Amlodipine, Valsartan and Hydrochlorothiazide Tablets

Type of Posting  Revision Bulletin
Posting Date  27–May–2016
Official Date  01–Jun–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 Amlodipine, Valsartan and Hydrochlorothiazide Tablets monograph. The purpose of this revision is to be consistent with the FDA-approved drug products and is described below.

- The acceptance criteria under Definition and Assay is widened from “NLT 95.0% and NMT 105.0%” to “NLT 92.5% and NMT 107.5%” for amlodipine, valsartan and hydrochlorothiazide.
- In the test for organic Impurities, the acceptance criteria for Benzothiadiazine related compound A is widened from NMT 0.4% to NMT 1.0%, Chlorothiazide and hydrochlorothiazide dimer from NMT 0.2% to NMT 0.50%, and the total degradation products is widened from NMT 1.5% to NMT 2.0%.
- A Dissolution Test 2 is added. The liquid chromatographic procedure is validated using an Inertsil ODS 3V brand of L1 column. The typical retention times for amlodipine, valsartan and hydrochlorothiazide are about 5.0 min and 7.5 min and 2.5 min respectively.
- A Dissolution Test 3 is added. The liquid chromatographic procedure is validated using an Oyster ODS 3 brand of L1 column. The typical retention times for hydrochlorothiazide and valsartan are about 2.3 min and 3.6 min respectively. The typical retention time for amlodipine is about 2.8 min.

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

The Amlodipine, Valsartan and Hydrochlorothiazide Tablets Revision Bulletin supersedes the currently official Amlodipine, Valsartan 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).
Amlodipine, Valsartan, and Hydrochlorothiazide Tablets

**DEFINITION**

**Change to read:**

Amlodipine, Valsartan, and Hydrochlorothiazide Tablets contain NLT 92.5% and NMT 107.5% each of the labeled amounts of amlodipine (C_{20}H_{25}ClN_{2}O_{5}), valsartan (C_{24}H_{29}N_{5}O_{3}), and hydrochlorothiazide (C_{7}H_{8}ClN_{3}O_{4}S_{2}).

**IDENTIFICATION**

- **A.** The UV absorption spectra of the amlodipine, valsartan, and hydrochlorothiazide peaks of Sample solution A, Sample solution B, and Sample solution C and those of the Standard solution exhibit maxima and minima at the same wavelengths, as obtained in the Assay.

- **B.** The retention times of the amlodipine, valsartan, and hydrochlorothiazide peaks of Sample solution A, Sample solution B, and Sample solution C correspond to those of the Standard solution, as obtained in the Assay.

**ASSAY**

**Change to read:**

- **PROCEDURE**
  
  Use amber glassware for all solutions containing drug substances.

  **Solution A:** Acetonitrile, water, and phosphoric acid (50:950:1)
  
  **Solution B:** Acetonitrile, water, and phosphoric acid (950:50:1)

  **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>95</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>95</td>
</tr>
<tr>
<td>10.1</td>
<td>95</td>
<td>5</td>
</tr>
<tr>
<td>15</td>
<td>95</td>
<td>5</td>
</tr>
</tbody>
</table>

  **Diluent:** Acetonitrile and water (500:500) 0.1% Phosphoric acid: Water and phosphoric acid (1000:1)

  **Standard solution:** 0.14 mg/mL of USP Amlodipine Besylate RS, 0.064 mg/mL of USP Valsartan RS, and 0.025 mg/mL of USP Hydrochlorothiazide RS in Diluent

  **Sample stock solution:** Transfer NLT 10 Tablets into a suitable volumetric flask. Add 0.1% Phosphoric acid to 4% of the total volume to disperse the Tablets. Sonicate for 10 min. Add 4% of the total volume of acetonitrile, swirl to mix, and add 60% of the total volume of Diluent. Sonicate for 20 min. Dilute with Diluent to volume to obtain solutions of nominal concentrations stated in Table 2. Centrifuge, and use the clear supernatant.

