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Candesartan Cilexetil Tablets

DEFINITION
Candesartan Cilexetil Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of candesartan cilexetil ($C_{33}H_{34}N_6O_6$).

IDENTIFICATION
• **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
• **B.** The UV absorption spectra of the major peak of the *Sample solution* exhibit maxima and minima at the same wavelengths as those of the *Standard solution*, as obtained in the *Assay*.

ASSAY
Change to read:
• **Procedure**

Mobile phase: ▲Acetonitrile and water (55:45). To each liter, add 1.0 mL of trifluoroacetic acid.▲ (USP 1-Dec-2022)

Diluent: Acetonitrile and water (70:30)

Standard solution: 0.8 mg/mL of USP Candesartan Cilexetil RS in *Diluent*. Sonication may be necessary for complete dissolution.▲▲ (USP 1-Dec-2022)

Sample solution: Nominally 0.8 mg/mL of candesartan cilexetil in *Diluent* prepared as follows. Transfer a number of Tablets (see *Table 1*) to a suitable volumetric flask.

Table 1

Tablet Strength (mg)	Number of Tablets (NLT)
4	10
8	10
16	5
32	5

Add *Diluent* to about 70% of the total volume and sonicate for about 25 min with intermittent shaking. Allow to cool and dilute with *Diluent* to volume. Pass through a suitable filter of 0.45-µm pore size.

Chromatographic system
(See *Chromatography ⟨621⟩, System Suitability*.)
Mode: LC
Detector: UV 282 nm. For *Identification B*, use a diode array detector ▲in the range of 210–400 nm.▲ (USP 1-Dec-2022)
Column: 4.6-mm × 15-cm; 5-µm packing L7
Column temperature: 30°
Flow rate: 1.5 mL/min
Injection volume: 10 µL
Run time: NLT 2.7 times the retention time of candesartan cilexetil

System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT ▲1.0%▲ (USP 1-Dec-2022)

Analysis
Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of candesartan cilexetil ($C_{33}H_{34}N_6O_6$) in the portion of Tablets taken:

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

r_U = peak response ▲of candesartan cilexetil▲ (USP 1-Dec-2022) from the *Sample solution*

r_S = peak response ▲of candesartan cilexetil▲ (USP 1-Dec-2022) from the *Standard solution*

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

C_U = nominal concentration of candesartan cilexetil in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• **Dissolution** ⟨711⟩

Medium

For Tablets labeled to contain 4, 8, or 16 mg: 0.35% polysorbate 20 in 0.05 M phosphate buffer, pH 6.5 ▲(dissolve 6.8 g of potassium phosphate, monobasic in a suitable container containing 500 mL of water; add 3.5 mL of polysorbate 20 and dilute with water to 1 L; adjust with 2 N sodium hydroxide solution to a pH of 6.5);▲ (USP 1-Dec-2022) 900 mL

For Tablets labeled to contain 32 mg: 0.70% polysorbate 20 in 0.05 M phosphate buffer, pH 6.5 ▲(dissolve 6.8 g of potassium phosphate, monobasic in a suitable container containing 500 mL of water; add 7.0 mL of polysorbate 20 and dilute with water to 1 L; adjust with 2 N sodium hydroxide solution to a pH of 6.5);▲ (USP 1-Dec-2022) 900 mL

Apparatus 2: 50 rpm

Time: 45 min

Mobile phase: ▲Acetonitrile and water (55:45). To each liter, add 1.0 mL of trifluoroacetic acid.▲ (USP 1-Dec-2022)

Standard stock solution: 0.45 mg/mL of USP Candesartan Cilexetil RS in acetonitrile. Sonication may be necessary for complete dissolution.

