

BRIEFING

**Escitalopram Tablets.** This monograph was posted on the USP Pending Monographs Web page as a draft USP Pending Monograph for public comment. The MD-PP Expert Committee has reviewed all comments received, and has approved the product as an Authorized USP Pending Monograph. The following is a summary of comments received and the Expert Committee responses:

**Comment 1:** Commenter requested that the limits proposed for impurities be revised to match ICH guidelines for qualification threshold and any other unspecified impurity as per identification threshold.

*Response 1:* Comment not incorporated. Commenter has been informed that the specifications for the impurities listed in the proposal are based on the tentatively approved limits between the monograph sponsor and the FDA and are not based on ICH guidelines. When commenter receives tentative/full approval from the FDA, USP will consider revising the impurities specification(s) at the appropriate time.

**Comment 2:** Commenter informed USP that their stability specification for the single largest unspecified degradant is 0.2%. Commenter requested that the proposed limit be widened from 0.1% to 0.2%, based on tentatively approved specification by the FDA.

*Response 2:* Comment incorporated. Specification for the single largest unspecified degradant widened from 0.1% to 0.2%.

**Comment 3:** Commenter claimed that the column used in the *Related compounds* test was not readily available.

*Response 3:* Comment not incorporated. USP performed a search on the Internet and was able to locate several distributors for the column.

**Comment 4:** Commenter suggested that the column temperature of 50° may significantly shorten the column life.

*Response 4:* Comment not incorporated. The USP general chapter *Chromatography* (621) allows column temperature to be adjusted by as much as  $\pm 10^\circ$ .

**Comment 5:** Commenter claimed that peak absorbances were very small, and that there appeared to be a potential tailing issue for the escitalopram peak.

*Response 5:* Comment not incorporated. The methods proposed in the draft are based on validated methods in the tentatively approved ANDA.

The proposed liquid chromatographic procedure in the test for *Related compounds* is based on analyses performed with the Macherey Nagel (MN) Nucleodur C18 Gravity brand of L1 column. The typical retention times for the escitalopram, escitalopram related compound A, and citalopram related compound D peaks are about 16.9, 7.9, and 8.8 minutes, respectively. The liquid chromatographic procedure in the *Assay* is based on analyses performed with the Inertsil C8-3 brand of L7 column. The typical retention time for the escitalopram peak is about 13 minutes. The liquid chromatographic procedure in the test for *Dissolution* is based on analyses performed with the Inertsil C8-3 brand of L7 column. The typical retention time for escitalopram oxalate is about 3.5 minutes.

(MD-PP: H. Ramanathan; R. Ravichandran; BPC: M. Marques) RTS—C62335

## Escitalopram Tablets

v.1 Authorized June 1, 2009

» Escitalopram Tablets contain escitalopram oxalate ( $C_{22}H_{23}FN_2O_5$ ) equivalent to not less than 90.0 percent and not more than 110.0 percent of the labeled amount of escitalopram ( $C_{20}H_{21}FN_2O$ ).

**Packaging and storage**—Preserve in well-closed containers. Store at controlled room temperature.

**USP Reference standards** (11)—*USP Citalopram Related Compound D RS. USP Escitalopram Oxalate RS. USP Escitalopram Related Compound A RS.*

**Identification**—

**A:** *Ultraviolet Absorption* (197U).

*Solution:* 10 µg per mL.

*Medium:* 0.1 N hydrochloric acid.

*Analytical wavelength:* 238 nm.

**B:** The retention time of the major peak in the *Assay preparation* matches the retention time of the major peak in the *Standard preparation*, as obtained in the *Assay*.

**Dissolution** (711)—

*Medium:* 0.1 N hydrochloric acid; 900 mL.

*Apparatus 2:* 75 rpm.

*Time:* 30 minutes.

*pH 2.5 Buffer*—Dissolve 6.8 g of potassium dihydrogen orthophosphate in 1000 mL of water. Add 5.0 mL of triethylamine. Adjust with orthophosphoric acid to a pH of 2.5.