  **Table 2**

<table>
<thead>
<tr>
<th>Tablet</th>
<th>Strength</th>
<th>Nominal Concentration of Amlodipine (mg/mL)</th>
<th>Nominal Concentration of Valsartan (mg/mL)</th>
<th>Nominal Concentration of Hydrochlorothiazide (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/160/12.5</td>
<td>0.1</td>
<td>3.2</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>10/160/12.5</td>
<td>0.2</td>
<td>3.2</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>5/160/25</td>
<td>0.1</td>
<td>3.2</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>10/160/25</td>
<td>0.2</td>
<td>3.2</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>10/320/25</td>
<td>0.1</td>
<td>3.2</td>
<td>0.25</td>
<td></td>
</tr>
</tbody>
</table>

  **Sample solution A:** Nominally equivalent to 0.1 mg/mL of amlodipine in Diluent from Sample stock solution

  **Sample solution B:** Nominally equivalent to 0.064 mg/mL of valsartan in Diluent from Sample stock solution

  **Sample solution C:** Nominally equivalent to 0.025 mg/mL of hydrochlorothiazide in Diluent from Sample stock solution

  **Chromatographic system**

  (See Chromatography (621), System Suitability.)

  **Mode:** LC

  **Detector:** Assay: 225 nm, Identification test A: Diode array, \textit{UV} 200–400 nm

  **Column:** 4.6-mm \textit{LC} Column: 4.6-mm × 15-cm; 3-µm packing L1

  **Column temperature:** 40°C

  **Flow rate:** 1.5 mL/min

  **Injection volume:** 10 µL

  **System suitability**

  **Sample:** Standard solution

  **Suitability requirements**

  **Tailing factor:** NMT 2.0 for amlodipine, valsartan, and hydrochlorothiazide

  **Relative standard deviation:** NMT 2.0% for amlodipine, valsartan, and hydrochlorothiazide

  **Analysis**

  **Samples:** Standard solution, Sample solution A, Sample solution B, and Sample solution C

  Calculate the percentage of the labeled amount of amlodipine (C_{20}H_{25}ClN_{2}O_{5}) in the portion of Tablets taken:

  \[ \text{Result} = \left( \frac{r_0}{r_s} \right) \times \left( \frac{C_s}{C_0} \right) \times \left( \frac{M_1}{M_2} \right) \times 100 \]

  \( r_0 = \) peak response of amlodipine from \textit{Sample solution A}

  \( r_s = \) peak response of amlodipine from the \textit{Standard solution}

  \( C_s = \) concentration of USP Amlodipine Besylate RS in the \textit{Standard solution} (mg/mL)

  \( C_0 = \) nominal concentration of amlodipine in \textit{Sample solution A} (mg/mL)

  \( M_1 = \) molecular weight of amlodipine, 408.88

  \( M_2 = \) molecular weight of amlodipine besylate, 567.05

  Calculate the percentage of the labeled amount of valsartan (C_{24}H_{29}N_{5}O_{3}) in the portion of Tablets taken:

  \[ \text{Result} = \left( \frac{r_0}{r_s} \right) \times \left( \frac{C_s}{C_0} \right) \times 100 \]

  \( r_0 = \) peak response of valsartan from \textit{Sample solution B}

  \( r_s = \) peak response of valsartan from the \textit{Standard solution}

  \( C_s = \) concentration of USP Valsartan RS in the \textit{Standard solution} (mg/mL)

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Amlodipine

\[ C_0 \text{ = nominal concentration of valsartan in } \text{Sample solution } B \text{ (mg/mL)} \]

Calculate the percentage of the labeled amount of hydrochlorothiazide (C7H8ClN3O4S2) in the portion of Tablets taken:

\[ \text{Result} = \left( \frac{r_o}{r_s} \right) \times \left( \frac{C_s}{C_0} \right) \times 100 \]

\[ r_o \text{ = peak response of hydrochlorothiazide from Sample solution } C \]
\[ r_s \text{ = peak response of hydrochlorothiazide from the Standard solution} \]
\[ C_s \text{ = concentration of USP Hydrochlorothiazide RS in the Standard solution (mg/mL)} \]
\[ C_0 \text{ = nominal concentration of hydrochlorothiazide in Sample solution C (mg/mL)} \]

Acceptance criteria: 92.5%–107.5% (8B 1-Jun-2016)

Performance tests

Change to read:

- **Dissolution (711)**

  Test 1: Dissolve 6.805 g of monobasic potassium phosphate and 0.896 g of sodium hydroxide in 1000 mL of water. Adjust with 0.2 N sodium hydroxide or 1 M phosphoric acid to a pH of 6.8.

