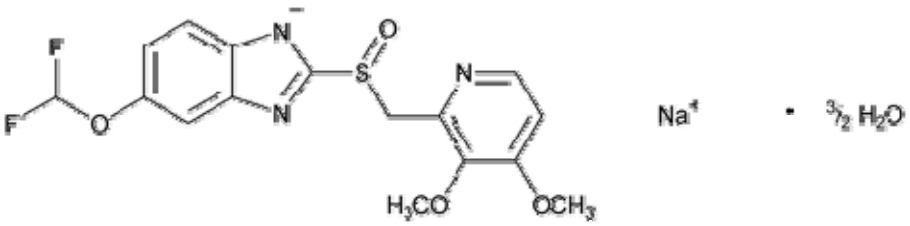
Pantoprazole Sodium

USP Method Pantoprazole Sodium RS
USP Method Pantoprazole Sodium Assay



Original Manufacturer:	Altana (Nycomed) and licensed in the USA to Wyeth (patent expiry 2009)
Brand Names:	Protonix, Somac, Pantoloc, Protium, Pantecta, Pantoheal, Fenix, Tecta, Protium, Inipomp, Eupantol, Pantozol, Pantodac, Perizole, Pansped, Zurcazol, Protonex, Pantup, Pantomed, TopZole, UXL-D, Pantid
Combination Drugs:	Pantazone (Domperidone and Pantoprazole) Pantop-D (Domperidone and Pantoprazole) Rantop-D (Domperidone and Pantoprazole)

Pantoprazole is a proton pump inhibitor drug that inhibits gastric acid secretion.

In 2007, Teva Pharmaceutical released an AB-rated generic alternative to Protonix. This was followed by generic equivalents from Sun Pharma and Kudco Pharma. Wyeth sued all three for patent infringement and launched its own generic version of Protonix with Nycomed.

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Pantoprazole Sodium

USP34 – NF29 S1

USP Columns:

Luna C18 Assay and Related Compounds 3.9 mm x 15 cm, 4 µm.

Hypersil-ODS Related compounds Related Compounds Test 2. 4 mm x 12.5 cm, 5 µm.

Equivalent Column:

Purospher®STAR RP-18 endcapped (5 µm) 150x4.6 mm	(1.51455.0001)
Purospher®STAR RP-18 endcapped (5 µm) 125x4.0 mm	(1.50036.0001)

Recommended Solvents and Reagents:

Acetonitrile	gradient grade for liquid chromatography LiChrosolv®	(1.00030)
Methanol	gradient grade for liquid chromatography LiChrosolv®	(1.06007)
Water	Water for chromatography LiChrosolv® or freshly purified water from Milli-Q water purification system	**(1.15333)**

Ammonium phosphate (mono basic)	Use ACS Reagent grade
Phosphoric Acid	Use ACS reagent grade
Ammonium Hydroxide	Use ACS Reagent grade
Potassium Phosphate, Dibasic	Use ACS Reagent grade

USP Standards

Pantoprazole Sodium (250 mg)	USP Product Number:	1494895
Pantoprazole Related Compound A (25 mg)	USP Product Number:	1494909
Pantoprazole Related Compound B (20 mg)	USP Product Number:	1494910
Pantoprazole Related Compound C (20 mg)	USP Product Number:	1494920
Pantoprazole Related Compounds D and F Mixture (20 mg)		1494931
Pantoprazole Related Compound E (20 mg)	USP Product Number:	1494942

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USP Method for Pantoprazole Sodium 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 mix (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.

USP Method for Pantoprazole Sodium Assay

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 (min)	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 components 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/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.

USP Method for Pantoprazole Sodium RS

[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/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.

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:

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

C_S and C_T = conc. in mg/mL, of Pantoprazole sodium in the Standard solution and the Test solution, respectively;
r_i = peak response of each impurity obtained from the Test solution;
r_S= Pantoprazole peak response obtained from the Standard solution.

The reporting level for impurities is 0.05%.

Table 1.

Compound	Relative Retention Time (RRT)	Limit (%)
Pantoprazole related compound A[1)]	0.52	0.20
Pantoprazole sodium	1.0	-
Pantoprazole related compound B[2)]	1.7	0.15
Any other individual impurity	1.5	0.1
Total impurities	-	0.5

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

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

USP Method for Pantoprazole Sodium RS – 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/mL.

Test solution
Prepare a solution of Pantoprazole Sodium in Diluent with known concentration of about 0.46 mg/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 degrees Celsius. The flow rate is about 1.0 mL per minute. The chromatograph is programmed as follows.

