Aripiprazole Tablets

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Expert Committee: Chemical Medicines Monographs 4
Reason for Revision: Compliance

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 4 Expert Committee has revised the Aripiprazole Tablets. The purpose for the revision is to add a dissolution test to accommodate drug products which were approved with different dissolution conditions and acceptance criteria. A Labeling section was also added.

- **Dissolution Test 2** was validated using a Zorbax SB C8 brand of column with L7 packing. The typical retention time for aripiprazole is about 3.7 min.

The Aripiprazole Tablets Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in the First Supplement to USP 41–NF 36.

Should you have any questions, please contact Heather Joyce, Ph.D., Senior Scientific Liaison (301–998–6792 or hri@usp.org).
Aripiprazole Tablets

**DEFINITION**

Aripiprazole Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of aripiprazole (C_{23}H_{27}Cl_{2}N_{3}O_{2}).

**IDENTIFICATION**

- **A. INFRARED ABSORPTION (197K)**
  - **Standard**: Add 30 mL of ethyl acetate to 30 mg of USP Aripiprazole RS. Shake for 10 min, centrifuge for NLT 5 min, and pass the supernatant through a suitable membrane filter. To the filtrate add 75 mL of water, shake for 5 min, and centrifuge for NLT 10 min. Transfer 20 mL of the upper layer to a container and add anhydrous magnesium sulfate, as needed. Shake well, pass through a suitable membrane filter, and evaporate the ethyl acetate on a water bath under reduced pressure. Use the residue. [**NOTE**—A centrifuge speed of 2000 rpm may be suitable.]
  - **Sample**: Grind a suitable number of Tablets and transfer a portion of the ground Tablets, equivalent to 30 mg of aripiprazole, to an appropriate container. Add 30 mL of ethyl acetate, shake for 10 min, centrifuge for NLT 5 min, and pass the supernatant through a suitable membrane filter. To the filtrate add 15 mL of water, shake for 5 min, and centrifuge for NLT 10 min. Transfer 20 mL of the upper layer to a container and add a suitable amount of anhydrous magnesium sulfate. Shake well, pass through a suitable membrane filter, and evaporate the ethyl acetate on a water bath under reduced pressure. Use the residue. [**NOTE**—A centrifuge speed of 2000 rpm may be suitable.]

**ASSAY**

**Change to read:**

**PROCEDURE**

- **Solution A**: 2.8 g/L of anhydrous sodium sulfate in water
- **Mobile phase**: Acetonitrile, methanol, Solution A, and glacial acetic acid (33:11:56:1)
- **Internal standard solution**: 0.33 mg/mL of USP Propylparaben RS in Mobile phase
- **Standard stock solution**: 1 mg/mL of USP Aripiprazole RS in Mobile phase
- **Standard solution**: 0.2 mg/mL of USP Aripiprazole RS prepared as follows. Transfer 10.0 mL of Standard stock solution and 10.0 mL of Internal standard solution to a 50-mL volumetric flask, and dilute with Mobile phase to volume.
- **Sample solution**: Nominally 0.2 mg/mL of aripiprazole from Tablets prepared as follows. Powder NLT 20 Tablets and transfer a suitable portion of the powder to an appropriate volumetric flask. Add 40% of the final flask volume of Mobile phase and 20% of the final flask volume of Internal standard solution. Shake for 10 min, and dilute with Mobile phase to volume. Centrifuge, if necessary, and pass the supernatant through a suitable filter of NMT 0.5-µm pore size, discard the first 1 mL of filtrate, and use the subsequent filtrate.

**Chromatographic system**

(See Chromatography (621), System Suitability.)

- **Mode**: LC
- **Detector**: UV 254 nm
- **Column**: 4.6-mm × 25-cm; 5-µm packing L1
- **Flow rate**: 1 mL/min
- **Injection volume**: 10 µL
- **Run time**: NLT 2 times the retention time of aripiprazole

**System suitability**

- **Sample**: Standard solution
  - [**NOTE**—The relative retention times for aripiprazole and propylparaben are about 1.0 and 1.5, respectively.]

