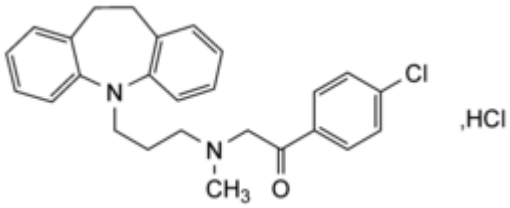
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Lofepramine Hydrochloride

General Notices



$C_{26}H_{27}ClN_2O,HCl$ 455.4 *26786-32-3*

Action and use

Monoamine reuptake inhibitor; tricyclic antidepressant.

Preparation

Lofepramine Tablets

DEFINITION

Lofepramine Hydrochloride is 5-(3-[*N*-(4-chlorophenacyl)-*N*-methylamino]propyl)10,11-dihydro-5*H*-dibenz[*b,f*]azepine hydrochloride. It contains not less than 98.5% and not more than 101.0% of $C_{26}H_{27}ClN_2O,HCl$, calculated with reference to the dried substance.

CHARACTERISTICS

A fine, yellowish white to greenish yellow powder.

Very soluble in *ethanol (96%)* and in *methanol*; slightly soluble in *acetone*; very slightly soluble in *water*.

It exhibits polymorphism.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the reference spectrum of *lofepramine hydrochloride (form A) (RS 399A)*.

B. 2 mL of a 1% w/v solution in *ethanol (96%)* complies with the test for *chlorides*, Appendix VI.

TESTS

Related substances

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Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Solution (1) contains 0.1% w/v of the substance being examined in the mobile phase. For solution (2) dilute 1 volume of solution (1) to 200 volumes with the mobile phase. Solution (3) contains 0.0002% w/v each of *desipramine hydrochloride BPCRS* and *imipramine hydrochloride BPCRS* in the mobile phase.

Inject 20 µL of solutions (1) and (2). Inject 20 µL of solution (3) and allow the chromatography to continue for 4 times the retention time of the principal peak.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with *base-deactivated end-capped octylsilyl silica gel for chromatography* (5 µm) (Lichrospher 60 RP-select B is suitable) maintained at 50°, (b) as the mobile phase with a flow rate of 1.5 mL per minute a 0.09% w/v solution of *sodium dodecyl sulfate* in a mixture of 550 volumes of *acetonitrile*, 325 volumes of *water* and 125 volumes of a buffer solution of pH 1.0 containing 0.015% w/v of *glycine*, 0.018% w/v of *sodium chloride* and 0.44% w/v of *hydrochloric acid* and (c) a detection wavelength of 254 nm.

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 0.9.

In the chromatogram obtained with solution (1) the area of any *secondary peak* is not greater than the area of the peak in the chromatogram obtained with solution (2) (0.5%) and the sum of the areas of any *secondary peaks* is not greater than twice the area of the peak in the chromatogram obtained with solution (2) (1%).

Loss on drying

When dried at a temperature of 100° at a pressure not exceeding 0.2 kPa, loses not more than 0.5% of its weight. Use 1 g.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Solution (1) contains 0.02% w/v of the substance being examined in the mobile phase. Solution (2) contains 0.02% w/v of *lofepramine hydrochloride BPCRS* in the mobile phase.

The chromatographic procedure described under the test for Related substances may be used.

Inject 20 µL of each solution.

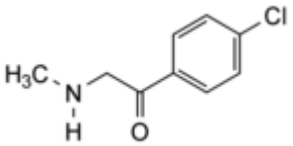
Calculate the content of $C_{26}H_{27}ClN_2O$,HCl from the chromatograms obtained and using the declared content of $C_{26}H_{27}ClN_2O$,HCl in *lofepramine hydrochloride BPCRS*.

STORAGE

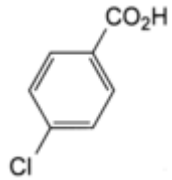
Lofepramine Hydrochloride should be kept in an airtight container and protected from light.

IMPURITIES

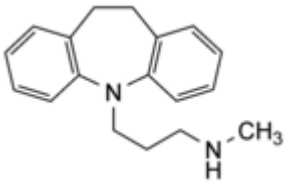
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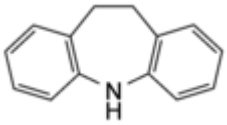
A. 1-methylamino-4′-chloroacetophenone,



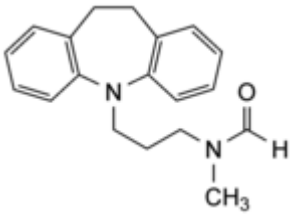
B. 4-chlorobenzoic acid,



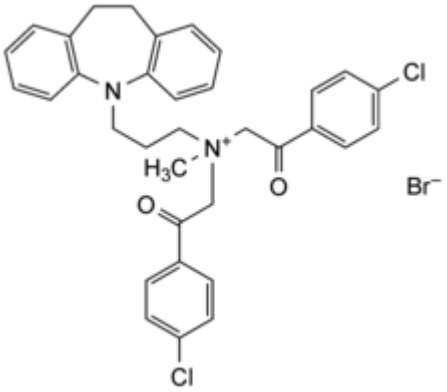
C. desipramine,



D. iminodibenzyl,

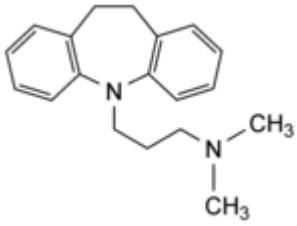


E. *N*-formyldesipramine,

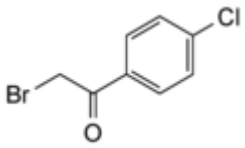


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F. *N,N*-bis(4′-chlorophenacyl)desipramine bromide,



G. imipramine,



H. 2-bromo-4′-chloroacetophenone.

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Lofepramine Tablets

General Notices

Action and use

Monoamine reuptake inhibitor; tricyclic antidepressant.

DEFINITION

Lofepramine Tablets contain Lofepramine Hydrochloride. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of lofepramine, $C_{26}H_{27}ClN_2O$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Remove the majority of the coating. Wash the tablet with *dichloromethane* to remove the remaining coating. Place the tablet core in an ultrasound bath for 30 minutes with 10 mL of *dichloromethane*, filter the resulting suspension through a 0.45-µm PTFE filter; evaporate the filtrate to dryness using a rotary evaporator and a water bath at 30° and dry the residue at 50° at a pressure not exceeding 2 kPa for 1 hour. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of lofepramine hydrochloride (form B) *(RS 399B)*.