Time (min)	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

USP Method for Pantoprazole Sodium RS – Test 2

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:

$100(1/F)(C_S/ C_U)(r_U/r_S)$

C_S = conc. in mg/mL, of Pantoprazole sodium in the Standard solution
C_U = conc. in mg/mL of Pantoprazole Sodium in the Test solution
F = the response factor of an individual Pantoprazole related compound relative to the response of Pantoprazole sodium (Table 2)
r_i = the peak response of each impurity obtained from the Test solution
r_S =the Pantoprazole peak response obtained from Standard solution.

Impurity Name	Rel. Ret. Time (RRT)	Rel. Resp. Factor (RRF)	Limit (%)
Pantoprazole related compound A	0.9	1.0	0.2
Pantoprazole related compound B	1.5	1.0	0.15
Pantoprazole related compound C[1]	0.6	3.3	0.1[2]
Pantoprazole related compound D[3] and F[5]	1.2	1.0	0.2[4]
Pantoprazole related compound E[6]	1.3	1.0	0.1
Any other individual impurity	-	-	0.1
Total impurities	-	-	0.5

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

[2] At 305 nm.

[3] 5-(Difluoromethoxy)-2-[(RS)-[(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-[(RS)-[(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)methyl]sulfinyl]-1H,1¢H-5,5¢-bibenzimidazolyl.

The Reporting level for impurities is 0.05%.

HPLC Application note 2029
USP Method Pantoprazole Sodium RS – Test 2

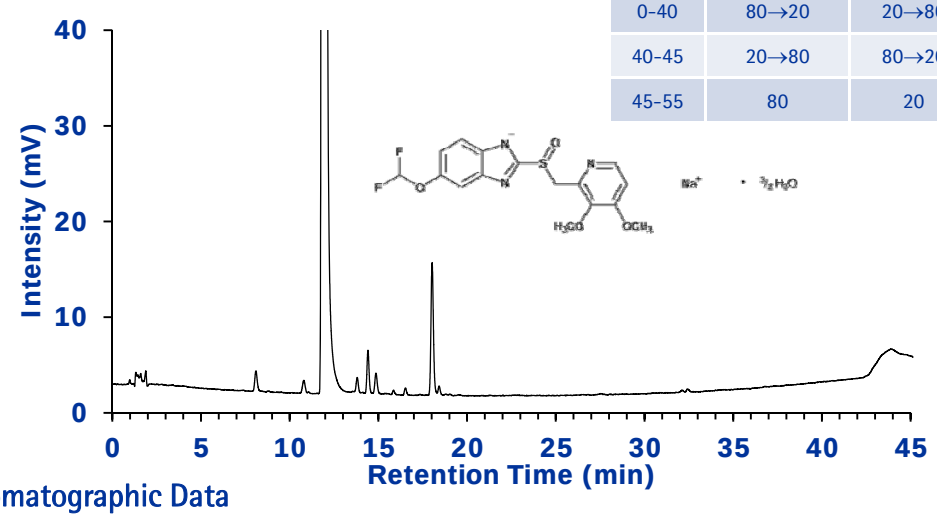
USP Method for Pantoprazole Sodium RS

Purospher®STAR RP-18endcapped

Chromatographic Conditions

Column:	Purospher®STAR RP-18endcapped (5 µm) 150x4.6 mm	1.51455.0001
Injection:	20 µL	
Detection:	Shimadzu Prominence, UV 290 nm	
Cell:	10 µL	
Flow Rate:	1.0 mL/min	
Mobile Phase (v/v):	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: acetonitrile	
Gradient:	see gradient table	
Temperature:	40°C	
Diluent	1:1 mixture of acetonitrile and 1 mM NaOH	
Sample:	460 ppm of Pantoprazole in Diluent	
Pressure Drop:	101 to 56 Bar (1465 to 812 psi)	

Time (min)	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



Chromatographic Data

No.	Compound	Time (min)	Relative Retention Time (RRT)	Resolution	Asymmetry (T_{USP})
1	Pantoprazole RS C	8.1	0.7	-	1.1
2	Pantoprazole RS A	10.8	0.9	-	1.0
	Pantoprazole Na	11.9	1.0	-	1.1
3	Pantoprazole RS F	13.8	1.2	-	1.1
4	Pantoprazole RS D	14.4	1.2	2.9	1.1
5	Pantoprazole RS E	14.7	1.2	2.0	1.1
6	Pantoprazole RS B	18.0	1.5	-	1.2

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