Esomeprazole Magnesium

Type of Posting	Notice of Intent to Revise
Posting Date	29-Jul-2022
Targeted Official Date	To Be Determined, Revision Bulletin
Expert Committee	Small Molecules 3

In accordance with the Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Small Molecules 3 Expert Committee intends to revise the Esomeprazole Magnesium monograph.

The purpose of this revision is to widen the *Acceptance criteria* for the *Content of Magnesium* test from 3.30%–3.55% on the anhydrous basis to 3.30%–3.70% on the anhydrous basis.

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.[1]

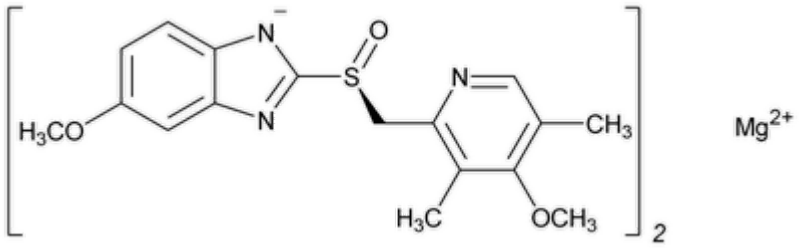
Should you have any questions, please contact Robyn Fales, Senior Scientist I (240-221-2047 or rnp@usp.org).

[1] This text is not the official version of a *USP–NF* monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the *USP–NF* for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product's final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the *Pharmacopeial Forum* must also meet the requirements outlined in the USP Guideline on Use of Accelerated Processes for Revisions to the *USP–NF*.

Notice of Intent to Revise
Official: To Be Determined

Esomeprazole Magnesium



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$C_{34}H_{36}MgN_6O_6S_2 \cdot 3H_2O$ Trihydrate: 767.17
$C_{34}H_{36}MgN_6O_6S_2 \cdot 2H_2O$ Dihydrate: 749.15
$C_{34}H_{36}MgN_6O_6S_2$ Anhydrous: 713.12

1*H*-Benzimidazole,5-methoxy-2-[(*S*)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-, magnesium salt (2:1)

5-Methoxy-2-[(*S*)-[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]benzimidazole, magnesium salt (2:1)

Trihydrate: CAS RN®: 217087-09-7; UNII: R6DXU4WAY9.
Dihydrate: CAS RN®: 217087-10-0; UNII: 36H71644EQ.

DEFINITION

Esomeprazole Magnesium contains NLT 98.0% and NMT 102.0% of esomeprazole magnesium ($C_{34}H_{36}MgN_6O_6S_2$), calculated on the anhydrous basis.

IDENTIFICATION

● **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197K. [Note—If a difference appears in the IR spectra of the analyte and the Standard, separately dissolve equal portions of the sample specimen and USP Esomeprazole Magnesium RS in equal volumes of methanol, evaporate the solution to dryness in similar containers under identical conditions, and repeat the test on the residues.]

● **B.** The *Sample solution*, prepared and tested as directed in the test for *Content of Magnesium*, exhibits a significant absorption at 285.2 nm.

● **C.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

● **Procedure**

Solution A: 0.181 g/L of sodium phosphate monobasic and 1.118 g/L of sodium phosphate dibasic anhydrous in water. If necessary, adjust with phosphoric acid to a pH of 7.6.

Solution B: Mix 11 mL of 0.25 M sodium phosphate tribasic with 22 mL of 0.5 M sodium phosphate dibasic, and dilute with water to 100 mL.

Mobile phase: Acetonitrile and *Solution A* (35:65)

Standard solution: 0.05 mg/mL of USP Omeprazole RS prepared as follows. Transfer 10 mg of USP Omeprazole RS to a 200-mL volumetric flask, and dissolve in about 10 mL of methanol. Add 10 mL of

Solution B, and dilute with water to volume.

Sample solution: 0.05 mg/mL of Esomeprazole Magnesium prepared as follows. Transfer 10 mg of Esomeprazole Magnesium to a 200-mL volumetric flask, and dissolve in about 10 mL of methanol. Add 10 mL of *Solution B*, and dilute with water to volume.

Chromatographic system

(See *Chromatography* ⟨621⟩*, System Suitability*.)

Mode: LC

Detector: UV 280 nm

Column: 4.0-mm × 12.5-cm or 4.6-mm × 15-cm; 5-µm packing L7. [Note—Alternatively, a 3.9-mm × 15-cm column; 4-µm packing L1 may be used.]

