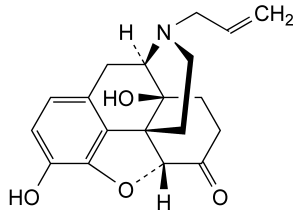
01/2008:0729

NALOXONE HYDROCHLORIDE DIHYDRATE

Naloxoni hydrochloridum dihydricum



, HCl , 2 H_2O

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

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*): – 170 to – 181 (anhydrous substance), determined on solution S.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.125 g of the substance to be examined in *0.1 M hydrochloric acid* and dilute to 25.0 ml with the same acid.

Reference solution (a). Dissolve 5 mg of *naloxone for peak identification CRS* (containing impurities A, B, C, D, E and F) in 1 ml of *0.1 M hydrochloric acid*.

Reference solution (b). Dilute 1.0 ml of the test solution to 20.0 ml with *0.1 M hydrochloric acid*. Dilute 1.0 ml of this solution to 25.0 ml with *0.1 M hydrochloric acid*.

Solution A. Dissolve 1.10 g of *sodium octanesulphonate R* in 1000 ml of *water R*, adjust to pH 2.0 with a 50 per cent *V/V* solution of *phosphoric acid R* and filter.

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 (20:40:940 *V/V/V*);
– *mobile phase B*: *tetrahydrofuran R, acetonitrile R*, solution A (40:170:790 *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);
– *impurity D*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 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.

Sulphated 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 $C_{19}H_{22}ClNO_4$.

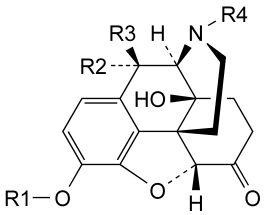
STORAGE

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*.



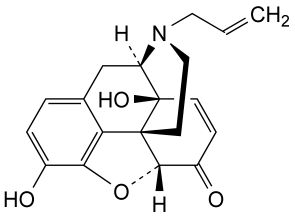
A. R1 = R2 = R3 = R4 = H: 4,5α-epoxy-3,14-dihydroxymorphinan-6-one (noroxymorphone),

B. R1 = R4 = CH_2-CH=CH_2, R2 = R3 = H: 4,5α-epoxy-14-hydroxy-17-(prop-2-enyl)-3-(prop-2-enyloxy)morphinan-6-one (3-*O*-allylnaloxone),

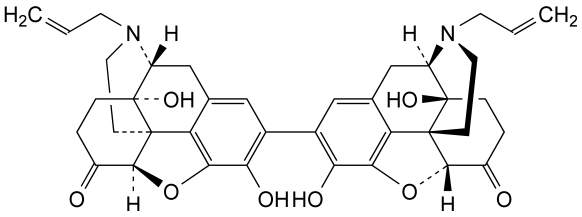
C. R1 = R3 = H, R2 = OH, R4 = CH_2-CH=CH_2: 4,5α-epoxy-3,10α,14-trihydroxy-17-(prop-2-enyl)morphinan-6-one (10α-hydroxynaloxone),

F. R1 = R2 = H, R3 = OH, R4 = CH_2-CH=CH_2: 4,5α-epoxy-3,10β,14-trihydroxy-17-(prop-2-enyl)morphinan-6-one (10β-hydroxynaloxone),

G. R1 = CH_3, R2 = R3 = H, R4 = CH_2-CH=CH_2: 4,5α-epoxy-14-hydroxy-3-methoxy-17-(prop-2-enyl)morphinan-6-one (3-*O*-methylnaloxone),



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

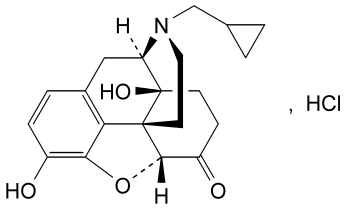


E. 4,5α:4′,5′α-diepoxy-3,3′,14,14′-tetrahydroxy-17,17′-bis(prop-2-enyl)-2,2′-bimorphinanyl-6,6′-dione (2,2′-binaloxone).

01/2008:1790

NALTREXONE HYDROCHLORIDE

Naltrexoni hydrochloridum



$C_{20}H_{24}ClNO_4$ M_r 377.9

DEFINITION

17-(Cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride. It may be anhydrous, a monohydrate or a dihydrate, a mixture or a solvate.

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

CHARACTERS

Appearance: white or almost white powder, very hygroscopic.

Solubility: freely soluble in water, slightly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Dissolve 20 mg in *water R* and dilute to 5 ml with the same solvent. Make alkaline with *dilute ammonia R1*. Shake with 10 ml of *methylene chloride R*, separate the organic layer and evaporate the solvent. Dry the residue obtained *in vacuo*.

Comparison: *naltrexone hydrochloride CRS*.

B. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S. Dissolve 0.40 g in *carbon dioxide-free water R* and dilute to 20.0 ml with the same solvent.