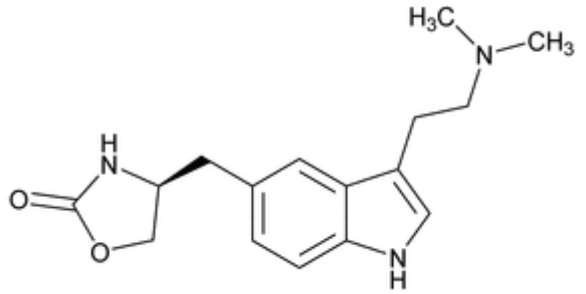
Zolmitriptan



$C_{16}H_{21}N_3O_2$ 287.36

2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1*H*-indol-5-yl]methyl]-, (*S*)-;
(*S*)-4-({3-[2-(Dimethylamino)ethyl]indol-5-yl}methyl)oxazolidin-2-one;
(*S*)-4-[[3-[2-(Dimethylamino)ethyl]indol-5-yl]methyl]-2-oxazolidinone [139264-17-8].

DEFINITION

Zolmitriptan contains NLT 97.0% and NMT 102.0% of zolmitriptan ($C_{16}H_{21}N_3O_2$), calculated on the anhydrous and solvent-free basis.

IDENTIFICATION

Change to read:

- **A. ▲Spectroscopic Identification Tests** ⟨197⟩**,** *Infrared Spectroscopy***:** 197K▲ (CN 1-May-2020)
- **B.** The migration time of the major peak of the *Sample solution* corresponds to that of the *System suitability solution*, as obtained in the test for *Limit of Zolmitriptan R-Isomer and Other Impurities*.

ASSAY

Change to read:

- **Procedure**

Mobile phase: Acetonitrile and water (135:865). For every liter of the mixture add 1 mL of trifluoroacetic acid and 0.25 mL of triethylamine.
System suitability solution: 0.12 µg/mL of USP Zolmitriptan Related Compound E RS and 25 µg/mL of USP Zolmitriptan RS in *Mobile phase*
Standard solution: 0.025 mg/mL of USP Zolmitriptan RS in *Mobile phase*
Sample solution: 0.025 mg/mL of Zolmitriptan in *Mobile phase*
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 225 nm
Column: 4.0-mm × 12.5-cm; 5-µm packing L1
Flow rate: 1 mL/min
Injection volume: 20 µL
Run time: ▲NLT▲ (IRA 1-May-2020) 3 times the retention time of zolmitriptan
System suitability
Sample: *System suitability solution*
[Note—The relative retention times for zolmitriptan and zolmitriptan related compound E are 1.0 and 1.6, respectively.]
Suitability requirements
Resolution: NLT 5 between zolmitriptan and zolmitriptan related compound E
Tailing factor: NMT 2.0 for zolmitriptan
▲Relative standard deviation: NMT 0.73%▲ (IRA 1-May-2020)
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of zolmitriptan ($C_{16}H_{21}N_3O_2$) in the portion of Zolmitriptan taken:

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

r_U = peak response ▲of zolmitriptan▲ (IRA 1-May-2020) from the *Sample solution*
r_S = peak response ▲of zolmitriptan▲ (IRA 1-May-2020) 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: 97.0%–102.0% on the anhydrous and solvent-free basis

IMPURITIES

- **Residue on Ignition** ⟨281⟩**:** NMT 0.1%
- **Limit of Zolmitriptan Related Compound H**

Perform this test only if zolmitriptan related compound H is a known process impurity. If this test is performed, then this is to be included in total impurities.
Standard solution: 0.1 mg/mL of USP Zolmitriptan Related Compound H RS in methanol
Sample solution: 200 mg/mL of Zolmitriptan in methanol
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: GC
Detector: Flame ionization
Column: 0.32-mm × 15-m; 1-µm coating of dimethylpolysiloxane phase G1
Temperatures
Injection port: 200°
Column: 130°
Detector: 250°
Carrier gas: Helium at 6 mL/min
Injection volume: 3 µL
Injection type: Split, split ratio 10:1
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of zolmitriptan related compound H in the portion of Zolmitriptan taken:

