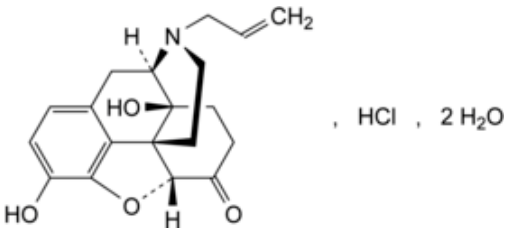
Edition: BP 2025 (Ph. Eur. 11.6 update)

Naloxone Hydrochloride

General Notices

(Naloxone Hydrochloride Dihydrate, Ph. Eur. monograph 0729)



, HCl , 2 H_2O

$C_{19}H_{22}ClNO_4,2H_2O$ 399.9 *51481-60-8*

Action and use

Opioid receptor antagonist.

Preparation

Naloxone Injection

Ph Eur

DEFINITION

4,5α-Epoxy-3,14-dihydroxy-17-(prop-2-enyl)morphinan-6-one hydrochloride dihydrate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, hygroscopic, crystalline powder.

Solubility

Freely soluble in water, soluble in ethanol (96 per cent), practically insoluble in toluene.

IDENTIFICATION

First identification: A, C.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *naloxone hydrochloride dihydrate CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 8 mg of the substance to be examined in 0.5 mL of *water R* and dilute to 1 mL with *methanol R*.

Reference solution Dissolve 8 mg of *naloxone hydrochloride dihydrate CRS* in 0.5 mL of *water R* and dilute to 1 mL with *methanol R*.

Plate *TLC silica gel G plate R*.

Mobile phase Mix 5 volumes of *methanol R* and 95 volumes of the upper layer from a mixture of 60 mL of *dilute ammonia R2* and 100 mL of *butanol R*.

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with a freshly prepared 5 g/L solution of *potassium ferricyanide R* in *ferric chloride solution R1*; examine in daylight.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. It gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 0.50 g in *carbon dioxide-free water R* and dilute to 25.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, *Method II*).

Acidity or alkalinity

To 10.0 mL of solution S add 0.05 mL of *methyl red solution R*. Not more than 0.2 mL of *0.02 M sodium hydroxide* or *0.02 M hydrochloric acid* is required to change the colour of the indicator.

Specific optical rotation (*2.2.7*)

-181 to -170 (anhydrous substance), determined on solution S.

Impurity D

Liquid chromatography (*2.2.29*).

Solution A Dissolve 1.58 g of *ammonium hydrogen carbonate R* in 950 mL of *water for chromatography R*, adjust to pH 9.0 with *concentrated ammonia R* and dilute to 1000 mL with *water for chromatography R*.

Test solution Dissolve 0.500 g of the substance to be examined in a 10.3 g/L solution of *hydrochloric acid R* and dilute to 20.0 mL with the same solution.

Reference solution (a) Dissolve 10.0 mg of *naloxone impurity D CRS* in a 10.3 g/L solution of *hydrochloric acid R* and dilute to 20.0 mL with the same solution. Dilute 5.0 mL of this solution to 100.0 mL with a 10.3 g/L solution of *hydrochloric acid R*.

Reference solution (b) Dilute 5.0 mL of reference solution (a) to 100.0 mL with a 10.3 g/L solution of *hydrochloric acid R*.

Reference solution (c) To 4.0 mL of the test solution add 2.0 mL of reference solution (a) and dilute to 20.0 mL with a 10.3 g/L solution of *hydrochloric acid R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: *acetonitrile R1*, solution A (20:80 *V/V*);

— *mobile phase B*: *acetonitrile R1*, solution A (40:60 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 50	100	0
50 - 51	100 → 0	0 → 100
51 - 60	0	100

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 10 µL of the test solution and reference solutions (b) and (c).

Relative retention With reference to naloxone (retention time = about 50 min): impurity D = about 0.8.

System suitability Reference solution (c):

— *symmetry factor*: maximum 1.8 for the peak due to impurity D.

Limit:

— *impurity D*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (75 ppm).

Related substances

Liquid chromatography (2.2.29).

Solution A Dissolve 1.10 g of sodium octanesulfonate R in 950 mL of water for chromatography R, adjust to pH 2.0 with a 50 per cent *V/V* solution of phosphoric acid R, filter and dilute to 1000 mL with water for chromatography R.

Test solution Dissolve 0.125 g of the substance to be examined in a 10.3 g/L solution of hydrochloric acid R and dilute to 25.0 mL with the same solution.

Reference solution (a) Dissolve the contents of a vial of naloxone for peak identification CRS (containing impurities A, B, C, D, E and F) in 1 mL of a 10.3 g/L solution of hydrochloric acid R.

Reference solution (b) Dilute 1.0 mL of the test solution to 20.0 mL with a 10.3 g/L solution of hydrochloric acid R. Dilute 1.0 mL of this solution to 25.0 mL with a 10.3 g/L solution of hydrochloric acid R.

