Blank: Methanol and Diluent (1:9)

Chromatographic system
(See Chromatography (621), System Suitability.)

Mode: LC

Detector: UV 285 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Flow rate: 0.8 mL/min

Injection size: 40 µL

System suitability
Sample: System suitability solution

Suitability requirements

Resolution: NLT 6 between lansoprazole and lansoprazole related compound A

Relative standard deviation: NMT 3%

Analysis
Samples: Standard solution, Sample solution, and Blank

Identify the lansoprazole peak and the peaks due to the impurities listed in Table 2. Measure the areas for the major peaks, excluding peaks obtained from the Blank.

Calculate the percentage of lansoprazole related compound B in the portion of Lansoprazole taken:

\[ \text{Result} = \left( \frac{r_B}{r_s} \right) \times \left( \frac{C_s}{C_B} \right) \times 100 \]

where:

- \( r_B \) = peak response for lansoprazole related compound B from the Sample solution
- \( r_s \) = peak response for lansoprazole related compound B from the Standard solution
- \( C_B \) = concentration of USP Lansoprazole Related Compound B RS in the Standard solution (µg/mL)
- \( C_s \) = concentration of Lansoprazole in the Sample solution (µg/mL)

Calculate the percentage of lansoprazole N-oxide, lansoprazole sulfone, and any other individual impurity in the portion of Lansoprazole taken:

\[ \text{Result} = \left( \frac{r_I}{r_s} \right) \times \left( \frac{C_s}{C_I} \right) \times (1/F) \times 100 \]

where:

- \( r_I \) = peak response for each impurity from the Sample solution
- \( r_s \) = peak response for lansoprazole from the Standard solution
- \( C_I \) = concentration of USP Lansoprazole Related Compound in the Sample solution (µg/mL)
- \( C_s \) = concentration of Lansoprazole in the Sample solution (µg/mL)
- \( F \) = relative response factor for each impurity (see Table 2)

Acceptance criteria:

Individual impurities: See Table 2. Disregard any peak below 0.05%.

Table 2 (Continued)

<table>
<thead>
<tr>
<th>Name</th>
<th>Retention Time</th>
<th>Response Factor</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lansoprazole related</td>
<td>1.1</td>
<td>0.82</td>
<td>0.4</td>
</tr>
<tr>
<td>compound (lansoprazole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sulfone)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lansoprazole N-oxide</td>
<td>0.8</td>
<td>1.3</td>
<td>0.1</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Specific Tests

•在美国药典, Method la (921)

Sample: 1.0 g

NOTE—Use 50 mL of a dehydrated mixture of pyridine and ethylene glycol (9:1 to 8:2) as the solvent.

Acceptance criteria: NMT 0.1%

Additional Requirements

• Packaging and Storage: Preserve in tight, light-resistant containers. Store at room temperature, and protect from excessive heat.

Change to read:

• USP Reference Standards (11)

USP Lansoprazole RS

USP Lansoprazole Related Compound A RS


C16H14F3N3OS 385.36

USP Lansoprazole Related Compound B RS

2-[[3-Methyl-4-(2,2,2-trifluoroethoxy)-pyridin-2-yl]sulfonfonyl]-1H-benzimidazole.

C16H14F3N3O5S 353.36

Lansoprazole Delayed-Release Capsules

Lansoprazole Delayed-Release Capsules contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of lansoprazole (C16H14F3N3O2S).

Packaging and storage—Preserve in tight containers, and store at controlled room temperature.

USP Reference standards (11)—

USP Lansoprazole RS

C16H14F3N3O5S 369.36

USP Lansoprazole Related Compound A RS


C16H14F3N3O5S 385.36

Identification—

A: Ultraviolet Absorption (197U)—Medium: methanol.

Procedure—Powder a portion of Capsule contents equivalent to 5 mg of lansoprazole. Add 5 mL of methanol, shake well,
and centrifuge. To 0.1 mL of the supernatant, add 10 mL of methanol.

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.

**Dissolution (711)—**Proceed as directed for Procedure for Method A under Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms.

**Acid Stage**—

Acid stage medium: 0.1 N hydrochloric acid: 500 mL

Apparatus 2: 75 rpm.

