

BRIEFING

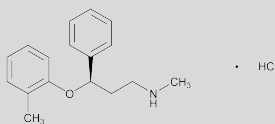
**Atomoxetine Hydrochloride.** A new USP Pending Monograph is proposed for this drug substance based on validated methods of analysis. The liquid chromatographic procedure in the *Assay* is based on analyses performed with the Lichrospher Cyano brand of L10 column. The typical retention time for atomoxetine is 19.4 min. The liquid chromatographic procedure in the test for *Organic Impurities, Procedure 1* is based on analyses performed with the Develosil ODS MG-5 brand of L1 column. The typical retention time for atomoxetine is 20.2 min. The liquid chromatographic procedure in the test for *Organic Impurities, Procedure 2* is based on analyses performed with the Spherisorb Cyano brand of L10 column. The typical retention time for atomoxetine is 11.4 min. The liquid chromatographic procedure in the test for *Enantiomeric Purity* is based on analyses performed with the Chiralcel ODH brand of L40 column. The typical retention time for atomoxetine is 16.4 min.

(MD-PP: H. Ramanathan, R. Ravichandran.) RTS—C84874

Add the following:

▶Atomoxetine Hydrochloride

Draft 1



$C_{17}H_{21}NO \cdot HCl$  291.82  
Benzenepropanamine, *N*-methyl- $\gamma$ -(2-methylphenoxy)-, hydrochloride, (-);  
(-)-*N*-Methyl-3-phenyl-3-(*o*-tolylxy)propylamine hydrochloride [82248-59-7].

**DEFINITION**

Atomoxetine Hydrochloride contains NLT 98.0% and NMT 102.0% of  $C_{17}H_{21}NO \cdot HCl$ , calculated on the dried basis.

**IDENTIFICATION**

- **A. INFRARED ABSORPTION (197K)**
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the test for *Enantiomeric Purity*.
- **C. IDENTIFICATION TESTS—GENERAL, Chloride (191):** Meets the requirements

**ASSAY**

• **PROCEDURE**

**Buffer:** 1.7 g/L of dibasic potassium phosphate in water. To 1 L of this solution, add 4.3 g of octanesulfonic acid sodium salt. Adjust with phosphoric acid to a pH of 6.0.  
**Solution A:** Methanol and *Buffer* (3:17)  
**Solution B:** Methanol and *Buffer* (3:1)  
**Diluent:** *Solution A* and *Solution B* (3:2)  
**Mobile phase:** See the gradient table below.

Time (min)	Solution A (%)	Solution B (%)
0.01	65	35
26.0	65	35
35.0	30	70
38.0	30	70

Time (min)	Solution A (%)	Solution B (%)
40.0	65	35
45.0	65	35

**Standard solution:** 0.05 mg/mL of USP Atomoxetine Hydrochloride RS in *Diluent*

**Sample solution:** 0.05 mg/mL of Atomoxetine Hydrochloride in *Diluent*

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 210 nm

**Column:** 4.0-mm × 25-cm; 5- $\mu$ m packing L10

**Column temperature:** 45°

**Flow rate:** 1 mL/min

**Injection size:** 10  $\mu$ L

**System suitability**

**Sample:** *Standard solution*

**Suitability requirements**

**Tailing factor:** NMT 2.5

**Relative standard deviation:** NMT 1.5%

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of  $C_{17}H_{21}NO \cdot HCl$  in the portion of Atomoxetine Hydrochloride taken:

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

$r_U$  = peak response of atomoxetine from the *Sample solution*

$r_S$  = peak response of atomoxetine from the *Standard solution*

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

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

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

**IMPURITIES**

**Inorganic Impurities**

- **RESIDUE ON IGNITION (281):** NMT 0.1%
- **HEAVY METALS, Method II (231):** NMT 10 ppm

**Organic Impurities**

- **PROCEDURE 1:** [NOTE—The *Sample solution* and *Standard solution* are stable for 6 h under refrigerated conditions.]

**Buffer:** 13.8 g/L of monobasic sodium phosphate in water.

To 1 L of this solution, add 4.3 g of octanesulfonic acid sodium salt. Adjust with phosphoric acid to a pH of 3.0.

