Leflunomide Tablets

Leflunomide Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of leflunomide (C₁₂H₉F₃N₂O₂).

Packaging and storage—Preserve in tight, light-, and humidity-resistant containers.

Add the following:

*Labeling—When more than one Dissolution test is given, the labeling states the Dissolution test used only if Test 1 is not used.*

USP Reference standards (11)—USP Leflunomide RS. USP Leflunomide Related Compound A RS. USP Leflunomide Related Compound B RS. USP Leflunomide Related Compound C RS.

Identification—

A: Ultraviolet Absorption (197U)—
Spectral range: 220 to 360 nm.
Solution: 0.01 mg per mL.
Medium: 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.

Change to read:

Dissolution (711)—

*TEST 1* (2-Nov-2009)

Medium: For Tablets labeled to contain 10 mg or 20 mg: water, 1000 mL, deaerated. For Tablets labeled to contain 100 mg: water containing 0.6% of polyoxyethylene lauryl ether; 1000 mL, deaerated.

Apparatus 2: 100 rpm.
Time: 30 minutes.

Determine the amount of C₁₂H₉F₃N₂O₂ dissolved employing one of the following methods.

SPECTROPHOTOMETRIC METHOD—

Procedure—Determine the amount of C₁₂H₉F₃N₂O₂ dissolved from UV absorbances at the wavelength of maximum absorbance at about 262 nm on portions of the solution under test passed through a suitable 0.45-µm filter, suitably diluted with Medium if necessary, in comparison with a Standard solution having a known concentration of USP Leflunomide RS in the same Medium. [NOTE—A volume of methanol not exceeding 2% of the final volume of the Standard solution may be used to dissolve leflunomide.] Chromatographic method—

Mobile phase—Prepare a filtrated and degassed mixture of acetonitrile and water (1:1). Make adjustments if necessary (see System Suitability under Chromatography (621)).

Standard solution—Transfer about 22 mg of USP Leflunomide RS, accurately weighed, to a 100-mL volumetric flask. Add 40 mL of acetonitrile, and sonicate until dissolved. Add about 40 mL of water, and cool to room temperature. Dilute with water to volume. Transfer 10.0 mL of this solution to a 100-mL volumetric flask, and dilute with water to volume.

Test solution—Use portions of the solution under test passed through a suitable 0.45-µm filter.

Chromatographic system—The liquid chromatograph is equipped with a 260-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 40 µL) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the amount of leflunomide (C₁₂H₉F₃N₂O₂) dissolved by the formula:

\[
\frac{r_s \times C_s \times (1000 \times 100)}{r_f \times L_c}
\]

in which \(r_s\) and \(r_f\) are the peak responses for the Standard solution and the Test solution, respectively; \(C_s\) is the concentration, in mg per mL, of the Standard solution; 1000 is the volume, in mL, of Medium; 100 is the conversion factor to percentage; and \(L_c\) is the Tablet label claim, in mg.

Tolerances—Not less than 80% (Q) of the labeled amount of C₁₂H₉F₃N₂O₂ 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.

Medium, Apparatus 2, Time, Spectrophotometric method, and Chromatographic method—Proceed as directed for Test 1.

Tolerances—Not less than 75% (Q) of the labeled amount of C₁₂H₉F₃N₂O₂ is dissolved in 30 minutes.

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

PROCEDURE FOR CONTENT UNIFORMITY—

Mobile phase, Standard preparation, System suitability preparations, and Chromatographic system—Prepare as directed in the Assay.

Test solution—Transfer 1 Tablet to a suitable volumetric flask, and prepare a solution having a concentration of about 1 mg of leflunomide per mL. Add Mobile phase 50% by volume, and shake to disintegrate the Tablet. After the Tablet is completely disintegrated, add acetonitrile 20% by volume, dilute with Mobile phase to volume, and shake again. Pass through a membrane filter.

Procedure—Proceed as directed in the Assay, except to use the Test solution instead of the Assay preparation.

Water, Method Ic (921): not more than 9.0%.

Related compounds—

Mobile phase, System suitability preparations, and Chromatographic system—Proceed as directed in the Assay.

Standard solution and Test solution—Prepare as directed for Standard preparation and Assay preparation, respectively, in the Assay.

Procedure—Separately inject equal volumes (about 10 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 individual impurity in the portion of Tablets taken by the formula:

\[
100(r_i / r_f)
\]

in which \(r_i\) is the peak response of each individual impurity in the chromatogram obtained from the Test solution; and \(r_f\) is the sum of all the related compounds and the leflunomide peak responses in the chromatogram obtained from the Test solution: not more than 0.1% of leflunomide related compound A is found; not more than 3.5% of leflunomide related compound B is found; not more than 0.2% of leflunomide related compound C is found; not more than 0.2% of any other individual impurity is found; and not more than 4.0% of total impurities is found.

Assay—

Mobile phase—Prepare a mixture of water, acetonitrile, and triethylamine (65:35:0.5), filter, and degas. Adjust with phosphoric acid to a pH of 4.0. Make adjustments if necessary (see System Suitability under Chromatography (621)).
Standard preparation—Dissolve an accurately weighed quantity of USP Leflunomide RS in a minimum volume of acetonitrile, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a known concentration of about 1 mg per mL.

System suitability preparation 1—Dissolve accurately weighed quantities of USP Leflunomide Related Compound A RS, USP Leflunomide Related Compound B RS, and USP Leflunomide Related Compound C RS in a minimum amount of acetonitrile, and dilute with Mobile phase to obtain a solution having known concentrations of about 10 µg per mL, 1 mg per mL, and 100 µg per mL, respectively.

System suitability preparation 2—Transfer about 100.0 mg of USP Leflunomide RS, accurately weighed, to a 100-mL volumetric flask. Dissolve in 2 mL of acetonitrile, add 1 mL of System suitability preparation 2 and 80 mL of Mobile phase, and shake by mechanical means for 10 minutes. Dilute with Mobile phase to volume, and mix.

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg of leflunomide, to a 100-mL volumetric flask. Add 20 mL of acetonitrile, dilute with Mobile phase to volume, and shake by mechanical means for 10 minutes. Pass through a membrane filter.

Chromatographic system (see Chromatography (621))—The liquid chromatograph is equipped with a 210-nm detector and a 4.0-mm × 12.5-cm column containing packing L1. The flow rate is about 1 mL per minute. Chromatograph System suitability preparation 2 and the Standard preparation, and record the peak responses as directed for Procedure: the relative retention times for leflunomide related compound A, leflunomide related compound B, leflunomide related compound C, and leflunomide are about 0.4, 0.2, 0.9, and 1.0, respectively; the resolution, R, between leflunomide related compound C and leflunomide is not less than 1.5; the tailing factor for leflunomide is not more than 3.0; and 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 responses for the major peaks. Calculate the quantity, in mg, of leflunomide (C12H9F3N2O2) in the portion of Tablets taken by the formula:

\[100C(r_U / r_S)\]

in which C is the concentration, in mg per mL, of USP Leflunomide RS in the Standard preparation; and \(r_U\) and \(r_S\) are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.