

BRIEFING

**Atomoxetine Hydrochloride.** This monograph was posted on the USP Website as Draft 1 on April 30, 2010. The SM4 Expert Committee received and considered the following comments, and has approved the monograph as an Authorized USP Pending Monograph, Version 1.

- **Comment 1:** Commenter observed that their assay procedure is better due to a lower tailing factor and also indicated that the draft pending monograph has three separate procedures for *Organic Impurities* to monitor enantiomeric purity as well as other organic impurities. They informed USP that their organic impurities method may be more appropriate since the three methods proposed in the draft have been reduced to two procedures to accomplish the same result.
- **Response 1:** Comment not incorporated. Commenter is an approved manufacturer and has submitted their validated procedures for USP's consideration. A proposed USP monograph for this drug substance is scheduled to appear in *PF 38(2)* [Mar.–Apr. 2012].
- **Comment 2:** Commenter observed that one of their process impurities elutes close to the *S*-enantiomer peak and thus the *Enantiomeric Purity* test lacks selectivity.
- **Response 2:** Comment not incorporated. Monograph sponsor submitted supporting data and informed USP that the use of the Chiralpak-IC brand of L## column improves selectivity of the *Enantiomeric Purity* method.

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 Chiralpak-IC brand of L## column. The typical retention time for atomoxetine is 16.4 min.

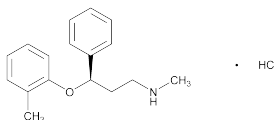
**Column information for the *Enantiomeric Purity* test**

**Chiralpak-IC:** Cellulose tris-(3,5-dichlorophenylcarbamate), immobilized on porous, spherical, silica particles, 3–5 μm in diameter

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**Atomoxetine Hydrochloride**

v.1 Authorized January 1, 2012



$C_{17}H_{21}NO \cdot HCl$  291.82  
Benzenepropanamine, *N*-methyl-γ-(2-methylphenoxy)-, hydrochloride, (–);  
(–)-*N*-Methyl-3-phenyl-3-(*o*-tolylloxy)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
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-μm packing L10

**Column temperature:** 45°

**Flow rate:** 1 mL/min

**Injection size:** 10 μL

**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.

## 2 / Atomoxetine Hydrochloride

**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 µg/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	—	—

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

**Impurity Table 1** (Continued)

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
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 L##

**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*-tolylloxy)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*-tolylloxy)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*-tolylloxy)propan-1-amine hydrochloride.

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