Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each impurity in the portion of Tablets 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 zolpidem from the *Standard solution*
C_S = concentration of USP Zolpidem Tartrate RS in the *Standard solution* (mg/mL)
C_U = concentration of zolpidem tartrate in the *Sample solution* (mg/mL)

Acceptance criteria
Individual impurities: See *Impurity Table 1*.
Total impurities: NMT 0.5%

Impurity Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Zolpidem acid[a]	0.23	0.3
Zolpidem related compound B[b]	0.58	0.3
Zolpidem related compound C[c]	0.70	0.3
Zolpidem tartrate	1.0	—
Zolpidem carbaldehyde[d]	1.45	0.3
Any individual unspecified degradation product	—	0.2

[a] 2-(6-Methyl-2-*p*-tolylimidazo[1,2-α]pyridin-3-yl)acetic acid.
[b] *N,N*-Dimethyl-2-(6-methyl-2-*p*-tolylimidazo[1,2-a]pyridin-3-yl)-2-oxoacetamide.
[c] 4-Methyl-*N*-(5-methylpyridin-2-yl)benzamide.
[d] 6-Methyl-2-*p*-tolylimidazo[1,2-α]pyridine-3-carbaldehyde.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers, and store at controlled room temperature.
- **USP REFERENCE STANDARDS ⟨11⟩**
  USP Zolpidem Impurities Mixture RS
  Contains at least 98.5% of zolpidem tartrate; 0.2% of zolpidem tartrate related compound B (*N,N,*6-trimethyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine-3-(2-oxoacetamide)); and 0.2% of zolpidem tartrate related compound C (5-methyl-2-(4-methylbenzamido)pyridine).
  USP Zolpidem Tartrate RS

Zolpidem Tartrate Extended-Release Tablets

DEFINITION

Zolpidem Tartrate Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of zolpidem tartrate ($C_{42}H_{48}N_6O_8$).

IDENTIFICATION

- **A. ULTRAVIOLET ABSORPTION ⟨197U⟩**
  Sample: 25 µg/mL of zolpidem tartrate in 0.01 M hydrochloric acid from a suitable quantity of powder obtained by grinding 1 Tablet
- **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**
  Buffer: 3.3 mL of phosphoric acid in 1 L of water. Adjust with triethylamine to a pH of 5.5.
  Mobile phase: Acetonitrile, methanol, and *Buffer* (4:5:11)
  Standard stock solution: 0.5 mg/mL of USP Zolpidem Tartrate RS in a mixture of alcohol and 0.01 M hydrochloric acid (4:1)
  Standard solution: 0.1 mg/mL of USP Zolpidem Tartrate RS in *Mobile phase* from the *Standard stock solution*
  Sample stock solution: Finely powder NLT 8 Tablets. Transfer the powder quantitatively to a suitable volumetric flask to obtain 0.5 mg/mL of zolpidem tartrate. Add 70% of the flask volume of a mixture of alcohol and 0.01 M hydrochloric acid (5:2), and stir on a magnetic stirrer for 1 h. Dilute with alcohol to volume. Allow solid particles to settle, and pass the supernatant through a suitable filter (Whatman 40 or equivalent).
  Sample solution: 0.1 mg/mL of zolpidem tartrate from filtered *Sample stock solution* in *Mobile phase*
  Chromatographic system
  (See *Chromatography* ⟨621⟩, *System Suitability*.)
  Mode: LC
  Detector: UV 240 nm
  Column: 4.6-mm × 15-cm; 5-µm packing L1
  Column temperature: 40°
  Flow rate: 1 mL/min
  Injection size: 15 µL
  System suitability
  Sample: *Standard solution*
  Suitability requirements
  Tailing factor: NMT 3.0 for zolpidem
  Relative standard deviation: NMT 2.0% for zolpidem
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of the labeled amount of zolpidem tartrate ($C_{42}H_{48}N_6O_8$) 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 Zolpidem Tartrate RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION ⟨711⟩**
  •Test 1• (RB 1-Jul-2011)
  Medium: 0.01 N hydrochloric acid; 500 mL
  Apparatus 1: 100 rpm
  Times: 30, 90, and 240 min
  Standard solution: Solution of USP Zolpidem Tartrate RS in *Medium* containing (*L*/500) mg/mL, where *L* is the label claim in mg/Tablet
  Sample solution: Pass a portion of the solution under test through a suitable filter.
  Detector: UV 295 nm
  Cell path: 1 cm
  Blank: *Medium*
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of the labeled amount of zolpidem tartrate ($C_{42}H_{48}N_6O_8$) dissolved:

$$\text{Result} = (A_U/A_S) \times (C_S/L) \times V \times 100$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)

L = label claim (mg/Tablet)
V = volume of *Medium*, 500 mL
Tolerances: See *Table 1*.