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

r_U = peak response of zolmitriptan related compound H from the *Sample solution*
r_S = peak response of zolmitriptan related compound H from the *Standard solution*
C_S = concentration of USP Zolmitriptan Related Compound H RS in the *Standard solution* (mg/mL)
C_U = concentration of Zolmitriptan in the *Sample solution* (mg/mL)

Acceptance criteria: NMT 0.1% of zolmitriptan related compound H

Change to read:

• **Limit of Zolmitriptan *R*-Isomer and Other Impurities**
Buffer: 19.1 g/L of sodium borate decahydrate in water. Adjust with phosphoric acid to a pH of 2.2.
Run buffer: 50 mg/mL of hydroxypropyl-β-cyclodextrin in *Buffer*
Diluent: 0.02 M hydrochloric acid
Internal standard solution: 0.05 mg/mL of tryptamine hydrochloride in *Diluent*
System suitability solution: 0.01 mg/mL of tryptamine hydrochloride from the *Internal standard solution*; 1 mg/mL of USP Zolmitriptan RS; and 0.01 mg/mL each of USP Zolmitriptan Related Compound F RS, USP Zolmitriptan Related Compound G RS, and USP Zolmitriptan *R*-Isomer RS in *Diluent*
Standard solution: 0.01 mg/mL of tryptamine hydrochloride from *Internal standard solution* and 0.001 mg/mL of USP Zolmitriptan RS in *Diluent*
Sample solution: 0.01 mg/mL of tryptamine hydrochloride from *Internal standard solution* and 1 mg/mL of Zolmitriptan in *Diluent*. Filter the solution and protect from light.
Capillary rinsing procedure: Use separate *Run buffer* vials for the capillary rinse and sample analysis. Condition the capillary by rinsing with 0.1 N sodium hydroxide followed by *Run buffer* before each injection. [Note—It may be suitable to rinse with 0.1 N sodium hydroxide using a pressure of 20 psi for NLT 1 min and then to rinse with *Run buffer* using a pressure of 20 psi for NLT 3 min.]
Electrophoretic system
Mode: CE
Detector: UV 200 nm
Column: 75-µm (ID) × 50-cm effective length, 60-cm total-length capillary uncoated fused-silica
Capillary temperature: 25°
Injection pressure: 0.5 psi for 5 s
Applied voltage: 15 kV
Run time: NLT 1.5 times the migration time of zolmitriptan
System suitability
Samples: *System suitability solution* and *Standard solution*
[Note—▲The relative migration time for tryptamine is 0.78;▲ (IRA 1-May-2020) see *Table 1* for ▲the other ▲ (IRA 1-May-2020) relative migration times.]
Suitability requirements
Resolution: NLT 1.5 between zolmitriptan and zolmitriptan *R*-isomer, ▲▲ (IRA 1-May-2020) *System suitability solution*
Relative standard deviation: NMT ▲15%▲ (IRA 1-May-2020) for the peak response ratio of zolmitriptan and tryptamine, ▲▲ (IRA 1-May-2020) *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the corrected peak responses:

$$\text{Result} = r/m$$

r = peak response
m = migration time of the peak (min)

Calculate the percentage of each 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 = corrected peak response ratio of the impurity to the internal standard from the *Sample solution*
R_S = corrected peak response ratio of zolmitriptan to the internal standard 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 (see *Table 1*)

Acceptance criteria: See *Table 1*. Disregard the peak due to zolmitriptan related compound E. The reporting threshold is 0.10%.

