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 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 4448968 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 (C₁₁₀H₁₁₂ClN₄O₂S).

**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 (C₁₁₀H₁₁₂ClN₄O₂S) in the portion of Capsules taken:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times \left( \frac{M_{r1}}{M_{r2}} \right) \times 100
\]

\[r_U = \text{peak response of ziprasidone from the Sample solution}
\]

\[r_S = \text{peak response of ziprasidone from the Standard solution}
\]

**Performance 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:** 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 Buffer, and then dilute with Buffer 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 (C₁₁₀H₁₁₂ClN₄O₂S) dissolved:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times V \times \left( \frac{M_{r1}}{M_{r2}} \right) \times 100
\]

\[r_U = \text{peak response of ziprasidone from the Sample solution}
\]

\[r_S = \text{peak response of ziprasidone from the Standard solution}
\]

\[C_S = \text{concentration of USP Ziprasidone Hydrochloride RS in the Standard solution (mg/mL)}
\]

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*K* = label claim (mg/Capsule)

\[ V = \text{volume of Medium}, \ 900 \text{ mL} \]

\[ M_1 = \text{molecular weight of ziprasidone free base}, \ 412.94 \]

\[ M_2 = \text{molecular weight of ziprasidone hydrochloride}, \ 467.41 \]

\[ L = \text{volume of Medium}, \ 900 \text{ mL} \]

**Tolerances:** NLT 75% (Q) of the labeled amount of ziprasidone (C\(_{21}H_{25}ClN_5OS\)) is dissolved.

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

**Test 2:** If the product complies with this test, the labeling indicates that the product meets USP Dissolution Test 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\(_{21}H_{25}ClN_5OS\)) 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); 900 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 R5 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 x 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\(_{21}H_{25}ClN_5OS\)) dissolved:

\[
\text{Result} = \left( \frac{r_1}{C_{\text{ClN}}/L} \right) \times \left( \frac{V}{M_1/M_2} \right) \times 100
\]

\[ r_1 = \text{peak response of ziprasidone from the Standard solution} \]

**Tolerances:** NLT 75% (Q) of the labeled amount of ziprasidone (C\(_{21}H_{25}ClN_5OS\)) 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

**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 R5 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

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**Table 1**

<table>
<thead>
<tr>
<th>Strength of Ziprasidone Capsules (mg)</th>
<th>Concentration of Ziprasidone (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>0.025</td>
</tr>
<tr>
<td>40</td>
<td>0.050</td>
</tr>
<tr>
<td>60</td>
<td>0.080</td>
</tr>
<tr>
<td>80</td>
<td>0.100</td>
</tr>
</tbody>
</table>

**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*

**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 (C₂₁H₂₅ClN₄OS) dissolved:

\[
\text{Result} = \left( \frac{r_s}{r_U} \right) \times C_s \times V \times D \times \left(1/L\right) \times (M_{r1}/M_{r2}) \times 100
\]

- \( r_U \) = 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 (C₂₁H₂₅ClN₄OS) 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**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>85</td>
<td>15</td>
</tr>
<tr>
<td>30</td>
<td>85</td>
<td>15</td>
</tr>
<tr>
<td>40</td>
<td>55</td>
<td>45</td>
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<tr>
<td>55</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>65</td>
<td>25</td>
<td>75</td>
</tr>
<tr>
<td>70</td>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>71</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>75</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

**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
- **Flow rate**: 1.5 mL/min
- **Injection volume**: 10 µL

**System suitability**

*Samples*: System suitability solution and *Standard solution*
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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:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times \left( \frac{1}{r} \right) \times 100
\]

- \( r_U \) = 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)
- \( r \) = relative response factor from the *Standard solution*

Calculate the percentage of a ziprasidone sulf oxide analog or any individual unspecified degradation product in the portion of Capsules taken:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times \left( \frac{1}{r} \right) \times 100
\]

- \( r_U \) = peak response of a ziprasidone sulf oxide analog or any individual unspecified degradation product from the *Sample solution*

**Acceptance criteria**: See Table 3. Disregard any peak with an area below 0.05% in the *Sample solution*.

### Table 3 (continued)

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th><em>Relative Response Factor</em></th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ziprasidone sulfoxide analog (if present)</td>
<td>0.11</td>
<td>0.49</td>
<td>0.5</td>
</tr>
<tr>
<td>Ziprasidone related compound A</td>
<td>0.22</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**ADDITONAL 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
  - USP Ziprasidone Related Compound F RS

- **Additional notes**

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