Eszopiclone Tablets

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Expert Committee	Chemical Medicines Monographs 4
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 4 Expert Committee has revised the Eszopiclone Tablets monograph. The purpose for the revision is to add *Dissolution Test 2* to accommodate drug products which were approved with different dissolution conditions and acceptance criteria. A *Labeling* section is also added and minor editorial changes have been made to update the monograph to current *USP* style.

Dissolution Test 2 was validated using a Kromasil C18 brand of column with L1 packing. The typical retention time of eszopiclone is about 4.9 min.

The Eszopiclone Tablets Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated into the *First Supplement* to *USP 41–NF 36*.

Should you have any questions, please contact Heather Joyce, Ph.D., Senior Scientific Liaison (301–998–6792 or hrj@usp.org).

Eszopiclone Tablets

DEFINITION

Eszopiclone Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of eszopiclone ($C_{17}H_{17}ClN_6O_3$).

IDENTIFICATION

- **A. INFRARED ABSORPTION ⟨197K⟩**

  Standard: USP Eszopiclone RS

  Sample: Nominally 37.5 mg of eszopiclone from Tablets prepared as follows. Powder a number of Tablets, and mix the resulting powder. Transfer a portion of powder, equivalent to 37.5 mg of eszopiclone, to a suitable container, add 30 mL of acetone, and shake. Dilute with acetone to 50 mL and pass the resulting solution through a suitable filter. Evaporate the filtrate to dryness on a water bath and dry the residue in an oven at 60° for 2 h.

  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**

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

  Mobile phase: Acetonitrile and *Solution A* (25:75) adjusted with dilute phosphoric acid to a pH of 6.5 ± 0.05

  Standard stock solution: 0.5 mg/mL of USP Eszopiclone RS prepared as follows. Transfer a suitable quantity of USP Eszopiclone RS to an appropriate volumetric flask and add 50% of the final flask volume of acetonitrile. Sonication may be used to promote dissolution. Dilute with acetonitrile to volume.

  Standard solution: 0.03 mg/mL of USP Eszopiclone RS from *Standard stock solution* in *Mobile phase* passed through a suitable filter of 0.45-µm pore size. Use the filtrate.

  Sample stock solution: Nominally 0.2 mg/mL of eszopiclone from Tablets prepared as follows. Transfer NLT 5 intact Tablets to a suitable volumetric flask. Add 5% of the final flask volume of *Solution A* and sonicate in cool water for 5 min with constant shaking. Add 30% of the final flask volume of acetonitrile and sonicate for 15 min. Dilute with acetonitrile to volume. Centrifuge the resulting solution and use the supernatant.

  Sample solution: Nominally 0.03 mg/mL of eszopiclone from *Sample stock solution* in *Mobile phase* passed through a suitable filter of 0.45-µm pore size. Use the filtrate.

  Chromatographic system
  (See *Chromatography* ⟨621⟩, *System Suitability*.)
  Mode: LC
  Detector: UV 303 nm
  Column: 4.6-mm × 15.0-cm; 5-µm packing L1
  Column temperature: 30°
  Flow rate: 1.5 mL/min
  Injection volume: 50 µL
  Run time: NLT 1.9 times the retention time of eszopiclone

  System suitability
  Sample: *Standard solution*
  Suitability requirements
  Tailing factor: NMT 2.0
  Relative standard deviation: NMT 2.0%

  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of the labeled amount of eszopiclone ($C_{17}H_{17}ClN_6O_3$) in the portion of Tablets 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 = nominal concentration of eszopiclone in the *Sample solution* (mg/mL)

  Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION ⟨711⟩**

  Test 1 (RB 1-Aug-2017)
  Medium: 0.1 N hydrochloric acid; 500 mL
  Apparatus 2: 50 rpm
  Time: 30 min
  Solution A: 1.4 g/L of anhydrous dibasic sodium phosphate in water
  Mobile phase: Acetonitrile and *Solution A* (30:70) adjusted with dilute phosphoric acid (1 in 10) to a pH of 6.5 ± 0.05
  Standard stock solution: 0.1 mg/mL of USP Eszopiclone RS in acetonitrile. Sonication may be used to promote dissolution.
  Standard solution: (*L*/500) mg/mL of USP Eszopiclone RS from *Standard stock solution* in *Medium*, where *L* is the Tablet label claim in mg. Pass the resulting solution through a suitable filter of 0.45-µm pore size and use the filtrate.
  Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size and use the filtrate.
  Chromatographic system
  (See *Chromatography* ⟨621⟩, *System Suitability*.)
  Mode: LC
  Detector: UV 303 nm
  Column: 4.6-mm × 15.0-cm; 5-µm packing L1
  Column temperature: 30°
  Flow rate: 1.2 mL/min
  Injection volume: 100 µL
  Run time: NLT 1.5 times the retention time of eszopiclone
  System suitability
  Sample: *Standard solution*
  Suitability requirements
  Tailing factor: NMT 2.0
  Relative standard deviation: NMT 2.0%
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of the labeled amount of eszopiclone ($C_{17}H_{17}ClN_6O_3$) dissolved:

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

  r_U = peak response from the *Sample solution*
  r_S = peak response from the *Standard solution*

C_S = concentration of USP Eszopiclone RS in the *Standard solution* (mg/mL)
V = volume of *Medium*, 500 mL
L = label claim (mg/Tablet)

Acceptance criteria: NLT 80% (*Q*) of the labeled amount of eszopiclone ($C_{17}H_{17}ClN_6O_3$) is dissolved.

