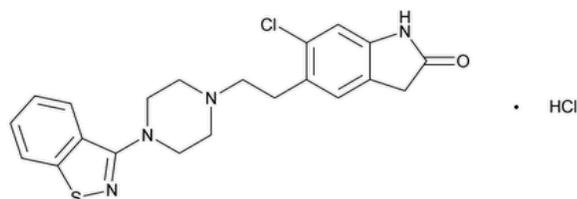


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Ziprasidone Hydrochloride



$C_{21}H_{21}ClN_4OS \cdot HCl$ 449.39

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

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

Monohydrate CAS RN[®]: 138982-67-9; UNII: 216X081ORU.

Anhydrous CAS RN[®]: 122883-93-6; UNII: JAL53626GG.

DEFINITION

Ziprasidone Hydrochloride contains NLT 97.5% and NMT 102.0% of ziprasidone hydrochloride ($C_{21}H_{21}ClN_4OS \cdot HCl$), calculated on the anhydrous and solvent-free basis.

IDENTIFICATION

- **A. SPECTROSCOPIC IDENTIFICATION TESTS (197), Infrared Spectroscopy:** 197A or 197K. If a difference appears in the spectra of the analyte and the Reference Standard, dissolve equal portions of the analyte and the Reference Standard in equal volumes of [methanol](#) separately, evaporate to dryness, and record new spectra using the residues.
- **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 (191), Chemical Identification Tests, Chloride**
Sample solution: Suspend 30 mg of the analyte in 2 mL of [water](#), acidify with 0.15 mL of [2 N nitric acid TS](#), and filter. Use the filtrate.
Acceptance criteria: Meets the requirements

ASSAY

PROCEDURE

Buffer: 6.8 g/L of [monobasic potassium phosphate](#) in [water](#). Adjust with [phosphoric acid](#) to a pH of 3.0.

Mobile phase: [Methanol](#) and *Buffer* (40:60)

Diluent: [Methanol](#) and [water](#) (60:40)

Standard solution: 0.23 mg/mL of [USP Ziprasidone Hydrochloride RS](#) in *Diluent*

Sample solution: 0.23 mg/mL of Ziprasidone Hydrochloride in *Diluent*. [NOTE—Because of its hygroscopic nature, the anhydrous form may be dried at 70° under vacuum for 2 h prior to the preparation of the *Sample solution*.]

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 volume: 20 μL

Run time: NLT 2 times the retention time of ziprasidone

System suitability

Sample: *Standard solution*

Suitability requirements**Tailing factor:** NMT 2.0**Relative standard deviation:** NMT 0.73%**Analysis****Samples:** *Standard solution* and *Sample solution*Calculate the percentage of ziprasidone hydrochloride ($C_{21}H_{21}ClN_4OS \cdot HCl$) in the portion of Ziprasidone Hydrochloride taken:

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

 r_U = peak response of ziprasidone from the *Sample solution* r_S = peak response of ziprasidone from the *Standard solution* C_S = concentration of [USP Ziprasidone Hydrochloride RS](#) in the *Standard solution* (mg/mL) C_U = concentration of Ziprasidone Hydrochloride in the *Sample solution* (mg/mL)**Acceptance criteria:** 97.5%–102.0% on the anhydrous and solvent-free basis**IMPURITIES**

- [RESIDUE ON IGNITION \(281\)](#): NMT 0.2%
- **LIMIT OF TETRAHYDROFURAN**

[NOTE—Perform this test only if tetrahydrofuran is likely to be present as the result of the manufacturing process.]

