– *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.20 per cent);
– *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 per cent);
– *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent).

Water (*2.5.12*): 1.5 per cent to 2.9 per cent, determined on 0.250 g.

Sulfated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

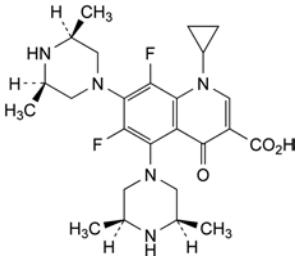
Dissolve 0.300 g in 100 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid* determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 39.54 mg of $C_{19}H_{20}F_3N_3O_3$.

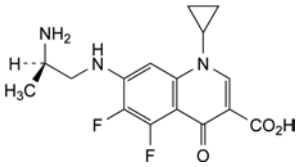
IMPURITIES

Specified impurities: *A, D*.

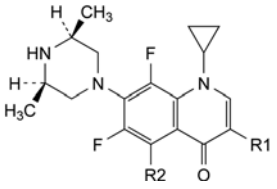
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical 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*): *B, C, E, F, G*.



A. 1-cyclopropyl-5,7-bis[(3*R*,5*S*)-3,5-dimethylpiperazin-1-yl]-6,8-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid,

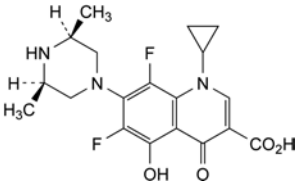


B. 7-[[(2*R*)-2-aminopropyl]amino]-1-cyclopropyl-5,6-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid,

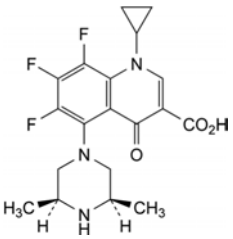


C. R1 = CO_2H, R2 = H : 1-cyclopropyl-7-[(3*R*,5*S*)-3,5-dimethylpiperazin-1-yl]-6,8-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid,

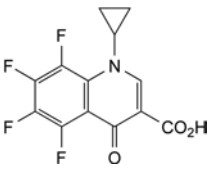
G. R1 = H, R2 = F: 1-cyclopropyl-7-[(3*R*,5*S*)-3,5-dimethylpiperazin-1-yl]-5,6,8-trifluoroquinolin-4(1*H*)-one,



D. 1-cyclopropyl-7-[(3*R*,5*S*)-3,5-dimethylpiperazin-1-yl]-6,8-difluoro-5-hydroxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid,



E. 1-cyclopropyl-5-[(3*R*,5*S*)-3,5-dimethylpiperazin-1-yl]-6,7,8-trifluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid,

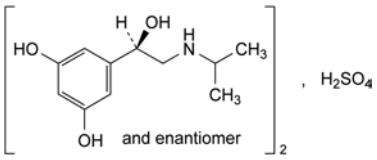


F. 1-cyclopropyl-5,6,7,8-tetrafluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

07/2008:1033
corrected 7.0

ORCIPRENALINE SULFATE

Orciprenalini sulfas



$C_{22}H_{36}N_2O_{10}S$ M_r 520.6
[5874-97-5]

DEFINITION

Bis[5-[(1*RS*)-1-hydroxy-2-[(1-methylethyl)amino]ethyl]-benzene-1,3-diol] sulfate.

Content: 98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white, slightly hygroscopic, crystalline powder.

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

IDENTIFICATION

First identification: *B, E*.

Second identification: *A, C, D, E*.

A. Ultraviolet and visible absorption spectrophotometry (*2.2.25*).

Test solution. Dissolve 50.0 mg in a 0.04 per cent *V/V* solution of *hydrochloric acid R* and dilute to 50.0 mL with the same solution. Dilute 5.0 mL of this solution to 50.0 mL with a 0.04 per cent *V/V* solution of *hydrochloric acid R*.

Spectral range: 240-350 nm.

Absorption maximum: at 278 nm.

Specific absorbance at the absorption maximum: 68.5 to 76.0 (anhydrous substance).

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *orciprenaline sulfate CRS*.

If the spectra obtained show differences, dissolve separately, with heating, 50 mg of the substance to be examined and 50 mg of the reference substance, in the minimum volume of *water R*. Add 10 mL of *acetone R* and centrifuge. Dry the precipitates at 40 °C under reduced pressure for 3 h 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 *ethanol (96 per cent) R* and dilute to 10 mL with the same solvent.

