Zolmitriptan Orally Disintegrating Tablets

Type of Posting	Revision Bulletin
Posting Date	24–Apr–2020
Official Date	01–May–2020
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 ($C_{16}H_{21}N_3O_2$).

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 *Mobile phase* from a suitable volume of *Standard stock solution*
Sample stock solution: 0.25 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 *Sample stock solution.* Pass a portion of the solution under test through a suitable membrane filter of 0.45-µm pore size.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
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°
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 ($C_{16}H_{21}N_3O_2$) in the portion of Tablets taken:

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

r_U = peak response 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_U = nominal concentration of zolmitriptan in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

- **DISINTEGRATION** ⟨701⟩**:** NMT 30 s

Change to read:

- **DISSOLUTION** ⟨711⟩

▲**Test 1**▲ (RB 1-May-2020)
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*.▲ (RB 1-May-2020)
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 from *Standard stock solution* 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 ($C_{16}H_{21}N_3O_2$) dissolved:

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

r_U = 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)
V = volume of *Medium,* 500 mL
L = label claim of zolmitriptan (mg/Tablet)

▲**Spectroscopic procedure**▲ (RB 1-May-2020)
Standard solution: 0.01 mg/mL of USP Zolmitriptan RS from *Standard stock solution* in *Medium*
Sample solution: Pass a portion of the solution under test through a suitable membrane filter of 0.2-µm pore size.
Instrumental conditions
Mode: UV
Analytical wavelength: About 283 nm
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of zolmitriptan ($C_{16}H_{21}N_3O_2$) dissolved:

$$\text{Result} = (A_U/A_S) \times C_S \times V \times (1/L) \times 100$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of 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 80% (Q) of the labeled amount of zolmitriptan ($C_{16}H_{21}N_3O_2$) 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.

Standard solution: (*L*/500) mg/mL of zolmitriptan from *Standard stock solution* in *Medium*, where *L* is the label claim of zolmitriptan in mg/Tablet

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

Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 225 nm
Column: 4.6-mm × 15-cm; 3-µm packing L1
Temperatures:
Autosampler: 5°
Column: 30°
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%

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of zolmitriptan ($C_{16}H_{21}N_3O_2$) dissolved:

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

r_U = 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)
V = volume of *Medium,* 500 mL
L = label claim of zolmitriptan (mg/Tablet)

Tolerances: NLT 75% (*Q*) of the labeled amount of zolmitriptan ($C_{16}H_{21}N_3O_2$) is dissolved. ▲ (RB 1-May-2020)

• **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

Time (min)	Solution A (%)	Solution B (%)
0	95	5
15	92	8
45	86	14
55	55	45
60	55	45
62	95	5
75	95	5

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: Nominally 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
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 L1
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:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of zolmitriptan related compound G at 235 nm from the *Sample solution*
r_S = 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:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

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

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Zolmitriptan related compound G	0.66	1.2	0.2
Zolmitriptan	1.0	—	—
Zolmitriptan related compound E	1.30	1.0	0.6
Any individual unspecified degradation product	—	1.0	0.2
Total degradation products	—	—	1.5

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.▲ (RB 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]-1*H*-indol-3-yl}ethanamine oxide.
  $C_{16}H_{21}N_3O_3$ 303.36
  USP Zolmitriptan Related Compound G RS
  (*S*)-4-(4-Aminobenzyl)oxazolidin-2-one.
  $C_{10}H_{12}N_2O_2$ 192.21