Flow rate: 1.0 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 1.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of esomeprazole magnesium ($C_{34}H_{36}MgN_6O_6S_2$) in the portion of Esomeprazole Magnesium taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times [M_{r1}/(2 \times M_{r2})] \times 100$$

r_U = peak response of esomeprazole from the *Sample solution*

r_S = peak response of omeprazole from the *Standard solution*

C_S = concentration of USP Omeprazole RS in the *Standard solution* (mg/mL)

C_U = concentration of Esomeprazole Magnesium in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of esomeprazole magnesium, 713.12

M_{r2} = molecular weight of omeprazole, 345.42

Acceptance criteria: 98.0%–102.0% on the anhydrous basis

OTHER COMPONENTS

Change to read:

- **Content of Magnesium**

Lanthanum solution: Transfer 58.7 g of lanthanum oxide to a 1000-mL volumetric flask, wet the substance with some water, and dissolve by cautious addition of 250 mL of hydrochloric acid in 20- to 30-mL portions, cooling between the additions. Add water while stirring, cool to room temperature, and dilute with water to volume. [Note—Store the solution in a plastic bottle.]

Standard stock solution: 1000 µg/mL of magnesium in water, from a commercially prepared atomic absorption standard solution. [Note—Store the solution in a plastic bottle.]

Standard solution A: Transfer 10.0 mL of *Standard stock solution* to a 500-mL volumetric flask, add 50 mL of 1 N hydrochloric acid, and dilute with water to volume. Transfer 20.0 mL of this solution to a

200-mL volumetric flask, and dilute with water to volume. [Note—This solution contains 2 µg/mL of magnesium.]

Standard solution B: Combine 5.0 mL of *Standard solution A* and 4.0 mL of *Lanthanum solution*, and dilute with water to 100.0 mL (0.1 µg/mL).

Standard solution C: Combine 10.0 mL of *Standard solution A* and 4.0 mL of *Lanthanum solution*, and dilute with water to 100.0 mL (0.2 µg/mL).

Standard solution D: Combine 15.0 mL of *Standard solution A* and 4.0 mL of *Lanthanum solution*, and dilute with water to 100.0 mL (0.3 µg/mL).

Standard solution E: Combine 20.0 mL of *Standard solution A* and 4.0 mL of *Lanthanum solution*, and dilute with water to 100.0 mL (0.4 µg/mL).

Standard solution F: Combine 25.0 mL of *Standard solution A* and 4.0 mL of *Lanthanum solution*, and dilute with water to 100.0 mL (0.5 µg/mL). [Note—Concentrations of the *Standard solutions* and the *Sample solution* may be modified to fit the linear or working range of the instrument. When using instruments with a linear calibration graph, the number of *Standard solutions* can be reduced.]

Sample solution: Transfer 250 mg of Esomeprazole Magnesium to a 100-mL volumetric flask, add 20 mL of 1 N hydrochloric acid, swirl until dissolved, and dilute with water to volume. Allow to stand for 30 min. Transfer 10.0 mL of this solution to a 200-mL volumetric flask, and dilute with water to volume. Transfer 10.0 mL of the solution to another 100-mL volumetric flask, add 4.0 mL of *Lanthanum solution*, and dilute with water to volume.

Blank: Transfer 4.0 mL of *Lanthanum solution* to a 100-mL volumetric flask, and dilute with water to volume.

Instrumental conditions

(See *Atomic Absorption Spectroscopy* ⟨852⟩.)

Mode: Atomic absorption spectrophotometry

Flame: Air–acetylene

Analytical wavelength: 285.2 nm

Analysis

Samples: *Standard solution B*, *Standard solution C*, *Standard solution D*, *Standard solution E*, *Standard solution F*, *Sample solution*, and *Blank*

Determine the concentration, C_S, in µg/mL, of magnesium in the *Sample solution* using the calibration graph.

Calculate the percentage of magnesium in the portion of Esomeprazole Magnesium taken:

$$\text{Result} = (C_S/C_U) \times [100/(100 - F)] \times 100$$

C_S = concentration of magnesium in the *Sample solution* as calculated above (µg/mL)

C_U = concentration of Esomeprazole Magnesium in the *Sample solution* (µg/mL)

F = content of water in Esomeprazole Magnesium, as determined in *Specific Tests, Water Determination* (%)

Acceptance criteria: ▲3.30%–3.70%▲ (TBD) on the anhydrous basis

IMPURITIES

• Organic Impurities

Solution A: Prepare as directed in the *Assay*.