B. In the Assay, the chromatogram obtained with solution (2) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (1).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) shake a quantity of tablets containing the equivalent of 0.35 g of lofepramine for 1 hour with 50 mL of a mixture of 250 volumes of *acetonitrile*, 250 volumes of *water* and 1 volume of *orthophosphoric acid (85%)*, dilute the resulting solution to 200 mL with the same solvent mixture, centrifuge and use the supernatant liquid. For solution (2) dilute 1 volume of solution (1) to 100 volumes with the same solvent mixture. Solution (3) contains 0.0002% w/v each of *desipramine hydrochloride BPCRS* and *imipramine hydrochloride BPCRS* in the mobile phase.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octylsilyl silica gel for chromatography* (5 µm) (Lichrospher 60 RP-select B is suitable) and maintained at 50°, (b) as the mobile phase with a flow rate of 1.5 mL per minute a 0.09% w/v solution of *sodium dodecyl sulfate* in a mixture of 550 volumes of *acetonitrile*, 325 volumes of *water*

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and 125 volumes of a buffer solution of pH 1.0 containing 0.015% w/v of *glycine*, 0.018% w/v of *sodium chloride* and 0.44% w/v of *hydrochloric acid* and (c) a detection wavelength of 254 nm.

Inject 20 µL of each solution. For solution (1) allow the chromatography to continue for 4 times the retention time of the principal peak.

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 0.9.

In the chromatogram obtained with solution (1), the area of any *secondary peak* is not greater than the area of the peak in the chromatogram obtained with solution (2) (1%) and the sum of the areas of any *secondary peaks* is not greater than twice the area of the peak in the chromatogram obtained with solution (2) (2%). Disregard any peak with a retention time of less than 3 minutes.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) shake 10 tablets for 1 hour with 300 mL of a mixture of 250 volumes of *acetonitrile*, 250 volumes of *water* and 1 volume of *orthophosphoric acid (85%)* and dilute to 500 mL with the same solvent mixture, mix and centrifuge; dilute the supernatant liquid with the same solvent mixture to produce a solution containing the equivalent of 0.028% w/v of lofepramine. Solution (2) contains 0.030% w/v of *lofepramine hydrochloride BPCRS* in the solvent mixture. Solution (3) contains 0.0002% w/v each of *desipramine hydrochloride BPCRS* and *imipramine hydrochloride BPCRS* in the mobile phase.

The chromatographic procedure described under Related substances may be used.

Inject 20 µL of each solution. The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 0.9.

Calculate the content of $C_{26}H_{27}ClN_2O$ in the tablets using the declared content of $C_{26}H_{27}ClN_2O$ in *lofepramine hydrochloride BPCRS*.

STORAGE

Lofepramine Tablets should be protected from light and moisture.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of lofepramine.

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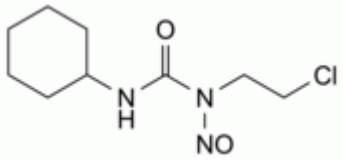
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Lomustine

General Notices

(Ph. Eur. monograph 0928)



$C_9H_{16}ClN_3O_2$ 233.7 *13010-47-4*

Action and use

Cytotoxic alkylating agent.

Preparation

Lomustine Capsules

Ph Eur

DEFINITION

1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

Yellow, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in acetone and in methylene chloride, soluble in ethanol (96 per cent).

Carry out the tests protected from light and prepare all the solutions immediately before use.

IDENTIFICATION

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Infrared absorption spectrophotometry (2.2.24).

Comparison lomustine CRS.

TESTS

Related substances

Liquid chromatography (2.2.29).

Phosphate buffer solution Dissolve 1.36 g of potassium dihydrogen phosphate R in 900 mL of water R, adjust to pH 3.0 with dilute phosphoric acid R and dilute to 1000 mL with water R.

Test solution Dissolve 50.0 mg of the substance to be examined in acetonitrile R1 and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 5.0 mg of dicyclohexylurea R (impurity C) in methanol R and dilute to 10.0 mL with the same solvent. Dilute 1.0 mL of the solution to 50.0 mL with acetonitrile R1. Mix 1.0 mL of this solution and 1.0 mL of the test solution.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with acetonitrile R1. Dilute 1.0 mL of this solution to 10.0 mL with acetonitrile R1.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: acetonitrile R1, phosphate buffer solution (20:80 *V/V*);

— *mobile phase B*: phosphate buffer solution, acetonitrile R1 (24:76 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	75	25
2 - 17	75 → 40	25 → 60
17 - 34	40 → 30	60 → 70
34 - 42	30	70

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 205 nm.

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Injection 20 µL.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity C.

Relative retention With reference to lomustine (retention time = about 23 min): impurity C = about 0.7.

System suitability Reference solution (a):

— *resolution*: minimum 5.0 between the peaks due to impurity C and lomustine.

Calculation of percentage contents:

— for each impurity, use the concentration of lomustine in reference solution (b).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent.

Chlorides (2.4.4)

Maximum 500 ppm.

Dissolve 0.24 g in 4 mL of *methanol R* and add 20 mL of *water R*. Allow to stand for 20 min and filter. To 10 mL of the filtrate, add 5 mL of *methanol R*. When preparing the standard, replace the 5 mL of *water R* with 5 mL of *methanol R*.

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 1.000 g by drying in a desiccator at a pressure not exceeding 0.7 kPa for 24 h.

ASSAY

Dissolve 0.200 g in about 3 mL of *ethanol (96 per cent) R* and add 20 mL of a 200 g/L solution of *potassium hydroxide R* and boil under a reflux condenser for 2 h. Add 75 mL of *water R* and 4 mL of *nitric acid R*. Cool and titrate with *0.1 M silver nitrate*, determining the end-point potentiometrically (2.2.20). Carry out a blank titration.

1 mL of *0.1 M silver nitrate* is equivalent to 23.37 mg of $C_9H_{16}ClN_3O_2$.

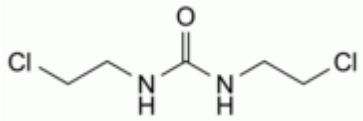
STORAGE

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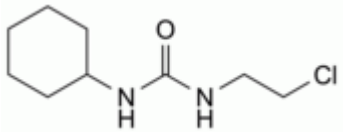
IMPURITIES

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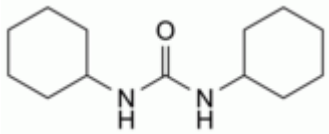
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C.*



A. 1,3-bis(2-chloroethyl)urea,



B. 1-(2-chloroethyl)-3-cyclohexylurea,



C. 1,3-dicyclohexylurea.

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Lomustine Capsules

General Notices

Action and use

Cytotoxic alkylating agent.

