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Candesartan Cilexetil and Hydrochlorothiazide Tablets

DEFINITION

Candesartan Cilexetil and Hydrochlorothiazide Tablets contain NLT 90.0% and NMT 110.0% each of the labeled amount of candesartan cilexetil ($C_{33}H_{34}N_6O_6$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$).

IDENTIFICATION

• **A.** The retention times of the major peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.

• **B.** The UV absorption spectra of the major peaks 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**

Solution A: ▲Acetonitrile and water (10:90). To each liter, add 1.0 mL of trifluoroacetic acid.▲ (USP 1-Aug-2024)

Solution B: ▲Acetonitrile and water (90:10). To each liter, add 1.0 mL of trifluoroacetic acid.▲ (USP 1-Aug-2024)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	90	10
4	90	10
6	30	70
15	30	70
17	90	10
20	90	10

Diluent: Acetonitrile and water (70:30)

Standard solution: Prepare solutions of USP Candesartan Cilexetil RS and USP Hydrochlorothiazide RS in *Diluent* as follows, at concentrations as given in *Table 2*. Transfer suitable amounts of USP Candesartan Cilexetil RS and USP Hydrochlorothiazide RS to a suitable volumetric flask. Add *Diluent* to about 50% of the total volume and sonicate to dissolve. Dilute with *Diluent* to volume.▲▲ (USP 1-Aug-2024)

Table 2

Tablet Strength Candesartan Cilexetil/Hydrochlorothiazide (mg/mg)	Concentration of ▲USP Candesartan Cilexetil RS▲ (USP 1-Aug-2024) (mg/mL)	Concentration of ▲USP Hydrochlorothiazide RS▲ (USP 1-Aug-2024) (mg/mL)
16/12.5	0.32	0.25
32/12.5	0.64	0.25
32/25	0.32	0.25

Sample solution: Nominally equivalent to the concentrations as given in *Table 2*, prepared as follows. Transfer NLT 5 Tablets to a suitable volumetric flask. Add *Diluent* to about 60% of the total volume and sonicate for about 25 min with intermittent shaking. Cool to room temperature 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-Aug-2024)

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

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

▲[NOTE—The relative retention times for hydrochlorothiazide and candesartan cilexetil are 0.4 and 1.0, respectively.]▲ (USP 1-AUG-2024)

Suitability requirements

Tailing factor: NMT 2.0 for candesartan cilexetil and hydrochlorothiazide

Relative standard deviation: NMT ▲1.0%▲ (USP 1-Aug-2024) for candesartan cilexetil and hydrochlorothiazide

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of candesartan cilexetil ($C_{33}H_{34}N_6O_6$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) 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 or hydrochlorothiazide from the *Sample solution*

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

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

C_U = nominal concentration of candesartan cilexetil or hydrochlorothiazide 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 16 mg/12.5 mg of candesartan cilexetil/hydrochlorothiazide: 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-Aug-2024) 900 mL

For Tablets labeled to contain 32 mg/12.5 mg and 32 mg/25 mg of candesartan cilexetil/hydrochlorothiazide: 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-Aug-2024) 900 mL

Apparatus 2: 50 rpm

Time: 45 min

Solution A and **Solution B:** Prepare as directed in the *Assay*.

Mobile phase: See *Table 3*.

Table 3

Time (min)	Solution A (%)	Solution B (%)
0	80	20
3.0	80	20
5.0	30	70

Time (min)	Solution A (%)	Solution B (%)
10.0	30	70
13.0	80	20
16.0	80	20

Standard stock solution A: 0.72 mg/mL of USP Candesartan Cilexetil RS in acetonitrile. ▲Sonicate to dissolve, if necessary.▲ (USP 1-Aug-2024)

Standard stock solution B: 0.28 mg/mL of USP Hydrochlorothiazide RS in acetonitrile. ▲Sonicate to dissolve, if necessary.▲ (USP 1-Aug-2024)

Standard solution: Prepare solutions of USP Candesartan Cilexetil RS and USP Hydrochlorothiazide RS from *Standard stock solution A* and *Standard stock solution B* in the appropriate *Medium*, at concentrations as given in *Table 4*.▲▲ (USP 1-Aug-2024)

Table 4

Tablet Strength Candesartan Cilexetil/Hydrochlorothiazide (mg/mg)	Concentration of ▲USP Candesartan Cilexetil RS▲ (USP 1-Aug-2024) (mg/mL)	Concentration of ▲USP Hydrochlorothiazide RS▲ (USP 1-Aug-2024) (mg/mL)
16/12.5	0.018	0.014
32/12.5	0.036	0.014
32/25	0.036	0.028

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

Chromatographic system

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

Mode: LC

Detector: UV 264 nm

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

Autosampler temperature: 10°

Flow rate: 1 mL/min

Injection volume: 50 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0 for candesartan cilexetil and hydrochlorothiazide

Relative standard deviation: NMT 2.0% for candesartan cilexetil and hydrochlorothiazide

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of candesartan cilexetil ($C_{33}H_{34}N_6O_6$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) dissolved:

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

r_U = peak response of candesartan cilexetil or hydrochlorothiazide from the *Sample solution*

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

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

V = volume of *Medium*, 900 mL

L = label claim (mg/Tablet)

Tolerances: NLT 80% (*Q*) the labeled amount of candesartan cilexetil ($C_{33}H_{34}N_6O_6$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) are dissolved

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

IMPURITIES

Change to read:

• **Organic Impurities**

Solution A and **Solution B:** Prepare as directed in the *Assay*.

Mobile phase: See *Table 5*.

