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

Candesartan Tablets

General Notices

Action and use

Angiotensin II (AT_1) receptor antagonist.

DEFINITION

Candesartan Tablets contain Candesartan Cilexetil.

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

Content of candesartan cilexetil, $C_{33}H_{34}N_6O_6$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 20 mg of Candesartan Cilexetil with 20 mL of *water* until the tablets have disintegrated and filter (a Whatman GF/C filter is suitable). Add the filter paper to 20 mL of *ethyl acetate*, mix with the aid of ultrasound and repeat the filtering process. Evaporate the filtrate to dryness under a stream of nitrogen. *The infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of candesartan cilexetil *(RS 494)*.

TESTS

Dissolution

For tablets containing 16 mg or less of candesartan cilexetil

Comply with the requirements in 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 a solution containing 0.35% w/v of *polysorbate 20* in *phosphate buffer pH 6.5*, at a temperature of 37°, as the medium.

PROCEDURE

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

(1) After 45 minutes withdraw a sample of the medium and filter (a Acrodisc GHP 25 0.45-µm filter is suitable). Dilute the filtered medium, if necessary, with sufficient dissolution medium to produce a solution expected to contain 0.00022% w/v of Candesartan Cilexetil.

(2) 0.00022% w/v of *candesartan cilexetil BPCRS* in the dissolution medium.
(3) 0.00022% w/v of *candesartan cilexetil for system suitability EPCRS* in the dissolution medium.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (4 µm) (Nova-Pak C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 0.8 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 254 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

1 volume of *glacial acetic acid*, 43 volumes of *water* and 57 volumes of *acetonitrile*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity B is at least 4.0.

DETERMINATION OF CONTENT

Calculate the total content of candesartan cilexetil, $C_{33}H_{34}N_6O_6$, in the medium from the chromatograms obtained and using the declared content of $C_{33}H_{34}N_6O_6$ in *candesartan cilexetil BPCRS*.

LIMITS

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

For tablets containing more than 16 mg of candesartan cilexetil

Comply with the requirements in 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 a solution containing 0.70% w/v of *polysorbate 20* in *phosphate buffer pH 6.5*, at a temperature of 37°, as the medium.

PROCEDURE

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

(1) After 45 minutes withdraw a sample of the medium and filter (a 0.45-µm Acrodisc GHP 25 filter is suitable). Dilute the filtered medium, if necessary, with sufficient dissolution medium to produce a solution expected to contain 0.00022% w/v of Candesartan Cilexetil.
(2) 0.00022% w/v of *candesartan cilexetil BPCRS* in the dissolution medium.
(3) 0.00022% w/v of *candesartan cilexetil for system suitability EPCRS* in the dissolution medium.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under the Dissolution test for tablets containing 16 mg or less of candesartan cilexetil may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity B is at least 4.0.

DETERMINATION OF CONTENT

Calculate the total content of candesartan cilexetil, $C_{33}H_{34}N_6O_6$, in the medium from the chromatograms obtained and using the declared content of $C_{33}H_{34}N_6O_6$ in *candesartan cilexetil BPCRS*.

LIMITS

The amount of candesartan cilexetil 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 in 60% v/v *acetonitrile* prepared immediately before use.

(1) To a quantity of the powdered tablets containing 20 mg of Candesartan Cilexetil, add 80 mL of 60% v/v *acetonitrile* and mix with the aid of ultrasound. Add sufficient 60% v/v *acetonitrile* to produce 100 mL and filter (a 0.45-µm PTFE filter is suitable).
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) 0.05% w/v of *candesartan cilexetil for system suitability EPCRS*.
(4) 0.05% w/v of *candesartan cilexetil for peak identification EPCRS*.
(5) 0.05% w/v of *candesartan cilexetil impurity standard BPCRS*.
(6) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (4 µm) (Nova-Pak C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 0.8 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 254 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 1 volume of *glacial acetic acid*, 43 volumes of *water* and 57 volumes of *acetonitrile*.

Mobile phase B 1 volume of *glacial acetic acid*, 10 volumes of *water* and 90 volumes of *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	100	0	isocratic
3-33	100→0	0→100	linear gradient
33-45	0	100	isocratic
45-47	0→100	100→0	linear gradient
47-55	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to candesartan cilexetil (retention time about 10 minutes) are: impurity G, about 0.2; impurity A, about 0.3; impurity B, about 0.5; impurity C, about 0.8; impurity D, about 1.2; impurity E, about 1.5; impurity F, about 2.0; impurity H, about 3.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5), the *peak-to-valley ratio* is at least 2.6, where *Hp* is the height above the baseline of the peak due to impurity D and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to candesartan cilexetil.

LIMITS

Use the chromatograms obtained with solutions (3) and (5) to identify the peaks due to impurities B, D and F.

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurities A, G and H using solutions (3) and (4) and multiply the area of these peaks by the corresponding correction factors: impurity A, 0.7; impurity G, 0.7; impurity H, 1.6.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity F is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any peak corresponding to impurity C, D or E is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5% of each);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (6) (0.2%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (6) (0.1%).

For tablets containing 16 mg or less of candesartan cilexetil

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity B is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%);

the sum of the areas of any *secondary peaks*, excluding the peak due to impurity B, is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3.0%).

For tablets containing more than 16 mg of candesartan cilexetil

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity B is not greater than 1.2 times the area of the principal peak in the chromatogram obtained with solution (2) (1.2%);

the sum of the areas of any *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of candesartan cilexetil must 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 in 60% v/v *acetonitrile*.

(1) Disperse one tablet in 25 mL of 60% v/v *acetonitrile* and mix with the aid of ultrasound for 10 minutes. Add sufficient 60% v/v *acetonitrile* to produce 50 mL and filter (a 0.45-µm PTFE filter is suitable). If necessary, dilute the filtrate with 60% v/v *acetonitrile* to produce a solution containing 0.0002% w/v of Candesartan Cilexetil.
(2) 0.0002 % w/v of *candesartan cilexetil BPCRS*.
(3) 0.015 % w/v of *candesartan cilexetil for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity B is at least 4.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{33}H_{34}N_6O_6$ in each tablet using the declared content of $C_{33}H_{34}N_6O_6$ in *candesartan cilexetil BPCRS*.

ASSAY

For tablets containing 2 mg or less and/or less than 2% w/w of candesartan cilexetil

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

For tablets containing more than 2 mg and 2% w/w or more of candesartan cilexetil

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

(1) To a quantity of the powdered tablets containing 20 mg of Candesartan Cilexetil, add 80 mL of 60% v/v *acetonitrile* and mix with the aid of ultrasound for 10 minutes. Dilute to 100 mL with 60% v/v *acetonitrile* and filter (a 0.45-µm PTFE filter is suitable). Add sufficient 60% v/v *acetonitrile* to the filtrate to produce a solution containing 0.002% w/v of Candesartan Cilexetil.
(2) 0.0002% w/v of *candesartan cilexetil BPCRS* in 60% v/v *acetonitrile*.
(3) 0.015% w/v of *candesartan cilexetil for system suitability EPCRS* in 60% v/v *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity B is at least 4.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{33}H_{34}N_6O_6$ in the tablets using the declared content of $C_{33}H_{34}N_6O_6$ in *candesartan cilexetil BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Candesartan Cilexetil.