Standard solution: ▲(*L*/900) mg/mL of USP Candesartan Cilexetil RS from the *Standard stock solution* in *Medium*, where *L* is the label claim in mg/Tablet▲ (USP 1-Dec-2022)

Sample solution: Pass a portion of solution under test through a suitable filter of 0.45-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 15-cm; 5-µm packing L7

Column temperature: 30°

Flow rate: 1.5 mL/min

Injection volume: 50 µL

Run time: NLT 1.8 times the retention time of candesartan cilexetil

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of candesartan cilexetil ($C_{33}H_{34}N_6O_6$) dissolved:

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

r_U = peak response ▲of candesartan cilexetil▲ (USP 1-Dec-2022) from the *Sample solution*

r_S = peak response ▲of candesartan cilexetil▲ (USP 1-Dec-2022) from the *Standard solution*

C_S = concentration of ▲USP Candesartan Cilexetil RS in▲ (USP 1-Dec-2022) the *Standard solution* (mg/mL)

V = volume of *Medium*, 900 mL

L = label claim (mg/Tablet)

Tolerances: NLT 80% (*Q*) of the labeled amount of candesartan cilexetil ($C_{33}H_{34}N_6O_6$) is dissolved.

• **Uniformity of Dosage Units** ⟨905⟩**:** Meet the requirements

IMPURITIES

Change to read:

• **Organic Impurities**

Solution A: ▲Acetonitrile and water (10:90). To each liter, add 1.0 mL of trifluoroacetic acid.▲ (USP 1-Dec-2022)

Solution B: ▲Acetonitrile and water (90:10). To each liter, add 1.0 mL of trifluoroacetic acid.▲ (USP 1-Dec-2022)

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	65	35
30	5	95
45	5	95
50	65	35
55	65	35

System suitability stock solution A: 0.05 mg/mL each of USP Candesartan Cilexetil Related Compound A RS, USP Candesartan Cilexetil Related Compound B RS, USP Candesartan Cilexetil Related Compound D RS, and USP Candesartan Cilexetil Related Compound F RS in acetonitrile

System suitability stock solution B: 0.1 mg/mL of USP Candesartan Cilexetil RS in acetonitrile

System suitability stock solution C: 0.5 mg/mL of USP Candesartan Cilexetil Related Compound G RS in methanol

System suitability solution: 0.0015 mg/mL each of USP Candesartan Cilexetil Related Compound A RS, USP Candesartan Cilexetil Related Compound B RS, USP Candesartan Cilexetil Related Compound D RS, and USP Candesartan Cilexetil Related Compound F RS; 0.001 mg/mL of USP Candesartan Cilexetil RS; and 0.005 mg/mL of USP Candesartan Cilexetil Related Compound G RS from *System suitability stock solution A*, *System suitability stock solution B*, and *System suitability stock solution C* in acetonitrile

Standard solution: 0.001 mg/mL of USP Candesartan Cilexetil RS in acetonitrile, from *System suitability stock solution B*

Sample solution: Nominally 1 mg/mL of candesartan cilexetil in acetonitrile prepared as follows. Transfer a suitable quantity of candesartan cilexetil from NLT 20 powdered Tablets to a suitable volumetric flask. Add acetonitrile to fill 60% of the total volume and sonicate for 15 min with intermittent shaking in cold water. Dilute with acetonitrile to volume and pass through a suitable filter of 0.45-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 10-cm; 3.5-µm packing L1

Autosampler temperature: 10°

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

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

▲[Note—See *Table 3* for the relative retention times.]▲ (USP 1-Dec-2022)

Suitability requirements

Resolution: NLT 5.0 between ▲candesartan cilexetil and candesartan cilexetil related compound D,▲ (USP 1-Dec-2022) *System suitability solution*

Tailing factor: NMT 2.0▲ (USP 1-Dec-2022) , *Standard solution*

Relative standard deviation: NMT ▲5.0%,▲ (USP 1-Dec-2022) *Standard solution*

▲Signal-to-noise ratio: NLT 10, *Standard solution*▲ (USP 1-Dec-2022)

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each ▲specified and unspecified degradation product▲ (USP 1-Dec-2022) in the portion of Tablets taken:

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

r_U = peak response of each ▲specified or unspecified degradation product▲ (USP 1-Dec-2022) from the *Sample solution*

r_S = peak response of candesartan cilexetil from the *Standard solution*

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

C_U = nominal concentration of candesartan cilexetil in the *Sample solution* (mg/mL)

F = relative response factor of each ▲specified or unspecified degradation product▲ (USP 1-Dec-2022) (see *Table 3*)

