Losartan Potassium and Hydrochlorothiazide Tablets

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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 Losartan Potassium and Hydrochlorothiazide Tablets monograph. The purpose for the revision is to add *Dissolution Test 2* to be consistent with the FDA approved specifications for a generic drug product.

The Liquid Chromatography based procedure for *Dissolution Test 2* is validated using a Symmetry C18 brand of L1 column. The typical retention time for losartan and hydrochlorothiazide are about 4.7 min and 3.3 min respectively.

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

The Losartan Potassium and Hydrochlorothiazide Tablets Revision Bulletin supersedes the currently official Losartan Potassium and Hydrochlorothiazide Tablets monograph. The Revision Bulletin will be incorporated in the *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).
Losartan Potassium and Hydrochlorothiazide Tablets

DEFINITION
Losartan Potassium and Hydrochlorothiazide Tablets contain NLT 95.0% and NMT 105.0% of the labeled amounts of losartan potassium \((C_{22}H_{22}ClKN_6O)\) and hydrochlorothiazide \((C_7H_8ClN_3O_4S_2)\).

IDENTIFICATION
• A. The retention times of the major peaks of the Sample solution correspond to those of the Standard solution, as obtained in the Assay.

ASSAY
• PROCEDURE
  Buffer A: 2.76 g/L of monobasic sodium phosphate in water. Adjust with phosphoric acid to a pH of 2.5.
  Buffer B: 1.25 g/L of monobasic potassium phosphate and 1.5 g/L of dibasic sodium phosphate in water. The pH of the resulting solution is about 7.0–7.5.
  Diluent: Acetonitrile and Buffer A (3:2).
  Solution A: Acetonitrile and Buffer B (7:93)
  Solution B: Use acetonitrile.
  Mobile phase: See Table 1.

Table 1

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>92</td>
<td>8</td>
</tr>
<tr>
<td>28</td>
<td>38</td>
<td>62</td>
</tr>
<tr>
<td>30</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>35</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

Standard solution: Transfer USP Losartan Potassium RS and USP Hydrochlorothiazide RS into a suitable volumetric flask and dissolve in Diluent (50% of the volume of the flask). Dilute with Buffer A to volume to obtain a solution having concentrations as directed in Table 2. Pass a portion of the solution through a PTFE or equivalent filter of 0.45-µm pore size.

Table 2

<table>
<thead>
<tr>
<th>Tablet Strength</th>
<th>Concentration of USP Losartan Potassium RS (mg/mL)</th>
<th>Concentration of USP Hydrochlorothiazide RS (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50/12.5</td>
<td>0.4</td>
<td>0.1</td>
</tr>
<tr>
<td>100/12.5</td>
<td>0.4</td>
<td>0.05</td>
</tr>
<tr>
<td>100/25</td>
<td>0.4</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Sample stock solution: Transfer 10 Tablets into a suitable volumetric flask and add Diluent as directed in Table 3. Mix well and mechanically shake or stir until the solid is dispersed. Dilute with Buffer A to volume, and sonicate.

Table 3

<table>
<thead>
<tr>
<th>Tablet Strength</th>
<th>Flask Size (mL)</th>
<th>Volume of Diluent (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50/12.5</td>
<td>250</td>
<td>210</td>
</tr>
<tr>
<td>100/12.5</td>
<td>500</td>
<td>420</td>
</tr>
<tr>
<td>100/25</td>
<td>500</td>
<td>420</td>
</tr>
</tbody>
</table>

Sample solution: Dilute a portion of the Sample solution first with acetonitrile (20% of the volume of the flask) and then with Buffer A, to obtain a solution having nominal concentrations as directed in Table 4. Pass a portion of this solution through a PTFE or equivalent filter of 0.45-µm pore size, and use the filtrate.

