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 hrj@usp.org).

Aripiprazole Tablets

DEFINITION

Aripiprazole Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of aripiprazole ($C_{23}H_{27}Cl_2N_3O_2$).

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 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 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 suitable 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.]

  Analysis

  Samples: *Standard* and *Sample*

  Acceptance criteria: Meet the requirements
- **B.** The retention time of the aripiprazole peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

Change to read:

- **Procedure**

  Solution A: •2.8 g/L of anhydrous sodium sulfate• (RB 1-Jun-2016) 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
  Tailing factor: NMT 1.7 for aripiprazole and for 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 ($C_{23}H_{27}Cl_2N_3O_2$) in the portion of Tablets taken:

$$\text{Result} = (R_U/R_S) \times (C_S/C_U) \times 100$$

  R_U = 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⟩

  •**Test 1**• (RB 1-Oct-2017)

  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,• (RB 1-Jun-2016) 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

  Procedure: Determine the percentage of the labeled amount of aripiprazole ($C_{23}H_{27}Cl_2N_3O_2$) 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

  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 the first 5 mL of filtrate.

Instrumental conditions
Mode: UV
Analytical wavelengths: 249 and 325 nm
Cell length: 1 cm
Blank: *Medium*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of aripiprazole ($C_{23}H_{27}Cl_2N_3O_2$) dissolved:

$$\text{Result} = (A_U/A_S) \times C_S \times V \times (1/L) \times 100$$

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)

Chromatographic procedure
Solution A: •2.8 g/L of anhydrous sodium sulfate• (RB 1-Jun-2016)
Solution B: 13.9 g/L of glacial acetic acid and 23.9 g/L of •sodium acetate• (RB 1-Jun-2016) in water
Mobile phase: Acetonitrile, methanol, *Solution A*, and glacial acetic acid (40:10:50:1)
Diluent: *Solution B* and methanol (50:50)
Internal standard solution: •0.67 µg/mL• (RB 1-Jun-2016) of USP Propylparaben RS in *Diluent*
Standard stock solution A: 1 mg/mL of USP Aripiprazole RS in *Mobile phase*
Standard stock solution B: 0.002 mg/mL of USP Aripiprazole RS from *Standard stock solution A* in *Medium* passed through a suitable filter of NMT 0.5-µm pore size, discarding the first 6 mL of filtrate
Standard solution: 0.001 mg/mL of USP Aripiprazole RS from *Standard stock solution B* prepared by combining 5 mL of *Standard stock solution B* and 5 mL of *Internal standard solution*
Sample stock solution: Pass a portion of the solution under test through a suitable filter of NMT 0.5-µm pore size, discarding NLT the first 6 mL of filtrate.
Sample solution: Combine 2 mL of *Sample stock solution* with 2 mL of *Internal standard solution.*
Chromatographic system: Proceed as directed in the *Assay* except as follows.
Injection volume: 100 µL
•• (RB 1-Oct-2017)
System suitability
Sample: *Standard solution*
[NOTE—The relative retention times for aripiprazole and propylparaben are about 1.0 and 1.8, respectively.]
Suitability requirements
Resolution: NLT 10 between aripiprazole and propylparaben
Relative standard deviation: NMT 1.5% 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 ($C_{23}H_{27}Cl_2N_3O_2$) dissolved:

$$\text{Result} = (R_U/R_S) \times C_S \times V \times (1/L) \times 100$$

R_U = 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)
V = volume of *Medium*, 900 mL
L = label claim (mg/Tablet)
Tolerances: NLT 75% (Q) of the labeled amount of aripiprazole ($C_{23}H_{27}Cl_2N_3O_2$) is dissolved.
•**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°
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 ($C_{23}H_{27}Cl_2N_3O_2$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/L) \times 100$$

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 ($C_{23}H_{27}Cl_2N_3O_2$) is dissolved.• (RB 1-Oct-2017)

• **UNIFORMITY OF DOSAGE UNITS ⟨905⟩:** Meet the requirements

IMPURITIES

Change to read:

• **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• (RB

1-Jun-2016) in water. Adjust with •11 g/L of dibasic ammonium citrate in water• (RB 1-Jun-2016) or •9.6 g/L of anhydrous citric acid in water• (RB 1-Jun-2016) 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*
[NOTE—See *Table 1* for the relative retention times.]
Suitability requirements
Resolution: NLT 3 between aripiprazole related compound G and aripiprazole
Signal-to-noise ratio: NLT 10 for aripiprazole related compound F and aripiprazole related compound G

Analysis
Sample: *Sample solution*
Calculate the percentage of each degradation product in the portion of Tablets taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response of each degradation product from the *Sample solution*

r_T = sum of all the peak responses from the *Sample solution*

Acceptance criteria: See *Table 1*. •Disregard peaks that are less than 0.1% of the aripiprazole peak.• (RB 1-Jun-2016)

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Aripiprazole related compound F	0.54	•0.3• (RB 1-Jun-2016)
Aripiprazole related compound G	0.81	•0.3• (RB 1-Jun-2016)
Aripiprazole	1.0	—
Any individual unspecified degradation product	—	•0.2• (RB 1-Jun-2016)
Total degradation products	—	1.0

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** ⟨11⟩
  USP Aripiprazole RS
  USP Aripiprazole Related Compound F RS
  4-(2,3-Dichlorophenyl)-1-[4-(2-oxo-1,2,3,4-tetrahydroquinolin-7-yloxy)butyl]piperazine 1-oxide.
  $C_{23}H_{27}Cl_2N_3O_3$ 464.38
  USP Aripiprazole Related Compound G RS
  7-{4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butoxy}quinolin-2(1*H*)-one.
  $C_{23}H_{25}Cl_2N_3O_2$ 446.37
  USP Propylparaben RS