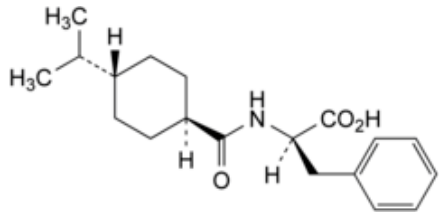
Edition: BP 2025 (Ph. Eur. 11.6 update)

Nateglinide

General Notices

(Ph. Eur. monograph 2575)



$C_{19}H_{27}NO_3$ 317.4 *105816-04-4*

Action and use

Stimulates insulin release; treatment of diabetes mellitus.

Ph Eur

DEFINITION

N-[[*trans*-4-(1-Methylethyl)cyclohexyl]carbonyl]-D-phenylalanine.

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 and in methylene chloride.

It shows polymorphism (*5.9*).

IDENTIFICATION

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

A. Specific optical rotation (2.2.7): -40.0 to -36.5 (dried substance).
Dissolve 0.200 g in a 4 g/L solution of *sodium hydroxide R* and dilute to 20.0 mL with the same solution.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *nateglinide CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

C. Test B for related substances (see Tests).

TESTS

Related substances

A. Impurity A and unspecified impurities. Liquid chromatography (2.2.29).

Test solution Dissolve 60.0 mg of the substance to be examined in 1 mL of *acetonitrile R1* and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 3.0 mg of *nateglinide impurity A CRS* in 1 mL of *acetonitrile R1* and dilute to 25.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve 3 mg of the substance to be examined in 1 mL of *acetonitrile R1*, add 4.0 mL of reference solution (a) and dilute to 10 mL with the mobile phase.

Reference solution (d) 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* = 0.05 m, Ø = 3.9 mm;

— *stationary phase*: spherical *end-capped octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase Mix 35 volumes of *acetonitrile R1* and 65 volumes of a 7.8 g/L solution of *sodium dihydrogen phosphate monohydrate R* previously adjusted to pH 2.5 with *phosphoric acid R*.

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 100 µL of the test solution and reference solutions (b), (c) and (d).

Run time 5 times the retention time of nateglinide.

Relative retention With reference to nateglinide (retention time = about 7 min): impurity A = about 0.5.

System suitability Reference solution (c):

— *resolution*: minimum 5.0 between the peaks due to impurity A and nateglinide.

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

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

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

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

B. Impurity B. Liquid chromatography (2.2.29).

Test solution Dissolve 0.200 g of the substance to be examined in *methanol R2* and dilute to 20.0 mL with the same solvent.

Reference solution (a) Dissolve 5 mg of *nateglinide impurity B CRS* in *methanol R2* and dilute to 10.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of the test solution to 50.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve 0.10 g of the substance to be examined in *methanol R2*. Add 1.0 mL of reference solution (a) and dilute to 10.0 mL with *methanol R2*.

Column:

— *size*: *l* = 0.25 m, *Ø* = 4.0 mm;

— *stationary phase*: urea type silica gel for chiral chromatography R (5 µm);

— *temperature*: 40 °C.

Mobile phase Dissolve 0.77 g of *ammonium acetate R* in *methanol R2* and dilute to 1000 mL with the same solvent.

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 220 nm.

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

Run time 1.5 times the retention time of nateglinide.

Relative retention With reference to nateglinide (retention time = about 21 min): impurity B = about 0.9.

System suitability Reference solution (c):

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

Limit:

— *impurity B*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent).

C. Impurities C and D. Liquid chromatography (2.2.29).

Sodium phosphate buffer Dissolve 8.5 g of anhydrous disodium hydrogen phosphate R in 950 mL of water R. Adjust to pH 7.5 with phosphoric acid R and dilute to 1000 mL with water R.

Test solution Dissolve 50.0 mg of the substance to be examined in 25 mL of methanol R2 and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 5.0 mg of phenylalanine CRS (impurity D) and 5 mg of nateglinide impurity C CRS in methanol R2 and dilute to 25.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of the test solution to 50.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve 20 mg of the substance to be examined in 10 mL of methanol R2, add 1.0 mL of reference solution (a) and dilute to 20.0 mL with sodium phosphate buffer.

Reference solution (d) Dilute 1.0 mL of reference solution (a) to 100.0 mL with the mobile phase.