DEFINITION

Lomustine Capsules contain Lomustine.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of lomustine, $C_9H_{16}ClN_3O_2$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

Carry out the following procedure in subdued light. Shake a quantity of the contents of the capsules containing 0.2 g of Lomustine with 10 mL of *methanol*, filter and evaporate the filtrate to dryness using a rotary evaporator on a water bath maintained at not more than 60°. The residue, after drying at 60° at a pressure not exceeding 0.7 kPa for 30 minutes, complies with the following tests.

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of lomustine *(RS 204)*.

B. *Melting point*, about 88°, Appendix V A.

TESTS

Related substances

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *methanol*.

(1) Shake a quantity of the contents of the capsules containing 0.20 g of Lomustine with 10 mL of *methanol* and filter.

(2) Dilute 1 volume of solution (1) to 25 volumes and further dilute 1 volume of this solution to 10 volumes.

(3) Dilute 1 volume of solution (2) to 2 volumes.

(4) Dissolve 10 mg of *lomustine EPCRS* and 10 mg of *1,3-dicyclohexylurea* and dilute to 10 mL.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel*.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

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(e) After removal of the plate, dry it at 110° for 1 hour. At the bottom of a chromatography tank, place an evaporating dish containing a mixture of 1 volume of 7M *hydrochloric acid*, 1 volume of *water* and 2 volumes of a 1.5% w/v solution of *potassium permanganate*, close the tank and allow to stand for 15 minutes. Place the dried plate in the tank and close the tank. Leave the plate in contact with the chlorine vapour for 5 minutes. Withdraw the plate and place it in a current of cold air until the excess of chlorine is removed and an area of coating below the line of application does not give a blue colour with a drop of *potassium iodide and starch solution*. Spray with *potassium iodide and starch solution*.

MOBILE PHASE

20 volumes of *glacial acetic acid* and 80 volumes of *toluene*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (4) shows two clearly separated principal spots.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.4%) and not more than one such spot is more intense than the spot in the chromatogram obtained with solution (3) (0.2%).

B. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *methanol*.

(1) Shake a quantity of the contents of the capsules containing 0.20 g of Lomustine with 10 mL of *methanol* and filter.

(2) Dilute 2 volumes of solution (1) to 100 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 to 10 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 230 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

50 volumes of *methanol* and 50 volumes of *water*.

When the chromatograms are recorded in the prescribed conditions, the retention time of lomustine is about 25 minutes.

LIMITS

In the chromatogram obtained with solution (1) the sum of the areas of any *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (2%).

Disregard any peak with an area less than 0.05 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

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Carry out the following procedure in subdued light. Shake a quantity of the mixed contents of 20 capsules containing 40 mg of Lomustine with 70 mL of *ethanol (96%)* for 20 minutes, dilute to 100 mL with the same solvent and filter. Dilute 5 mL of the filtrate to 100 mL with *ethanol (96%)* and measure the *absorbance* of the resulting solution at the maximum at 230 nm, Appendix II B. Calculate the content of $C_9H_{16}ClN_3O_2$ taking 260 as the value of A(1%, 1 cm) at the maximum at 230 nm.

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Loperamide Capsules

General Notices

Action and use

Opioid receptor agonist; antidiarrhoeal.

DEFINITION

Loperamide Capsules contain Loperamide Hydrochloride.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of loperamide hydrochloride, $C_{29}H_{33}ClN_2O_2,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the contents of the capsules containing 10 mg of Loperamide Hydrochloride with 10 mL of *methanol* for 5 minutes and filter.

(2) 0.1% w/v of *loperamide hydrochloride BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

2.5 volumes of *acetate buffer pH 4.7*, 17.5 volumes of *methanol*, 27 volumes of *ethyl acetate* and 53 volumes of *dichloromethane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

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Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 500 mL of a buffer solution prepared by mixing 20 volumes of 1M *acetic acid* with 60 volumes of *water*, adjusting the pH to 4.7 with 1M *sodium hydroxide* and diluting to 100 volumes with *water*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a 10-mL sample of the medium and filter. Dilute the filtrate, if necessary, with dissolution medium to produce a solution expected to contain 0.0004% w/v of Loperamide Hydrochloride.

(2) 0.0004% w/v of *loperamide hydrochloride BPCRS* in the dissolution medium.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (4 µm) (Novapak C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 226 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.005M *sodium octanesulfonate* containing, per 1000 mL, 1 mL of 13.5M *ammonia* and 0.5 mL of *triethylamine* and adjusted to pH 3.2 with *orthophosphoric acid* (solvent A).

45 volumes of solvent A and 55 volumes of *acetonitrile*.

DETERMINATION OF CONTENT

Calculate the total content of loperamide hydrochloride, $C_{29}H_{33}ClN_2O_2$,HCl, in the medium from the chromatograms obtained and using the declared content of $C_{29}H_{33}ClN_2O_2$,HCl in *loperamide hydrochloride BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following freshly prepared solutions in solvent B.

35 volumes of 0.085M *potassium dihydrogen orthophosphate*, adjusted to pH 2.1 with *orthophosphoric acid*, and 65 volumes of *methanol* (solvent B).

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(1) Shake a quantity of the contents of the capsules with a sufficient volume of solvent B to produce a solution containing 0.0035% w/v of Loperamide Hydrochloride. Filter and use the filtrate.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) Dilute 1 volume of solution (2) to 5 volumes.

(4) 0.0035% w/v of *loperamide hydrochloride BPCRS* and 0.000035% w/v of *loperamide N-oxide BPCRS* (impurity F).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (7.5 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel* (5 µm) (Phenomenex Luna C18(2) is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 219 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for 3 times the retention time of loperamide.

