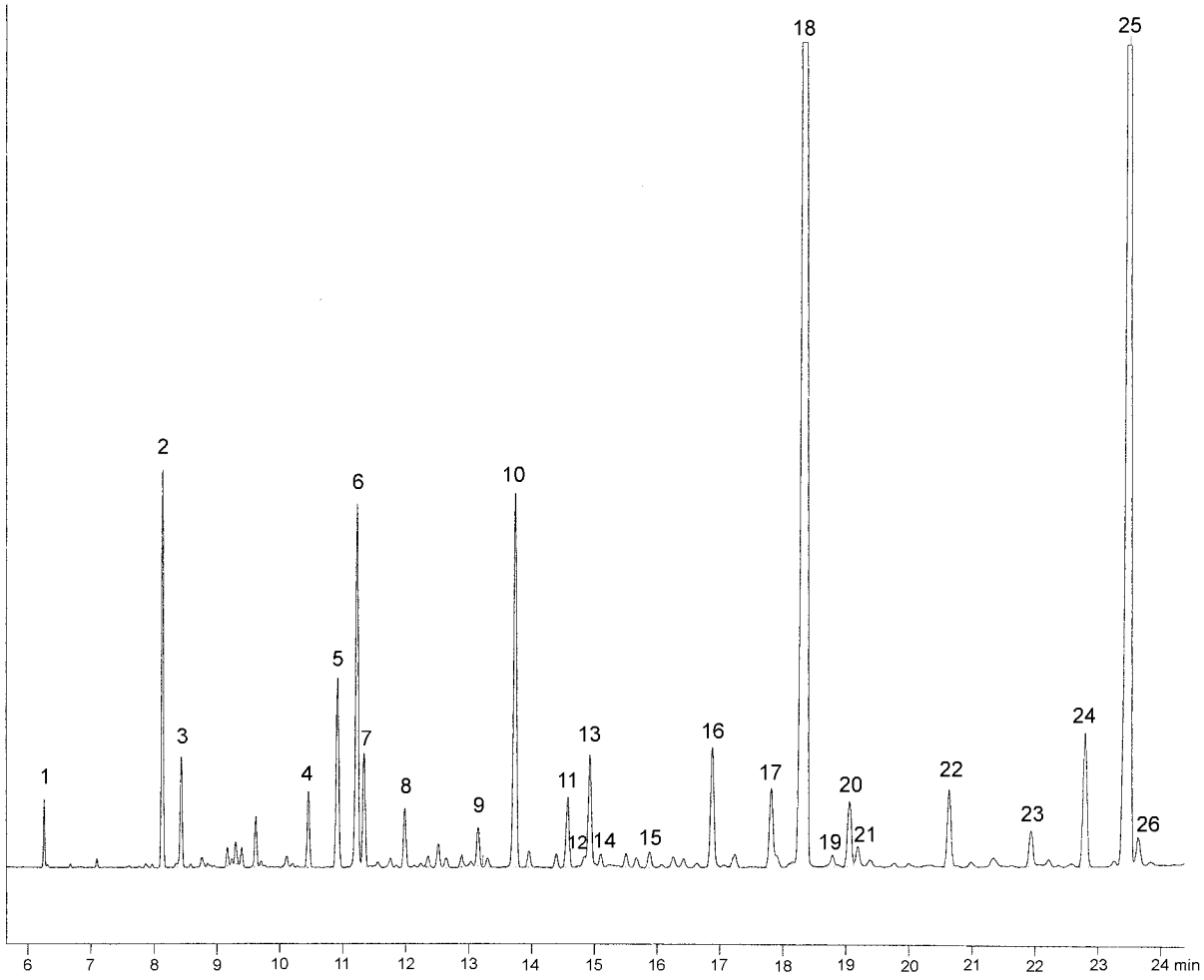


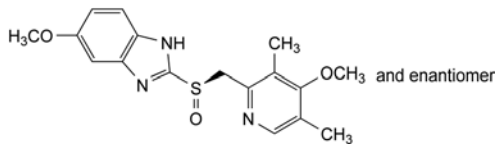

| | | | | | | |
|---|---|---|---|---|---|---|
| 1. C14:0 | 5. C18:0 | 9. C18:3 n-3 | 13. C20:1 n-9 | 17. C20:4 n-3 | 21. C22:1 n-9 | 25. DHA |
| 2. C16:0 | 6. C18:1 n-9 | 10. C18:4 n-3 | 14. C20:1 n-7 | 18. EPA | 22. C21:5 n-3 | 26. C24:1 n-9 |
| 3. C16:1 n-7 | 7. C18:1 n-7 | 11. C20:0 | 15. C20:2 n-6 | 19. C22:0 | 23. C22:5 n-6 | |
| 4. C16:4 n-1 | 8. C18:2 n-6 | 12. C20:1 n-11 | 16. C20:4 n-6 | 20. C22:1 n-11 | 24. C22:5 n-3 | |

Figure 1352.-2. – *Chromatogram for the assays*

**07/2010:0942**

# 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]sulfinyl]-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

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.

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 350 ppm for the sum of the contents.

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

**Related substances**. Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

*Test solution.* Dissolve 3 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.

