Amiodarone Hydrochloride Tablets

Type of Posting                  Revision Bulletin
Posting Date                    25–Oct–2019
Official Date                   01–Dec–2019
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 Amiodarone Hydrochloride Tablets monograph. The purpose for the revision is to add Dissolution Test 2 to accommodate FDA-approved drug products with different dissolution conditions and tolerances than the existing dissolution test. A Labeling section has also been added.

The Amiodarone Hydrochloride Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Edith Chang, Senior Scientific Liaison—Team Leader (301-816-8392 or yec@usp.org).
Amiodarone Hydrochloride Tablets

**DEFINITION**
Amiodarone Hydrochloride Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of amiodarone hydrochloride (C\(_{25}\)H\(_{29}\)I\(_{2}\)NO\(_{4}\) · HCl).

**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 spectrum of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay.

**ASSAY**

**PROCEDURE**
- **Buffer:** Add 3 mL of acetic acid, glacial to 1 L of water. Adjust with ammonia water, 25 percent to a pH of 3.0.
- **Mobile phase:** Acetonitrile and Buffer (40:60)
- **Standard solution:** 0.1 mg/mL of USP Amiodarone Hydrochloride RS in Mobile phase
- **Sample stock solution:** Nominally 1 mg/mL of amiodarone hydrochloride inMobile phase prepared as follows. Transfer a quantity, equivalent to 100 mg of amiodarone hydrochloride, from NLT 20 finely powdered Tablets to a 100-mL volumetric flask. Add Mobile phase to about 50% of the final flask volume. Sonicate with occasional shaking to dissolve. Cool the solution and dilute with Mobile phase to volume.
- **Sample solution:** Nominally 0.1 mg/mL of amiodarone hydrochloride inMobile phase from Sample stock solution. Pass a portion of the solution through a suitable filter of 0.45-µm pore size, discard the first few milliliters, and collect the filtrate.

**Chromatographic system**
(See Chromatography (621), System Suitability.)
**Mode:** LC
**Detector:** UV 240 nm. For Identification B, use a diode array detector in the range of 200–400 nm.
**Column:** 4.6-mm × 25-cm; 5-µm packing L1
**Column temperature:** 30°
**Flow rate:** 1 mL/min
**Injection volume:** 10 µL
**Run time:** NLT 2.5 times the retention time of amiodarone

**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 amiodarone hydrochloride (C\(_{25}\)H\(_{29}\)I\(_{2}\)NO\(_{4}\) · HCl) dissolved:**

\[
\text{Result} = \left( \frac{A_u}{A_s} \right) \times \left( \frac{C_i}{C_0} \right) \times 100
\]

- \(A_u\) = absorbance of amiodarone from the Sample solution
- \(A_s\) = absorbance of amiodarone from the Standard solution
- \(C_i\) = concentration of USP Amiodarone Hydrochloride RS in the Standard solution (mg/mL)
- \(D\) = dilution factor for the Sample solution
- \(V\) = volume of Medium, 1000 mL
- \(L\) = label claim of amiodarone hydrochloride (mg/Tablet)

- **Tolerances:** NLT 80% (Q) of the labeled amount of amiodarone hydrochloride (C\(_{25}\)H\(_{29}\)I\(_{2}\)NO\(_{4}\) · HCl) is dissolved.

- **Test 2:** If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 2.
  - **Medium:** 0.2% (v/v) polysorbate 80 in 0.05 N hydrochloric acid prepared as follows. Add 26 mL of hydrochloric acid and 12 mL of polysorbate 80 to 6 L of deaerated water; 900 mL
  - **Apparatus 2:** 75 rpm
  - **Time:** 30 min

**Instrumental conditions**
- **Mode:** UV

**PERFORMANCE TESTS**

**Change to read:**

- **Dissolution (711)**
  - **Test 1**
    - **Medium:** 1% (w/v) sodium dodecyl sulfate; 1000 mL
    - **Apparatus 2:** 100 rpm
    - **Time:** 60 min
  - **Standard stock solution:** 0.2 mg/mL of USP Amiodarone Hydrochloride RS prepared as follows. Transfer an appropriate quantity of USP Amiodarone Hydrochloride RS to a suitable volumetric flask and add methanol to 50% of the final flask volume. Sonicate to dissolve and dilute with Medium to volume.
  - **Standard solution:** 0.01 mg/mL of USP Amiodarone Hydrochloride RS in Medium from Standard stock solution
  - **Sample solution:** Dilute a portion of the solution under test with Medium to a concentration similar to that of the Standard solution. Pass a portion of the solution through a suitable filter of 0.45-µm pore size, discard the first few milliliters, and collect the filtrate.

