Pantoprazole Sodium

C_{16}H_{15}F_{2}N_{3}O_{3}S \cdot 1.5H_{2}O 432.37

1H-Benzimidazole, 5-(difluoromethoxy)-2-[[3,4-dimethoxy-2-pyridyl][methyl]sulfinyl]-1H-benzimidazole.

C_{16}H_{15}F_{2}N_{3}O_{3}S 399.37

USP Pantoprazole Related Compound B RS

5-(Difluoromethoxy)-2-[[3,4-dimethoxy-2-pyridyl][methyl][thio]-1H-benzimidazole.

C_{12}H_{17}F_{2}N_{3}O_{3}S 376.37

USP Pantoprazole Related Compound C RS

5-(Difluoromethoxy)-1H-benzimidazole-2-thiol.

C_{12}H_{17}F_{2}N_{3}O_{3}S 216.21

USP Pantoprazole Related Compound D and F Mixture RS

A mixture of 5-(difluoromethoxy)-2-[[RS]-[3,4-dimethoxy-2-yl]methyl][sulfinyl]-1-methyl-1H-benzimidazole and 6-(difluoromethoxy)-2-[[RS]-[3,4-dimethoxy-2-yl]methyl][sulfinyl]-1-methyl-1H-benzimidazole.

C_{12}H_{17}F_{2}N_{3}O_{3}S 398.40

USP Pantoprazole Related Compound E RS

A mixture of the stereoisomers of 6,6′-bis(difluoromethoxy)-2,2′-bis[[3,4-dimethoxy-2-yl]methyl][sulfinyl]-1H,1′H-5,5′-biphenylbenzimidazolyl.

C_{12}H_{26}F_{4}N_{6}O_{8}S_{2} 764.74

Identification—

A: Infrared Absorption (197K).

B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

C: It meets the requirements of the pyroantimonate precipitate test for Sodium (191).

Water, Method I (921); between 5.0% and 8.0%.

Heavy metals, Method II (231): not more than 0.002%.

Related compounds—[NOTE—On the basis of the synthetic route, perform either Test 1 or Test 2. Test 2 is recommended when impurities C, D, E, and F are potential related compounds.]

TEST 1—[NOTE—Protect all solutions from light, and use amber autosampler vials and low-actinic glassware.]

Diluent, Mobile phase, System suitability preparation, and Chromatographic system—Procedures as directed in the Assay.

Standard solution—Transfer about 20 mg of USP Pantoprazole Sodium RS, accurately weighed, to a 50-mL volumetric flask, dilute in 5 to 10 mL of a mixture of acetonitrile and water (1:1), and dilute with Diluent to volume. Further dilute with Diluent quantitatively, and stepwise if necessary, to obtain solutions having a known concentration of about 0.004 mg per mL.

Test solution—Transfer about 20 mg of Pantoprazole Sodium, accurately weighed, to a 50-mL volumetric flask, dilute in 5 to 10 mL of a mixture of acetonitrile and water (1:1), dilute with Diluent to volume, and mix.

Chromatographic system (see Chromatography (621))—Procedures as directed in the Assay. Chromatograph the system suitability preparation, and record the peak responses as directed for Procedure. Identify the components on the basis of their relative retention times (Table 1): the resolution, R, between the pantoprazole related compound A and pantoprazole peaks is not less than 10.0.

| Name                              | Relative Retention Time | Limit (%) |
|-----------------------------------|-------------------------|-----------|
| Pantoprazole related compound A   | 0.52                    | 0.20      |
| Pantoprazole sodium               | 1.00                    | N/A       |
| Pantoprazole related compound B   | 1.70                    | 0.15      |
| Any other individual impurity     | —                       | 0.10      |
| Total impurities                  | —                       | 0.5       |

1 5-(Difluoromethoxy)-2-[[3,4-dimethoxy-2-pyridyl][methyl][sulfinyl]]-1H-benzimidazole.
2 USP Pantoprazole Related Compound A RS, USP Pantoprazole Related Compound B RS, USP Pantoprazole Related Compound C RS, USP Pantoprazole Related Compound D and F Mixture RS.

