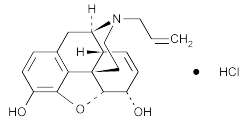
mg, of $C_{12}H_{12}N_2O_3$ in the portion of Tablets taken by the formula:

$$(12{,}500 / 3)(C)(R_U / R_S)$$

in which the terms are as defined therein.

Nalorphine Hydrochloride



$C_{19}H_{21}NO_3 \cdot HCl$ 347.84
Morphinan-3,6-diol, 7,8-didehydro-4,5-epoxy-17-(2-propenyl)-(5α,6α)-, hydrochloride.
17-Allyl-7,8-didehydro-4,5α-epoxymorphinan-3,6α-diol hydrochloride [57-29-4].

» Nalorphine Hydrochloride contains not less than 97.0 percent and not more than 103.0 percent of $C_{19}H_{21}NO_3 \cdot HCl$, calculated on the dried basis.

Packaging and storage—Preserve in tight, light-resistant containers. Store at 25°, excursions permitted between 15° and 30°.

USP Reference standards ⟨11⟩**—**
USP Nalorphine Hydrochloride RS

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: *Ultraviolet Absorption* ⟨197U⟩—

Solution: 100 µg per mL.

Medium: water.

C: A solution of it responds to the tests for *Chloride* ⟨191⟩.

Specific rotation ⟨781S⟩**:** between –122° and –125°.

Test solution: 20 mg per mL, in water.

Loss on drying ⟨731⟩**—**Dry it in vacuum at 100° for 2 hours: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩**:** not more than 0.1%.

Assay—Transfer about 25 mg of Nalorphine Hydrochloride, accurately weighed, to a 250-mL volumetric flask, dissolve in and dilute with water to volume, and mix. Concomitantly determine the absorbances of this solution and of a Standard solution of USP Nalorphine Hydrochloride RS in the same medium having a known concentration of about 100 µg per mL in 1-cm cells at the wavelength of maximum absorbance at about 285 nm, with a suitable spectrophotometer, using water as the blank. Calculate the quantity, in mg, of $C_{19}H_{21}NO_3 \cdot HCl$ in the Nalorphine Hydrochloride taken by the formula:

$$0.25C(A_U / A_S)$$

in which C is the concentration, in µg per mL, of USP Nalorphine Hydrochloride RS in the Standard solution; and A_U and A_S are the absorbances of the solution of Nalorphine Hydrochloride and the Standard solution, respectively.

Nalorphine Hydrochloride Injection

» Nalorphine Hydrochloride Injection is a suitably buffered, sterile solution of Nalorphine Hydrochloride in Water for Injection. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of nalorphine hydrochloride ($C_{19}H_{21}NO_3 \cdot HCl$).

Packaging and storage—Preserve in single-dose or in multiple-dose containers, preferably of Type I glass.

USP Reference standards ⟨11⟩**—**
USP Endotoxin RS
USP Nalorphine Hydrochloride RS

Identification—Apply 15 µL of Injection and 15 µL of a Standard solution of USP Nalorphine Hydrochloride RS in methanol containing 5 mg per mL to a suitable thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of chromatographic silica gel mixture. Allow the applications to dry, and develop the chromatogram in an equilibrated chamber containing methanol until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Observe the plate under short- and long-wavelength UV light: the R_F value of the principal spot obtained from the Injection corresponds to that obtained from the Standard solution.

Bacterial endotoxins ⟨85⟩**—**It contains not more than 11.6 USP Endotoxin Units per mg of nalorphine hydrochloride.

pH ⟨791⟩: between 6.0 and 7.5.

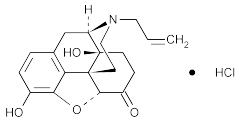
Other requirements—It meets the requirements under *Injections* ⟨1⟩.