**Suitability requirements**

- **Resolution**: NLT 8 between aripiprazole and propylparaben
- **Relative standard deviation**: NMT 2.0% for the peak response ratio of aripiprazole to propylparaben

**Analysis**

- **Samples**: Standard solution and Sample solution
  - Calculate the percentage of the labeled amount of aripiprazole (C_{23}H_{27}Cl_{2}N_{3}O_{2}) in the portion of Tablets taken:
    
    \[ \text{Result} = \left( \frac{R_d}{R_s} \right) \times \left( \frac{C_s}{C_u} \right) \times 100 \]

    - \( R_d \) = peak response ratio of aripiprazole to propylparaben from the Sample solution
    - \( R_s \) = peak response ratio of aripiprazole to propylparaben from the Standard solution
    - \( C_s \) = concentration of USP Aripiprazole RS in the Standard solution (mg/mL)
    - \( C_u \) = nominal concentration of aripiprazole in the Sample solution (mg/mL)

- **Acceptance criteria**: 95.0%–105.0%

**PERFORMANCE TESTS**

**Change to read:**

- **DISSOLUTION (711)**
  - **Medium**: pH 1.2 hydrochloric acid buffer (Transfer 250 mL of 14.9 g/L of potassium chloride in water to a 1-L volumetric flask, add 425 mL of 0.2 N hydrochloric acid, and dilute with water to volume. Degas the resulting solution or pass the resulting solution through a filter under vacuum.), degassed; 900 mL
  - **Apparatus 2**: 60 rpm
  - **Time**: 30 min

**Procedures**

- **Determine the percentage of the labeled amount of aripiprazole (C_{23}H_{27}Cl_{2}N_{3}O_{2}) dissolved by using either the Spectrometric procedure or the Chromatographic procedure described below.**

**Spectrometric procedure**

- **Standard stock solution**: 1 mg/mL of USP Aripiprazole RS in alcohol
- **Sample solution**: (L/900) mg/mL of USP Aripiprazole RS from Standard stock solution in Medium, where L is the label claim, in mg/Tablet

**Sample solution**: Pass a portion of the solution under test through a suitable filter, discounting the first 5 mL of filtrate.
Aripiprazole

Instrumental conditions
Mode: UV
Analytical wavelengths: 249 and 325 nm
Cell length: 1 cm

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of aripiprazole (C$_{23}$H$_{27}$Cl$_2$N$_3$O$_2$) dissolved:

\[
\text{Result} = \left( \frac{A_U}{A_S} \right) \times C_S \times V \times \left( \frac{1}{L} \right) \times 100
\]

\(A_U\) = absorbance at 249 nm minus the absorbance at 325 nm of the Sample solution
\(A_S\) = absorbance at 249 nm minus the absorbance at 325 nm of the Standard solution
\(C_S\) = concentration of USP Aripiprazole RS in the Standard solution (mg/mL)
\(V\) = volume of Medium, 900 mL
\(L\) = label claim (mg/Tablet)

Tolerances: NLT 75% (Q) of the labeled amount of aripiprazole (C$_{23}$H$_{27}$Cl$_2$N$_3$O$_2$) dissolved.

\(\star\)Test 2: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 2.
Medium: 0.1 N hydrochloric acid VS; 900 mL
Apparatus 2: 60 rpm
Time: 15 min
Buffer: 6.8 g/L of monobasic potassium phosphate in water. Adjust with 1 N phosphoric acid TS to a pH of 3.0.

Mobile phase: Acetonitrile and Buffer (40:60)

Standard stock solution: 0.11 mg/mL of USP Aripiprazole RS in solution prepared as follows. Transfer a suitable amount of USP Aripiprazole RS to an appropriate volumetric flask. Add 2% of the flask volume of acetonitrile and 70% of the flask volume of Medium. Sonication may be used to promote dissolution. Dilute with Medium to volume.

Standard solution: (L/900) mg/mL of USP Aripiprazole RS from Standard stock solution in Medium, where L is the label claim, in mg/Tablet
Sample solution: Pass a portion of the solution under test through a suitable filter, discarding NLT the first 5 mL of filtrate.

