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

Repaglinide Tablets

General Notices

Action and use

Stimulates insulin release; treatment of diabetes mellitus.

DEFINITION

Repaglinide Tablets contain Repaglinide.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of repaglinide, $C_{27}H_{36}N_2O_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions prepared in *methanol*.
(1) Mix with the aid of ultrasound a quantity of powdered tablets containing 5 mg of Repaglinide with 15 mL of *methanol*. Dilute to 50 mL, filter (a 0.45-µm nylon filter is suitable) and use the filtrate.
(2) 0.01% w/v of *repaglinide BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).
(b) Use the mobile phase as described below.
(c) Apply 25 µL of each solution.
(d) Develop the plate to 5 cm.
(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

25 volumes of *methanol*, 30 volumes of *toluene* and 45 volumes of *dichloromethane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.
(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 30 minutes withdraw a sample of the medium and filter (a 0.45-µm Millex LCR PTFE filter is suitable). Use the filtered medium, diluted with the dissolution medium if necessary to produce a solution expected to contain 0.00006% w/v of Repaglinide.
(2) 0.006% w/v of *repaglinide BPCRS* in *methanol*. Dilute 1 volume to 100 volumes with the medium.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 40°.
(e) Use fluorimetric detection with an excitation wavelength of 244 nm and an emission wavelength of 348 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

11 volumes of *methanol*, 40 volumes of 0.01M *potassium dihydrogen orthophosphate* adjusted to pH 2.3 with *orthophosphoric acid* and 49 volumes of *acetonitrile*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *symmetry factor* of the peak due to repaglinide is between 0.8 and 1.8.

DETERMINATION OF CONTENT

Calculate the total content of repaglinide, $C_{27}H_{36}N_2O_4$, in the medium from the chromatograms obtained and using the declared content of $C_{27}H_{36}N_2O_4$, in *repaglinide BPCRS*.

LIMITS

The amount of repaglinide released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, protected from light and prepared in a mixture of equal volumes of *acetonitrile R1* and mobile phase A (solution A).

(1) Shake a quantity of the powdered tablets containing 5 mg of Repaglinide in 2 mL of water. Add 10 mL of solution A, mix with the aid of ultrasound and dilute to 20 mL. Centrifuge and use the supernatant liquid.
(2) Dilute 1 volume of solution (1) to 100 volumes. Further dilute 1 volume of this solution to 5 volumes.
(3) Dilute 1 volume of *repaglinide impurity standard solution BPCRS* to 10 volumes with solution A.
(4) 0.1% w/v of *repaglinide for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped extra-dense bonded octylsilyl silica gel for chromatography* (5 µm) (Zorbax Eclipse XDB C8 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 40°.
(e) Use detection wavelengths of 210 nm and 240 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 0.02M *potassium dihydrogen orthophosphate* adjusted to pH 2.9 with *orthophosphoric acid*.

Mobile phase B *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-4	75	25	isocratic
4-30	75→50	25→50	linear gradient
30-40	50	50	isocratic
40-41	50→75	50→25	linear gradient
41-50	75	25	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to repaglinide (retention time about 24 minutes) are: impurity A, about 0.1; impurity B, about 0.4; impurity C, about 0.6; impurity 1, about 1.05; and impurity D, about 1.6.

SYSTEM SUITABILITY

The test is not valid unless:

At 210 nm

in the chromatogram obtained with solution (2), the *signal to noise ratio* of the peak due to repaglinide is at least 40;

At 240 nm

in the chromatogram obtained with solution (3), the *resolution* between the peaks due to repaglinide and impurity 1 is at least 1.8.

LIMITS

At 210 nm

Identify any peak corresponding to impurity C in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (4), and multiply the area of this peak by a correction factor of 2.2.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater than 2.5 times the area of the peak in the chromatogram obtained with solution (2) (0.5%).

At 240 nm

Identify any peak corresponding to impurities A and B in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (4), and multiply the areas of these peak by a correction factor of: 0.6 and 0.7 respectively.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than 2.5 times the area of the peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

The sum of all impurities, including impurity C, is not greater than 1.0%.

Uniformity of content

Repaglinide Tablets containing less than 2 mg and/or less than 2% w/w of Repaglinide comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To one tablet add 3 mL of the mobile phase, mix with the aid of ultrasound and shake for 15 minutes. Dilute to 5 mL with mobile phase and filter (a 0.45-µm Millex LCR PTFE filter is suitable). Dilute the filtrate, if necessary, with mobile phase to produce a solution containing the equivalent of 0.01% w/v of repaglinide.
(2) 0.1% w/v of *repaglinide BPCRS* in *methanol*. Dilute 1 volume to 10 volumes with the mobile phase.
(3) Dilute 1 volume of *repaglinide impurity standard solution BPCRS* to 10 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped extra-dense bonded octylsilyl silica gel for chromatography* (5 µm) (Zorbax Eclipse XDB C8 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 45°.
(e) Use a detection wavelength of 242 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

25 volumes of 0.007M *potassium dihydrogen orthophosphate* adjusted to pH 2.5 with *orthophosphoric acid* and 75 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions, the retention time of repaglinide is about 6 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between impurity 1 and repaglinide is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of repaglinide, $C_{27}H_{36}N_2O_4$, in the tablets from the chromatograms obtained and using the declared content of $C_{27}H_{36}N_2O_4$ in *repaglinide BPCRS*.

ASSAY

For tablets containing the equivalent of less than 2 mg and/or less than 2% w/w of Repaglinide

Use the average of the individual results determined in the test for Uniformity of content.

For tablets containing the equivalent of 2 mg or more and 2% w/w or more of Repaglinide

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 75 mL of the mobile phase to 10 whole tablets, mix with the aid of ultrasound and shake for 15 minutes. Dilute to 100 mL with mobile phase and filter (a 0.45-µm Millex LCR PTFE filter is suitable). Further dilute this solution, if necessary, with the mobile phase to produce a solution containing 0.01% w/v of Repaglinide.
(2) 0.1% w/v of *repaglinide BPCRS* in *methanol*. Dilute 1 volume to 10 volumes with the mobile phase.
(3) Dilute 1 volume of *repaglinide impurity standard solution BPCRS* to 10 volumes with solution A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Uniformity of content may be used.

SYSTEM SUITABILITY

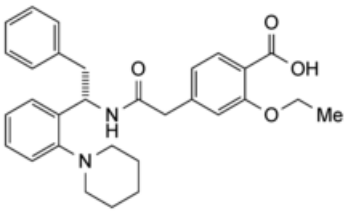
The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between impurity 1 and repaglinide is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of repaglinide, $C_{27}H_{36}N_2O_4$, in the tablets from the chromatograms obtained and using the declared content of $C_{27}H_{36}N_2O_4$ in *repaglinide BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Repaglinide and:



1. 2-ethoxy-4-(2-{(1*S*)-1-[2-(pyrolidin-1-yl)phenyl]-2-phenylethylamino}-2-oxoethyl)benzoic acid.