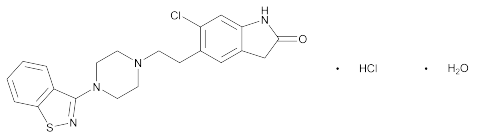
Ziprasidone Hydrochloride



$C_{21}H_{21}ClN_4OS \cdot HCl \cdot H_2O$ 467.41

2*H*-Indol-2-one, 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl] ethyl]-6-chloro-1,3-dihydro-, monohydrochloride, monohydrate;

5-[2-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-2-indolinone monohydrochloride, monohydrate [138982-67-9].

DEFINITION

Ziprasidone Hydrochloride contains NLT 98.0% and NMT 102.0% of $C_{21}H_{21}ClN_4OS \cdot HCl$, calculated on the anhydrous and solvent-free 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*.
- **C. Identification Tests—General,** *Chloride* ⟨**191**⟩**:** Meets the requirements

ASSAY

- **Procedure**

Buffer: 6.8 g/L of monobasic potassium phosphate in water. Adjust with 85% phosphoric acid to a pH of 3.0.
Mobile phase: Methanol and *Buffer* (2:3)
Diluent: Methanol and water (3:2)
Standard solution: 0.23 mg/mL of USP Ziprasidone Hydrochloride RS in *Diluent*
Sample solution: 0.23 mg/mL of Ziprasidone Hydrochloride in *Diluent*
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 229 nm
Column: 4.6-mm × 15-cm; 5-µm packing L7
Column temperature: 40°
Flow rate: 1.5 mL/min
Injection size: 20 µL
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 $C_{21}H_{21}ClN_4OS \cdot HCl$ in the portion of Ziprasidone Hydrochloride 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 Ziprasidone Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of Ziprasidone Hydrochloride in the *Sample solution* (mg/mL)

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

IMPURITIES

Inorganic Impurities

- **Residue on Ignition** ⟨**281**⟩**:** NMT 0.1%
- **Heavy Metals,** *Method II* ⟨**231**⟩**:** NMT 20 ppm

Organic Impurities

- **Procedure 1: Limit of Tetrahydrofuran**

Standard solution: 0.05 mg/mL in dimethyl sulfoxide. Transfer 4 mL of this solution to a 20-mL headspace vial, and seal.
Sample solution: Transfer 40 mg of Ziprasidone Hydrochloride and 4.0 mL of dimethyl sulfoxide to a 20-mL headspace vial, seal, and mix.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: GC with headspace injector
Detector: Flame ionization
Column: 30-m × 0.32-mm fused silica column coated with a 1.8-µm film of phase G43
Temperature
Injection port: 180°
Detector: 260°
Column: See the temperature program table below.

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
40	0	40	5
40	2	90	0
90	30	225	2

Injector split ratio: 30:1
Carrier gas: Helium
Flow rate: 1.6 mL/min
Injection size: 2 mL
System suitability
Sample: *Standard solution*
Suitability requirements
Relative standard deviation: NMT 5%
Analysis: [NOTE—The headspace vials are maintained at 105° for 60 min prior to headspace injection.]
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of tetrahydrofuran in the portion of Ziprasidone Hydrochloride taken:

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

r_U = peak response of tetrahydrofuran from the *Sample solution*
r_S = peak response of tetrahydrofuran from the *Standard solution*
C_S = concentration of tetrahydrofuran in the *Standard solution* (mg/mL)
C_U = nominal concentration of Ziprasidone Hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria
Tetrahydrofuran: NMT 0.4%

- **Procedure 2: Limit of Early-Eluting Impurities**

Mobile phase and **Chromatographic system:** Proceed as directed in the *Assay*.
Diluent A: Methanol, water, and hydrochloric acid (20:5:0.01)
Diluent B: Methanol and water (3:2)
Standard solution A: 0.5 µg/mL of USP Ziprasidone Related Compound A RS and 0.8 µg/mL of USP Ziprasidone Related Compound B RS in *Diluent A*
Standard solution B: 0.4 µg/mL of USP Ziprasidone Related Compound B RS in *Diluent A*
System suitability solution: 0.24 mg/mL of USP Ziprasidone Hydrochloride RS in *Standard solution A*
Sample solution A: 0.4 mg/mL of Ziprasidone Hydrochloride in *Diluent A*
Sample solution B: 0.2 mg/mL of Ziprasidone Hydrochloride in *Diluent B*

System suitability
Sample: *System suitability solution*
Suitability requirements
Resolution: NLT 1.5 between the ziprasidone related compound B and ziprasidone peaks
Relative standard deviation: NMT 10% for the ziprasidone related compound B peak
Analysis: [NOTE—Run the *Sample solution* NLT 7 times the ziprasidone retention time in *Sample solution A*.]
Samples: *Standard solution A* and *Sample solution A*
Calculate the percentages of ziprasidone related compounds A and B relative to the content of ziprasidone free base in the portion of Ziprasidone Hydrochloride taken:

