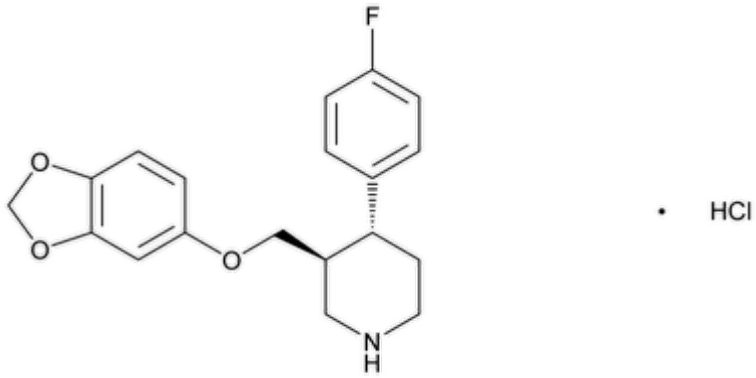
Interim Revision Announcement
Official: May 1, 2021

Paroxetine Hydrochloride

Change to read:



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$C_{19}H_{20}FNO_3 \cdot HCl$ 365.83
▲$C_{19}H_{20}FNO_3 \cdot HCl \cdot ½H_2O$▲ (IRA 1-May-2021) 374.83
Piperidine, 3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)-, hydrochloride, (3*S*-*trans*)-;
(−)-(3*S*,4*R*)-4-(*p*-Fluorophenyl)-3-[(3,4-methylenedioxy)phenoxy]methylpiperidine hydrochloride;
▲(3*S*,4*R*)-3-[(Benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine hydrochloride.▲ (IRA 1-May-2021)
Anhydrous [78246-49-8]; UNII: 3I3T11UD2S.
Hemihydrate [110429-35-1]; UNII: X2ELS050D8.

DEFINITION

Paroxetine Hydrochloride is anhydrous or contains one-half molecule of water of hydration. It contains NLT 98.5% and NMT 102.0% of paroxetine hydrochloride ($C_{19}H_{20}FNO_3 \cdot HCl$), calculated on the anhydrous and solvent-free basis.

IDENTIFICATION

- **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197M, 197K, or 197A

  Standard: Dissolve USP Paroxetine Hydrochloride RS in a mixture of water and isopropyl alcohol (1 in 10). Heat to 70° to dissolve, recrystallize, and dry the residue under vacuum at 50° for 3 h.

  Sample: Dissolve Paroxetine Hydrochloride in a mixture of water and isopropyl alcohol (1 in 10). Heat to 70° to dissolve, recrystallize, and dry the residue under vacuum at 50° for 3 h.

  Acceptance criteria: Meets the requirements

- **B. Identification Tests—General ⟨191⟩, *Chemical Identification Tests, Chloride***

  Sample solution: 10 mg/mL of Paroxetine Hydrochloride in methanol and water (50:50)

  Acceptance criteria: Meets the requirements

- **C.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution* as obtained in the *Assay*.

ASSAY

Change to read:

- **Procedure**

  Buffer: 0.05 M ammonium acetate in water. Adjust with glacial acetic acid to a pH of 4.5.

Mobile phase: Acetonitrile, *Buffer*, and triethylamine (30:70:1). [NOTE—The ratio for acetonitrile, *Buffer*, and triethylamine may be varied between 25:75:1 and 40:70:1 to meet system suitability requirements.] Adjust with glacial acetic acid to a pH of 5.5.

System suitability solution: 0.5 mg/mL each of USP Paroxetine Hydrochloride RS and USP Paroxetine Related Compound B RS ▲in water▲ (IRA 1-May-2021)

Standard solution: 0.5 mg/mL of USP Paroxetine Hydrochloride RS ▲in water▲ (IRA 1-May-2021)

Sample solution: 0.5 mg/mL of Paroxetine Hydrochloride ▲in water▲ (IRA 1-May-2021)

Chromatographic system

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

Mode: LC

Detector: UV 295 nm

Column: 4.6-mm × 25-cm; 5-µm packing L13

Flow rate: 1 mL/min

Injection volume: 10 µL

▲**Run time:** NLT 1.5 times the retention time of paroxetine▲ (IRA 1-May-2021)

System suitability

Sample: *System suitability solution*

[NOTE—The approximate relative retention times for paroxetine related compound B and paroxetine are about 0.9 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.0 between paroxetine related compound B and paroxetine

Tailing factor: NMT 2.0 for paroxetine

Relative standard deviation: NMT ▲0.73%▲ (IRA 1-May-2021) for paroxetine

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of paroxetine hydrochloride ($C_{19}H_{20}FNO_3 \cdot HCl$) in the portion of Paroxetine Hydrochloride taken:

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

r_U = peak response ▲of paroxetine▲ (IRA 1-May-2021) from the *Sample solution*

r_S = peak response ▲of paroxetine▲ (IRA 1-May-2021) from the *Standard solution*

C_S = concentration of ▲USP Paroxetine Hydrochloride RS in▲ (IRA 1-May-2021) the *Standard solution* (mg/mL)

C_U = concentration of ▲Paroxetine Hydrochloride in▲ (IRA 1-May-2021) the *Sample solution* (mg/mL)

Acceptance criteria: 98.5%–102.0% on the anhydrous and solvent-free basis

IMPURITIES

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

Change to read:

- **LIMIT OF PAROXETINE RELATED COMPOUND C**

Mobile phase: *n*-Hexane, absolute alcohol, trifluoroacetic acid, and water (900:100:2:2)

Diluent: *n*-Hexane and absolute alcohol (50:50)

System suitability solution: 0.1 mg/mL each of ▲USP Paroxetine Hydrochloride RS▲ (IRA 1-May-2021) and USP Paroxetine Related Compound C RS in *Diluent*

Standard solution: 0.1 mg/mL of USP Paroxetine Related Compound C RS in *Diluent*

Sample solution: 5 mg/mL of Paroxetine Hydrochloride in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 295 nm

Column: 4.6-mm × 25-cm; 10-µm packing L51

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 5 µL

▲**Run time:** NLT 2.3 times the retention time of paroxetine▲ (IRA 1-May-2021)

System suitability

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

[Note—The relative retention times for paroxetine related compound C and paroxetine are about 0.6 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.0 between paroxetine and paroxetine related compound C, *System suitability solution*

Tailing factor: NMT 2.5 for the paroxetine related compound C peak, *System suitability solution*

Relative standard deviation: NMT 10.0% for paroxetine related compound C, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of paroxetine related compound C in the portion of Paroxetine Hydrochloride taken:

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

r_U = peak response ▲of paroxetine related compound C▲ (IRA 1-May-2021) from the *Sample solution*

r_S = peak response ▲of paroxetine related compound C▲ (IRA 1-May-2021) from the *Standard solution*

C_S = concentration of USP Paroxetine Related Compound C RS in the *Standard solution* (mg/mL)

C_U = concentration of Paroxetine Hydrochloride, ▲on the anhydrous basis,▲ (IRA 1-May-2021) in the *Sample solution* (mg/mL)

Acceptance criteria: NMT 0.1% ▲▲ (IRA 1-May-2021)

Change to read:

• **Limit of ▲Paroxetine Related Compound E▲** (IRA 1-May-2021)

[Note—Perform this test only if ▲paroxetine related compound E▲ (IRA 1-May-2021) is a known process impurity.]

Solution A: Dissolve 30 g of sodium perchlorate in 900 mL of water. Add 3.5 mL of phosphoric acid and 2.4 mL of triethylamine. Dilute with water to 1000 mL. Adjust with phosphoric acid or triethylamine to

a pH of 2.0.

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	85	15
▲2	85	15▲ (IRA 1-May-2021)
20	80	20
▲20.1▲ (IRA 1-May-2021)	55	45
▲25▲ (IRA 1-May-2021)	55	45
▲26▲ (IRA 1-May-2021)	85	15
▲35▲ (IRA 1-May-2021)	85	15

Diluent: Acetonitrile and water (20:80)

▲**Sensitivity solution:** 0.006 µg/mL of USP Paroxetine Related Compound E RS (equivalent to 0.005 µg/mL of paroxetine related compound E free base) in *Diluent*▲ (IRA 1-May-2021)

Standard solution: ▲0.012 µg/mL of USP Paroxetine Related Compound E RS (equivalent to 0.010 µg/mL of paroxetine related compound E free base)▲ (IRA 1-May-2021) in *Diluent*

Sample solution: ▲10,000 µg/mL▲ (IRA 1-May-2021) of Paroxetine Hydrochloride in *Diluent*. Sonicate as needed to aid dissolution.

Chromatographic system

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

Mode: LC

Detector: UV 242 nm

Column: ▲3.0-mm × 15-cm; 3-µm packing▲ (IRA 1-May-2021)L1

Column temperature: ▲35°▲ (IRA 1-May-2021)

Flow rate: ▲0.6▲ (IRA 1-May-2021) mL/min

Injection volume: ▲100▲ (IRA 1-May-2021) µL

System suitability

Sample: ▲*Sensitivity solution* and▲ (IRA 1-May-2021)*Standard solution*

[NOTE—The relative retention times for ▲paroxetine related compound E▲ (IRA 1-May-2021) and paroxetine are about 0.6 and 1.0, respectively.]

