Candesartan Cilexetil and Hydrochlorothiazide Tablets

Candesartan Cilexetil and Hydrochlorothiazide Tablets contain not less than 90.0 per cent and not more than 110.0 per cent of stated amount of candesartan cilexetil, \( \text{C}_{33}\text{H}_{34}\text{N}_{6}\text{O}_{6} \) and hydrochlorothiazide, \( \text{C}_{7}\text{H}_{8}\text{ClN}_{3}\text{O}_{4}\text{S}_{2} \).

**Usual strength.** Candesartan Cilexetil, 16 mg and hydrochlorothiazide, 12.5 mg.

**Identification**

In the Assay, the principal peaks in the chromatogram obtained with the test solution correspond to the peaks in the chromatogram obtained with reference solution (c).

**Tests**

**Dissolution (2.5.2)**

Apparatus No.1,

Medium. 900 ml of a 0.35 per cent w/v polysorbate 20 in 0.05 M phosphate buffer pH 6.5.

Speed and Time: 50 rpm and 45 min.

Withdraw a suitable volume of the medium and filter.

Determine by liquid chromatography (2.4.14).

*Test solution.* Dilute the filtrate, if necessary, with the dissolution medium.

*Reference solution (a).* A 0.072 per cent w/v solution of candesartan cilexetil RS in acetonitrile.

*Reference solution (b).* A 0.028 per cent w/v solution of hydrochlorothiazide RS in acetonitrile.

*Reference solution (c).* Dilute suitable volume of reference solution (a) and reference solution (b) in dissolution medium to obtain a solution having similar concentration to that of the test solution.

**Chromatographic system**

– a stainless steel column 15 cm x 4.6 mm, packed with octylsilane bonded to porous silica (5 µm),
– sample temperature: 10°.
– mobile phase: A. a mixture of 10 volumes of acetonitrile, 90 volumes of water and 0.1 volume of trifluoroacetic acid,

\[ \text{B. a mixture of 90 volumes of acetonitrile, 10 volumes of water and 0.1 volume of trifluoroacetic acid,} \]

– flow rate: 1 ml per minute,
– a gradient programme using the conditions given below,
– spectrophotometer set at 264 nm,
– injection volume: 50 µl.

<table>
<thead>
<tr>
<th>Time (in min)</th>
<th>Mobile phase A (per cent)</th>
<th>Mobile phase B (per cent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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<td>20</td>
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<tr>
<td>3</td>
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<tr>
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<td>20</td>
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<tr>
<td>16</td>
<td>80</td>
<td>20</td>
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</tbody>
</table>

Inject reference solution (c). The test is not valid unless the tailing factor is not more than 2.0 and the relative standard deviation for both the peaks is not more than 2.0 per cent.

Inject reference solution (c) and the test solution.

D. Not less than 80 per cent each of the stated amount of of \( \text{C}_{33}\text{H}_{34}\text{N}_{6}\text{O}_{6} \) and \( \text{C}_{7}\text{H}_{8}\text{ClN}_{3}\text{O}_{4}\text{S}_{2} \).

**Related substances.** Determined by liquid chromatography (2.4.14).

*Solvent mixture A.* 70 volumes of acetonitrile and 30 volumes of water.

*Solvent mixture B.* 50 volumes of acetonitrile and 50 volumes of water.
Test solution. Weigh and powder 20 tablets. Disperse a quantity of powder containing 75 mg of Candesartan Cilexetil in 30 ml of solvent mixture A with the aid of ultrasound for 20 minutes with intermittent shaking in cold water and dilute to 50.0 ml with solvent mixture A.

Reference solution (a). A solution containing 0.005 per cent w/v each of benzothiadiazine related compound A RS, hydrochlorothiazide RS and 0.01 per cent w/v of chlorothiazide RS in solvent mixture B. Dilute 5.0 ml of the solution to 100.0 ml with solvent mixture A.

Reference solution (b). A solution containing 0.16 per cent w/v of candesartan cilexetil RS and 0.06 per cent w/v of hydrochlorothiazide RS in solvent mixture A. Dilute 1.0 ml of the solution to 200.0 ml with the solvent mixture A.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octysilane bonded to porous silica (5 µm),
- column temperature: 35°C,
- mobile phase: A. a mixture of 10 volumes of acetonitrile, 90 volumes of water and 0.1 volume of trifluoroacetic acid,
- B. a mixture of 90 volumes of acetonitrile, 10 volumes of water and 0.1 volume of trifluoroacetic acid,
- flow rate: 1.5 ml per minute,
- a gradient programme using the conditions given below,
- spectrophotometer set at 265 nm,
- injection volume: 10 µl.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Mobile phase A (per cent v/v)</th>
<th>Mobile phase B (per cent v/v)</th>
</tr>
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<tbody>
<tr>
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<tr>
<td>70</td>
<td>95</td>
<td>5</td>
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</table>

