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Esomeprazole for Injection

General Notices

Details for the public consultation of this monograph are as follows:

EAG/Panel/Working Party	Medicinal Chemicals 1
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Notes	Revised monograph If limits are too restrictive, please provide batch/stability data to demonstrate that an increase is required. Enantiomeric purity Test solution concentrations aligned with Ph. Eur. Esomeprazole Sodium monograph Related substances Revised test based on Ph. Eur. Esomeprazole Sodium monograph Assay Standard solution preparation and System suitability requirement modified

Action and use

Proton pump inhibitor; treatment of peptic ulcer disease.

DEFINITION

Esomeprazole for Injection is a sterile material consisting of [Esomeprazole Sodium](#) with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under [Parenteral Preparations](#) and with the following requirements.

Content of esomeprazole, C₁₇H₁₉N₃O₃S

95.0 to 105.0% of the stated amount.

IDENTIFICATION

- A. The powder for injection complies with the test for Esomeprazole Impurity B.
- B. In the test for Esomeprazole Impurity B, the UV spectrum, in the range 210 nm to 400 nm, of the principal peak obtained with solution (1) is similar to that of the peak to esomeprazole in the chromatogram obtained with solution (3).

TESTS

Alkalinity

pH of a solution containing the equivalent of 0.8% w/v of esomeprazole in 0.9% w/v of [sodium chloride](#) in [water for injections](#), 9.0 to 11.0, [Appendix V L](#).

Esomeprazole impurity B (enantiomeric purity)

Carry out the method for [liquid chromatography](#), [Appendix III D](#), using the following solutions.

Solution A Dilute a mixture of 11 volumes of 0.25M [trisodium orthophosphate](#) and 22 volumes of 0.5 M [disodium hydrogen orthophosphate](#) to 100 volumes with [water](#). Adjust to pH 11.0 with [orthophosphoric acid](#) or 10M [sodium hydroxide](#).

- (1) Disperse a quantity of the powder containing the equivalent of 40 mg of esomeprazole in 5 mL of [methanol](#), dilute to 50 mL with solution A and filter (a 0.45-µm nylon filter is suitable). Further dilute 1 volume to 25 volumes with solution A.
- (2) 0.0004% w/v of [omeprazole BPCRS](#) in solution A.
- (3) 0.0008% w/v of [omeprazole BPCRS](#) in solution A.

CHROMATOGRAPHIC CONDITIONS

- (a) Use a stainless steel column (10 cm × 4.0 mm) packed with [α₁-acid-glycoprotein silica gel for chiral separation](#) (5 µm) (Chiralpak AGP is suitable).
- (b) Use isocratic elution and the mobile phase described below.
- (c) Use a flow rate of 0.6 mL per minute.
- (d) Use an ambient column temperature.
- (e) Use a detection wavelength of 302 nm.
- (f) Use a diode array detector (for identification A).
- (g) Inject 20 µL of each solution.

MOBILE PHASE

13 volumes of [acetonitrile](#) and 87 volumes of a solution containing 0.0025M [disodium hydrogen orthophosphate](#) and 0.005M [sodium dihydrogen orthophosphate](#).

When the chromatograms are recorded under the prescribed conditions, the relative retention with reference to esomeprazole (retention time about 5 minutes) is: (*R*)-omeprazole (impurity B), about 0.7.

SYSTEM SUITABILITY

The test is not valid unless in the chromatogram obtained with solution (2), the [resolution](#) between the peaks due to (*R*)-omeprazole and esomeprazole is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the peak of any area due to impurity B is not greater than 0.2% by [normalisation](#).

disregard any peak with an area less than 0.1% of that of the area of the peak due to esomeprazole.

Related substances

Carry out the method for [liquid chromatography](#), [Appendix III D](#), using the following solutions prepared in mobile phase A. Solutions (1) and (4) should be freshly prepared and injected within 15 minutes.

- (1) Disperse a quantity of the powder containing the equivalent of 0.2 g of esomeprazole in 100 mL and dilute to 1 volume to 10 volumes.
- (2) Dilute 1 volume of solution (1) to 200 volumes.
- (3) 0.0005% w/v each of [omeprazole BPCRS](#) and [omeprazole impurity D EPCRS](#) dissolving first in a minimum quantity of [acetonitrile](#).
- (4) 0.01% w/v of [omeprazole impurity standard BPCRS](#) dissolving first in a minimum quantity of [acetonitrile](#).
- (5) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

- (a) Use a stainless steel column (10 cm × 4.6 mm) packed with [octadecylsilyl silica gel for chromatography](#) (3 µm) (MicroSpher C18 is suitable).
- (b) Use gradient elution and the mobile phase described below.
- (c) Use a flow rate of 1 mL per minute.
- (d) Use an ambient column temperature
- (e) Use an autosampler temperature of 5°
- (f) Use a detection wavelength of 302 nm.
- (g) Inject 20 µL of each solution.

MOBILE PHASE

Solution B 0.57% w/v [disodium hydrogen orthophosphate](#) and 0.07% w/v of [orthophosphoric acid](#) in [water](#) adjusted to pH 7.6 with [sodium hydroxide](#).

Mobile phase A 1 volume of **solution B** mixed with 1 volume of [acetonitrile R](#) and diluted to 10 volumes with [water](#).

Mobile phase B 10 volume of **solution B** mixed with 800 volumes of [acetonitrile R](#) and diluted to 1000 volumes with [water](#).

