Zolmitriptan Nasal Spray

Type of Posting	Notice of Intent to Revise
Posting Date	24–April–2020
Targeted Official Date	To Be Determined, Revision Bulletin
Expert Committee	Chemical Medicines Monographs 4

In accordance with section 7.04 (c) of the 2015–2020 Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Chemical Medicines Monographs 4 Expert Committee intends to revise the Zolmitriptan Nasal Spray monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to broaden the acceptance range for pH ⟨791⟩ in order to accommodate drug products having different compositions.

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.[1]

Should you have any questions, please contact Nicholas Garito, Scientific Liaison to the Chemical Medicines Monographs 4 Expert Committee (301-816-8321 or njg@usp.org).

[1] This text is not the official version of a *USP–NF* monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the *USP–NF* for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product's final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the *Pharmacopeial Forum* must also meet the requirements outlined in the USP Guideline on Use of Accelerated Processes for Revisions to the *USP–NF*.

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-Dimethylamino)ethyl)-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

Change to read:

• **pH** ⟨791⟩: ▲4.5–5.3▲ (TBD)

• **MICROBIAL ENUMERATION TESTS** ⟨61⟩ and **TESTS FOR SPECIFIED MICROORGANISMS** ⟨62⟩
Total aerobic viable count: $\leq 10^2$ cfu/mL
Total combined yeasts and molds count: $\leq 10^1$ 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