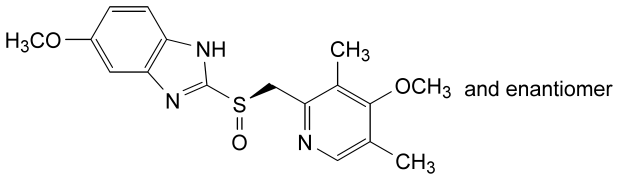
01/2008:0942

OMEPRAZOLE

Omeprazolum



$C_{17}H_{19}N_3O_3S$ M_r 345.4
[73590-58-6]

DEFINITION

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

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 methylene chloride, sparingly soluble in ethanol (96 per cent) and in methanol. It dissolves in dilute solutions of alkali hydroxides.

It shows polymorphism (*5.9*).

IDENTIFICATION

First identification: B.

Second identification: A, C.

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.

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

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *omeprazole 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. 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 from *acetic acid R*. The spots rapidly turn brown.

TESTS

Solution S. Dissolve 0.50 g in *methylene chloride R* and dilute to 25 ml with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*).

Impurities F and G: maximum 0.035 per cent for the sum of the contents.

The absorbance (*2.2.25*) of solution S measured at 440 nm is not greater than 0.10.

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

Solvent mixture: *methanol R, methylene chloride R* (50:50 *V/V*).

Test solution (a). Dissolve 0.10 g of the substance to be examined in 2.0 ml of the solvent mixture.

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

Reference solution (a). Dissolve 10 mg of *omeprazole CRS* in 2.0 ml of *methanol R*.

Reference solution (b). Dilute 1 ml of test solution (a) to 10 ml with the solvent mixture. Dilute 1 ml of this solution to 100 ml with the solvent mixture.

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.

Limits: 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 principal 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 mg of *omeprazole CRS* and 1 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 A = about 0.4; impurity E = about 0.6; impurity D = about 0.8; impurity B = about 0.9.

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 mobile phase or the concentration of *acetonitrile R*; an increase in the pH will improve the resolution.

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 $C_{17}H_{19}N_3O_3S$.

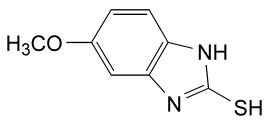
STORAGE

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

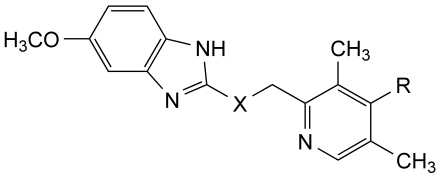
IMPURITIES

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,

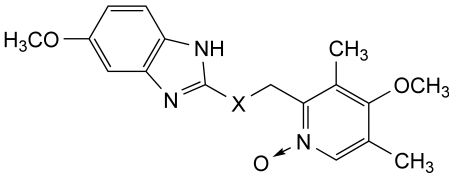


B. R = H, X = SO: 2-[(*RS*)-[(3,5-dimethylpyridin-2-yl)methyl]sulphinyl]-5-methoxy-1*H*-benzimidazole,

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

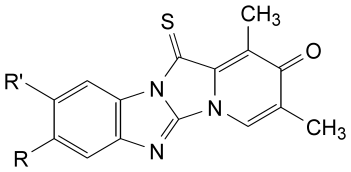
D. R = OCH_3, X = SO_2: 5-methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulphonyl]-1*H*-benzimidazole (omeprazole sulphone),

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,



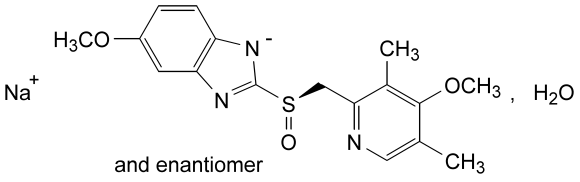
F. R = OCH_3, R′ = H: 8-methoxy-1,3-dimethyl-12-thioxopyrido[1′,2′:3,4]imidazo[1,2-*a*]benzimidazol-2(12*H*)-one,

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).