Reference solution (e) Dissolve 50.0 mg of nateglinide CRS in 25 mL of methanol R2 and dilute to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 6.0 mm;

— *stationary phase*: polymethacrylate gel R (6 µm);

— *temperature*: 30 °C.

Mobile phase methanol R2, sodium phosphate buffer (45:55 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

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

Run time 1.4 times the retention time of nateglinide.

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

Relative retention With reference to nateglinide (retention time = about 18 min): impurity D = about 0.2; impurity C = about 0.9.

System suitability Reference solution (c):

— peak-to-valley ratio: minimum 1.5, 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 nateglinide.

Limits:

— *impurity C*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *impurity D*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.2 per cent).

Limits:

— *total for impurities A, B, C, D and sum of unspecified impurities*: maximum 0.5 per cent;

— *disregard limit for impurities A, B, C and D*: 0.05 per cent for each impurity.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

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 C for related substances with the following modification.

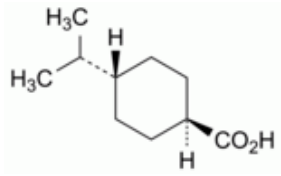
Injection Test solution and reference solution (e).

Calculate the percentage content of $C_{19}H_{27}NO_3$ taking into account the assigned content of *nateglinide CRS*.

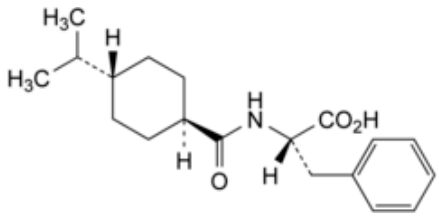
IMPURITIES

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

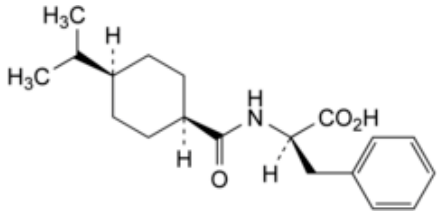
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical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



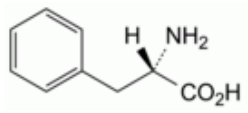
A. *trans*-4-(1-methylethyl)cyclohexanecarboxylic acid,



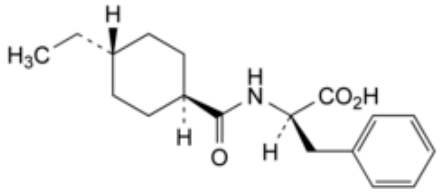
B. *N*-[[*trans*-4-(1-methylethyl)cyclohexyl]carbonyl]-L-phenylalanine (L-phenylalanine isomer),



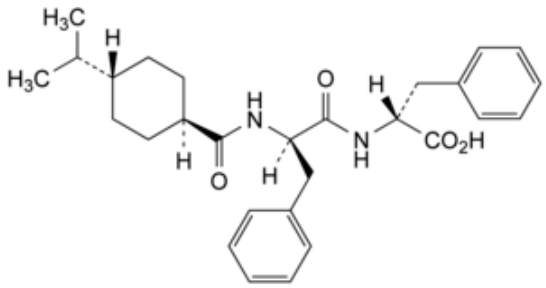
C. *N*-[[*cis*-4-(1-methylethyl)cyclohexyl]carbonyl]-D-phenylalanine (*cis*-isomer),



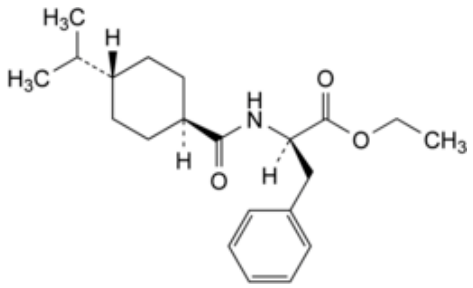
D. (2*S*)-2-amino-3-phenylpropanoic acid (phenylalanine),



E. *N*-[(*trans*-4-ethylcyclohexyl)carbonyl]-D-phenylalanine,



F. *N*-[[*trans*-4-(1-methylethyl)cyclohexyl]carbonyl]-D-phenylalanyl-D-phenylalanine,



G. ethyl *N*-[[*trans*-4-(1-methylethyl)cyclohexyl]carbonyl]-D-phenylalaninate.

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