Mobile phase: dissolve 0.95 g of *sodium hexanesulfonate R* in 1000 mL of a mixture of 25 volumes of *acetonitrile R* and 75 volumes of *water R* and add 4 mL of *acetic acid R*.

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 215 nm.

Injection: 20 µL.

Run time: 10 times the retention time of esketamine.

Relative retention with reference to esketamine: impurity A = about 1.6; impurity B = about 3.3; impurity C = about 4.6.

System suitability: reference solution (a):

– *retention time*: esketamine = 3.0 min to 4.5 min,
– *resolution*: minimum 1.5 between the peaks due to impurity A and esketamine.

Limits:

– *impurities A, B, C*: for each impurity, not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent),
– *any other impurity*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent),
– *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent),
– *disregard limit*: 0.2 times 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.

Dilute 12.5 mL of solution S to 20 mL with *water R*. 12 mL of the solution complies with limit test A. Prepare the standard using *lead standard solution (2 ppm Pb) R*.

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

ASSAY

Dissolve 0.200 g in 50 mL of *methanol R* and add 1.0 mL of *0.1 M hydrochloric acid*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

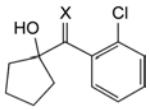
1 mL of *0.1 M sodium hydroxide* is equivalent to 27.42 mg of $C_{13}H_{17}Cl_2NO$.

STORAGE

Protected from light.

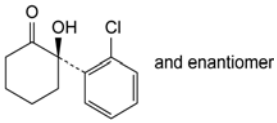
IMPURITIES

Specified impurities: A, B, C, D.

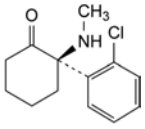


A. X = N-CH_3: 1-[(2-chlorophenyl)(methylimino)methyl]cyclopentanol,

C. X = O: (2-chlorophenyl)(1-hydroxycyclopentyl)methanone,



B. (2*RS*)-2-(2-chlorophenyl)-2-hydroxycyclohexanone,

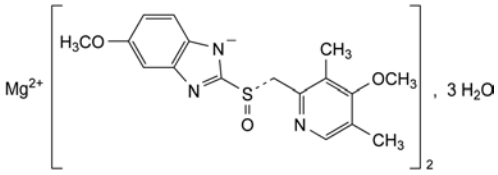


D. (2*R*)-2-(2-chlorophenyl)-2-(methylamino)cyclohexanone ((*R*)-ketamine).

01/2009:2372
corrected 6.7

ESOMEPRAZOLE MAGNESIUM TRIHYDRATE

Esomeprazolum magnesicum trihydricum



$C_{34}H_{36}MgN_6O_6S_2,3H_2O$ M_r 767.2
[217087-09-7]

DEFINITION

Magnesium bis[5-methoxy-2-[(*S*)-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfinyl]-1*H*-benzimidazol-1-ide] trihydrate.

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

CHARACTERS

Appearance: white or slightly coloured powder, slightly hygroscopic.

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

IDENTIFICATION

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

A. Specific optical rotation (*2.2.7*): – 137 to – 155.

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: *esomeprazole magnesium trihydrate 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. Enantiomeric purity (see Tests).

E. 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 0.20 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. *Use freshly prepared solutions.*

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 the *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.

Monographs D-E

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 esomeprazole.

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 esomeprazole (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:

– *impurity D*: maximum 0.2 per cent;

– *impurity E*: maximum 0.1 per cent;

– *unspecified impurities*: for each impurity, maximum 0.10 per cent;

– *total*: maximum 0.5 per cent;

– *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Enantiomeric purity. Liquid chromatography (*2.2.29*).

Buffer solution pH 6.0. Mix 70 mL of a 156.0 g/L solution of *sodium dihydrogen phosphate R* with 20 mL of a 179.1 g/L solution of *disodium hydrogen phosphate R*. Dilute to 1000 mL with *water R*, then dilute 250 mL of this solution to 1000.0 mL with *water R*.

Buffer solution pH 11.0. Mix 11 mL of a 95.0 g/L solution of *trisodium phosphate dodecahydrate R* with 22 mL of a 179.1 g/L solution of *disodium hydrogen phosphate R*, then dilute to 1000.0 mL with *water R*.

Test solution. Dissolve 40 mg of the substance to be examined in 5 mL of *methanol R* and dilute to 25 mL with buffer solution pH 11.0. Dilute 1.0 mL of this solution to 50.0 mL with buffer solution pH 11.0.

Reference solution (a). Dissolve 2 mg of *omeprazole CRS* in buffer solution pH 11.0 and dilute to 10.0 mL with the same buffer solution. Dilute 1.0 mL of this solution to 50.0 mL with buffer solution pH 11.0.

Reference solution (b). Dilute 1.0 mL of reference solution (a) to 50.0 mL with buffer solution pH 11.0.

Column:

– *size*: *l* = 0.1 m, Ø = 4.0 mm;

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

Mobile phase: *acetonitrile R*, buffer solution pH 6.0 (65:435 *V/V*).

Flow rate: 0.6 mL/min.

Detection: spectrophotometer at 302 nm.

Injection: 20 µL.

Elution order: impurity F, esomeprazole.

Retention time: esomeprazole = about 4 min.

System suitability:

– *resolution*: minimum 3.0 between the peaks due to impurity F and esomeprazole in the chromatogram obtained with reference solution (a);

– *signal-to-noise ratio*: minimum 10 for the peak due to impurity F in the chromatogram obtained with reference solution (b).