Standard solution: 0.05 mg/mL of [tetrahydrofuran](#) 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; coated with a 1.8- μ m film of phase [G43](#)**Temperatures****Injection port:** 180°**Detector:** 260°**Column:** See [Table 1](#).**Table 1**

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

Carrier gas: Helium**Flow rate:** 1.6 mL/min**Injection volume:** 2 mL**Injection type:** Headspace; split ratio, 30:1**Vial treatment:** Maintain at 105° for 60 min prior to injection**System suitability****Sample:** *Standard solution***Suitability requirements****Relative standard deviation:** NMT 5%**Analysis****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 = concentration of Ziprasidone Hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: NMT 0.4% of tetrahydrofuran

Change to read:

• **ORGANIC IMPURITIES**

Buffer: 6.8 g/L of [monobasic potassium phosphate](#) in [water](#)

Solution A: [Methanol](#) and *Buffer* (33:67). Adjust with [phosphoric acid](#) to a pH of 3.0.

Solution B: [Acetonitrile](#), [methanol](#), and *Buffer* (55:5:40). Adjust with ▲[potassium hydroxide solution](#)▲ (ERR 1-Sep-2023) to a pH of 6.0.

Mobile phase: See [Table 2](#).

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	100	0
15	100	0
20	85	15
30	85	15
40	55	45
55	40	60
65	25	75
70	20	80
71	100	0
75	100	0

Diluent: [Acetonitrile](#), [methanol](#), and [water](#) (40:10:50). Adjust with [phosphoric acid](#) to a pH of 2.5.

System suitability solution: 0.5 mg/mL of [USP Ziprasidone Hydrochloride RS](#) and 0.05 mg/mL each of [USP Ziprasidone Related Compound A RS](#), [USP Ziprasidone Related Compound B RS](#), [USP Ziprasidone Related Compound C RS](#), [USP Ziprasidone Related Compound D RS](#), and [USP Ziprasidone Related Compound F RS](#) in *Diluent*. [NOTE—Ziprasidone related compound F is stable for 6 h at 10° in this solution.]

Sensitivity solution: 0.5 µg/mL of [USP Ziprasidone Hydrochloride RS](#) in *Diluent*

Standard solution: 0.001 mg/mL of [USP Ziprasidone Hydrochloride RS](#) and 0.002 mg/mL each of [USP Ziprasidone Related Compound A RS](#), [USP Ziprasidone Related Compound B RS](#), [USP Ziprasidone Related Compound C RS](#), and [USP Ziprasidone Related Compound D RS](#) in *Diluent*

Sample solution: 1.0 mg/mL of Ziprasidone Hydrochloride in *Diluent*. [NOTE—Because ziprasidone related compound F is stable only for 6 h at 10°, it is recommended that the freshly prepared *Sample solution* be analyzed.]

Chromatographic system

(See [Chromatography \(621\)](#), [System Suitability](#).)

Mode: LC

Detector: UV 229 nm

Column: 4.6-mm × 15-cm; 5-µm packing [L7](#)

Temperatures

Autosampler: 10°

Column: 30°

Flow rate: 1.5 mL/min

Injection volume: 10 µL

System suitability

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

[NOTE—The relative retention times in [Table 3](#) are provided as information that could aid to peak assignment.]

Table 3

Name	Relative Retention Time
Ziprasidone related compound A	0.22
Chloroindolinone ^a	0.59
Ziprasidone related compound B	0.70
Ziprasidone related compound F	0.84
Ziprasidone	1.0
Ziprasidone related compound C	1.84
Ziprasidone related compound D	2.18

^a 6-Chloroindolin-2-one.

Suitability requirements

Resolution: NLT 1.5 between ziprasidone related compound B and related compound F; NLT 2.0 between ziprasidone related compound F and ziprasidone, *System suitability solution*

Tailing factor: NMT 1.5 for ziprasidone, *Standard solution*

Relative standard deviation: NMT 5.0% for ziprasidone, ziprasidone related compound B, ziprasidone related compound C, and ziprasidone related compound D, *Standard solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Samples: *Standard solution and Sample solution*

Calculate the percentage of ziprasidone related compounds A, B, C, and D, relative to the content of ziprasidone free base, in the portion of Ziprasidone Hydrochloride taken:

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

r_U = peak response of ziprasidone related compounds A, B, C, and D from the *Sample solution*

r_S = peak response of the corresponding USP Reference Standard from the *Standard solution*

