Atomoxetine Capsules

Type of Posting	Revision Bulletin
Posting Date	31–Jan–2020
Official Date	01–May–2020
Expert Committee	Chemical Medicines Monographs 4
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 4 Expert Committee has revised the Atomoxetine Capsules monograph. The purpose for the revision is to accommodate FDA-approved drug products with slightly different dissolution conditions (no deaeration of the *Medium* and use of different sinkers).

The Atomoxetine Capsules Revision Bulletin replaces the version that is scheduled to become official on May 1, 2020. Please note that General Notices, 3.10 Applicability of Standards discusses early adoption. For questions regarding compliance, please consult your relevant regulatory authority.

Should you have any questions, please contact Heather Joyce, Senior Scientific Liaison (301-998-6792 or hrj@usp.org).

Atomoxetine Capsules

DEFINITION

Atomoxetine Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of atomoxetine ($C_{17}H_{21}NO$).

IDENTIFICATION

Change to read:

- **A. ▲SPECTROSCOPIC IDENTIFICATION TESTS** ⟨197⟩**,** *Infrared Spectroscopy***:** 197K or 197A▲ (CN 1-May-2020)

Standard: 6 mg/mL of USP Atomoxetine Hydrochloride RS in methanol. Dry the solution to a dry powder under an air or nitrogen purge for a minimum of 3 h.

Sample: Shake the contents of a sufficient number of Capsules, equivalent to about 60 mg of atomoxetine, with 10 mL of methanol. Centrifuge at 4000 rpm for 5 min. Evaporate the solution to a dry powder with the aid of a current of air or stream of nitrogen.

Acceptance criteria: The IR spectrum exhibits main bands at (±2) wavenumbers (cm^{-1}) 2955, 2855, 1599–1604, 1492, 1048, 1023, and 1010.

- **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**

Buffer: 5.8 g/L of monobasic potassium phosphate in water. To each liter of this solution add 3.0 mL of triethylamine, and adjust with phosphoric acid to a pH of 2.5.

Mobile phase: Acetonitrile and *Buffer* (38:62)

System suitability solution: 0.1 mg/mL of atomoxetine (free base) from USP Atomoxetine Hydrochloride RS and 0.02 mg/mL of *o*-cresol in *Mobile phase*. Sonicate to aid in dissolution.

Standard solution: 0.1 mg/mL of atomoxetine (free base) from USP Atomoxetine Hydrochloride RS in *Mobile phase*. Sonicate to aid in dissolution.

Sample stock solution: From NLT 10 Capsules (including shells) prepared as follows. Add the intact Capsules to a suitable volumetric flask. Add *Mobile phase* to fill 65% of the final volume. Allow to stand for at least 10 min, then shake for 20 min. Dilute with *Mobile phase* to volume.

Sample solution: Nominally 0.1 mg/mL of atomoxetine, prepared by diluting a suitable volume of *Sample stock solution* with *Mobile phase*

Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 220 nm
Column: 4.6-mm × 7.5-cm; 3.5-µm packing L7
Column temperature: 35°
Flow rate: 1.5 mL/min
Injection volume: 10 µL
Run time: 1.7 times the retention time of atomoxetine

System suitability
Samples: *System suitability solution* and *Standard solution*
[NOTE—The relative retention times for atomoxetine and *o*-cresol are 1.0 and 1.3, respectively.]
Suitability requirements
Resolution: NLT 3.5 between atomoxetine and *o*-cresol, *System suitability solution*
Tailing factor: NMT 2.0 for atomoxetine, *System suitability solution*
Relative standard deviation: NMT 1.0% for atomoxetine, *Standard solution*

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of atomoxetine ($C_{17}H_{21}NO$) in the portion of Capsules 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 atomoxetine in the *Standard solution* (mg/mL)
C_U = nominal concentration of atomoxetine in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION** ⟨711⟩

Medium: 0.1 N hydrochloric acid; 1000 mL, deaerated, ▲if needed▲ (RB 1-May-2020)

Apparatus 2: 50 rpm, with ▲suitable▲ (RB 1-May-2020) sinker

Time: 30 min

Buffer and **Mobile phase:** Prepare as directed in the *Assay*.

