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 monograph. The purpose for the revision is to revise the acceptance criteria within the test for *Organic Impurities* to accommodate recently approved drug products and clarify the form of sodium sulfate needed in the *Assay*.

- Correct the reference from sodium sulfate to anhydrous sodium sulfate in *Solution A* within the *Assay* and test for *Dissolution*.
- Revise the concentration of the *Internal standard solution* within the test for *Dissolution* from 0.35 µg/mL to from 0.67 µg/mL so that the peak sizes of the internal standard and aripiprazole in the *Sample solution* and *Standard solution* chromatograms will be similar.
- Add a statement indicating that peaks with area less than 0.1% of the aripiprazole peak may be disregarded in the test for *Organic Impurities*.
- Widen the acceptance criteria for aripiprazole related compound F from NMT 0.20% to NMT 0.3% in Table 1.
- Widen the acceptance criteria for aripiprazole related compound G from NMT 0.20% to NMT 0.3% in Table 1.
- Widen the acceptance criteria for any individual unspecified degradation product from NMT 0.10% to NMT 0.2% in Table 1.

Additionally, minor editorial changes have been made to update the monograph to current *USP* style.

The Aripiprazole Tablets Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in *USP 40–NF 35*.

Should you have any questions, please contact Heather Joyce, Ph.D. (301–998–6792 or hrj@usp.org).

Add the following:

▲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⟩
  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
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 1.8, 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.

• **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.

- **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
  ▲*USP39*