  Buffer: Dissolve 6.805 g of monobasic potassium phosphate and 0.896 g of sodium hydroxide in 1000 mL of water. Adjust with 0.2 N sodium hydroxide or 1 M phosphoric acid to a pH of 6.8.

  Medium: Buffer, 900 mL

  Apparatus 2: 50 rpm for 5/160/12.5, 10/160/12.5, 5/160/25, and 10/160/25 (mg/mg/mg) of Tablet strengths (amlodipine/valsartan/hydrochlorothiazide); 55 rpm for 10/320/25 (mg/mg/mg) of Tablet strengths (amlodipine/valsartan/hydrochlorothiazide)

  Time: 30 min

  Solution A: Acetonitrile, water, and phosphoric acid (50:950:1)

  Solution B: Acetonitrile, water, and phosphoric acid (950:50:1)

  Mobile phase: See Table 3.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>67</td>
<td>33</td>
</tr>
<tr>
<td>2.50</td>
<td>23</td>
<td>77</td>
</tr>
<tr>
<td>2.51</td>
<td>67</td>
<td>33</td>
</tr>
<tr>
<td>4.00</td>
<td>67</td>
<td>33</td>
</tr>
</tbody>
</table>

  Diluent: 1 mg/mL of polysorbate 80 in Buffer

  Standard stock solution A: 0.07 mg/mL of USP Amlodipine Besylate and 0.124 mg/mL of USP Hydrochlorothiazide RS. Initially dissolve with 4% of the total volume of methanol, and dilute with Diluent to volume.

  Standard stock solution B: 3.2 mg/mL of USP Valsartan RS in methanol

  Standard solution: 0.014 mg/mL of USP Amlodipine Besylate RS, 0.16 mg/mL of USP Valsartan RS, and 0.0248 mg/mL of USP Hydrochlorothiazide RS in Diluent from Standard stock solution A and Standard stock solution B, respectively

  Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-μm pore size. Discard at least the first 10 mL of the filtrate.

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

Mode: LC
Detector: UV 250 nm
Column: 4.6-mm x 5-cm; 3-μm packing L1
Column temperature: 30°
Flow rate: 1.5 mL/min
Injection volume: 5 μL for 10/320/25 (mg/mg/mg) of Tablet strengths (amlodipine/valsartan/hydrochlorothiazide); 10 μL for 5/160/12.5, 10/160/12.5, 5/160/25, and 10/160/25 (mg/mg/mg) of Tablet strengths (amlodipine/valsartan/hydrochlorothiazide)

System suitability

Sample: Standard solution
Suitability requirements

Resolution: NLT 3.0 between amlodipine and valsartan

Tailing factor: NMT 2.0 for amlodipine, valsartan, and hydrochlorothiazide

Relative standard deviation: NMT 2.0% for amlodipine, valsartan, and hydrochlorothiazide

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of the labeled amount of amlodipine (C20H25ClN2O5) dissolved:

\[ \text{Result} = \left( \frac{r_o}{r_s} \right) \times C_s \times V \times \left( \frac{M_r}{M_2} \right) \times \left( \frac{1}{L_1} \right) \times 100 \]

\[ r_o \text{ = peak response of amlodipine from the Sample solution} \]
\[ r_s \text{ = peak response of amlodipine from the Standard solution} \]
\[ C_s \text{ = concentration of USP Amlodipine Besylate RS in the Standard solution (mg/mL)} \]
\[ V \text{ = volume of Medium, 900 mL} \]
\[ M_1 \text{ = molecular weight of amlodipine, 408.88} \]
\[ M_2 \text{ = molecular weight of amlodipine besylate, 567.05} \]
\[ L_1 \text{ = label claim for amlodipine (mg/Tablet)} \]