- **Instrumental conditions**
  - **Mode:** UV
  - **Analytical wavelength:** 243 nm
  - **Cell:** 1 cm
  - **Blank:** Medium
  - **Analysis**
    - **Samples:** Standard solution and Sample solution
    - **Calculate the percentage of the labeled amount of amiodarone hydrochloride (C\(_{25}\)H\(_{29}\)I\(_{2}\)NO\(_{4}\) · HCl) dissolved:**

\[
\text{Result} = \left( \frac{A_u}{A_s} \right) \times \left( \frac{C_i}{C_0} \right) \times 100
\]

- **Acceptance criteria:** 90.0%–110.0%
2 Amiodarone

Analysis wavelength: 244 nm
Cell: 0.1 cm
Blank: Medium

Analysis Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of amiodarone hydrochloride (C_{27}H_{28}I_{3}NO_{8}·HCl) dissolved:

\[
\text{Result} = \frac{A_0}{A_s} \times \frac{C_s}{C} \times V \times \frac{1}{L} \times 100
\]

- \( A_0 \) = absorbance of amiodarone from the Sample solution
- \( A_s \) = absorbance of amiodarone from the Standard solution
- \( C_s \) = concentration of USP Amiodarone Hydrochloride RS in the Standard solution (mg/mL)
- \( V \) = volume of Medium, 900 mL
- \( L \) = label claim of amiodarone hydrochloride (mg/Tablet)

Tolerances: NLT 75% (Q) of the labeled amount of amiodarone hydrochloride (C_{27}H_{28}I_{3}NO_{8}·HCl) is dissolved. ▲ (RB 1-Dec-2019)

• Uniformity ofDosage Units (905): Meet the requirements

Impurities
• Organic Impurities
Buffer: Add 3 mL of acetic acid, glacial to 800 mL of water. Adjust with 10% (v/v) ammonia hydroxide solution to a pH of 4.9. Dilute with water to 1000 mL.
Mobile phase: Acetonitrile, methanol, and Buffer (40:30:30)
Diluent: Acetonitrile and water (50:50)
Standard solution: 0.01 mg/mL of USP Amiodarone Hydrochloride RS in Diluent
Sensitivity solution: 0.3 µg/mL of USP Amiodarone Hydrochloride RS in Diluent from the Standard solution
Sample solution: Nominally 1 mg/mL of amiodarone hydrochloride in Diluent prepared as follows. Transfer a quantity equivalent to 50 mg of amiodarone hydrochloride from NLT 20 finely powdered Tablets to a 50-mL volumetric flask. Add Diluent to 50% of the final flask volume. Sonicate with occasional shaking to dissolve. Cool the solution and dilute with Diluent to volume. Pass a portion of the solution through a suitable filter of 0.45-µm pore size, discard the first few milliliters, and collect the filtrate.

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 240 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Column temperature: 30°C
Flow rate: 1 mL/min
Injection volume: 10 µL
Run time: NLT 1.7 times the retention time of amiodarone for the Standard solution; NLT 3.4 times the retention time of amiodarone for the Sample solution

System suitability
Samples: Standard solution and Sensitivity solution
Suitability requirements
- Relative standard deviation: NMT 10.0%, Standard solution

Signal-to-noise ratio: NLT 10, Sensitivity solution

Analysis Samples: Standard solution and Sample solution
Calculate the percentage of amiodarone related compound D or any unspecified degradation product in the portion of Tablets taken:

Result = \( \left( \frac{r_U}{r_s} \right) \times \left( \frac{C_s}{C_U} \right) \times \frac{1}{F} \times 100 \)

- \( r_U \) = peak response of amiodarone related compound D or any unspecified degradation product from the Sample solution
- \( r_s \) = peak response of amiodarone from the Standard solution
- \( C_s \) = concentration of USP Amiodarone Hydrochloride RS in the Standard solution (mg/mL)
- \( C_U \) = nominal concentration of amiodarone hydrochloride in the Sample solution (mg/mL)
- \( F \) = relative response factor (see Table 1)

Acceptance criteria: See Table 1. The reporting threshold is 0.03%.

Table 1

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Relative Response Factor</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone related compound A(^{a, b})</td>
<td>0.22</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Amiodarone related compound D(^c)</td>
<td>0.29</td>
<td>0.90</td>
<td>0.5</td>
</tr>
<tr>
<td>Amiodarone related compound C(^d)</td>
<td>0.52</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>1.00</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Any unspecified degradation product</td>
<td>—</td>
<td>1.00</td>
<td>0.2</td>
</tr>
<tr>
<td>Total degradation products</td>
<td>—</td>
<td>—</td>
<td>1.0</td>
</tr>
</tbody>
</table>

\(^{a}\) (2-Butylbenzofuran-3-yl)[4-[2-(diethylamino)ethoxy]phenyl]methanone.
\(^{b}\) Process impurity included in the table for identification only. Process impurities are controlled in the drug substance and are not to be reported or included in the total degradation products for the drug product.
\(^{c}\) (2-Butylbenzofuran-3-yl)(4-hydroxy-3,5-diiodophenyl)methanone.
\(^{d}\) (2-Butylbenzofuran-3-yl)[4-[2-(diethylamino)ethoxy]-3-iodophenyl]methanone.

Additional Requirements
- Packaging and Storage: Preserve in tight and light-resistant containers, and store at controlled room temperature.

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. ▲ (RB 1-Dec-2019)
- **USP Reference Standards** (11)
  USP Amiodarone Hydrochloride RS ▲ (USP 1-Dec-2019)