

BRIEFING

Eszopiclone. This monograph was posted on the USP Website as a Draft on March 25, 2011. No comments were received. The SM4 Expert Committee has approved the monograph as an Authorized USP Pending Monograph, Version 1.

The liquid chromatographic procedures in the *Assay* and in the test for *Organic Impurities* are based on analyses performed with the Inerstil ODS 3V brand of L1 column. The typical retention time for eszopiclone is about 28 min. The liquid chromatographic procedure in the test for *Limit of Zopiclone R-Isomer* is based on analyses performed with the Chiralcel OJ-H brand of L# column. The typical retention time for eszopiclone is about 13.8 min.

Description and Solubility: A white to slightly yellowish powder. Soluble in methylene chloride and in dilute mineral acids; practically insoluble in water and in alcohol.

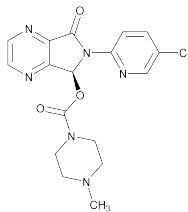
Column information for the Limit of Zopiclone R-Isomer test:

Chiralcel OJ-H: Cellulose tris(4-methylbenzoate)-coated, porous, spherical, silica particles, 5-µm in diameter

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Eszopiclone

v. 1 Authorized November 1, 2011



C₁₇H₁₇ClN₆O₃ 388.81
1-Piperazinecarboxylic acid, 4-methyl-, (5S)-6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester;
(+)-(5S)-6-(5-Chloropyridin-2-yl)-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-yl 4-methylpiperazine-1-carboxylate [138729-47-2].

DEFINITION

Eszopiclone contains NLT 98.0% and NMT 102.0% of C₁₇H₁₇ClN₆O₃, calculated on the anhydrous and solvent-free basis.

IDENTIFICATION

- A. INFRARED ABSORPTION (197K)**
- B.** The retention time of the major peak in the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

PROCEDURE

Buffer: Dissolve 8.1 g of sodium dodecyl sulfate and 1.6 g of monobasic sodium phosphate in 1 L of water. Adjust with 10% phosphoric acid to a pH of 4.0.

Mobile phase: Acetonitrile and *Buffer* (38:62)

Standard solution: 0.5 mg/mL of USP Eszopiclone RS in *Mobile phase*

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

Chromatographic system

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

Mode: LC

Detector: UV 303 nm

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

Column temperature: 30°

Flow rate: 1.5 mL/min

Injection size: 10 µL

Run time: 2 times the retention time of eszopiclone

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 1.5%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of eszopiclone (C₁₇H₁₇ClN₆O₃) 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 Eszopiclone RS in the *Standard solution* (mg/mL)

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

Acceptance criteria: 98.0%–102.0% on the anhydrous and solvent-free basis

IMPURITIES

- HEAVY METALS, Method II (231):** NMT 10 ppm
- RESIDUE ON IGNITION (281):** NMT 0.1%
- ORGANIC IMPURITIES**

[NOTE—The *Standard solution* and *Sample solution* are stable for 48 h at refrigerated conditions.]

Buffer and Mobile phase: Proceed as directed in the *Assay*.

Standard solution: 4.0 µg/mL of USP Eszopiclone RS in *Mobile phase*

System suitability solution: 0.04 mg/mL of USP Eszopiclone Related Compound A RS and 0.04 mg/mL of USP Eszopiclone RS from the *Standard solution*, in *Mobile phase*

Sample solution: 4.0 mg/mL of Eszopiclone in *Mobile phase*

Chromatographic system: Proceed as directed in the *Assay*.

Injection size: 20 µL

System suitability

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

Suitability requirements

Resolution: NLT 3.0 between eszopiclone related compound A and eszopiclone, *System suitability solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of any individual impurity in the portion of Eszopiclone taken:

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

r_U = peak response of any individual impurity from the *Sample solution*

r_S = peak response of eszopiclone from the *Standard solution*

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

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

F = relative response factor for the corresponding impurity peak (see *Table 1*)

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Acceptance criteria: See Table 1.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Zopiclone alcohol ^a	0.13	1.4	0.15
Pyrolopyrazinone analog ^b	0.24	1.6	0.15
Eszopiclone related compound A ^c	0.60	0.88	0.15
Eszopiclone	1.0	—	—
Any individual unspecified impurity	—	1.0	0.10
Total impurities	—	—	0.4

^a 6-(5-Chloropyridin-2-yl)-7-hydroxy-6,7-dihydro-5H-pyrrolo[3,4-*b*]pyrazin-5-one.

^b 6-(5-Chloropyridin-2-yl)-6,7-dihydro-5H-pyrrolo[3,4-*b*]pyrazin-5-one.

^c 6-(5-Chloropyridin-2-yl)-7-oxo-6,7-dihydro-5H-pyrrolo [3,4,*b*] pyrazin-5-yl 4-methylpiperazine-1-carboxylate 4-oxide.

• **LIMIT OF ZOPICLONE R-ISOMER**

[NOTE—The *Sample solution* is stable for 48 h at refrigerated conditions.]

Mobile phase: Absolute alcohol, *n*-hexane, and diethyl amine (700: 300: 0.2)

System suitability solution: 0.1 mg/mL each of USP Eszopiclone RS and USP Zopiclone R-Isomer RS in methanol

Sample solution: 1.0 mg/mL of Eszopiclone in methanol

Chromatographic system

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

Mode: LC

Detector: UV 303 nm

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

Flow rate: 1 mL/min

Injection size: 10 μL

Run time: 1.5 times the retention time of eszopiclone

System suitability

Sample: *System suitability solution*

[NOTE—The relative retention times for zopiclone R-isomer and eszopiclone are 0.68 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.0 between the zopiclone R-isomer and eszopiclone peaks

Analysis

Sample: *Sample solution*

Calculate the percentage of zopiclone R-isomer in the portion of Eszopiclone taken:

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

r_U = peak response of zopiclone R-isomer from the *Sample solution*

r_T = sum of the peak responses from the *Sample solution*

Acceptance criteria: NMT 1.0%

SPECIFIC TESTS

- **WATER DETERMINATION, Method Ia (921):** NMT 0.5%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers. Store at controlled room temperature.

- **USP REFERENCE STANDARDS (11)**

USP Eszopiclone RS

USP Eszopiclone Related Compound A RS

6-(5-Chloropyridin-2-yl)-7-oxo-6,7-dihydro-5H-pyrrolo [3,4,*b*] pyrazin-5-yl 4-methylpiperazine-1-carboxylate 4-oxide.

C₁₇H₁₇ClN₆O₄ 404.81

USP Zopiclone R-Isomer RS

(-)-(5*R*)-6-(5-Chloropyridin-2-yl)-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-*b*]pyrazin-5-yl 4-methylpiperazine-1-carboxylate.

C₁₇H₁₇ClN₆O₃ 388.81