Mobile phase: Acetonitrile and *Solution A* (11:29). [NOTE—To improve the resolution, the composition may be changed to 1:3, if necessary.]

System suitability solution: 0.04 mg/mL each of USP Omeprazole RS and USP Omeprazole Related Compound A RS in *Mobile phase*.

Sample solution: 0.16 mg/mL of Esomeprazole Magnesium in *Mobile phase*. [NOTE—Prepare this solution fresh.]

Chromatographic system

(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: LC

Detector: UV 280 nm

Column: 4.0-mm × 12.5-cm or 4.6-mm × 15-cm; 5-µm packing L7. [NOTE—Alternatively, a 3.9-mm × 15-cm column; 4-µm packing L1 may be used.]

Flow rate: 0.8–1.0 mL/min

Injection volume: 50 µL

Run time: NLT 4.5 times the retention time of omeprazole

System suitability

Sample: *System suitability solution*

Suitability requirements

Resolution: NLT 3 between omeprazole related compound A and omeprazole

Analysis

Sample: *Sample solution*

Calculate the percentage of any individual impurity in the portion of Esomeprazole Magnesium taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response of any individual impurity from the *Sample solution*

r_T = sum of all the peak responses from the *Sample solution*

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Omeprazole *N*-oxide[a]	0.45	0.1
Omeprazole related compound A	0.8	0.2
Esomeprazole	1.0	—
Any other individual impurity	—	0.1
Total impurities	—	0.5

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

- **Enantiomeric Purity**

Solution A: Mix 70 mL of 1 M sodium phosphate monobasic with 20 mL of 0.5 M sodium phosphate dibasic, and dilute with water to 1000 mL. Dilute 250 mL of this solution with water to 1000 mL.

Mobile phase: Acetonitrile and *Solution A* (15:85)

Diluent: Mix 11 mL of 0.25 M sodium phosphate tribasic with 22 mL of 0.5 M sodium phosphate dibasic, and dilute with water to 1000 mL.

System suitability solution: 0.004 mg/mL of USP Omeprazole RS in *Diluent*

Sample solution: 0.03 mg/mL of Esomeprazole Magnesium prepared as follows. Dissolve 40 mg of Esomeprazole Magnesium in 5 mL of methanol, and dilute with *Diluent* to 25 mL. Dilute 1 mL of this solution with *Diluent* to 50 mL.

Chromatographic system

(See *Chromatography* ⟨621⟩*, System Suitability*.)

Mode: LC

Detector: UV 302 nm

Column: 4.0-mm × 10-cm; 5-µm packing L41

Flow rate: 0.6 mL/min

Injection volume: 20 µL

System suitability

Sample: *System suitability solution*

Suitability requirements

Resolution: NLT 3 between the enantiomer peaks. [Note—The elution order is the *R*-enantiomer, followed by the esomeprazole peak, which is the *S*-enantiomer.]

Analysis

Sample: *Sample solution*

Calculate the percentage of the *R*-enantiomer in the portion of Esomeprazole Magnesium taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response of the *R*-enantiomer from the *Sample solution*

r_T = sum of the peak responses for esomeprazole and *R*-enantiomer from the *Sample solution*

Acceptance criteria: NMT 0.2% of the *R*-enantiomer

SPECIFIC TESTS

- **Water Determination** ⟨921⟩*, Method I*

If labeled as trihydrate: 6.0%–8.0%

If labeled as dihydrate: 4.5%–7.0%

If labeled as amorphous: 7.0%–10.0%

- **Crystallinity** ⟨695⟩(if it is labeled as amorphous)**:** Most of the particles do not exhibit birefringence and extinction positions.

- **Color of Solution**

Sample solution: 20 mg/mL of Esomeprazole Magnesium in methanol, filtered

Analysis: Determine the absorbance of this solution at 440 nm, in 1-cm cells, using methanol as the blank.

Acceptance criteria: NMT 0.2

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers, protected from light. Store at room temperature. If it is labeled as amorphous, store at 2°–8° under nitrogen atmosphere.
- **Labeling:** Where it is a dihydrate form, the label so indicates. Where it is an amorphous form, the label so indicates.
- **USP Reference Standards** ⟨11⟩

  USP Esomeprazole Magnesium RS

  USP Omeprazole RS

  USP Omeprazole Related Compound A RS

  Omeprazole sulfone;

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

  $C_{17}H_{19}N_3O_4S$ 361.42

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