**Solution A:** Acetonitrile and *Buffer* (3:7)

**Solution B:** Acetonitrile, methanol, and *Buffer* (9:5:6)

**Diluent:** *Solution A* and *Solution B* (4:1)

**Mobile phase:** See the gradient table below.

Time (min)	Solution A (%)	Solution B (%)
0	80	20
10	60	40
15	50	50
20	40	60
30	30	70
50	30	70
55	80	20
65	80	20

**Standard stock solution:** 0.5 mg/mL of USP Atomoxetine Hydrochloride RS in *Diluent*

**Standard solution:** 1  $\mu$ g/mL each of USP Atomoxetine Hydrochloride RS from the *Standard stock solution* and USP Atomoxetine Related Compound A RS in *Diluent*

**Sample solution:** 1 mg/mL of Atomoxetine Hydrochloride in *Diluent*

**Chromatographic system**

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

**Mode:** LC  
**Detector:** UV 210 nm  
**Column:** 4.6-mm × 25-cm; 5-μm packing L1  
**Flow rate:** 1 mL/min  
**Injection size:** 20 μL

**System suitability**

[NOTE—See *Impurity Table 1* for the relative retention times of atomoxetine and atomoxetine related compound A.]

**Samples:** *Standard stock solution* and *Standard solution*

**Suitability requirements**

**Tailing factor:** NMT 2.0, *Standard stock solution*  
**Relative standard deviation:** NMT 10.0% for the atomoxetine peak, *Standard solution*

**Analysis**

**Samples:** *Standard solution* and *Sample solution*  
 Calculate the percentage of any individual impurity in the portion of Atomoxetine Hydrochloride taken:

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

- $r_U$  = peak response of each individual impurity from the *Sample solution*  
 $r_S$  = peak response of atomoxetine from the *Standard solution*  
 $C_S$  = concentration of USP Atomoxetine Hydrochloride RS in the *Standard solution* (mg/mL)  
 $C_U$  = concentration of Atomoxetine Hydrochloride in the *Sample solution* (mg/mL)  
 $F$  = relative response factor for the corresponding impurity peak (see *Impurity Table 1*)

**Acceptance criteria**

**Individual impurities:** See *Impurity Table 1*.

**Impurity Table 1**

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Atomoxetine related compound A <sup>a</sup>	0.21	0.72	0.15
Atomoxetine	1.0	—	—
Any other individual, unspecified impurities	—	1.0	0.10
Total impurities	—	—	0.50

<sup>a</sup> [3-(Methylamino)-1-phenylpropan-1-ol].

**PROCEDURE 2**

**Mobile phase:** *n*-Hexane, absolute alcohol, and diethylamine (970:30:0.5)

**System suitability stock solution:** 2.0 mg/mL each of USP Atomoxetine Related Compound B RS and USP Atomoxetine Related Compound C RS, prepared by first dissolving in absolute alcohol, using 50% of final volume. Dilute with *Mobile phase* to volume.

**System suitability solution:** 2.0 mg/mL of USP Atomoxetine Hydrochloride RS and 2 μg/mL each of USP Atomoxetine Related Compound B RS and USP Atomoxetine Related Compound C RS, from the *System suitability stock solution*, prepared by first dissolving USP Atomoxetine Hydrochloride RS in absolute alcohol, using 50% of final volume. Dilute with *Mobile phase* to volume.

**Sample solution:** 2.0 mg/mL of Atomoxetine Hydrochloride, prepared by first dissolving in absolute alcohol, using 50% of final volume. Dilute with *Mobile phase* to volume.

**Chromatographic system**

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

**Mode:** LC  
**Detector:** UV 230 nm  
**Column:** 4.6-mm × 25-cm; 5-μm packing L10  
**Column temperature:** 30°  
**Flow rate:** 2 mL/min  
**Injection size:** 30 μL  
**Run time:** 2.6 times the retention time of atomoxetine

**System suitability**

**Sample:** *System suitability solution*

**Suitability requirements**

**Tailing factor:** NMT 2.5 for the atomoxetine peak  
**Resolution:** NLT 3.0 between atomoxetine and atomoxetine related compound B