Time: 60 minutes.

Procedure—Withdraw a 25-mL aliquot and then proceed immediately as directed for Test solution in the Buffer stage, leaving the remaining 475 mL in the vessel for use in the Buffer stage. Using a filtered portion of the aliquot, determine the amount of C<sub>16</sub>H<sub>14</sub>F<sub>3</sub>N<sub>3</sub>O<sub>2</sub>S dissolved by employing UV absorption at the wavelength of maximum absorbance at about 306 nm, using Acid stage medium as the blank. Concomitantly determine the absorbance of the Acid stage test solution in comparison with a Standard solution of USP Lansoprazole RS having a known concentration equivalent to about 8% of the labeled amount of lansoprazole dissolved per 500 mL of Acid stage medium.

**Tolerances**—Not more than 10% of the labeled amount of C<sub>16</sub>H<sub>14</sub>F<sub>3</sub>N<sub>3</sub>O<sub>2</sub>S is dissolved in 60 minutes.

**Buffer Stage**—

Buffer concentrate—Transfer 65.4 g of monobasic sodium phosphate, 28.2 g of sodium hydroxide, and 12 g of sodium dodecyl sulfate to a suitable container, and add enough water to dissolve. Dilute with water to 4 L, and mix well.

Blank solution—Prepare a mixture of Acid stage medium and Buffer concentrate (19:17). Adjust, if necessary, with either phosphoric acid or sodium hydroxide to a pH of 6.8.

Test solution—Add 425 mL of Buffer concentrate to the remaining 475 mL of solution in each vessel from the Acid stage. Adjust, if necessary, with either phosphoric acid or sodium hydroxide to a pH of 6.8.

Apparatus 2: 75 rpm.

Time: 60 minutes.

Procedure—Determine the amount of C<sub>16</sub>H<sub>14</sub>F<sub>3</sub>N<sub>3</sub>O<sub>2</sub>S dissolved in filtered portions of the Test solution, using the difference between the absorbances at the wavelengths of about 286 nm and 650 nm, with Blank solution as the blank. Concomitantly determine the absorbance of the Test solution in comparison with a Standard solution of USP Lansoprazole RS having a known concentration equivalent to about 70% of the labeled amount of lansoprazole dissolved in 900 mL of Blank solution.

**Tolerances**—Not more than 80% (Q) of the labeled amount of C<sub>16</sub>H<sub>14</sub>F<sub>3</sub>N<sub>3</sub>O<sub>2</sub>S is dissolved in 60 minutes.

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

**Procedure for Content Uniformity**—

Test solution—Transfer the contents of 1 Capsule to a 100-mL volumetric flask, add 30 mL of 0.1 M sodium hydroxide, and sonicate to disintegrate. Add 65 mL of acetonitrile, cool, and dilute with acetonitrile to volume. Centrifuge a portion of the suspension and pass through a membrane filter having a 0.5-µm or finer porosity. Quantitatively dilute a volume of the filtrate with a mixture of acetonitrile and 0.1 M sodium hydroxide (7:3) to obtain a solution containing about 0.012 mg of lansoprazole per mL, in 1-cm cells, at the wavelength of maximum absorbance at about 294 nm, with a suitable spectrophotometer, using a mixture of acetonitrile and 0.1 M sodium hydroxide (7:3) as the blank. Calculate the quantity, in mg, of C<sub>16</sub>H<sub>14</sub>F<sub>3</sub>N<sub>3</sub>O<sub>2</sub>S in the Capsule taken by the formula:

\[
\left(\frac{L}{D}\right)\left(\frac{A_c}{A_s}\right)
\]

in which \(L\) is the labeled quantity of lansoprazole in the Capsule; \(C\) is the concentration, in mg per mL, of USP Lansoprazole RS in the Standard preparation; \(D\) is the concentration, in mg per mL, of lansoprazole in the Test solution, based on the labeled quantity of lansoprazole per Capsule and the extent of dilution; and \(A_c\) and \(A_s\) are the absorbances of the Test solution and the Standard solution, respectively.

**Loss on Drying (731)—**Dry about 1 g of the Capsule contents in vacuum over phosphorus pentoxide at a pressure not exceeding 5 mm of mercury at 60° for 5 hours: it loses not more than 5.0% of its weight.

