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Nateglinide

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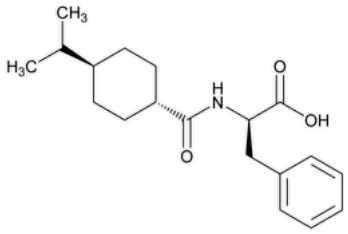

▲ (ERR 1-Nov-2020) $C_{19}H_{27}NO_3$ 317.42

D-Phenylalanine, *N*-[[*trans*-4-(1-methylethyl)cyclohexyl] carbonyl]-;

(−)-*N*-[(*trans*-4-Isopropylcyclohexyl)carbonyl-D-phenylalanine CAS RN®: 105816-04-4; UNII: 41X3PWK4O2.

DEFINITION

Nateglinide contains NLT 98.0% and NMT 102.0% of $C_{19}H_{27}NO_3$, calculated on the dried basis.

IDENTIFICATION

- **A.** **Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197K
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay.*

ASSAY

- **Procedure**

Buffer: 8.5 g/L of anhydrous dibasic sodium phosphate in water. Adjust with phosphoric acid to a pH of 7.5.

Mobile phase: Methanol and *Buffer* (1:1)

System suitability stock solution: 0.2 mg/mL each of USP Nateglinide Related Compound C RS and DL-phenylalanine in methanol. [Note—Sonicate, if necessary.]

System suitability solution: Transfer USP Nateglinide RS to a suitable volumetric flask, dissolve first in methanol, using 45% of the final volume, add *System suitability stock solution* equal to 5% of the final volume, and then dilute with *Buffer* to volume to obtain a solution containing about 1.0 mg/mL of nateglinide and about 0.01 mg/mL each of nateglinide related compound C and DL-phenylalanine.

Standard solution: 1.0 mg/mL of nateglinide prepared as follows: transfer USP Nateglinide RS to a suitable volumetric flask, dissolve first in methanol, using 50% of the final volume, and then dilute with *Buffer* to volume.

Sample solution: Transfer about 100 mg of Nateglinide to a 100-mL volumetric flask, dissolve in 50 mL of methanol, and dilute with *Buffer* to volume.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 210 nm

Column: 6-mm × 15-cm; 6-µm packing L71 (see *Chromatographic Reagents* under *Reagents, Indicators, and Solutions*)

Column temperature: 30°

Flow rate: 1 mL/min

Injection size: 20 µL

System suitability

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 0.9 between nateglinide related compound C and nateglinide, *System suitability solution*

Relative standard deviation: NMT 1.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of nateglinide ($C_{19}H_{27}NO_3$) in the portion of Nateglinide taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Nateglinide RS in the *Standard solution* (mg/mL)

C_U = concentration of Nateglinide in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the dried basis

IMPURITIES

- **Residue on Ignition ⟨281⟩:** NMT 0.1%
- **Limit of Nateglinide Related Compound A and Other Impurities**

Buffer: 7.8 g/L of monobasic sodium phosphate in water. Adjust with phosphoric acid to a pH of 2.5.

Mobile phase: Acetonitrile and *Buffer* (7:13)

System suitability stock solution: Dissolve USP Nateglinide Related Compound A RS in acetonitrile to obtain a solution containing about 0.6 mg/mL. Further dilute this solution with *Mobile phase* to obtain a solution containing about 0.12 mg/mL.

System suitability solution: Transfer an amount of USP Nateglinide RS to a suitable volumetric flask, dissolve first in acetonitrile using 10% of the final volume, then add *System suitability stock solution* equal to 10% of the final volume, and dilute with *Mobile phase* to volume to obtain a solution containing about 6 mg/mL of nateglinide and about 0.012 mg/mL of nateglinide related compound A.

Standard solution: Dissolve USP Nateglinide RS in acetonitrile to obtain a solution having a known concentration of about 0.3 mg/mL. Further dilute this solution with *Mobile phase* to obtain a solution having a known concentration of about 0.06 mg/mL.

Sample solution: Transfer 60 mg of Nateglinide to a 10-mL volumetric flask, dissolve in a minimal amount of acetonitrile, and dilute with *Mobile phase* to volume.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 210 nm

Column: 3.9-mm × 5-cm; 5-µm packing L7

Column temperature: 40°

Flow rate: 2 mL/min

Injection size: 100 µL

Run time: 5 times the retention time of nateglinide

System suitability

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 2.5 between nateglinide related compound A and nateglinide, *System suitability solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Nateglinide taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of each impurity from the *Sample solution*

r_S = peak response of nateglinide from the *Standard solution*

C_S = concentration of USP Nateglinide RS in the *Standard solution* (mg/mL)

C_U = concentration of Nateglinide in the *Sample solution* (mg/mL)

F = relative response factor (see *Table 1*)

Acceptance criteria

Individual impurities: See *Table 1*.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Nateglinide related compound A[a]	0.5	0.015	0.2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Ethyl analog[b]	0.6	1.0	0.1
Nateglinide	1.0	—	—
IPP impurity[c]	3.1	1.0	0.1
Ester impurity[d]	4.1	0.94	0.1
Any other individual impurity	—	1.0	0.1

[a] *trans*-4-Isopropylcyclohexylcarboxylic acid.