*Reference solution (c).* Dissolve 3 mg of *omeprazole for peak identification CRS* (containing impurity E) in the mobile phase and dilute to 20.0 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 obtained with reference solution (a) to identify the peak due to impurity D; 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.

*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).

**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.

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

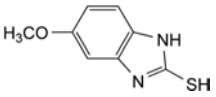
STORAGE

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

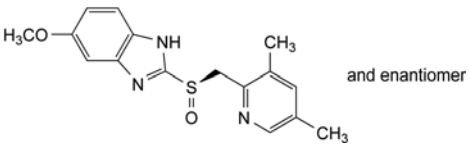
IMPURITIES

*Specified impurities: D, E, F, G.*

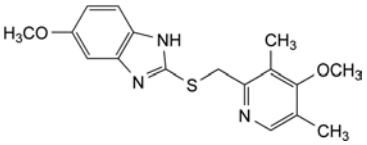
*Other detectable impurities* (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical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



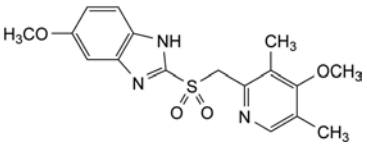
A. 5-methoxy-1*H*-benzimidazole-2-thiol,



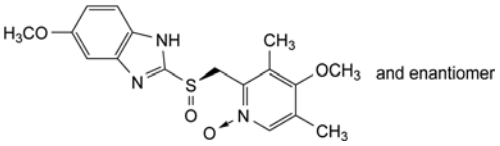

B. 2-[(*RS*)-[(3,5-dimethylpyridin-2-yl)methyl]sulfinyl]-5-methoxy-1*H*-benzimidazole,



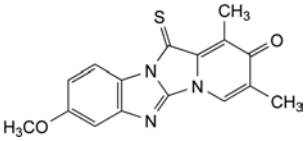
C. 5-methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfanyl]-1*H*-benzimidazole (ufiprazole),



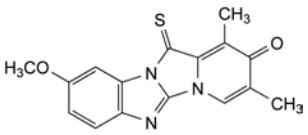
D. 5-methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfonyl]-1*H*-benzimidazole (omeprazole sulfone),



