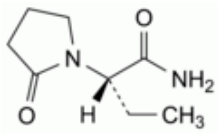
Edition: BP 2025 (Ph. Eur. 11.6 update)

Levetiracetam

General Notices

(Ph. Eur. monograph 2535)



$C_8H_{14}N_2O_2$ 170.2 *102767-28-2*

Action and use

Antiepileptic.

Ph Eur

DEFINITION

(2*S*)-2-(2-Oxopyrrolidin-1-yl)butanamide.

Content

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

CHARACTERS

Appearance

White or almost white powder.

Solubility

Very soluble in water, soluble in acetonitrile, practically insoluble in heptane.

IDENTIFICATION

Carry out either tests A, B or tests B, C.

A. Specific optical rotation (2.2.7): -82 to -76.
Dissolve 0.500 g in water R and dilute to 25.0 mL with the same solvent.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison levetiracetam CRS.

C. Enantiomeric purity (see Tests).

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution BY_6 (2.2.2, Method II).

Dissolve 2.0 g in water R and dilute to 10.0 mL with the same solvent.

Enantiomeric purity

Liquid chromatography (2.2.29): use the normalisation procedure.

Test solution Dissolve 0.200 g of the substance to be examined in 2-propanol R and dilute to 10.0 mL with the same solvent. Dilute 1.0 mL of the solution to 20.0 mL with the mobile phase.

Reference solution (a) Dissolve 5 mg of the substance to be examined and 5 mg of levetiracetam impurity D CRS in the mobile phase and dilute to 5.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: cellulose derivative of silica gel for chiral separation R (10 µm).

Mobile phase 2-propanol R, heptane R (18:82 *V/V*).

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 205 nm.

Injection 20 µL.

Run time 1.4 times the retention time of levetiracetam.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity D.

Relative retention With reference to levetiracetam (retention time = about 12 min): impurity D = about 0.8.

System suitability Reference solution (a):

— *resolution*: minimum 1.5 between the peaks due to impurity D and levetiracetam;

— *symmetry factor*: maximum 2.4 for the peak due to levetiracetam.

Limit:

— *impurity D*: maximum 0.8 per cent.

— *reporting threshold*: 0.10 per cent (reference solution (b)).

Impurity G

Liquid chromatography (*2.2.29*).

Buffer solution Dissolve 1.22 g of *sodium decanesulfonate R* in 850 mL of *water for chromatography R*, add 1.3 mL of *phosphoric acid R*, adjust to pH 3.0 with a 200 g/L solution of *potassium hydroxide R* and dilute to 1000.0 mL with *water for chromatography R*.

Test solution Dissolve 20 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 2.0 mg of *levetiracetam impurity G CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 20.0 mL with the mobile phase.

Reference solution (c) To 1.0 mL of reference solution (a) add 1.0 mL of the test solution and dilute to 20.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 27 °C.

Mobile phase *acetonitrile R1*, buffer solution (15:85 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 200 nm.

Injection 50 µL of the test solution and reference solutions (b) and (c).

Run time 5 times the retention time of levetiracetam.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity G.

Relative retention With reference to levetiracetam (retention time = about 4 min): impurity G = about 3.8.

System suitability Reference solution (c):

— *resolution*: minimum 5.0 between the peaks due to levetiracetam and impurity G.

Calculation of percentage content:

— for impurity G, use the concentration of impurity G in reference solution (b).

Limit:

— *impurity G*: maximum 0.05 per cent.

Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 50.0 mg of the substance to be examined in mobile phase A and dilute to 10.0 mL with mobile phase A.

Test solution (b) Dilute 1.0 mL of test solution (a) to 50.0 mL with mobile phase A.

Reference solution (a) Dissolve 5 mg of *levetiracetam impurity A CRS* and 5 mg of *levetiracetam impurity E CRS* in mobile phase A, add 1.0 mL of test solution (a) and dilute to 100.0 mL with mobile phase A.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 20.0 mL with mobile phase A.

Reference solution (c) Dissolve 5.0 mg of *levetiracetam impurity C CRS* in mobile phase A and dilute to 100.0 mL with mobile phase A. Dilute 1.0 mL of the solution to 40.0 mL with mobile phase A.

Reference solution (d) Dissolve 50.0 mg of *levetiracetam CRS* in mobile phase A and dilute to 10.0 mL with mobile phase A. Dilute 1.0 mL of the solution to 50.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

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

Mobile phase:

— *mobile phase A*: *acetonitrile R1*, *phosphate buffer solution pH 5.5 R* (5:95 *V/V*);

— *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	100	0
3 - 20	100 → 71	0 → 29
20 - 25	71	29

Flow rate 0.9 mL/min.

Detection Spectrophotometer at 205 nm.

Injection 10 µL of test solution (a) and reference solutions (a), (b) and (c).

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A and E; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity C.

Relative retention With reference to levetiracetam (retention time = about 11 min): impurity C = about 0.5; impurity A = about 0.7; impurity E = about 0.9.

System suitability Reference solution (a):

— *resolution*: minimum 3.5 between the peaks due to impurity E and levetiracetam.

Calculation of percentage contents:

— for impurity C, use the concentration of impurity C in reference solution (c);

— for impurities other than C, use the concentration of levetiracetam in reference solution (b).

Limits:

— *impurity A*: maximum 0.3 per cent;

— *impurity C*: maximum 250 ppm;

— *unspecified impurities*: for each impurity, maximum 0.05 per cent;

— *total*: maximum 0.4 per cent;

— *reporting threshold*: 0.03 per cent, except for impurity C.

Water (*2.5.32*)

Maximum 0.5 per cent, determined on 0.300 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

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

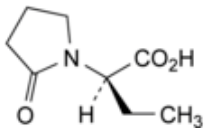
Injection Test solution (b) and reference solution (d).

Calculate the percentage content of $C_8H_{14}N_2O_2$ taking into account the assigned content of *levetiracetam CRS*.

IMPURITIES

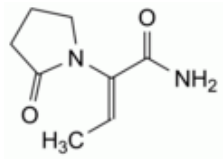
Specified impurities *A, C, D, G.*

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, E.*

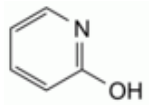


and enantiomer

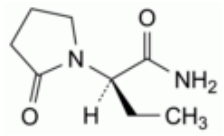
A. (2*RS*)-2-(2-oxopyrrolidin-1-yl)butanoic acid,



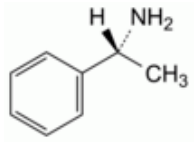
B. (2*Z*)-2-(2-oxopyrrolidin-1-yl)but-2-enamide,



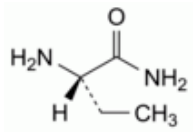
C. pyridin-2-ol,



D. (2*R*)-2-(2-oxopyrrolidin-1-yl)butanamide ((*R*)-etiracetam),



E. (1*R*)-1-phenylethan-1-amine,



G. (2*S*)-2-aminobutanamide.

Ph Eur