

Add the following:

Pantoprazole Sodium Delayed-Release Tablets

» Pantoprazole Sodium Delayed-Release Tablets contain an amount of Pantoprazole Sodium equivalent to not less than 90.0 percent and not more than 110.0 percent of the labeled amount of pantoprazole ($C_{16}H_{15}F_2N_3O_4S$).

Packaging and storage—Preserve in well-closed containers. Store at controlled room temperature.

Labeling—Label Tablets to indicate that they must not be split, chewed, or crushed before administration. When more than one *Dissolution* test is given, the labeling states the test used only if *Test 1* is not used.

USP Reference standards (11)—*USP Pantoprazole Sodium RS*. *USP Pantoprazole Related Compound A RS*. *USP Pantoprazole Related Compound B RS*.

Identification—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*.

Dissolution (711)—

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

ACID STAGE—

Acid stage medium: 0.1 N hydrochloric acid; 1000 mL.

Apparatus 2: 75 rpm.

Time: 120 minutes.

Procedure—After 120 minutes, withdraw an aliquot, pass through a suitable 0.45- μ m filter, 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*. Determine the amount of pantoprazole dissolved in the *Acid stage* using the following procedure.

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

Mobile phase—Prepare a filtered and degassed mixture of water, acetonitrile, and triethylamine (60 : 40 : 1). Adjust with phosphoric acid to a pH of 7.0 ± 0.05 .

Standard stock solution—Transfer about 20 mg of USP Pantoprazole Sodium RS, accurately weighed, 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.

Working 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—The liquid chromatograph is equipped with a 290-nm detector and a 4.6-mm \times 7.5-cm column that contains 3- μ m packing L1. The column is maintained at 30°. The flow rate is about 1.0 mL per minute. Chromatograph the *Working standard solution*, and record the peak responses as directed for *Procedure*: the tailing factor is not more than 2.5, and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 μ L) of the *Working standard solution* and the solution under test into the chromatograph, record the chromatograms, and measure the peak re-

sponses for the major peaks. Calculate the amount of pantoprazole released in the *Acid stage* by the formula:

$$\frac{r_U \times C_S \times 383.37 \times 1000 \times 100}{r_S \times 405.35 \times L}$$

in which r_U and r_S are the peak responses of pantoprazole obtained from the solution under test and the *Working standard solution*, respectively; C_S is the concentration, in mg per mL, of pantoprazole sodium in the *Working standard solution*; 383.37 is the molecular weight of pantoprazole; 1000 is the volume, in mL, of *Medium*; 100 is the conversion factor to percentage; 405.35 is the molecular weight of pantoprazole sodium; and L is the Tablet label claim, in mg.

Tolerances—Not more than 10% of the labeled amount of pantoprazole is dissolved in 120 minutes.

BUFFER STAGE—

Buffer stage medium: pH 6.8 phosphate buffer; 1000 mL.

Apparatus 2: 75 rpm.

Time: 30 minutes.

Procedure—After 30 minutes, withdraw an aliquot, pass through a suitable 0.45- μ m filter, and immediately dilute a portion of the filtrate by a factor of 2 with 0.5 N sodium hydroxide. Determine the amount of pantoprazole dissolved in the *Buffer stage* using the same procedure as for the *Acid stage*.

Tolerances—Not less than 75% (Q) of the labeled amount of pantoprazole is dissolved in 30 minutes.

Test 2—If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 2*.

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

ACID STAGE—

Acid stage medium: 0.1 N hydrochloric acid; 1000 mL.

Apparatus 2: 100 rpm.

Time: 2 hours.

Standard stock solution—Transfer an accurately weighed quantity of USP Pantoprazole Sodium RS to a suitable volumetric flask, dissolve first in 0.1 N sodium hydroxide, using 10% of the final volume, then dilute to volume with pH 6.8 phosphate buffer, to obtain a solution having a known concentration of about 0.46 mg of pantoprazole sodium per mL. Mix well until a clear solution is obtained. Calculate the concentration in mg of pantoprazole per mL, the molecular weights of pantoprazole and pantoprazole sodium being 383.37 and 405.35, respectively.

