

## Candesartan Cilexetil Tablets

<b>Type of Posting</b>	Revision Bulletin
<b>Posting Date</b>	18–Nov–2016
<b>Official Date</b>	01–Dec–2016
<b>Expert Committee</b>	Chemical Medicines Monographs 2
<b>Reason for Revision</b>	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](mailto: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- $\mu$ m 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- $\mu$ m 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  $\times$  15-cm; 5- $\mu$ m packing L7

**Column temperature:** 30°

**Flow rate:** 1.5 mL/min

**Injection volume:** 10  $\mu$ L

**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- $\mu$ m pore size.

#### Chromatographic system

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

**Mode:** LC

**Detector:** UV 254 nm

**Column:** 4.6-mm  $\times$  15-cm; 5- $\mu$ m packing L7

**Column temperature:** 30°

**Flow rate:** 1.5 mL/min

**Injection volume:** 50  $\mu$ L

**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

## 2 Candesartan

### 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- $\mu$ m pore size.

#### Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

**Mode:** LC

**Detector:** UV 254 nm

**Column:** 4.6-mm  $\times$  10-cm; 3.5- $\mu$ m packing L1

**Sample cooler temperature:** 10°

**Flow rate:** 1 mL/min

**Injection volume:** 10  $\mu$ L

#### 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 <sup>a</sup>	0.17	1.30	1.0
Candesartan cilexetil related compound A <sup>b,c</sup>	0.46	1.16	—
Candesartan cilexetil related compound B <sup>d</sup>	0.77	1.00	1.5
Candesartan cilexetil	1.0	—	—
Candesartan cilexetil related compound D <sup>e</sup>	1.15	1.00	0.5
Candesartan cilexetil related compound F <sup>f</sup>	1.47	0.88	1.5
Any unspecified impurity	—	1.00	0.2
Total impurities	—	—	4.0 <sup>g</sup> (RB 1, Dec-2016)

<sup>a</sup> 1-[[2'-(1*H*-Tetrazol-5-yl)biphenyl-4-yl]methyl]-2-ethoxybenzimidazole-7-carboxylic acid.

<sup>b</sup> Ethyl 1-[[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-2-ethoxybenzimidazole-7-carboxylate.

<sup>c</sup> Process-related impurity not included in total impurities.

<sup>d</sup> 1-(Cyclohexyloxy)carbonyloxy)ethyl 1-[[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-2-hydroxybenzimidazole-7-carboxylate.

<sup>e</sup> 1-[[[(Cyclohexyloxy)carbonyloxy]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.

<sup>f</sup> 1-(Cyclohexyloxy)carbonyloxy)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<sub>26</sub>H<sub>24</sub>N<sub>6</sub>O<sub>3</sub> 468.51

USP Candesartan Cilexetil Related Compound B RS

1-(Cyclohexyloxy)carbonyloxy)ethyl 1-[[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-2-hydroxybenzimidazole-7-carboxylate.

C<sub>31</sub>H<sub>30</sub>N<sub>6</sub>O<sub>6</sub> 582.61

USP Candesartan Cilxetil Related Compound D RS  
1-[[Cyclohexyloxy-carbonyloxy]carbonyl]oxyethyl 3-  
[2'-(2-ethyl-2*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-  
2-oxo-2,3-dihydro-1*H*-benzimidazole-4-carboxylate.  
C<sub>33</sub>H<sub>34</sub>N<sub>6</sub>O<sub>6</sub> 610.67

USP Candesartan Cilxetil Related Compound F RS  
1-(Cyclohexyloxy-carbonyloxy)ethyl 2-ethoxy-1-[[2'-  
(2-ethyltetrazol-5-yl)biphenyl-  
4-yl]methyl]benzimidazole-7-carboxylate.

C<sub>35</sub>H<sub>38</sub>N<sub>6</sub>O<sub>6</sub> 638.71

USP Candesartan Cilxetil Related Compound G RS  
1-[[2'-(1*H*-Tetrazol-5-yl)biphenyl-4-yl]methyl]-2-ethox-  
ybenzimidazole-7-carboxylic acid.  
C<sub>24</sub>H<sub>20</sub>N<sub>6</sub>O<sub>3</sub> 440.45