Table 4

<table>
<thead>
<tr>
<th>Tablet Strength</th>
<th>Concentration of USP Losartan Potassium RS (mg/mL)</th>
<th>Concentration of USP Hydrochlorothiazide RS (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50/12.5</td>
<td>0.4</td>
<td>0.1</td>
</tr>
<tr>
<td>100/12.5</td>
<td>0.4</td>
<td>0.05</td>
</tr>
<tr>
<td>100/25</td>
<td>0.4</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 280 nm
Column: 3.9-mm × 15-cm; 5-µm packing L7
Column temperature: 35°
Flow rate: 1 mL/min
Injection volume: 20 µL
System suitability
Sample: Standard solution
Suitability requirements
Tailing factor: Less than 2.5 for the losartan peak
Relative standard deviation: Less than 2.0% for both hydrochlorothiazide and losartan peaks

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of losartan potassium \((C_{22}H_{22}ClKN_6O)\) or hydrochlorothiazide \((C_7H_8ClN_3O_4S_2)\) in the portion of Tablets taken:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times 100
\]

where
\[
\begin{align*}
  r_U & = \text{peak response of losartan or hydrochlorothiazide from the Sample solution} \\
  r_S & = \text{peak response of losartan or hydrochlorothiazide from the Standard solution} \\
  C_S & = \text{concentration of USP Losartan Potassium RS or USP Hydrochlorothiazide RS in the Standard solution (mg/mL)} \\
  C_U & = \text{nominal concentration of losartan potassium or hydrochlorothiazide in the Sample solution (mg/mL)}
\end{align*}
\]
Acceptance criteria: 95.0%-105.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION (711)**
  - **Test 1 (88-1-Jun-2016)**
    - Medium: Water; 900 mL, deaerated
    - Apparatus 1: 100 rpm
    - Time: 30 min for both losartan and hydrochlorothiazide
  - **Buffer**: Dissolve 1.36 g/L of monobasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 2.5.
  - **Mobile phase**: Acetonitrile and Buffer (2:3)
  - **Losartan potassium stock solution**: 0.44 mg/mL of USP Losartan Potassium RS in Medium
  - **Hydrochlorothiazide stock solution**: 0.14 mg/mL of USP Hydrochlorothiazide RS prepared by dissolving in methanol (10% of the volume of the flask). Dilute with Medium to volume.
  - **Standard solution**: Transfer the appropriate volumes of Losartan potassium stock solution and Hydrochlorothiazide stock solution to a 100-mL volumetric flask according to the dilution schemes in Table 5. Dilute with Medium to volume.

<table>
<thead>
<tr>
<th>Tablet Strength Losartan Potassium/Hydrochlorothiazide (mg)</th>
<th>Aliquot of Losartan Potassium Stock Solution (mL)</th>
<th>Aliquot of Hydrochlorothiazide Stock Solution (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50/12.5</td>
<td>12.5</td>
<td>10.0</td>
</tr>
<tr>
<td>100/12.5</td>
<td>25.0</td>
<td>10.0</td>
</tr>
<tr>
<td>100/25</td>
<td>25.0</td>
<td>20.0</td>
</tr>
</tbody>
</table>

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-μm pore size.

Chromatographic system
(See Chromatography (621), System Suitability.)

- **Mode**: LC
- **Detector**: UV 230 nm
- **Column**: 4.6-mm × 25-cm; 10-μm packing L7
- **Column temperature**: 35°C
- **Flow rate**: 2.3 mL/min
- **Injection volume**: 20 μL

System suitability
Sample: Standard solution

Suitability requirements
- **Resolution**: NLT 2 between the hydrochlorothiazide and losartan peaks
- **Relative standard deviation**: NMT 2.0% for both the hydrochlorothiazide and losartan peaks

Analysis
Samples: Standard solution and Sample solution

Calculate the percentage of the labeled amount of losartan potassium (C22H22ClKN6O) or hydrochlorothiazide (C6H6ClIN5O2S2) dissolved:

\[
\text{Result} = \left( \frac{r_u}{r_s} \right) \times \left( \frac{C_i}{L} \right) \times V \times 100
\]

\[
r_u = \text{peak response of losartan or hydrochlorothiazide from the Sample solution}
\]

\[
r_s = \text{peak response of losartan or hydrochlorothiazide from the Standard solution}
\]

\[
C_i = \text{concentration of USP Losartan Potassium RS or USP Hydrochlorothiazide RS in the Standard solution (mg/mL)}
\]

\[
L = \text{label claim (mg/Tablet)}
\]

\[
V = \text{volume of Medium, 900 mL}
\]

Tolerances: NLT 85% (Q) of the labeled amount of losartan potassium (C22H22ClKN6O) and NLT 75% (Q) of the labeled amount of hydrochlorothiazide (C6H6ClIN5O2S2) is dissolved.