Acceptance criteria: See *Table 3*. ▲The reporting threshold is 0.1%.▲ (USP 1-Dec-2022)

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Candesartan cilexetil related compound G▲▲ (USP 1-Dec-2022)	0.17	1.30	1.0
Candesartan cilexetil related compound A▲▲ (USP 1-Dec-2022) [a]	0.46	▲—▲ (USP 1-Dec-2022)	—
Candesartan cilexetil related compound B▲▲ (USP 1-Dec-2022)	0.77	1.00	1.5
Candesartan cilexetil	1.0	—	—
Candesartan cilexetil related compound D▲▲ (USP 1-Dec-2022)	1.15	1.00	0.5
Candesartan cilexetil related compound F▲▲ (USP 1-Dec-2022)	1.47	0.88	1.5
Any unspecified ▲degradation product▲ (USP 1-Dec-2022)	—	1.00	0.2
Total ▲degradation products▲ (USP 1-Dec-2022)	—	—	4.0

[a] Process-related impurity is not included in total ▲degradation products.▲ (USP 1-Dec-2022)

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight, light-resistant containers. Store at controlled room temperature.

Change to read:

• **USP Reference Standards** ⟨11⟩

USP Candesartan Cilexetil RS

USP Candesartan Cilexetil Related Compound A RS

▲Ethyl 2-ethoxy-1-{[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl}benzimidazole-7-carboxylate;
Also known as▲ (USP 1-Dec-2022) Ethyl 1-{[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl}-2-ethoxybenzimidazole-7-carboxylate.

$C_{26}H_{24}N_6O_3$ 468.51

USP Candesartan Cilexetil Related Compound B RS

▲1-Cyclohexyloxycarbonyloxyethyl 1-{[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl}-2-oxo-2,3-dihydrobenzimidazole-7-carboxylate;
Also known as (1-{[(Cyclohexyloxy)carbonyl]oxy}ethyl 3-({2'-(1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl}methyl)-2-oxo-2,3-dihydro-1*H*-benzo[d]imidazole-4-carboxylate).▲ (USP 1-Dec-2022)

$C_{31}H_{30}N_6O_6$ ▲582.62▲ (USP 1-Dec-2022)

USP Candesartan Cilexetil Related Compound D RS

▲1-{[(Cyclohexyloxy)carbonyl]oxy}ethyl 1-{[2′-(2-ethyl-2*H*-tetrazol-5-yl)biphenyl-4-yl]methyl}-2-oxo-2,3-dihydrobenzimidazole-7-carboxylate;
Also known as 1-{[(Cyclohexyloxy)carbonyl]oxy}ethyl 3-({2'-(2-ethyl-2*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl}methyl)-2-oxo-2,3-dihydro-1*H*-benzimidazole-4-carboxylate).▲ (USP 1-Dec-2022)

$C_{33}H_{34}N_6O_6$ 610.67

USP Candesartan Cilexetil Related Compound F RS

▲1-Cyclohexyloxycarbonyloxyethyl 2-ethoxy-1-{[2′-(2-ethyl-2*H*-tetrazol-5-yl)biphenyl-4-yl]methyl}benzimidazole-7-carboxylate;
Also known as (1-(Cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-{[2'-(2-ethyl-2*H*-tetrazol-5-yl)biphenyl-4-yl]methyl}-1*H*-benzimidazole-7-carboxylate).▲ (USP 1-Dec-2022)

$C_{35}H_{38}N_6O_6$ ▲638.73▲ (USP 1-Dec-2022)

USP Candesartan Cilexetil Related Compound G RS

▲2-Ethoxy-1-{[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl}benzimidazole-7-carboxylic acid;
Also known as▲ (USP 1-Dec-2022) 1-{[2'-(1*H*-Tetrazol-5-yl)biphenyl-4-yl]methyl}-2-ethoxybenzimidazole-7-carboxylic acid.

$C_{24}H_{20}N_6O_3$ ▲440.46▲ (USP 1-Dec-2022)

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

Topic/Question	Contact	Expert Committee
CANDESARTAN CILEXETIL TABLETS	Documentary Standards Support	SM22020 Small Molecules 2

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