Procedure—Separately inject equal volumes (about 20 µL) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each impurity in the portion of Pantoprazole Sodium taken by the formula:

\[
100 \left( \frac{C_t}{C_s} \varepsilon \right) \]

in which \(C_t\) and \(C_s\) are the concentrations, in mg/mL, of pantoprazole sodium in the Standard solution and the Test solution, respectively; \(\varepsilon\) is the peak response of each impurity obtained from the Test solution; and \(r_1\) is the pantoprazole peak response obtained from the Standard solution. The reporting level for impurities is 0.05%.

TEST 2—Diluent—Prepare a mixture of acetonitrile and 0.001 N sodium hydroxide solution (50:50).

Standard solution—Dissolve an accurately weighed quantity of USP Pantoprazole Sodium RS in Diluent, and dilute quantitatively to obtain a solution having a known concentration of about 0.03 mg per mL.

Test solution—Prepare a solution of Pantoprazole Sodium in Diluent having a known concentration of about 0.46 mg per mL.

System suitability solution—Dissolve suitable amounts of USP Pantoprazole Sodium RS, USP Pantoprazole Related Compound A RS, USP Pantoprazole Related Compound B RS, USP Pantoprazole Related Compound C RS, USP Pantoprazole Related Compound D and F Mixture RS, and USP Pantoprazole Related Compound E RS in Diluent to obtain a solution containing about 0.46 mg of pantoprazole sodium per mL and about 1.3 µg each of related compounds A, B, C, and E per mL, and about 1.3 µg of the D and F mixture per mL.
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**Solution A**—Prepare a solution of dibasic potassium phosphate (1.74 g/L) adjusted with a solution of phosphoric acid (330 g/L) to a pH of 7.00 ± 0.05.

**Solution B**—Use acetonitrile.

**Mobile phase**—Use variable mixtures of Solution A and Solution B as directed below for Chromatographic system. Make adjustments as necessary (see System Suitability under Chromatography (621)).

**Chromatographic system** (see Chromatography (621))—The liquid chromatograph is equipped with either a programmable variable wavelength detector or two separate detectors capable of monitoring at 290 nm and at 305 nm, and a 4-mm × 12.5-cm column that contains 5-μm packing L1. The column temperature is maintained at 40°. The flow rate is about 1.0 mL per minute. The chromatograph is programmed as follows:

| Time (minutes) | Solution A (%) | Solution B (%) | Elution |
|----------------|----------------|----------------|---------|
| 0–40           | 80–20          | 20–80          | linear gradient |
| 40–45          | 20–80          | 80–20          | linear gradient |
| 45–55          | 80             | 20             | re-equilibration |

Chromatograph the System suitability solution, and record the peak responses at 290 nm as directed for Procedure. Identify the components based on relative retention times (Table 2): the resolution, R, between pantoprazole related compound E and pantoprazole related compounds D and F is not less than 1.5. Chromatograph the Standard solution at 290 nm, and record the peak responses as directed for Procedure: the tailing factor is not more than 2; and the relative standard deviation for replicate injections is not more than 5.0%.

**Procedure**—Separately inject equal volumes (about 20 μL) of the Standard solution and the Test solution into the chromatograph, record the chromatograms at 290 nm and 305 nm, and measure the responses for the major peaks. [NOTE—Pantoprazole related compound C is monitored using a wavelength of 305 nm, and all other compounds are monitored at 290 nm.] Calculate the percentage of each impurity in the portion of Pantoprazole Sodium taken by the formula:

\[ 100 \left( \frac{1}{R} \right) \frac{C_i}{C_{i}} (r/f) \]

where C is the concentration, in mg per mL, of pantoprazole sodium in the Standard solution; C is the concentration, in mg per mL of Pantoprazole Sodium in the Test solution; F is the response factor of an individual pantoprazole related compound relative to the response of pantoprazole sodium (Table 2); r is the peak response of each impurity obtained from the Test solution; and fi is the pantoprazole peak response obtained from the Standard solution. The reporting level for impurities is 0.05%.