Standard stock solution: 0.1 mg/mL of atomoxetine (free base) from USP Atomoxetine Hydrochloride RS in *Medium*. Sonicate to aid in dissolution.

Standard solution: Dilute the *Standard stock solution* with *Medium* to obtain a final concentration of (*L*/1000) mg/mL, where *L* is the Capsule label claim in mg.

Sample solution: Pass a portion of the solution under test through a suitable filter.

Chromatographic system: Proceed as directed in the *Assay*.

System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 1.4%

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of atomoxetine ($C_{17}H_{21}NO$) dissolved:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of atomoxetine in the *Standard solution* (mg/mL)
L = label claim (mg/Capsule)
V = volume of *Medium* (mL)

Tolerances: NLT 80% (*Q*) of the labeled amount of atomoxetine ($C_{17}H_{21}NO$) is dissolved.

- **UNIFORMITY OF DOSAGE UNITS** ⟨905⟩**:** Meet the requirements

IMPURITIES

- **ORGANIC IMPURITIES**

Buffer: Dissolve 4.9 g of sodium 1-decanesulfonate and 6.9 g of monobasic potassium phosphate in 1 L of water. Adjust with phosphoric acid to a pH of 3.1.

Mobile phase: Acetonitrile and *Buffer* (41:59)

Sensitivity solution: 0.1 µg/mL of atomoxetine in *Mobile phase*

System suitability solution: 1 mg/mL of atomoxetine containing atomoxetine *N*-amide prepared as follows.

Weigh equal amounts of USP Atomoxetine Hydrochloride RS and urea, and place in a volumetric flask. Add water to fill 10% of the final volume. Sonicate for 3 min. Place the flask in an 85° oven for 40 min. Allow the solution to cool to room temperature. Dilute with *Mobile phase* to volume. [NOTE—The oven temperature and time in the oven can be adjusted to give a suitable level of atomoxetine *N*-amide peak.]

Sample solution: 1 mg/mL of atomoxetine in *Mobile phase*, from the contents of NLT 5 Capsules prepared as follows. Transfer the Capsule contents to a suitable volumetric flask. Fill 50% of the final volume with *Mobile phase*. Swirl, and let stand for 15 min. Dilute with *Mobile phase* to volume.

Chromatographic system

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

Mode: LC

Detector: UV 215 nm

Column: 4.6-mm × 15-cm; 3.5-µm packing L7

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 10 µL

Run time: 2.3 times the retention time of atomoxetine

System suitability

Samples: *Sensitivity solution* and *System suitability solution* [NOTE—See *Table 1* for the relative retention times.]

Suitability requirements

Resolution: NLT 2.6 between atomoxetine and atomoxetine *N*-amide, *System suitability solution*

Relative standard deviation: NMT 5%, *Sensitivity solution*

Analysis

Sample: *Sample solution*

Calculate the percentage of each individual impurity in the portion of Capsules taken:

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

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

r_T = sum of all the peak responses from the *Sample solution*

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Desmethyl atomoxetine[a]	0.76	0.3
Atomoxetine	1.0	—
Atomoxetine *N*-amide[b]	1.2	0.2
Any individual unspecified degradation product	—	0.2
Total impurities	—	1.0

[a] (*R*)-*N*-Methyl-3-phenoxy-3-phenylpropan-1-amine.
[b] (*R*)-1-Methyl-1-[3-phenyl-3-(*o*-tolyloxy)propyl]urea.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers. Store at controlled room temperature.
- **USP REFERENCE STANDARDS** ⟨11⟩
  USP Atomoxetine Hydrochloride RS