Esomeprazole Magnesium Trihydrate

Published on: 07 February, 2024 **Last date for comments:** 22 March, 2024

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Manufacturers, regulatory authorities, health authorities, researchers, and other stakeholders are invited to provide their feedback and comments on this draft proposal. Manufacturers are also invited to submit samples of their products to the IPC to ensure that the proposed monograph adequately controls the quality of the product(s) they manufacture. Comments and samples received after the last date will not be considered by the IPC before finalizing the monograph.

Please send any comments you may have on this draft document to lab.ipc@gov.in, with a copy to Dr. Gaurav Pratap Singh (email: gpsingh.ipc@gov.in) before the last date for comments.

Document History and Schedule for the Adoption Process

Description	Details
Document version	1.0
First draft published on IPC website for public comments	February 7, 2024
Last date for comments	**March 22, 2024**
Monograph revisions proposed for inclusion in	**IP 2026**
Tentative effective date of monograph revisions	**July, 2026**
Draft revision published on IPC website for public comments	--
Further follow-up action as required.	

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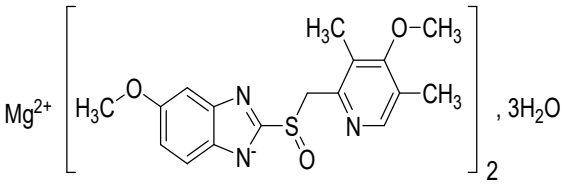
Change **to**: **Esomeprazole Magnesium Trihydrate**



$(C_{17}H_{18}N_3O_3S)_2$, $Mg.3H_2O$ Mol. Wt. 767.2

Esomeprazole Magnesium Trihydrate is 5-methoxy-2-{(*S*)- [(4-methoxy-3,5-dimethy1-2-pyridinyl)methy]sulfinyl}-1*H*-benzimidazolemagnesium trihydrate.

Esomeprazole Magnesium Trihydrate contains not less than 98.0 per cent and not more than 102.0 per cent of $(C_{17}H_{18}N_3O_3S)_2$,Mg, calculated on the anhydrous basis.

Category. Antiulcer.

Description. A white to slightly coloured powder.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *esomeprazole magnesium IPRS* or with the reference spectrum esomeprazole magnesium.

B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

Tests

Magnesium. 3.30 per cent to 3.55 per cent, calculated on the anhydrous basis.

Dissolve 0.4 g of the substance under examination in 25 ml of *methanol* and sonicate to dissolve. Add 25 ml of *water*, 10 ml of *concentrated ammonia*, 20.0 ml of *0.05 M disodium edentate* and 50 mg of *mordant black 11*. Titrate the excess of *disodium edetate* with *0.05 M zinc sulphate* until the colour change from blue to violet. Carry out a blank titration.

1 ml of *0.05 M disodium edetate* is equivalent to 0.00121525 g of magnesium.

Related substances. Determine by liquid chromatography (2.4.14).

NOTE- Prepare solutions immediately before use.

Test solution. Dissolve 80 mg of the substance under examination in the mobile phase and dilute to 100.0 ml with the mobile phase. Dilute 10.0 ml of the solution to 50.0 ml with the mobile phase.

Reference solution. A solution containing 0.004 per cent w/v, each of, *omeprazole IPRS* and *omeprazole related compound A IPRS* in the mobile phase.

Chromatographic system

– a stainless steel column 12.5 cm x 4.0 mm, packed with octylsilane bonded to porous silica (5 µm) (Such as Lichrosorb RP-8),

- mobile phase: a mixture of 72.5 volumes of a buffer solution prepared by dissolving 1.12 g of *disodium hydrogen orthophosphate anhydrous* and 0.18 g of *sodium dihydrogen orthophosphate* in 1000 ml of *water*, adjusted to pH 7.6 with *orthophosphoric acid* and27.5 volumes of *acetronitrile,*
- flow rate: 0.8 ml per minute,
- spectrophotometer set at 280 nm,
- injection volume: 50 µl.

