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Zolmitriptan Nasal Spray

DEFINITION

Zolmitriptan Nasal Spray is an aqueous solution of zolmitriptan, supplied in a form suitable for nasal administration. It contains NLT 90.0% and NMT 110.0% of the labeled amount of zolmitriptan ($C_{16}H_{21}N_3O_2$).

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197K**▲ (CN 1-May-2020)

Standard: Add 300 µL of a solution of 2.5 mg/mL of USP Zolmitriptan RS in methylene chloride to about 200 mg of dried potassium bromide. Allow the mixture to dry. Grind the residue.

Sample: Add the contents of NLT 5 units of Nasal Spray to a container with 3 mL of 0.1 M sodium hydroxide. Extract into a sufficient volume of methylene chloride to obtain a final concentration of about 1.0–2.5 mg/mL of zolmitriptan in the extract. Dry the extract over anhydrous sodium sulfate. Add a suitable volume of the extract containing about 0.8 mg of zolmitriptan to about 200 mg of dried potassium bromide. Allow the mixture to dry. Grind the residue.

Acceptance criteria: Meets the requirements

• **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**

Diluent: 0.02 M hydrochloric acid

Mobile phase: Acetonitrile and water (135:865). Add 1 mL of trifluoroacetic acid and 0.25 mL of triethylamine to each liter of the mixture.

Standard stock solution: 0.5 mg/mL of USP Zolmitriptan RS in *Diluent*

Standard solution: 0.025 mg/mL of USP Zolmitriptan RS from *Standard stock solution* and *Mobile phase*

System suitability stock solution: 0.005 mg/mL each of USP Zolmitriptan Related Compound E RS and USP Zolmitriptan Related Compound G RS in *Mobile phase*

System suitability solution: Dilute 1 mL of *System suitability stock solution* with 9 mL of *Standard solution*.

Sample stock solution: Nominally 0.5 mg/mL of zolmitriptan prepared as follows. Discharge the contents of NLT 10 units of Nasal Spray to a suitable container. Transfer an amount of the composite solution containing about 5 mg of zolmitriptan to a 10-mL volumetric flask. Dilute with *Diluent* to volume.

Sample solution: Nominally 0.025 mg/mL of zolmitriptan from *Sample stock solution* in *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 15-cm; 3-µm packing L1

Column temperature: 40°

Flow rate: 1.6 mL/min

Injection volume: 20 µL

Run time: NLT 3 times the retention time of zolmitriptan

System suitability

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

[Note—See *Table 1* for the relative retention times.]

Suitability requirements

Resolution: NLT 4.0 between zolmitriptan and zolmitriptan related compound E, *System suitability solution*

Tailing factor: NMT 2.0 for zolmitriptan, *Standard solution*

Relative standard deviation: NMT 1.0%, *Standard solution*

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 Nasal Spray 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 = nominal concentration of zolmitriptan in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• **Delivered Dose Uniformity**

Diluent, Mobile phase, Standard solution, and **System suitability solution:** Prepare as directed in the *Assay*.

Sample solution: Nominally 0.025 mg/mL of zolmitriptan prepared as follows. Discharge the contents of a single unit into a suitable volumetric flask. Dilute with *Mobile phase* to volume.

Repeat this procedure with 9 additional units.

Chromatographic system and **System suitability:** Proceed as directed in the *Assay*.

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of zolmitriptan in each dose of Nasal Spray taken:

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

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)

V = volume of the *Sample solution*

L = label claim of zolmitriptan (mg/dose)

Acceptance criteria

Tier 1

1. The mean of 10 units is within 85.0%–115.0% of the labeled amount of zolmitriptan ($C_{16}H_{21}N_3O_2$).
2. NMT 1 dosage unit outside of 80%–120% of the labeled amount of zolmitriptan ($C_{16}H_{21}N_3O_2$)
3. None outside of 75%–125% of the labeled amount of zolmitriptan ($C_{16}H_{21}N_3O_2$) for 10 units

If criterion 2 in *Tier 1* cannot be met, proceed to *Tier 2*.

Tier 2: Test an additional 20 units. All 30 results (including the results from *Tier 1*) meet the following acceptance criteria.