Suitability requirements

Relative standard deviation: ▲NMT 10.0%, *Standard solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution* ▲ (IRA 1-May-2021)

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of ▲paroxetine related compound E ▲ (IRA 1-May-2021) in the portion of Paroxetine Hydrochloride taken:

$$\text{▲Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100 \text{▲ (IRA 1-May-2021)}$$

r_U = peak response ▲of paroxetine related compound E ▲ (IRA 1-May-2021) from the *Sample solution*

r_S = peak response ▲of paroxetine related compound E ▲ (IRA 1-May-2021) from the *Standard solution*

C_S = concentration of ▲USP Paroxetine Related Compound E RS ▲ (IRA 1-May-2021) in the *Standard solution* ▲(µg/mL) ▲ (IRA 1-May-2021)

C_U = concentration of ▲Paroxetine Hydrochloride, on the anhydrous basis, ▲ (IRA 1-May-2021) in the *Sample solution* ▲(µg/mL)

M_{r1} = molecular weight of paroxetine related compound E (free base), 191.25

M_{r2} = molecular weight of paroxetine related compound E (hydrochloride salt), 227.71 ▲ (IRA 1-May-2021)

Acceptance criteria: NMT 0.0001%

Change to read:

• Organic Impurities, Procedure 1

Perform either *Organic Impurities, Procedure 1* or *Organic Impurities, Procedure 2*, depending on the synthetic route. *Organic Impurities, Procedure 2* is recommended if paroxetine related compound F or paroxetine related compound G are potential impurities.

Solution A: Tetrahydrofuran, water, and trifluoroacetic acid (20:180:1)

Solution B: Acetonitrile, tetrahydrofuran, and trifluoroacetic acid (180:20:1)

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	80	20
30	80	20
50	20	80
60	20	80
70	80	20

Diluent: Tetrahydrofuran and water (1:9)

System suitability solution: 1 mg/mL of USP Paroxetine System Suitability Mixture A RS in *Diluent*. Sonication may be necessary to achieve complete dissolution.

Standard solution: 0.001 mg/mL of USP Paroxetine Hydrochloride RS in *Diluent*

Sample solution: 1 mg/mL of Paroxetine Hydrochloride in *Diluent*. Sonicate to dissolve.

Chromatographic system

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

Mode: LC

Detector: UV 285 nm

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

Column temperature: 40°

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Sample: *System suitability solution*

▲[NOTE—See *Table 3* for relative retention times.]▲ (IRA 1-MAY-2021)

Suitability requirements

Resolution: NLT 2.0 between paroxetine related compound A and paroxetine related compound B

Tailing factor: 0.8–2.0 for paroxetine related compound A

Relative standard deviation: NMT 2.0% for paroxetine related compound A

Analysis

Samples: *Diluent*, *Standard solution*, and *Sample solution*

Calculate the percentage of each impurity in the portion of Paroxetine Hydrochloride taken:

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

r_U = peak area of each impurity from the *Sample solution*, excluding peaks from the chromatogram of the *Diluent*

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

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

C_U = concentration of Paroxetine Hydrochloride, on the anhydrous basis, in the *Sample solution* (mg/mL)

Acceptance criteria: See *Table 3*.

Table 3

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Paroxetine related compound A	0.66	0.1
Paroxetine related compound B	0.73	0.3
Paroxetine	1.0	—
Any unspecified impurity	—	0.1
Total impurities	—	1.0

Change to read:

- **Organic Impurities, Procedure 2**

Buffer: Dissolve 3.4 g of monobasic potassium phosphate and 3.4 g of tetrabutylammonium hydrogen sulfate in 1.0 L of water.

Solution A: Acetonitrile and *Buffer* (2:98)

Solution B: Acetonitrile and *Buffer* (40:60)

Mobile phase: See *Table 4*.

Table 4

Time (min)	Solution A (%)	Solution B (%)
0	100	0
5	100	0
70	40	60
90	0	100
95	0	100
95.1	100	0
110	100	0

Diluent: Acetonitrile and *Buffer* (10:90)

Identification solution: 2 mg/mL of USP Paroxetine Hydrochloride RS, 0.01 mg/mL of USP Paroxetine Related Compound B RS, 0.01 mg/mL of USP Paroxetine Related Compound F RS, and 0.004 mg/mL of USP Paroxetine Related Compound G RS in *Diluent*

Standard solution: 0.004 mg/mL of USP Paroxetine Hydrochloride RS, 0.01 mg/mL of USP Paroxetine Related Compound B RS, 0.01 mg/mL of USP Paroxetine Related Compound F RS, and 0.004 mg/mL of USP Paroxetine Related Compound G RS in *Diluent*

