

BRIEFING

Zolmitriptan. A new USP Pending monograph based on validated methods of analysis is proposed for this drug substance. The liquid chromatographic procedures in the *Assay* and the test for *Organic Impurities* are based on analyses performed with a Xterra RP18 brand of L1 column. The typical retention time for zolmitriptan is about 5.3 min for the *Assay* and about 14 min for the *Organic Impurities* test. The liquid chromatographic procedure in the test for *Limit of Zolmitriptan R-Isomer* is based on analysis performed with a Chiralpal AD-H brand of L51 column. The typical retention time for zolmitriptan is about 9 min.

Description and Solubility: White to off-white crystalline powder.

Soluble in methanol; sparingly soluble in dichloromethane; practically insoluble in toluene.

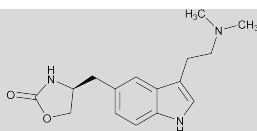
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Add the following:

►Zolmitriptan

Draft 1



C₁₆H₂₁N₃O₂ 287.36
2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (S)-;
(S)-4-[[3-[2-(Dimethylamino)ethyl]indol-5-yl]methyl]-2-oxazolidinone [139264-17-8].

DEFINITION

Zolmitriptan contains NLT 98.0% and NMT 102.0% of C₁₆H₂₁N₃O₂, calculated on the dried basis.

IDENTIFICATION

- A. INFRARED ABSORPTION** (197K)
- B.** The retention time of the major peak in the *Sample solution* corresponds to that of zolmitriptan (*S* enantiomer) peak in the *System suitability solution* in the test for *Limit of Zolmitriptan R-Isomer*.

ASSAY

• **PROCEDURE**

Buffer solution: 1.2 g/L of ammonium dihydrogen phosphate in water. Adjust with dilute ammonia solution to a pH of 9.8.

Mobile phase: Acetonitrile and *Buffer solution* (30:70)

Diluent: Acetonitrile and water (50:50)

Standard solution: 0.1 mg/mL of USP Zolmitriptan RS in *Diluent*. Sonicate to dissolve.

Sample solution: 0.1 mg/mL of Zolmitriptan in *Diluent*. Sonicate to dissolve.

Chromatographic system

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

Mode: LC

Detector: UV 225 nm

Column: 4.6-mm × 25-cm; 5-μm packing L1

Column temperature: 30 ± 5°

Flow rate: 1 mL/min

Injection size: 10 μL

Run time: 3 times the retention time of the zolmitriptan peak

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 zolmitriptan (C₁₆H₂₁N₃O₂) in the portion of sample taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Zolmitriptan RS in the *Standard solution* (mg/mL)

C_U = concentration of Zolmitriptan in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the dried basis

IMPURITIES

• **HEAVY METALS, Method I** (231): NMT 10 ppm

• **RESIDUE ON IGNITION** (281): NMT 0.1%

• **ORGANIC IMPURITIES**

Buffer solution, Diluent, and Chromatographic system: Proceed as directed in the *Assay*.

Solution A: Methanol, acetonitrile, and *Buffer solution* (20:10:70)

Solution B: Acetonitrile and *Buffer solution* (70:30)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
10	100	0
30	45	55
35	45	55
36	100	0

Standard solution: 0.5 mg/mL of USP Zolmitriptan RS and 0.75 μg/mL each of USP Zolmitriptan Related Compound A RS, USP Zolmitriptan Related Compound B RS, USP Zolmitriptan Related Compound C RS, and USP Zolmitriptan Related Compound D RS in *Diluent*. Sonicate to dissolve.

Sample solution: 0.5 mg/mL of Zolmitriptan in *Diluent*. Sonicate to dissolve.

System suitability

[NOTE—Refer to *Table 2* for relative retention times.]

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 4.0 between the zolmitriptan related compound B and zolmitriptan peaks

Relative standard deviation: NMT 2.0% for the zolmitriptan peak

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of zolmitriptan related compounds A, B, C, D, and any other impurity in the portion of Zolmitriptan 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 A, zolmitriptan related compound B, zolmitriptan related compound C, zolmitriptan related compound D, or any other impurity from the *Sample solution*

r_S = peak response of USP Zolmitriptan RS from the *Standard solution*

C_S = concentration of USP Zolmitriptan RS in the *Standard solution* (mg/mL)

C_U = concentration of Zolmitriptan in the *Sample solution* (mg/mL)

F = relative response factor for the corresponding impurity peak (see *Table 2*)

Acceptance criteria: See Table 2.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Zolmitriptan related compound A ^a	0.43	0.64	0.15
Zolmitriptan related compound B ^b	0.59	0.48	0.15
Zolmitriptan	1.0	—	—
Zolmitriptan related compound C ^c	1.4	0.70	0.15
Zolmitriptan related compound D ^d	1.7	0.46	0.15
Any unspecified individual impurity	—	1.0	0.10
Total impurities	—	—	0.50

^a (S)-4-({3-[2-(Methylamino)ethyl]-1H-indol-5-yl)methyl}oxazolidin-2-one.

^b (S)-2-Amino-3-{3-[2-(dimethylamino)ethyl]-1H-indol-5-yl}propan-1-ol.

^c 1-[2-(Dimethylamino)ethyl]-6,6a,7,11-tetrahydrooxazolo[3,4-b]pyrrolo[2,3-h]isoquinolin-9(3H)-one.

