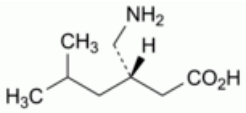
Edition: BP 2025 (Ph. Eur. 11.6 update)

Pregabalin

General Notices

(Ph. Eur. monograph 2777)



$C_8H_{17}NO_2$ 159.2 *148553-50-8*

Action and use

Antiepileptic.

Preparations

Pregabalin Capsules

Pregabalin Oral Solution

Ph Eur

DEFINITION

(3*S*)-3-(Aminomethyl)-5-methylhexanoic acid.

Content

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

CHARACTERS

Appearance

White or almost white powder.

Solubility

Sparingly soluble in water, very slightly soluble in methanol, practically insoluble in heptane.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *pregabalin CRS*.

B. Examine the chromatograms obtained in the test for enantiomeric purity.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with the reference solution.

TESTS

Enantiomeric purity

Liquid chromatography (*2.2.29*): use the normalisation procedure.

Test solution Dissolve 20 mg of the substance to be examined in *water R* and dilute to 10.0 mL with the same solvent. Derivatise the solution as described under Derivatisation.

Reference solution Dissolve 2 mg of *pregabalin impurity B CRS* in *water R* and dilute to 20.0 mL with the same solvent. Dilute 1.0 mL of the solution to 10.0 mL with *water R*. To 20 mg of *pregabalin CRS*, add 1.0 mL of this solution and dilute to 10.0 mL with *water R*. Derivatise this solution as described under Derivatisation.

Derivatisation Transfer 500 µL of the solution to a reaction vial. Add 500 µL of a 5 g/L solution of *1-fluoro-2,4-dinitrophenyl-5-L-alaninamide R* in *acetonitrile R*. Add 50 µL of an 84 g/L solution of *sodium hydrogen carbonate R*. Seal the vial, mix and derivatise by maintaining the vial at 40 °C for 1 h in a heating/stirring module. Stop the reaction by adding about 50 µL of a 103 g/L solution of *hydrochloric acid R*. Mix thoroughly. To 200 µL of the derivatised solution add 800 µL of the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

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

— *temperature*: 30 °C.

Mobile phase *acetonitrile R*, 1 per cent *V/V* solution of *triethylamine R* previously adjusted to pH 3.0 with *phosphoric acid R* (38:62 *V/V*).

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 340 nm.

Injection 20 µL.

Run time 2.5 times the retention time of the pregabalin derivative.

Relative retention With reference to the pregabalin derivative (retention time = about 10 min): impurity B derivative = about 1.3.

System suitability Reference solution:

— *resolution*: minimum 4.4 between the peaks due to the pregabalin derivative and impurity B derivative.

Limit:

— *impurity B*: maximum 0.15 per cent.

Related substances

A. Polar impurities eluting before pregabalin. Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.100 g of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 0.100 g of *pregabalin CRS* in the mobile phase and dilute to 10.0 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.

Reference solution (c) Dissolve 5 mg of *mandelic acid R* (impurity C) in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 0.5 mL of the solution to 5.0 mL with the test solution.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography compatible with 100 per cent aqueous mobile phases R* (5 µm);

— *temperature*: 30 °C.

Mobile phase *methanol R2*, 3.40 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 6.3 with *concentrated ammonia R* (15:85 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 20 µL of the test solution and reference solutions (b) and (c).

Run time 1.3 times the retention time of pregabalin.

Relative retention With reference to pregabalin (retention time = about 10 min): impurity C = about 0.6.

System suitability Reference solution (c):

— *resolution*: minimum 5.0 between the peaks due to impurity C and pregabalin.

Calculation of percentage contents:

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

Limits:

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

— *reporting threshold*: 0.05 per cent.

B. Non-polar impurities eluting after pregabalin. Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.100 g of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) 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.

Reference solution (b) Dissolve 2.5 mg of *pregabalin impurity D CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase (solution A). Dissolve the contents of a vial of *pregabalin impurity A CRS* in the mobile phase, add 1.0 mL of solution A and dilute to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography compatible with 100 per cent aqueous mobile phases R* (5 µm);

— *temperature*: 30 °C.

Mobile phase 3.40 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 6.3 with *concentrated ammonia R*, *methanol R2* (45:55 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 20 µL.

Run time 4 times the retention time of pregabalin.

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

Relative retention With reference to pregabalin (retention time = about 4 min): impurity A = about 2.4; impurity D = about 3.0.

System suitability Reference solution (b):

— *resolution*: minimum 3.5 between the peaks due to impurities A and D.

Calculation of percentage contents:

— for impurities A and D, use the concentration of each impurity in reference solution (b);

— for impurities other than A and D, use the concentration of pregabalin in reference solution (a).

Limits:

— *impurity A*: maximum 0.15 per cent;

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

— *reporting threshold*: 0.05 per cent.

Limit:

— *total for tests A and B*: maximum 0.5 per cent.

Water (*2.5.12*)

Maximum 0.5 per cent, determined on 0.130 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 test A for related substances with the following modification.

Injection Test solution and reference solution (a).

Calculate the percentage content of $C_8H_{17}NO_2$ taking into account the assigned content of *pregabalin CRS*.

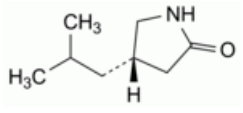
IMPURITIES

Test A for related substances: C.

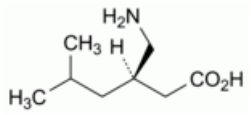
Test B for related substances: A, D.

Specified impurities *A, B.*

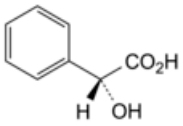
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical 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.*



A. (4*S*)-4-(2-methylpropyl)pyrrolidin-2-one,

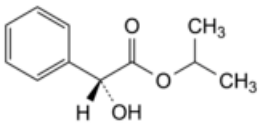


B. (3*R*)-3-(aminomethyl)-5-methylhexanoic acid (pregabalin enantiomer),



and enantiomer

C. (2*RS*)-2-hydroxy-2-phenylacetic acid (mandelic acid),



and enantiomer

D. 1-methylethyl (2*RS*)-2-hydroxy-2-phenylacetate.

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