Sample solution: 0.5 mg/mL of Paroxetine Hydrochloride in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 3.9-mm × 15-cm; 5-µm packing L1

Flow rate: 1.0 mL/min

Injection volume: 25 µL

System suitability

Sample: *Standard solution*

▲[Note—See *Table 5* for relative retention times.]▲ (IRA 1-May-2021)

Suitability requirements

Relative standard deviation: NMT 10.0% for each of paroxetine related compound B, paroxetine related compound F, paroxetine hydrochloride, and paroxetine related compound G

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of paroxetine related compound B, paroxetine related compound F, and paroxetine related compound G in the portion of Paroxetine Hydrochloride taken:

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

r_U = peak response of the corresponding impurity from the *Sample solution*

r_S = peak response of the corresponding impurity from the *Standard solution*

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

C_U = concentration of Paroxetine Hydrochloride, on the anhydrous basis, in the *Sample solution* (mg/mL)

Calculate the percentage of any individual unspecified impurity in the portion of Paroxetine Hydrochloride taken:

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

r_U = peak response of any individual unspecified impurity from the *Sample solution*

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

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

C_U = concentration of Paroxetine Hydrochloride, on the anhydrous basis, in the *Sample solution* (mg/mL)

Acceptance criteria: See *Table 5*.

Table 5

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Paroxetine related compound B	0.91	0.5
Paroxetine related compound F	0.96	0.2
Paroxetine	1.0	—
Paroxetine related compound G	1.34	0.2
Any unspecified impurity	—	0.1
Total impurities	—	1.0

SPECIFIC TESTS

- **Water Determination** ⟨921⟩, *Method I*

Anhydrous form: NMT 1.5%

Hemihydrate form: 2.2%–2.8%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve the anhydrous form in tight containers. Preserve the hemihydrate form in well-closed containers. Store at room temperature.

• **Labeling:** Label the article to indicate whether it is the anhydrous form or the hemihydrate form, and label it to indicate with which *Organic Impurities* test the article complies.

Change to read:

• **USP Reference Standards** ⟨11⟩

USP Paroxetine Hydrochloride RS

USP Paroxetine Related Compound B RS

(3*S*,4*R*)-3-[(Benzodioxol-5-yloxy)methyl]-4-phenylpiperidine hydrochloride.

$C_{19}H_{21}NO_3 \cdot HCl$ 347.84

USP Paroxetine Related Compound C RS

(3*R*,4*S*)-3-[(Benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine hydrochloride;

▲Also known as▲ (IRA 1-May-2021) (+)-*trans*-Paroxetine hydrochloride.

$C_{19}H_{20}FNO_3 \cdot HCl$ 365.83

▲ USP Paroxetine Related Compound E RS

4-(4-Fluorophenyl)-1-methyl-1,2,3,6-tetrahydropyridine hydrochloride.

$C_{12}H_{14}FN \cdot HCl$ 227.71

[Note—Paroxetine related compound E was previous identified as 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine hydrochloride.]▲ (IRA 1-May-2021)

USP Paroxetine Related Compound F RS

(3*S*,4*R*)-3-[(Benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)-1-methylpiperidine.

$C_{20}H_{22}FNO_3$ 343.39

USP Paroxetine Related Compound G RS

▲(3*SR*,4*RS*)-3-[(Benzodioxol-5-yloxy)methyl]-4-(4′-fluorobiphenyl-4-yl)piperidine hydrochloride;

Also known as▲ (IRA 1-May-2021)(±)*trans*-3-[(1,3-Benzodioxol-5-yloxy)methyl]-4-(4′′-fluorophenyl-4′-phenyl)piperidine hydrochloride.

$C_{25}H_{24}FNO_3 \cdot HCl$ ▲441.93▲ (IRA 1-May-2021)

USP Paroxetine System Suitability Mixture A RS

▲Contains a mixture of the following three compounds:

Paroxetine hydrochloride.

Paroxetine related compound A: (3*S*,4*R*)-3-[(Benzodioxol-5-yloxy)methyl]-4-(4-methoxyphenyl)piperidine hydrochloride;

Also known as piperidine, 3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-methoxyphenyl)-, hydrochloride (3*S*-*trans*)-.

$C_{20}H_{23}NO_4 \cdot HCl$ 377.86

Paroxetine related compound B: (3*S*,4*R*)-3-[(Benzodioxol-5-yloxy)methyl]-4-phenylpiperidine hydrochloride;

Also known as piperidine, 3-[(1,3-benzodioxol-5-yloxy)methyl]-4-phenyl-,hydrochloride (3*S*-*trans*)-.

$C_{19}H_{21}NO_3 \cdot HCl$ 347.84▲ (IRA 1-May-2021)

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