^d (S)-Ethyl 3-[2-(dimethylamino)ethyl]-5-[(2-oxooxazolidin-4-yl)methyl]-1H-indole-2-carboxylate.

• LIMIT OF ZOLMITRIPTAN R-ISOMER

Mobile phase: Hexane, isopropyl alcohol, methanol, and diethylamine (75:10:15:0.3)

System suitability solution: 0.75 µg/mL each of USP Zolmitriptan RS and USP Zolmitriptan R-Isomer RS in *Mobile phase*

Sample solution: 0.5 mg/mL of Zolmitriptan in *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: UV 225 nm

Column: 4.6-mm × 25-cm; 5-µm packing L51

Flow rate: 1 mL/min

Injection size: 10 µL

Run time: 2.8 times the retention time of the zolmitriptan peak

System suitability

[NOTE—The relative retention time for zolmitriptan R-isomer and zolmitriptan are 0.70 and 1.0, respectively.]

Sample: *System suitability solution*

Suitability requirements:

Resolution: NLT 3.5 between the zolmitriptan R-isomer and zolmitriptan peaks

Relative standard deviation: NMT 2.0% for the zolmitriptan peak

Analysis

Sample: *Sample solution*

Calculate the percentage of zolmitriptan R-isomer in the portion of Zolmitriptan taken:

$$\text{Result} = (r_u/r_T) \times 100$$

r_u = peak response of zolmitriptan R-isomer from the *Sample solution*

r_T = sum of the peak responses of zolmitriptan R-isomer and zolmitriptan from the *Sample solution*

Acceptance criteria: NMT 0.15% of zolmitriptan R-isomer

• LIMIT OF NICKEL

[NOTE—Perform this test if nickel is a known process impurity.]

Diluent: 3% nitric acid

Standard stock solution: 10 ppm nickel in *Diluent* from commercially available NIST traceable nickel ICP standard (1000 ppm)

Standard solutions: Prepare three different of calibration solutions having concentrations of 0.05, 0.5, and 1.0 ppm in *Diluent* from the *Standard stock solution*

Sample solution: To 0.5 g of Zolmitriptan in a teflon beaker, add 15 mL nitric acid and 6 mL perchloric acid, and digest

the solution at 300° on a hot plate by covering the beaker. Reduce the volume of acid by 1/4 the total volume and until the evolution of brown fumes stops and the solution becomes clear. If any precipitation occurs, digest the sample with 5 mL of nitric acid. Cool and transfer the contents to a 10-mL volumetric flask, and dilute with *Diluent* to volume.

Blank solution: Prepare as directed for the *Sample solution*, omitting Zolmitriptan.

Instrumental conditions:

(See *Plasma Spectrochemistry* (730).)

Mode: ICP-OES

Analytical wavelength: 231.604 nm

Other instrumental settings: Optimized as directed by the manufacturer

System suitability

Samples: *Standard solutions*

Suitability requirements

Correlation coefficient: NLT 0.99 for the calibration curve using the three *Standard solutions*

Analysis

Samples: *Blank solution* and *Sample solution*

Aspirate the *Sample solution* and *Blank solution* into the instrument, and measure the response. Determine the concentration from the curve obtained from the *Standard solutions*. If the nickel concentration measured in the *Sample solution* is greater than the 1.0 ppm standard, dilute the sample and re-analyze.

Calculate the amount of nickel, in ppm, in the portion of Zolmitriptan taken:

$$\text{Result} = \{[V \times (C_U - C_B)]\} / W$$

V = dilution volume (mL)

C_U = concentration of nickel measured in the *Sample solution* (ppm)

C_B = concentration of nickel measured in the *Blank solution* (ppm)

W = sample weight (g)

Acceptance criteria: NMT 10 ppm

SPECIFIC TESTS

• **LOSS ON DRYING** (731): Dry a sample in vacuum at 60° for 3 h; it loses NMT 0.5% of its weight.

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in light-resistant containers. Store at controlled room temperature.

• USP REFERENCE STANDARDS (11)

USP Zolmitriptan RS

USP Zolmitriptan Related Compound A RS

(S)-4-({3-[2-(Methylamino)ethyl]-1H-indol-5-yl)methyl}oxazolidin-2-one.

$C_{15}H_{19}N_3O_2$ 273.33

USP Zolmitriptan Related Compound B RS

(S)-2-Amino-3-{3-[2-(dimethylamino)ethyl]-1H-indol-5-yl}propan-1-ol.

$C_{15}H_{23}N_3O$ 261.36

USP Zolmitriptan Related Compound C RS

1-[2-(Dimethylamino)ethyl]-6,6a,7,11-tetrahydrooxazolo[3,4-b]pyrrolo[2,3-h]isoquinolin-9(3H)-one.

$C_{17}H_{21}N_3O_2$ 299.37

USP Zolmitriptan Related Compound D RS

(S)-Ethyl 3-[2-(dimethylamino)ethyl]-5-[(2-oxooxazolidin-4-yl)methyl]-1H-indole-2-carboxylate.

$C_{19}H_{25}N_3O_4$ 359.42

USP Zolmitriptan R-Isomer RS

(R)-4-[[3-[2-(Dimethylamino)ethyl]indol-5-yl]methyl]-2-oxazolidinone.

$C_{16}H_{21}N_3O_2$ 287.36 ◀ (1-Sep-2011)