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

r_U = peak response of the ziprasidone related compound from *Sample solution A*
r_S = peak response of the ziprasidone related compound from *Standard solution A*
C_S = concentration of the ziprasidone related compound in *Standard solution A* (mg/mL)
C_U = nominal concentration of Ziprasidone Hydrochloride in *Sample solution A* (mg/mL)
M_{r1} = molecular weight of ziprasidone free base, 412.94
M_{r2} = molecular weight of ziprasidone hydrochloride, 467.41

Samples: *Standard solution B* and *Sample solution B*
Calculate the percentage of ziprasidone open ring relative to the content of ziprasidone free base in the portion of Ziprasidone Hydrochloride taken:

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

r_U = peak response of ziprasidone open ring from *Sample solution B*
r_S = peak response of ziprasidone related compound B from *Standard solution B*
C_S = concentration of ziprasidone related compound B in *Standard solution B* (mg/mL)
C_U = nominal concentration of Ziprasidone Hydrochloride in *Sample solution B* (mg/mL)
M_{r1} = molecular weight of ziprasidone free base, 412.94
M_{r2} = molecular weight of ziprasidone hydrochloride, 467.41

Samples: *Diluent A*, *Diluent B*, *Standard solution B*, and *Sample solution A*
Calculate the percentage of unspecified impurity eluting before ziprasidone relative to the content of ziprasidone free base in the portion of Ziprasidone Hydrochloride taken:

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

r_U = peak response of each unspecified impurity from *Sample solution A*
r_S = peak response of ziprasidone related compound B from *Standard solution B*
C_S = concentration of ziprasidone related compound B in *Standard solution B* (mg/mL)
C_U = nominal concentration of Ziprasidone Hydrochloride in *Sample solution A* (mg/mL)
M_{r1} = molecular weight of ziprasidone free base, 412.94
M_{r2} = molecular weight of ziprasidone hydrochloride, 467.41

[NOTE—Disregard the peaks in the injections of *Diluent A* and *Diluent B*.]

Acceptance criteria
Individual impurities: See *Impurity Table 1*.

Impurity Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Ziprasidone related compound A	0.4	0.1
Ziprasidone related compound B	0.8	0.2
Ziprasidone open ring[a]	0.9	0.2
Ziprasidone	1.0	—
Any individual unspecified impurity eluting before ziprasidone	—	0.1

[a] 2-(2-Amino-5-(2-(4-(benzo[*d*]isothiazol-3-yl)piperazin-1-yl)ethyl)-4-chlorophenyl)acetic acid.

• **PROCEDURE 3: LIMIT OF LATE-ELUTING IMPURITIES**
Buffer: 6.8 g/L of monobasic potassium phosphate in water. Adjust with 5 N potassium hydroxide to a pH of 6.0.
Mobile phase: Acetonitrile, methanol, and *Buffer* (11:1:8)
Diluent: Methanol, water, and hydrochloric acid (20:5:0.01)
Standard solution: 0.8 µg/mL each of USP Ziprasidone Related Compound C RS and USP Ziprasidone Related Compound D RS in *Diluent*
System suitability solution: 0.24 mg/mL of USP Ziprasidone Hydrochloride RS in the *Standard solution*
Sample solution: 0.45 mg/mL of Ziprasidone Hydrochloride in *Diluent*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 229 nm
Column: 4.6-mm × 15-cm; 5-µm packing L7
Column temperature: 35°
Flow rate: 1 mL/min
Injection size: 20 µL
System suitability
Sample: *System suitability solution*
Suitability requirements
Resolution: NLT 6.0 between the ziprasidone and ziprasidone related compound C peaks
Relative standard deviation: NMT 10% for the ziprasidone related compound C peak
Analysis: [NOTE—Run the *Sample solution* NLT 12 times the ziprasidone retention time in the *Sample solution*.]
Samples: *Standard solution* and *Sample solution*
Calculate the percentages of ziprasidone related compounds C and D relative to the content of ziprasidone free base in the portion of Ziprasidone Hydrochloride taken:

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

r_U = peak response of the ziprasidone related compound from the *Sample solution*
r_S = peak response of the ziprasidone related compound from the *Standard solution*
C_S = concentration of the ziprasidone related compound in the *Standard solution* (mg/mL)
C_U = nominal concentration of Ziprasidone Hydrochloride in the *Sample solution* (mg/mL)
M_{r1} = molecular weight of ziprasidone hydrochloride free base, 412.94
M_{r2} = molecular weight of ziprasidone hydrochloride, 467.41

Samples: *Diluent*, *Standard solution,* and *Sample solution*
Calculate the percentage of unspecified impurity eluting after ziprasidone relative to the content of ziprasidone

free base in the portion of Ziprasidone Hydrochloride taken:

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

r_U = peak response of each unspecified impurity from the *Sample solution*
r_S = peak response of ziprasidone related compound D from the *Standard solution*
C_S = concentration of ziprasidone related compound D in the *Standard solution* (mg/mL)
C_U = nominal concentration of Ziprasidone Hydrochloride in the *Sample solution* (mg/mL)
M_{r1} = molecular weight of ziprasidone hydrochloride free base, 412.94
M_{r2} = molecular weight of ziprasidone hydrochloride, 467.41

[NOTE—Disregard the peaks in the injection of the *Diluent*.]