Table 1

Time (min)	Amount Dissolved
30	50%–70%
90	70%–90%
240	NLT 85%

The percentages of the labeled amount of zolpidem tartrate ($C_{42}H_{48}N_6O_8$) dissolved in the times specified conform to *Acceptance Table 2* in *Dissolution* ⟨711⟩.

•**Test 2:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.
Medium, Apparatus, and **Times:** Proceed as directed for *Test 1*.
Standard solution: Solution of USP Zolpidem Tartrate RS in *Medium* containing (L/500) mg/mL, where L is the label claim in mg/Tablet
Sample solution: Pass a portion of the solution under test through a suitable filter.
Detector: UV 295 nm
Blank: *Medium*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of zolpidem tartrate ($C_{42}H_{48}N_6O_8$) dissolved:

$$\text{Result} = (A_U/A_S) \times (C_S/L) \times V \times 100$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
L = label claim (mg/Tablet)
V = volume of *Medium*, 500 mL
Tolerances: See *Table 2*.

Table 2

Time (min)	Amount Dissolved
30	55%–75%
90	70%–90%
240	NLT 85%

The percentages of the labeled amount of zolpidem tartrate ($C_{42}H_{48}N_6O_8$) dissolved in the times specified conform to *Acceptance Table 2* in *Dissolution* ⟨711⟩.

Test 3: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.
Medium: 0.01 N hydrochloric acid; 500 mL
Apparatus 1: 100 rpm
Times: 30, 90, and 120 min
Standard solution: Solution of USP Zolpidem Tartrate RS in *Medium* containing (L/500) mg/mL, where L is the label claim in mg/Tablet
Sample solution: Pass a portion of the solution under test through a suitable filter.
Detector: UV 237 nm
Blank: *Medium*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of zolpidem tartrate ($C_{42}H_{48}N_6O_8$) dissolved:

$$\text{Result} = (A_U/A_S) \times (C_S/L) \times V \times 100$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
L = label claim (mg/Tablet)
V = volume of *Medium*, 500 mL
Tolerances: See *Table 3*.

Table 3

Time (min)	Amount Dissolved
30	25%–45%
90	65%–85%
120	NLT 80%

The percentages of the labeled amount of zolpidem tartrate ($C_{42}H_{48}N_6O_8$) dissolved in the times specified conform to *Acceptance Table 2* in *Dissolution* ⟨711⟩.• (RB 1-Jul-2011)

• **Uniformity of Dosage Units ⟨905⟩:** Meet the requirements

IMPURITIES

Change to read:

• **Organic Impurities**
Buffer, Mobile phase, Standard stock solution, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.
System suitability solution: Dissolve a suitable amount of USP Zolpidem Related Compound A RS in *Standard stock solution* to obtain a solution containing 1 µg/mL of zolpidem related compound A. Dilute 1 mL of the resulting solution with *Mobile phase* to 5 mL.
System suitability
Sample: *System suitability solution*
Suitability requirements
Resolution: NLT 1.5 between zolpidem related compound A and zolpidem
Tailing factor: NMT 3.0 for the zolpidem peak
Relative standard deviation: NMT 2.0% for the zolpidem peak
Analysis
Sample: *Sample solution*
Calculate the percentage of each impurity in the portion of Tablets taken:

$$\text{Result} = (r_U/r_T) \times (1/F) \times 100$$

r_U = peak response for each impurity from the *Sample solution*
r_T = sum of the peak responses for all the peaks from the *Sample solution*
F = relative response factor of the corresponding impurity from *Table 4*
Acceptance criteria: See *Table 4*.