1. NMT 3 of the 30 dosage units outside of 80%–120% of the labeled amount of zolmitriptan ($C_{16}H_{21}N_3O_2$)
2. None of the 30 dosage units are outside of 75%–125% of the labeled amount of zolmitriptan ($C_{16}H_{21}N_3O_2$).

IMPURITIES

• **Organic Impurities**

Diluent, Mobile phase, Standard solution, System suitability solution, and **Sample stock solution:** Prepare as directed in the *Assay*.

Sensitivity solution: 0.1 µg/mL of USP Zolmitriptan RS in *Mobile phase* from *Standard solution*

Sample solution: Nominally 0.1 mg/mL of zolmitriptan from *Sample stock solution* in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 15-cm; 3-µm packing L1

Column temperature: 40°

Flow rate: 1.6 mL/min

Injection volume: 20 µL

Run time: NLT 8 times the retention time of zolmitriptan

System suitability

Samples: *System suitability solution* and *Sensitivity solution*

[NOTE—See *Table 1* for the relative retention times.]

Suitability requirements

Resolution: NLT 4.0 between zolmitriptan and zolmitriptan related compound E, *System suitability solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Sample: *Sample solution*

Calculate the percentage of each degradation product in the portion of Nasal Spray taken:

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

r_I = peak response of each degradation product from the *Sample solution*

r_U = peak response of zolmitriptan from the *Sample solution*

Acceptance criteria: See *Table 1*. The reporting threshold is 0.1%.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Zolmitriptan related compound G[a]	0.27	—
Zolmitriptan hydroxy ketone analog[b]	0.34	0.6
Zolmitriptan pyrrolo analog quaternary salt[c]	0.42	1.3
Zolmitriptan hydroxymethyl quaternary salt[d]	0.89	0.4
Zolmitriptan	1.0	—
Zolmitriptan related compound E[a]	1.3	—
Zolmitriptan related compound F[a,e]	1.8	—
Zolmitriptan methylene dimer[f]	6.0	0.3
Any other individual degradation product	—	0.2
Total degradation products	—	2.5

[a] Process impurity; included for peak identification and/or resolution check only; controlled in the drug substance. Not to be included in total degradation products.

[b] (4*S*)-4-({3-[2-(Dimethylamino)ethyl]-3-hydroxy-2-oxoindolin-5-yl}methyl)oxazolidin-2-one.

[c] 3a-Hydroxy-1,1-dimethyl-5-{[(*S*)-2-oxooxazolidin-4-yl]methyl}-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-1-ium; may also be known as (4*S*)-4-[(8*b*-Hydroxy-3,3-dimethyl-1,2,3a,4-tetrahydropyrrolo[2,3-*b*]indol-3-ium-7-yl)methyl]oxazolidin-2-one.

[d] (*S*)-*N*-(Hydroxymethyl)-*N*,*N*-dimethyl-2-{5-[(2-oxooxazolidin-4-yl)methyl]-1*H*-indol-3-yl}ethan-1-aminium; may also be known as (4*S*)-4-[[3-(2-Dimethylaminoethyl)-1-(hydroxymethyl)indol-5-yl]methyl]oxazolidin-2-one.

[e] 2,2'-[4-(Dimethylamino)butane-1,1-diyl]bis{5-[(*S*)-(2-oxooxazolidin-4-yl)methyl]-3-(2-dimethylaminoethyl)indole}.

[f] (*S*)-4-({3-[2-(Dimethylamino)ethyl]-1-[(3-[2-(dimethylamino)ethyl]-5-{[(*S*)-2-oxooxazolidin-4-yl]methyl}-1*H*-indol-2-yl)methyl]-1*H*-indol-5-yl}methyl)oxazolidin-2-one.

SPECIFIC TESTS

- **pH** ⟨791⟩**:** 4.7–5.3
- **Microbial Enumeration Tests** ⟨61⟩ and **Tests for Specified Microorganisms** ⟨62⟩

Total aerobic viable count: ≤10^2 cfu/mL

Total combined yeasts and molds count: ≤10^1 cfu/mL

Bile-tolerant Gram-negative bacteria per mL: NMT 10

Tests for the absence of *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Escherichia coli*: Meets the requirements

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in a tight, light-resistant container. Store at controlled room temperature.
- **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

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
ZOLMITRIPTAN NASAL SPRAY	Documentary Standards Support	SM52020 Small Molecules 5
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM52020 Small Molecules 5

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