MOBILE PHASE

5 volumes of *tetrahydrofuran*, 37 volumes of *acetonitrile R1* and 58 volumes of a solution containing 0.46% w/v *ammonium dihydrogen phosphate* and 0.61% w/v *sodium decanesulfonate*, previously adjusted to pH 2.1 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions the retention relative to loperamide (retention time about 15 minutes) is: impurity F, about 1.2.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to loperamide and impurity F is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity F is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of the areas of any other *secondary peaks*, excluding impurity F, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

Uniformity of content

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Capsules containing less than 2 mg and/or less than 2% w/w of Loperamide Hydrochloride comply with the requirements stated under Capsules using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 150 mL of *water* to one whole capsule and mix with the aid of ultrasound for 30 minutes, shake mechanically for 30 minutes and dilute to 200 mL with *acetonitrile*, filter and use the filtrate.
(2) 0.001% w/v of *loperamide hydrochloride BPCRS* in a mixture of 45 volumes of *water* and 55 volumes of *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{29}H_{33}ClN_2O_2$,HCl in each capsule using the declared content of $C_{29}H_{33}ClN_2O_2$,HCl in *loperamide hydrochloride BPCRS*.

ASSAY

For capsules containing the equivalent of less than 2 mg and/or less than 2% w/w of loperamide hydrochloride

Use the average of the individual results obtained in the test for Uniformity of content.

For capsules containing the equivalent of 2 mg or more and 2% w/w or more of loperamide hydrochloride

Weigh and powder the contents of 20 capsules. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix a quantity of the mixed capsule contents containing 20 mg of Loperamide Hydrochloride with 90 mL of *water* with the aid of ultrasound for 10 minutes, shake for 30 minutes, dilute to 200 mL with *acetonitrile* and filter.
(2) 0.01% w/v of *loperamide hydrochloride BPCRS* in a mixture of 45 volumes of *water* and 55 volumes of *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{29}H_{33}ClN_2O_2$,HCl in the capsules using the declared content of $C_{29}H_{33}ClN_2O_2$,HCl in *loperamide hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurity F listed under Loperamide Hydrochloride.

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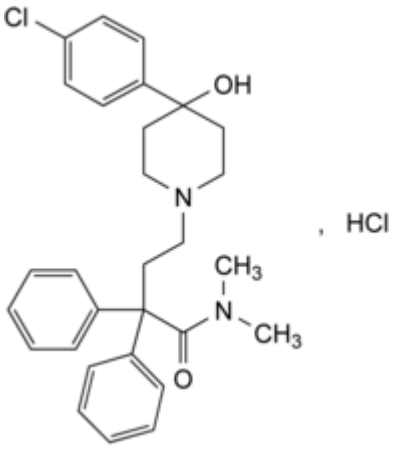
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Loperamide Hydrochloride

General Notices

(Ph. Eur. monograph 0929)



$C_{29}H_{34}Cl_2N_2O_2$ 513.5 *34552-83-5*

Action and use

Opioid receptor agonist; antidiarrhoeal.

Preparations

Loperamide Capsules

Loperamide Oral Solution

Loperamide Oral Suspension

Loperamide Tablets

Loperamide Orodispersible Tablets

Ph Eur

DEFINITION

4-[4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl]-*N*,*N*-dimethyl-2,2-diphenylbutanamide hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

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CHARACTERS

Appearance

White or almost white powder.

Solubility

Slightly soluble in water, freely soluble in ethanol (96 per cent) and in methanol.

It shows polymorphism (5.9).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *loperamide hydrochloride CRS*.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *methylene chloride R*, evaporate to dryness and record new spectra using the residues.

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.100 g of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 10.0 mg of *loperamide for system suitability CRS* (containing impurities A, B, D, E, G and H) in *methanol R* and dilute to 1.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 35 °C.

Mobile phase:

— *mobile phase A*: 17.0 g/L solution of *tetrabutylammonium hydrogen sulfate R1*;

— *mobile phase B*: *acetonitrile for chromatography R*;

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	90 → 30	10 → 70
15 - 17	30	70

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *loperamide for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, D, E, G and H.

Relative retention With reference to loperamide (retention time = about 6 min): impurity D = about 0.8; impurity G = about 1.20; impurity H = about 1.25; impurity E = about 1.45; impurity A = about 1.50; impurity B = about 1.9.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity G and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity H; minimum 1.5, where H_p = height above the baseline of the peak due to impurity E and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity A.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity D by 1.7;

— for each impurity, use the concentration of loperamide hydrochloride in reference solution (b).

Limits:

— *impurities B, D*: for each impurity, maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (*2.4.14*)

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Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.400 g in 50 mL of *ethanol (96 per cent) R* and add 5.0 mL of *0.01 M hydrochloric acid*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 51.35 mg of $C_{29}H_{34}Cl_2N_2O_2$.

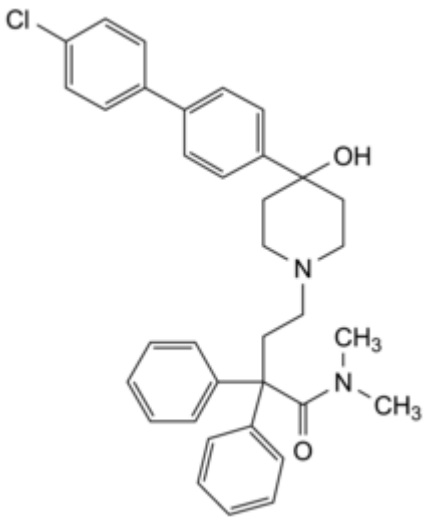
STORAGE

Protected from light.

IMPURITIES

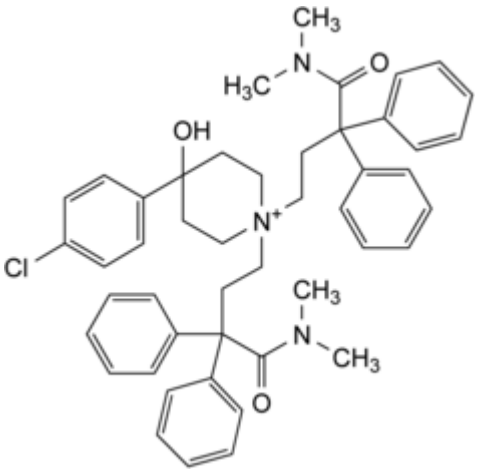
Specified impurities *B, D.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, C, E, F, G, H.*