Column:

— *size*: *l* = 0.125 m, Ø = 4.0 mm;

— *stationary phase*: end-capped octylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: acetonitrile R, tetrahydrofuran R, solution A (2:4:94 *V/V/V*);

— *mobile phase B*: tetrahydrofuran R, acetonitrile R, solution A (4:17:79 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 40	100 → 0	0 → 100
40 - 50	0	100

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 20 µL.

Relative retention With reference to naloxone (retention time = about 11 min): impurity C = about 0.6; impurity A = about 0.8; impurity F = about 0.9; impurity D = about 1.1; impurity E = about 3.0; impurity B = about 3.2.

Identification of impurities Use the chomatogram supplied with naloxone for peak identification CRS and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, C, D, E and F.

System suitability Reference solution (a):

— peak-to-valley ratio: minimum 2.0, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to naloxone.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity E by 0.5;

— *impurities A, B, C, E, F*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.8 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (*2.5.12*)

7.5 per cent to 11.0 per cent, determined on 0.200 g.

Sulfated ash (*2.4.14*)

Maximum 0.2 per cent, determined on 0.50 g.

ASSAY

Dissolve 0.300 g in 50 mL of *ethanol (96 per cent) R* and add 5.0 mL of *0.01 M hydrochloric acid*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M ethanolic sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M ethanolic sodium hydroxide* is equivalent to 36.38 mg of $C_{19}H_{22}ClNO_4$.

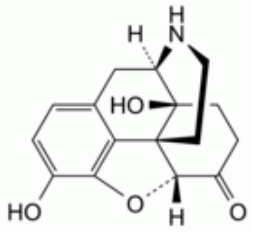
STORAGE

In an airtight container, protected from light.

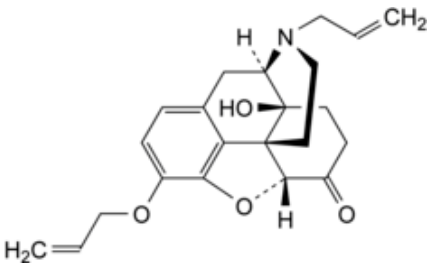
IMPURITIES

Specified impurities *A, B, C, D, E, F.*

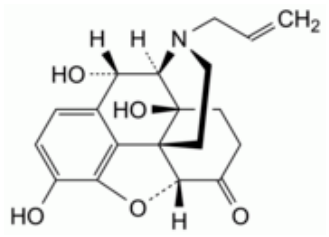
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *G.*



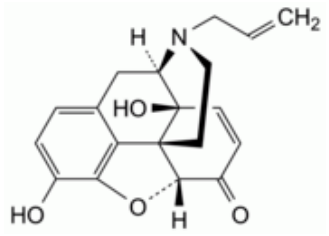
A. 4,5α-epoxy-3,14-dihydroxymorphinan-6-one (noroxymorphone),



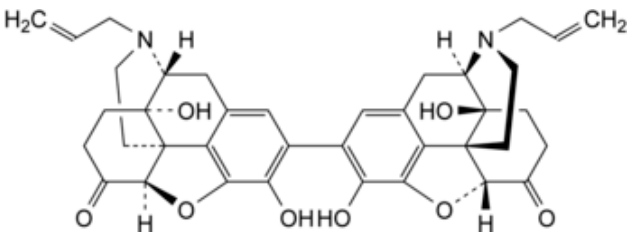
B. 4,5α-epoxy-14-hydroxy-17-(prop-2-enyl)-3-(prop-2-enyloxy)morphinan-6-one (3-*O*-allylnaloxone),



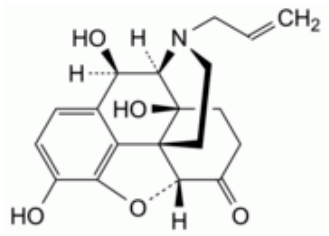
C. 4,5α-epoxy-3,10α,14-trihydroxy-17-(prop-2-enyl)morphinan-6-one (10α-hydroxynaloxone),



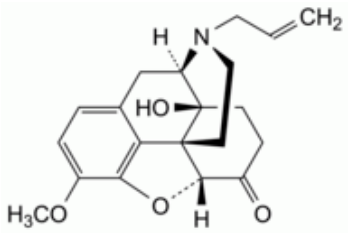
D. 7,8-didehydro-4,5α-epoxy-3,14-dihydroxy-17-(prop-2-enyl)morphinan-6-one (7,8-didehydronaloxone),



E. 4,5α:4′,5′α-diepoxy-3,3′,14,14′-tetrahydroxy-17,17′-bis(prop-2-enyl)-2,2′-bimorphinanyl-6,6′-dione (2,2′-binaloxone),



F. 4,5α-epoxy-3,10β,14-trihydroxy-17-(prop-2-enyl)morphinan-6-one (10β-hydroxynaloxone),



G. 4,5α-epoxy-14-hydroxy-3-methoxy-17-(prop-2-enyl)morphinan-6-one (3-*O*-methylnaloxone).

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