Acid stage working standard solution—Dilute an appropriate volume of the *Standard stock solution* to 1 L with *Acid stage medium* in such a way to obtain a final concentration of about 10% of the Tablet label claim per L.

Test solution—Pass a portion of the solution under test through a suitable 10- μ m filter.

Procedure—Determine the amount of pantoprazole dissolved by employing UV absorption at the wavelength of \bullet (RB 01-Dec-2009) about 305 nm on portions of the *Test solution* in comparison to *Acid stage working standard solution* using a 4-cm path length cell and *Acid stage medium* as blank. Drain the *Acid stage medium* from each vessel and replace with *Buffer stage medium*. Calculate the amount of pantoprazole dissolved by the formula:

$$\frac{A_U \times C_S \times 1 \times 100}{A_S \times L}$$

in which A_U and A_S are the absorbances obtained from the *Test solution* and the *Acid stage working standard solution*, respectively; C_S is the concentration, in mg per L, of pantoprazole in the *Acid stage working standard solution*; 1 is the volume, in L, of *Acid stage me-*

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dium; 100 is the conversion factor to percentage; and L is the Tablet label claim in mg.

Tolerances—Not more than 10% of the labeled amount of pantoprazole is dissolved in 2 hours.

BUFFER STAGE—

Buffer stage medium: pH 6.8 phosphate buffer; 1000 mL.

Apparatus 2: 100 rpm.

Time: 45 minutes.

Buffer stage working standard solution—Dilute an appropriate volume of the *Standard stock solution* to 250 mL with *Buffer stage medium* in such a way to obtain a final concentration of about 100% of the Tablet label claim per L.

Test solution—Pass a portion of the solution under test through a suitable 10- μ m filter.

Procedure—Determine the amount of pantoprazole dissolved by employing UV absorption at the wavelength of maximum absorbance at about 288 nm on portions of the *Test solution* in comparison to *Buffer stage working standard solution* using a 0.5-cm path length cell and *Buffer stage medium* as blank. Calculate the amount of pantoprazole dissolved by the formula:

$$\frac{A_U \times C_S \times 1 \times 100}{A_S \times L}$$

in which A_U and A_S are the absorbances obtained from the *Test solution* and the *Buffer stage working standard solution*, respectively; C_S is the concentration, in mg per L, of pantoprazole in the *Buffer stage working standard solution*; 1 is the volume, in L, of *Buffer stage medium*; 100 is the conversion factor to percentage, and L is the Tablet label claim in mg.

Tolerances—Not less than 75% (Q) of the labeled amount of pantoprazole is dissolved in 45 minutes.

Test 3—If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 3*.

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

ACID STAGE—

Acid stage medium: 0.1 N hydrochloric acid; 1000 mL.

Apparatus 2: 100 rpm.

Time: 2 hours.

Determination of the amount of pantoprazole remaining in the Tablet employing the following procedure.

Dilute ammonia solution—Transfer 40 mL of strong ammonia solution to a 100-mL volumetric flask, and dilute with water to volume.

Buffer solution—Transfer 1.5 g of ammonium acetate to a 1000-mL volumetric flask, dissolve in and dilute with water to volume. Adjust the pH to 7.0 ± 0.1 with *Dilute ammonia solution*.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and methanol (3 : 2). Make adjustments if necessary (see *System Suitability* under *Chromatography* (621)).

Standard solution—Transfer an accurately weighed quantity of USP Pantoprazole Sodium RS to a suitable volumetric flask, add 10% of the final volume of methanol, sonicate until dissolved, and dilute with *Mobile phase* to volume to obtain a solution having a known concentration of about 0.4 mg per mL.

Test solution—After 2 hours in the *Acid stage medium*, decant the medium from the vessel, remove the Tablet from the vessel, and dry it with tissue paper. Transfer the Tablet to a suitable volumetric flask, add 20% of the final volume of methanol, and sonicate for about 20 minutes. Dilute with *Mobile phase* to volume to obtain a final concentration of about 0.4 mg of pantoprazole per mL. Mix well, centrifuge, and use the supernatant.

