Zolmitriptan Orally Disintegrating 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 Zolmitriptan Orally Disintegrating Tablets monograph. The purpose for the revision is to add Dissolution Test 2 to accommodate FDA-approved drug products with different dissolution conditions and/or tolerances than the existing dissolution test. A Labeling section has also been added.

- Dissolution Test 2 was validated using an Alltima C18 brand of L1 column. The typical retention time for zolmitriptan is about 4.4 min.

The Zolmitriptan Orally Disintegrating Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Nicholas Garito Jr., Scientific Liaison (301-816-8321 or njg@usp.org).
Zolmitriptan Orally Disintegrating Tablets

**Definition**
Zolmitriptan Orally Disintegrating Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of zolmitriptan (C_16H_21N_3O_2).

**Identification**
- A. The UV spectrum of the zolmitriptan peak of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay.
- B. The retention time of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay.

**Assay**

**Procedure**
Buffer: Dissolve 2 mL of triethylamine in 1 L of water. Adjust with phosphoric acid to a pH of 3.0.
Mobile phase: Acetonitrile and Buffer (15:85)
Standard stock solution: 0.25 mg/mL of USP Zolmitriptan RS in methanol
Standard solution: 0.025 mg/mL of USP Zolmitriptan RS in methanol
Sample stock solution: 0.025 mg/mL of zolmitriptan in methanol, prepared as follows. Transfer NLT 20 Tablets to a suitable volumetric flask. Add 75% of the flask volume of methanol. Sonicate for 30 min. Allow to cool to room temperature and dilute with methanol to volume.
Sample solution: Nominally 0.025 mg/mL of zolmitriptan in Mobile phase from a suitable volume of Standard stock solution.

**Chromatographic system**
Mode: LC
Detector: UV 225 nm. For Identification test A, use a diode-array detector in the wavelength range of 200–300 nm.
Column: 4.6-mm × 15-cm; 5-μm packing L1
Column temperature: 30°C
Flow rate: 1 mL/min
Injection volume: 20 μL
Run time: NLT 2.5 times the retention time of zolmitriptan

**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 zolmitriptan (C_16H_21N_3O_2) dissolved:

\[
\text{Result} = \left( \frac{r_v}{r_s} \times \frac{C_s}{C_v} \right) \times 100
\]

\( r_v \): peak response of zolmitriptan from the Sample solution
\( r_s \): peak response of zolmitriptan from the Standard solution
\( C_s \): concentration of USP Zolmitriptan RS in the Standard solution (mg/mL)
\( C_v \): nominal concentration of zolmitriptan in the Sample solution (mg/mL)

**Acceptance criteria:** 90.0%–110.0%

**Performance tests**

**Disintegration** (701): NMT 30 s

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**Change to read:**

- **Dissolution** (711)

  **Test 1 (85):**
  - Medium: 0.1 N hydrochloric acid; 500 mL
  - Apparatus 2: 50 rpm
  - Time: 15 min
  - Analyze the sample under test using either the Chromatographic procedure or the Spectroscopic procedure.

  **Chromatographic procedure**
  Buffer, Mobile phase, Standard stock solution, Chromatographic system, and System suitability: Proceed as directed in the Assay.
  Standard solution: 0.005 mg/mL of USP Zolmitriptan RS in Medium
  Sample solution: Pass a portion of the solution under test through a suitable membrane filter of 0.45-μm pore size.

  **Analysis**
  Samples: Standard solution and Sample solution
  Calculate the percentage of the labeled amount of zolmitriptan (C_16H_21N_3O_2) dissolved:

  \[
  \text{Result} = \left( \frac{A_v}{A_s} \times \frac{C_v}{C_s} \right) \times 100
  \]

  \( A_v \): absorbance of the Sample solution
  \( A_s \): absorbance of the Standard solution
  \( C_v \): concentration of USP Zolmitriptan RS in the Standard solution (mg/mL)
  \( V \): volume of Medium, 500 mL
  \( L \): label claim of zolmitriptan (mg/Tablet)

  **Tolerances:** NLT 80% (Q) of the labeled amount of zolmitriptan (C_16H_21N_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; 500 mL
  - Apparatus 2: 50 rpm
  - Time: 15 min
  - Buffer: Add 7.8 g of monobasic sodium phosphate to 1000 mL of water. Adjust with phosphoric acid to a pH of 2.5.
  - Mobile phase: Acetonitrile and Buffer (15:85)
  - Standard stock solution: 0.33 mg/mL of USP Zolmitriptan RS prepared as follows. Transfer a suitable quantity of USP
Zolmitriptan RS to an appropriate volumetric flask and add 70% of the flask volume of Medium. Sonicate to aid dissolution. Dilute with Medium to volume.