Calculate the percentage content of impurity F using the following expression:

$$100 \left(\frac{r_i}{r_s} \right)$$

r_i = area of the peak due to impurity F in the chromatogram obtained with the test solution;

r_s = sum of the areas of the peaks due to esomeprazole and impurity F in the chromatogram obtained with the test solution.

Limits:

– *impurity F*: maximum 0.2 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 mL of a 103 g/L solution of *hydrochloric acid R*, adding the acid slowly, and dilute to 100.0 mL with *water R*. Dilute 10.0 mL of this solution to 200.0 mL with *water R*. To 10.0 mL of the solution obtained 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*, diluted as necessary with a mixture of 1 mL of a 103 g/L solution of *hydrochloric acid R* in 1000.0 mL of *water R*.

Wavelength: 285.2 nm.

Water (*2.5.12*): 6.0 per cent to 8.0 per cent, determined on 0.200 g.

ASSAY

Liquid chromatography (*2.2.29*).

Buffer solution pH 11.0. Mix 11 mL of a 95.0 g/L solution of *trisodium phosphate dodecahydrate R* with 22 mL of a 179.1 g/L solution of *disodium hydrogen phosphate R*, and dilute to 100.0 mL with *water R*.

Test solution. Dissolve 10.0 mg of the substance to be examined in about 10 mL of *methanol R*, add 10 mL of buffer solution pH 11.0 and dilute to 200.0 mL with *water R*.

Reference solution. Dissolve 10.0 mg of *omeprazole CRS* in about 10 mL of *methanol R*, add 10 mL of buffer solution pH 11.0 and dilute to 200.0 mL with *water R*.

Column:

– *size*: *l* = 0.125 m, Ø = 4 mm;

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

Mobile phase: mix 35 volumes of *acetonitrile R* with 65 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: 20 µL.

Run time: 1.5 times the retention time of esomeprazole.

Retention time: esomeprazole = about 4 min.

Calculate the percentage content of $C_{34}H_{36}MgN_6O_6S_2$ from the declared content of *omeprazole CRS*.

1 g of omeprazole is equivalent to 1.032 g of esomeprazole magnesium.

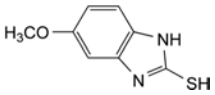
STORAGE

In an airtight container, protected from light.

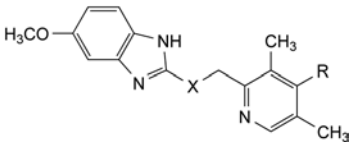
IMPURITIES

Specified impurities: *D, E, F.*

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.*



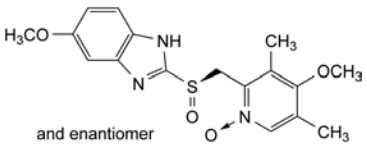
A. 5-methoxy-1*H*-benzimidazole-2-thiol,



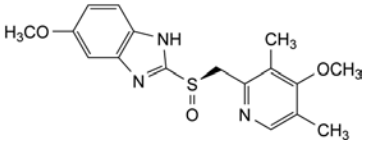
B. R = H, X = SO: 2-[(*RS*)-[(3,5-dimethylpyridin-2-yl)methyl]sulfinyl]-5-methoxy-1*H*-benzimidazole,

C. R = OCH_3, X = S: 5-methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfanyl]-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 sulfone),



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

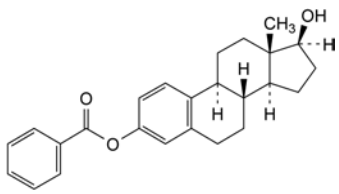


F. 5-methoxy-2-[(*R*)-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfinyl]-1*H*-benzimidazole((*R*)-omeprazole).

04/2008:0139

ESTRADIOL BENZOATE

Estradioli benzoas



$C_{25}H_{28}O_3$ M_r 376.5

[50-50-0]

DEFINITION

17β-Hydroxyestra-1,3,5(10)-trien-3-yl benzoate.

Content: 97.0 per cent to 103.0 per cent (dried substance).

CHARACTERS

Appearance: almost white, crystalline powder or colourless crystals.

Solubility: practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in acetone, slightly soluble in methanol.

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *estradiol benzoate CRS.*

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *acetone R*, evaporate to dryness and record new spectra using the residues.

TESTS

Specific optical rotation (*2.2.7*): + 55.0 to + 59.0 (dried substance).

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

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 20 mg of the substance to be examined in *acetonitrile R1* and dilute to 10.0 mL with the same solvent.

Reference solution (a). Dissolve 5 mg of *estradiol benzoate for system suitability CRS* (containing impurities A, B, C, E and G) in *acetonitrile R1* and dilute to 2.5 mL with the same solvent.

Reference solution (b). Dilute 0.5 mL of the test solution to 100.0 mL with *acetonitrile R1.*

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;
– *stationary phase*: *end-capped octylsilyl silica gel for chromatography R* (5 μm).

Mobile phase:

– *mobile phase A*: *water R, acetonitrile R1* (40:60 *V/V*);
– *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 20	100	0
20 - 21	100 → 10	0 → 90
21 - 31	10	90

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 230 nm.

Injection: 10 μL.

Identification of impurities: use the chromatogram supplied with *estradiol benzoate for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, C, E and G.

Relative retention with reference to estradiol benzoate (retention time = about 19 min): impurity A = about 0.3; impurity E = about 1.1; impurity B = about 1.2; impurity G = about 1.3; impurity C = about 1.5.

System suitability: reference solution (a):

– *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity E and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to estradiol benzoate.

Limits:

– *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 3.3; impurity C = 0.7;
– *impurity C*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);