**Table 2**

| Impurity Name | Relative Retention Time (%) | Relative Response Factor (%) | Limit (%)  |
|---------------|---------------------------|-----------------------------|------------|
| Related compound A | 0.9                      | 1.0                         | 0.20       |
| Related compound B | 1.5                      | 1.0                         | 0.15       |
| Related compound C¹ | 0.6                      | 3.3                         | 0.10²      |
| Related compounds D¹ and F ² | 1.2                      | 1.0                         | 0.20⁴      |
| Related compound E⁵ | 1.3                      | 1.0                         | 0.10       |

¹ 5-(Difluoromethoxy)-1H-benzimidazole-2-thiol.
² At 305 nm.
³ 5-(Difluoromethoxy)-2-[(3,4-dimethoxypyridin-2-yl)methyl][sulfinyl]-1-methyl-1H-benzimidazole.
⁴ Impurities D and F are not fully resolved and should be integrated together.
⁵ 6-(Difluoromethoxy)-2-[(3,4-dimethoxypyridin-2-yl)methyl][sulfinyl]-1-methyl-1H-benzimidazole.
⁶ Mixture of the stereoisomers of 6,6'-bis(difluoromethoxy)-2,2'-bis[[3,4-dimethoxypyridin-2-yl][sulfinyl]-1H,1'H-5,5'-bifentramizidazolyl.

**Assay**—[NOTE—Protect all solutions from light, and use amber autosampler vials and low-actinic glassware.]

**Ammonium phosphate buffer**—Dissolve 1.32 g of dibasic ammonium phosphate in 1000 mL of water. Adjust with phosphoric acid to a pH of 7.5.

**Acetonitrile–methanol mixture**—Prepare a mixture of acetonitrile and methanol (7:3).

**Solution A**—Use a filtered and degassed mixture of Ammonium phosphate buffer and Acetonitrile–methyl alcohol mixture (85:15).

**Solution B**—Use Acetonitrile–methanol mixture.

**Diluent**—Transfer 25 mL of ammonium hydroxide to a suitable container, and dilute with water to 500 mL.

**Procedure**—Use variable mixtures of Solution A and Solution B as directed for Chromatographic system. Make adjustments as necessary (see System Suitability under Chromatography (621)).

**System suitability preparation**—Dissolve suitable amounts of USP Pantoprazole Sodium RS, USP Pantoprazole Related Compound A RS, and USP Pantoprazole Related Compound B RS in a mixture of acetonitrile and water (1:1) to obtain a solution having about 0.5 mg of each component per mL. Transfer 1 mL of this solution to a 100-mL volumetric flask, and dilute with Diluent to volume.

**Standard preparation**—Transfer about 20 mg of USP Pantoprazole Sodium RS, accurately weighed, to a 50-mL volumetric flask, dissolve in 5 to 10 mL of a mixture of acetonitrile and water (1:1), and dilute with Diluent to volume. Further dilute with Diluent quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.06 mg per mL.

**Assay preparation**—Transfer about 20 mg of Pantoprazole Sodium, accurately weighed, to a 50-mL volumetric flask, dissolve in 5 to 10 mL of a mixture of acetonitrile and water (1:1), and dilute with Diluent to volume. Further dilute with Diluent quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.06 mg per mL.

