Esomeprazole Magnesium

Type of Posting	Revision Bulletin
Posting Date	25–Mar–2016
Official Date	01–Apr–2016
Expert Committee	Chemical Medicines Monographs 3
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines 3 Expert Committee has revised the Esomeprazole Magnesium monograph. The purpose for the revision is to add an amorphous form of the drug substance to the monograph, to accommodate generic products recently approved by the FDA. The changes listed below were previously published on the USP Pending Monographs website as a part of the Authorized Pending Monograph.

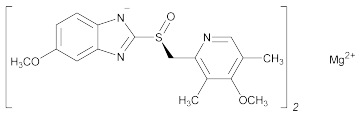
- The test for *Water Determination* was revised to add an acceptance criteria for the material labeled as amorphous form of “7.0%–10.0”.
- A test for *Crystallinity* was added to distinguish between amorphous and crystalline forms of the drug substance.
- *Labeling* section was revised to include the amorphous form
- *Packaging and Storage* section was revised to include storage conditions for the amorphous form

The Esomeprazole Magnesium Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated into *USP 40–NF 35*.

Should you have any questions, please contact Elena Gonikberg, Ph.D, Principal Scientific Liaison (301–816-8251 or eg@usp.org)

Esomeprazole Magnesium

Change to read:



$C_{34}H_{36}MgN_6O_6S_2 \cdot 3H_2O$ Trihydrate: 767.17

•$C_{34}H_{36}MgN_6O_6S_2 \cdot 2H_2O$ Dihydrate: 749.15• (RB 1-Dec-2015)

$C_{34}H_{36}MgN_6O_6S_2$ Anhydrous: 713.12

1*H*-Benzimidazole,5-methoxy-2-[(*S*)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-, magnesium salt (2:1)•• (RB 1-Dec-2015)

5-Methoxy-2-[(*S*)-[(4-methoxy-3,5-dimethyl-2-pyridyl) methyl]sulfinyl]benzimidazole, magnesium salt (2:1)•• (RB 1-Dec-2015)

Trihydrate: [217087-09-7].

•Dihydrate: [217087-10-0].• (RB 1-Dec-2015)

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

Change to read:

- **A. INFRARED ABSORPTION ⟨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 the USP Reference Standard in equal volumes of methanol, evaporate the solution to dryness in similar containers under identical conditions, and repeat the test on the residues.]• (RB 1-Dec-2015)
- **B.** The *Sample solution*, prepared and tested as directed in the test for *Content of Magnesium*, exhibits a significant absorption at 285.2 nm.

ASSAY

- **PROCEDURE**

Solution A: Dissolve 0.725 g of monobasic sodium phosphate and 4.472 g of anhydrous dibasic sodium phosphate in 300 mL of water, and dilute with water to 1000 mL. Dilute 250 mL of this solution with water to 1000 mL. If necessary, adjust with phosphoric acid to a pH of 7.6.

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

Mobile phase: Acetonitrile and *Solution A* (7:13)

Standard solution: 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. [NOTE—This solution contains 0.05 mg/mL of omeprazole.]

Sample solution: 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. [NOTE—This solution contains 0.05 mg/mL of esomeprazole magnesium.]

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 that contains 4-µm packing L1 may be used.]

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 2000 theoretical plates

Relative standard deviation: NMT 2.0%

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 from the *Sample solution*

r_S = peak response 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 solu-*

tion 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⟩.)• (CN 1-May-2016)

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%–3.55% on the anhydrous basis

IMPURITIES

• **ORGANIC IMPURITIES**

Solution A: Dissolve 0.725 g of monobasic sodium phosphate and 4.472 g of anhydrous dibasic sodium phosphate in 300 mL of water, and dilute with water to 1000 mL. Dilute 250 mL of this solution with water to 1000 mL. If necessary, adjust with phosphoric acid to a pH of 7.6.

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: 1 mg each of USP Omeprazole RS and USP Omeprazole Related Compound A RS in 25 mL of *Mobile phase*. [NOTE—Omeprazole related compound A is omeprazole sulfone.]

Sample solution: 4 mg of Esomeprazole Magnesium in 25 mL of *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 that contains 4-µm packing L1 may be used.]

Flow rate: 0.8–1 mL/min

Injection volume: 50 µL

System suitability

Sample: *System suitability solution*

[NOTE—For relative retention times, see *Table 1*.]

Suitability requirements

Resolution: NLT 3 between omeprazole related compound A and omeprazole

Analysis

Sample: *Sample solution*

Record the chromatogram for at least 4.5 times the retention time of the omeprazole peak, and measure the peak responses. Identify the impurities based on the retention times shown in *Table 1*.

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 each impurity from the *Sample solution*

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

Acceptance criteria

Individual impurities: See *Table 1*.

Total impurities: NMT 0.5%

Table 1

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

[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 monobasic sodium phosphate with 20 mL of 0.5 M dibasic sodium phosphate, and dilute with water to 1000 mL. Dilute 250 mL of this solution with water to 1000 mL.

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

Mobile phase: Acetonitrile and *Solution A* (3:17)

System suitability solution: 2 mg of USP Omeprazole RS in 10 mL of *Diluent*. Dilute 1.0 mL of this solution with *Diluent* to 50 mL.

Sample solution: 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; 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

Change to read:

- **WATER DETERMINATION** ⟨**921**⟩**,** *Method I***:** 6.0%–8.0% •for the trihydrate form• (RB 1-Apr-2016)
  •**If labeled as dihydrate:** 4.5%–7.0%• (RB 1-Dec-2015)
  •**If labeled as amorphous:** 7.0%–10.0%• (RB 1-Apr-2016)

Add the following:

•• **CRYSTALLINITY** ⟨**695**⟩**:** If it is labeled as amorphous, most of the particles do not exhibit birefringence and extinction positions.• (RB 1-Apr-2016)
- **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

Change to read:

- **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.• (RB 1-Apr-2016)

Change to read:

•• **LABELING:** Where it is a dihydrate form, the label so indicates. •Where it is an amorphous form, the label so indicates.• (RB 1-Apr-2016)• (RB 1-Dec-2015)
- **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 [CAS-88546-55-8].