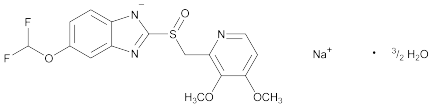
- **BEYOND-USE DATE:** NMT 14 days after the date on which it was compounded when stored at controlled cold temperature
- **USP REFERENCE STANDARDS** ⟨11⟩
  USP Pantoprazole Sodium RS

Pantoprazole Sodium



$C_{16}H_{14}F_2N_3NaO_4S \cdot 1.5H_2O$ 432.37
1*H*-Benzimidazole, 5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-, sodium salt, hydrate (2:3).
5-(Difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]benzimidazole, sodium salt, sesquihydrate [164579-32-2].

» Pantoprazole Sodium contains not less than 98.0 percent and not more than 102.0 percent of $C_{16}H_{14}F_2N_3NaO_4S$, calculated on the anhydrous basis.

Packaging and storage—Preserve in well-closed, light-resistant containers. Store at room temperature.

Labeling—If a test for *Related compounds* other than *Test 1* is used, then the labeling states the test with which the article complies.

USP Reference standards ⟨11⟩**—**
USP Pantoprazole Sodium RS
USP Pantoprazole Related Compound A RS
5-(Difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)-methyl]sulfonyl]-1*H*-benzimidazole.
$C_{16}H_{15}F_2N_3O_5S$ 399.37
USP Pantoprazole Related Compound B RS
5-(Difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)-methyl]thio]-1*H*-benzimidazole.
$C_{16}H_{15}F_2N_3O_3S$ 367.37
USP Pantoprazole Related Compound C RS
5-(Difluoromethoxy)-1*H*-benzimidazole-2-thiol.
$C_8H_6F_2N_2OS$ 216.21
USP Pantoprazole Related Compound D and F Mixture RS
A mixture of 5-(difluoromethoxy)-2-[(*RS*)-[(3,4-dimethoxypyridin-2-yl)methyl]sulfinyl]-1-methyl-1*H*-benzimidazole and 6-(difluoromethoxy)-2-[(*RS*)-[(3,4-dimethoxypyridin-2-yl)methyl]sulfinyl]-1-methyl-1*H*-benzimidazole.
$C_{17}H_{17}F_2N_3O_4S$ 398.40
USP Pantoprazole Related Compound E RS
A mixture of the stereoisomers of 6,6′-bis(difluoromethoxy)-2,2′-bis[[(3,4-dimethoxypyridin-2-yl)methyl]sulfinyl]-1*H*,1′*H*-5,5′-bibenzimidazolyl.
$C_{32}H_{28}F_4N_6O_8S_2$ 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*—Proceed as directed in the *Assay.*

Standard solution—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 0.0004 mg per mL.

Test solution—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), dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—Prepare 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.

Table 1

Name	Relative Retention Time	Limit (%)
Pantoprazole related compound A[1]	0.52	0.20
Pantoprazole sodium	1.0	N/A
Pantoprazole related compound B[2]	1.7	0.15
Any other individual impurity	—	0.10
Total impurities	—	0.5

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

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:

$$100(C_S / C_T)(r_i / r_S)$$

in which C_S and C_T are the concentrations, in mg per mL, of pantoprazole sodium in the *Standard solution* and the *Test solution,* respectively; r_i is the peak response of each impurity obtained from the *Test solution;* and r_S 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.

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:

$$100\ (1 / F)(C_S / C_U)(r_i / r_S)$$

in which C_S is the concentration, in mg per mL, of pantoprazole sodium in the *Standard solution;* C_U 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_i is the peak response of each impurity obtained from the *Test solution;* and r_S 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 (*F*)	Limit (%)
Related compound A	0.9	1.0	0.20
Related compound B	1.5	1.0	0.15
Related compound C[1]	0.6	3.3	0.10[2]
Related compounds D[3] and F[5]	1.2	1.0	0.20[4]
Related compound E[6]	1.3	1.0	0.10
Any other individual impurity	—		0.10
Total impurities	—		0.5

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

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–methanol 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.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system.* Make adjustments if 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 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-

ponents based on their relative retention times (*Table 1*): the resolution, *R,* between the pantoprazole related compound A and pantoprazole peaks is not less than 10.0. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of $C_{16}H_{14}F_2N_3NaO_4S$ in the portion of Pantoprazole Sodium taken by the formula:

$$100(C_S / C_U)(r_U / r_S)$$

in which C_S and C_U are the concentrations, in mg per mL, of pantoprazole sodium in the *Standard preparation* and the *Assay preparation,* respectively; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

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 ($C_{16}H_{15}F_2N_3O_4S$).

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 × 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 $C_{16}H_{15}F_2N_3O_4S$ in the portion of Tablets taken:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Pantoprazole Sodium RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of pantoprazole in the *Sample solution* (mg/mL)
M_{r1} = molecular weight of pantoprazole, 383.37
M_{r2} = molecular weight of pantoprazole sodium, 405.35

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

- **DISSOLUTION** ⟨711⟩

Test 1: Proceed as directed for *Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms, Method B, Procedure*.

Acid stage
Acid stage medium: 0.1 N hydrochloric acid; 1000 mL
Apparatus 2: 75 rpm
Time: 120 min

Determine the amount of pantoprazole dissolved in the *Acid stage* using the following procedure.

Sample solution: After 120 min, withdraw an aliquot, pass through a suitable filter of 0.45-µm pore size, and immediately dilute a portion of the filtrate by a factor of 2 with 0.5 N sodium hydroxide. Transfer the Tablets to the vessels containing the *Buffer stage medium*.

Diluent: Prepare a mixture of pH 6.8 phosphate buffer and 0.5 N sodium hydroxide (1:1).

Mobile phase: Acetonitrile, triethylamine, and water (40:1:60). Adjust with phosphoric acid to a pH of 7.0 ± 0.05.

Standard stock solution: Transfer about 20 mg of USP Pantoprazole Sodium RS to a 50-mL volumetric flask. Add about 30 mL of 0.02 N sodium hydroxide, and sonicate until dissolved. Add 2 mL of acetonitrile, and dilute with 0.02 N sodium hydroxide to volume.

Standard solution: Transfer 1.0 mL of the *Standard stock solution* to a 20-mL volumetric flask, and dilute with *Diluent* to volume.

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