*Mobile phase*—Prepare a filtered and degassed mixture of *pH 2.5 Buffer*, acetonitrile, and methanol (18 : 11 : 11). Make adjustments if necessary (see *System Suitability under Chromatography* (621)).

*Standard solution*—Accurately weigh a portion of USP Escitalopram Oxalate RS, and dilute with *Medium* to obtain a solution with a final concentration of  $L/1000$  mg per mL, where  $L$  is the Tablet label claim, in mg.

*Test solution*—Pass a portion of the solution under test through a suitable 0.45-µm filter. Dilute with *Medium*, if necessary.

*Chromatographic system*—The chromatograph is equipped with a 240-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L7. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure*: the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

*Procedure*—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of escitalopram dissolved by the formula:

$$(r_v/r_s) \times (C_s/L) \times (324.4/414.4) \times 900 \times 100$$

in which  $r_v$  and  $r_s$  are the peak responses obtained from the *Test solution* and the *Standard solution*, respectively;  $C_s$  is the concentration of escitalopram oxalate, in mg per mL, in the *Standard solution*;  $L$  is the Tablet label claim of escitalopram, in mg; 324.4 is the molecular weight of escitalopram; 414.4 is the molecular weight of escitalopram oxalate; and 900 is the volume, in mL, of *Medium*.

**Tolerances**—Not less than 80% ( $Q$ ) of the labeled amount of escitalopram is dissolved in 30 minutes.

**Uniformity of dosage units** (905): meets the requirements.

**Related compounds**—

*Buffer*—Prepare a filtered buffer solution by dissolving 1.32 g of dibasic ammonium phosphate in 1000 mL of water. Add 2 mL of triethylamine, and adjust with orthophosphoric acid to a pH of  $7.0 \pm 0.1$ . Dissolve in the resulting solution 1.88 g of sodium 1-hexanesulfonate, and mix. Pass through a 0.45-µm membrane filter.

*Mobile phase*—Prepare a degassed mixture of *Buffer*, methanol, and acetonitrile (10:9:1). Make adjustments as necessary (see *System Suitability under Chromatography* (621)).

2 / Escitalopram Tablets

**System suitability solution**—Dissolve an accurately weighed quantity of USP Citalopram Related Compound D RS and USP Escitalopram Related Compound A RS in *Mobile phase* to obtain a solution having a known concentration of about 5 µg per mL each of citalopram related compound D and escitalopram related compound A.

**Standard solution**—Dissolve an accurately weighed quantity of USP Escitalopram Oxalate RS in *Mobile phase* to obtain a solution having a known concentration of about 2.5 µg per mL of escitalopram oxalate.

**Test solution**—Weigh and finely powder not fewer than 10 Tablets. Transfer a weighed portion of the composite, equivalent to 50 mg of escitalopram to a 50-mL volumetric flask. Dissolve in and dilute with *Mobile phase* to volume. Centrifuge a portion of the solution, pass the supernatant through a 0.45-µm filter, and collect the filtrate to obtain a solution having a nominal concentration of about 1 mg per mL.

**Chromatographic system** (see *Chromatography* <621>)—The liquid chromatograph is equipped with a 240-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 1.5 mL per minute; and the column temperature is maintained at about 50 ± 2°. Chromatograph the *System suitability solution*, and record the peak responses as directed for *Procedure*: the resolution, *R*, between citalopram related compound D and escitalopram related compound A is not less than 1.2. Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure*: the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 15% for the escitalopram peak.

**Procedure**—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, and record the chromatograms for about 2.4 times the retention time of the escitalopram peak. Measure the peak areas of all the peaks in the *Test solution*. Identify the peaks using the relative retention time values given in *Table 1*.

Table 1

Impurity Name	Relative Retention Time	Relative Response Factor ( <i>F</i> )	Limit (%)
Amide escitalopram <sup>1</sup>	0.35	0.70	0.2
Escitalopram related compound A <sup>2</sup>	0.47	0.87	0.2
Citalopram related compound D <sup>3</sup>	0.52	0.62	0.2
3-Oxo escitalopram <sup>4</sup>	0.74	0.47	0.2
Escitalopram	1.0	—	—
Any other unspecified impurity	—	1.0	0.2
Total impurities	—	—	1.0

<sup>1</sup> 1-[3-(Dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carboxamide.

