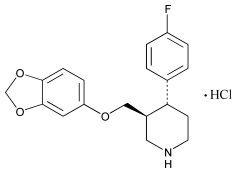
Paroxetine Hydrochloride



$C_{19}H_{20}FNO_3 \cdot HCl$ 365.83
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] methyl]piperidine hydrochloride [*78246-49-8*].
Hemihydrate 374.83

» Paroxetine Hydrochloride is anhydrous or contains one-half molecule of water of hydration. It contains not less than 98.5 percent and not more than 102.0 percent of $C_{19}H_{20}FNO_3 \cdot HCl$, calculated on the anhydrous and solvent-free basis.

Packaging and storage—Preserve the anhydrous form in tight containers. Preserve the hemihydrate form in well-closed containers. Store at controlled room temperature.
Labeling—Label it to indicate whether it is the anhydrous or the hemihydrate form. Label it to indicate with which impurity tests the article complies.

USP Reference standards ⟨11⟩**—***USP Paroxetine Hydrochloride RS. USP Paroxetine System Suitability Mixture A RS. USP Paroxetine Related Compound B RS. USP Paroxetine Related Compound C RS. USP Paroxetine Related Compound E Mixture RS. USP Paroxetine Related Compound F RS. USP Paroxetine Related Compound G RS.*

Identification—

A: *Infrared Absorption* ⟨197M⟩—

Test specimen—Dissolve a suitable portion of Paroxetine Hydrochloride in a solution of water in isopropyl alcohol (1 in 10), heat to 70° to dissolve, recrystallize, and dry the residue under vacuum at 50° for 3 hours.

Standard specimen: a similar preparation of USP Paroxetine Hydrochloride RS.

B: A solution (1 in 100) in a mixture of methanol and water (1 : 1) meets the requirements of the test for *Chloride* ⟨191⟩.

Water, *Method I* ⟨921⟩**:** not more than 1.5% for the anhydrous form and between 2.2% and 2.8% for the hemihydrate form.
Residue on ignition ⟨281⟩**:** not more than 0.1%.
Heavy metals, *Method II* ⟨231⟩**:** 0.002%.
Limit of related compound C—

Mobile phase—Prepare a mixture of *n*-hexane, absolute alcohol, water, and trifluoroacetic acid (900 : 100 : 2 : 2). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent: a mixture of absolute alcohol and *n*-hexane (1 : 1).

Standard solution—Dissolve an accurately weighed quantity of USP Paroxetine Related Compound C RS, and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 1 mg per mL.

Test solution—Transfer about 125 mg of Paroxetine Hydrochloride, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix.

System suitability solution—Dilute known volumes of the *Test solution* and the *Standard solution* with *Diluent* to obtain a solution having known concentrations of about 0.1 mg per mL each of Paroxetine Hydrochloride and of USP Paroxetine Related Compound C RS.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 295-nm detector and a 4.6-mm × 25-cm column that contains packing L51. The flow rate is about 1.0 mL per minute, and the column temperature is maintained at 30°. Chromatograph the *System suitability solution*, and record the peak responses as directed for *Procedure:* the relative retention times for paroxetine and paroxetine related compound C are 1.0 and about 0.6, respectively; the resolution, *R*, between paroxetine and paroxetine related compound C is not less than 2.0; and the tailing factor for paroxetine related compound C is not greater than 2.5. Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0% for the paroxetine related compound C.

Procedure—Separately inject equal volumes (about 5 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of paroxetine related compound C in the portion of Paroxetine Hydrochloride taken by the formula:

$$2500(C/W)(r_i / r_S)$$

in which C is the concentration, in mg per mL, of USP Paroxetine Related Compound C RS in the *Standard solution; W* is the weight, in mg, of Paroxetine Hydrochloride, on the anhydrous basis, used to prepare the *Test solution;* and r_i and r_S are the peak areas for paroxetine related compound C in the *Test solution* and the *Standard solution*, respectively: not more than 0.1% of paroxetine related compound C is found.

Limit of 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine—

Solution A—Dissolve about 30 g of sodium perchlorate in about 900 mL of water. Add 3.5 mL of phosphoric acid and 2.4 mL of triethylamine. Dilute with water to volume, and mix. Adjust with phosphoric acid or triethylamine to a pH of 2.0. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Solution B: acetonitrile, filtered and degassed.

Diluent: a mixture of water and acetonitrile (4 : 1).