Table 5

Time (min)	Solution A (%)	Solution B (%)
0	95	5
8	95	5
15	60	40
20	60	40
30	40	60
35	30	70
45	20	80
50	0	100
60	0	100
62	95	5
70	95	5

Diluent A: Acetonitrile and water (70:30)

Diluent B: Acetonitrile and water (50:50)

Peak identification 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

Peak identification stock solution B: 0.1 mg/mL of USP Candesartan Cilexetil RS in acetonitrile

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

Peak identification 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 *Peak identification stock solution A*, *Peak identification stock solution B*, and *Peak identification stock solution C* in acetonitrile

System suitability stock solution: 0.05 mg/mL each of USP Benzothiadiazine Related Compound A RS and USP Hydrochlorothiazide RS, and 0.1 mg/mL of USP Chlorothiazide RS in *Diluent B*

System suitability solution: 2.5 µg/mL each of USP Benzothiadiazine Related Compound A RS and USP Hydrochlorothiazide RS and 5 µg/mL of USP Chlorothiazide RS in *Diluent A*, from *System suitability stock solution*

▲▲ (USP 1-Aug-2024)

Standard solution: 0.008 mg/mL of USP Candesartan Cilexetil RS and 0.003 mg/mL of USP Hydrochlorothiazide RS in *Diluent A*. ▲Sonicate to dissolve, if necessary.▲ (USP 1-Aug-2024)

Sample solution: Nominally 1.5 mg/mL of candesartan cilexetil in acetonitrile prepared as follows. Transfer about 75 mg of candesartan cilexetil, from finely powdered Tablets (NLT 20), to a 50-mL volumetric flask. Add 30 mL of *Diluent A* and sonicate for 20 min with intermittent shaking in cold water. Allow it to reach room temperature, dilute with *Diluent A* 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 265 nm

Column: 4.6-mm × 25-cm; 5-µm packing L7

Column temperature: 35°

Flow rate: 1.5 mL/min

Injection volume: 10 µL

System suitability

Samples: ▲*Peak identification solution*,▲ (USP 1-Aug-2024) *System suitability solution*, and *Standard solution*

▲[NOTE—See *Table 6* for the relative retention times.]▲ (USP 1-AUG-2024)

Suitability requirements

Resolution: NLT 1.5 between benzothiadiazine related compound A and chlorothiazide; NLT 1.5 between chlorothiazide and hydrochlorothiazide, *System suitability solution*

Tailing factor: NMT 2.0 for candesartan cilexetil and hydrochlorothiazide, *Standard solution*

Relative standard deviation: NMT ▲5.0%▲ (USP 1-Aug-2024) for candesartan cilexetil and hydrochlorothiazide, *Standard solution*

▲**Signal-to-noise ratio:** NLT 10 for candesartan cilexetil, *Peak identification solution*▲ (USP 1-Aug-2024)

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each ▲specified degradation product▲ (USP 1-Aug-2024) of candesartan cilexetil and any unspecified ▲degradation product▲ (USP 1-Aug-2024) 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 degradation product of candesartan cilexetil or any unspecified degradation product▲ (USP 1-Aug-2024) 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 (see *Table 6*)

Calculate the percentage of benzothiadiazine related compound A and chlorothiazide 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 benzothiadiazine related compound A ▲or▲ (USP 1-Aug-2024) chlorothiazide from the *Sample solution*

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

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

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

F = relative response factor (see *Table 6*)

Acceptance criteria: See *Table 6*. ▲The reporting threshold is 0.1%.▲ (USP 1-Aug-2024)

Table 6

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Benzothiadiazine related compound A▲▲ (USP 1-Aug-2024)	▲0.15▲ (USP 1-Aug-2024)	1.15	1.0
Chlorothiazide▲▲ (USP 1-Aug-2024)	▲0.17▲ (USP 1-Aug-2024)	0.48	0.5
▲Hydrochlorothiazide	0.20	—	—▲ (USP 1-Aug-2024)
Candesartan cilexetil related compound G▲▲ (USP 1-Aug-2024)	0.51	1.11	1.0
Candesartan cilexetil related compound A▲▲ (USP 1-Aug-2024) [a]	0.73	—	—

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Candesartan cilexetil related compound B▲ (USP 1-Aug-2024)	0.89	0.90	1.75
Candesartan cilexetil	1.00	—	—
Candesartan cilexetil related compound D▲ (USP 1-Aug-2024)	1.06	0.91	0.5
Candesartan cilexetil related compound F▲ (USP 1-Aug-2024)	1.24	0.83	1.5
Any unspecified degradation product	—	1.00	0.2
Total ▲degradation products▲ (USP 1-Aug-2024)	—	—	4.0

[a] Process-related impurity is not included in total ▲degradation products.▲ (USP 1-Aug-2024)

ADDITIONAL REQUIREMENTS

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

Change to read:

• **USP Reference Standards** ⟨11⟩

USP Benzothiadiazine Related Compound A RS
4-Amino-6-chloro-1,3-benzenedisulfonamide.
$C_6H_8ClN_3O_4S_2$ 285.73

USP Candesartan Cilexetil RS

USP Candesartan Cilexetil Related Compound A RS
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-Aug-2024)
$C_{31}H_{30}N_6O_6$ ▲582.62▲ (USP 1-Aug-2024)

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-Aug-2024)
$C_{33}H_{34}N_6O_6$ 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-Aug-2024)
$C_{35}H_{38}N_6O_6$ ▲638.73▲ (USP 1-Aug-2024)

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-Aug-2024) 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-Aug-2024)

USP Chlorothiazide RS

USP Hydrochlorothiazide RS

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

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

Topic/Question	Contact	Expert Committee
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM22020 Small Molecules 2

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