**Sample solution:** Pass a portion of the solution under test through a suitable filter.

**Chromatographic system**
(See Chromatography (621), System Suitability.)

Mode: LC
Solution A: 2.7 g/L of monobasic potassium phosphate in Methanol and water (25:75)
Solution B: Acetonitrile

**Mobile phase:**

**Detector:** UV 225 nm
**Column:** 4.6-mm × 15-cm; 3-μm packing
**Temperatures:** Autosampler: 5°
**Flow rate:** 1 mL/min
**Injection volume:** 10 μL
**Run time:** NLT 2 times the retention time of zolmitriptan

**System suitability**

Sample: Standard solution
Suitability requirements:
- **Tailing factor:** NMT 2.0
- **Relative standard deviation:** NMT 2.0%
- **Resolution:** NLT 5.0 between zolmitriptan and any other unspecified degradation products:
- **Relative standard deviation:** NMT 5.0%, Standard solution
- **Relative standard deviation:** NMT 5.0%, Standard solution

**Analysis**

Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of zolmitriptan (C₂₃H₂₆N₅O₂) dissolved:

\[
\text{Result} = \left( \frac{r_s}{r_f} \right) \times \frac{C_s}{L} \times \frac{V}{1/L} \times 100
\]

- \(r_s\) = peak response of zolmitriptan from the Sample solution
- \(r_f\) = peak response of zolmitriptan from the Standard solution
- \(C_s\) = concentration of USP Zolmitriptan RS in the Standard solution (mg/mL)
- \(V\) = volume of Medium, 500 mL
- \(L\) = label claim of zolmitriptan (mg/Tablet)

Tolerances: NLT 75% (Q) of the labeled amount of zolmitriptan (C₂₃H₂₆N₅O₂) dissolved.

- **Uniformity of dosage units** (905): Meet the requirements

**Impurities**

- **Organic impurities**

  **Diluent:** Methanol and water (25:75)
  **Solution A:** 2.7 g/L of monobasic potassium phosphate in water
  **Solution B:** Acetonitrile
  **Mobile phase:** See Table 1.

**Table 1**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>95</td>
<td>5</td>
</tr>
<tr>
<td>15</td>
<td>92</td>
<td>8</td>
</tr>
<tr>
<td>45</td>
<td>86</td>
<td>14</td>
</tr>
<tr>
<td>55</td>
<td>55</td>
<td>45</td>
</tr>
<tr>
<td>60</td>
<td>55</td>
<td>45</td>
</tr>
<tr>
<td>62</td>
<td>95</td>
<td>5</td>
</tr>
<tr>
<td>75</td>
<td>95</td>
<td>5</td>
</tr>
</tbody>
</table>

**Impurities stock solution:** 0.2 mg/mL each of USP Zolmitriptan Related Compound E RS and USP Zolmitriptan Related Compound G RS in methanol

**System suitability solution:** 0.25 mg/mL of USP Zolmitriptan RS and 0.002 mg/mL each of USP Zolmitriptan Related Compound E RS and USP Zolmitriptan Related Compound G RS in Diluent prepared as follows. Dissolve a suitable quantity of USP Zolmitriptan RS in a suitable volumetric flask containing 50% of the flask volume of Diluent. Sonicate to dissolve. Transfer a suitable volume of Impurities stock solution to the flask. Dilute with Diluent to volume.