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 215 nm
Column: 4.6-mm × 15-cm; 5-μm packing L7
Column temperature: 40°C
Flow rate: 1 mL/min
Injection volume: 5 μL
Run time: NLT 1.6 times the retention time of aripiprazole

System suitability
Sample: Standard solution
Suitability requirements
Tailing factor: NMT 1.5
Relative standard deviation: NMT 1.0%

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of aripiprazole (C$_{23}$H$_{27}$Cl$_2$N$_3$O$_2$) dissolved:

\[
\text{Result} = \left( \frac{R_U}{R_S} \right) \times C_S \times V \times \left( \frac{1}{L} \right) \times 100
\]

\(R_U\) = peak response of aripiprazole from the Sample solution
\(R_S\) = peak response of aripiprazole from the Standard solution
\(C_S\) = concentration of USP Aripiprazole RS in the Standard solution (mg/mL)
\(V\) = volume of Medium, 900 mL
\(L\) = label claim (mg/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of aripiprazole (C$_{23}$H$_{27}$Cl$_2$N$_3$O$_2$) is dissolved.

\(\star\)Uniformity of Dosage Units (905): Meet the requirements

IMPURITIES

Change to read:

\(\star\)Organic Impurities
Protect solutions from light.
Buffer: 9.6 g/L of dibasic ammonium citrate, 1.6 g/L of citric acid, and 2.9 g/L of sodium dodecyl sulfate

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Aripiprazole

in water. Adjust with 11 g/L of dibasic ammonium citrate in water or 9.6 g/L of anhydrous citric acid in water to a pH of 4.7, if needed.

**Mobile phase:** Acetonitrile and Buffer (45:55)

**Diluent:** Acetonitrile, water, and glacial acetic acid (40:60:1)

**System suitability solution:** 0.5 mg/mL of USP Aripiprazole RS, and 0.0005 mg/mL each of USP Aripiprazole Related Compound F RS and USP Aripiprazole Related Compound G RS in Diluent

**Sample solution:** Nominally 0.5 mg/mL of aripiprazole from Tablets prepared as follows. Powder NLT 20 Tablets, transfer a suitable portion of the powder equivalent to NLT 4 mg of aripiprazole to an appropriate container, and add a suitable volume of Diluent. Shake for 10 min and centrifuge, if necessary. Pass the supernatant through a suitable filter of NMT 0.5-μm pore size, discard the first 1 mL of filtrate, and use the subsequent filtrate.

**Chromatographic system**

(See Chromatography (621), System Suitability.)

- **Mode:** LC
- **Detector:** UV 254 nm
- **Column:** 4.6-mm × 15-cm; 5-μm packing L1
- **Flow rate:** 1 mL/min
- **Injection volume:** 20 μL
- **Run time:** NLT 2 times the retention time of aripiprazole

**System suitability**

- **Sample:** System suitability solution
- **Suitability requirements**
  - **Resolution:** NLT 3 between aripiprazole related compound G and aripiprazole
  - **Signal-to-noise ratio:** NLT 10 for aripiprazole related compound G and aripiprazole related compound F

**Analysis**

- **Sample:** Sample solution

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

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

\(r_0\) is the peak response of each degradation product from the Sample solution.

**Acceptance criteria:** See Table 1. Disregard peaks that are less than 0.1% of the aripiprazole peak.

**Table 1**

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole related compound F</td>
<td>0.54</td>
<td>( \bullet 0.3 ) (RB 1-Jun-2016)</td>
</tr>
<tr>
<td>Aripiprazole related compound G</td>
<td>0.81</td>
<td>( \bullet 0.3 ) (RB 1-Jun-2016)</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>1.0</td>
<td>( \bullet )</td>
</tr>
<tr>
<td>Any individual unspecified degradation product</td>
<td>—</td>
<td>( \bullet 0.2 ) (RB 1-Jun-2016)</td>
</tr>
<tr>
<td>Total degradation products</td>
<td>—</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**ADDITIONAL REQUIREMENTS**

- **Packaging and Storage:** Preserve in tight containers. Store at controlled room temperature.

**Add the following:**

**Labeling:** The labeling states the Dissolution test used only if Test 1 is not used. (RB 1-Oct-2017)

- **USP Reference Standards**
  - USP Aripiprazole RS
  - USP Aripiprazole Related Compound F RS
  - USP Aripiprazole Related Compound G RS
  - USP Propylparaben RS

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