Naloxone hydrochloride (Naloxoni hydrochloridum)

**Naloxone hydrochloride, anhydrous**

**Naloxone hydrochloride, dihydrate**

**Molecular formula.** \( \text{C}_{19}\text{H}_{21}\text{NO}_4\text{HCl} \) (anhydrous); \( \text{C}_{19}\text{H}_{21}\text{NO}_4\text{HCl,2H}_2\text{O} \) (dihydrate).

**Relative molecular mass.** 363.8 (anhydrous); 399.9 (dihydrate).

**Graphic formula.**

![Graphic formula](image)

**Chemical name.** (-)-17-Allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride; 4,5α-epoxy-3,14-dihydroxy-17-(2-propenyl)morphinan-6-one hydrochloride; (-)-12-allyl-7,7a,8,9-tetrahydro-3,7a-dihydroxy-4aH-8,9c-imino-ethanophenanthro[4,5-bcd]furan-5(6H)-one hydrochloride; CAS Reg. No. 357-08-4 (anhydrous).

(-)-17-Allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride dihydrate; 4,5α-epoxy-3,14-dihydroxy-17-(2-propenyl)morphinan-6-one hydrochloride dihydrate; (-)-12-allyl-7,7a,8,9-tetrahydro-3,7a-dihydroxy-4aH-8,9c-imino-ethanophenanthro[4,5-bcd]furan-5(6H)-one hydrochloride dihydrate; CAS Reg. No. 51481-60-8 (dihydrate).

**Description.** A white or almost white powder.

**Solubility.** Soluble in water; slightly soluble in ethanol (~750 g/l) TS; practically insoluble in ether R.

**Category.** Narcotic antagonist.

**Storage.** Naloxone hydrochloride should be kept in a tightly closed container, protected from light.

**Labelling.** The designation on the container of Naloxone hydrochloride should state whether the substance is in the anhydrous form or is the dihydrate.

**Additional information.** Even in the absence of light, Naloxone hydrochloride is gradually degraded on exposure to a humid atmosphere, the decomposition being faster at higher temperatures. It melts at about 177°C.

**Requirements**

**Definition.** Naloxone hydrochloride contains not less than 98.0% and not more than 102.0% of \( \text{C}_{19}\text{H}_{21}\text{NO}_4\text{HCl} \), calculated with reference to the dried substance.

**Identity tests**

- Either test A or tests B and C may be applied.
  
  **A.** Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from naloxone hydrochloride RS or with the *reference spectrum* of naloxone hydrochloride.

  **B.** Dissolve 0.05 g in 5 mL of hydrochloric acid (0.1 mol/l) VS and add 0.3 mL of ferric chloride (25 g/l) TS; a purplish blue colour is produced.

  **C.** A 0.05 g/mL solution yields reaction A described under 2.1 General identification tests as characteristic of chlorides.
**Specific optical rotation.** Use a 25 mg/mL solution and calculate with reference to the dried substance; $[\alpha]_{D}^{20^\circ\text{C}} = -170^\circ\text{ to } -181^\circ$.

**Loss on drying.** Dry to constant weight at 105°C; anhydrous Naloxone hydrochloride loses not more than 5.0 mg/g. Naloxone hydrochloride dihydrate loses not more than 110 mg/g.

**Related substances.** Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R1 as the coating substance, and as the mobile phase prepare the following solution: shake 100 mL of 1-butanol R with 60 mL of ammonia (~17 g/l) TS, discard the lower layer, and mix 95 volumes of the upper layer with 5 volumes of methanol R. Dry the plate in a current of air. Apply separately to the plate 5μl of each of the two following solutions. For solution (A) dissolve 40 mg of Naloxone hydrochloride in 2 mL of water and dilute to 5 mL with methanol R. For solution (B) dilute 0.5 mL of solution A to 100 mL with methanol R. Develop the chromatogram protected from light. After removing the plate from the chromatographic chamber, allow it to dry in air, spray with ferric chloride/potassium ferricyanide TS, and examine the chromatogram in daylight.

Any spot obtained with solution A, other than the principal spot, is not more intense than that obtained with solution B (0.5%). Disregard any spot remaining at the point of application.

**Chlorides content.** Dissolve about 0.3 g, accurately weighed, in 50 mL of methanol R. Add 5 mL of glacial acetic acid R and 0.1 mL of eosin Y (5 g/l) TS, and titrate with silver nitrate (0.1 mol/l) VS until a pink colour is produced. Each mL of silver nitrate (0.1 mol/l) VS is equivalent to 3.545 mg of Cl; the content of chlorides is not less than 95.4 mg/g and not more than 99.4 mg/g, calculated with reference to the dried substance.

**Assay.** Dissolve 0.300 g in 50 mL of dehydrated ethanol R and add 5.0 mL of hydrochloric acid (0.01 mol/L) VS. Carry out a potentiometric titration using sodium hydroxide/ethanol (0.1 mol/L) VS, as described under 2.6 Non-aqueous titration. Read the volume added between the two points of inflexion.

1 mL of sodium hydroxide/ethanol (0.1 mol/L) VS is equivalent to 36.38 mg of $C_{19}H_{21}NO_{4}$HCl.

**Additional requirements for Naloxone hydrochloride for parenteral use**

Complies with the monograph for "Parenteral preparations".

**Bacterial endotoxins.** Carry out the test as described under 3.4 Test for bacterial endotoxins; contains not more than 500 IU of endotoxin RS per mg.