Reference solution (a). Dissolve 10 mg of *orciprenaline sulfate CRS* in *ethanol (96 per cent) R* and dilute to 10 mL with the same solvent.

Reference solution (b). Dissolve 10 mg of *orciprenaline sulfate CRS* and 10 mg of *salbutamol CRS* in *ethanol (96 per cent) R* and dilute to 10 mL with the same solvent.

Plate: *TLC silica gel G plate R*.

Mobile phase: *ammonia R, water R, aldehyde-free methanol R* (1.5:10:90 *V/V/V*).

Application: 2 µL.

Development: over 2/3 of the plate.

Drying: in air.

Detection: spray with a 10 g/L solution of *potassium permanganate R*.

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 about 20 mg in 2 mL of *ethanol (96 per cent) R*. Add 2 mL of a 1 g/L solution of *dichloroquinonechlorimide R* in *ethanol (96 per cent) R* and 1 mL of *sodium carbonate solution R*. A violet colour is produced, turning to brown.

E. It gives reaction (a) of sulfates (*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 colourless (*2.2.2, Method II*).

pH (*2.2.3*): 4.0 to 5.5 for solution S.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 20 mg of the substance to be examined in the mobile phase and dilute to 20 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 2 mg of *orciprenaline for system suitability CRS* (containing impurities A and B) in 2.0 mL of the mobile phase.

Column:

– *size*: *l* = 0.125 m, Ø = 4.0 mm;

– *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

– *temperature*: 45 °C.

Mobile phase. Dissolve 9.1 g of *potassium dihydrogen phosphate R* and 4.6 g of *sodium octanesulfonate R* in *water R*, adjust to pH 4.0 with *dilute phosphoric acid R* and dilute to 1000 mL with *water R*. Add 140 mL of *acetonitrile R*.

Flow rate: 1.5 mL/min.

Detection: spectrophotometer at 280 nm.

Injection: 10 µL.

Run time: twice the retention time of orciprenaline.

Identification of impurities: use the chromatogram supplied with *orciprenaline for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and B.

Relative retention with reference to orciprenaline (retention time = about 7 min): impurity A = about 0.9; impurity B = about 1.3.

System suitability: reference solution (b):

– *resolution*: minimum 2.0 between the peaks due to impurity A and orciprenaline.

Limits:

– *correction factor*: for the calculation of content, multiply the peak area of impurity B by 0.3;

– *impurities A, B*: 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 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).

Phenone: maximum 0.1 per cent.

Dissolve 0.50 g in a 0.04 per cent *V/V* solution of *hydrochloric acid R* and dilute to 25.0 mL with the same solution. The absorbance (*2.2.25*) of the solution measured at 328 nm is not greater than 0.16.

Iron (*2.4.9*): maximum 20 ppm.

The residue obtained in the test for sulfated ash complies with the test. Prepare the reference solution using *iron standard solution (2 ppm Fe) R*.

Heavy metals (*2.4.8*): maximum 20 ppm.

1.0 g complies with test C. Prepare the reference solution using 2 mL of *lead standard solution (10 ppm Pb) R*.

Water (*2.5.12*): maximum 2.0 per cent, determined on 1.000 g.

Sulfated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.400 g in 5 mL of *anhydrous formic acid R* and add 30 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid* using 0.1 mL of *crystal violet solution R* as indicator.

1 mL of *0.1 M perchloric acid* is equivalent to 52.06 mg of $C_{22}H_{36}N_2O_{10}S$.

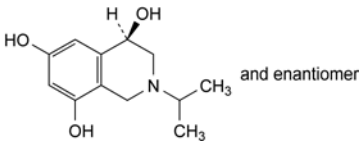
STORAGE

In an airtight container, protected from light.

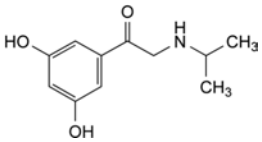
IMPURITIES

Specified impurities: A, B.

