Naloxone Hydrochloride Injection

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Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 2 Expert Committee has revised the Naloxone Hydrochloride Injection monograph. The purpose for the revision is to update the *Packaging and Storage* requirements from "Preserve in single-dose or in multiple-dose containers of Type I glass," to "Preserve in single-dose or in multiple-dose containers, preferably of Type I glass," in order to allow flexibility and accommodate FDA-approved drug product applications.

The Naloxone Hydrochloride Injection Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Tsion Bililign, Scientific Liaison (301-816-8286 or tb@usp.org).

Revision Bulletin
Official: September 1, 2020

Naloxone Hydrochloride Injection

DEFINITION

Naloxone Hydrochloride Injection is a sterile, isotonic solution of Naloxone Hydrochloride in Water for Injection. It contains NLT 90.0% and NMT 110.0% of the labeled amount of naloxone hydrochloride ($C_{19}H_{21}NO_4 \cdot HCl$). It may contain suitable preservatives.

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*.

• **B.** The UV absorption spectrum of the naloxone peak of the *Sample solution* exhibits maxima and minima at the same wavelengths as those of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• **Procedure**

Mobile phase: A mixture of 1.36 g of sodium 1-octanesulfonate (anhydrous), 1.0 g of sodium chloride, 580 mL of water, 420 mL of methanol, and 1.0 mL of phosphoric acid

Diluent: Transfer 150 mg of edetate disodium to a 2000-mL volumetric flask, and add 0.9 mL of hydrochloric acid. Dilute with water to volume, and mix.

Standard solution: 10 µg/mL of USP Naloxone RS in *Diluent*

Sample solution: Nominally 10 µg/mL of naloxone hydrochloride prepared as follows. Transfer an adequate volume from NLT 5 Injections to a suitable volumetric flask. Dilute with *Diluent* to volume.

Chromatographic system

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

Mode: LC

Detector: UV 229 nm. For *Identification B*, use a diode array detector in the range of 200–400 nm.

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

Flow rate: 1 mL/min

Injection volume: 100 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 1.5%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of naloxone hydrochloride ($C_{19}H_{21}NO_4 \cdot HCl$) in the portion of Injection taken:

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

r_U = peak area of naloxone from the *Sample solution*

r_S = peak area of naloxone from the *Standard solution*

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

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

M_{r1} = molecular weight of naloxone hydrochloride (anhydrous), 363.84

M_{r2} = molecular weight of naloxone (anhydrous), 327.38

Acceptance criteria: 90.0%–110.0%

IMPURITIES

- **Limit of 2,2′-Bisnaloxone**

Standard solution A: Prepare as directed for the *Standard solution* in the *Assay*.

Mobile phase, Diluent, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay* by using *Standard solution A* in place of the *Standard solution*.

Standard solution B: 0.2 µg/mL of USP Naloxone RS in *Diluent* from *Standard solution A*

Ferric chloride solution: 4% (v/v) ferric chloride TS in water

Peak identification solution: Dissolve 10 mg of naloxone in 100 mL of 0.1 N hydrochloric acid. Transfer 10.0 mL of the resulting solution to a 100-mL volumetric flask, and add 0.5 mL of the *Ferric chloride solution*. Heat on a steam bath for 10 min, cool, dilute with water to volume, and mix.

Sample solution: Nominally 10 µg/mL of naloxone hydrochloride prepared as follows. Transfer an adequate volume from NLT 5 Injections to a suitable volumetric flask. Dilute with *Diluent* to volume.

Analysis

Samples: *Standard solution B*, *Peak identification solution*, and *Sample solution*

[Note—The relative retention times for naloxone and 2,2′-bisnaloxone (4,5′:4′,5″-diepoxy-3,3′,14,14′-tetrahydroxy-17,17′-bis(prop-2-enyl)-2,2′-bimorphinanyl-6,6′-dione) are 1.0 and 2.8, respectively.]

Calculate the percentage of 2,2′-bisnaloxone in the portion of Injection taken:

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

r_U = peak area of 2,2′-bisnaloxone from the *Sample solution*

r_S = peak area of naloxone from *Standard solution B*

C_S = concentration of USP Naloxone RS in *Standard solution B* (µg/mL)

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

F = relative response factor of 2,2′-bisnaloxone to naloxone hydrochloride, 1.8

M_{r1} = molecular weight of naloxone hydrochloride (anhydrous), 363.84

M_{r2} = molecular weight of naloxone (anhydrous), 327.38

Acceptance criteria: NMT 4.0%

SPECIFIC TESTS

- **pH** ⟨791⟩**:** 3.0–6.5
- **Bacterial Endotoxins Test** ⟨85⟩**:** NMT 500 USP Endotoxin Units/mg of naloxone hydrochloride
- **Other Requirements:** It meets the requirements in *Injections and Implanted Drug Products* ⟨1⟩.

ADDITIONAL REQUIREMENTS

Change to read:

- **Packaging and Storage:** Preserve in single-dose or in multiple-dose containers, ▲preferably▲ (RB 1-Sep-2020) of Type I glass, protected from light, and store at controlled room temperature.
- **USP Reference Standards** ⟨11⟩

USP Naloxone RS

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