Candesartan Cilexetil Tablets

Type of Posting                  Revision Bulletin
Posting Date                    18–Nov–2016
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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 (C₃₃H₃₄N₆O₆).

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

<table>
<thead>
<tr>
<th>Tablet Strength (mg)</th>
<th>Number of Tablets (NLT)</th>
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<tbody>
<tr>
<td>4</td>
<td>10</td>
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<tr>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>32</td>
<td>5</td>
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</table>

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
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: 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 (C₃₃H₃₄N₆O₆) in the portion of Tablets taken:

\[
\text{Result} = \left( \frac{r_0}{r_1} \right) \times C_3 \times V \times \left( \frac{1}{L} \right) \times 100
\]

r₀ = peak response from the Sample solution
r₁ = peak response from the Standard solution
C₃ = concentration of USP Candesartan Cilexetil RS in the Standard solution (mg/mL)
V = volume of medium, 900 mL
L = label claim (mg/Tab)

Tolerances:
NLT 80% (Q) of the labeled amount of candesartan cilexetil (C₃₃H₃₄N₆O₆) is dissolved.

• UNIFORMITY OF DOSAGE UNITS (905): Meet the requirements
ORGANIC IMPURITIES

• Change to read:

Samples:

ORGANIC IMPURITIES

Relative standard deviation:

Mobile phase:

Chromatographic system

Sample solution:

Nominally 1 mg/mL of candesartan cilexetil-7-carboxylate.

0.001 mg/mL of USP CandesartanStandard solution:

System suitability solution:

0.0015 mg/mL of 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 solution:

0.0015 mg/mL each of USP Candesartan Cilexetil Related Compound A RS, USP Candesartan Cilexetil Related Compound D RS, and 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 solution B.

System suitability stock solution C:

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 C:

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

Solution A:

Sample solution:

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Sample solution:

Nominally 1 mg/mL of candesartan cilexetil in acetonitrile prepared as follows. Transfer a solution B.
USP Candesartan Cilexetil Related Compound D RS
1-(((Cyclohexyloxycarbonyloxy)carbonyloxy)ethyl) 3-(2'- (2-ethyl-2H-tetrazol-5-yl)biphenyl-4-yl)methyl)-2-oxo-2,3-dihydro-1H-benimidazole-4-carboxylate.
C_{13}H_{16}N_{6}O_{6} 638.71

USP Candesartan Cilexetil Related Compound G RS
1-(((2'- (2-ethyl-2H-tetrazol-5-yl)biphenyl-4-yl)methyl)-2-ethoxy-1H-benimidazole-7-carboxylic acid.
C_{23}H_{20}N_{6}O_{3} 440.45

USP Candesartan Cilexetil Related Compound F RS
1-(Cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-(2'- (2-ethyltetrazol-5-yl)biphenyl-4-yl)methyl)benimidazole-7-carboxylate.