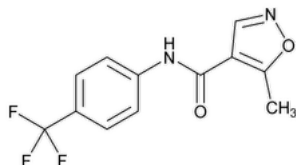


Status: Currently Official on 15-Feb-2025
 Official Date: Official as of 01-May-2020
 Document Type: USP Monographs
 DocId: GUID-4F190681-ABE3-4A78-AC0E-28C3E6B04B0A_5_en-US
 DOI: https://doi.org/10.31003/USPNF_M44450_05_01
 DOI Ref: fw4tg

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Leflunomide



$C_{12}H_9F_3N_2O_2$ 270.21

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

α,α -Trifluoro-5-methyl-4-isoxazolecarboxy-*p*-toluidide CAS RN®: 75706-12-6; UNII: G162GK9U4W.

DEFINITION

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

IDENTIFICATION

Change to read:

- **A.** ▲ [SPECTROSCOPIC IDENTIFICATION TESTS \(197\)](#), [Infrared Spectroscopy: 197K](#) ▲ (CN 1-MAY-2020)

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 μ L

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%

Change to read:

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 stock solution:** Proceed as directed in the *Standard solution* in the Assay.

Standard solution: 0.5 µg/mL of [USP Leflunomide RS](#) from the *Standard stock solution* in *Mobile phase* ▲ (ERR 1-Feb-2019)

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 *Sensitivity 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)

Impurity Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
5-Methylisoxazole-carboxylic acid	0.05	1.0	0.1



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