Table 2

Name	Detection Mode	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)[a]	Acceptance Criteria, NMT (%)[b]
6α-Hydroxy ethinyl estradiol[c]	Fl (215 nm/315 nm)[g]	0 .25	0.73	0.3	0.3
6β-Hydroxy ethinyl estradiol[d]	Fl (215 nm/315 nm)	0.27	0.64	0.3	0.3
6-Keto ethinyl estradiol[e]	UV 222 nm	0.41	2.3	1.5	0.5
Ethinyl estradiol related compound B[f]	Fl (215 nm/344 nm)	0.88	—	1.0	1.0
Ethinyl estradiol	Fl (215 nm/315 nm)	1.0	—	—	—
Any unspecified degradation product	Fl (215 nm/315 nm) and UV 222[h]	—	1.0	0.3	0.5
Total degradation product	—	—	—	3.0	2.5

[a] Limits for drug products labeled to contain 3 mg of drospirenone and 0.03 mg of ethinyl estradiol.
[b] Limits for drug products labeled to contain 3 mg of drospirenone and 0.02 mg of ethinyl estradiol.
[c] 19-Nor-6α,17α-pregna-1,3,5(10)-trien-20-yne-3,6,17-triol.
[d] 19-Nor-6β,17α-pregna-1,3,5(10)-trien-20-yne-3,6,17-triol.
[e] 19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol-6-one.
[f] Δ9,11-Ethinyl estradiol. 19-Nor-17α-pregna-1,3,5(10),9(11)-tetraen-20-yne-3,17-diol.
[g] Fl = Fluorescence.
[h] Determine unknown impurities using both modes of detection. Report the values from the detection mode that yield higher impurity levels.

Table 3

Name	Detection Mode (λ nm)	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)[a]	Acceptance Criteria, NMT (%)[b]
Drospirenone	UV 222	0.75	—	—	—
17-Epidrospirenone[c]	UV 222	0.83	1.0	0.3	0.3
Ethinyl estradiol	UV 222	1.0	—	—	—
Any unspecified degradation product	UV 222	—	1.0	0.3	0.5
Total degradation product	—	—	—	0.5	1.0

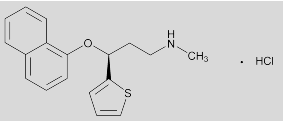
[a] Limits for drug products labeled to contain 3 mg of drospirenone and 0.03 mg of ethinyl estradiol.
[b] Limits for drug products labeled to contain 3 mg of drospirenone and 0.02 mg of ethinyl estradiol.
[c] 17-Hydroxy-6β,7β:15β,16β-dimethylene-3-oxo-17β-pregn-4-ene-21-carboxylic acid, γ-lactone.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers.
- **LABELING:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.
- **USP REFERENCE STANDARDS** ⟨**11**⟩
  USP Drospirenone RS
  USP Ethinyl Estradiol RS
  USP Ethinyl Estradiol Related Compound B RS
  19-Nor-17α-pregna-1,3,5(10),9(11)-tetraen-20-yne-3,17-diol.
  $C_{20}H_{22}O_2$ 294.39■2S (*USP35*)

Add the following:

■Duloxetine Hydrochloride



$C_{18}H_{19}NOS \cdot HCl$ 333.88
2-Thiophenepropanamine, *N*-methyl-γ-(1-naphthalenyloxy)-, hydrochloride, (*S*)-;
(+)-(*S*)-*N*-Methyl-γ-(1-naphthyloxy)-2-thiophenepropylamine hydrochloride [136434-34-9].

DEFINITION

Duloxetine Hydrochloride contains NLT 97.0% and NMT 102.0% of $C_{18}H_{19}NOS \cdot HCl$, calculated on the dried basis.