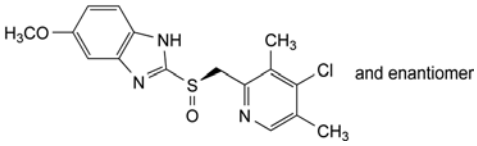

E. 4-methoxy-2-[[(*RS*)-(5-methoxy-1*H*-benzimidazol-2-yl)sulfinyl]methyl]-3,5-dimethylpyridine 1-oxide,



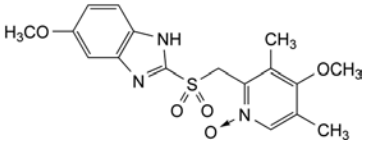
F. 8-methoxy-1,3-dimethyl-12-thioxopyrido[1′,2′:3,4]imidazo-[1,2-*a*]benzimidazol-2(12*H*)-one,



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



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

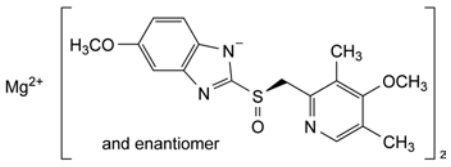


I. 4-methoxy-2-[[(5-methoxy-1*H*-benzimidazol-2-yl)sulfonyl]methyl]-3,5-dimethylpyridine 1-oxide.

**01/2009:2374**
**corrected 6.7**

# OMEPRAZOLE MAGNESIUM

## Omeprazolum magnesicum



$C_{34}H_{36}MgN_6O_6S_2$ $M_r$ 713
[95382-33-5]

DEFINITION

Magnesium bis[5-methoxy-2-[(*RS*)-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfinyl]-1*H*-benzimidazol-1-ide]. It contains a variable quantity of water.

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

CHARACTERS

*Appearance*: white or almost white, hygroscopic powder.

*Solubility*: very slightly soluble in water, sparingly soluble in methanol, practically insoluble in heptane.

IDENTIFICATION

Carry out either tests A, B, C or tests A, B, D.

A. Optical rotation (*2.2.7*): − 0.10° to + 0.10°.

Dissolve 0.250 g in *methanol R* and dilute to 25.0 mL with the same solvent.

B. Infrared absorption spectrophotometry (*2.2.24*).

*Comparison*: *omeprazole magnesium CRS*.

C. Atomic absorption spectrometry (*2.2.23*) as described in the test for magnesium.

The test solution shows the absorption maximum at 285.2 nm.

D. Ignite about 0.5 g of the substance to be examined according to the procedure for the sulfated ash test (*2.4.14*). Dissolve the residue in 10 mL of *water R*. 2 mL of this solution gives the reaction of magnesium (*2.3.1*).

TESTS

**Absorbance** (*2.2.25*): maximum 0.10 at 440 nm.

Dissolve 0.500 g in *methanol R* and dilute to 25.0 mL with the same solvent. Filter the solution through a membrane filter (nominal pore size 0.45 µm).

**Related substances**. Liquid chromatography (*2.2.29*): use the normalisation procedure. *Prepare the solutions immediately before use.*

*Test solution.* Dissolve 3.5 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).* Dissolve 3 mg of *omeprazole for peak identification CRS* (containing impurity E) in the mobile phase 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 10.0 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 (b) 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 its proportion of acetonitrile; an increase in the pH will improve the resolution.

*Limits*:

– *impurities D, E*: for each impurity, maximum 0.1 per cent;
– *unspecified impurities*: for each impurity, maximum 0.10 per cent;
– *total*: maximum 0.5 per cent;
– *disregard limit*: half the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

**Magnesium**: 3.30 per cent to 3.55 per cent (anhydrous substance).

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

*Test solution.* Dissolve 0.250 g in 20.0 mL of a 103 g/L solution of *hydrochloric acid R* by slow addition of the acid and dilute to 100.0 mL with *water R*. Dilute 10.0 mL of the solution to 200.0 mL with *water R*. To 10.0 mL of this solution add 4 mL of *lanthanum chloride solution R* and dilute to 100.0 mL with *water R*.

*Reference solutions.* Prepare the reference solutions using *magnesium standard solution (1000 ppm Mg) R*, diluting with a mixture of 1 mL of a 103 g/L solution of *hydrochloric acid R* and 1000.0 mL of *water R*.