Table 4

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Zolpidem acid[a]	0.3	•1.2• (RB 1-Jul-2011)	0.20
Zolpidem related compound A[b]	0.9	1.0	0.20
Zolpidem	1.0	—	—
Any unspecified degradation product	—	1.0	0.20
Total impurities	—	—	0.5

[a] 2-(6-Methyl-2-*p*-tolylimidazo[1,2-*a*]pyridin-3-yl)acetic acid.
[b] *N,N*-Dimethyl-2-(7-methyl-2-*p*-tolylimidazo[1,2-*a*]pyridin-3-yl)acetamide.

ADDITIONAL REQUIREMENTS

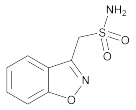
• **Packaging and Storage:** Preserve in well-closed containers, and store at controlled room temperature.

Add the following:

•• **LABELING:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.• (RB 1-Jul-2011)

• **USP REFERENCE STANDARDS** ⟨**11**⟩
USP Zolpidem Related Compound A RS
N,N-Dimethyl-2-(7-methyl-2-*p*-tolylimidazo[1,2-*a*]pyridin-3-yl)acetamide.
$C_{19}H_{21}N_3O$ 307.39
USP Zolpidem Tartrate RS

Zonisamide



$C_8H_8N_2O_3S$ 212.23
1,2-Benzisoxazole-3-methanesulfonamide [68291-97-4].

DEFINITION
Zonisamide contains NLT 98.0% and NMT 102.0% of $C_8H_8N_2O_3S$, calculated on the anhydrous basis.

IDENTIFICATION
• **A. INFRARED ABSORPTION** ⟨**197K**⟩
• **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**
Buffer: 1.36 g/L of monobasic potassium phosphate in water. Adjust the pH to 3.0 ± 0.1 with 10% phosphoric acid.
Mobile phase: Acetonitrile, methanol, and *Buffer* (1:1:8)
Standard solution: 0.1 mg/mL of USP Zonisamide RS in *Mobile phase*
Sample solution: 0.1 mg/mL of Zonisamide in *Mobile phase*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 240 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Flow rate: 1.5 mL/min
Injection size: 20 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Column efficiency: NLT 5000 theoretical plates
Tailing: NMT 1.8
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of $C_8H_8N_2O_3S$ in the portion of Zonisamide taken:

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

r_U = peak response of zonisamide from the *Sample solution*
r_S = peak response of zonisamide from the *Standard solution*
C_S = concentration of USP Zonisamide RS in the *Standard solution* (mg/mL)
C_U = concentration of Zonisamide in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the anhydrous basis

IMPURITIES
Inorganic Impurities
• **HEAVY METALS,** *Method II* ⟨**231**⟩**:** NMT 10 ppm
• **RESIDUE ON IGNITION** ⟨**281**⟩**:** NMT 0.1%
Organic Impurities
• **PROCEDURE**
Mobile phase: Prepare as directed in the *Assay.*
Standard solution: 1 µg/mL of USP Zonisamide RS and 1.5 µg/mL of USP Zonisamide Related Compound A RS in *Mobile phase*
Sample solution: 1.0 mg/mL of Zonisamide in *Mobile phase*
Chromatographic system: Prepare as directed in the *Assay.*
Run time: 2 times the retention time of the zonisamide peak
System suitability
Sample: *Standard solution*
Suitability requirements
Resolution: NLT 10.0 between zonisamide related compound A and zonisamide
Relative standard deviation: NMT 10.0% for both zonisamide and zonisamide related compound A peaks
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of zonisamide related compound A in the portion of Zonisamide taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of zonisamide related compound A from the *Sample solution*
r_S = peak response of zonisamide related compound A from the *Standard solution*
C_S = concentration of USP Zonisamide Related Compound A RS in the *Standard solution* (mg/mL)
C_U = concentration of zonisamide related compound A in the *Sample solution* (mg/mL)
M_{r1} = molecular weight of zonisamide related compound A (free acid), 213.23
M_{r2} = molecular weight of USP Zonisamide Related Compound A RS (sodium salt), 235.23

Calculate the percentage of any unspecified impurity in the portion of Zonisamide 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 zonisamide from the *Standard solution*
C_S = concentration of USP Zonisamide RS in the *Standard solution* (mg/mL)
C_U = concentration of Zonisamide in the *Sample solution* (mg/mL)