Chromatographic system—The liquid chromatograph is equipped with a 290-nm detector and a 4.6-mm \times 25-cm column that contains

5- μ m packing L1. The column is maintained at ambient temperature, and the autosampler is maintained at 4°. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure*: the column efficiency is not less than 7500 theoretical plates; the tailing factor is not more than 2.0, and the relative standard deviation for six replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 μ L) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak response for the major peaks. Calculate the amount of pantoprazole released by the formula:

$$A - \left[\frac{r_U \times C_S \times D_U \times 383.37 \times 100}{r_S \times L \times 405.35} \right]$$

in which A is the percentage of pantoprazole as determined in the *Assay*; r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution*, respectively; C_S is the concentration, in mg per mL, of the *Standard solution*; 383.37 is the molecular weight of pantoprazole; 100 is the conversion factor to percentage; D_U is the dilution factor of the *Test solution*; L is the Tablet label claim, in mg; and 405.35 is the molecular weight of pantoprazole sodium.

Tolerances—Not more than 10% of the labeled amount of pantoprazole is dissolved in 2 hours.

BUFFER STAGE—

Buffer stage medium: pH 6.8 phosphate buffer; 1000 mL.

Apparatus 2: 100 rpm.

Time: 45 minutes.

Standard solution—Further dilute an appropriate volume of the *Standard solution* prepared in the *Acid stage* with *Buffer stage medium* to obtain a solution having a known concentration of about 0.04 mg per mL.

Test solution—Transfer a separate Tablet to the vessel containing *Acid stage medium*, and proceed as directed for the *Acid stage*. After 2 hours, decant the *Acid stage medium*, add the *Buffer stage medium*, and operate the apparatus at the specified conditions. After 45 minutes, withdraw 10 mL of the solution under test and pass through a suitable 0.45- μ m filter.

Determine the amount of pantoprazole released to the *Buffer stage medium* using the same chromatographic procedure as directed for the *Acid stage* with the exception of injecting about 50 μ L of the *Standard solution* and the *Test solution* into the chromatograph. Calculate the amount of pantoprazole released by the formula:

$$\frac{r_U \times C_S \times 1000 \times 383.37 \times 100}{r_S \times L \times 405.35}$$

in which r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution*, respectively; C_S is the concentration, in mg per mL, of the *Standard solution*; 1000 is the volume, in mL, of *Buffer stage medium*; 383.37 is the molecular weight of pantoprazole; 100 is the conversion factor to percentage; L is the Tablet label claim, in mg; and 405.35 is the molecular weight of pantoprazole sodium.

Tolerances—Not less than 75% (Q) of the labeled amount of pantoprazole is dissolved in 45 minutes.

Test 4—If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 4*.

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

ACID STAGE—

Acid stage medium: 0.1 N hydrochloric acid; 1000 mL, degassed.

Apparatus 2: 100 rpm, with sinkers.

Time: 2 hours.

Determine the amount of pantoprazole remaining in the Tablet employing the following procedure.

Diluent—Prepare a mixture of water and acetonitrile (7 : 3).

Buffer solution—Dissolve 771 mg of ammonium acetate in 1000 mL of water. Adjust the pH to 8.5 ± 0.1 with acetic acid or ammonium hydroxide.

Solution A—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (7 : 3).

Solution B: acetonitrile.

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 solution—Prepare a solution containing 0.0068 mg of pantoprazole sulfone per mL in *Diluent*. Transfer 10 mL of this solution to a 100-mL volumetric flask, add 23 mg of USP Pantoprazole Sodium RS, and dilute with *Diluent* to volume.

Acid stage standard solution—Prepare a solution containing 0.23 mg of USP Pantoprazole Sodium RS per mL in *Diluent*.

Test solution—After 2 hours in the *Acid stage medium*, carefully remove the Tablet from the vessel and transfer to a suitable volumetric flask. Add 50% of the final volume of *Diluent*, and sonicate for 20 minutes (but not more than 60 minutes), swirling the flask every few minutes. Dilute with *Diluent* to volume to obtain a final concentration of about 0.2 mg of pantoprazole per mL.