**Assay**—

Diluent, Mobile phase, and Resolution solution—Prepare as directed in the Assay under Lansoprazole.

**Internal standard solution**—Dissolve an accurately weighed quantity of 4′-ethoxycetophenone in acetonitrile to obtain a solution having a known concentration of about 7.5 mg per mL.

**Standard preparation**—Dissolve an accurately weighed quantity of USP Lansoprazole RS in a mixture of 0.1 M sodium hydroxide and acetonitrile (3:2) to obtain a solution having a known concentration of 3.0 mg per mL. Transfer 25.0 mL of this solution and 5.0 mL of Internal standard solution to a 50-mL volumetric flask, dilute with Diluent to volume, and mix. Quantitatively dilute with Diluent to obtain a solution having a known concentration of about 0.1 mg of USP Lansoprazole RS per mL.

**Assay preparation**—Transfer the contents of not fewer than 10 Capsules, equivalent to about 300 mg of lansoprazole, to a 300-mL conical flask containing 60.0 mL of 0.1 M sodium hydroxide, and sonicate until completely disintegrated. Add 20.0 mL of acetonitrile and 20.0 mL of Internal standard solution, shake well, and centrifuge a portion of the suspension. Quantitatively dilute a volume of the supernatant with Diluent to obtain a solution containing about 0.1 mg of lansoprazole per mL, and pass through a membrane filter having a 0.5-µm or finer porosity.

**Chromatographic system** (see Chromatography (621))—The liquid chromatograph is equipped with a 285-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1 mL per minute. Chromatograph the Resolution solution, and record the peak responses as directed for Procedure: the resolution, \(R\), between the two major peaks is not less than 5. 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 10 µL) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the quantity, in mg, of lansoprazole (C<sub>16</sub>H<sub>14</sub>F<sub>3</sub>N<sub>3</sub>O<sub>2</sub>S) in each Capsule taken by the formula:

\[
\left(\frac{L}{D}\right)\left(\frac{A_c}{A_s}\right)
\]

in which \(L\) is the labeled quantity, in mg, of lansoprazole in each Capsule taken; \(C\) is the concentration, in mg per mL, of USP Lansoprazole RS in the Standard preparation; \(D\) is the concentration, in mg per mL, of lansoprazole in the Assay preparation, based on the labeled quantity of lansoprazole in the Capsules taken and the extent of dilution; and \(A_c\) and \(A_s\) are the peak response ratios obtained from the Assay preparation and the Standard preparation, respectively.
Leflunomide

\[
\text{C}_{12}\text{H}_{9}\text{F}_{3}\text{N}_{2}\text{O}_{2}
\]

270.21

4-Isoxazolocarboxamide, S-methyl-N-[4-(trifluoromethyl)-phenyl]-; α,α,α-Trifluoro-5-methyl-4-isoxazolocarboxy-p-toluidide [75706-12-6].

**DEFINITION**

Leflunomide contains NLT 98.0% and NMT 102.0% of \( \text{C}_{12}\text{H}_{9}\text{F}_{3}\text{N}_{2}\text{O}_{2} \) calculated on the dried basis.

**IDENTIFICATION**

- **A. INFRARED ABSORPTION (197K)**
  - Sample: Dry the substance for 10 min at 130°C.
  - Procedure: The retention time of the major peak of the Sample solution corresponds to that of the USP Leflunomide Reference Standard solution in Mobile phase, as obtained in the Assay.