Calculate the percentage of the labeled amount of valsartan (C24H29N5O3) dissolved:

\[ \text{Result} = \left( \frac{r_o}{r_s} \right) \times C_s \times V \times \left( \frac{1}{L_1} \right) \times 100 \]

\[ r_o \text{ = peak response of valsartan from the Sample solution} \]
\[ r_s \text{ = peak response of valsartan from the Standard solution} \]
\[ C_s \text{ = concentration of USP Valsartan RS in the Standard solution (mg/mL)} \]
\[ V \text{ = volume of Medium, 900 mL} \]
\[ L_2 \text{ = label claim for valsartan (mg/Tablet)} \]

Calculate the percentage of the labeled amount of hydrochlorothiazide (C7H8ClN3O4S2) dissolved:

\[ \text{Result} = \left( \frac{r_o}{r_s} \right) \times C_s \times V \times \left( \frac{1}{L_1} \right) \times 100 \]

\[ r_o \text{ = peak response of hydrochlorothiazide from the Sample solution} \]
\[ r_s \text{ = peak response of hydrochlorothiazide from the Standard solution} \]
\[ C_s \text{ = concentration of USP Hydrochlorothiazide RS in the Standard solution (mg/mL)} \]
\[ V \text{ = volume of Medium, 900 mL} \]
\[ L_3 \text{ = label claim for hydrochlorothiazide (mg/Tablet)} \]

Tolerances: NLT 75% (Q) of the labeled amount of amlodipine (C20H25ClN2O5) is dissolved, NLT 80% (Q) of the labeled amount of valsartan (C24H29N5O3) is dissolved, and NLT 80% (Q) of hydrochlorothiazide (C7H8ClN3O4S2) is dissolved.

Test 2: If the product complies with this test, the labeling indicates that the product meets USP Dissolution Test 2.
Medium: Proceed as directed under Dissolution Test 1, 900 mL

Apparatus 2
For Tablets labeled to contain amlodipine/valsartan/hydrochlorothiazide, 5/160/12.5, 10/160/12.5, 5/160/25, 10/160/25, and 5/80/12.5 (mg/mg/mg): 55 rpm
For Tablets labeled to contain amlodipine/valsartan/hydrochlorothiazide, 10/320/25 (mg/mg/mg): 30 rpm

Time: 30 min for valsartan and hydrochlorothiazide, 45 min for amlodipine
Buffer: Mix 7.0 mL of triethylamine with 1000 mL of water. Adjust with phosphoric acid to a pH of 3.0.
Solution A: Acetonitrile and Buffer (10:90).
Solution B: Acetonitrile and Buffer (90:10).
Mobile phase: See Table 4.

Table 4

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>90</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>8</td>
<td>90</td>
<td>10</td>
</tr>
<tr>
<td>15</td>
<td>90</td>
<td>10</td>
</tr>
</tbody>
</table>

Standard stock solution A: 0.35 mg/mL of USP Amlodipine Besylate RS prepared as follows. Initially dissolve in 10% of the final volume of methanol and dilute with Medium to volume.
Standard stock solution B: 1.6 mg/mL of USP Val- sartan RS in methanol
Standard stock solution C: 0.7 mg/mL of USP Hydrochlorothiazide RS prepared as follows. Initially dissolve in 25% of the final volume of methanol and dilute with Medium to volume.
Standard solution: (L1/1000) mg/mL of amlodipine, (L2/1000) mg/mL of valsartan, and (L3/1000) mg/mL of hydrochlorothiazide in Diluent from Standard stock solution A, Standard stock solution B, and Standard stock solution C, where L1 is the label claim of valsartan in mg/Tablet, L2 is the label claim of amlodipine in mg/Tablet, and L3 is the label claim of hydrochlorothiazide in mg/Tablet.
Sample solution: Pass a portion of the solution under test through a suitable filter of 1-μm pore size.