**Test 2**: If the product complies with this test, the labeling indicates that the product meets USP Dissolution Test 2.

- **Medium, Apparatus 1, and Time**: Proceed as directed in Test 1.
- **Buffer**: Dissolve 1.78 g of dibasic sodium phosphate dihydrate in 1 L of water. Adjust with phosphoric acid to a pH of 6.5.
- **Mobile phase**: Acetonitrile and Water (40:60)
- **Standard stock solution 1**: 1.1 mg/mL of USP Losartan Potassium RS in Diluent. Sonication may be necessary for complete dissolution.
- **Standard stock solution 2**: 0.28 mg/mL of USP Hydrochlorothiazide RS in Diluent. Sonication may be necessary for complete dissolution.

Standard solution: Transfer appropriate volumes of Standard stock solution 1 and Standard stock solution 2 to a 100-mL volumetric flask according to the dilution schemes in Table 6. Dilute with Medium to volume.

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-μm pore size.

Chromatographic system
(See Chromatography (621), System Suitability.)

- **Mode**: LC
- **Detector**: UV 225 nm
- **Column**: 4.6-mm × 25-cm; 5-μm packing L1
- **Autosampler temperature**: 8°C
- **Flow rate**: 1.2 mL/min
- **Injection volume**: 10 μL

System suitability
Sample: Standard solution

Suitability requirements
Relative standard deviation: NMT 2.0% for both the hydrochlorothiazide and losartan peaks

Analysis
Samples: Standard solution and Sample solution

Calculate the percentage of the labeled amount of losartan potassium (C22H22ClKN6O) or hydrochlorothiazide (C6H6ClIN5O2S2) dissolved:

\[
\text{Result} = \left( \frac{r_u}{r_s} \right) \times \left( \frac{C_i}{L} \right) \times V \times 100
\]

\[
r_u = \text{peak response of losartan or hydrochlorothiazide from the Sample solution}
\]

\[
r_s = \text{peak response of losartan or hydrochlorothiazide from the Standard solution}
\]

\[
C_i = \text{concentration of USP Losartan Potassium RS or USP Hydrochlorothiazide RS in the Standard solution (mg/mL)}
\]

\[
L = \text{label claim (mg/Tablet)}
\]

\[
V = \text{volume of Medium, 900 mL}
\]
**UNIFORMITY OF DOSAGE UNITS**

- **Tablet Strength**
  - **Losartan Potassium/Hydrochlorothiazide**

<table>
<thead>
<tr>
<th>Tablet Strength</th>
<th>Concentration of USP Losartan Potassium RS (mg/mL)</th>
<th>Concentration of USP Hydrochlorothiazide RS (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50/12.5</td>
<td>0.06</td>
<td>0.014</td>
</tr>
<tr>
<td>100/12.5</td>
<td>0.06</td>
<td>0.007</td>
</tr>
<tr>
<td>100/25</td>
<td>0.06</td>
<td>0.014</td>
</tr>
</tbody>
</table>

  **Sample stock solution:** Transfer 1 Tablet into a suitable volumetric flask, and add Diluent as directed in Table 8. Mix well, and mechanically shake for 30 min or until the solid is finely dispersed. Dilute with Buffer A to volume, and mix well.

**Sample solution:** Dilute 10 mL of the Sample stock solution in a 100-mL volumetric flask, with 45 mL of Diluent, and then dilute with Buffer A to volume. Pass an aliquot of the solution through a PTFE equivalent filter of 0.45-µm pore size, and use the filtrate.

## IMPURITIES

- **Organic Impurities**

  **Buffer A, Buffer B, Diluent, Solution A, Solution B, Mobile phase, Standard solution, Sample solution, and Chromatographic system:** Proceed as directed in the Assay.

