Limits:

– *impurities A, B, D, 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 the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent).

Chloroform and methylene chloride. Head-space gas chromatography (*2.2.28*): use the standard additions method.

Test solution. Place 0.50 g of the substance to be examined in a 10 ml vial. Add 4.0 ml of *dimethylacetamide R* and stopper the vial.

Column:

– *material*: fused silica;

– *size*: *l* = 30 m, Ø = 0.32 mm;

– *stationary phase*: cross-linked *poly[(cyanopropyl)-(phenyl)][dimethyl]siloxane R* (film thickness 1.8 µm).

Carrier gas: *nitrogen for chromatography R*.

Static head-space conditions that may be used:

– *equilibration temperature*: 80 °C;

– *equilibration time*: 1 h.

Detection: flame ionisation.

Limits:

– *methylene chloride*: maximum 100 ppm;

– *chloroform*: maximum 50 ppm.

Loss on drying (*2.2.32*): maximum 0.2 per cent, determined on 1.000 g by drying under high vacuum at 60 °C for 4 h.

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

ASSAY

Dissolve 1.100 g in a mixture of 10 ml of *water R* and 40 ml of *ethanol (96 per cent) R*. Titrate with *0.5 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 ml of *0.5 M sodium hydroxide* is equivalent to 0.1727 g of $C_{17}H_{19}N_3O_3S$.

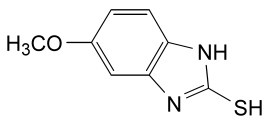
STORAGE

In an airtight container, protected from light, at a temperature of 2 °C to 8 °C.

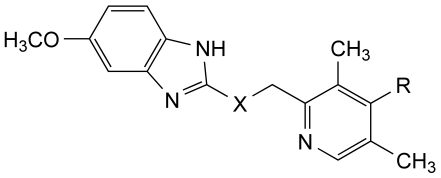
IMPURITIES

Specified impurities: A, B, C, D, 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*): *H, I.*



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

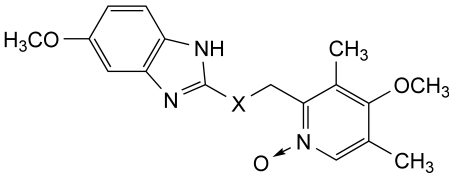


B. R = H, X = SO: 2-[(*RS*)-[(3,5-dimethylpyridin-2-yl)methyl]sulphinyl]-5-methoxy-1*H*-benzimidazole,

C. R = OCH_3, X = S: 5-methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulphanyl]-1*H*-benzimidazole (ufiprazole),

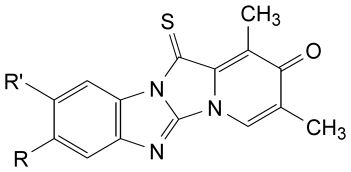
D. R = OCH_3, X = SO_2: 5-methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulphonyl]-1*H*-benzimidazole (omeprazole sulphone),

H. R = Cl, X = SO: 2-[(*RS*)-[(4-chloro-3,5-dimethylpyridin-2-yl)methyl]sulfinyl]-5-methoxy-1*H*-benzimidazole,



E. X = SO: 4-methoxy-2-[[(*RS*)-(5-methoxy-1*H*-benzimidazol-2-yl)sulphinyl]methyl]-3,5-dimethylpyridine 1-oxide,

I. X = SO_2: 4-methoxy-2-[[(5-methoxy-1*H*-benzimidazol-2-yl)sulphonyl]methyl]-3,5-dimethylpyridine 1-oxide,



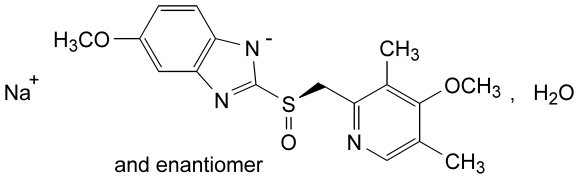
F. R = OCH_3, R′ = H: 8-methoxy-1,3-dimethyl-12-thioxopyrido[1′,2′:3,4]imidazo[1,2-*a*]benzimidazol-2(12*H*)-one,

G. R = H, R′ = OCH_3: 9-methoxy-1,3-dimethyl-12-thioxopyrido[1′,2′:3,4]imidazo[1,2-*a*]benzimidazol-2(12*H*)-one.

01/2008:1032

OMEPRAZOLE SODIUM

Omeprazolum natricum



$C_{17}H_{18}N_3NaO_3S,H_2O$ M_r 385.4
[95510-70-6]

DEFINITION

Sodium 5-methoxy-2-[(*RS*)-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulphinyl]-1*H*-benzimidazole monohydrate.

Content: 98.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white, hygroscopic powder.