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 237 nm
Column: 4.6-mm × 15-cm; 5-μm packing L1
Temperatures
Autosampler: 10°
Column: 50°
Flow rate: 1.5 mL/min
Injection volume: 20 μL
System suitability
Sample: Standard solution
Suitability requirements
Tailing factor: NMT 2.0 for each peak
Relative standard deviation: NMT 2.0% for each peak.
Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of amlodipine (C20H25ClN2O5) dissolved:

\[ \text{Result} = \left( \frac{r_u}{r_s} \right) \times C_s \times V \times \left( \frac{M_r}{M_i} \right) \times \left( \frac{1}{L_i} \right) \times 100 \]

\( r_u \) = peak response of amlodipine from the Sample solution
\( r_s \) = peak response of amlodipine from the Standard solution
\( C_s \) = concentration of USP Amlodipine Besylate RS in the Standard solution (mg/mL)
\( V \) = volume of Medium, 900 mL
\( M_r \) = molecular weight of amlodipine, 408.88
\( M_i \) = molecular weight of amlodipine, 67.05
\( L_i \) = label claim for amlodipine (mg/Tablet)
Calculate the percentage of the labeled amount of valsartan (C24H29N5O3) dissolved:

\[ \text{Result} = \left( \frac{r_u}{r_s} \right) \times C_s \times V \times \left( \frac{1}{L_i} \right) \times 100 \]

\( r_u \) = peak response of valsartan from the Sample solution
\( r_s \) = peak response of valsartan from the Standard solution
\( C_s \) = concentration of USP Valsartan RS in the Standard solution (mg/mL)
\( V \) = volume of Medium, 900 mL
\( L_i \) = label claim for valsartan (mg/Tablet)
Calculate the percentage of the labeled amount of hydrochlorothiazide (C7H8ClN3O4S2) dissolved:

\[ \text{Result} = \left( \frac{r_u}{r_s} \right) \times C_s \times V \times \left( \frac{1}{L_i} \right) \times 100 \]

\( r_u \) = peak response of hydrochlorothiazide from the Sample solution
\( r_s \) = peak response of hydrochlorothiazide from the Standard solution
\( C_s \) = concentration of USP Hydrochlorothiazide RS in the Standard solution (mg/mL)
\( V \) = volume of Medium, 900 mL
\( L_i \) = label claim for hydrochlorothiazide (mg/Tablet)

Tolerances: NLT 75% (Q) of the labeled amount of amlodipine (C20H25ClN2O5) is dissolved, NLT 80% (Q) of the labeled amount of valsartan (C24H29N5O3) is dissolved, and NLT 80% (Q) of the labeled amount of hydrochlorothiazide (C7H8ClN3O4S2) is dissolved.

Test 3: If the product complies with this test, the labeling indicates that the product meets USP Dissolution Test 3.
Medium: Dissolve 6.80 g of monobasic potassium phosphate in 1000 mL of water. Adjust with 10% sodium hydroxide solution to a pH of 6.8.; 1000 mL for valsartan and hydrochlorothiazide; 900 mL for amlodipine.

Apparatus 2: 50 rpm for valsartan and hydrochlorothiazide; 55 rpm for amlodipine in Tablets labeled to contain amlodipine/valsartan/hydrochlorothiazide, 10/320/25 (mg/mg/mg); and 50 rpm for amlodipine in Tablets labeled to contain amlodipine/valsartan/hydrochlorothiazide, 5/160/12.5, 10/160/12.5, 5/160/25, 10/160/25, and 5/80/12.5 (mg/mg/mg).
Times: 30 min for valsartan and hydrochlorothiazide, 45 min for amlodipine.

Solution A: Acetonitrile, trifluoroacetic acid and water (100:0.1:90)
Solution B: Acetonitrile, trifluoroacetic acid and water (90:0.1:10)
Mobile phase: See Table 5.

Table 5

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01</td>
<td>90</td>
<td>10</td>
</tr>
<tr>
<td>2.5</td>
<td>10</td>
<td>90</td>
</tr>
</tbody>
</table>
Diluent: Acetonitrile and water (50:50)

Standard stock solution A: 0.15 mg/mL of USP Amlodipine Besylate RS in Medium prepared as follows. Initially dissolve and sonicate in 10% of the final volume of Diluent and dilute with Medium to volume.