Chromatographic system (see Chromatography (621))—The liquid chromatograph is equipped with a 285-nm detector and a 3.9-mm × 15-cm column that contains 4-μm packing L1. The flow rate is about 1 mL per minute. The column temperature is maintained at 30°, and the autosampler temperature is maintained at 4°. The chromatograph is programmed as follows:

| Time (minutes) | Solution A (%) | Solution B (%) | Elution |
|----------------|----------------|----------------|---------|
| 0–10           | 86             | 14             | isocratic |
| 10–35          | 86–42          | 14–58          | linear gradient |
| 35–36          | 42–86          | 58–14          | linear gradient |
| 36–46          | 86             | 14             | re-equilibration |

Chromatograph the System suitability preparation, and record the peak responses as directed for Procedure. Identify the com-
Pantoprazole Sodium Delayed-Release Tablets

**DEFINITION**

Pantoprazole Sodium Delayed-Release Tablets contain an amount of Pantoprazole Sodium equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of pantoprazole (C_{16}H_{14}F_{2}N_{3}NaO_{4}S).

**IDENTIFICATION**

- 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:** Dissolve 3.85 g of ammonium acetate and 1.1 g of tetrabutylammonium hydrogen sulfate in 1 L of water, and adjust with ammonium hydroxide solution diluted 1:1 with water to a pH of 7.9.

  **Diluent:** Mixture of acetonitrile and 0.02 N sodium hydroxide (1:1)

  **Mobile phase:** Prepare a mixture of acetonitrile and Solution A (35:65).

  **Standard solution:** Transfer a weighed quantity of USP Pantoprazole Sodium RS to a suitable volumetric flask, add 0.02 N sodium hydroxide to about 60% of the final volume, sonicate for 5 min to dissolve, add about 2% of acetonitrile, and dilute with 0.02 N sodium hydroxide to volume to obtain a solution having a known concentration of about 0.2 mg/mL of pantoprazole sodium.

  **System suitability solution:** Prepare a solution in 0.02 N sodium hydroxide, using sonication if necessary, containing about 0.2 mg/mL of pantoprazole sodium and about 0.0004 mg/mL each of USP Pantoprazole Related Compound A RS and USP Pantoprazole Related Compound B RS.

  **Sample solution:** Transfer 5 Tablets into a suitable volumetric flask. [NOTE—Use 50- or 100-mL volumetric flasks for Tablets containing 20 or 40 mg of pantoprazole per Tablet, respectively.] Add Diluent to about 60% of the final volume, shake mechanically for about 60 min, and dilute with Diluent to volume. Pass through a suitable filter, and dilute the filtrate with 0.02 N sodium hydroxide to obtain a solution having a known concentration of about 0.2 mg/mL of pantoprazole, based on the label claim.

**Chromatographic system**

(See Chromatography (621), System Suitability.)

- **Mode:** LC
- **Detector:** UV 290 nm
- **Column:** 4.6-mm x 25-cm; 5-µm packing L1
- **Flow rate:** 1 mL/min
- **Injection size:** 20 µL

**System suitability**

- **Samples:** Standard solution and System suitability solution

**Suitability requirements**

- **Resolution:** NLT 3 between pantoprazole and pantoprazole related compound A, System suitability solution
- **Tailing factor:** NMT 2.0, System suitability solution
- **Relative standard deviation:** NMT 2.0% for replicate injections, Standard solution

**Analysis**

- **Samples:** Standard solution and Sample solution

  Calculate the percentage of C_{16}H_{14}F_{2}N_{3}O_{4}S in the portion of Tablets taken:

  \[
  \text{Result} = \left( \frac{r_u}{r_s} \right) \times \left( \frac{C_s}{C_u} \right) \times \left( \frac{M_1}{M_2} \right) \times 100
  \]

  \( r_u \) = peak response from the Sample solution

  \( r_s \) = peak response from the Standard solution

  \( C_s \) = concentration of USP Pantoprazole Sodium RS in the Standard preparation (mg/mL)

  \( C_u \) = nominal concentration of pantoprazole in the Sample preparation (mg/mL)

  \( M_1 \) = molecular weight of pantoprazole, 383.37

  \( M_2 \) = molecular weight of pantoprazole sodium, 405.35

  **Acceptance criteria:** 90.0%–110.0%