Assay—Transfer an accurately measured volume of Injection, equivalent to about 10 mg of nalorphine hydrochloride, to a 25-mL centrifuge separator, add 1 mL of 3 N hydrochloric acid, and dilute with water to about 10 mL. Extract with five 5-mL portions of chloroform, separating the layers by centrifugation before drawing off each chloroform extract, and discard the chloroform extracts. Transfer the aqueous layer to a 100-mL volumetric flask with the aid of water, dilute with water to volume, and mix. Proceed as directed in the *Assay* under *Nalorphine Hydrochloride*, beginning with "Concomitantly determine the absorbances." Calculate the quantity, in mg, of $C_{19}H_{21}NO_3 \cdot HCl$ in each mL of the Injection taken by the formula:

$$(0.1C / V)(A_U / A_S)$$

in which V is the volume, in mL, of Injection taken, and C, A_U, and A_S are as defined therein.

Naloxone Hydrochloride



$C_{19}H_{21}NO_4 \cdot HCl$ 363.84
Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, hydrochloride, (5α)-.
17-Allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride [357-08-4].
Dihydrate 399.87 [51481-60-8].

» Naloxone Hydrochloride is anhydrous or contains two molecules of water of hydration. It contains not less than 98.0 percent and not more than 100.5 percent of $C_{19}H_{21}NO_4 \cdot HCl$, calculated on the dried basis.

Packaging and storage—Preserve in tight, light-resistant containers. Store at 25°, excursions permitted between 15° and 30°.

USP Reference standards ⟨11⟩**—**
USP Naloxone RS
USP Noroxymorphone Hydrochloride RS

Identification, *Infrared Absorption* ⟨197K⟩**—**

Test specimen—Dissolve about 150 mg in 25 mL of water in a small separator, add a few drops of 6 N ammonium hydroxide slowly until no more white precipitate is formed. Extract with three 5-mL portions of chloroform, pass the extracts through a dry filter, collecting the filtrate in a small flask. Evaporate the filtrate on a steam bath to dryness, and dry the residue at 105° for one hour.

Specific rotation ⟨781S⟩**:** between –170° and –181°.

Test solution: 25 mg per mL, in water.

Loss on drying ⟨731⟩**—**Dry it at 105° to constant weight: the anhydrous form loses not more than 0.5% of its weight, and the hydrous form loses not more than 11.0% of its weight.

Noroxymorphone hydrochloride [(–)-4,5α-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride] and other impurities—Transfer about 40 mg, accurately weighed, to a 5-mL volumetric flask, dissolve completely in 2.0 mL of water, add methanol to volume, and mix, to obtain the test solution. Prepare a solution of USP Naloxone RS in chloroform containing about 7.6 mg per mL. Prepare a solution of USP Noroxymorphone Hydrochloride RS in dilute methanol (3 in 5) containing 0.084 mg per mL. Apply 5 µL each of the test solution and the two Standard solutions to a thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of chromatographic silica gel that previously has been activated by heating for 15 minutes at 105°. Immediately place the plate in a suitable chromatographic chamber containing a 1 in 20 solution of methanol in ammoniacal butanol previously prepared by shaking 100 mL of butyl alcohol with 60 mL of ammonium hydroxide solution (1 in 100) and discarding the lower layer. Develop the chromatogram, protected from light, until the solvent front has moved about 10 cm from the point of application. Remove the plate, dry thoroughly, and spray with ferric chloride-potassium ferricyanide reagent prepared, immediately prior to use, by dissolving 100 mg of potassium ferricyanide in 20 mL of ferric chloride solution (1 in 10). Other than the principal spot corresponding in R_F value to that of USP Naloxone RS and the spot at the origin (ammonium chloride), no other spot is more intense than the spot corresponding to that of USP Noroxymorphone Hydrochloride RS (1.0%).

Chloride content—Dissolve about 300 mg, accurately weighed, in 50 mL of methanol contained in a 125-mL conical flask, add 5 mL of glacial acetic acid and 2 drops of eosin Y TS, and titrate with 0.1 N silver nitrate VS to a pink endpoint. Each mL of 0.1 N silver nitrate is equivalent to 3.545 mg of chloride. Not less than 9.54% and not more than 9.94%, calculated on the dried basis, is found.