Standard stock solution B: 1.6 mg/mL of USP Val- sartan RS in Medium prepared as follows. Initially dis- solve and sonicate in 20% of the final volume of Dilu- ent and dilute with Medium to volume.

Standard stock solution C: 0.25 mg/mL of USP Hy- drochlorothiazide RS in Medium prepared as follows. Initially dissolve and sonicate in 10% of the final vol- ume of Diluent and dilute with Medium to volume.

Standard stock solution D: Standard stock solution A, Standard stock solution B, and Standard stock solution C, where \( L_1 \) is the label claim of amlodipine in mg/Tablet, \( L_2 \) is the label claim of valsartan in mg/Tablet, and \( L_3 \) is the label claim of hydrochlorothiazide in mg/Tablet.

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Discard at least the first few mL of the filtrate.

Chromatographic system

(See Chromatography (621), System Suitability.)

Mode: LC

Detector: UV 237 for amlodipine and UV 270 nm for valsartan and hydrochlorothiazide

Column: 4.6-mm x 10-cm; 5-µm packing L1

Flow rate: 1.5 mL/min

Injection volume: 10 µL

System suitability

Sample: Standard solution

Suitability requirements

Tailing factor: NMT 2.0 for each peak

Relative standard deviation: NMT 2.0% for each peak

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of the labeled amount of amlodipine (\( C_{\text{Aml}} \)) dissolved:

\[
\text{Result} = \left( \frac{r_o}{r_u} \right) \times C_i \times V \times (M_i/\dot{M}_g) \times (1/L_i) \times 100
\]

\( r_o \) = peak response of valsartan from the Sample solution

\( r_u \) = peak response of valsartan from the Standard solution

\( C_i \) = concentration of USPValsartan RS in the Standard solution (mg/mL)

\( V \) = volume of Medium, 1000 mL

\( L_i \) = label claim for valsartan (mg/Tablet)

\( r_o \) = peak response of amlodipine from the Sample solution

\( r_u \) = peak response of amlodipine from the Standard solution

\( C_{\text{Aml}} \) = concentration of USP Amlodipine RS in the Standard solution (mg/mL)

\( V \) = volume of Medium, 1000 mL

\( L_i \) = label claim for hydrochlorothiazide (mg/Tablet)

\( r_o \) = peak response of hydrochlorothiazide from the Sample solution

\( r_u \) = peak response of hydrochlorothiazide from the Standard solution

\( C_{\text{HCO3}} \) = concentration of USP Hydrochlorothiazide RS in the Standard solution (mg/mL)

\( V \) = volume of Medium, 1000 mL

\( L_i \) = label claim for hydrochlorothiazide (mg/Tablet)

**Tolerances**


- NLT 75% (Q) of the labeled amount of amlodipine (\( C_{20H25ClN2O5} \)) is dissolved, NLT 80% (Q) of the labeled amount of valsartan (\( C_{24H29N5O3} \)) is dissolved, and NLT 80% (Q) of the labeled amount of hydrochlorothiazide (\( C_{7H8ClN3O4S2} \)) is dissolved.

For Tablets labeled to contain amlodipine/valsartan/hydrochlorothiazide, 5/160/25, 10/ 320/25 (mg/mg):

- NLT 70% (Q) of the labeled amount of amlodipine (\( C_{20H25ClN2O5} \)) is dissolved, NLT 80% (Q) of the labeled amount of valsartan (\( C_{24H29N5O3} \)) is dissolved, and NLT 80% (Q) of the labeled amount of hydrochlorothiazide (\( C_{7H8ClN3O4S2} \)) is dissolved.

**Uniformity of Dosage Units (905):** Meet the requirements.

**IMPURIITIES**

**Change to read:**

- **Organic Impurities**

  Use amber glassware for all solutions containing drug substances.

  **Mobile phase, Diluent, Sample solution A, Sample so- lution B, Sample solution C, and Chromatographic system:** Proceed as directed in the Assay.

