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.

Reference solution (c). Dissolve 3 mg of *omeprazole for peak identification CRS* (containing impurity E) in the mobile phase and dilute to 25.0 mL with the mobile phase.

Column:

– *size*: *l* = 0.125 m, Ø = 4.6 mm;

– *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: mix 27 volumes of *acetonitrile R* and 73 volumes of a 1.4 g/L solution of *disodium hydrogen phosphate R*, previously adjusted to pH 7.6 with *phosphoric acid R*.

Flow rate: 1 mL/min.

Detection: spectrophotometer at 280 nm.

Injection: 40 µL.

Run time: 5 times the retention time of omeprazole.

Identification of impurities: use the chromatogram supplied with *omeprazole for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity E; use the chromatogram obtained with reference solution (a) to identify the peak due to impurity D.

Relative retention with reference to omeprazole (retention time = about 9 min): impurity E = about 0.6; impurity D = about 0.8.

System suitability: reference solution (a):

– *resolution*: minimum 3.0 between the peaks due to impurity D and omeprazole; if necessary adjust the pH of the aqueous part of the mobile phase or the concentration of *acetonitrile R*; an increase in the pH will improve the resolution.

Limits:

– *impurities D, E*: 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 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).

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*): 4.5 per cent to 10.0 per cent, determined on 0.300 g.

ASSAY

Dissolve 0.300 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* corresponds to 36.74 mg of $C_{17}H_{18}N_3NaO_3S$.

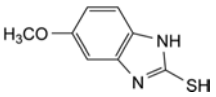
STORAGE

In an airtight container, protected from light.

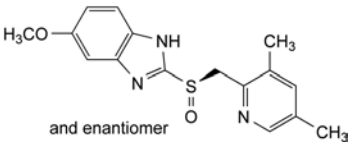
IMPURITIES

Specified impurities: D, E.

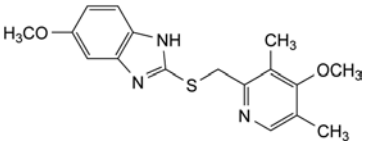
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical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



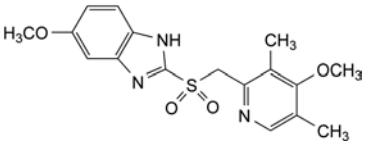
A. 5-methoxy-1*H*-benzimidazole-2-thiol,



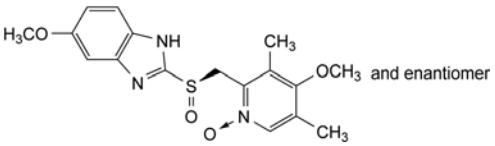
B. 2-[(*RS*)-[(3,5-dimethylpyridin-2-yl)methyl]sulfinyl]-5-methoxy-1*H*-benzimidazole,



C. 5-methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfanyl]-1*H*-benzimidazole (ufiprazole),



D. 5-methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfonyl]-1*H*-benzimidazole (omeprazole-sulfone),

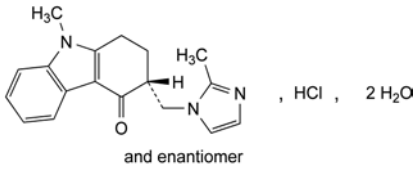


E. 4-methoxy-2-[[(*RS*)-(5-methoxy-1*H*-benzimidazol-2-yl)sulfinyl]methyl]-3,5-dimethylpyridine 1-oxide.

01/2008:2016

ONDANSETRON HYDROCHLORIDE DIHYDRATE

Ondansetroni hydrochloridum dihydricum



$C_{18}H_{20}ClN_3O,2H_2O$ M_r 365.9

DEFINITION

(3*RS*)-9-Methyl-3-[(2-methyl-1*H*-imidazol-1-yl)methyl]-1,2,3,9-tetrahydro-4*H*-carbazol-4-one hydrochloride dihydrate.

Content: 97.5 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white powder.

Solubility: sparingly soluble in water and in alcohol, soluble in methanol, slightly soluble in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *ondansetron hydrochloride dihydrate CRS*.

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

TESTS

Impurity B. Thin-layer chromatography (*2.2.27*).

Test solution. Dissolve 0.125 g of the substance to be examined in a mixture of 0.5 volumes of *concentrated ammonia R*, 100 volumes of *alcohol R* and 100 volumes of *methanol R*, and dilute to 10.0 mL with the same mixture of solvents.

Reference solution (a). Dissolve 12.5 mg of *ondansetron for TLC system suitability CRS* in a mixture of 0.5 volumes of *concentrated ammonia R*, 100 volumes of *alcohol R* and 100 volumes of *methanol R*, and dilute to 1.0 mL with the same mixture of solvents.