•**Test 2**

Medium: 0.1 N hydrochloric acid VS; 500 mL
Apparatus 2: 50 rpm
Time: 20 min
Buffer: To each liter of water add 1.0 mL of phosphoric acid and adjust with 2 N sodium hydroxide TS to a pH of 4.0.
Mobile phase: Acetonitrile and *Buffer* (20:80)
Standard stock solution: 0.1 mg/mL of USP Eszopiclone RS in *Medium*. Sonication may be used to promote dissolution.
Standard solution: (*L*/500) mg/mL of USP Eszopiclone RS from *Standard stock solution* in *Medium*, where *L* is the label claim in mg/Tablet. Pass the resulting solution through a suitable filter of 0.45-µm pore size and use the filtrate.
Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size and use the filtrate.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 303 nm
Column: 4.6-mm × 15.0-cm; 5-µm packing L1
Column temperature: 45°
Flow rate: 1 mL/min
Injection volume: 80 µL
Run time: NLT 1.5 times the retention time of eszopiclone
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of eszopiclone ($C_{17}H_{17}ClN_6O_3$) dissolved:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Eszopiclone RS in the *Standard solution* (mg/mL)
V = volume of *Medium*, 500 mL
L = label claim (mg/Tablet)

Tolerances: NLT 80% (*Q*) of the labeled amount of eszopiclone ($C_{17}H_{17}ClN_6O_3$) is dissolved.• (RB 1-Aug-2017)

- **UNIFORMITY OF DOSAGE UNITS ⟨905⟩:** Meets the requirements

IMPURITIES

Change to read:

- **ORGANIC IMPURITIES**

Protect all solutions from light.
Solution A: 8.1 g/L of •sodium dodecyl sulfate• (RB 1-Aug-2017) and 6.9 g/L of monobasic sodium phosphate in water. Sonicate for NLT 15 min and do not let the temperature of the water bath exceed 25°. Pass the resulting solution through a suitable filter of 0.45-µm pore size. Foam may form during filtration.
Mobile phase: Acetonitrile and *Solution A* (37:63) adjusted with dilute phosphoric acid (1 in 100) to a pH of 4.8 ± 0.05
Diluent: Acetonitrile and *Solution A* (37:63) adjusted with dilute phosphoric acid (1 in 100) to a pH of 2.5 ± 0.05
System suitability solution: 0.008 mg/mL each of USP Eszopiclone Related Compound A RS and USP Eszopiclone RS in *Diluent*. Sonication may be used to promote dissolution.
Standard solution: 0.008 mg/mL of USP Eszopiclone RS in *Diluent* passed through a suitable membrane filter of 0.45-µm pore size. Use the filtrate. Sonication may be used to promote dissolution.
Sample solution: Nominally 0.8 mg/mL of eszopiclone in *Diluent* prepared as follows. Crush NLT 20 Tablets to a fine powder and transfer a suitable portion to an appropriate volumetric flask. Add 60% of the final flask volume of *Diluent*, sonicate for 15 min in cold water with periodic shaking, and dilute with *Diluent* to volume. Pass the resulting solution through a suitable membrane filter of 0.45-µm pore size, and use the filtrate.
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 volume: 50 µL
Run time: NLT 2 times the retention time of eszopiclone
System suitability
Samples: *System suitability solution* and *Standard solution*
Suitability requirements
Resolution: NLT 10 between eszopiclone related compound A and eszopiclone, *System suitability solution*
Tailing factor: NMT 2.0 for eszopiclone, *Standard solution*
Relative standard deviation: NMT 5.0%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each degradation product in the portion of Tablets taken:

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

r_U = peak response of each degradation product 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 = nominal concentration of eszopiclone in the *Sample solution* (mg/mL)
F = relative response factor (see *Table 1*)

Acceptance criteria: See *Table 1*. Disregard peaks less than 0.04%.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Zopiclone alcohol[a]	0.11	1.7	1.0
2-Amino-5-chloropyridine	0.21	0.76	1.0
Eszopiclone related compound A	0.44	0.86	1.0
Eszopiclone	1.0	—	—
Any individual unspecified degradation product	—	1.0	0.50
Total degradation products	—	—	2.0

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

ADDITIONAL REQUIREMENTS

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

Add the following:

- **LABELING:** The labeling states the *Dissolution* test used only if *Test 1* is not used. (RB 1-Aug-2017)
- **USP REFERENCE STANDARDS** ⟨11⟩
  USP Eszopiclone RS
  USP Eszopiclone Related Compound A RS
  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