Edition: BP 2025 (Ph. Eur. 11.6 update)

Leflunomide Tablets

General Notices

Action and use

Immunomodulator.

DEFINITION

Leflunomide Tablets contain Leflunomide.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of leflunomide, $C_{12}H_9F_3N_2O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 50 mg of Leflunomide with 20 mL of *methanol* and filter. Dilute 1 volume of the filtrate to 50 volumes with *methanol* and dilute 1 volume of the resulting solution to 5 volumes with *methanol*. The *light absorption*, Appendix II B, of the final solution in the range 220 to 360 nm shows a maximum at about 260 nm.
B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 100 revolutions per minute.
(b) For tablets containing less than 100 mg of leflunomide, use 1000 mL of *water*, at a temperature of 37°, as the medium.
(c) For tablets containing 100 mg or more of leflunomide, use 1000 mL of 0.6% w/v *polyoxyethylene 23 lauryl ether*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 30 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with *water* if necessary, to produce a solution expected to contain 0.001% w/v of Leflunomide.
(2) 0.01% w/v of *leflunomide BPCRS* in *acetonitrile*. Dilute 1 volume to 10 volumes with *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Inertsil ODS-3V is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 260 nm.
(f) Inject 40 µL of each solution.

MOBILE PHASE

Equal volumes of *acetonitrile* and *water*.

DETERMINATION OF CONTENT

Calculate the total content of leflunomide, $C_{12}H_9F_3N_2O_2$, in the medium from the chromatograms obtained and using the declared content of $C_{12}H_9F_3N_2O_2$, in *leflunomide BPCRS*.

LIMITS

The amount of leflunomide released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, prepared in the mobile phase.

(1) Shake a quantity of powdered tablets containing 100 mg of Leflunomide with 20 mL of *acetonitrile R1*, add sufficient mobile phase to produce 100 mL and filter.
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) 0.1% w/v of *leflunomide for peak identification EPCRS*.
(4) Dissolve 10 mg of *leflunomide impurity A EPCRS* in 5 mL of *acetonitrile R1* and dilute to 100 mL with the mobile phase. Dilute 1 volume of the resulting solution to 100 volumes with the mobile phase and dilute 1 volume of this solution to 10 volumes.
(5) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4 mm) packed with *base-deactivated octadecylsilyl silica gel for chromatography* (5 µm) (Kromasil C18 is suitable is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 210 nm.
(f) Inject 10 µL of each solution.
(g) Allow the chromatography to proceed for twice the retention time of leflunomide.

MOBILE PHASE

Mix 5 volumes of *triethylamine* with 650 volumes of *water*, adjust to pH 3.4 with *orthophosphoric acid* and add 350 volumes of *acetonitrile R1*.

When the chromatograms are recorded under the prescribed conditions the retention times relative to leflunomide (retention time about 22 minutes) are impurity B, about 0.2; impurity A, about 0.4; impurity C, about 0.9.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the resolution between the peaks due to impurity C and leflunomide is at least 1.5

The test is not valid unless, in the chromatogram obtained with solution (4), the *signal-to-noise ratio* of the peak due to Impurity A is at least 10

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity B is not greater than 3.5 times the area of the principal peak in the chromatogram obtained with solution (2) (3.5%);

the area of any peak corresponding to impurity A is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (0.01%);

the area of any other secondary peak is not greater than twice the area of the principal peak in the chromatogram obtained with solution (5) (0.2%);

the sum of all impurities is not greater 4.0%.

Disregard any peak, with the exception of impurity A, with an area less than half the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, prepared in the mobile phase.

(1) Shake a quantity of powdered tablets containing 100 mg of Leflunomide with 20 mL of *acetonitrile*, add sufficient mobile phase to produce 100 mL and filter. Dilute 1 volume of this solution to 4 volumes with mobile phase.
(2) 0.025% w/v of *leflunomide BPCRS*.
(3) 0.1% w/v of *leflunomide for peak identification EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

When the chromatograms are recorded under the prescribed conditions the retention time of leflunomide is about 8 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the resolution between the peaks due to impurity C and leflunomide is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{12}H_9F_3N_2O_2$ in the tablets from the chromatograms obtained using the declared content of $C_{12}H_9F_3N_2O_2$ in *leflunomide BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include the impurities listed under *Leflunomide*.