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6.0

volume 2

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EUROPEAN PHARMACOPOEIA 6th EDITION

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replaces the 5th Edition on 1 January 2008

Volumes 1 and 2 of this publication 6.0 constitute the 6th Edition of the European Pharmacopoeia. They will be complemented by **non-cumulative supplements** that are to be kept for the duration of the 6th Edition. 2 supplements will be published in 2007 and 3 supplements in each of the years 2008 and 2009. A cumulative list of reagents will be published in supplements 6.4 and 6.7.

If you are using the 6th Edition at any time later than 1 April 2008, make sure that you have all the published supplements and consult the index of the most recent supplement to ensure that you use the latest versions of the monographs and general chapters.

EUROPEAN PHARMACOPOEIA - ELECTRONIC VERSION

The 6th Edition is also available in an electronic format (CD-ROM and online version) containing all of the monographs and general chapters found in the printed version. With the publication of each supplement the electronic version is replaced by a new, fully updated, cumulative version.

In addition to the official English and French online versions, a Spanish online version is also available for the convenience of users.

PHARMEUROPA

Quarterly Forum Publication

Pharmeuropa contains preliminary drafts of all new and revised monographs proposed for inclusion in the European Pharmacopoeia and gives an opportunity for all interested parties to comment on the specifications before they are finalised. Pharmeuropa also contains information on the work programme and on certificates of suitability to monographs of the European Pharmacopoeia issued by the EDQM, and articles of general interest. Pharmeuropa is available on subscription from the EDQM. The subscription also includes Pharmeuropa Bio and Pharmeuropa Scientific Notes (containing scientific articles on pharmacopoeial matters). Pharmeuropa Online is also available as a complementary service for subscribers to the printed version of Pharmeuropa.

INTERNATIONAL HARMONISATION

See the information given in chapter *5.8. Pharmacopoeial Harmonisation*.

WEBSITE

http://www.edqm.eu

http://www.edqm.eu/store (for prices and orders)

HELPDESK

To send a question or to contact the EDQM, use the HELPDESK, accessible through the EDQM website (visit http://www.edqm.eu/site/page_521.php).

KNOWLEDGE

Consult KNOWLEDGE, the new free database at http://www.edqm.eu to obtain information on the work programme of the European Pharmacopoeia, the volume of Pharmeuropa and of the European Pharmacopoeia in which a text has been published, trade names of the reagents (for example, chromatography columns) that were used at the time of the elaboration of the monographs, the history of the revisions of a text since its publication in the 5th Edition, reference chromatograms, the list of reference standards used, and the list of certificates granted.

COMBISTATS

CombiStats is a computer program for the statistical analysis of data from biological assays in agreement with chapter *5.3* of the 6th Edition of the European Pharmacopoeia. For more information, visit the website (http://www.edqm.eu/combistats).

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EUROPEAN PHARMACOPOEIA

SIXTH EDITION

Volume 2

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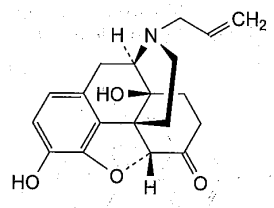
NALOXONE HYDROCHLORIDE DIHYDRATE

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);

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– *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 $C_{19}H_{22}ClNO_4$.

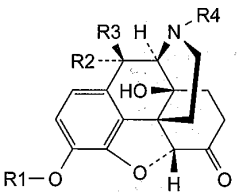
STORAGE

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*.



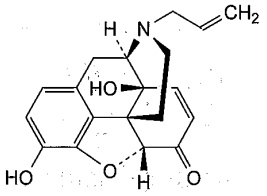
A. R1 = R2 = R3 = R4 = H: 4,5α-epoxy-3,14-dihydroxymorphinan-6-one (noroxymorphone),

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),

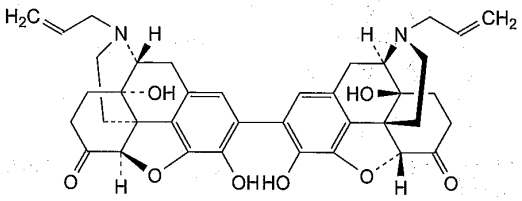
C. R1 = R3 = H, R2 = OH, R4 = CH_2-CH=CH_2: 4,5α-epoxy-3,10α,14-trihydroxy-17-(prop-2-enyl)morphinan-6-one (10α-hydroxynaloxone),

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).

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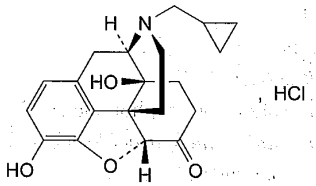
NALTREXONE HYDROCHLORIDE

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.

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