  **System suitability solution:** 0.02 mg/mL each of USP Benzothiadiazine Related Compound A RS and USP Val- sartan Related Compound B RS, 0.005 mg/mL of USP Amlodipine Related Compound A RS, 0.14 mg/mL of USP Amlodipine Besylate RS, 0.064 mg/mL of USP Val- sartan RS, and 0.025 mg/mL of USP Hydrochlorothi- azone RS in Diluent

  **Sensitivity solution:** 0.14 µg/mL of USP Amlodipine Besylate RS, 0.064 µg/mL of USP Valsartan RS, and 0.025 µg/mL of USP Hydrochlorothiazide RS in Diluent

  **Standard solution:** 0.0005 mg/mL of USP Amlodipine Related Compound A RS, 0.0001 mg/mL of USP Benzo- thiadiazine Related Compound A RS, 0.0003 mg/mL of USP Amlodipine Besylate RS, 0.00015 mg/mL of USP Valsartan RS, and 0.00005 mg/mL of USP Hydro- chlorothiazide RS in Diluent

  **System suitability**

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

  **Suitability requirements**

  **Signal-to-noise ratio:** NLT 10 for amlodipine, val- sartan, and hydrochlorothiazide, Sensitivity solution
**Amlodipine**

**Resolution:** NLT 2.0 between any adjacent peaks of benzothiadiazine related compound A, hydrochlorothiazide, amlodipine related compound A, amlodipine, valsartan related compound B, and valsartan, System suitability solution.

**Relative standard deviation:** NMT 5.0% for amlodipine related compound A, benzothiadiazine related compound A, amlodipine, valsartan, and hydrochlorothiazide, Standard solution.

**Analysis**

**Samples:** Sample solution A, Sample solution B, Sample solution C, and Standard solution.

Calculate the percentage of amlodipine related compound A in the portion of Tablets taken:

\[
\text{Result} = \left( \frac{r_1}{r_2} \right) \times \left( \frac{C_S}{C_U} \right) \times \left( \frac{M_1}{M_2} \right) \times 100
\]

where:

- \( r_1 \) = peak response of amlodipine related compound A from Sample solution A
- \( r_2 \) = peak response of amlodipine related compound A from the Standard solution
- \( C_S \) = concentration of USP Amlodipine Related Compound A RS in the Standard solution (mg/mL)
- \( C_U \) = nominal concentration of amlodipine in Sample solution A (mg/mL)
- \( M_1 \) = molecular weight of amlodipine besylate, 406.86
- \( M_2 \) = molecular weight of amlodipine related compound A fumarate, 522.93

Calculate the percentage of any valsartan related degradation product in the portion of Tablets taken:

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

where:

- \( r_1 \) = peak response of any valsartan related degradation product from Sample solution B
- \( r_2 \) = peak response of valsartan from the Standard solution
- \( C_S \) = concentration of USP Valsartan RS in the Standard solution (mg/mL)
- \( C_U \) = nominal concentration of valsartan in Sample solution B (mg/mL)

Calculate the percentage of benzothiadiazine related compound A in the portion of Tablets taken:

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

where:

- \( r_1 \) = peak response of benzothiadiazine related compound A from Sample solution C
- \( r_2 \) = peak response of benzothiadiazine related compound A from the Standard solution
- \( C_S \) = concentration of USP Benzothiadiazine Related Compound A RS in the Standard solution (mg/mL)
- \( C_U \) = nominal concentration of benzothiadiazine in Sample solution C (mg/mL)

Calculate the percentage of hydrochlorothiazide and hydrochlorothiazide dimer in the portion of Tablets taken:

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

where:

- \( r_1 \) = peak response of hydrochlorothiazide or hydrochlorothiazide dimer from Sample solution C
- \( r_2 \) = peak response of hydrochlorothiazide from the Standard solution
- \( C_S \) = concentration of USP Hydrochlorothiazide RS in the Standard solution (mg/mL)
- \( C_U \) = nominal concentration of hydrochlorothiazide in Sample solution C (mg/mL)