**Analysis**

**Samples:** *Sample solution*

Calculate the percentage of atomoxetine related compound B and atomoxetine related compound C in the portion of Atomoxetine Hydrochloride taken:

$$\text{Result} = (r_U/r_T) \times 100$$

- $r_U$  = peak response of atomoxetine related compound B or atomoxetine related compound C from the *Sample solution*  
 $r_T$  = sum of the responses of all peaks from the *Sample solution*

**Acceptance criteria**

**Individual impurities:** See *Impurity Table 2*.

**Impurity Table 2**

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Atomoxetine	1.0	—
Atomoxetine related compound B <sup>a</sup>	1.2	0.15
Atomoxetine related compound C <sup>b</sup>	1.3	0.15

<sup>a</sup> (R)-N-Methyl-3-phenyl-3-(*m*-tolylloxy)propan-1-amine.

<sup>b</sup> (R)-N-Methyl-3-phenyl-3-(*p*-tolylloxy)propan-1-amine.

**SPECIFIC TESTS**

• **ENANTIOMERIC PURITY:** [NOTE—The *Sample solution* is stable for 1.5 h under refrigerated conditions.]

**Mobile phase:** *n*-Hexane, 2-propanol, and diethylamine (970:30:5)

**System suitability solution:** 1.0 mg/mL of USP Atomoxetine Hydrochloride RS and 1.5 μg/mL of USP Atomoxetine *S*-Isomer RS, prepared by first dissolving in 2-propanol, using 20% of final volume. Dilute with *Mobile phase* to volume.

**Sample solution:** 1.0 mg/mL of Atomoxetine Hydrochloride prepared by first dissolving in 2-propanol, using 20% of final volume. Dilute with *Mobile phase* to volume. [NOTE—Use a freshly prepared solution.]

**Chromatographic system**

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

**Mode:** LC  
**Detector:** UV 270 nm  
**Column:** 4.6-mm × 25-cm; 5-μm packing L40  
**Flow rate:** 1 mL/min  
**Injection size:** 50 μL  
**Run time:** 1.8 times the retention time of atomoxetine

**System suitability**

**Sample:** *System suitability solution*

**Suitability requirements**

[NOTE—The relative retention times for atomoxetine *S*-isomer and atomoxetine are 0.71 and 1.0, respectively.]

**Resolution:** NLT 3.0 between atomoxetine *S*-isomer and atomoxetine

**Tailing factor:** NMT 2.5 for the atomoxetine peak

**Relative standard deviation:** NMT 10.0% for the atomoxetine peak

**Analysis**

**Sample:** *Sample solution*

Calculate the percentage of atomoxetine *S*-isomer in the portion of Atomoxetine Hydrochloride taken:

$$\text{Result} = (r_U/r_T) \times 100$$

$r_U$  = peak response of the atomoxetine *S*-isomer from the *Sample solution*

$r_T$  = sum of the responses of the atomoxetine *S*-isomer and atomoxetine peaks from the *Sample solution*

**Acceptance criteria:** NMT 0.15% of the *S*-enantiomer is found.

- **Loss on Drying (731):** Dry a sample in vacuum at 105° for 3 h: it loses NMT 0.5% of its weight.

**ADDITIONAL REQUIREMENTS**

- **PACKAGING AND STORAGE:** Preserve in well-closed containers, protected from light. Store at room temperature.
- **USP REFERENCE STANDARDS (11)**  
USP Atomoxetine Hydrochloride RS

USP Atomoxetine Related Compound A RS

[3-(methylamino)-1-phenylpropan-1-ol]

(C<sub>10</sub>H<sub>15</sub>NO 165.23)

USP Atomoxetine Related Compound B RS

[(*R*)-*N*-methyl-3-phenyl-3-(*m*-tolylxy)propan-1-amine hydrochloride]

(C<sub>17</sub>H<sub>21</sub>NO · HCl 291.82)

USP Atomoxetine Related Compound C RS

[(*R*)-*N*-methyl-3-phenyl-3-(*p*-tolylxy)propan-1-amine hydrochloride]

(C<sub>17</sub>H<sub>21</sub>NO · HCl 291.82)

USP Atomoxetine *S*-Isomer RS

[(*S*)-*N*-methyl-3-phenyl-3-(*o*-tolylxy)propan-1-amine hydrochloride]

(C<sub>17</sub>H<sub>21</sub>NO · HCl 291.82)◀(1-Nov-2010)