**ASSAY**

- **PROCEDURE**
  - Standard solution: 0.5 mg/mL of USP Leflunomide RS in acetonitrile and Mobile phase (1:9). [NOTE—First dissolve in acetonitrile. Protect solutions from light.]
  - System suitability solution: 0.5 mg/mL of USP Leflunomide RS, 0.15 mg/mL of USP Leflunomide Related Compound B RS, and 0.05 mg/mL of USP Leflunomide Related Compound C RS in Mobile phase. [NOTE—Dissolve the Reference Standards in acetonitrile, and dilute with Mobile phase.]
  - Sample solution: 0.5 mg/mL of Leflunomide in acetonitrile and Mobile phase (1:9). [NOTE—First dissolve in acetonitrile. Protect solutions from light.]
  - Chromatographic system:
    - Mode: LC
    - Detector: UV 210 nm
    - Column: 4-mm × 12.5-cm; packing L1
    - Flow rate: 1 mL/min
    - Injection size: 20 µL
  - System suitability:
    - Sample: System suitability solution
    - [NOTE—The relative retention times for leflunomide related compound B and leflunomide related compound C are 0.2 and 0.9, respectively.]
    - Suitability requirements:
      - Resolution: NLT 1.0 between the leflunomide and leflunomide related compound C peaks
  - Analysis:
    - Samples: Standard solution and Sample solution
    - Calculate the percentage of \( \text{C}_{12}\text{H}_{9}\text{F}_{3}\text{N}_{2}\text{O}_{2} \) in the portion of Leflunomide taken:
      \[
      \text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times 100
      \]
      \[r_U = \text{peak response from the Sample solution}\]
      \[r_S = \text{peak response from the Standard solution}\]
      \[C_S = \text{concentration of USP Leflunomide RS in the Standard solution (mg/mL)}\]
      \[C_U = \text{nominal concentration of Leflunomide in the Sample solution (mg/mL)}\]

**Acceptance criteria:** 98.0%–102.0% on the dried basis

**IMPURITIES**

**Inorganic Impurities**

- **RESIDUE ON IGNITION (281):** NMT 0.1%
- **HEAVY METALS, Method II (231):** NMT 20 ppm

**Organic Impurities**

- **PROCEDURE 1: LIMIT OF LEFLUNOMIDE RELATED COMPOUND A**
  - Mobile phase, System suitability solution, and Chromatographic system: Proceed as directed in the Assay.
  - Standard stock solution: 0.125 mg/mL of USP Leflunomide Related Compound A RS, in acetonitrile and Mobile phase (1:9)
  - Standard solution: 0.5 µg/mL of USP Leflunomide Related Compound A RS, from the Standard stock solution in Mobile phase
  - Sample solution: 2.5 mg/mL of Leflunomide, in acetonitrile and Mobile phase (1:9)
  - Injection size: 20 µL
  - Analysis:
    - Samples: Standard solution and Sample solution
    - Calculate the percentage of leflunomide related compound A in the portion of Leflunomide taken:
      \[
      \text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times 100
      \]
      \[r_U = \text{peak area of leflunomide related compound A from the Sample solution}\]
      \[r_S = \text{peak area of leflunomide related compound A from the Standard solution}\]
      \[C_S = \text{concentration of USP Leflunomide Related Compound A RS in the Standard solution (mg/mL)}\]
      \[C_U = \text{concentration of Leflunomide in the Sample solution (mg/mL)}\]
    - Acceptance criteria: NMT 0.02%

- **PROCEDURE 2**
  - Mobile phase, Sample solution, System suitability solution, and Chromatographic system: Proceed as directed in the Assay.
  - Standard stock solution: 0.5 µg/mL of USP Leflunomide RS, from the Standard solution in Mobile phase
  - Sensitivity solution: 0.25 µg/mL of Leflunomide, from the Standard solution in Mobile phase
  - System suitability
    - Samples: System suitability solution and Sensitivity solution
    - Resolution: NLT 1.0 between leflunomide and leflunomide related compound C
  - Signal-to-noise ratio: NLT 10, Sensitivity solution
  - Analysis:
    - Samples: Standard solution and Sample solution
      - [NOTE—Disregard any peak with an area less than the leflunomide peak from the System suitability solution. Continue the elution for two times the retention time of the leflunomide peak.]
      - Calculate the percentage of each related compound and any unknown impurity (see Impurity Table 1) in the portion of Leflunomide taken:
        \[
        \text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times 100
        \]
        \[r_U = \text{peak area for each impurity from the Sample solution}\]
        \[r_S = \text{peak area of leflunomide from the Standard solution}\]
        \[C_S = \text{concentration of USP Leflunomide RS in the Standard solution (mg/mL)}\]
        \[C_U = \text{concentration of Leflunomide in the Sample solution (mg/mL)}\]