Assay—Dissolve about 300 mg of Naloxone Hydrochloride, previously dried and accurately weighed, in a mixture of 40 mL of glacial acetic acid and 10 mL of acetic anhydride; add 10 mL of mercuric acetate TS and 1 drop of methyl violet TS; and titrate with 0.1 N perchloric acid VS. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 36.38 mg of $C_{19}H_{21}NO_4 \cdot HCl$.

Naloxone Hydrochloride Injection

» Naloxone Hydrochloride Injection is a sterile, isotonic solution of Naloxone Hydrochloride in Water for Injection. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of naloxone hydrochloride ($C_{19}H_{21}NO_4 \cdot HCl$). It may contain suitable preservatives.

Packaging and storage—Preserve in single-dose or in multiple-dose containers of Type I glass, protected from light.

USP Reference standards ⟨11⟩**—**
USP Endotoxin RS
USP Naloxone RS

Identification—The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that of the *Standard preparation* as obtained in the *Assay*.

Bacterial endotoxins ⟨85⟩**—**It contains not more than 500 USP Endotoxin Units per mg of Naloxone Hydrochloride.

pH ⟨791⟩: between 3.0 and 6.5.

Limit of 2,2′-bisnaloxone —

Mobile phase, Diluting solvent, System suitability preparation, and *Chromatographic system*—Prepare as directed in the *Assay*.

Ferric chloride solution—Transfer 4 mL of ferric chloride TS to a 100-mL volumetric flask, dilute with water to volume, and mix.

Identification solution—Dissolve 10 mg of naloxone in 100 mL of 0.1 N hydrochloric acid. Transfer 10.0 mL of this solution to a 100-mL volumetric flask, and add 0.5 mL of *Ferric chloride solution*. Heat on a steam bath for 10 minutes, cool, dilute with water to volume, and mix.

Standard solution—Transfer 2.0 mL of the *Standard preparation* prepared as directed in the *Assay* to a 100-mL volumetric flask, dilute with *Diluting solvent* to volume, and mix.

Test solution—Use the *Assay preparation*.

Procedure—Separately inject equal volumes (about 100 µL) of the *Identification solution*, the *Standard solution*, and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas of the peak responses for naloxone and 2,2′-bisnaloxone. The relative retention times are about 2.8 for the naloxone dimer and 1.0 for naloxone. Calculate the percentage of 2,2′-bisnaloxone in the volume of Injection taken by the formula:

$$(100 / L)(363.84 / 327.38)(C / 1.8)(V_b / V)(r_U / r_S)$$

in which L is the labeled quantity, in µg per mL, of naloxone hydrochloride ($C_{19}H_{21}NO_4 \cdot HCl$) in the Injection taken, 363.84 and 327.38 are the molecular weights of anhydrous naloxone hydrochloride and naloxone, respectively, C is the concentration, in µg per mL, of USP Naloxone RS in the *Standard solution*, 1.8 is the ratio of UV absorptivity of 2,2′-bisnaloxone to that of naloxone hydrochloride, V_b is the volume, in mL, of the *Test solution*, V is the volume, in mL, of Injection taken, r_U is the peak response for 2,2′-bisnaloxone obtained from the *Test solution*, and r_S is the peak response for naloxone obtained from the *Standard solution*. Not more than 4.0% is found.

Other requirements—It meets the requirements under *Injections* ⟨1⟩.

Assay—

Mobile phase—Prepare a filtered and degassed mixture of 1.36 g of sodium 1-octanesulfonate, 1.0 g of sodium chloride, 580 mL of water, 420 mL of methanol, and 1.0 mL of phosphoric acid. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluting solvent—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 preparation—Dissolve an accurately weighed quantity of USP Naloxone RS in *Diluting solvent*, and dilute quantitatively, and stepwise if necessary, with *Diluting solvent* to obtain a solution having a known concentration of about 10 µg per mL.

Assay preparation 1 (for Injection labeled to contain not more than 100 µg of naloxone hydrochloride per mL)—Transfer an accurately measured volume of Injection, equivalent to