Name | Relative retention time | Correction factor
--- | ----------------------- | ------------------
Candesartan cilexetil related compound G \(^1\) | 0.51 | 0.90
Candesartan cilexetil related compound A \(^2\) | 0.73 | —
Benzothiadiazine related compound A \(^3\) | 0.75 | 0.87
Chlorothiazide \(^4\) | 0.85 | 2.08
Candesartan cilexetil related compound B \(^5\) | 0.89 | 1.11
Candesartan cilexetil | 1.00 | —
Candesartan cilexetil related compound D \(^6\) | 1.06 | 1.10
Candesartan cilexetil related compound F \(^7\) | 1.24 | 1.20

1. \(2\)-(1H-Tetrazol-5-yl)benzophenone-4-carboxylic acid.  
2. \(2\)-(1H-Tetrazol-5-yl)benzophenone-4-carboxylic acid.  
3. Process related to purity not included in Total impurities.  
4. 4-Amino-6-chloro-1,3-benzenedisulfonamide.  
6. 6-Chloro-2-H,1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide.  
7. 1-(Cyclohexyloxycarbonyloxy)ethyl 1-\([2\)-[12]-[1H-tetrazol-5-yl]benzophenone-4-carboxylic acid.  
8. 1-(Cyclohexyloxycarbonyloxy)ethyl 1-\([2\)-[12]-[1H-tetrazol-5-yl]benzophenone-4-carboxylic acid.  
9. 1-(Cyclohexyloxycarbonyloxy)ethyl 1-\([2\)-[12]-[1H-tetrazol-5-yl]benzophenone-4-carboxylic acid.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks corresponding to benzothiadiazine related compound A and chlorothiazide is not less than 1.5, chlorothiazide and hydrochlorothiazide is not less than 1.5 in the chromatogram obtained with reference solution (a). The tailing factor is not more than 2.0 and relative standard deviation for replicate injection is not more than 10.0 per cent for both candesartan cilexetil and hydrochlorothiazide peaks in the chromatogram obtained with reference solution (b).
Inject reference solution (b) and the test solution. In the chromatogram obtained with the test solution, the area of any peak due to candesartan cilexetil related compound G is not more than 1.9 times the area of the candesartan cilexetil peak in the chromatogram obtained with reference solution (b) (1.0 per cent), the area of any peak due to benzothiadiazine related compound A is not more than 5 times the area of the hydrochlorothiazide peak in the chromatogram obtained with reference solution (b) (1.0 per cent), the area of any peak due to chlorothiazide is not more than 2.5 times the area of the hydrochlorothiazide peak in the chromatogram obtained with reference solution (b) (0.5 per cent), the area of any peak due to candesartan cilexetil related compound B is not more than 3.28 times the area of the candesartan cilexetil peak in the chromatogram obtained with reference solution (b) (1.75 per cent), the area of any peak due to candesartan cilexetil related compound D is not more than 0.94 times the area of the candesartan cilexetil peak in the chromatogram obtained with reference solution (b) (0.5 per cent), the area of any peak due to candesartan cilexetil related compound F is not more than 2.82 times the area of the candesartan cilexetil peak in the chromatogram obtained with reference solution (b) (1.5 per cent), the area of any other secondary peak is not more than 0.38 times the area of the candesartan cilexetil peak in the chromatogram obtained with reference solution (b) (0.2 per cent) and the sum of areas of all the secondary peaks is not more than 7.5 times the area of the candesartan cilexetil peak in the chromatogram obtained with reference solution (b) (4.0 per cent).

Other tests. Comply with the tests stated under Tablets.

Assay. Determine by liquid chromatography (2.4.14).

Solvent mixture. 70 volumes of acetonitrile and 30 volumes of water.

Test solution. Weigh and powder 20 tablets. Disperse a quantity of the powder containing 32 mg of Candesartan Cilexetil in the solvent mixture with the aid of ultrasound for about 25 minutes with intermediate shaking and dilute to 100.0 ml with the solvent mixture.

Reference solution (a). A 0.32 per cent w/v solution of candesartan cilexetil RS in the solvent mixture.

Reference solution (b). A 0.125 per cent w/v solution of hydrochlorothiazide RS in the solvent mixture.

Reference solution (c). Dilute suitable volume of reference solution (a) and reference solution (b) in the solvent mixture to obtain a solution having similar concentration to that of the test solution.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with octylsilane bonded to porous silica (5 µm),
- mobile phase: A. a mixture of 10 volumes of acetonitrile, 90 volumes of water and 0.1 volume of trifluoroacetic acid,
  B. a mixture of 90 volumes of acetonitrile, 10 volumes of water and 0.1 volume of trifluoroacetic acid,
- flow rate: 1 ml per minute,
- a gradient programme using the conditions given below,
- spectrophotometer set at 282 nm,
- injection volume: 10 µl.

<table>
<thead>
<tr>
<th>Time (in min)</th>
<th>mobile phase A (per cent)</th>
<th>mobile phase B (per cent)</th>
</tr>
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<tbody>
<tr>
<td>0</td>
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<tr>
<td>20</td>
<td>90</td>
<td>10</td>
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</tbody>
</table>

Inject reference solution (c). The test is not valid unless the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 2.0 per cent for both the components.

Inject reference solution (c) and the test solution.

Calculate the content of C₉H₇N₃O₁₈ and C₉H₆ClN₅O₆S₂.

Storage: store protected from light and moisture, at a temperature not exceeding 30°.