C_S = concentration of the corresponding USP Reference Standard in the *Standard solution* (mg/mL)

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

M_{r1} = molecular weight of ziprasidone hydrochloride in the sample taken, 467.41 for the monohydrate, [▲]449.39_▲ (ERR 1-Sep-2023) for the anhydrous form

M_{r2} = molecular weight of ziprasidone free base, 412.94

Calculate the percentage of chloroindolinone, ziprasidone related compound F, and any unspecified impurity, relative to the content of ziprasidone free base, in the portion of Ziprasidone Hydrochloride taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times (M_{r1}/M_{r2}) \times (M_{r3}/M_{r1}) \times 100$$

r_U = peak response of chloroindolinone, ziprasidone related compound F, or any unspecified impurity from the *Sample solution*

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

C_S = concentration of [USP Ziprasidone Hydrochloride RS](#) in the *Standard solution* (mg/mL)

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

F = relative response factor (see [Table 4](#))

M_{r1} = molecular weight of ziprasidone free base, 412.94

1

M_{r2} = molecular weight of ziprasidone hydrochloride anhydrous form, \blacktriangle 449.39 \blacktriangle (ERR 1-Sep-2023)

2

M_{r3} = molecular weight of ziprasidone hydrochloride in the sample taken, 467.41 for the monohydrate, \blacktriangle 449.39 \blacktriangle (ERR 1-Sep-2023) for the anhydrous form

3

Acceptance criteria: See [Table 4](#). The reporting threshold is 0.05%.

Table 4

Name	Relative Response Factor	Acceptance Criteria, NMT (%)
Ziprasidone related compound A	—	0.1
Chloroindolinone ^a	0.47	0.15
Ziprasidone related compound B	—	0.2
Ziprasidone related compound F	0.83	0.2
Ziprasidone related compound C	—	0.2
Ziprasidone related compound D	—	0.2
Any unspecified impurity	1.0	0.1
Total impurities	—	0.5

^a A process impurity specific to a manufacturing process; may not be present in all manufacturing processes.

SPECIFIC TESTS

• [WATER DETERMINATION \(921\), Method I](#)

Monohydrate: 3.7%–5.0%

Anhydrous: NMT 2.0%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers, and store at room temperature.
- **LABELING:** If this is an anhydrous form, it is so labeled.

• **USP REFERENCE STANDARDS (11).**

USP Ziprasidone Hydrochloride RS

USP Ziprasidone Related Compound A RS

3-(Piperazin-1-yl)benzothiazole monohydrochloride;
also known as 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-(Benzoisothiazol-3-yl)piperazin-1-yl]ethyl}-6-chloroindoline-2,3-dione;
also known as 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-(benzothiazol-3-yl)piperazin-1-yl]ethyl}-6,6'-dichloro-3-hydroxy-3,3'-biindoline-2,2'-dione;
also known as 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-(Benzoisothiazol-3-yl)-5-{2-[4-(benzothiazol-3-yl)piperazin-1-yl]ethyl}-6-chloroindolin-2-one;
also known as 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

USP Ziprasidone Related Compound F RS

Sodium 2-(2-amino-5-{2-[4-(benzothiazol-3-yl)piperazin-1-yl]ethyl}-4-chlorophenyl)acetate monohydrate;
also known as Sodium 2-(2-amino-5-{2-[4-(benzo[d]isothiazol-3-yl)piperazin-1-yl]ethyl}-4-chlorophenyl)acetate monohydrate.
 $C_{21}H_{22}ClN_4NaO_2S \cdot H_2O$ 470.95

Auxiliary Information - Please [check for your question in the FAQs](#) before contacting USP.

Topic/Question	Contact	Expert Committee
ZIPRASIDONE HYDROCHLORIDE	Documentary Standards Support	SM42020 Small Molecules 4
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM42020 Small Molecules 4

Chromatographic Database Information: [Chromatographic Database](#)

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