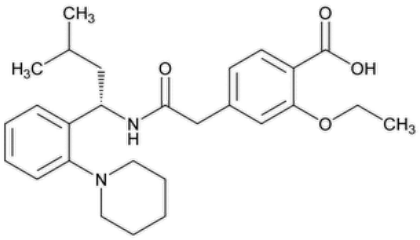
Status: Currently Official on 16-Feb-2025
Official Date: Official as of 01-May-2020
Document Type: USP Monographs
DocId: GUID-DB25DE8F-D766-4E43-ABC3-3ABCEBAC56FF_4_en-US
DOI: https://doi.org/10.31003/USPNF_M73165_04_01
DOI Ref: m1lwb

Repaglinide



$C_{27}H_{36}N_2O_4$ 452.59

(*S*)-2-Ethoxy-4-[2-{methyl-1-[2-(1-piperidinyl)phenyl]butylamino}-2-oxoethyl]-benzoic acid;

(+)-2-Ethoxy-α-[[(*S*)-α-isobutyl-*o*-piperidinobenzyl]carbamoyl]-*p*-toluic acid CAS RN®: 135062-02-1; UNII: 668Z8C33LU.

DEFINITION

Repaglinide contains NLT 98.0% and NMT 102.0% of repaglinide ($C_{27}H_{36}N_2O_4$), calculated on the dried basis.

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197K**▲ (CN 1-May-2020)

• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *System suitability solution*, as obtained in the test for *Enantiomeric Purity*.

ASSAY

• **Procedure**

Buffer: 1 g/L of monobasic potassium phosphate solution, adjusted with phosphoric acid to a pH of 2.5

Mobile phase: Methanol and *Buffer* (8:2)

Standard solution: 0.5 mg/mL of USP Repaglinide RS in methanol

Sample solution: 0.5 mg/mL of Repaglinide in methanol

Chromatographic system

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

Mode: LC

Detector: UV 240 nm

Column: 4.6-mm × 12.5-cm; 5-µm packing L1

Column temperature: 45°

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 0.73%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of repaglinide ($C_{27}H_{36}N_2O_4$) in the portion of Repaglinide 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 the *Standard solution* (mg/mL)

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

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

IMPURITIES

• **Residue on Ignition ⟨281⟩**

Ignition temperature: 600° ± 25°

Acceptance criteria: NMT 0.1%

• **Organic Impurities**

Solution A: 3 mg/mL of monobasic potassium phosphate solution, adjusted with 1 N sodium hydroxide to a pH of 7.0

Solution B: Methanol

Identification solution: 6 mg/mL of USP Repaglinide RS, 60 µg/mL of USP Repaglinide Related Compound A RS, 60 µg/mL of USP Repaglinide Related Compound B RS, and 60 µg/mL of USP Repaglinide Related Compound C RS in methanol

Sample solution: 6 mg/mL of Repaglinide in methanol

Standard solution: 0.06 mg/mL of repaglinide in methanol, from the *Sample solution*

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	50	50
2	30	70
8	30	70
12	5	95
15	5	95

Return to original conditions and re-equilibrate the system.

Chromatographic system

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

Mode: LC

Detector: UV 240 nm

Column: 4.6-mm × 12.5-cm; 5-µm packing L1

Column temperature: 45°

Flow rate: 1 mL/min

Injection volume: 5 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 10% of repaglinide, *Standard solution*

Analysis

Samples: *Identification solution*, *Sample solution*, and *Standard solution*

Chromatograph the *Identification solution*, and identify the components on the basis of their relative retention times, given in *Table 2*.

Calculate the percentage of each impurity in the portion of Repaglinide 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 repaglinide from the *Standard solution*

C_S = concentration of repaglinide in the *Standard solution* (mg/mL)

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

F = relative response factor (see Table 2)

Acceptance criteria: See Table 2.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
4-(Carboxymethyl)-2-ethoxybenzoic acid	0.15	1.4	0.1
Repaglinide related compound B	0.31	1.7	0.1
Repaglinide related compound C	0.96	1.0	0.1
Repaglinide	1.0	—	—
Repaglinide related compound A	1.6	0.5	0.1
Repaglinide ethyl ester[a]	1.9	1.3	0.1
Any other individual impurity	—	1.0	0.1
Total impurities	—	—	0.5

[a] (*S*)-Ethyl 2-ethoxy-4-[2-({3-methyl-1-[2-(piperidin-1-yl)phenyl]butyl}amino)-2-oxoethyl]benzoate.