Name	Relative retention time
Omeprazole N- oxide[1]	0.45
Omeprazole related compound A[2]	0.80
Esomeprazole	1.0

[1]4-Methoxy-2-[[(*RS*)-(5-methoxy-1*H*-benzimidazol-2-yl)sulfinyl]methyl]-3,5-dimethylpyridine 1-oxide,
[2]5-Methoxy-2-{[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfonyl}-1*H*-benzimidazole.

Inject the reference solution. The test is not valid unless the resolution between the peaks due to omeprazole related compound A and omeprazole is not less than 3.0.

Inject the test solution. Run the chromatograms 4.5 times of the principal peak. The area of any peak corresponding to omeprazole N-oxide is not more than 0.1 per cent, the area of any peak corresponding to omeprazole related compound A, is not more than 0.2 per cent, the area of any other secondary peak is not more than 0.10 per cent and the sum of areas of all the secondary peaks is not more than 0.5 per cent, calculated by area normalization.

Enantiomeric purity. Determine by liquid chromatography (2.4.14).

Solution A. Mix 70 ml of *1 M sodium dihydrogen orthophosphate* with 20 ml of *0.5 M disodium hydrogen ortho phosphate* and dilute to 1000 ml with *water.* Dilute 250 ml of the solution to 1000 ml with *water*.

Solvent mixture. Mix 11 ml of *0.25 M trisodium orthophosphate* with22 ml of *0.5 M disodium hydrogen ortho phosphate* and dilute to 1000 ml with *water*.

Test solution. Dissolve 40 mg of the substance under examination in 5 ml of *methanol* and dilute to 25.0 ml with the solvent mixture. Dilute 1.0 ml of the solution to 50.0 ml with the solvent mixture.

Reference solution. A 0.0004 per cent w/v solution of *omeprazole IPRS* in the solvent mixture.

Chromatographic system
- a stainless steel column 10 cm x 4.0 mm, packed with immobilised α-1 acid glycoprotein on spherical silica particles (5µm) (Such as Chiral-AGP),
- mobile phase: a mixture of 85 volumes of solution A and 15 volumes of *acetonitrile,*
- flow rate: 0.6 ml per minute,
- spectrophotometer set at 302 nm,
- injection volume: 20 µl.

Inject the reference solution. The test is not valid unless the resolution between the peaks due to R- enantiomer and S - enantiomer is not less than 3.0.
[NOTE -The elution order is R-enantiomer, followed by Esomeprazole peak (S-enantiomer)].

Inject the test solution. The area of any peak due to R-enantiomer is not more than 0.2 per cent, calculated by area normalization.

Heavy metals (2.3.13). 1.0 g complies with the limit test for heavy metals, Method B (20 ppm).

Water (2.3.43). 6.0 per cent to 8.0 per cent, determined on 0.2 g.

Assay. Determine by liquid chromatography (2.4.14).

Solvent mixture. Mix 11 ml of *0.25 M trisodium orthophosphate* with22 ml of *0.5 M disodium hydrogen ortho phosphate* and dilute to 100 ml with *water*.

Test solution. Weigh and transfer 10 mg of the substance under examination to a 200-ml volumetric flask, add 10 ml of *methanol* and mix to dissolve. Add10 ml of the solvent mixture and dilute to volume with *water*.

Reference solution. Transfer 10 mg of *omeprazole IPRS* to a 200-ml volumetric, add 10 ml of *methanol* and mix to dissolve. Add10 ml of the solvent mixture and dilute to volume with *water*.

Chromatographic system

- a stainless steel column 12.5 cm x 4.0 mm, packed with octylsilane bonded to porous silica (5 µm),
- mobile phase: a mixture of 65 volumes of a buffer solution prepared by dissolving 1.12 g of *disodium hydrogen orthophosphate anhydrous* and 0.18 g of *sodium dihydrogen orthophosphate* in 1000 ml of *water*, adjusted to pH 7.6 with *orthophosphoric acid* and35 volumes of *acetonitrile,*
- flow rate: 1 ml per minute,
- spectrophotometer set at 280 nm,
- injection volume: 20 µl.

Inject the reference solution. The test is not valid unless the tailing factor is not more than 1.5 and the relative standard deviation for replicate injections is not more than 1.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $(C_{17}H_{18}N_3O_3S)_2$, $Mg.3H_2O$.

Storage. Store protected from light and moisture, at a temperature not exceeding 30°.