**Standard stock solution:** 0.25 mg/mL of USP Zolmitriptan RS in methanol
**Standard solution:** 0.001 mg/mL of USP Zolmitriptan RS from Standard stock solution in Diluent

**Sample solution:** Nominal 0.25 mg/mL of zolmitriptan from NLT 5 Tablets prepared as follows. Transfer the required number of Tablets to a suitable volumetric flask. Add 25% of the flask volume of methanol. Sonicate for 30 min with intermittent shaking. Cool to room temperature. Dilute with water to volume. Pass through a suitable filter of 0.45-μm pore size.

**Chromatographic system**
(See Chromatography (621), System Suitability.)

Mode: LC
Detector: UV 223 nm

For zolmitriptan and zolmitriptan related compound E and any other unspecified degradation products: UV 223 nm

For zolmitriptan and zolmitriptan related compound G: UV 235 nm

**Column:** 4.6-mm × 25-cm; 5-μm packing
**Column temperature:** 30°
**Flow rate:** 1.5 mL/min
**Injection volume:** 20 μL

**System suitability**

Samples: System suitability solution and Standard solution

[Note—See Table 2 for relative retention times.]

Suitability requirements: Use 223 nm for system suitability evaluation.

**Resolution:** NLT 5.0 between zolmitriptan and zolmitriptan related compound E, System suitability solution

Tailing factor: NMT 2.0 for zolmitriptan, Standard solution

Relative standard deviation: NMT 5.0%, Standard solution

**Analysis**

Samples: Standard solution and Sample solution
Calculate the percentage of zolmitriptan related compound G in the portion of Tablets taken:

\[
\text{Result} = \left( \frac{r_s}{r_f} \right) \times \frac{C_s}{C_u} \times \frac{F}{1/F} \times 100
\]

- \(r_s\) = peak response of zolmitriptan related compound G at 235 nm from the Sample solution
- \(r_f\) = peak response of zolmitriptan at 235 nm from the Standard solution
- \(C_s\) = concentration of USP Zolmitriptan RS in the Standard solution (mg/mL)
- \(C_u\) = nominal concentration of zolmitriptan in the Sample solution (mg/mL)
- \(F\) = relative response factor for zolmitriptan related compound G (see Table 2)

Calculate the percentage of zolmitriptan related compound E and any other unspecified degradation product in the portion of Tablets taken:
Result = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times \left( \frac{1}{F} \right) \times 100

- \( r_U \) = peak response of zolmitriptan related compound E or any other unspecified degradation product at 223 nm from the Sample solution
- \( r_S \) = peak response of zolmitriptan at 223 nm from the Standard solution
- \( C_S \) = concentration of USP Zolmitriptan RS in the Standard solution (mg/mL)
- \( C_U \) = nominal concentration of zolmitriptan in the Sample solution (mg/mL)
- \( F \) = relative response factor (see Table 2)

Acceptance criteria: See Table 2. Disregard any impurity less than 0.05%.

**Table 2**

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Relative Response Factor</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zolmitriptan related compound G</td>
<td>0.66</td>
<td>1.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Zolmitriptan related compound E</td>
<td>1.30</td>
<td>1.0</td>
<td>0.6</td>
</tr>
<tr>
<td>Any individual unspecified degradation product</td>
<td>—</td>
<td>1.0</td>
<td>0.2</td>
</tr>
</tbody>
</table>

**Table 2 (continued)**

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Relative Response Factor</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total degradation products</td>
<td>—</td>
<td>—</td>
<td>1.5</td>
</tr>
</tbody>
</table>

**ADDITIONAL REQUIREMENTS**

- **PACKAGING AND STORAGE:** Preserve in well-closed, light-resistant containers. 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. (BB 1-May-2020)
- **USP REFERENCE STANDARDS** (11)
  - USP Zolmitriptan RS
  - USP Zolmitriptan Related Compound E RS
    - (S)-N,N-Dimethyl-2-\{5-[(2-oxooxazolidin-4-yl)methyl]-1H-indol-3-yl\}ethanamine oxide.
    - C₁₆H₂₁N₃O₃ 303.36
  - USP Zolmitriptan Related Compound G RS
    - (S)-4-(4-Aminobenzyl)oxazolidin-2-one.
    - C₁₀H₁₂N₂O₂ 192.21