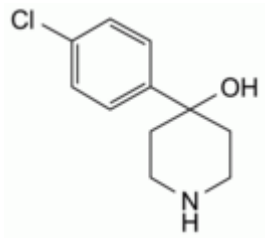


A. 4-[4-(4′-chloro-[1,1′-biphenyl]-4-yl)-4-hydroxypiperidin-1-yl]-*N*,*N*-dimethyl-2,2-diphenylbutanamide,

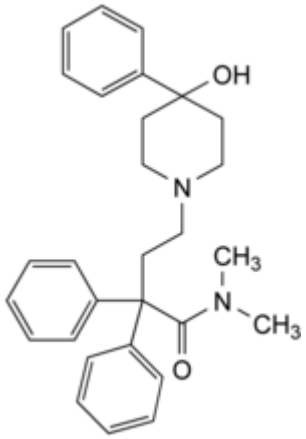
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B. 4-(4-chlorophenyl)-1,1-bis[4-(dimethylamino)-4-oxo-3,3-diphenylbutyl]-4-hydroxypiperidin-1-ium,

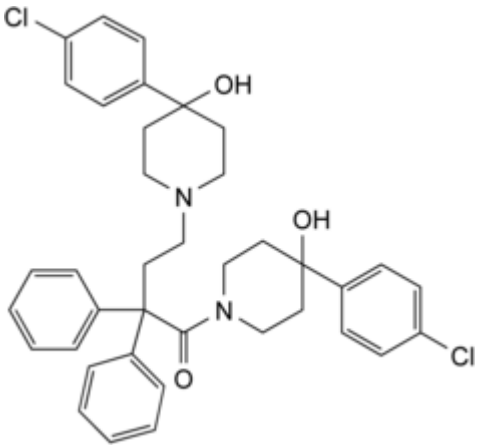


C. 4-(4-chlorophenyl)piperidin-4-ol,

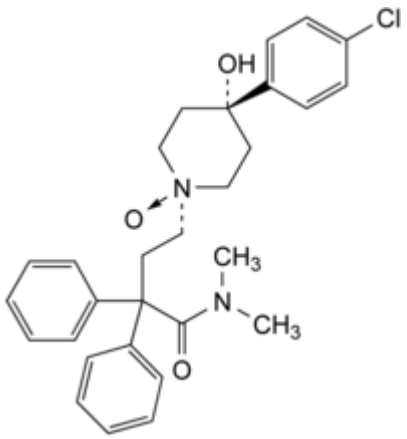


D. 4-(4-hydroxy-4-phenylpiperidin-1-yl)-*N*,*N*-dimethyl-2,2-diphenylbutanamide,

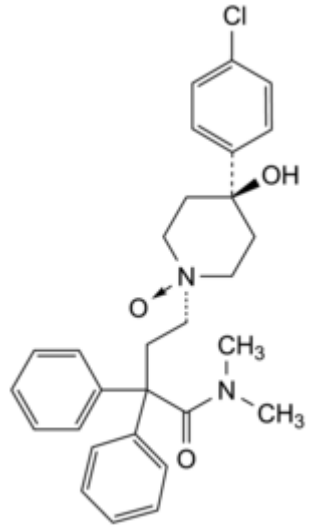
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E. 1,4-bis[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]-2,2-diphenylbutan-1-one,

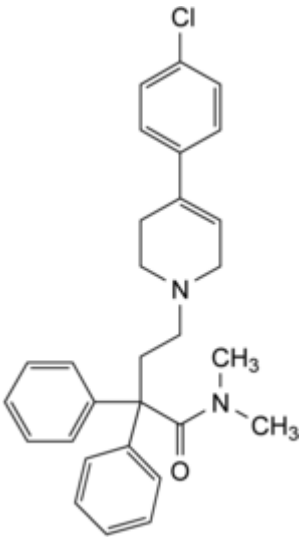


F. (1*r*,4*r*)-4-(4-chlorophenyl)-1-[4-(*N*,*N*-dimethylamino)-3,3-diphenyl-4-oxobutyl]-4-hydroxypiperazine 1-oxide (loperamide oxide),



G. (1*s*,4*s*)-4-(4-chlorophenyl)-1-[4-(*N*,*N*-dimethylamino)-3,3-diphenyl-4-oxobutyl]-4-hydroxypiperazine 1-oxide,

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H. 4-[4-(4-chlorophenyl)-3,6-dihydropyridin-1(2*H*)-yl]-*N*,*N*-dimethyl-2,2-diphenylbutanamide.

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Loperamide Oral Solution

General Notices

Action and use

Opioid receptor agonist; antidiarrhoeal.

DEFINITION

Loperamide Oral Solution contains Loperamide Hydrochloride.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of loperamide hydrochloride, $C_{29}H_{33}ClN_2O_2,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) To a weighed quantity of the oral solution containing 4 mg of Loperamide Hydrochloride, add 1 mL of 1M *sodium hydroxide* and mix using a vortex mixer. Add 2 mL of *dichloromethane* and shake vigorously. Centrifuge and use the lower liquid layer.

(2) 0.2% w/v of *loperamide hydrochloride BPCRS* in *dichloromethane*.

(3) 0.2% w/v each of *loperamide hydrochloride BPCRS* and *loperamide N-oxide BPCRS* in *dichloromethane*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* F_{254}.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air.

MOBILE PHASE

1 volume of *formic acid*, 15 volumes of *methanol* and 85 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

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B. In the Assay, the principal peak in the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 4.0 to 6.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following freshly prepared solutions in solvent A.

35 volumes of 0.085M *potassium dihydrogen orthophosphate*, adjusted to pH 2.1 with *orthophosphoric acid*, and 65 volumes of *methanol* (solvent A).

(1) Dilute a quantity of the oral solution with a sufficient volume of solvent A to produce a solution containing 0.0035% w/v of Loperamide Hydrochloride. Filter and use the filtrate.
(2) Dilute 1 volume of solution (1) to 100 volumes. Dilute 1 volume to 5 volumes.
(3) 0.0035% w/v of *loperamide hydrochloride BPCRS* and 0.000035% w/v of *loperamide N-oxide BPCRS* (impurity F).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (7.5 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel* (5 µm) (Phenomenex Luna C18(2) is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 30°.
(e) Use a detection wavelength of 219 nm.
(f) Inject 20 µL of each solution.
(g) For solution (1), allow the chromatography to proceed for 3 times the retention time of loperamide.

MOBILE PHASE

5 volumes of *tetrahydrofuran*, 37 volumes of *acetonitrile R1* and 58 volumes of a solution containing 0.46% w/v of *ammonium dihydrogen phosphate* and 0.61% w/v of *sodium decanesulfonate*, previously adjusted to pH 2.1 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions the retention time relative to loperamide (retention time about 15 minutes) is: impurity F, about 1.2.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to loperamide and impurity F is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

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the area of any peak corresponding to impurity F is not greater than 3.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.7%);

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any other *secondary peaks*, excluding impurity F, is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.8%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following freshly prepared solutions in solvent A, described under Related substances.

