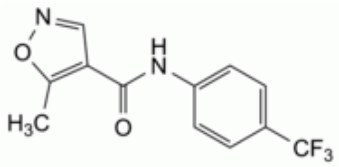
Edition: BP 2025 (Ph. Eur. 11.6 update)

Leflunomide

General Notices

(Ph. Eur. monograph 2330)



$C_{12}H_9F_3N_2O_2$ 270.2

Action and use

Immunomodulator.

Preparation

Leflunomide Tablets

Ph Eur

DEFINITION

5-Methyl-*N*-[4-(trifluoromethyl)phenyl]isoxazole-4-carboxamide.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, freely soluble in methanol, sparingly soluble in methylene chloride.

It shows polymorphism (5.9).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Preparation Heat the substance to be examined and the reference substance at 130 °C for 10 min.

Comparison leflunomide CRS.

TESTS

Related substances

Liquid chromatography (2.2.29). *Store all solutions protected from light.*

Test solution (a) Dissolve 25.0 mg of the substance to be examined in 5 mL of acetonitrile for chromatography R and dilute to 50.0 mL with the mobile phase.

Test solution (b) Dissolve 0.125 g of the substance to be examined in 5 mL of acetonitrile for chromatography R and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dilute 5.0 mL of test solution (a) to 50.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve 12.5 mg of leflunomide impurity A CRS in 5 mL of acetonitrile for chromatography R and dilute to 100.0 mL with the mobile phase. Dilute 10.0 mL of the solution to 100.0 mL with the mobile phase. Dilute 2.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (c) Dissolve 25.0 mg of leflunomide CRS in 5 mL of acetonitrile for chromatography R and dilute to 50.0 mL with the mobile phase.

Reference solution (d) Dissolve the contents of 1 vial of leflunomide for peak identification CRS (containing impurities B and C) in 2.0 mL of the mobile phase and sonicate for 10 min.

Column:

— *size*: *l* = 0.125 m, Ø = 4.0 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm).

Mobile phase Mix 5 volumes of triethylamine R with 650 volumes of water for chromatography R, adjust to pH 3.4 ± 0.1 with phosphoric acid R and add 350 volumes of acetonitrile for chromatography R.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 20 µL of test solutions (a) and (b) and reference solutions (a), (b) and (d).

Run time Twice the retention time of leflunomide.

Identification of impurities Use the chromatogram supplied with leflunomide for peak identification CRS and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities B and C.

Relative retention With reference to leflunomide (retention time = about 25 min): impurity B = about 0.2; impurity A = about 0.4; impurity C = about 0.9.

System suitability Reference solution (d):

— *peak-to-valley ratio*: minimum 3, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to leflunomide.

Limits Test solution (a):

— *impurity B*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *sum of impurities C and E*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *sum of impurities other than B*: not more twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Limit Test solution (b):

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.01 per cent).

Loss on drying (*2.2.32*)

Maximum 0.3 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C for 4 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution (a) and reference solution (c).

Calculate the percentage content of $C_{12}H_9F_3N_2O_2$ from the declared content of *leflunomide CRS*.

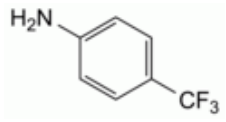
STORAGE

Protected from light.

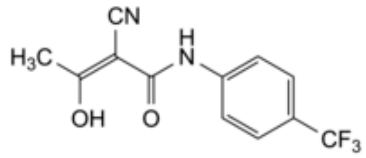
IMPURITIES

Specified impurities *A, B.*

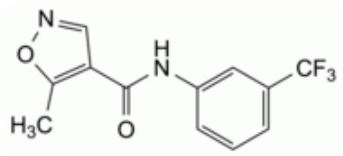
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, D, E, F, G, H.*



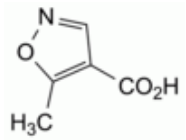
A. 4-(trifluoromethyl)aniline,



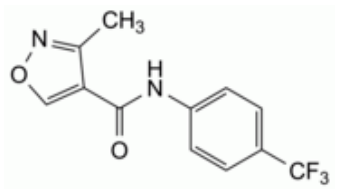
B. (2*Z*)-2-cyano-3-hydroxy-*N*-[4-(trifluoromethyl)phenyl]but-2-enamide (teriflunomide),



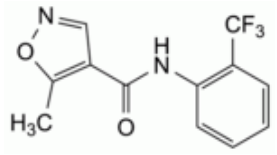
C. 5-methyl-*N*-[3-(trifluoromethyl)phenyl]isoxazole-4-carboxamide,



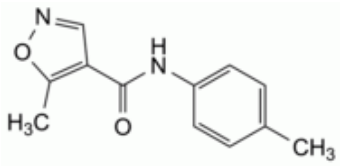
D. 5-methylisoxazole-4-carboxylic acid,



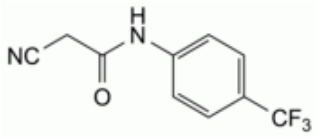
E. 3-methyl-*N*-[4-(trifluoromethyl)phenyl]isoxazole-4-carboxamide,



F. 5-methyl-*N*-[2-(trifluoromethyl)phenyl]isoxazole-4-carboxamide,



G. 5-methyl-*N*-(4-methylphenyl)isoxazole-4-carboxamide,



H. 2-cyano-*N*-[4-(trifluoromethyl)phenyl]acetamide.

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