• **Enantiomeric Purity**

[Note—Protect all solutions containing repaglinide from light.]

Buffer: Dissolve 1 g of monobasic potassium phosphate in 1 L of water. If needed, adjust with 2 N sodium hydroxide or with dilute phosphoric acid to a pH of 4.7.

Solution A: *Buffer*

Solution B: Acetonitrile

Mobile phase: See Table 3. [Note—Equilibrate after installation of the column as follows. Using water, slowly increase the flow rate from 0.2 mL/min to 0.5 mL/min. Maintain the flow rate at 0.5 mL/min for 5 min. The column must be washed with water for 1 h at a flow rate of 1 mL/min, and for 1 h with *Mobile phase* at the initial composition prior to the first analysis.]

Table 3

Time (min)	Solution A (%)	Solution B (%)
0	80	20
4	60	40
6	60	40

Return to the original conditions and re-equilibrate the system.

System suitability solution: 1.0 mg/mL of USP Repaglinide RS and 0.02 mg/mL of USP Repaglinide Related Compound E RS in methanol

Standard solution: 2.0 µg/mL of USP Repaglinide Related Compound E RS in methanol

Sample solution: 1.0 mg/mL of Repaglinide in methanol

Chromatographic system

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

Mode: LC

Detector: UV 240 nm

Column: 4.0-mm × 10-cm; 5-µm packing L41

Flow rate: 1.0 mL/min

Injection volume: 10 µL

System suitability

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

[NOTE—The typical relative retention times for repaglinide and repaglinide related compound E are 1.0 and 1.5, respectively.]

Suitability requirements

Resolution: NLT 1.5 between repaglinide and repaglinide related compound E, *System suitability solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of repaglinide related compound E in the portion of Repaglinide taken:

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

r_U = peak response of repaglinide related compound E in the *Sample solution*

r_S = peak response of repaglinide related compound E in the *Standard solution*

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

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

Acceptance criteria: NMT 0.2%

SPECIFIC TESTS

• **LOSS ON DRYING ⟨731⟩**

Analysis: Dry at 105° to constant weight.

Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight containers. Protect from light.

• **USP REFERENCE STANDARDS ⟨11⟩**

USP Repaglinide RS

USP Repaglinide Related Compound A RS

(*S*)-3-Methyl-1-[2-(1-piperidinyl)phenyl]butylamine, *N*-acetyl-L-glutamate salt.

$C_{16}H_{26}N_2 \cdot C_7H_{11}NO_5$ 435.6

USP Repaglinide Related Compound B RS

3-Ethoxy-4-ethoxycarbonylphenylacetic acid.

$C_{13}H_{16}O_5$ 252.27

USP Repaglinide Related Compound C RS

(*S*)-2-Ethoxy-4-[2-[[2-phenyl-1-[2-(1-piperidinyl)phenyl]ethyl]amino]-2-oxoethyl]benzoic acid.

$C_{30}H_{34}N_2O_4$ 486.61

USP Repaglinide Related Compound E RS

(*R*)-2-Ethoxy-4-[2-({3-methyl-1-[2-(piperidin-1-yl)phenyl]butyl}amino)-2-oxoethyl]benzoic acid.

$C_{27}H_{36}N_2O_4$ 452.59

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

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

Topic/Question	Contact	Expert Committee
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM32020 Small Molecules 3

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 39(6)

Current DocID: GUID-DB25DE8F-D766-4E43-ABC3-3ABCEBAC56FF_4_en-US
DOI: https://doi.org/10.31003/USPNF_M73165_04_01
DOI ref: m1lwb