  **Chlorothiazide standard solution:** 0.1 mg/mL of USP Chlorothiazide RS prepared by dissolving in Diluent (50% of the volume of the flask). Dilute with Buffer A to volume, and sonicate.

  **Benzothiadiazine related compound A standard solution:** 0.1 mg/mL of USP Benzothiadiazine Related Compound A RS prepared by dissolving in Diluent (50% of the volume of the flask). Dilute with Buffer A to volume, and sonicate.

  **Stressed losartan solution:** [NOTE—This solution contains the degradates 1-H-dimer and 2-H-dimer and losartan potassium.] Weigh 12 mg of the USP Losartan Potassium RS in a 50-mL flask. Dissolve in 5 mL of water. Pipet 5.0 mL of 0.1 N hydrochloric acid into this solution, and place it in an oven at 105° for 1–2 h. Remove from the oven and allow to cool to room temperature. Pipet 5.0 mL of 0.1 N sodium hydroxide into the flask, and dilute with water to volume.

  **Diluted standard solution:** Dilute portions of the Standard solution and Benzothiadiazine related compound A standard solution first with acetonitrile (30% of the volume of the flask), then with Buffer A to obtain a solution having nominal concentrations based on Tablet strength as listed in Table 9.

**Chromatographic system**

(See Chromatography (621), System Suitability.)

- **Mode:** LC
- **Detector:** UV 230 nm
- **Column:** 4.6-mm × 25-cm; 10-µm packing L7
- **Column temperature:** 35°
- **Flow rate:** 2.3 mL/min
- **Injection volume:** 20 µL

**System suitability**

- **Sample:** Standard solution

**Suitability requirements**

- **Resolution:** NLT 2 between the hydrochlorothiazide and losartan peaks
- **Relative standard deviation:** NMT 2.0% for both the hydrochlorothiazide and losartan peaks

**Analysis**

**Samples:** Standard solution and Sample solution

Calculate the percentage of the labeled amount of losartan potassium (C₂₂H₂₂ClKN₆O₇) or hydrochlorothiazide (C₇H₈ClN₃O₄S₂) in the Tablet taken:

\[ \text{Result} = \left( \frac{r_2}{r_1} \right) \times \left( \frac{C_S}{C_D} \right) \times 100 \]

Where:

- \( r_2 \) = peak response of losartan or hydrochlorothiazide from the Sample solution
- \( r_1 \) = peak response of losartan or hydrochlorothiazide from the Standard solution
- \( C_S \) = concentration of USP Losartan Potassium RS or USP Hydrochlorothiazide RS in the Standard solution (mg/mL)
- \( C_D \) = nominal concentration of losartan potassium or hydrochlorothiazide in the Sample solution (mg/mL)

**Acceptance criteria:** Meet the requirements

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C172288_160301-M45938-CHM22015, Rev. 0 20160527
Losartan

Table 9

<table>
<thead>
<tr>
<th>Tablet Strength</th>
<th>Losartan Potassium/ Hydrochlorothiazide (mg)</th>
<th>Concentration of USP Losartan Potassium RS (µg/mL)</th>
<th>Concentration of USP Hydrochlorothiazide RS (µg/mL)</th>
<th>Concentration of USP Benzothiadiazine Related Compound A RS (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50/12.5</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>100/12.5</td>
<td>4</td>
<td>0.5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>100/25</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

System suitability solution: Dissolve weighed quantities of USP Losartan Potassium RS and USP Hydrochlorothiazide RS in a suitable volumetric flask in Diluent (50% of the volume of the flask). Add the Stressed losartan solution, about 25% of the volume of the flask, into the same flask. Transfer appropriate amounts of Chlorothiazide standard solution and Benzothiazide related compound A standard solution into the same flask, and dilute with Buffer A to volume to obtain a solution having a known concentration of about 0.4 mg/mL of losartan, 0.1 mg/mL of hydrochlorothiazide, and 0.001 mg/mL each of benzothiadiazine related compound A and chlorothiazide. Adjust with phosphoric acid to a pH of 2.5, and mix well. Pass an aliquot of the solution through a PTFE or equivalent filter of 0.45-µm pore size, and use the filtrate.