Calculate the percentage of each unspecified degradation product in the portion of Tablets taken:

\[
\text{Result} = \left( \frac{r_1}{r_2} \right) \times \left( \frac{C_S}{C_U} \right) \times \left( \frac{M_1}{M_2} \right) \times 100
\]

where:

- \( r_1 \) = peak response of each unspecified degradation product from Sample solution A
- \( r_2 \) = peak response of amlodipine from the Standard solution
- \( C_S \) = concentration of USP Amlodipine Related Compound A RS in the Standard solution (mg/mL)
- \( C_U \) = nominal concentration of amlodipine in Sample solution A (mg/mL)
- \( M_1 \) = molecular weight of amlodipine, 408.88
- \( M_2 \) = molecular weight of amlodipine besylate, 567.05

**Acceptance criteria:** See Table 6. Disregard amlodipine ethyl analog peak, valsartan related compound B peak, and any peaks below 0.1%.

**Table 6**

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzothiadiazine related compound A</td>
<td>0.60</td>
<td>1.0 (RB 1-Jun-2016)</td>
</tr>
<tr>
<td>Chlorothiazide</td>
<td>0.62</td>
<td>0.50 (RB 1-Jun-2016)</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Devamoy valsartan</td>
<td>0.71</td>
<td>0.2</td>
</tr>
<tr>
<td>Hydrochlorothiazide dimer</td>
<td>0.89</td>
<td>0.50 (RB 1-Jun-2016)</td>
</tr>
<tr>
<td>Amlodipine related compound A</td>
<td>0.96</td>
<td>0.5</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>1.00</td>
<td>—</td>
</tr>
<tr>
<td>Valsartan related degradation product 1</td>
<td>1.04</td>
<td>0.2</td>
</tr>
<tr>
<td>Amlodipine ethyl analog</td>
<td>1.08</td>
<td>—</td>
</tr>
<tr>
<td>Valsartan related compound B</td>
<td>1.22</td>
<td>—</td>
</tr>
<tr>
<td>Valsartan related degradation product 2</td>
<td>1.27</td>
<td>0.2</td>
</tr>
<tr>
<td>Valsartan</td>
<td>1.36</td>
<td>—</td>
</tr>
<tr>
<td>Valsartan related degradation product 3</td>
<td>1.51</td>
<td>0.2</td>
</tr>
</tbody>
</table>

1. 4-Amino-6-chloro-1,3-benzenedisulfonamide.
2. 6-Chloro-2 H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.
3. 4-Chloro-6-[2-(1H-Tetrazole-5-syl)biphenyl-4-syl][methyl]-l-valine.
4. 6-Chloro-N-[6-chloro-7-sulfamoyl-2,3-dihydro-4H-1,2,4-benzothiadiazine-4-sulfonic acid methyl][3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.
5. 3,5-Dimethyl-5-(2-aminoethyl)-4-(2-chlorophenyl)-6-methyl-3,5-pyridinedicarboxylate.

These are specified unidentified degradation products. No information is available about chemical structures or chemical names for these impurities.

6. Diethyl 2-[2-(aminoethoxy)ethyl][4-(2-chlorophenyl)-6-methyl-3,5-pyridinedicarboxylate].
7. Process related impurity given for information only. (RB 1-Jun-2016)
8. 3-(N-Butyl)-N-[2-(1H-Tetrazole-5-syl)bisphenyl-4-syl][methyl]-l-valine.
### ADDITIONAL REQUIREMENTS

**LABELING:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if test 1 is not used. (RB 1-Jun-2016)

**USP REFERENCE STANDARDS** (11)
- USP Amlodipine Besylate RS
- USP Amlodipine Related Compound A RS
  \(C_{20}H_{23}ClN_2O_5\cdot C_4H_4O_4\) 522.93
- USP Benzothiadiazine Related Compound A RS
- 4-Amino-6-chloro-1,3-benzenedisulfonamide. 
  \(C_6H_8ClN_3O_4S_2\) 285.73
- USP Hydrochlorothiazide RS
- USP Valsartan RS

**PACKAGING AND STORAGE:** Store at controlled room temperature in tight containers in a dry place.