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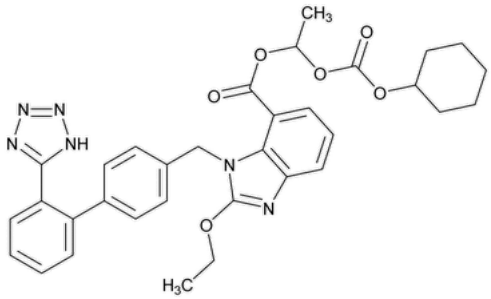
Candesartan Cilexetil

Change to read:



$C_{33}H_{34}N_6O_6$ ▲610.67▲ (USP 1-Dec-2022)

1*H*-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-, 1-[[(cyclohexyloxy)carbonyl]oxy]ethyl ester, (±); (±)-1-Hydroxyethyl 2-ethoxy-1-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]-7-benzimidazolecarboxylate, cyclohexyl carbonate (ester); ▲1-Cyclohexyloxycarbonyloxyethyl 2-ethoxy-1-{[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl}benzimidazole-7-carboxylate▲ (USP 1-Dec-2022) CAS RN®: 145040-37-5; UNII: R85M2X0D68.

Change to read:

DEFINITION

Candesartan Cilexetil contains NLT ▲98.0%▲ (USP 1-Dec-2022) and NMT ▲102.0%▲ (USP 1-Dec-2022) of candesartan cilexetil ($C_{33}H_{34}N_6O_6$), calculated on anhydrous basis.

IDENTIFICATION

Change to read:

• **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** ▲197A or▲ (USP 1-Dec-2022) 197K. If the spectra obtained show differences, proceed with the samples prepared as follows. Separately dissolve a quantity of USP Candesartan Cilexetil RS and Candesartan Cilexetil in alcohol. [Note—Heating the solution may be necessary for complete dissolution.] Cool the solution in an ice bath, filter the crystals, and dry at 105°.

Change to read:

• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the ▲*Assay*.▲ (USP 1-Dec-2022)

ASSAY

Change to read:

• **Procedure**

▲**Solution A:** Acetonitrile and water (57:43). To each liter, add 10 mL of glacial acetic acid.

Solution B: Acetonitrile and water (90:10). To each liter, add 10 mL of glacial acetic acid.

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
3	100	0
33	0	100
33.1	100	0

Diluent: Acetonitrile and water (60:40)

Standard solution: 0.04 mg/mL of USP Candesartan Cilexetil RS in *Diluent*. Sonicate as necessary.

Sample solution: 0.04 mg/mL of Candesartan Cilexetil in *Diluent*. Sonicate as necessary.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 3.9-mm × 15-cm; 4-µm packing L1

Flow rate: 0.8 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 0.73%

Analysis

Samples: *Standard solution* and *Sample solution*

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

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

r_U = peak response of candesartan cilexetil 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 = concentration of Candesartan Cilexetil in the *Sample solution* (mg/mL)▲ (USP 1-Dec-2022)

Acceptance criteria: ▲98.0%–102.0%▲ (USP 1-Dec-2022) on the anhydrous basis

IMPURITIES

• **Residue on Ignition ⟨281⟩**

Sample: 1 g

Acceptance criteria: NMT 0.1%

Change to read:

• **Organic Impurities**

▲**Solution A, Solution B, Mobile phase, Diluent,** and **Chromatographic system:** Proceed as directed in the *Assay*.▲ (USP 1-Dec-2022)

System suitability solution: ▲0.4 mg/mL of USP Candesartan Cilexetil RS, and 0.4 µg/mL each of USP Candesartan Cilexetil Related Compound A RS, USP Candesartan Cilexetil Related Compound B RS, USP Candesartan Cilexetil Related Compound D RS, USP Candesartan Cilexetil Related Compound F RS, and USP Candesartan Cilexetil Related Compound G RS in *Diluent*▲ (USP 1-Dec-2022)

Standard solution: ▲0.4 µg/mL▲ (USP 1-Dec-2022) of USP Candesartan Cilexetil RS in *Diluent*

▲**Sensitivity solution:** 0.2 µg/mL of USP Candesartan Cilexetil RS in *Diluent*, from *Standard solution*▲ (USP 1-Dec-2022)

Sample solution: 0.4 mg/mL of Candesartan Cilexetil in *Diluent*

▲▲ (USP 1-Dec-2022)

System suitability▲▲ (USP 1-Dec-2022)

Samples: *System suitability solution*, ▲*Standard solution*, and *Sensitivity solution*

[Note—See *Table 2* for the relative retention times.]▲ (USP 1-Dec-2022)

Suitability requirements

Resolution: ▲NLT 4.0 between candesartan cilexetil related compound A and candesartan cilexetil related compound B; NLT 2.0 between candesartan cilexetil and candesartan cilexetil related compound D, *System suitability solution*▲ (USP 1-Dec-2022)

Tailing factor: NMT 1.5 for candesartan cilexetil, ▲*Standard solution*▲ (USP 1-Dec-2022)

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

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of ▲any specified and unspecified▲ (USP 1-Dec-2022) impurity in the portion of Candesartan Cilexetil taken:

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

r_U = peak response of ▲any specified or unspecified▲ (USP 1-Dec-2022) impurity 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 = concentration of Candesartan Cilexetil in the *Sample solution* (mg/mL)

▲F = relative response factor (see *Table 2*)▲ (USP 1-Dec-2022)

Acceptance criteria: See *Table 2*. ▲The reporting threshold is 0.05%.▲ (USP 1-Dec-2022)

Table 2

Name	Relative Retention Time	▲Relative Response Factor▲ (USP 1-Dec-2022)	Acceptance Criteria, NMT (%)
▲Candesartan cilexetil related compound G	0.19	1.2	0.2▲ (USP 1-Dec-2022)
▲Candesartan cilexetil related compound A	0.35	1.1▲ (USP 1-Dec-2022)	0.2
▲Candesartan cilexetil related compound B	0.47	0.93▲ (USP 1-Dec-2022)	0.3
Candesartan cilexetil	1.0	▲—▲ (USP 1-Dec-2022)	—
▲Candesartan cilexetil related compound D	1.14	0.83	0.10▲ (USP 1-Dec-2022)
▲Candesartan cilexetil related compound F	2.09	0.78▲ (USP 1-Dec-2022)	0.2
▲Trityl candesartan cilexetil[a]	3.62	0.40	0.15▲ (USP 1-Dec-2022)
Any ▲unspecified▲ (USP 1-Dec-2022) impurity	—	▲1.0▲ (USP 1-Dec-2022)	0.10
Total impurities	—	▲—▲ (USP 1-Dec-2022)	0.6

[a] 1-Cyclohexyloxycarbonyloxyethyl 2-ethoxy-1-{[2'-(1-trityl-1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl}benzimidazole-7-carboxylate.

SPECIFIC TESTS

Change to read:

• **Water Determination** ⟨921⟩, *Method I,* ▲*Method Ia* *(USP 1-Dec-2022)*▲: NMT 0.3%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers, and 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 (Ethyl 1-{[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl}-2-ethoxybenzimidazole-7-carboxylate).

$C_{26}H_{24}N_6O_3$ 468.52

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).

$C_{31}H_{30}N_6O_6$ 582.62

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).

$C_{33}H_{34}N_6O_6$ 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).

$C_{35}H_{38}N_6O_6$ 638.73

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 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	Documentary Standards Support	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

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