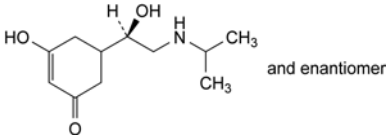
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical 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.*



A. (4*RS*)-2-(1-methylethyl)-1,2,3,4-tetrahydroisoquinoline-4,6,8-triol,



B. 1-(3,5-dihydroxyphenyl)-2-[(1-methylethyl)amino]ethanone,

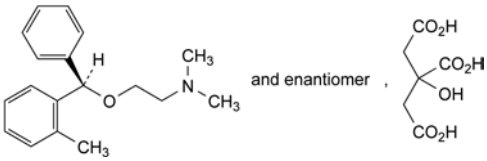


C. 3-hydroxy-5-[(1*RS*)-1-hydroxy-2-[(1-methylethyl)amino]-ethyl]cyclohex-2-enone.

07/2010:1759

ORPHENADRINE CITRATE

Orphenadrini citras



$C_{24}H_{31}NO_8$ M_r 461.5
[4682-36-4]

DEFINITION

(*RS*)-*N*,*N*-Dimethyl-2-[(2-methylphenyl)phenylmethoxy]ethanamine dihydrogen 2-hydroxypropane-1,2,3-tricarboxylate.

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

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: sparingly soluble in water, slightly soluble in ethanol (96 per cent).

mp: about 137 °C.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *orphenadrine citrate CRS*.

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and its absorbance (*2.2.25*) at 436 nm has a maximum of 0.050.

Dissolve 1.0 g in a 3.6 per cent *V/V* solution of *hydrochloric acid R* in *ethanol (96 per cent) R* and dilute to 10.0 mL with the same acid solution.

Related substances. Gas chromatography (*2.2.28*): use the normalisation procedure.

Test solution. Dissolve 0.500 g of the substance to be examined in *water R* and dilute to 50 mL with the same solvent. Add 2 mL of *concentrated ammonia R* and shake with 3 quantities, each of 10 mL, of *toluene R*. To the combined upper layers add *anhydrous sodium sulfate R*, shake, filter and evaporate the filtrate, at a temperature not exceeding 50 °C, using a rotary evaporator. Take up the residue with *toluene R* and dilute to 20.0 mL with the same solvent.

Reference solution (a). Dissolve 30 mg of *orphenadrine citrate CRS* and 30 mg of *orphenadrine impurity E CRS* in 20 mL of *water R*. Add 1 mL of *concentrated ammonia R* and shake with 3 quantities, each of 5 mL, of *toluene R*. To the combined upper layers add *anhydrous sodium sulfate R*, shake, filter and evaporate the filtrate, at a temperature not exceeding 50 °C, using a rotary evaporator. Take up the residue with *toluene R* and dilute to 20.0 mL with the same solvent.

Reference solution (b). Dissolve the contents of a vial of *orphenadrine for peak identification CRS* (containing impurities A, B, C, D and F) in 1.0 mL of *toluene R*.

Column:

– *size*: *l* = 60 m, Ø = 0.32 mm;
– *stationary phase*: *poly(dimethyl)(diphenyl)siloxane R* (film thickness 1.0 µm).

Carrier gas: *helium for chromatography R*.

Flow rate: 1 mL/min.

Split ratio: 1:25.

Temperature:

– *column*: 240 °C;
– *injection port and detector*: 290 °C.

Detection: flame ionisation.

Injection: 2 µL.

Run time: 1.3 times the retention time of orphenadrine.

Identification of impurities: use the chromatogram supplied with *orphenadrine for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C, D and F. Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity E.

Relative retention with reference to orphenadrine (retention time = about 13 min): impurity B = about 0.5; impurity A = about 0.6; impurity D = about 0.8; impurity C = about 0.9; impurity E = about 0.98; impurity F = about 1.1.

System suitability: reference solution (a):

– *resolution*: minimum of 1.5 between the peaks due to impurity E and orphenadrine.

Limits:

– *impurities A, B, C, D, E, F*: for each impurity, not more than 0.3 per cent;
– *unspecified impurities*: for each impurity, not more than 0.10 per cent;
– *total*: maximum 1.0 per cent;
– *disregard limit*: 0.05 per cent.

Heavy metals (*2.4.8*): maximum 10 ppm.

2.0 g complies with test C. Prepare the reference solution using 2 mL of *lead standard solution (10 ppm Pb) 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 for 3 h.

Sulfated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

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 46.15 mg of $C_{24}H_{31}NO_8$.

STORAGE

Protected from light. If the substance is sterile, store in a sterile, airtight, tamper-proof container, protected from light.

IMPURITIES

Specified impurities: *A, B, C, D, E, F*.