Ziprasidone Capsules

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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 Ziprasidone capsules monograph. The purpose for the revision is to add *Dissolution Test* 2 to accommodate the FDA approved specifications for the sponsor product. The labeling information is also incorporated to support the inclusion of *Dissolution Test 2.*

- *Dissolution Test* 2 was validated using Zorbax Eclipse XDB-C18 brand of L1 column. The typical retention time for Ziprasidone is about 3.4 min.

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

The Ziprasidone Capsules Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in the *Second Supplement* to *USP 41–NF 36*.

Should you have any questions, please contact Sridevi Ramachandran, PhD., Associate Scientific Liaison (sdr@usp.org).

Ziprasidone Capsules

DEFINITION

Ziprasidone Capsules contain an amount of ziprasidone hydrochloride equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of ziprasidone ($C_{21}H_{21}ClN_4OS$).

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: 0.3% (v/v) of triethylamine in water

Mobile phase: Acetonitrile and *Buffer* (35:65). Adjust with glacial acetic acid to a pH of 6.0.

Diluent: Acetonitrile, water, and glacial acetic acid (70:30:5)

Standard stock solution: 1.0 mg/mL of USP Ziprasidone Hydrochloride RS in *Diluent*

Standard solution: 0.2 mg/mL of USP Ziprasidone Hydrochloride RS from the *Standard stock solution* in *Mobile phase*

Sample stock solution: Nominally 1 mg/mL of ziprasidone prepared as follows. Empty the contents of NLT 20 Capsules into a container. Blend the contents. Transfer an amount of the contents, equivalent to NLT 50 mg of ziprasidone, to a suitable volumetric flask. Dissolve the contents in 60% of the flask volume of *Diluent*. Sonicate for NLT 5 min. Dilute with *Diluent* to volume. Pass a portion of the solution through a suitable filter of 0.45-µm pore size and use the filtrate to prepare the *Sample solution*.

Sample solution: Nominally 0.2 mg/mL of ziprasidone prepared from the filtered *Sample stock solution* and *Mobile phase*

Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 254 nm. For *Identification B*, a diode array detector may be used in the wavelength range of 200–300 nm.
Column: 4.6-mm × 15-cm; 5-µm packing L1
Flow rate: 2.0 mL/min
Injection volume: 20 µL
Run time: 1.5 times the retention time of ziprasidone

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 ziprasidone ($C_{21}H_{21}ClN_4OS$) in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of ziprasidone from the *Sample solution*
r_S = peak response of ziprasidone from the *Standard solution*
C_S = concentration of USP Ziprasidone Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of ziprasidone in the *Sample solution* (mg/mL)
M_{r1} = molecular weight of ziprasidone free base, 412.94
M_{r2} = molecular weight of ziprasidone hydrochloride; 467.41 for the monohydrate, 449.40 for the anhydrous form

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION** ⟨711⟩

•Test 1• (RB 1-Nov-2017)

Tier 1

Phosphate buffer, pH 7.5: Dissolve 7.8 g of monobasic sodium phosphate dihydrate and 20 g of sodium dodecyl sulfate in 1 L water. Sonicate to dissolve and adjust with phosphoric acid or sodium hydroxide to a pH of 7.5.

Medium: *Phosphate buffer, pH 7.5*; 900 mL
Apparatus 2: 75 rpm. Use a suitable sinker, if necessary.
Time: 45 min
Buffer: 0.3% (v/v) of triethylamine in water. Adjust with glacial acetic acid to a pH of 6.0.
Mobile phase: Acetonitrile and *Buffer* (45:55)
Diluent: Acetonitrile, water, and glacial acetic acid (70:30:5)
Standard stock solution: 0.24 mg/mL of USP Ziprasidone Hydrochloride RS prepared as follows. Dissolve a suitable amount of USP Ziprasidone Hydrochloride RS in a suitable volumetric flask first in 60% of the flask volume of *Diluent*, and then dilute with *Diluent* to volume.
Standard solution: 0.024 mg/mL of USP Ziprasidone Hydrochloride RS in *Medium* from the *Standard stock solution*
Sample solution: Pass a portion of the solution through a suitable filter of 0.45-µm pore size. Dilute with *Medium* to a concentration similar to that of the *Standard solution*.
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: 1.5 mL/min
Injection volume: 10 µL
Run time: 1.5 times the retention time of ziprasidone
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 1.5
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of ziprasidone ($C_{21}H_{21}ClN_4OS$) dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times V \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of ziprasidone from the *Sample solution*
r_S = peak response of ziprasidone from the *Standard solution*
C_S = concentration of USP Ziprasidone Hydrochloride RS in the *Standard solution* (mg/mL)

L = label claim (mg/Capsule)
V = volume of *Medium*, 900 mL
M_{r1} = molecular weight of ziprasidone free base, 412.94
M_{r2} = molecular weight of ziprasidone hydrochloride; 467.41 for the monohydrate, 449.40 for the anhydrous form

Tolerances: NLT 75% (Q) of the labeled amount of ziprasidone ($C_{21}H_{21}ClN_4OS$) is dissolved.