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system*. Make adjustments to either solution as necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Paroxetine Related Compound E Mixture RS, and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 42 ng per mL of 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine.

Test solution—Transfer about 420 mg of Paroxetine Hydrochloride, accurately weighed, to a 10-mL volumetric flask, and dissolve in about 7 mL of *Diluent* with sonication. Dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 242-nm detector and a 4.0-mm × 25-cm column that contains packing L1. The column temperature is maintained at 30°. The flow rate is about 1.5 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	85	15	equilibration
0–20	85→80	15→20	linear gradient
20–27	80→55	20→45	linear gradient
27–36	55	45	isocratic
36–38	55→85	45→15	linear gradient
38–45	85	15	re-equilibration

Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure:* the relative retention times are 0.6 for 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine and 1.0 for paroxetine; and the relative standard deviation for replicate injections is not more than 15.0% for the 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine peak.

Procedure—Separately inject equal volumes (about 75 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of 1-methyl-4-(*p*-fluorophenyl)-

1,2,3,6-tetrahydropyridine in the portion of Paroxetine Hydrochloride taken by the formula:

$$1000(CI/W)\ (r_i / r_S)$$

in which C is the concentration, in mg per mL, of USP Paroxetine Related Compound E Mixture RS in the *Standard solution; I* is the fraction, by weight, of 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine in USP Paroxetine Related Compound E Mixture RS; W is the weight, in mg, of Paroxetine Hydrochloride, on the anhydrous basis, used to prepare the *Test solution;* and r_i and r_S are the peak areas for 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.0001% of 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine is found.

Chromatographic purity—[NOTE—Perform all related impurities methods unless the manufacturer has assurance, based on knowledge of the manufacturing process, that one of the tests is not relevant to their material.]

TEST 1—

Solution A—Prepare a filtered and degassed mixture of water, tetrahydrofuran, and trifluoroacetic acid (180 : 20 : 1).

Solution B—Prepare a filtered and degassed mixture of acetonitrile, tetrahydrofuran, and trifluoroacetic acid (180 : 20 : 1).

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent: a mixture of water and tetrahydrofuran (9 : 1).

Standard solution—Dissolve an accurately weighed quantity of USP Paroxetine Hydrochloride RS, and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 1 µg per mL.

System suitability solution—Dissolve, by sonication if necessary, a suitable quantity of USP Paroxetine System Suitability Mixture A RS in *Diluent* to obtain a solution having a known concentration of about 1 mg per mL.

Test solution—Transfer about 25 mg of Paroxetine Hydrochloride, accurately weighed, to a 25-mL volumetric flask, dissolve in 20 mL of *Diluent,* sonicate, dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 285-nm detector and a 4.6-mm × 25-cm column that contains packing L7. The flow rate is about 1 mL per minute. The column temperature is maintained at 40°. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	80	20	equilibration
0–30	80	20	isocratic
30–50	80→20	20→80	linear gradient
50–60	20	80	isocratic
60–70	20→80	80→20	linear gradient

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.66 for paroxetine related compound A, 0.73 for paroxetine related compound B, and 1.0 for paroxetine; the resolution, R, between paroxetine related compound A and paroxetine related compound B is not less than 2.0; the tailing factor of the paroxetine related compound A peak is between 0.8 and 2.0; and the relative standard deviation for replicate injections is not more than 2.0% for paroxetine related compound A.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution,* the *Test solution,* and the *Diluent* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of each impurity in the portion of Paroxetine Hydrochloride taken by the formula:

$$2500(C/W)(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Paroxetine Hydrochloride RS in the *Standard solution; W* is the weight, in mg, of Paroxetine Hydrochloride, on the anhydrous basis, used to prepare the *Test solution;* r_U is the peak area of each impurity in the *Test solution,* excluding the peaks obtained from the chromatogram of the *Diluent;* and r_S is the peak area of paroxetine obtained from the *Standard solution:* not more than 0.3% of any peak at a retention time of paroxetine related compound B is found; not more than 0.1% of any other individual impurity is found; and not more than 1.0% of total impurities is found.

TEST 2—

Phosphate 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—Prepare a filtered and degassed mixture of *Phosphate buffer* and acetonitrile (98 : 2).

Solution B—Prepare a filtered and degassed mixture of *Phosphate buffer* and acetonitrile (6 : 4).

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent: a mixture of *Phosphate buffer* and acetonitrile (9 : 1).

