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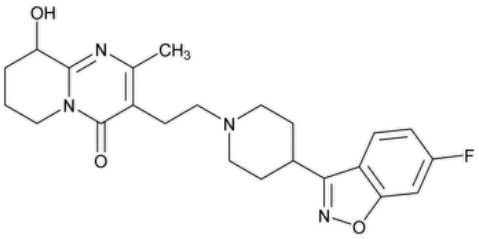
Paliperidone



$C_{23}H_{27}FN_4O_3$ 426.48

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-9-hydroxy-2-methyl-; (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 CAS RN®: 144598-75-4; UNII: 838F01T721.

DEFINITION

Paliperidone contains NLT 98.0% and NMT 102.0% of paliperidone ($C_{23}H_{27}FN_4O_3$).

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197K**▲ (CN 1-May-2020) Do not dry the sample.

• **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**

Protect the *System suitability solution, Standard solution*, and *Sample solution* from light.

Buffer: 28 mM Tetrabutylammonium hydrogen sulfate

Mobile phase: See *Table 1*.

Solution A: Methanol and *Buffer* (10:90)

Solution B: Methanol

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
5	100	0
35	85	15
37	100	0
45	100	0

Diluent: Dissolve 0.71 g of dibasic sodium phosphate and 0.62 g of monobasic sodium phosphate in 1 L of water.

System suitability solution: 0.5 mg/mL of USP Paliperidone Resolution Mixture RS prepared as follows. Dissolve first in methanol using 50% of the final flask volume, and dilute with *Diluent*.

Standard solution: 0.5 mg/mL of USP Paliperidone RS prepared as follows. Dissolve first in methanol using 50% of the final flask volume, and dilute with *Diluent*.

Sample solution: 0.5 mg/mL of Paliperidone prepared as follows. Dissolve first in methanol using 50% of the final flask volume, and dilute with *Diluent*.

Chromatographic system

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

Mode: LC

Detector: UV 275 nm

Column: 4.6-mm × 10-cm; 3-µm packing L1

Column temperature: 40°

Flow rate: 0.9 mL/min

Injection volume: 10 µL

System suitability

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

[NOTE—See *Table 2* for relative retention times.]

Suitability requirements

Resolution: NLT 2.0 between paliperidone related compound B and paliperidone; NLT 2.0 between paliperidone and paliperidone hydroxybenzoyl analog, *System suitability solution*

Tailing factor: NMT 2.0, *Standard solution*

Relative standard deviation: NMT 0.73%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of paliperidone ($C_{23}H_{27}FN_4O_3$) in the portion of Paliperidone 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 Paliperidone RS in the *Standard solution* (mg/mL)

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

Acceptance criteria: 98.0%–102.0%

IMPURITIES

• **RESIDUE ON IGNITION ⟨281⟩:** NMT 0.1%

• **ORGANIC IMPURITIES**

Protect the *System suitability solution*, *Standard solution*, and *Sample solution* from light.

Diluent, Mobile phase, System suitability solution, Standard solution, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

Sensitivity solution: 0.5 µg/mL of USP Paliperidone RS in *Diluent* from *Standard solution*

System suitability

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

[NOTE—See *Table 2* for relative retention times.]

Suitability requirements

Resolution: NLT 2.0 between paliperidone related compound B and paliperidone; NLT 2.0 between paliperidone and paliperidone hydroxybenzoyl analog, *System suitability solution*

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

Relative standard deviation: NMT 5.0%, *Sensitivity solution*

Analysis:

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of any individual impurity in the portion of Paliperidone taken:

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

r_U = peak response for each impurity from the *Sample solution*

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

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

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

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

Acceptance criteria: See *Table 2*. Disregard any peak with area less than 0.05%.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Paliperidone related compound C[a]	0.57	1.0	0.10
Paliperidone related compound B[b]	0.83	1.0	0.10
Paliperidone	1.00	—	—
Paliperidone hydroxybenzoyl analog[c]	1.1	1.0	0.10
Paliperidone ketone[d]	1.27	0.58	0.50
Any other individual unspecified impurity	—	1.0	0.10
Total impurities	—	—	0.70

[a] 3-(2-Chloroethyl)-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one.

[b] 6-Fluoro-3-(piperidin-4-yl)benzoisoxazole.

[c] 3-{2-[4-(4-Fluoro-2-hydroxybenzoyl)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-(6-Fluorobenzo[*d*]isoxazol-3-yl)piperidin-1-yl]ethyl}-2-methyl-7,8-dihydro-4*H*-pyrido[1,2-*a*]pyrimidine-4,9(6*H*)-dione.

SPECIFIC TESTS

• **Water Determination,** *Method Ia* ⟨921⟩**:** NMT 0.5%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed containers.

• **USP Reference Standards** ⟨11⟩

USP Paliperidone RS

USP Paliperidone Resolution Mixture RS

This contains paliperidone as the major component; it also contains paliperidone related compound B, paliperidone related compound C, paliperidone hydroxybenzoyl analog, and paliperidone ketone as minor components.

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

Topic/Question	Contact	Expert Committee
PALIPERIDONE	Documentary Standards Support	SM42020 Small Molecules 4

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

Chromatographic Database Information: Chromatographic Database

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