<sup>2</sup> 4-[(4-Dimethylamino)-1-(4-fluorophenyl)-1-(hydroxybutyl)]-3-hydroxy-methyl benzonitrile.

<sup>3</sup> 1-(4'-Fluorophenyl)-1-(3-methylaminopropyl)-1,3-dihydroisobenzofuran-5-carbonitrile.

<sup>4</sup> 1-(3-Dimethylamino)propyl-1-(4-fluorophenyl)-3-oxo-1,3-dihydroisobenzofuran-5-carbonitrile.

Calculate the percentage of each impurity relative to escitalopram in the portion of the Tablets taken by the formula:

$$(r_i / r_s) \times (C_s / C_U) \times (1/F) \times (324.4/414.4) \times 100$$

in which *r<sub>i</sub>* is the peak response of each individual impurity obtained from the *Test solution*; *r<sub>s</sub>* is the response of the escitalopram peak obtained from the *Standard solution*; *C<sub>s</sub>* is the concentration, in µg per mL, of escitalopram oxalate in the *Standard solution*; *C<sub>U</sub>* is the nominal concentration of escitalopram, in µg per mL, based on the label claim, in the *Test solution*; *F* is the relative response factor for each of the impurities as given in *Table 1*; 324.4 is the molecular weight of escitalopram; and 414.4 is the molecular weight of escitalopram oxalate. [NOTE—Disregard the peak due to oxalate at the relative retention time of 0.1.]

**Assay**—

**Buffer**—Dissolve 1.5 g of ammonium acetate in 1000 mL of water. Add 5 mL of triethylamine, and adjust with orthophosphoric acid to a pH of 6.8. Pass through a suitable filter.

**Mobile phase**—Prepare a degassed mixture of *Buffer*, methanol, and acetonitrile (6 : 3 : 1). Make adjustments as necessary (see *System Suitability* under *Chromatography* <621>).

**Standard preparation**—Dissolve an accurately weighed quantity of USP Escitalopram Oxalate RS in *Mobile phase* to obtain a solution having a known concentration of about 0.06 mg per mL.

**Assay preparation**—Weigh and finely powder not fewer than 20 Tablets. Transfer a portion of the powder equivalent to 100 mg of escitalopram to a 200-mL volumetric flask. Dissolve in and dilute with 0.1 N hydrochloric acid to volume. Centrifuge a portion of the solution, and dilute 5.0 mL of the supernatant with *Mobile phase* to 50.0 mL. Pass the solution through a 0.45-µm filter to obtain a solution having a nominal concentration of about 0.05 mg per mL of escitalopram.

**Chromatographic system** (see *Chromatography* <621>)—The liquid chromatograph is equipped with a 240-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L7. The flow rate is about 2.0 mL per minute, and the column temperature is maintained at 35°. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure*: the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0% for the escitalopram peak.

**Procedure**—Separately inject equal volumes (about 20 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 percentage of label claim of escitalopram (C<sub>20</sub>H<sub>21</sub>FN<sub>2</sub>O) in the portion of the Tablets taken by the formula:

$$(r_U / r_S) \times (C_S / C_U) \times (324.4/414.4) \times 100$$

in which *r<sub>U</sub>* is the peak response of the escitalopram peak obtained from the *Assay preparation*; *r<sub>S</sub>* is the peak response of the escitalopram peak obtained from the *Standard preparation*; *C<sub>S</sub>* is the concentration of escitalopram oxalate, in mg per mL, in the *Standard preparation*; *C<sub>U</sub>* is the nominal concentration of escitalopram, in mg per mL, in the *Assay preparation*, based on the label claim; 324.4 is the molecular weight of escitalopram; and 414.4 is the molecular weight of escitalopram oxalate.