Standard solution—Dissolve an accurately weighed quantity of USP Paroxetine Hydrochloride RS, USP Paroxetine Related Compound B RS, USP Paroxetine Related Compound F RS, and USP Paroxetine Related Compound G RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having known concentrations of about 4 µg per mL, 10 µg per mL, 10 µg per mL, and 4 µg per mL, respectively.

Identification solution—Dissolve an accurately weighed quantity of USP Paroxetine Hydrochloride RS, USP Paroxetine Related Compound B RS, USP Paroxetine Related Compound F RS, and USP Paroxetine Related Compound G RS in *Diluent* to obtain a solution having known concentrations of about 2 mg per mL, 10 µg per mL, 10 µg per mL, and 4 µg per mL, respectively.

Test solution—Transfer about 25 mg of Paroxetine Hydrochloride, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 3.9-mm × 15-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	100	0	equilibration
0–5	100	0	isocratic
5–70	100→40	0→60	linear gradient
70–90	40→0	60→100	linear gradient
90–95	0	100	isocratic
95–95.1	0→100	100→0	linear gradient
95.1–110	100	0	re-equilibration

Chromatograph the *Identification solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.91 for paroxetine related compound B, about 0.96 for paroxetine related compound F, 1.0 for paroxetine, and about 1.34 for paroxetine related compound G. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 10.0% for the paroxetine related compound B, paroxetine related compound F, paroxetine hydrochloride, and paroxetine related compound G peaks.

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of paroxetine related compound B, paroxetine related compound F, and paroxetine related compound G in the portion of Paroxetine Hydrochloride taken by the formula:

$$5000(C/W)(r_i / r_S)$$

in which C is the concentration, in mg per mL, of the appropriate USP Reference Standard in the *Standard solution; W* is the weight, in mg, of Paroxetine Hydrochloride, on the anhydrous basis, used to prepare the *Test solution;* and r_i and r_S are the peak areas for the

corresponding impurity in the *Test solution* and the *Standard solution,* respectively: not more than 0.5% of paroxetine related compound B is found; not more than 0.2% of paroxetine related compound F is found; and not more than 0.2% of paroxetine related compound G is found. Calculate the percentage of any unknown impurity in the portion of Paroxetine Hydrochloride taken by the formula:

$$5000(C/W)(r_i / r_S)$$

in which C is the concentration, in mg per mL, of USP Paroxetine Hydrochloride RS in the *Standard solution; W* is the weight, in mg, of Paroxetine Hydrochloride, on the anhydrous basis, used to prepare the *Test solution;* r_i is the peak area for any unknown impurity in the *Test solution;* and r_S is the peak area of paroxetine in the *Standard solution:* not more than 0.1% of any single unknown impurity is found, and not more than 1.0% of total impurities is found. **Organic volatile impurities,** *Method V* ⟨467⟩**:** meets the requirements.

(Official until July 1, 2008)

Assay—

Acetate buffer—Prepare a 0.05 M solution of ammonium acetate in water, adjust with glacial acetic acid to a pH of 4.5, mix, and filter.

Mobile phase—Prepare a filtered and degassed mixture of *Acetate buffer,* acetonitrile, and triethylamine (70 : 30 : 1). [NOTE—The *Acetate buffer*–acetonitrile–triethylamine ratio can be varied between 70 : 40 : 1 and 75 : 25 : 1 to meet the system suitability requirements.] Adjust with glacial acetic acid to a pH of 5.5. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Dissolve suitable quantities of USP Paroxetine Related Compound B RS and USP Paroxetine Hydrochloride RS in water to obtain a solution having known concentrations of about 0.5 mg of each USP Reference Standard per mL.

Standard preparation—Dissolve an accurately weighed quantity of USP Paroxetine Hydrochloride RS in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.5 mg per mL.

Assay preparation—Transfer about 50 mg of Paroxetine Hydrochloride, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 295-nm detector and a 4.6-mm × 25-cm column that contains packing L13. The flow rate is about 1 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between paroxetine related compound B and paroxetine is not less than 2.0; the tailing factor for the paroxetine peak is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%. [NOTE—For information purposes, the approximate relative retention times are about 0.9 for paroxetine related compound B and 1.0 for paroxetine.]

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{19}H_{20}FNO_3 \cdot HCl$ in the portion of Paroxetine Hydrochloride taken by the formula:

$$100C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Paroxetine Hydrochloride RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.