If the above tolerance cannot be met, proceed to *Tier 2*.

Tier 2

Solution A: Dissolve 7.8 g of monobasic sodium phosphate dihydrate in 1 L of water. Sonicate to dissolve and adjust with phosphoric acid or sodium hydroxide to a pH of 7.5. Dissolve 10 g of pancreatin in the resulting solution.

Solution B: Dissolve 7.8 g of monobasic sodium phosphate dihydrate in 1 L of water. Adjust with phosphoric acid or sodium hydroxide to a pH of 7.5. Dissolve 90 g of sodium dodecyl sulfate in the resulting solution. Sonicate to dissolve.

Medium: Transfer 700 mL of *Solution A* to the dissolution vessel and equilibrate at 37° for 15 min. Add 200 mL of *Solution B*; 900 mL.

Apparatus 2: 75 rpm. Use a suitable sinker, if necessary.

Time: 45 min

Analyze the *Sample solution* using the liquid chromatographic procedure described in *Tier 1*.

Tolerances: NLT 75% (Q) of the labeled amount of ziprasidone ($C_{21}H_{21}ClN_4OS$) is dissolved.

• **Test 2:** If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 2*.

Tier 1

Medium: 2% sodium lauryl sulfate in pH 7.5 phosphate buffer (dissolve 6.9 g of monobasic sodium phosphate monohydrate and 1.6 g of sodium hydroxide in 900 mL of water, adjust with 1 N sodium hydroxide to a pH of 7.5 and dilute with water to 1000 mL); 900 mL

Apparatus 2: 75 rpm. Use a suitable sinker, if necessary.

Time: 60 min

Tier 2

Medium A: pH 7.5 phosphate buffer (dissolve 6.9 g of monobasic sodium phosphate monohydrate and 1.6 g of sodium hydroxide in 900 mL of water, adjust with 1 N sodium hydroxide to a pH of 7.5 and dilute with water to 1000 mL) with 1% pancreatin; 700 mL

Medium B: pH 7.5 phosphate buffer with 9% of sodium lauryl sulfate; 200 mL

Apparatus 2: 75 rpm. Use a suitable sinker, if necessary.

Time: 15 min for *Medium A*; 45 min for *Medium A* with the addition of *Medium B*

Solution A: Dissolve 2.7 g of monobasic sodium phosphate monohydrate in 1 L of water. Adjust with 1 N sodium hydroxide to a pH of 6.0.

Mobile phase: Acetonitrile and *Solution A* (50:50)

Diluent: Acetonitrile and water (50:50)

Standard stock solution: 0.48 mg/mL of USP Ziprasidone Hydrochloride RS in *Diluent*

Standard solution: (L/900) mg/mL of USP Ziprasidone Hydrochloride RS in *Medium* from *Standard stock solution*, where L is the label claim of ziprasidone in mg/Capsules

Sample solution: Pass a portion of the solution through a suitable filter of 0.45-µm pore size.

Procedure: Perform the test using the conditions in *Tier 1*. In the presence of cross-linking repeat the test with new Capsules using the conditions in *Tier 2* as follows. After 15 min with 700 mL of *Medium A*, stop the dissolution bath and timer and add 200 mL of *Medium B* pre-equilibrated at 37 ± 0.5°. Restart the bath and timer, and continue the dissolution for an additional 45 min.

Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 254 nm
Column: 3.9-mm × 15-cm; 5-µm packing L1
Column temperature: 40°
Flow rate: 1.5 mL/min
Injection volume: 20 µL
Run time: 1.8 times the retention time of ziprasidone

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 ziprasidone ($C_{21}H_{21}ClN_4OS$) dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times V \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of ziprasidone from the *Sample solution*
r_S = peak response of ziprasidone from the *Standard solution*
C_S = concentration of USP Ziprasidone Hydrochloride RS in the *Standard solution* (mg/mL)
L = label claim (mg/Capsule)
V = volume of *Medium*, 900 mL
M_{r1} = molecular weight of ziprasidone, 412.94
M_{r2} = molecular weight of ziprasidone hydrochloride; 467.41 for the monohydrate form, 449.40 for the anhydrous form

Tolerances: NLT 75% (Q) of the labeled amount of ziprasidone ($C_{21}H_{21}ClN_4OS$) is dissolved. • (RB 1-Nov-2017)

• **Uniformity of Dosage Units ⟨905⟩:** Meet the requirements

IMPURITIES

• **Organic Impurities**

Buffer: 0.05 M monobasic potassium phosphate

Solution A: Methanol and *Buffer* (33:67). Adjust with phosphoric acid to a pH of 3.0.