Limit of quantitation solution: Pipet 5.0 mL of the Diluted standard solution into a 50-mL volumetric flask. Add 15 mL of acetonitrile, dilute with Buffer A to volume, and mix well.

System suitability
Samples: Standard solution, Diluted standard solution, System suitability solution, and Limit of quantitation solution

Suitability requirements
Resolution: Greater than 1.5 between chlorothiazide and benzothiadiazine related compound A; greater than 1.5 between the benzothiadiazine related compound A and hydrochlorothiazide peak, System suitability solution

Tailing factor: Less than 2.5 for the losartan peak, Standard solution

Relative standard deviation: Less than 2.0% for both the hydrochlorothiazide and losartan peaks, Standard solution; less than 10.0% for both the hydrochlorothiazide and losartan peaks, Diluted standard solution

Signal-to-noise ratio: NLT 10 for each component from the first injection. If this is not met, then the signal-to-noise ratio must be greater than 3 with a relative standard deviation of area counts less than 25% for three replicate injections, Limit of quantitation solution

Analysis
Samples: Sample solution and Diluted standard solution

For Tablet strengths of 50/12.5 and 100/25 for losartan potassium/hydrochlorothiazide, respectively, calculate the percentage of any other impurity in the portion of Tablets taken:

\[ \text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_i}{C_d} \right) \times 100 \]

For a Tablet strength of 100/12.5 for losartan potassium/hydrochlorothiazide, calculate the percentage of any other impurity in the portion of Tablets taken:

\[ \text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_i}{C_d} \right) \times 100 \]

\[ r_U \] = peak response of each individual impurity from the Sample solution

\[ r_S \] = peak response of losartan from the Diluted standard solution

\[ C_i \] = concentration of USP Losartan Potassium RS in the Diluted standard solution (mg/mL)

\[ C_d \] = nominal concentration of losartan potassium in the Sample solution (mg/mL)

Acceptance criteria See Table 10.
Table 10

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorothiazide&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.57</td>
<td>—</td>
</tr>
<tr>
<td>Benzothiadiazine related compound A</td>
<td>0.69</td>
<td>1.0</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Losartan</td>
<td>2.7</td>
<td>—</td>
</tr>
<tr>
<td>1-H-Dimer&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.3</td>
<td>0.5</td>
</tr>
<tr>
<td>2-H-Dimer&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Total impurities&lt;sup&gt;d&lt;/sup&gt;</td>
<td>—</td>
<td>2.0</td>
</tr>
</tbody>
</table>

<sup>a</sup> This process impurity (not a degradation product) is related to hydrochlorothiazide and is controlled in the drug substance.

<sup>b</sup> Related to losartan potassium: 5-{4′-[[2-butyl-5-[[2-butyl-4-chloro-5-hydroxymethyl-1H-imidazol-1-yl]methyl]biphenyl-2-yl]-1H-tetrazol-1-yl]methyl]-4-chloro-1H-imidazol-1-yl]methyl][biphenyl-2-yl][tetrazol, potassium salt.

<sup>c</sup> Related to losartan potassium: 5-{4′-[[2-butyl-5-[[2-butyl-4-chloro-5-hydroxymethyl-1H-imidazol-1-yl]methyl]biphenyl-2-yl]-2H-tetrazol-2-yl]methyl]-4-chloro-1H-imidazol-1-yl]methyl][biphenyl-2-yl][tetrazol, potassium salt.

<sup>d</sup> Total impurities include the sum of all the specified impurities and the unspecified impurities that are equal to or greater than 0.1%.

### ADDITIONAL REQUIREMENTS

**Add the following:**

- **LABELING:** When more than one Dissolution test is given, the labeling states the test used only if Test 1 is not used.

**PACKAGING AND STORAGE:** Preserve in tightly closed containers protected from light, and store at controlled room temperature.

**USP REFERENCE STANDARDS (11)**

- USP Benzothiadiazine Related Compound A RS
- 4-Amino-6-chloro-1,3-benzenedisulfonamide.
  
  $\text{C}_9\text{H}_6\text{CIN}_1\text{O}_6\text{S}_2$ 285.73
- USP Chlorothiazide RS
- USP Hydrochlorothiazide RS
- USP Losartan Potassium RS