

BRIEFING

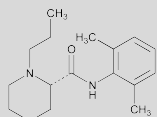
Ropivacaine. A new USP Pending Monograph for this drug substance, based on validated methods of analysis, is being proposed. The liquid chromatographic procedures in the test for *Organic Impurities* and in the *Assay* are based on analyses performed with an Xtera RP18 brand of L1 column. The typical retention time for ropivacaine is about 14 min. The liquid chromatographic procedure in the test for *Enantiomeric Purity* is based on analysis performed with a Chiral AGP brand of L41 column. The typical retention time for ropivacaine is about 14.2 min.

(MD-PS: M. Puderbaugh, M. Waddell.) RTS—C59061

Add the following:

►Ropivacaine

Draft 1



C₁₇H₂₆N₂O 274.4

(S)-(-)-1-Propylpiperidine-2-carboxylic acid (2,6-dimethylphenyl)-amide;

(S)-(-)-1-Propyl-2',6'-pipecoloxylidide [84057-95-4].

DEFINITION

Ropivacaine contains NLT 98.5% and NMT 101.0% of C₁₇H₂₆N₂O, calculated on the anhydrous basis.

IDENTIFICATION

- **A. INFRARED ABSORPTION** (197K)
- **B.** The retention time of the ropivacaine peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the test for *Enantiomeric Purity*.

ASSAY

• **PROCEDURE**

Solution A: 138 mg/mL of monobasic sodium phosphate

Solution B: 89 mg/mL of dibasic sodium phosphate dihydrate

Buffer: Mix 1.3 mL of *Solution A* with 32.5 mL of *Solution B*, and dilute with water to 1000 mL. Adjust the pH to 8.0 if necessary.

Diluent: Use the *Mobile phase*.

Mobile phase: Acetonitrile and *Buffer* (2:3)

Standard solution: 0.15 mg/mL of USP Ropivacaine RS in *Mobile phase*. [NOTE—Dissolve in acetonitrile before diluting with *Mobile phase* to volume.]

Sample solution: 0.15 mg/mL of Ropivacaine in *Mobile phase*. [NOTE—Dissolve in acetonitrile before diluting with *Mobile phase* to volume.]

Chromatographic system

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

Mode: LC

Detector: UV 240 nm

Column: 4.6-mm × 15-cm column; 3.5-μm packing L1

Flow rate: 1 mL/min

Injection size: 20 μL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.2

Relative standard deviation: NMT 1.0%

Analysis

[NOTE—The run time is about 2 times the retention time of the ropivacaine peak.]

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of C₁₇H₂₆N₂O in the portion of ropivacaine taken:

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

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

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

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

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

Acceptance criteria: 98.5%–101.0% on the anhydrous basis

IMPURITIES

Inorganic Impurities

- **RESIDUE ON IGNITION** (281): NMT 0.1%

• **HEAVY METALS** (231)

Solution A: Dilute 10.0 mL of *Standard Lead Solution* (containing 10 μg/mL of lead) to 100 mL to obtain a solution that contains the equivalent of 1 μg/mL of lead.

Solution B: Dissolve about 6.0 g of sodium sulfide in 40 g of glycerol, then dilute with water to 100 mL. Filter using a cotton pad, and store in a glass container protected from light.

Sample stock solution: Prepare as directed for the *Test Preparation under Heavy Metals, Method II* (231), using about 1 g of Ropivacaine.

Standard solution: Combine 10.0 mL of *Solution A* with 2 mL of *Sample stock solution* and 2 mL of *pH 3.5 Acetate Buffer*, and mix.

Sample solution: Combine 12 mL of *Sample stock solution* with 2 mL of *pH 3.5 Acetate Buffer*, and mix.

Blank solution: Combine 10.0 mL of water with 2 mL of *Sample stock solution* and 2 mL of *pH 3.5 Acetate Buffer*, and mix.

Analysis: Transfer the *Blank solution* to a color-comparison tube. Transfer the *Standard solution* and the *Sample solution* to individual color-comparison tubes each containing 1 drop of *Solution B*. After 1 min, compare the colors, viewing downward over a white surface.

Acceptance criteria: 10 ppm. The *Standard solution* shows a slight brown color compared to the *Blank solution*, and the *Sample solution* is not darker than the *Standard solution*.

Organic Impurities

• **PROCEDURE 1: LIMIT OF 2,6-DIMETHYLANILINE**

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

System suitability solution: 10 μg/mL each of USP Ropivacaine RS and USP Bupivacaine Hydrochloride RS in *Mobile phase*. [NOTE—Dissolve in acetonitrile before diluting with *Mobile phase* to volume.]

Standard solution: 0.1 μg/mL of USP Ropivacaine Related Compound A RS in *Mobile phase*

Sample solution: 10 mg/mL of Ropivacaine in *Mobile phase*. [NOTE—Dissolve in acetonitrile before diluting with *Mobile phase* to volume.]

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

System suitability

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

[NOTE—The relative retention times for 2,6-dimethylaniline and ropivacaine are 0.4 and 1.00, respectively.]

Suitability requirements

Resolution: NLT 6.0 between ropivacaine and bupivacaine hydrochloride, *System suitability solution*

Signal-to-noise ratio: NLT 10, *Standard solution*

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

Analysis

[NOTE—The run time is about 2 times the retention time of the ropivacaine peak.]