Acceptance criteria

Individual impurities: See *Impurity Table 2*.

Total impurities: NMT 0.5%. [NOTE—The total impurities are the sum of related compounds A, B, C, D, ziprasidone open ring, and all unspecified impurities found in *Procedure 2: Limit of Early-Eluting Impurities* and *Procedure 3: Limit of Late-Eluting Impurities*.]

Impurity Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Ziprasidone	1.0	—
Ziprasidone related compound C	2.0	0.2
Ziprasidone related compound D	3.0	0.2
Any individual unspecified impurity eluting after ziprasidone	—	0.1

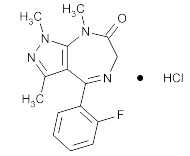
SPECIFIC TESTS

- **WATER DETERMINATION,** *Method I* ⟨**921**⟩**:** Between 3.7% and 5.0%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers, and store at room temperature.
- **USP REFERENCE STANDARDS** ⟨**11**⟩
  USP Ziprasidone Hydrochloride RS
  USP Ziprasidone Related Compound A RS
  3-(Piperazin-1-yl)benzo[*d*]isothiazole monohydrochloride.
  $C_{11}H_{13}N_3S \cdot HCl$ 255.77
  USP Ziprasidone Related Compound B RS
  5-(2-(4-(Benzo[*d*]isothiazol-3-yl)piperazin-1-yl)ethyl)-6-chloroindoline-2,3-dione.
  $C_{21}H_{19}ClN_4O_2S$ 426.92
  USP Ziprasidone Related Compound C RS
  5,5′-Bis(2-(4-(benzo[*d*]isothiazol-3-yl)piperazin-1-yl)ethyl)-6,6′-dichloro-3-hydroxy-3,3′-biindoline-2,2′-dione.
  $C_{42}H_{40}Cl_2N_8O_3S_2$ 839.85
  USP Ziprasidone Related Compound D RS
  3-(Benzo[*d*]isothiazol-3-yl)-5-(2-(4-(benzo[*d*]isothiazol-3-yl)piperazin-1-yl)ethyl)-6-chloroindolin-2-one.
  $C_{28}H_{24}ClN_5OS_2$ 546.11

Zolazepam Hydrochloride



$C_{15}H_{15}FN_4O \cdot HCl$ 322.77

Pyrazolo[3,4-*e*][1,4]diazepin-7(1*H*)-one, 4-(2-fluorophenyl)-6,8-dihydro-1,3,8-trimethyl-, monohydrochloride.

4-(*o*-Fluorophenyl)-6,8-dihydro-1,3,8-trimethylpyrazolo[3,4-*e*][1,4]diazepin-7(1*H*)-one monohydrochloride [33754-49-3].

» Zolazepam Hydrochloride contains not less than 97.0 percent and not more than 103.0 percent of $C_{15}H_{15}FN_4O \cdot HCl$.

Packaging and storage—Preserve in tight containers.

Labeling—Label it to indicate that it is for veterinary use only. Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms.

USP Reference standards ⟨11⟩**—**
USP Endotoxin RS
USP Zolazepam Hydrochloride RS

Clarity of solution—Dissolve 2.0 g of it in 10 mL of water: the solution is clear.

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: *Ultraviolet Absorption* ⟨197U⟩—

Solution: 0.015 mg per mL.

Medium: 0.1 N hydrochloric acid.

Absorptivities at 223 nm do not differ by more than 3.0%.

C: It responds to the tests for *Chloride* ⟨191⟩.

Bacterial endotoxins ⟨85⟩—Where the label states that Zolazepam Hydrochloride is sterile or must be subjected to further processing during the preparation of injectable dosage forms, it contains not more than 0.07 USP Endotoxin Unit per mg of zolazepam.

Sterility ⟨71⟩—Where the label states that Zolazepam Hydrochloride is sterile, it meets the requirements when tested as directed for *Membrane Filtration* under *Test for Sterility of the Product to be Examined*.

pH ⟨791⟩: between 1.5 and 3.5, in a solution (1 in 10).

Loss on drying ⟨731⟩**—**Dry it at 105° for 4 hours: it loses not more than 1.0% of its weight.

Residue on ignition ⟨281⟩: not more than 0.5%.

Heavy metals, *Method II* ⟨231⟩: 0.002%.

Chromatographic purity—

Modified Dragendorff's reagent—Dissolve 1.7 g of bismuth subnitrate in 80 mL of water and 20 mL of glacial acetic acid, warming, if necessary. Cool, add 100 mL of potassium iodide solution (1 in 2), and mix. Refrigerate this stock solution for prolonged storage. For use, dilute 10 mL of this stock solution with water to 100 mL, add 10 mL of glacial acetic acid, and mix. Then add 120 mg of iodine crystals, and shake until the iodine has completely dissolved. Store refrigerated, and discard after 2 weeks.

Procedure—Prepare a test solution of Zolazepam Hydrochloride in methanol containing 100 mg per mL. Prepare a Standard solution in methanol containing 2.0 mg of USP Zolazepam Hydrochloride RS per mL. Prepare a thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of chromatographic silica gel mixture. Separately apply 5 µL of