(1) Dilute a weighed quantity of the oral solution with a sufficient volume of solvent A to produce a solution containing 0.0035% w/v of Loperamide Hydrochloride.
(2) 0.0035% w/v of *loperamide hydrochloride BPCRS*.
(3) 0.0035% w/v of *loperamide hydrochloride BPCRS* and 0.000035% w/v of *loperamide N-oxide BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to loperamide and impurity F is at least 1.5.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_{29}H_{33}ClN_2O_2$,HCl, weight in volume, using the declared content of $C_{29}H_{33}ClN_2O_2$,HCl, in *loperamide hydrochloride BPCRS*

IMPURITIES

The impurities limited by the requirements of this monograph include impurity F listed under Loperamide Hydrochloride.

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Loperamide Oral Suspension

General Notices

NOTE: *This monograph has been developed to cover unlicensed formulations.*

Action and use

Opioid receptor agonist; antidiarrhoeal.

DEFINITION

Loperamide Oral Suspension is a suspension of Loperamide Hydrochloride in a suitable vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral suspension also complies with the requirements stated under Unlicensed Medicines.

Content of loperamide hydrochloride, $C_{29}H_{33}ClN_2O_2,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) To a quantity of the oral suspension containing 5 mg of Loperamide Hydrochloride, add 1 mL of 1M *sodium hydroxide* and mix using a vortex mixer. Add 2 mL of *dichloromethane* and shake vigorously. Centrifuge and use the lower liquid layer.

(2) 0.25% w/v of *loperamide hydrochloride BPCRS* in *dichloromethane*.

(3) 0.2% w/v of each of *loperamide hydrochloride BPCRS* and *loperamide N-oxide BPCRS* in *dichloromethane*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* F_{254}.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air.

MOBILE PHASE

1 volume of *formic acid*, 15 volumes of *methanol* and 85 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

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The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 4.0 to 6.5, Appendix V L.

Dissolution

Complies with the requirements stated under Unlicensed Medicines, Oral Suspensions. Use a volume of the oral suspension containing one dose.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following freshly prepared solutions in a mixture of 35 volumes of 0.085M *potassium dihydrogen orthophosphate*, adjusted to pH 2.1 with *orthophosphoric acid*, and 65 volumes of *methanol* (solution A).

(1) Dilute a quantity of the oral suspension to produce a solution containing 0.005% w/v of Loperamide Hydrochloride. Dilute 7 volumes of this solution to 10 volumes.
(2) Dilute 1 volume of solution (1) to 100 volumes; further dilute 1 volume to 5 volumes.
(3) 0.0035% w/v of *loperamide hydrochloride BPCRS* and 0.000035% w/v of *loperamide N-oxide BPCRS* (impurity F).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (7.5 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Phenomenex Luna C18(2) is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 30°.
(e) Use a detection wavelength of 219 nm.
(f) Inject 20 µL of each solution.
(g) For solution (1), allow the chromatography to proceed for 3 times the retention time of loperamide.

MOBILE PHASE

5 volumes of *tetrahydrofuran*, 37 volumes of *acetonitrile R1* and 58 volumes of a solution containing 0.46% w/v *ammonium dihydrogen orthophosphate* and 0.61% w/v *sodium decanesulfonate*, previously adjusted to pH 2.1 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions the retention time of loperamide is about 15 minutes and the relative retention of impurity F is about 1.2.

SYSTEM SUITABILITY

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The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to loperamide and impurity F is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity F is not greater than 3.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.7%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any other *secondary peaks*, excluding impurity F, is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.8%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following freshly prepared solutions in solution A as described under Related substances.

(1) Dilute a weighed quantity of the oral suspension to produce a solution containing 0.005% w/v of Loperamide Hydrochloride. Dilute 7 volumes of this solution to 10 volumes.
(2) 0.0035% w/v of *loperamide hydrochloride BPCRS*.
(3) 0.0035% w/v of *loperamide hydrochloride BPCRS* and 0.000035% w/v of *loperamide N-oxide BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to loperamide and impurity F is at least 1.5.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_{29}H_{33}ClN_2O_2$,HCl, weight in volume, using the declared content of $C_{29}H_{33}ClN_2O_2$,HCl, in *loperamide hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurity F listed under Loperamide Hydrochloride.

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Loperamide Orodispersible Tablets

General Notices

Orodispersible Loperamide Tablets

Action and use

Opioid receptor agonist; antidiarrhoeal.

DEFINITION

Loperamide Orodispersible Tablets contain Loperamide Hydrochloride in a suitable orodispersible basis.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of loperamide hydrochloride, $C_{29}H_{33}ClN_2O_2,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of powdered tablets containing 10 mg of Loperamide Hydrochloride with 10 mL of *methanol* for 5 minutes and filter.

(2) 0.1% w/v of *loperamide hydrochloride BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

2.5 volumes of *acetate buffer pH 4.7*, 17.5 volumes of *methanol*, 27 volumes of *ethyl acetate* and 53 volumes of *dichloromethane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

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TESTS

Dissolution

Complies with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 500 mL of a buffer solution prepared by mixing 20 volumes of 1M *acetic acid* with 60 volumes of *water*, adjusting the pH to 4.7 with 1M *sodium hydroxide* and diluting to 100 volumes with *water*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

0.005M *sodium octanesulfonate* containing, per 1000 mL, 1 mL of 13.5M *ammonia* and 0.5 mL of *triethylamine* and adjust the pH to 3.2 with *orthophosphoric acid* (solvent A).

(1) After 10 minutes withdraw a 10-mL sample of the medium and filter. Dilute the filtrate, if necessary, with dissolution medium to produce a solution containing 0.0004% w/v of Loperamide Hydrochloride.

(2) 0.0004% w/v of *loperamide hydrochloride BPCRS* in the dissolution medium.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (4 µm) (Novapak C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 226 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

45 volumes of solvent A and 55 volumes of *acetonitrile*.

DETERMINATION OF CONTENT

Calculate the total content of loperamide hydrochloride, $C_{29}H_{33}ClN_2O_2$,HCl, in the medium from the chromatograms obtained and using the declared content of $C_{29}H_{33}ClN_2O_2$,HCl in *loperamide hydrochloride BPCRS*.

LIMITS

The amount of loperamide hydrochloride released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following freshly prepared solutions in solvent B.

