

BRIEFING

Escitalopram Oral Solution. A new USP Pending Monograph for this drug product, based on validated methods of analyses, is proposed. The liquid chromatographic procedure in the *Assay* is based on analyses performed with the Hypersil BDS C-18 brand of L1 column. The typical retention time for escitalopram is about 5.6 min. The liquid chromatographic procedure in the test for *Organic Impurities* is based on analyses performed with the Atlantis d C18 brand of L1 column. The typical retention time for escitalopram is about 18.5 min.

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Add the following:

Escitalopram Oral Solution

Draft 1

DEFINITION

Escitalopram Oral Solution contains an amount of escitalopram oxalate equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of escitalopram (C₂₀H₂₁FN₂O).

IDENTIFICATION

- A.** 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: 6.1 g/L of monobasic potassium phosphate. To each L of this solution add 1.5 mL of triethylamine. Adjust with phosphoric acid to a pH of 2.5.

Mobile phase: Acetonitrile and *Buffer* (32:68)

Diluent: Acetonitrile and *Buffer* (25:75)

Standard solution: 33 µg/mL of USP Escitalopram Oxalate RS in *Diluent*

Sample solution: Nominally, 25 µg/mL of escitalopram from a suitable volume of Oral Solution, prepared as follows. Fill 50% of the flask volume with *Diluent*, and sonicate for 10 min with intermittent shaking. Allow the solution to cool, and dilute with *Diluent* to volume.

Chromatographic system

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

Mode: LC

Detector: UV 240 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Flow rate: 2 mL/min

Injection volume: 20 µL

Run time: 2.1 times the retention time of escitalopram

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of escitalopram (C₂₀H₂₁FN₂O) in the portion of Oral Solution taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of escitalopram from the *Sample solution*

r_S = peak response of escitalopram from the *Standard solution*

C_S = concentration of USP Escitalopram Oxalate RS in the *Standard solution* (µg/mL)

C_U = nominal concentration of escitalopram in the *Sample solution* (µg/mL)

M_{r1} = molecular weight of escitalopram free base, 324.39

M_{r2} = molecular weight of escitalopram oxalate, 414.43

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

- DELIVERABLE VOLUME (698):** Meets the requirement

IMPURITIES

ORGANIC IMPURITIES

Solution A: 6.6 g/L of dibasic ammonium phosphate in water. To each L of this solution add 2 mL of triethylamine. Adjust with phosphoric acid to a pH of 3.0.

Solution B: Acetonitrile and methanol (60:40)

Diluent: Acetonitrile and *Solution A* (30:70)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	80	20
10	70	30
20	60	40
35	60	40
36	80	20
45	80	20

Standard stock solution: 0.33 mg/mL of USP Escitalopram Oxalate RS in *Diluent*

System suitability solution: 1.0 µg/mL of USP Citalopram Related Compound C RS in the *Standard stock solution*

Standard solution: 3.3 µg/mL of USP Escitalopram Oxalate RS in *Diluent* from the *Standard stock solution*

Sample solution: Nominally, 0.25 mg/mL of escitalopram from a suitable volume of Oral Solution in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 15-cm; 3-µm packing L1

Flow rate: 1.5 mL/min

Injection volume: 20 µL

System suitability

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0 for escitalopram, *System suitability solution*

Resolution: NLT 2.0 between citalopram related compound C and escitalopram, *System suitability solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Oral Solution taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times (1/F) \times 100$$

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

r_S = peak response of escitalopram from the *Standard solution*

C_S = concentration of USP Escitalopram Oxalate RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of escitalopram in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of escitalopram free base, 324.39

M_{r2} = molecular weight of escitalopram oxalate, 414.43

F = relative response factor for each individual impurity (see Table 2)

Acceptance criteria: See Table 2.

[NOTE—Disregard any peaks less than 0.05%.]

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Oxalic acid ^a	0.06	—	—
Citalopram related compound A ^b	0.48	1.0	0.2
Desfluorocitalopram ^{c,h}	0.90	—	—
Citalopram related compound C ^d	0.92	2.56	0.3
Escitalopram	1.0	—	—
Citalopram chloromethyl quaternary ammonium salt ^{e,h}	1.1	—	—
Citalopram alkene dimer ^{f,h}	1.6	—	—
Citalopram related compound H ^{g,h}	1.7	—	—
Any individual unspecified degradation product	—	1.0	0.20
Total impurities	—	—	0.7

^a Not included in total impurities. For identification purposes only.

^b 1-(3-(Dimethylamino)propyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carboxamide.

^c 1-[3-(Dimethylamino)propyl]-1-phenyl-1,3-dihydroisobenzofuran-5-carbonitrile.

^d 3-[3-(Dimethylamino)-1-propyl] (4-fluorophenyl)-6-cyano-1(3H)-isobenzofuranone.

^e N-Chloromethyl-3-[5-cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-N,N-dimethylpropan-1-quaternary ammonium salt.

^f 3-[5-Cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-N-[5-cyano-2-[4-(dimethylamino)-1-(4-fluorophenyl)but-1-enyl]benzyl]-N,N-dimethylpropan-1-ammonium chloride.

^g 1-(4'-Fluorophenyl)-1-(3-dimethylaminopropyl)-5-bromophthalane.

^h Process impurity listed for information only.

SPECIFIC TESTS

• **PH** (791): 4.0–5.0

• **MICROBIAL ENUMERATION TESTS** (61) and **TESTS FOR SPECIFIED MICROORGANISMS** (62): The total aerobic microbial count

does not exceed 10² cfu/mL. The total yeasts and molds count does not exceed 10¹ cfu/mL. It meets the requirement of the test for absence of *Escherichia coli*.

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in light-resistant containers. Store at controlled room temperature.

• **USP REFERENCE STANDARDS** (11):

USP Escitalopram Oxalate RS

USP Citalopram Related Compound C RS

3-[3-(Dimethylamino)-1-propyl](4-fluorophenyl)-6-cyano-1(3H)-isobenzofuranone oxalate.

C₂₂H₂₁FN₂O₆ 428.41 (1-Mar-2012)