Chromatographic system—The liquid chromatograph is equipped with a 290-nm detector and a 3.9-mm x 15-cm column that contains 5-µm packing L1. The flow rate is about 1 mL per minute. The column is maintained at 30° and the autosampler at 4°. The chromatograph is programmed as follows:

Time (minutes)	Solution A (%)	Solution B (%)	Elution
0–6	100	0	isocratic
6–17	27	73	linear gradient
17–18	100	0	linear gradient
18–22	100	0	isocratic

Chromatograph the *System suitability solution* and record the peak responses as area as directed for *Procedure*: the resolution between the pantoprazole sulfone and pantoprazole peaks is not less than 1.5. Chromatograph the *Acid stage standard solution*, and record the peak responses as area 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 *Acid stage standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak area response for the major peaks. Calculate the amount of pantoprazole released by the formula:

$$A - \left[\frac{r_U \times C_S \times D_U \times 383.37 \times 100}{r_S \times L \times 405.35} \right]$$

in which *A* is the percentage of pantoprazole as determined in the *Assay*; *r_U* and *r_S* are the peak area responses obtained from the *Test solution* and *Acid stage standard solution*, respectively; *C_S* is the concentration, in mg per mL, of the *Acid stage standard solution*; 383.37 is the molecular weight of pantoprazole; 100 is the conversion factor to percentage; *D_U* is the dilution factor of the *Test solu-*

tion; *L* is the Tablet label claim in mg; and 405.35 is the molecular weight of pantoprazole sodium.

Tolerances—Not more than 10% (*Q*) of the labeled amount of pantoprazole is dissolved in 2 hours.

BUFFER STAGE—

Buffer stage medium: pH 6.8 phosphate buffer (prepared by dissolving 76.0 g of sodium phosphate tribasic dodecahydrate in 1000 mL of water, adding 250 mL of this solution to 750 mL of *Acid stage medium*, adjusting the pH to 6.80 ± 0.05 with hydrochloric acid or sodium hydroxide); 1000 mL, degassed.

Apparatus 2: 100 rpm, with sinkers.

Time: 45 minutes.

Buffer stage standard solution—Prepare a solution in methanol containing 1.6 mg of USP Pantoprazole Sodium RS per mL. This solution is stable for 5 days at room temperature and 7 days when refrigerated. Dilute this solution with *Buffer stage medium* to obtain a concentration of *L*/1000 mg per mL, where *L* is the Tablet label claim in mg.

Test solution—Transfer a Tablet with the sinker to the vessel containing *Acid stage medium*, and proceed as directed for the *Acid stage*. After 2 hours, remove the *Acid stage medium*, add the *Buffer stage medium* and operate the apparatus at the specified conditions. After 45 minutes, withdraw 10 mL of the solution under test and pass it through a suitable 0.45-µm filter.

Procedure—Determine the amount of pantoprazole released to the *Buffer stage medium* by employing UV absorption at the wavelength of maximum absorbance at about 289 nm on portions of the *Test solution* in comparison to the *Buffer stage standard solution*, using 1 cm path length cell and *Buffer stage medium* as blank. Calculate the percentage of pantoprazole released by the formula:

$$\frac{A_U \times C_S \times 1000 \times 383.37 \times 100}{A_S \times L \times 405.35}$$

in which *A_U* and *A_S* are the absorbances obtained from the *Test solution* and the *Buffer stage standard solution*, respectively; *C_S* is the concentration, in mg per mL, of the *Buffer stage standard solution*; 383.37 is the molecular weight of pantoprazole; 100 is the conversion factor to percentage; 1000 is the volume, in mL, of *Buffer stage medium*; *L* is the Tablet label claim in mg, and 405.35 is the molecular weight of pantoprazole sodium.

Tolerances—Not less than 75% (*Q*) of the labeled amount of pantoprazole is dissolved in 45 minutes.

• (RB 01-Dec-2009)

Uniformity of dosage units (905): meet the requirements.

Chromatographic purity—

Mobile phase and *System suitability preparation*—Prepare as directed in the *Assay*.