Table 1

Name	Relative Migration Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Zolmitriptan related compound G	0.68	0.52	0.1
Zolmitriptan related compound F	0.71	0.41	1.2
▲▲ (IRA 1-May-2020)	▲▲ (IRA 1-May-2020)	▲▲ (IRA 1-May-2020)	▲▲ (IRA 1-May-2020)
Zolmitriptan	1.0	—	—
Zolmitriptan *R*-isomer	1.07	1.0	0.2
Any individual unspecified impurity	—	1.0	0.1

Change to read:

• **Organic Impurities**
Mobile phase: Acetonitrile and water (135:865). For every liter of the mixture add 1 mL of trifluoroacetic acid and 0.25 mL of triethylamine.
System suitability solution: 0.5 µg/mL of USP Zolmitriptan Related Compound E RS and 0.1 mg/mL of USP Zolmitriptan RS in *Mobile phase*
Sample solution: 0.1 mg/mL of Zolmitriptan in *Mobile phase*
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 225 nm
Column: 4.0-mm × 12.5-cm; 5-µm packing L1
Flow rate: 1 mL/min
Injection volume: 20 µL
Run time: NLT 6 times the retention time of zolmitriptan
System suitability
Sample: *System suitability solution*
[Note—See *Table 2* for relative retention times.]
Suitability requirements
Resolution: NLT 5 between zolmitriptan and zolmitriptan related compound E▲▲ (IRA 1-May-2020)
Tailing factor: NMT 3.0 for zolmitriptan
Analysis
Sample: *Sample solution*
Calculate the percentage of each impurity in the portion of Zolmitriptan taken:

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

r_U = peak response of each impurity from the *Sample solution*
r_T = sum of the peak responses from the *Sample solution*

Acceptance criteria: See *Table 2*. The reporting threshold is 0.05%.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Zolmitriptan related compound B[a]	0.36	0.2
Zolmitriptan	1.0	—
Zolmitriptan related compound E	1.6	0.2
Zolmitriptan related compound F[b]	2.3	—
Any individual unspecified impurity	—	0.1
Total impurities[c]	—	0.5

[a] (*S*)-2-Amino-3-{3-[2-(dimethylamino)ethyl]-1*H*-indol-5-yl}propan-1-ol.
[b] Included for identification purposes only. Not reported here as it is monitored under the *Limit of Zolmitriptan R-Isomer and Other Impurities* test. Not to be included in total impurities.
[c] Includes all impurities except zolmitriptan related compound F. Also includes zolmitriptan related compound H from the test for *Limit of Zolmitriptan Related Compound H* if it is a known process impurity, as well as impurities from the test for *Limit of Zolmitriptan R-Isomer and Other Impurities* with the exception of zolmitriptan related compound F.

SPECIFIC TESTS

- **Water Determination** ⟨921⟩**,** *Method I, Method Ia***:** NMT 1.0%

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed containers. Store at room temperature.

Change to read:

- **USP Reference Standards** ⟨11⟩

USP Zolmitriptan RS

USP Zolmitriptan *R*-Isomer RS
▲(*R*)-4-({3-[2-(Dimethylamino)ethyl]indol-5-yl}methyl)oxazolidin-2-one;
Also known as▲ (IRA 1-May-2020) (*R*)-4-[[3-[2-(Dimethylamino)ethyl]indol-5-yl]methyl]-2-oxazolidinone.
$C_{16}H_{21}N_3O_2$ 287.36

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 F RS
2,2′-[4-(Dimethylamino)butane-1,1-diyl]bis{5-[(*S*)-(2-oxooxazolidin-4-yl)methyl]-3-(2-dimethylaminoethyl)indole}.
$C_{38}H_{53}N_7O_4$ ▲671.89▲ (IRA 1-May-2020)

USP Zolmitriptan Related Compound G RS
(*S*)-4-(4-Aminobenzyl)oxazolidin-2-one.
$C_{10}H_{12}N_2O_2$ ▲192.22▲ (IRA 1-May-2020)

USP Zolmitriptan Related Compound H RS
4,4-Diethoxy-*N,N*-dimethylbutan-1-amine.
$C_{10}H_{23}NO_2$ 189.30