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* ▲▲*USP35*
Suitability requirements
Resolution: NLT 6 between lansoprazole and lansoprazole related compound A ▲▲*USP35*
Relative standard deviation: NMT 3% ▲▲*USP35*
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:

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

r_U = 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_S = concentration of USP Lansoprazole Related Compound B RS in the *Standard solution* (µg/mL)
C_U = concentration of Lansoprazole in the *Sample solution* (µg/mL)▲*USP35*

Calculate the percentage of ▲lansoprazole *N*-oxide, lansoprazole sulfone, and any other individual▲*USP35* impurity in the portion of Lansoprazole taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response for each impurity from the *Sample solution*
r_S = peak response for lansoprazole from the *Standard solution*
C_S = concentration of USP Lansoprazole RS in the *Standard solution* (µg/mL)
C_U = 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%.▲*USP35*

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Lansoprazole *N*-oxide[a]	0.8	1.3	0.1
Lansoprazole	1.0	—	—
Lansoprazole related compound A (lansoprazole sulfone)[b]	1.1	0.82	0.4
▲Lansoprazole related compound B▲*USP35* (lansoprazole sulfide)[c]	1.2	▲—▲*USP35*	0.1
Other individual impurity	—	1.00	0.1
Total impurities	—	—	0.6

[a] [[(1*H*-Benzimidazole-2-yl)sulfinyl]methyl]-3-methyl-4-(2,2,2-trifluoroethoxy)-pyridine 1-oxide.
[b] 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfonyl]benzimidazole.
[c] 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-pyridin-2-yl]methyl]sulfanyl]-1*H*-benzimidazole.

SPECIFIC TESTS
• **WATER DETERMINATION,** *Method Ia* ⟨**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
2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfonyl]benzimidazole.
$C_{16}H_{14}F_3N_3O_3S$ 385.36
▲USP Lansoprazole Related Compound B RS
2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-pyridin-2-yl]methyl]sulfanyl]-1*H*-benzimidazole.
$C_{16}H_{14}F_3N_3OS$ 353.36▲*USP35*

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 ($C_{16}H_{14}F_3N_3O_2S$).

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

USP Reference standards ⟨11⟩**—**
USP Lansoprazole RS
$C_{16}H_{14}F_3N_3O_2S$ 369.36
USP Lansoprazole Related Compound A RS
2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfonyl]benzimidazole.
$C_{16}H_{14}F_3N_3O_3S$ 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 $C_{16}H_{14}F_3$ N_3O_2S 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.* [NOTE—A volume of methanol not to exceed 0.5% of the total volume of the Standard solution may be used to dissolve USP Lansoprazole RS prior to dilution with *Acid stage medium.*]

Tolerances—Not more than 10% of the labeled amount of $C_{16}H_{14}F_3N_3O_2S$ 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 $C_{16}H_{14}F_3N_3O_2S$ 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 absorbances 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.* [NOTE—An amount of methanol not to exceed 2% of the total volume of the Standard solution may be used to dissolve USP Lansoprazole RS prior to dilution with *Blank solution*.]

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{16}H_{14}F_3N_3O_2S$ 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.

Procedure—Concomitantly determine the absorbances of the *Test solution* and a solution of USP Lansoprazole RS in the same medium and having a known concentration of 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 $C_{16}H_{14}F_3N_3O_2S$ in the Capsule taken by the formula:

$$(LC/D)(A_U / A_S)$$

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 solution; 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_U 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′-ethoxyacetophenone 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.

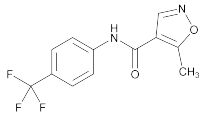
Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 285-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1 mL per minute. Chromatograph the *Resolution solution*, and record the peak responses as directed for *Procedure:* 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 ($C_{16}H_{14}F_3N_3O_2S$) in each Capsule taken by the formula:

$$(LC/D)(R_U / R_S)$$

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 R_U and R_S are the peak response ratios obtained from the *Assay preparation* and the *Standard preparation*, respectively.

Leflunomide



$C_{12}H_9F_3N_2O_2$ 270.21

4-Isoxazolecarboxamide, 5-methyl-*N*-[4-(trifluoromethyl)-phenyl]-;

α,α,α-Trifluoro-5-methyl-4-isoxazolecarboxy-*p*-toluidide [75706-12-6].

DEFINITION

Leflunomide contains NLT 98.0% and NMT 102.0% of $C_{12}H_9F_3N_2O_2$, calculated on the dried basis.

IDENTIFICATION

- **A. Infrared Absorption** ⟨**197K**⟩
  Sample: Dry the substance for 10 min at 130°.
- **B.** 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**
  Mobile phase: Acetonitrile, triethylamine, and water (70:1:130). Adjust with phosphoric acid to a pH of 4.
  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
  (See *Chromatography* ⟨621⟩, *System Suitability*.)
  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 $C_{12}H_9F_3N_2O_2$ in the portion of Leflunomide taken:

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

  r_U = peak response from the *Sample solution*
  r_S = peak response from the *Standard solution*
  C_S = concentration of USP Leflunomide RS in the *Standard solution* (mg/mL)
  C_U = 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* (1:19)
  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:

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

  r_U = peak area of leflunomide related compound A from the *Sample solution*
  r_S = peak area of leflunomide related compound A from the *Standard solution*
  C_S = concentration of USP Leflunomide Related Compound A RS in the *Standard solution* (mg/mL)
  C_U = 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 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:

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

  r_U = peak area for each impurity from the *Sample solution*
  r_S = peak area of leflunomide from the *Standard solution*
  C_S = concentration of USP Leflunomide RS in the *Standard solution* (mg/mL)
  C_U = concentration of Leflunomide in the *Sample solution* (mg/mL)