Solution B: Acetonitrile, methanol, and *Buffer* (55:5:40). Adjust with potassium hydroxide to a pH of 6.0.

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
15	100	0
20	85	15
30	85	15
40	55	45
55	40	60
65	25	75
70	20	80

Table 1 *(Continued)*

Time (min)	Solution A (%)	Solution B (%)
71	100	0
75	100	0

Diluent: Acetonitrile, methanol, and water (40:10:50). Adjust with phosphoric acid to a pH of 2.5.
System suitability solution: 0.5 mg/mL of USP Ziprasidone Hydrochloride RS and 0.05 mg/mL each of USP Ziprasidone Related Compound B RS and USP Ziprasidone Related Compound F RS in *Diluent*
Standard solution: 0.002 mg/mL each of USP Ziprasidone Hydrochloride RS and USP Ziprasidone Related Compound B RS in *Diluent*. Sonication may be used to aid in dissolution.
Sample solution: Nominally 1.0 mg/mL of ziprasidone in *Diluent* from a portion of contents of Capsules (NLT 20) prepared as follows. Transfer a suitable amount of Capsule contents to a suitable volumetric flask. Add 60% of the flask volume of *Diluent*. Sonicate for 10 min. Dilute with *Diluent* to volume. Pass through a suitable filter of 0.45-µm pore size.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 229 nm
Column: 4.6-mm × 15-cm; 5-µm packing L7
Column temperature: 30°
Flow rate: 1.5 mL/min
Injection volume: 10 µL
System suitability
Samples: *System suitability solution* and *Standard solution*
Suitability requirements
Resolution: NLT 2.0 between ziprasidone related compound B and related compound F; NLT 2.0 between ziprasidone related compound F and ziprasidone, *System suitability solution*
Tailing factor: NMT 1.5 for ziprasidone, *Standard solution*
Relative standard deviation: NMT 5.0% for both ziprasidone and ziprasidone related compound B, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of ziprasidone related compound B in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of ziprasidone related compound B from the *Sample solution*
r_S = peak response of ziprasidone related compound B from the *Standard solution*
C_S = concentration of USP Ziprasidone Related Compound B RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of ziprasidone in the *Sample solution* (mg/mL)

Calculate the percentage of any other unspecified degradation product in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of each unspecified degradation product from the *Sample solution*
r_S = peak response of ziprasidone from the *Standard solution*
C_S = concentration of USP Ziprasidone Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of ziprasidone in the *Sample solution* (mg/mL)
M_{r1} = molecular weight of ziprasidone free base, 412.94
M_{r2} = molecular weight of ziprasidone hydrochloride; 467.41 for the monohydrate, 449.40 for the anhydrous form

Acceptance criteria: See *Table 2*. Disregard any peak with an area below 0.05% in the *Sample solution*.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Ziprasidone related compound A[a,b]	0.22	—
Chloroindolinone[a,c]	0.59	—
Ziprasidone related compound B	0.70	0.20
Ziprasidone related compound F[a]	0.84	—
Ziprasidone	1.0	—
Ziprasidone related compound C[a,d]	1.84	—
Ziprasidone related compound D[a,e]	2.18	—
Any individual unspecified degradation product	—	0.20
Total degradation products	—	0.50

[a] Process impurity included in the table for identification only; controlled in the drug substance. Process impurities are controlled in the drug substance and are not to be reported or included in the total impurities for the drug product.
[b] 3-(Piperazin-1-yl)benzo[*d*]isothiazole.
[c] 6-Chloroindolin-2-one.
[d] 5,5′-Bis{2-[4-(benzo[*d*]isothiazol-3-yl)piperazin-1-yl]ethyl}-6,6′-dichloro-3-hydroxy-3,3′-biindoline-2,2′-dione.
[e] 3-(Benzo[*d*]isothiazol-3-yl)-5-{2-[4-(benzo[*d*]isothiazol-3-yl)piperazin-1-yl]ethyl}-6-chloroindolin-2-one.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers, and store at controlled room temperature.

Add the following:

- **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-Nov-2017)
- **USP REFERENCE STANDARDS** ⟨11⟩
  USP Ziprasidone Hydrochloride RS
  USP Ziprasidone Related Compound B RS
  5-{2-[4-(Benzo[*d*]isothiazol-3-yl)piperazin-1-yl]ethyl}-6-chloroindoline-2,3-dione.
  $C_{21}H_{19}ClN_4O_2S$ 426.92
  USP Ziprasidone Related Compound F RS
  2-(2-Amino-5-{2-[4-(benzo[*d*]isothiazol-3-yl)piperazin-1-yl]ethyl}-4-chlorophenyl)acetic acid.
  $C_{21}H_{23}ClN_4O_2S$ 430.95