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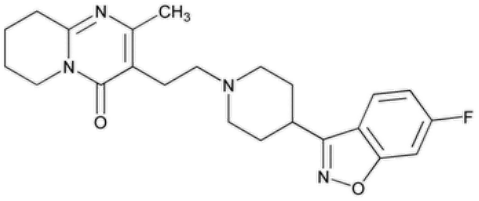
Risperidone



$C_{23}H_{27}FN_4O_2$ 410.48

4*H*-Pyrido[1,2-*a*]pyrimidin-4-one, 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-;
3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one CAS RN®: 106266-06-2.

DEFINITION

Risperidone contains NLT 98.0% and NMT 102.0% of risperidone ($C_{23}H_{27}FN_4O_2$), 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 *Standard solution*, as obtained in the *Assay*.

ASSAY

• **Procedure**

Buffer: 5 g/L of ammonium acetate. Adjust with glacial acetic acid to a pH of 6.0, and pass the solution through a suitable filter.

Solution A: Acetonitrile and tetrahydrofuran (80:20)

Mobile phase: *Buffer* and *Solution A* (80:20)

Standard stock solution: 1 mg/mL of USP Risperidone RS in solution prepared as follows. Dissolve a suitable amount of USP Risperidone RS in 20% of the final volume with methanol. Dilute with *Mobile phase* to final volume. Sonication may be used to aid in dissolution.

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

System suitability solution: 20 µg/mL of USP Risperidone Related Compound G RS in *Standard solution*

Sample stock solution: 1 mg/mL of Risperidone in solution prepared as follows. Dissolve a suitable amount of Risperidone in 20% of the final volume with methanol. Dilute with *Mobile phase* to final volume. Sonication may be used to aid in dissolution.

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

Chromatographic system

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

Mode: LC

Detector: UV 275 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Column temperature: 50°

Flow rate: 1.5 mL/min

Injection volume: 10 µL

Run time: 2 times the retention time of risperidone

System suitability

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

[Note—The relative retention times for risperidone and risperidone related compound G are 1.0 and 1.1, respectively.]

Suitability requirements

Resolution: NLT 1.5 between risperidone and risperidone related compound G, *System suitability solution*

Tailing factor: NMT 2.0 for risperidone, *Standard solution*

Relative standard deviation: NMT 1.0% for risperidone, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of risperidone ($C_{23}H_{27}FN_4O_2$) in the portion of Risperidone 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 Risperidone RS in the *Standard solution* (mg/mL)

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

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

IMPURITIES

- **Residue on Ignition ⟨281⟩**

Sample: 2.0 g of Risperidone

Acceptance criteria: NMT 0.1%

- **Organic Impurities**

Solution A: 5 g/L of ammonium acetate. Adjust with glacial acetic acid to a pH of 6.0, and pass the solution through a suitable filter.

Solution B: Acetonitrile and methanol (40:60)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0.01	70	30
12	65	35
18	65	35
25	35	65
35	30	70
40	30	70
42	70	30
50	70	30

System suitability solution: 20 µg/mL of USP Risperidone Related Compound G RS and 10 mg/mL of USP Risperidone RS in methanol. Sonication may be used to aid in dissolution.

Standard solution: 20 µg/mL of USP Risperidone RS in methanol. Sonication may be used to aid in dissolution.

Sample solution: 10 mg/mL of Risperidone in methanol. Sonication may be used to aid in dissolution.

Chromatographic system

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

Mode: LC

Detector: UV 260 nm

Column: 4.6-mm × 25-cm; 5-µm packing L7

Column temperature: 50°

Flow rate: 2 mL/min

Injection volume: 10 µL

System suitability

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

[NOTE—Identify the peaks using *Table 2*.]

Suitability requirements

Resolution: NLT 1.5 between risperidone and risperidone related compound G, *System suitability solution*

Tailing factor: NMT 2.0 for risperidone, *Standard solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

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

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

r_U = peak area of each impurity from the *Sample solution*

r_S = peak area of risperidone from the *Standard solution*

C_S = concentration of USP Risperidone RS in the *Standard solution* (mg/mL)

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

F = relative response factor for each impurity (see *Table 2*)

Acceptance criteria: See *Table 2*.

[NOTE—Disregard the impurity peaks less than 0.05%.]

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
E-Oxime[a]	0.52	1.0	0.20
Z-Oxime[b]	0.64	1.0	0.20
9-Hydroxyrisperidone[c]	0.71	1.0	0.20
Desfluoro risperidone[d,e]	0.79	1.0	0.10
Risperidone difluoroketone[f]	0.90	1.4	0.10
5-Fluororisperidone[g]	0.94	1.0	0.20
Risperidone	1.00	1.0	—
Risperidone related compound G[e]	1.08	2.5	0.10
6-Methylrisperidone[h]	1.44	1.0	0.20
Any unspecified individual impurity	—	1.0	0.10
Total impurities	—	—	0.30

[a] 3-(2-[4-[(*E*)-(2,4-Difluorophenyl)(hydroxyimino)methyl]piperidin-1-yl]ethyl)-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one.

[b] 3-[2-[4-[(*Z*)-(2,4-Difluorophenyl)(hydroxyimino)methyl]piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one.

[c] (9*RS*)-3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one.

[d] 3-{2-[4-(Benzisoxazol-3-yl)piperidin-1-yl]ethyl}-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one.

[e] This impurity may not be relevant to all manufacturing processes.

[f] 3-[2-[4-(2,4-Difluorobenzoyl)piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one.

[g] 3-[2-[4-(5-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (also known as 5-fluororisperidone).

[h] (6*RS*)-3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2,6-dimethyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one.

SPECIFIC TESTS

- **Loss on Drying ⟨731⟩**

  Analysis: Dry under vacuum at 80° for 4 h.

  Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed containers. Store at room temperature.
- **USP Reference Standards ⟨11⟩**

  USP Risperidone RS

  USP Risperidone Related Compound G RS

  3-[2-[4-(4-Fluoro-2-hydroxybenzoyl)piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-α]pyrimidin-4-one hydrochloride.

  $C_{23}H_{28}FN_3O_3 \cdot HCl$ 448.94

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

Topic/Question	Contact	Expert Committee
RISPERIDONE	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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