Reference solution (b). Dilute 1 mL of the test solution to 100 mL with a mixture of 0.5 volumes of *concentrated ammonia R*, 100 volumes of *alcohol R* and 100 volumes of *methanol R*. Dilute 4.0 mL to 10.0 mL with a mixture of 0.5 volumes of *concentrated ammonia R*, 100 volumes of *alcohol R* and 100 volumes of *methanol R*.

Plate: *TLC silica gel F_{254} plate R.*

Mobile phase: *concentrated ammonia R, methanol R, ethyl acetate R, methylene chloride R* (2:40:50:90 *V/V/V/V*).

Application: 20 µL.

Development: over 3/4 of the plate.

Drying: in air.

Detection: examine in ultraviolet light at 254 nm.

Order of elution: ondansetron, impurity B, impurity A.

System suitability: the chromatogram obtained with reference solution (a) shows 3 clearly separated spots.

Limit:

– *impurity B*: any spot corresponding to impurity B in the chromatogram obtained with the test solution is not more intense than the principal spot in the chromatogram obtained with reference solution (b) (0.4 per cent).

Related substances. Liquid chromatography (*2.2.29*).

Test solution (a). Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Test solution (b). Dissolve 90.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 10.0 mL to 100.0 mL with the mobile phase.

Reference solution (a). Dilute 2.0 mL of test solution (a) to 100.0 mL with the mobile phase. Dilute 10.0 mL to 100.0 mL with the mobile phase.

Reference solution (b). Dissolve 10.0 mg of *imidazole R* and 10.0 mg of *2-methylimidazole R* in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 1.0 mL to 100.0 mL with the mobile phase.

Reference solution (c). Dissolve 5.0 mg of *ondansetron for LC system suitability CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (d). Dissolve 5.0 mg of *ondansetron impurity D CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 1.0 mL to 100.0 mL with the mobile phase.

Reference solution (e). Dissolve 90.0 mg of *ondansetron hydrochloride dihydrate CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 10.0 mL to 100.0 mL with the mobile phase.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm,

– *stationary phase*: spherical *nitrile silica gel for chromatography R* (5 µm) with a specific surface area of 220 m^2/g and a pore size of 8 nm.

Mobile phase: mix 20 volumes of *acetonitrile R* and 80 volumes of a 2.8 g/L solution of *sodium dihydrogen phosphate monohydrate R* previously adjusted to pH 5.4 with a 40 g/L solution of *sodium hydroxide R*.

Flow rate: 1.5 mL/min.

Detection: spectrophotometer at 216 nm.

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

Run time: 1.5 times the retention time of ondansetron.

Relative retentions with reference to ondansetron (retention time = about 18 min): impurity E = about 0.1; impurity F = about 0.2; impurity C = about 0.4; impurity D = about 0.5; impurity H = about 0.7; impurity A = about 0.8; impurity G = about 0.9.

System suitability:

– *resolution*: minimum of 1.3 between the peak due to impurity E (first peak) and the peak due to impurity F (second peak) in the chromatogram obtained with reference solution (b) and minimum of 2.5 between the peak due to impurity C (first peak) and the peak due to impurity D (second peak) in the chromatogram obtained with reference solution (c).

Limits:

– *correction factor*: for the calculation of contents, multiply the peak area of impurity C by 0.6,

– *impurity C*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent),

– *impurity D*: not more than the area of the principal peak in the chromatogram obtained with reference solution (d) (0.1 per cent),

– *impurity E*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.2 per cent),

– *impurity F*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.2 per cent),

– *any other impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 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*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.04 per cent).

Water (*2.5.12*): 9.0 per cent to 10.5 per cent, determined on 0.200 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.

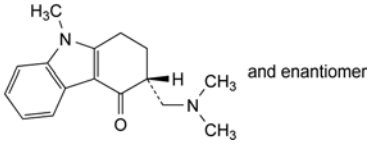
Injection: test solution (b) and reference solution (e).

Calculate the percentage content of $C_{18}H_{20}ClN_3O$.

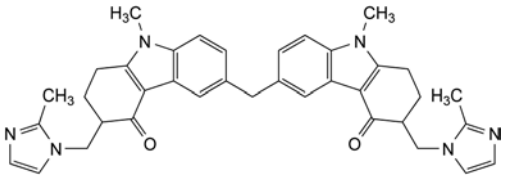
STORAGE

Protected from light.