Standard solution—Dilute an accurately measured volume of the *Standard preparation*, prepared as directed in the *Assay*, with 0.02 N sodium hydroxide to obtain a solution having a known concentration of about 0.0004 mg of pantoprazole sodium per mL.

Test solution—Use the *Assay preparation*.

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 and pantoprazole related compound A peaks is not less than 3; and the tailing factor for the pantoprazole peak is not more than 2.0. Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure*: the relative standard deviation for replicate injections is not more than 10.0%.

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Table 1

Component Name	Relative Retention Time	Limit (%)
Pantoprazole	1.0	N/A
Related compounds D ³ and F ⁴	1.2	0.5 ⁵
Pantoprazole related compound A ¹	1.3	0.5
Pantoprazole related compound B ²	2.7	0.3
Any other individual impurity	—	0.2
Total impurities	—	1.0

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

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

³5-(Difluoromethoxy)-2-[(RS)-[(3,4-dimethoxypyridin-2-yl)methyl]sulfinyl]-1-methyl-1H-benzimidazole.

⁴6-(Difluoromethoxy)-2-[(RS)-[(3,4-dimethoxypyridin-2-yl)methyl]sulfinyl]-1-methyl-1H-benzimidazole.

⁵Impurities D and F are not fully resolved and should be integrated together.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms for at least three times the retention time of the pantoprazole peak, and measure the peak responses. Calculate the percentage of each impurity in the portion of Tablets taken by the formula:

$$100(383.37/405.35)(C_S / C_T)(r_i / r_S)$$

in which 383.37 and 405.35 are the molecular weights of pantoprazole and pantoprazole sodium, respectively; C_S is the concentration, in mg per mL, of pantoprazole sodium in the *Standard solution*; C_T is the concentration, in mg per mL, of pantoprazole in the *Test solution*, based on the labeled quantity per Tablet and the extent of dilution; r_i is the peak response for each impurity obtained from the *Test solution*; and r_S is the peak response for pantoprazole obtained from the *Standard solution*. Reporting level for impurities is 0.1%.

Assay—

Buffer solution—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—Prepare a mixture of 0.02 N sodium hydroxide and acetonitrile (1 : 1).

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (65 : 35).

Standard preparation—Transfer an accurately 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 minutes 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 of pantoprazole sodium per mL.

System suitability preparation—Prepare a solution in 0.02 N sodium hydroxide, using sonication if necessary, containing about 0.2 mg of pantoprazole sodium per mL and about 0.0004 mg each of pantoprazole related compound A and pantoprazole related compound B per mL.

Assay preparation—Transfer 5 Tablets into a suitable volumetric flask. [NOTE—Use 50-mL or 100-mL volumetric flasks for Tablets containing 20 mg or 40 mg of pantoprazole per Tablet, respectively.] Add *Diluent* to about 60% of the final volume, shake mechanically for about 60 minutes, 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 of pantoprazole per mL, based on the label claim.

Chromatographic system (see *Chromatography* <621>)—The liquid chromatograph is equipped with a 290-nm detector and a 25-cm × 4.6-mm column that contains 5-µm packing L1. The flow rate is about 1 mL per minute. Chromatograph the *System suitability preparation*, and record the peak responses as directed for *Procedure*: the resolution, R , between the pantoprazole and pantoprazole related compound A peaks is not less than 3; and the tailing factor for the pantoprazole peak is not more than 2.0. 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 the labeled amount of $C_{16}H_{15}F_2N_3O_4S$ in the portion of Tablets taken by the formula:

$$100(383.37/405.35)(C_S / C_U)(r_U / r_S)$$

in which 383.37 and 405.35 are the molecular weights of pantoprazole and pantoprazole sodium, respectively; C_S is the concentration, in mg per mL, of pantoprazole sodium in the *Standard preparation*; C_U is the concentration, in mg per mL, of pantoprazole in the *Assay preparation*, based on the labeled quantity per Tablet and the extent of dilution; and r_U and r_S are the peak responses of pantoprazole obtained from the *Assay preparation* and the *Standard preparation*, respectively.●₃