Candesartan Cilexetil Tablets

Type of Posting	Revision Bulletin
Posting Date	18–Nov–2016
Official Date	01–Dec–2016
Expert Committee	Chemical Medicines Monographs 2
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 2 Expert Committee has revised the Candesartan Cilexetil Tablets monograph. The purpose of this revision is to widen the total impurities limit from NMT 3.0% to NMT 4.0% in accordance with the FDA-approved drug products.

Minor editorial changes have been made to update the monograph to the current *USP* style.

The Candesartan Cilexetil Tablets Revision Bulletin supersedes the currently official Candesartan Cilexetil Tablets monograph. The Revision Bulletin will be incorporated in the *Second supplement* to *USP 40–NF 35.*

Should you have any questions, please contact Sujatha Ramakrishna, Ph.D., MBA. Senior Scientific Liaison (301–816–8349 or sxr@usp.org).

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 corresponding peak from the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **PROCEDURE**

Mobile phase: Acetonitrile, trifluoroacetic acid, and water (550:1:450)

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. Pass through a suitable filter of 0.45-µm pore size.

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 fill 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
Detectors
Assay: UV 282 nm
Identification test B: Diode array
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 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of candesartan cilexetil ($C_{33}H_{34}N_6O_6$) in the portion of Tablets taken:

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

r_U = peak response from the *Sample solution*
r_S = peak response 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

- **DISSOLUTION** ⟨711⟩

Medium for Tablets labeled to contain 4 mg, 8 mg, and 16 mg: 0.35% polysorbate 20 in 0.05 M phosphate buffer, pH 6.5; 900 mL

Medium for Tablets labeled to contain 32 mg: 0.70% polysorbate 20 in 0.05 M phosphate buffer, pH 6.5; 900 mL

Apparatus 2: 50 rpm

Time: 45 min

Mobile phase: Acetonitrile, trifluoroacetic acid, and water (550:1:450)

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

Standard solution: Prepare solutions in *Medium* from *Standard stock solution* (see *Table 2* for concentrations).

Table 2

Tablet Strength (mg)	Concentration (mg/mL)
4	0.0045
8	0.009
16	0.018
32	0.036

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 from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of 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, trifluoroacetic acid, and water (10: 0.1: 90)

Solution B: Acetonitrile, trifluoroacetic acid, and water (90: 0.1: 10)

Mobile phase: See *Table 3*.

Table 3

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, 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 into 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

Sample cooler temperature: 10°

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

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

Suitability requirements

Resolution: NLT 5.0 between candesartan cilexetil related compound B and candesartan cilexetil, *System suitability solution*

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

Relative standard deviation: NMT 10.0% for candesartan cilexetil peak, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity 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 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 = nominal concentration of candesartan cilexetil in the *Sample solution* (mg/mL)

F = relative response factor of each impurity (see *Table 4*)

Acceptance criteria: See *Table 4*.

Table 4

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Candesartan cilexetil related compound G[a]	0.17	1.30	1.0
Candesartan cilexetil related compound A[b,c]	0.46	1.16	—
Candesartan cilexetil related compound B[d]	0.77	1.00	1.5
Candesartan cilexetil	1.0	—	—
Candesartan cilexetil related compound D[e]	1.15	1.00	0.5
Candesartan cilexetil related compound F[f]	1.47	0.88	1.5
Any unspecified impurity	—	1.00	0.2
Total impurities	—	—	●4.0● (RB 1-Dec-2016)

[a] 1-{[2′-(1*H*-Tetrazol-5-yl)biphenyl-4-yl]methyl}-2-ethoxybenzimidazole-7-carboxylic acid.

[b] Ethyl 1-{[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl}-2-ethoxybenzimidazole-7-carboxylate.

[c] Process-related impurity not included in total impurities.

[d] 1-(Cyclohexyloxycarbonyloxy)ethyl 1-{[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl}-2-hydroxybenzimidazole-7-carboxylate.

[e] 1-{[(Cyclohexyloxy)carbonyl]oxy}ethyl 3-({2′-(2-ethyl-1*H*-tetrazol-5-yl)-[1,1′-biphenyl]-4-yl}methyl)-2-oxo-2,3-dihydro-1*H*-benzimidazole-4-carboxylate.

[f] 1-(Cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-{[2′-(2-ethyltetrazol-5-yl)biphenyl-4-yl]methyl}benzimidazole-7-carboxylate.

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers. Store at controlled room temperature.

• **USP REFERENCE STANDARDS** ⟨11⟩

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-(Cyclohexyloxycarbonyloxy)ethyl 1-{[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl}-2-hydroxybenzimidazole-7-carboxylate.

$C_{31}H_{30}N_6O_6$ 582.61

USP Candesartan Cilexetil Related Compound D RS
1-{[(Cyclohexyloxycarbonyloxy)carbonyl]oxy}ethyl 3-{[2′-(2-ethyl-2*H*-tetrazol-5-yl)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-(Cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-{[2′-(2-ethyltetrazol-5-yl)biphenyl-4-yl]methyl}benzimidazole-7-carboxylate.
$C_{35}H_{38}N_6O_6$ 638.71

USP Candesartan Cilexetil Related Compound G RS
1-{[2′-(1*H*-Tetrazol-5-yl)biphenyl-4-yl]methyl}-2-ethoxybenzimidazole-7-carboxylic acid.
$C_{24}H_{20}N_6O_3$ 440.45