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of 2,6-dimethylaniline in the portion of Ropivacaine taken:

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

r_U = peak area for 2,6-dimethylaniline from the *Sample solution*

r_S = peak area for 2,6-dimethylaniline from the *Standard solution*

C_S = concentration of USP Ropivacaine Related Compound A RS in the *Standard solution* (mg/mL)

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

M_{r1} = molecular weight of 2,6-dimethylaniline, 121.18

M_{r2} = molecular weight of ropivacaine related compound A, 157.64

Acceptance criteria: NMT 0.001%

PROCEDURE 2

Buffer, Mobile phase, and System suitability solution: Prepare as directed for *Procedure 1*.

Standard solution: 1.25 µg/mL of USP Ropivacaine RS in *Mobile phase*. [NOTE—Dissolve in acetonitrile before diluting with *Mobile phase* to volume.]

Sample solution: 2.5 mg/mL of Ropivacaine in *Mobile phase*. [NOTE—Dissolve in acetonitrile before diluting with *Mobile phase* to volume.]

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

Samples: *System suitability solution* and *Standard solution* [NOTE—The relative retention times are listed in *Impurity Table 1*.]

Suitability requirements

Resolution: NLT 6.0 between ropivacaine and bupivacaine, *System suitability solution*

Signal-to-noise ratio: NLT 10, *Standard solution*

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

Analysis

[NOTE—The run time is about 3 times the retention time of the ropivacaine peak.]

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of any individual impurity in the portion of Ropivacaine taken:

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

r_U = response for any individual impurity from the *Sample solution*

r_S = response for Ropivacaine from the *Standard solution*

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

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

F = relative response factor (See *Impurity Table 1*.)

Acceptance criteria

Individual impurities: See *Impurity Table 1*.

Total impurities: NMT 0.50%

Impurity Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
2,6-dimethylaniline ^a	0.4	—	—
Pipecoloxylidide ^b	0.2	0.95	0.10
Bupivacaine ^c	1.6	0.76	0.20
Any other unknown individual impurity	—	1.0	0.05

^a Disregard peak due to 2,6-dimethylaniline.

^b *N*-(2,6-Dimethylphenyl)piperidine-2-carboxamide.

^c 1-Butyl-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide.

SPECIFIC TESTS

• **BACTERIAL ENDOTOXINS (85):** The level of bacterial endotoxins is such that the requirements under the relevant dosage form monograph(s) in which Ropivacaine is used can be met. Where the label states that Ropivacaine must be subjected to further processing during the preparation of injectable dosage forms, the level of bacterial endotoxins is such that the requirements under the relevant dosage form monograph(s) in which Ropivacaine is used can be met.

• **ENANTIOMERIC PURITY**

Buffer: 1.38 mg/mL of monobasic sodium phosphate. Adjust with sodium hydroxide solution (10% w/v) to a pH of 7.0.

Mobile phase: Isopropyl alcohol and *Buffer* (1:9)

System suitability solution: 20 µg/mL each of USP Ropivacaine RS and USP Ropivacaine Related Compound B RS in *Mobile phase*. [NOTE—Dissolve in isopropyl alcohol before diluting with *Mobile phase* to volume.]

Standard solution: 0.1 mg/mL of USP Ropivacaine RS in *Mobile phase*. [NOTE—Dissolve in isopropyl alcohol before diluting with *Mobile phase* to volume.]

Sample solution: 0.1 mg/mL of Ropivacaine in *Mobile phase*. [NOTE—Dissolve in isopropyl alcohol before diluting with *Mobile phase* to volume.]

Chromatographic system

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

Mode: LC

Detector: UV 202 nm

Column: 4.0-mm × 15-cm; 5-µm packing L41

Flow rate: 0.9 mL/min

Injection size: 20 µL

System suitability

Sample: *System suitability solution*

Suitability requirements

Resolution: NLT 1.8 between ropivacaine related compound B and ropivacaine

Analysis

[NOTE—The run time is about 25 min.]

Samples: *Standard solution* and *Sample solution*

[NOTE—Verify the identification of the ropivacaine peak based on the chromatogram of the *Standard solution*. The relative retention times of ropivacaine related compound B and ropivacaine are 0.84 and 1.00 respectively.]

Calculate the percentage of ropivacaine related compound B in the portion of Ropivacaine taken:

$$\text{Result} = 100 \times [r_U/(r_U + r_S)]$$

r_U = peak response of ropivacaine related compound B from the *Sample solution*

r_S = peak response of ropivacaine from the *Sample solution*

Acceptance criteria: NMT 0.5% of ropivacaine related compound B

• **COLOR**

Blank: Dilute 5 mL of 0.5 N hydrochloric acid with water to 25 mL.

Sample solution: Using a 25-mL volumetric flask, suspend 410 mg of Ropivacaine in 15 mL of water, add 5 mL of 0.5 N hydrochloric acid, and dilute with water to volume. Pass the solution through a 0.2- μ m nylon filter.

Spectrometric conditions

Mode: UV-Vis

Analytical wavelengths: 405 and 436 nm

Cell: 1 cm

Analysis

Samples: *Blank* and *Sample solution*

Measure the absorbances of the solutions.

Acceptance criteria: NMT 0.030 at 405 nm and NMT 0.025 at 436 nm

- **WATER DETERMINATION, Method Ia (921):** NMT 0.5%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers. Store at room temperature.

- **LABELING:** Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms.

• **USP REFERENCE STANDARDS (11)**

USP Bupivacaine Hydrochloride RS

USP Endotoxin RS

USP Ropivacaine RS

USP Ropivacaine Related Compound A RS

USP Ropivacaine Related Compound B RS (1-Jan-2010)