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35 volumes of 0.085M *potassium dihydrogen phosphate*, adjusted to pH 2.1 with *orthophosphoric acid*, and 65 volumes of *methanol* (solvent B).

(1) Shake a quantity of powdered tablets with a sufficient volume of solvent B to produce a solution containing 0.0035% w/v of Loperamide Hydrochloride. Filter and use the filtrate.
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) Dilute 1 volume to of solution (2) to 5 volumes.
(4) 0.0035% w/v of *loperamide hydrochloride BPCRS* and 0.000035% w/v of *loperamide N-oxide BPCRS* (impurity F).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (7.5 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel* (5 µm) (Phenomenex Luna C18(2) is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 30°.
(e) Use a detection wavelength of 219 nm.
(f) Inject 20 µL of each solution.
(g) For solution (1), allow the chromatography to proceed for 3 times the retention time of loperamide.

MOBILE PHASE

5 volumes of *tetrahydrofuran*, 37 volumes of *acetonitrile R1* and 58 volumes of a solution containing 0.46% w/v *ammonium dihydrogen phosphate* and 0.61% w/v *sodium decanesulfonate*, previously adjusted to pH 2.1 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions the retention time relative to loperamide (retention time about 15 minutes) is: impurity F, about 1.2.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to loperamide and impurity F is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity F is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of the areas of any *secondary peaks*, excluding impurity F, is not greater the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

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Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Loperamide Hydrochloride comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 150 mL of *water* to one whole tablet and mix with the aid of ultrasound for 30 minutes, shake mechanically for 30 minutes and dilute with sufficient *acetonitrile* to produce a solution expected to contain 0.001% w/v of Loperamide Hydrochloride and filter.
(2) 0.001% w/v of *loperamide hydrochloride BPCRS* in a mixture of 45 volumes of *water* and 55 volumes of *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{29}H_{33}ClN_2O_2$,HCl in each tablet using the declared content of $C_{29}H_{33}ClN_2O_2$,HCl in *loperamide hydrochloride BPCRS*.

ASSAY

For tablets containing less than 2 mg and/or less than 2% w/w of loperamide hydrochloride

Use the average of the 10 individual results obtained in the test for Uniformity of content.

For tablets containing 2 mg or more and 2% w/w or more of loperamide hydrochloride

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix a quantity of the powdered tablets containing 20 mg of Loperamide Hydrochloride with 90 mL of *water* with the aid of ultrasound for 10 minutes, shake for 30 minutes, dilute to 200 mL with *acetonitrile* and filter.
(2) 0.01% w/v of *loperamide hydrochloride BPCRS* in a mixture of 45 volumes of *water* and 55 volumes of *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{29}H_{33}ClN_2O_2$,HCl in the tablets using the declared content of $C_{29}H_{33}ClN_2O_2$,HCl in *loperamide hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurity F listed under Loperamide Hydrochloride.

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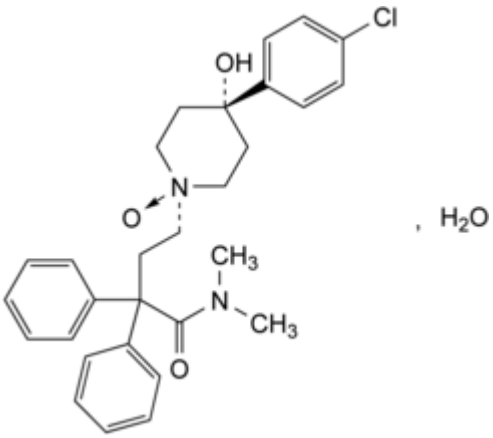
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This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Loperamide Oxide Monohydrate

General Notices

(Ph. Eur. monograph 1729)



$C_{29}H_{33}ClN_2O_3,H_2O$ 511.1

Action and use

Opioid receptor agonist; antidiarrhoeal.

Ph Eur

DEFINITION

4-[*trans*-4-(4-Chlorophenyl)-4-hydroxy-1-oxidopiperidin-1-yl]-*N*,*N*-dimethyl-2,2-diphenylbutanamide monohydrate.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder, slightly hygroscopic.

Solubility

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Practically insoluble in water, freely soluble in ethanol (96 per cent) and in methylene chloride.

mp

About 152 °C, with decomposition.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *loperamide oxide monohydrate CRS*.

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.100 g of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 5.0 mg of *loperamide hydrochloride CRS* in *methanol R*, add 0.5 mL of the test solution and dilute to 100.0 mL with *methanol R*.

Reference solution (b) Dilute 1.0 mL of the test solution to 20.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 25.0 mL with *methanol R*.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm,

— *stationary phase*: *base-deactivated octadecylsilyl silica gel for chromatography R* (3 µm),

— *temperature*: 35 °C.

Mobile phase:

— *mobile phase A*: 17.0 g/L solution of *tetrabutylammonium hydrogen sulfate R1*,

— *mobile phase B*: *acetonitrile R*,

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	90 → 30	10 → 70
15 - 17	30	70

Flow rate 1.5 mL/min.

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Detection Spectrophotometer at 220 nm.

Injection 10 µL.

Relative retention With reference to loperamide oxide (retention time = about 7 min): impurity A = about 0.9; impurity B = about 1.11; impurity C = about 1.13.

System suitability Reference solution (a):

— *resolution*: minimum 3.8 between the peaks due to loperamide oxide and impurity A.

Limits:

— *impurities A, B, C*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent),

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent),

— *total*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent),

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (2.5.12)

3.4 per cent to 4.2 per cent, determined on 0.500 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.350 g in 50 mL of a mixture of 1 volume of *anhydrous acetic acid R* and 7 volumes of *methyl ethyl ketone R*. Titrate with *0.1 M perchloric acid* using 0.2 mL of *naphtholbenzein solution R* as indicator.

1 mL of *0.1 M perchloric acid* is equivalent to 49.30 mg of $C_{29}H_{33}ClN_2O_3$.

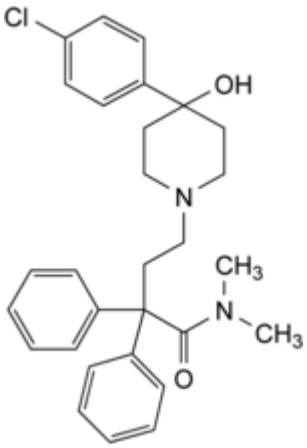
STORAGE

In an airtight container, protected from light.