IDENTIFICATION

- **A. INFRARED ABSORPTION** ⟨**197K**⟩
  Sample solution: 5 mg/mL in methanol
  Acceptance criteria: Meets the requirements
- **B.** The retention time of the major peak in the *Sample solution* corresponds to that of the duloxetine *S*-isomer from the *System suitability solution* in the test for *Limit of Duloxetine Related Compound A*.
- **C. IDENTIFICATION TESTS—GENERAL,** *Chloride* ⟨**191**⟩**:** Meets the requirements

ASSAY

- **PROCEDURE**
  Protect solutions of duloxetine from light.
  Buffer: 2.9 g/L of phosphoric acid in water. Adjust with sodium hydroxide solution to a pH of 2.5. To each L of this solution add 10.3 g of sodium 1-hexanesulfonate monohydrate, and dissolve.
  Mobile phase: Acetonitrile, *n*-propanol, and *Buffer* (13:17:70)
  Diluent: Acetonitrile and water (25:75)
  System suitability solution: 0.2 mg/mL of USP Duloxetine Hydrochloride RS in *Mobile phase*. Heat the solution to at least 40° for a minimum of 1 h. [NOTE—The resulting solution contains duloxetine impurity B, duloxetine impurity C, duloxetine impurity D, duloxetine impurity E, and duloxetine related compound F.]
  Standard solution: 0.1 mg/mL of USP Duloxetine Hydrochloride RS in *Diluent*
  Sample solution: 0.1 mg/mL of Duloxetine Hydrochloride in *Diluent*

Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 230 nm
Column: 4.6-mm × 15-cm; 3.5-µm packing L7
Column temperature: 40 ± 3°
Flow rate: 1 mL/min
Injection size: 10 µL
Run time: 2 times the retention time of duloxetine
System suitability
Sample: *System suitability solution*
[NOTE—See *Table 1* for relative retention times.]
Suitability requirements
Resolution: NLT 1.5 between duloxetine and duloxetine related compound F peaks
Tailing factor: NMT 1.5 for the duloxetine peak
Relative standard deviation: NMT 1.0% for the duloxetine peak
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of duloxetine hydrochloride ($C_{18}H_{19}NOS \cdot HCl$) in the portion of sample 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 USP Duloxetine Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = concentration of Duloxetine Hydrochloride in the *Sample solution* (mg/mL)
Acceptance criteria: 97.0%–102.0% on the dried basis

IMPURITIES

- **HEAVY METALS,** *Method II* ⟨**231**⟩**:** NMT 10 ppm
- **RESIDUE ON IGNITION** ⟨**281**⟩**:** NMT 0.2%
- **ORGANIC IMPURITIES**

Protect solutions of duloxetine from light.
Buffer, Mobile phase, Diluent, and **System suitability solution:** Proceed as directed in the *Assay*.
Sensitivity solution: 0.2 µg/mL of USP Duloxetine Hydrochloride RS in *Diluent*
Sample solution: 0.2 mg/mL of Duloxetine Hydrochloride in *Diluent*
Chromatographic system: Proceed as directed in the *Assay*
Run time: 2.4 times the retention time of duloxetine
System suitability
Samples: *System suitability solution* and *Sensitivity solution*
[NOTE—See *Table 1* for relative retention times.]
Suitability requirements
Resolution: NLT 1.5 between duloxetine impurity C and duloxetine impurity D; NLT 1.5 between duloxetine and duloxetine related compound F, *System suitability solution*
Tailing factor: NMT 1.5 for the duloxetine peak, *System suitability solution*
Relative standard deviation: NMT 1.0% for the duloxetine peak, *System suitability solution*
Signal-to-noise ratio: NLT 20 for the duloxetine peak, *Sensitivity solution*
Analysis
Sample: *Sample solution*
Calculate the percentage of any individual impurity in the portion of Duloxetine Hydrochloride taken:

$$\text{Result} = (r_U/r_T) \times (1/F) \times 100$$

r_U = peak response of each impurity from the *Sample solution*
r_T = sum of the responses of all the peaks from the *Sample solution*
F = relative response factor (see *Table 1*)
Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Tme	Relative Response Factor	Acceptance Criteria NMT (%)
Duloxetine impurity B[a,g]	0.15	0.36	—
Duloxetine impurity C[b,g]	0.43	1.0	—
Duloxetine impurity D[c,g]	0.48	1.8	—
Duloxetine impurity E[d,g]	0.74	1.0	—
Duloxetine	1.0	—	—
Duloxetine related compound F[e]	1.1	1.0	0.5
Duloxetine impurity G [f,g]	1.4	0.51	—
Any individual unspecified impurity	—	1.0	0.1
Total impurities	—	—	0.6

[a] 3-(Methylamino)-1-(thiophen-2-yl)propan-1-ol.
[b] 4-[3-(Methylamino)-1-(thiophen-2-yl)propyl]naphthalen-1-ol.
[c] Naphthalen-1-ol.
[d] 1-(3-(Methylamino)-1-(thiophen-2-yl)propyl)naphthalen-2-ol.
[e] (*S*)-*N*-Methyl-3-(naphthalen-1-yloxy)-3-(thiophen-3-yl)propan-1-amine.
[f] 1-Fluoronaphthalene.
[g] Controlled at *Any individual unspecified impurity* level.

- **LIMIT OF DULOXETINE RELATED COMPOUND A**

Mobile phase: Hexane and isopropyl alcohol (83:17). To 1 L of this mixture add 2 mL of diethylamine.
System suitability solution: 0.1 mg/mL each of USP Duloxetine Hydrochloride RS and USP Duloxetine Related Compound A RS in *Mobile phase*. Sonication may be used to aid in dissolution.
Sensitivity solution: 0.1 µg/mL of USP Duloxetine Hydrochloride RS in *Mobile phase*
Sample solution: 0.1 mg/mL of Duloxetine Hydrochloride in *Mobile phase*. Sonication may be used to aid in dissolution.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 230 nm
Column: 4.6-mm × 25-cm; 5-µm packing L40
Column temperature: 40°
Flow rate: 1 mL/min
Injection size: 10 µL
Run time: 2 times the retention time of duloxetine
System suitability
Samples: *Sensitivity solution* and *System suitability solution*
[NOTE—The relative retention times for duloxetine and duloxetine related compound A are 1.0 and 1.3, respectively.]
Suitability requirements
Resolution: NLT 3.5 between duloxetine and duloxetine related compound A, *System suitability solution*
Tailing: Between 0.8 and 1.5 each for duloxetine and duloxetine related compound A peaks, *System suitability solution*
Relative standard deviation: NMT 5.0% for the duloxetine peak, *System suitability solution*

Signal-to-noise ratio: NLT 3, *Sensitivity solution*
Analysis
Sample: *Sample solution*
Calculate the percentage of duloxetine related compound A in the portion of Duloxetine Hydrochloride taken:

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

r_U = peak response for duloxetine related compound A from the *Sample solution*
r_T = sum of the responses of duloxetine and duloxetine related compound A peaks from the *Sample solution*

Acceptance criteria: NMT 0.5%

SPECIFIC TESTS
- **LOSS ON DRYING ⟨731⟩:** Dry at 105° for 3 h: it loses NMT 0.5% of its weight.

ADDITIONAL REQUIREMENTS
- **PACKAGING AND STORAGE:** Protect from light. Store at room temperature.
- **USP REFERENCE STANDARDS ⟨11⟩:**
USP Duloxetine Hydrochloride RS
USP Duloxetine Related Compound A RS
(*R*)-*N*-Methyl-3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propan-1-amine hydrochloride.
$C_{18}H_{19}NOS \cdot HCl$ 333.88 ■2S (*USP35*)

Add the following:

▪Duloxetine Delayed-Release Capsules

DEFINITION
Duloxetine Delayed-Release Capsules contain an amount of Duloxetine Hydrochloride equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of duloxetine ($C_{18}H_{19}NOS$).

