Ziprasidone Capsules

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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 update the specification limits in the *Organic Impurities* test to accommodate FDA-approved drug products. The details are as follows:

- Incorporation of ziprasidone sulfoxide analog at NMT 0.5% with a relative retention time of 0.11. Add the relative response factor to *Table 3*.
- Revision of any individual unspecified degradation products from NMT 0.20% to NMT 0.2%.
- Revision of the total degradation products from NMT 0.50% to NMT 0.8%.
- Revision to update the calculation to accommodate the ziprasidone sulfoxide analog.
- Addition of alternate chemical names for ziprasidone related compound A, ziprasidone related compound C, and ziprasidone related compound D as footnotes for *Table 3*.
- Addition of an alternate chemical name for USP Ziprasidone Related Compound B RS and a revision to USP Ziprasidone Related Compound F RS in the *USP Reference Standards* section.

The Ziprasidone Capsules Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Pavani Jagu, Associate Scientific Liaison (+91 40 44488968 or pavani.jagu@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

- **DISSOLUTION** ⟨711⟩

Test 1

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.

Test 3: If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 3*.

Tier 1

Medium: 2% sodium lauryl sulfate in pH 7.5 phosphate buffer (6.9 g/L of monobasic sodium phosphate pH adjusted with 5 N sodium hydroxide); 900 mL
Apparatus 2: 75 rpm. Use a suitable sinker.
Time: 60 min

Tier 2

Medium A: pH 7.5 phosphate buffer (6.9 g/L of monobasic sodium phosphate pH adjusted with 5 N sodium hydroxide) with 1% pancreatin; 700 mL
Medium B: pH 7.5 phosphate buffer (6.9 g/L of monobasic sodium phosphate pH adjusted with 5 N sodium hydroxide) with 9% sodium lauryl sulfate; 200 mL
Apparatus 2: 75 rpm. Use a suitable sinker.
Time: 15 min for *Medium A*; 45 min for *Medium A* with the addition of *Medium B*
Buffer: 6.8 g/L g of monobasic potassium phosphate. To each liter of this solution, add 1 mL of triethylamine and adjust with phosphoric acid to a pH of 3.0.
Mobile phase: Acetonitrile and *Buffer* (30:70)
Diluent
Diluent 1: Acetonitrile and methanol (35:65)

Diluent 2
Tier 1: *Medium*
Tier 2: *Medium A* and *Medium B* (70:20)
Standard stock solution 1: 0.5 mg/mL of USP Ziprasidone Hydrochloride RS in *Diluent 1*
Standard stock solution 2: Prepare solutions of USP Ziprasidone Hydrochloride RS in *Diluent 2* at concentrations given in *Table 1* as follows. Transfer a suitable volume of *Standard stock solution* into a suitable volumetric flask and dilute with *Diluent 2* to volume.

Table 1

Strength of Ziprasidone Capsules (mg)	Concentration of Ziprasidone (mg/mL)
20	0.025
40	0.050
60	0.080
80	0.100

Standard solution: Transfer 5 mL of *Standard stock solution 2* to a 25-mL volumetric flask and dilute with *Mobile phase* to volume.
Sample solution: Centrifuge a portion of the solution under test. Dilute the supernatant with *Mobile phase* to volume to obtain nominal concentration of ziprasidone similar to that of the *Standard solution*. Pass through a suitable filter of 0.45-µm pore size. [NOTE—A centrifuge speed of 4000 rpm for 10 min may be suitable.]
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 230 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Flow rate: 1.3 mL/min
Injection volume: 10 µL
Run time: 1.3 times the retention time of ziprasidone
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 1.5%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of ziprasidone ($C_{21}H_{21}ClN_4OS$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times D \times (1/L) \times (M_{r1}/M_{r2}) \times 100$$

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)
V = volume of *Medium* (*Tier 1* or *Tier 2*), 900 mL
D = dilution factor for the *Sample solution*, 5
L = label claim (mg/Capsule)
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 70% (Q) of the labeled amount of ziprasidone ($C_{21}H_{21}ClN_4OS$) is dissolved.
• **UNIFORMITY OF DOSAGE UNITS** ⟨905⟩**:** Meet the requirements

IMPURITIES

Change to read:

• **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 2*.