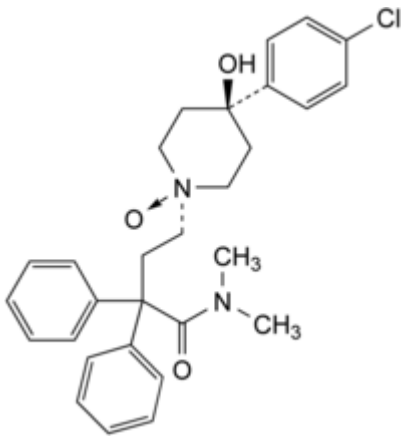
IMPURITIES

Specified impurities *A, B, C.*

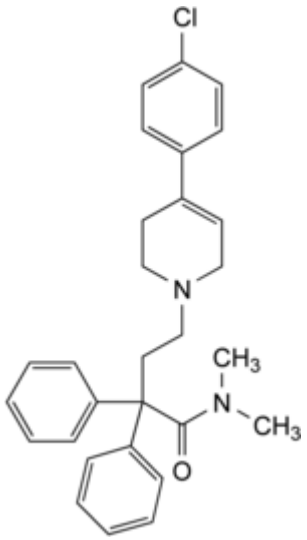
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A. 4-[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]-*N*,*N*-dimethyl-2,2-diphenylbutanamide (loperamide),



B. 4-[*cis*-4-(4-chlorophenyl)-4-hydroxy-1-oxidopiperidin-1-yl]-*N*,*N*-dimethyl-2,2-diphenylbutanamide,



C. 4-[4-(4-chlorophenyl)-3,6-dihydropyridin-1(2*H*)-yl]-*N*,*N*-dimethyl-2,2-diphenylbutanamide.

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Loperamide Tablets

General Notices

Action and use

Opioid receptor agonist; antidiarrhoeal.

DEFINITION

Loperamide Tablets contain Loperamide Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of loperamide hydrochloride, $C_{29}H_{33}ClN_2O_2,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of powdered tablets containing 10 mg of Loperamide Hydrochloride with 10 mL of *methanol* for 5 minutes and filter.

(2) 0.1% w/v of *loperamide hydrochloride BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

2.5 volumes of *acetate buffer pH 4.7*, 17.5 volumes of *methanol*, 27 volumes of *ethyl acetate* and 53 volumes of *dichloromethane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

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Dissolution

Complies with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 500 mL of a buffer solution prepared by mixing 20 volumes of 1M *acetic acid* with 60 volumes of *water*, adjusting the pH to 4.7 with 1M *sodium hydroxide* and diluting to 100 volumes with *water*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

0.005M *sodium octanesulfonate* containing, per 1000 mL, 1 mL of 13.5M *ammonia* and 0.5 mL of *triethylamine* and adjust the pH to 3.2 with *orthophosphoric acid* (solvent A).

(1) After 45 minutes withdraw a 10-mL sample of the medium and filter. Dilute the filtrate, if necessary, with dissolution medium to produce a solution expected to contain 0.0004% w/v of Loperamide Hydrochloride.

(2) 0.0004% w/v of *loperamide hydrochloride BPCRS* in the dissolution medium.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (4 µm) (Novapak C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 226 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

45 volumes of solvent A and 55 volumes of *acetonitrile*.

DETERMINATION OF CONTENT

Calculate the total content of loperamide hydrochloride, $C_{29}H_{33}ClN_2O_2$,HCl, in the medium from the chromatograms obtained and using the declared content of $C_{29}H_{33}ClN_2O_2$,HCl in *loperamide hydrochloride BPCRS*.

LIMITS

The amount of loperamide hydrochloride released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following freshly prepared solutions in solvent B.

35 volumes of 0.085M *potassium dihydrogen orthophosphate*, adjusted to pH 2.1 with *orthophosphoric acid*, and 65 volumes of *methanol* (solvent B).

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(1) Shake a quantity of powdered tablets with a sufficient volume of solvent B to produce a solution containing 0.0035% w/v of Loperamide Hydrochloride. Filter and use the filtrate.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) Dilute 1 volume of solution (2) to 5 volumes.

(4) 0.0035% w/v of *loperamide hydrochloride BPCRS* and 0.000035% w/v of *loperamide N-oxide BPCRS* (impurity F).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (7.5 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel* (5 µm) (Phenomenex Luna C18(2) is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 219 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for 3 times the retention time of loperamide.

MOBILE PHASE

5 volumes of *tetrahydrofuran*, 37 volumes of *acetonitrile R1* and 58 volumes of a solution containing 0.46% w/v *ammonium dihydrogen phosphate* and 0.61% w/v *sodium decanesulfonate*, previously adjusted to pH 2.1 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions the retention time relative to loperamide (retention time about 15 minutes) is: impurity F, about 1.2.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to loperamide and impurity F is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity F is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of the areas of any *secondary peaks*, excluding impurity F, is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

Uniformity of content

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Tablets containing less than 2 mg and/or less than 2% w/w of Loperamide Hydrochloride comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 150 mL of *water* to one whole tablet and mix with the aid of ultrasound for 30 minutes, shake mechanically for 30 minutes and dilute with sufficient *acetonitrile* to produce a solution expected to contain 0.001% w/v of Loperamide Hydrochloride and filter.
(2) 0.001% w/v of *loperamide hydrochloride BPCRS* in a mixture of 45 volumes of *water* and 55 volumes of *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{29}H_{33}ClN_2O_2$,HCl in each tablet using the declared content of $C_{29}H_{33}ClN_2O_2$,HCl in *loperamide hydrochloride BPCRS*.

ASSAY

For tablets containing less than 2 mg and/or less than 2% w/w of loperamide hydrochloride

Use the average of the individual results obtained in the test for Uniformity of content.

For tablets containing 2 mg or more and 2% w/w or more of loperamide hydrochloride

Weigh and powder 20 tablets. Prepare. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix a quantity of the powdered tablets containing 20 mg of Loperamide Hydrochloride with 90 mL of *water* with the aid of ultrasound for 10 minutes, shake for 30 minutes, dilute to 200 mL with *acetonitrile* and filter.
(2) 0.01% w/v of *loperamide hydrochloride BPCRS* in a mixture of 45 volumes of *water* and 55 volumes of *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{29}H_{33}ClN_2O_2$,HCl in the tablets using the declared content of $C_{29}H_{33}ClN_2O_2$,HCl in *loperamide hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurity F listed under Loperamide Hydrochloride.

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