[b] *N*-(*trans*-4-Ethylcyclohexylcarbonyl)-D-phenylalanine.

[c] *N*-(*trans*-4-Isopropylcyclohexylcarbonyl)-D-phenylalanine-D-phenylalanine.

[d] *N*-(*trans*-4-isopropylcyclohexylcarbonyl)-D-phenylalanine-ethyl ester.

• **Limit of Nateglinide Related Compound B**

Mobile phase: 0.77 g/L of ammonium acetate in methanol.

[Note—The following solutions are stable for up to 48 h when stored in a refrigerator.]

System suitability solution: 10 mg/mL of USP Nateglinide RS and 0.02 mg/mL of USP Nateglinide Related Compound B RS in methanol

Standard solution: 0.02 mg/mL of USP Nateglinide Related Compound B RS in methanol. [Note—Nateglinide related compound B is *N*-(*trans*-4-isopropyl-cyclohexylcarbonyl)-L-phenylalanine.]

Sample solution: 10 mg/mL of Nateglinide in methanol

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 220 nm

Column: 4-mm × 25-cm or 4.6-mm × 25-cm; 5-µm packing L72 (see *Chromatographic Reagents* under *Reagents, Indicators, and Solutions*)

Column temperature: 40°

Flow rate: 0.8 mL/min. [Note—The flow rate can be adjusted as needed to achieve a recommended retention time of nateglinide related compound B at about 25 min.]

Injection size: 10 µL

System suitability

[Note—The elution order is nateglinide related compound B, followed by the nateglinide peak.]

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 0.8 between nateglinide related compound B and nateglinide, *System suitability solution*

Relative standard deviation: NMT 5%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of nateglinide related compound B in the portion of Nateglinide taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of nateglinide related compound B from the *Sample solution*

r_S = peak response of nateglinide related compound B from the *Standard solution*

C_S = concentration of USP Nateglinide Related Compound B RS in the *Standard solution* (mg/mL)

C_U = concentration of Nateglinide in the *Sample solution* (mg/mL)

Acceptance criteria: NMT 0.2%

• **Limit of Nateglinide Related Compound C and Phenylalanine**

Mobile phase, System suitability solution, Standard solution, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

Diluted standard solution: Dilute the *Standard solution* with *Mobile phase* to obtain a solution having a known concentration of about 0.01 mg/mL of nateglinide.

Analysis

Samples: *Sample solution* and *Diluted standard solution*

Calculate the percentage of each specified impurity listed in *Table 2* in the portion of Nateglinide taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of each impurity from the *Sample solution*

r_S = peak response of nateglinide from the *Diluted standard solution*

C_S = concentration of nateglinide in the *Diluted standard solution* (mg/mL)

C_U = concentration of Nateglinide in the *Sample solution* (mg/mL)

F = relative response factor of each individual impurity (see *Table 2*)

Acceptance criteria

Individual impurities: See *Table 2*.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Phenylalanine	0.2	1.5	0.2
Nateglinide *cis*-isomer[a] (related compound C)	0.9	0.97	0.2
Nateglinide	1.0	—	—

[a] *N*-(*cis*-4-isopropylcyclohexylcarbonyl)-D-phenylalanine.

Total impurities: The sum of all impurities found in the tests for *Limit of Nateglinide Related Compound A and Other Impurities*, *Limit of Nateglinide Related Compound B*, and *Limit of Nateglinide Related Compound C and Phenylalanine* is NMT 0.5%.

SPECIFIC TESTS

• **Loss on Drying ⟨731⟩:** Dry a sample at 105° for 2 h: it loses NMT 0.5% of its weight.

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers. Store at room temperature.

• **USP Reference Standards ⟨11⟩**

USP Nateglinide RS

(−)-*N*-[(*trans*-4-Isopropylcyclohexyl)carbonyl-D-phenylalanine.

$C_{19}H_{27}NO_3$ 317.42

USP Nateglinide Related Compound A RS

trans-4-Isopropylcyclohexylcarboxylic acid.

$C_{10}H_{18}O_2$ 170.2

USP Nateglinide Related Compound B RS

N-(*trans*-4-Isopropylcyclohexylcarbonyl)-L-phenylalanine.

$C_{19}H_{27}NO_3$ 317.4

USP Nateglinide Related Compound C RS

Nateglinide *cis*-isomer, *N*-(*cis*-4-isopropylcyclohexylcarbonyl)-D-phenylalanine.

$C_{19}H_{27}NO_3$ 317.4

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
NATEGLINIDE	Documentary Standards Support	SM32020 Small Molecules 3

Chromatographic Database Information: Chromatographic Database

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