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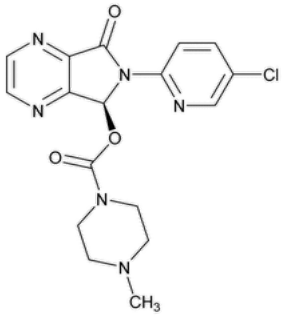
Eszopiclone



$C_{17}H_{17}ClN_6O_3$ 388.81

1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5*H*-pyrrolo[3,4-*b*]pyrazin-5-yl ester, (5*S*)-;

(+)-(5*S*)-6-(5-Chloropyridin-2-yl)-7-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyrazin-5-yl 4-methylpiperazine-1-carboxylate CAS RN®: 138729-47-2; UNII: UZX80K71OE.

DEFINITION

Eszopiclone contains NLT 98.5% and NMT 101.0% of eszopiclone ($C_{17}H_{17}ClN_6O_3$), calculated on the dried basis.

IDENTIFICATION

Change to read:

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

• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the second peak of the *System suitability solution*, as obtained in the *Limit of R-Isomer* test.

ASSAY

• **Procedure**

Solution A: 1.4 g/L of anhydrous dibasic sodium phosphate in water

Mobile phase: Acetonitrile and *Solution A* (25:75) adjusted with phosphoric acid to a pH of 6.5

Standard stock solution: 1 mg/mL of USP Eszopiclone RS prepared as follows. Transfer a suitable quantity of USP Eszopiclone RS to an appropriate volumetric flask and add 15% of the final flask volume of acetonitrile. Add 15% of the final flask volume of *Mobile phase*. Sonication may be used to promote dissolution. Dilute with *Mobile phase* to volume.

Standard solution: 0.2 mg/mL of USP Eszopiclone RS from *Standard stock solution* in *Mobile phase*

Sample stock solution: 1 mg/mL of Eszopiclone prepared as follows. Transfer a suitable quantity of Eszopiclone to an appropriate volumetric flask and add 15% of the final flask volume of acetonitrile. Add 15% of the final flask volume of *Mobile phase*. Sonication may be used to promote dissolution. Dilute with *Mobile phase* to volume.

Sample solution: 0.2 mg/mL of Eszopiclone from *Sample stock solution* in *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: UV 303 nm

Column: 4.6-mm × 15.0-cm; 5-µm packing L1

Flow rate: 1.5 mL/min

Injection volume: 20 µL

Run time: NLT 2.5 times the retention time of eszopiclone

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 1.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of eszopiclone ($C_{17}H_{17}ClN_6O_3$) in the portion of Eszopiclone 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: 98.5%–101.0% on the dried basis

IMPURITIES

- **Residue on Ignition ⟨281⟩:** NMT 0.10%
- **Organic Impurities**

Solution A: 8.1 g/L of sodium lauryl sulfate and 2.1 g/L of monobasic sodium phosphate in water

Mobile phase: Acetonitrile and *Solution A* (628:1000) adjusted with phosphoric acid to a pH of 4.0

System suitability solution: 0.04 mg/mL each of USP Eszopiclone Related Compound A RS and USP Eszopiclone RS in *Mobile phase*. Sonication may be used to promote dissolution.

Standard stock solution: 0.4 mg/mL of USP Eszopiclone RS in *Mobile phase*. Sonication may be used to promote dissolution.

Standard solution: 0.004 mg/mL of USP Eszopiclone RS from *Standard stock solution* in *Mobile phase*

Sample solution: 4 mg/mL of Eszopiclone in *Mobile phase*. Sonication may be used to promote dissolution.

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

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

Column temperature: 30°

Flow rate: 1.5 mL/min

Injection volume: 20 µL

Run time: 2.7 times the retention time of eszopiclone

System suitability

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

Suitability requirements

Resolution: NLT 2.0 between eszopiclone related compound A and eszopiclone, *System suitability solution*

Tailing factor: NMT 1.5 for eszopiclone, *System suitability solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Eszopiclone taken:

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

r_U = peak response of each 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)

Acceptance criteria: See *Table 1*. Disregard peaks below 0.05%.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Zopiclone alcohol[a]	0.14	0.10
Eszopiclone related compound A	0.93	0.10

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Eszopiclone	1.0	—
Any individual unspecified impurity	—	0.10
Total impurities	—	0.3

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

• **Limit of *R*-Isomer**

Mobile phase: 1 mL of diethylamine in 1000 mL of absolute alcohol. Sonication may be used to promote dissolution.

System suitability solution: 0.5 mg/mL of USP Eszopiclone RS and 0.1 mg/mL of USP Zopiclone R-Isomer RS prepared as follows. Transfer suitable amounts of USP Eszopiclone RS and USP Zopiclone R-Isomer RS to an appropriate volumetric flask. Add 20% of the flask volume of dichloromethane. Sonication may be used to promote dissolution. Dilute with absolute alcohol to volume.

Sample solution: 0.5 mg/mL of Eszopiclone prepared as follows. Transfer a suitable amount of Eszopiclone to an appropriate volumetric flask. Add 20% of the flask volume of dichloromethane. Sonication may be used to promote dissolution. Dilute with absolute alcohol to volume.

Chromatographic system

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

Mode: LC

Detector: UV 303 nm

Column: 4.6-mm × 25.0-cm; 5-µm packing L40

Flow rate: 0.5 mL/min

Injection volume: 20 µL

Run time: NLT 1.3 times the retention time of eszopiclone

System suitability

Sample: *System suitability solution*

[Note—The relative retention times of zopiclone *R*-isomer and eszopiclone are about 0.7 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 3.0 between zopiclone *R*-isomer and eszopiclone

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 0.30%

SPECIFIC TESTS

• **Loss on Drying ⟨731⟩**

Analysis: Dry at 105° under vacuum for 3 h.

Acceptance criteria: NMT 0.50%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers. Store at controlled room temperature.

Change to read:

• **USP Reference Standards ⟨11⟩**

USP Eszopiclone RS

USP Eszopiclone Related Compound A RS

[Note—This material may be available in the free base or salt form.]

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

$C_{17}H_{17}ClN_6O_4$ 404.81

6-(5-Chloropyridin-2-yl)-7-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyrazin-5-yl 4-methylpiperazine-1-carboxylate 4-oxide, 3-▲chlorobenzoate▲ (ERR 1-Jun-2018) salt (1:1).

$C_{17}H_{17}ClN_6O_4 \cdot$ ▲$C_7H_5ClO_2$▲ (ERR 1-Jun-2018) 561.38

USP Zopiclone R-Isomer RS

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

$C_{17}H_{17}ClN_6O_3$ 388.81

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

Topic/Question	Contact	Expert Committee
ESZOPICLONE	Documentary Standards Support	SM42020 Small Molecules 4

Chromatographic Database Information: Chromatographic Database

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