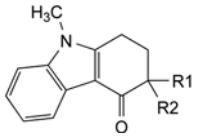
IMPURITIES



A. (3*RS*)-3-[(dimethylamino)methyl]-9-methyl-1,2,3,9-tetrahydro-4*H*-carbazol-4-one,



B. 6,6′-methylenebis[(3*RS*)-9-methyl-3-[(2-methyl-1*H*-imidazol-1-yl)methyl]-1,2,3,9-tetrahydro-4*H*-carbazol-4-one],

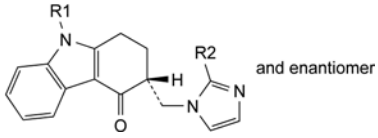


C. R1 = R2 = H: 9-methyl-1,2,3,9-tetrahydro-4*H*-carbazol-4-one,

D. R1 + R2 = CH_2: 9-methyl-3-methylene-1,2,3,9-tetrahydro-4*H*-carbazol-4-one,

E. R = H: 1*H*-imidazole,

F. R = CH_3: 2-methyl-1*H*-imidazole,



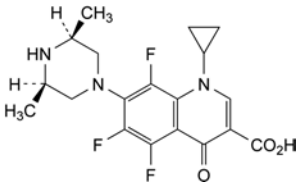
G. R1 = CH_3, R2 = H: (3*RS*)-3-[(1*H*-imidazol-1-yl)methyl]-9-methyl-1,2,3,9-tetrahydro-4*H*-carbazol-4-one (*C*-demethylondansetron),

H. R1 = H, R2 = CH_3: (3*RS*)-3-[(2-methyl-1*H*-imidazol-1-yl)methyl]-1,2,3,9-tetrahydro-4*H*-carbazol-4-one (*N*-demethylondansetron).

01/2010:2259
corrected 7.0

ORBIFLOXACIN FOR VETERINARY USE

Orbifloxacinum ad usum veterinarium



$C_{19}H_{20}F_3N_3O_3$ M_r 395.4
[113617-63-3]

DEFINITION

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

Content: 99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or pale yellow, crystals or crystalline powder.

Solubility: very slightly soluble in water, soluble in glacial acetic acid, practically insoluble in anhydrous ethanol.

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *orbifloxacin CRS*.

If the spectra obtained in the solid state show differences, dissolve 0.1 g of the substance to be examined and 0.1 g of the reference substance separately in 12 mL of *methanol R*. Heat to boiling while shaking. Filter the solutions and let them cool slowly to room temperature. Filter under vacuum and wash the residues with cooled *methanol R*. Dry the residues under vacuum 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 GY_4 (*2.2.2, Method II*).

Dissolve 0.4 g in a 4 g/L solution of *sodium hydroxide R* and dilute to 20 mL with the same solution.

Related substances. Liquid chromatography (*2.2.29*).

Buffer solution. Dissolve 5.9 g of *sodium citrate R* in 800 mL of *water R*, add 90 mL of *glacial acetic acid R* and mix. Adjust to pH 3.5 with a 240 g/L solution of *sodium hydroxide R* in *water R* and dilute to 1000 mL with *water R*.

Test solution. Dissolve 10 mg of the substance to be examined in the buffer solution and dilute to 50.0 mL with the buffer solution.

Reference solution (a). Dilute 1.0 mL of the test solution to 50.0 mL with the buffer solution. Dilute 1.0 mL of this solution to 10.0 mL with the buffer solution.

Reference solution (b). Dissolve 10.0 mg of *methyl 4-aminobenzoate R* in the buffer solution and dilute to 100.0 mL with the buffer solution. Mix 10.0 mL of the solution with 5.0 mL of the test solution and dilute to 50.0 mL with the buffer solution. Dilute 1.0 mL of this solution to 50.0 mL with the buffer solution.

Reference solution (c). Dissolve the contents of a vial of *orbifloxacin impurity mixture CRS* (impurities A and D) in 1.0 mL of the buffer solution.

Reference solution (d). Dilute 0.25 mL of reference solution (c) to 1.0 mL of the buffer solution.

Column:

– *size*: *l* = 33 mm, Ø = 4.6 mm;
– *stationary phase*: *base-deactivated octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase: *dioxane R, methanol R,* buffer solution (4:11:86 *V/V/V*).

Flow rate: 1 mL/min.

Detection: spectrophotometer at 290 nm.

Injection: 10 µL.

Run time: 9 times the retention time of orbifloxacin.

Identification of the impurities: use the chromatogram supplied with *orbifloxacin impurity mixture CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and D.

Relative retention with reference to orbifloxacin (retention time = about 2 min): impurity A = about 0.5; methyl 4-aminobenzoate = about 1.2; impurity D = about 2.5.

System suitability:

– *resolution*: minimum 2.0 between the peaks due to orbifloxacin and methyl 4-aminobenzoate in the chromatogram obtained with reference solution (b);
– *signal-to-noise ratio*: minimum 10 for the peak due to impurity A in the chromatogram obtained with reference solution (d).

Limits:

– *correction factors*: for the calculation of contents, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 2.8; impurity D = 1.4;
– *impurities A, D*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);