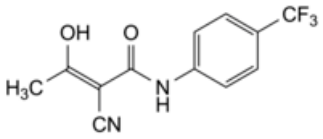
Edition: BP 2025 (Ph. Eur. 11.6 update)

Teriflunomide

General Notices

(Ph. Eur. monograph 3036)



$C_{12}H_9F_3N_2O_2$ 270.2 *163451-81-8*

Action and use

Immunomodulator; treatment of multiple sclerosis.

Preparation

Teriflunomide Tablets

Ph Eur

DEFINITION

(2*Z*)-2-Cyano-3-hydroxy-*N*-[4-(trifluoromethyl)phenyl]but-2-enamide.

Content

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

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, slightly soluble in anhydrous ethanol, practically insoluble in heptane.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *teriflunomide CRS*.

TESTS

Related substances

Liquid chromatography (*2.2.29*). *Use freshly prepared solutions.*

Buffer solution 3.85 g/L solution of *ammonium acetate R* in *water for chromatography R* adjusted to pH 5.5 with *glacial acetic acid R*.

Solvent mixture Buffer solution, *acetonitrile R* (20:80 *V/V*).

Test solution Dissolve 20.0 mg of the substance to be examined in 40 mL of the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 10 mg of *leflunomide impurity A CRS* (teriflunomide impurity A) in *acetonitrile R* and dilute to 250 mL with the same solvent. Dilute 1 mL of the solution to 200 mL with the solvent mixture.

Reference solution (c) Dissolve 5 mg of *teriflunomide impurity B CRS* in *acetonitrile R* and dilute to 100 mL with the same solvent. Dilute 2 mL of the solution to 50 mL with the solvent mixture. To 1 mL of this solution add 1 mL of reference solution (b) and dilute to 10 mL with the solvent mixture.

Reference solution (d) Dissolve 20.0 mg of *teriflunomide for assay CRS* in 40 mL of the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped solid core octadecylsilyl silica gel for chromatography R* (2.7 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: *acetonitrile for chromatography R*, buffer solution (10:90 *V/V*);

— *mobile phase B*: buffer solution, *acetonitrile for chromatography R* (10:90 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	76	24
2 - 12	76 → 23	24 → 77

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 249 nm.

Injection 5 µL of the test solution and reference solutions (a) and (c).

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and B.

Relative retention With reference to teriflunomide (retention time = about 5 min): impurity B = about 1.5; impurity A = about 1.6.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurities B and A;

— *signal-to-noise ratio*: minimum 10 for the peak due to impurity A.

Calculation of percentage contents:

— for each impurity, use the concentration of teriflunomide in reference solution (a).

Limits:

— *impurity A*: maximum 0.01 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent; do not disregard the peak due to impurity A.

Water (*2.5.32*)

Maximum 0.5 per cent, determined on 0.100 g by direct sample introduction.

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 modifications.

Injection Test solution and reference solution (d).

System suitability Reference solution (d):

— *symmetry factor*: maximum 2.0 for the peak due to teriflunomide;

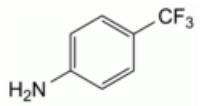
— *repeatability*: maximum relative standard deviation of 1.2 per cent determined on 6 injections.

Calculate the percentage content of $C_{12}H_9F_3N_2O_2$ taking into account the assigned content of *teriflunomide for assay CRS*.

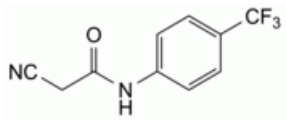
IMPURITIES

Specified impurities *A*.

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) *B*.



A. 4-(trifluoromethyl)aniline (leflunomide impurity A),



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