Solubility: freely soluble in water and in ethanol (96 per cent), soluble in propylene glycol, very slightly soluble in methylene chloride.

IDENTIFICATION

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

Test solution. Dissolve 2.0 mg in *0.1 M sodium hydroxide* and dilute to 100.0 ml with the same solvent.

Spectral range: 230-350 nm.

Absorption maxima: at 276 nm and 305 nm.

Absorption ratio: A_{305} / A_{276} = 1.6 to 1.8.

B. Examine the chromatograms obtained in the test for impurity C.

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). Place the plate in a tank saturated with vapour of *acetic acid R*. The spots rapidly turn brown.

C. Ignite 1 g and cool. Add 1 ml of *water R* to the residue and neutralise with *hydrochloric acid R*. Filter and dilute the filtrate to 4 ml with *water R*. 0.1 ml of the solution gives reaction (b) of sodium (*2.3.1*).

TESTS

Solution S. Dissolve 0.50 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 not more intensely coloured than reference solution B_6 (*2.2.2, Method II*).

pH (*2.2.3*): 10.3 to 11.3 for solution S.

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

Test solution (a). Dissolve 0.10 g of the substance to be examined in 2.0 ml of *methanol R*.

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

Reference solution (a). Dissolve 9 mg of *omeprazole CRS* in 2.0 ml of *methanol R*.

Reference solution (b). Dilute 1.0 ml of test solution (b) to 100 ml with *methanol R*.

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

Mobile phase: mix 20 volumes of *2-propanol R*, 40 volumes of *methylene chloride R* previously shaken with *concentrated ammonia R* (shake 100 ml of *methylene chloride R* with 30 ml of *concentrated ammonia R* in a separating funnel, allow the layers to separate and use the lower layer) and 40 volumes of *methylene chloride R*.

Application: 10 µl.

Development: over a path of 15 cm.

Drying: in air.

Detection: examine in ultraviolet light at 254 nm.

Limit: test solution (a):

– *impurity C*: any spot with a higher R_F value than that of the spot due to omeprazole is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.1 per cent).

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 3.0 mg of the substance to be examined in the mobile phase and dilute to 25.0 ml with the mobile phase.

Reference solution (a). Dissolve 1.0 mg of *omeprazole CRS* and 1.0 mg of *omeprazole impurity D CRS* in the mobile phase and dilute to 10.0 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 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: 3 times the retention time of omeprazole.

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

System suitability: reference solution (a):

– *resolution*: minimum 3 between the peaks due to impurity D and omeprazole; if necessary adjust the pH of the mobile phase or the concentration of *acetonitrile R*; an increase in the pH will improve the resolution.

Limit:

– *any 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).

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 $C_{17}H_{18}N_3NaO_3S$.

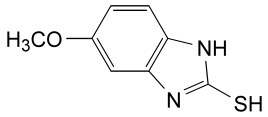
STORAGE

In an airtight container, protected from light.

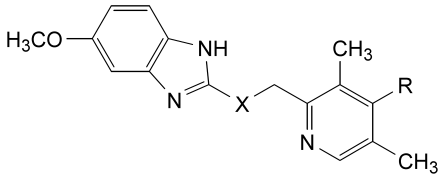
IMPURITIES

Specified impurities: 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, B, D, E.*



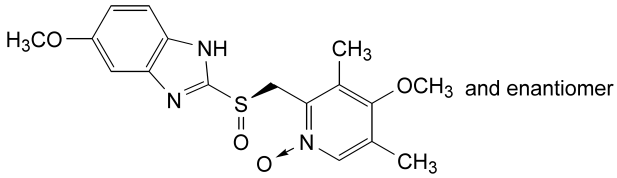
A. 5-methoxy-1*H*-benzimidazole-2-thiol,



B. R = H, X = SO: 2-[(*RS*)-[(3,5-dimethylpyridin-2-yl)methyl]sulphinyl]-5-methoxy-1*H*-benzimidazole,

C. R = OCH_3, X = S: 5-methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]thio]-1*H*-benzimidazole (ufiprazole),

D. R = OCH_3, X = SO_2: 5-methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfonyl]-1*H*-benzimidazole (omeprazole-sulphone),

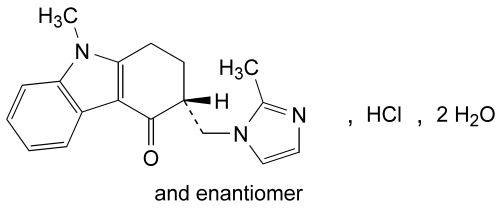


E. 4-methoxy-2-[[(*RS*)-(5-methoxy-1*H*-benzimidazol-2-yl)sulphinyl]methyl]-3,5-dimethylpyridine 1-oxide,

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.