IDENTIFICATION
- **A. INFRARED ABSORPTION ⟨197S⟩**
Spectral range: 1650 cm^{-1} to 900 cm^{-1}
Standard: 1 mg/mL of USP Duloxetine Hydrochloride RS in methylene chloride. Shake the contents, and sonicate for 1 min. Transfer 15 mL of filtrate into a separatory funnel, and add 15 mL of pH 7.5 phosphate buffer. Collect the organic layer, and evaporate to dryness. Redissolve the residue with a few drops of methylene chloride, and transfer to a KBr or NaCl plate. Allow it to dry.
Sample: 1 mg/mL of duloxetine, from the contents of NLT 10 Capsules in methylene chloride. Proceed as directed for the *Standard*.
- **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**
Protect solutions of duloxetine from light.
Buffer A: 3.4 g/L of monobasic potassium phosphate in water. To 1 L of this solution add 15 mL of triethylamine, and adjust with phosphoric acid to a pH of 5.5.
Buffer B: 0.2 g/L of monobasic ammonium phosphate and 4.5 g/L of dibasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 8.0.
Mobile phase: Methanol, tetrahydrofuran, and *Buffer A* (323:90:587)
Diluent: Methanol and *Buffer B* (50:50)
System suitability solution: 0.1 mg/mL USP Duloxetine Hydrochloride RS, 0.05 mg/mL of 1-naphthol, 0.01 mg/mL of USP Duloxetine Related Compound F RS, and 0.025 mg/mL of USP Duloxetine Related Compound H RS, in *Diluent*. [NOTE—Add 1 mL of methanol before diluting to volume to assist with dissolving contents. Duloxetine related compound H is used for peak identification purposes in this solution.]
Standard solution: 0.1 mg/mL of USP Duloxetine Hydrochloride RS in *Diluent*
Sample solution: Nominally 0.1 mg/mL of duloxetine from the contents of NLT 5 Capsules, in *Diluent*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
[NOTE—It is recommended to preheat the *Mobile phase* to 45°.]
Mode: LC
Detector: UV 230 nm
Column: 4.6-mm × 7.5-cm; 3- or 3.5-µm packing L7
Column temperature: 45°
Flow rate: 1.5 mL/min
Injection size: 10 µL
Run time: 6 times the retention time of duloxetine
System suitability
Samples: *System suitability solution* and *Standard solution*
[NOTE—See *Table 1* under *Organic Impurities* for relative retention times.]
Suitability requirements
Resolution: NLT 1.6 between duloxetine and duloxetine related compound F; NLT 2 between 1-naphthol and duloxetine related compound H, *System suitability solution*
Relative standard deviation: NMT 1.5%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of duloxetine ($C_{18}H_{19}NOS$) in the portion of Capsules taken:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Duloxetine Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of duloxetine in the *Sample solution* (mg/mL)
M_{r1} = molecular weight of duloxetine free base, 297.42
M_{r2} = molecular weight of duloxetine hydrochloride, 333.88

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS
- **DISSOLUTION ⟨711⟩**
Acid stage medium: 0.1 N hydrochloric acid; 1000 mL
Time: 2 h
Buffer stage medium: pH 6.8 phosphate buffer; 1000 mL
Time: 60 min for Capsules containing 20% w/w pellets; 90 min for Capsules containing 32% w/w pellets
Apparatus 1: 100 rpm
Buffer A and **Mobile phase:** Proceed as directed in the *Assay*.
Standard stock solution: 0.28 mg/mL of USP Duloxetine Hydrochloride RS in *Buffer stage medium*. Use a small amount of methanol, not exceeding 2% of the final volume, to dissolve duloxetine.
Acid stage standard solution: 2.3 µg/mL of duloxetine hydrochloride, from the *Standard stock solution* diluted with *Buffer stage medium*
Buffer stage standard solution: 23 µg/mL of duloxetine hydrochloride, from the *Standard stock solution* diluted with *Buffer stage medium*