Table 2

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
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 ▲ziprasidone sulfoxide analog or any individual▲ (RB 1-Oct-2019) unspecified degradation product in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times \text{▲}(1/F)\text{▲ (RB 1-Oct-2019)} \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of ▲ziprasidone sulfoxide analog or▲ (RB 1-Oct-2019) 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)

▲F = relative response factor▲ (RB 1-Oct-2019)

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 3*. Disregard any peak with an area below 0.05% in the *Sample solution*.

Table 3

Name	Relative Retention Time	▲Relative Response Factor▲ (RB 1-Oct-2019)	Acceptance Criteria, NMT (%)
▲Ziprasidone sulfoxide analog (if present)[a]	0.11	0.49	0.5▲ (RB 1-Oct-2019)
Ziprasidone related compound A[b, c]	0.22	▲—▲ (RB 1-Oct-2019)	—
Chloroindolinone[b, d]	0.59	▲—▲ (RB 1-Oct-2019)	—
Ziprasidone related compound B	0.70	▲—▲ (RB 1-Oct-2019)	0.20
Ziprasidone related compound F[b]	0.84	▲—▲ (RB 1-Oct-2019)	—
Ziprasidone	1.0	▲—▲ (RB 1-Oct-2019)	—
Ziprasidone related compound C[b, e]	1.84	▲—▲ (RB 1-Oct-2019)	—
Ziprasidone related compound D[b, f]	2.18	▲—▲ (RB 1-Oct-2019)	—
Any individual unspecified degradation product	—	▲1.0	0.2▲ (RB 1-Oct-2019)
Total degradation products	—	▲—	0.8▲ (RB 1-Oct-2019)

[a] 6-Chloro-5-{2-[4-(1-oxidobenzisothiazol-3-yl)piperazin-1-yl]ethyl}indolin-2-one.

[b] 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.

[c] 3-(Piperazin-1-yl)benzo[*d*]isothiazole; ▲also known as 3-(Piperazin-1-yl) benzisothiazole monohydrochloride.▲ (RB 1-Oct-2019)

[d] 6-Chloroindolin-2-one.

[e] 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; ▲also known as 5,5′-Bis{2-[4-(benzisothiazol-3-yl)piperazin-1-yl]ethyl}-6,6′-dichloro-3-hydroxy-3,3′-biindoline-2,2′-dione.▲ (RB 1-Oct-2019)

[f] 3-(Benzo[*d*]isothiazol-3-yl)-5-{2-[4-(benzo[*d*]isothiazol-3-yl)piperazin-1-yl] ethyl}-6-chloroindolin-2-one; ▲also known as 3-(Benzisothiazol-3-yl)-5-{2-[4-(benzisothiazol-3-yl)piperazin-1-yl]ethyl}-6-chloroindolin-2-one.▲ (RB 1-Oct-2019)

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers, and store at controlled room temperature.
- **LABELING:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.

Change to read:

- **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; ▲also known as 5-{2-[4-(Benzisothiazol-3-yl)piperazin-1-yl]ethyl}-6-chloroindoline-2,3-dione.▲ (RB 1-Oct-2019)

$C_{21}H_{19}ClN_4O_2S$ 426.92

USP Ziprasidone Related Compound F RS

▲Sodium 2-(2-amino-5-{2-[4-(benzo[d]isothiazol-3-yl) piperazin-1-yl]ethyl}-4-chlorophenyl)acetate monohydrate; also known as Sodium 2-(2-amino-5-{2-[4-(benzisothiazol-3-yl)piperazin-1-yl]ethyl}-4-chlorophenyl)acetate monohydrate

$C_{21}H_{22}ClN_4NaO_2S.\ H_2O$ 470.95▲ (RB 1-Oct-2019)