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	100	0	isocratic

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
5-15	100→80	0→20	linear gradient
15-35	80→0	20→100	linear gradient
35-38	0→100	100→0	linear gradient
38-45	100	0	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the [resolution](#) between the peaks due to omeprazole and impurity D and is at least 3.0.

CALCULATION OF IMPURITIES

For each impurity, use the concentration of omeprazole in solution (2).

For the reporting threshold, use the concentration of omeprazole in solution (5).

For peak identification, use solutions (3) and (4).

Omeprazole retention time: about 7 minutes.

Relative retention: impurity 3, about 0.2; impurity 1, about 0.37; impurity A, about 0.46; impurity 5, about 0.49; impurity D; about 0.97; impurity 2, about 1.07.

LIMITS

- impurity 5: not more than 1.3%;
- impurity 2: not more than 0.9%;
- impurity D: not more than 0.5%;
- unspecified impurities: for each impurity, not more than 0.2%;
- total impurities: not more than 2.6%;
- reporting threshold: 0.1%.

ASSAY

Determine the weight of the contents of 10 containers as described in the test for [uniformity of weight](#), [Appendix XII C1](#), Powders for Parenteral Administration.

Carry out the method for [liquid chromatography](#), [Appendix III D](#), using the following solutions.

Solution A Dilute a mixture of 11 volumes of 0.25M [trisodium orthophosphate](#) and 22 volumes of 0.5M [disodium hydrogen orthophosphate](#) to 100 volumes with [water](#). Adjust to pH 11.0 with

orthophosphoric acid or 10M sodium hydroxide.

- (1) Disperse a quantity of the mixed contents of 10 containers containing the equivalent of 20 mg of esomeprazole with 20 mL of ethanol, dilute to 100 mL with solution A and filter (a 0.45-µm glass fibre filter is suitable). Dilute 1 volume to 5 volumes with water.
- (2) 0.02% w/v of omeprazole BPCRS in a mixture of 1 volume of ethanol and 4 volumes of solution A. Dilute 1 volume to 5 volumes with water.
- (3) 0.0005% w/v of omeprazole BPCRS and omeprazole impurity D EPCRS, each prepared by dissolving the reference material in 1 volume of ethanol and diluting to 5 volumes with solution A. Mix 1 volume of each solution and dilute to 10 volumes with water.

CHROMATOGRAPHIC CONDITIONS

- (a) Use a stainless steel column (15 cm × 4.6 mm) packed with end-capped extra-dense bonded octadecylsilyl silica gel for chromatography (5 µm) (XDB-C18 is suitable).
- (b) Use isocratic elution and the mobile phase described below.
- (c) Use a flow rate of 1 mL per minute.
- (d) Use a column temperature of 20°.
- (e) Use a detection wavelength of 302 nm.
- (f) Use an autosampler temperature of 5°.
- (f) Inject 20 µL of each solution.

MOBILE PHASE

Solution D Dilute a mixture of 10.5 volumes of 1M sodium dihydrogen orthophosphate monohydrate and 60 volumes of 0.5M disodium hydrogen orthophosphate dihydrate to 1000 volumes with water. Adjust to pH 7.3 with orthophosphoric acid or 10M sodium hydroxide.

33 volumes of acetonitrile, 52 volumes of solution D and dilute to 100 volumes with water.

When the chromatograms are recorded under the prescribed conditions, the retention time of esomeprazole is about 5 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the resolution between the peaks due to impurity D and omeprazole is greater than 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{17}H_{19}N_3O_3S$ in a container of average content weight from the chromatograms obtained and from the declared content of $C_{17}H_{19}N_3O_3S$ in omeprazole BPCRS.

LABELLING

The label of the sealed container states the quantity of Esomeprazole Sodium contained in it in terms of the equivalent amount of esomeprazole.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A and C to G listed under [Esomeprazole Sodium](#) and:

-  1. 2-hydroxy-5-methoxybenzimidazole (5-methoxy-2-benzimidazolinone)
1. 2-hydroxy-5-methoxybenzimidazole (5-methoxy-2-benzimidazolinone)
-  2. 5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1-methyl-1H-benzimidazole and 6-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1-methyl-1H-benzimidazole, regioisomers
2. 5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1-methyl-1*H*-benzimidazole and 6-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1-methyl-1*H*-benzimidazole, regioisomers
-  3. 1,4-dihydro-1-(5-methoxy-1H-benzimidazol-2-yl)-3,5-dimethyl-4-oxo-2-pyridinecarboxylic acid
3. 1,4-dihydro-1-(5-methoxy-1*H*-benzimidazol-2-yl)-3,5-dimethyl-4-oxo-2-pyridinecarboxylic acid
-  4. [1-(5-methoxy-1H-benzimidazol-2-yl)-3,5-dimethyl-4-oxo-1,4-dihydropyridin-2-yl] methanesulfinic acid
4. [1-(5-methoxy-1*H*-benzimidazol-2-yl)-3,5-dimethyl-4-oxo-1,4-dihydropyridin-2-yl] methanesulfinic acid
-  5. 2{[(5-methoxy-1H-benzimidazol-2-yl)sulfinyl]methyl}-3,5-dimethyl-4(1H)-pyridone
5. 2{[(5-methoxy-1*H*-benzimidazol-2-yl)sulfinyl]methyl}-3,5-dimethyl-4(1*H*)-pyridone