Naltrexone hydrochloride

EUROPEAN PHARMACOPOEIA 6.0

**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).

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.

D. 7,8-didehydro-4,5α-epoxy-3,14-dihydroxy-17-prop-2-enylmorphinan-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).
**Appearance of solution.** Solution S is clear (2.2.1) and not more intensely coloured than reference solution Y₆ or B₆ (2.2.2, Method II).

**Acidity and alkalinity.** To 10 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): – 187 to – 195 (anhydrous substance).

Dissolve 0.40 g in water R and dilute to 20.0 ml with the same solvent.

**Related substances.** Liquid chromatography (2.2.29).

**Test solution.** Dissolve 20.0 mg of the substance to be examined in 0.1 M hydrochloric acid and dilute to 10.0 ml with the same solvent.

**Reference solution (a).** Dissolve 5.0 mg of naltrexone impurity C CRS in 0.1 M hydrochloric acid and dilute to 2.5 ml with the same solvent.

**Reference solution (b).** Dilute 1.0 ml of the test solution and 1.0 ml of reference solution (a) to 100.0 ml with 0.1 M hydrochloric acid. Dilute 1.0 ml of this solution to 10.0 ml with 0.1 M hydrochloric acid.

**Column:**

- size: l = 0.15 m, Ø = 4.6 mm,
- stationary phase: octadecylsilyl silica gel for chromatography R1 (5 µm),
- temperature: 40 °C.

**Mobile phase:**

- mobile phase A: 1.1 g/l solution of sodium octanesulphonate R adjusted to pH 2.3 with phosphoric acid R;
- mobile phase B: acetonitrile R;

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<thead>
<tr>
<th>Time (min)</th>
<th>Mobile phase A (per cent V/V)</th>
<th>Mobile phase B (per cent V/V)</th>
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<tbody>
<tr>
<td>0 - 45</td>
<td>90 → 55</td>
<td>10 → 45</td>
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<tr>
<td>45 - 47</td>
<td>55 → 90</td>
<td>45 → 10</td>
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<tr>
<td>47 - 55</td>
<td>90</td>
<td>10</td>
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**Flow rate:** 1.2 ml/min.

**Detection:** spectrophotometer at 230 nm.

**Equilibration:** 8 min.

**Injection:** 10 µl.

**Relative retention** with reference to naltrexone (retention time = about 16 min): impurity A = about 0.4; impurity B = about 0.7; impurity F = about 0.8; impurity C = about 0.9; impurity C = about 1.05; impurity H = about 1.1; impurity I = about 1.2; impurity J = about 1.3; impurity D = about 1.4; impurity E = 1.7.

**System suitability:** reference solution (b):

- resolution: minimum 2.0 between the peaks due to naltrexone and impurity C.

**Limits:**

- correction factor: for the calculation of content, multiply the peak area of impurity D by 0.4;

- impurities C, D, E, F, G: for each impurity, not more than twice the area of the peak due to naltrexone in the chromatogram obtained with reference solution (b) (0.2 per cent);

- impurities A, B, H, I, J: for each impurity, not more than the area of the peak due to naltrexone in the chromatogram obtained with reference solution (b) (0.1 per cent);

- any other impurity: for each impurity, not more than the area of the peak due to naltrexone in the chromatogram obtained with reference solution (b) (1.0 per cent);

- disregard limit: 0.5 times the area of the peak due to naltrexone in the chromatogram obtained with reference solution (b) (0.05 per cent).

**Ethanol (2.4.24, System A):** maximum 3.0 per cent.

**Test solution.** Dissolve 0.25 g of the substance to be examined in water R and dilute to 10.0 ml with the same solvent.

**Reference solution.** Dilute 0.750 g of anhydrous ethanol R to 1000.0 ml with water R.

**Water (2.5.12):** maximum 10.0 per cent, determined on 0.200 g.

**Sulphated ash (2.4.14):** maximum 0.1 per cent, determined on 1.0 g.

**ASSAY**

Dissolve 0.200 g in 60 ml of ethanol (96 per cent) R, add 1.0 ml of 0.1 M hydrochloric acid. Carry out a potentiometric titration (2.2.20), using 0.1 M sodium hydroxide. The curve shows 3 points of inflexion. Read the volume added between the first 2 points of inflexion.

1 ml of 0.1 M sodium hydroxide is equivalent to 37.79 mg of C₂₀H₂₄ClNO₄.

**STORAGE**

In an airtight container. Protected from light.

**IMPURITIES**

**Specified impurities: A, B, C, D, E, F, G, H, I, J.**

- A = CHO: 17-formyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one,
- B = H: 4,5α-epoxy-3,14-dihydroxymorphinan-6-one (noroxymorphone),
- C = CH₂CH₂CH₂=CH₂: 17-but-3-enyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one,
- H. R = CH₂CH₂CH₂CH₂: 17-butyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one,
Nandrolone decanoate

**DEFINITION**

3-Oxoestr-4-en-17β-yl decanoate.

**Content:** 97.0 per cent to 103.0 per cent (dried substance).

**CHARACTERS**

**Appearance:** white or almost white, crystalline powder.

**Solubility:** practically insoluble in water, very soluble in ethanol (96 per cent) and in methylene chloride.

**IDENTIFICATION**

A. Melting point (2.2.14): 34 °C to 38 °C.

B. Infrared absorption spectrophotometry (2.2.24).

**Comparison:** nandrolone decanoate CRS.

**TESTS**

**Appearance of solution.** The solution is clear (2.2.1) and not more intensely coloured than reference solution Y₆ (2.2.2, Method II).

Dissolve 0.20 g in 10 ml of methanol R.

**Specific optical rotation** (2.2.7): +35.0 to +40.0 (dried substance).

Dissolve 0.200 g in anhydrous ethanol R and dilute to 20.0 ml with the same solvent.

**Impurities A, B, C.** Thin-layer chromatography (2.2.27).

Test solution. Dissolve 50 mg of the substance to be examined in methylene chloride R and dilute to 5.0 ml with the same solvent.

Reference solution (a). Dilute 1.0 ml of the test solution to 10.0 ml with methylene chloride R.

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 10.0 ml with methylene chloride R.

Reference solution (c). Dilute 1.0 ml of reference solution (a) to 20.0 ml with methylene chloride R.

Reference solution (d). Dissolve 5 mg of nandrolone decanoate for system suitability CRS (containing impurities A, B, C) in 0.5 ml of methylene chloride R.

**Plate:** TLC silica gel plate R.

**Mobile phase:** acetone R, heptane R (30:70 V/V).

Application: 10 µl of the test solution and reference solutions (b), (c) and (d).

Development: over 2/3 of the plate.

Drying: in air.

Detection: treat with alcoholic solution of sulphuric acid R and heat at 130 °C until the spots appear. Examine in ultraviolet light at 366 nm.

**Retention factors:** nandrolone decanoate = about 0.37; impurity A = about 0.45; impurity B = about 0.55; impurity C = about 0.58.

**System suitability:** reference solution (d):

- the chromatogram shows 4 clearly separated spots.

**Limits:**

- **impurity A:** any spot due to impurity A is not more intense than the principal spot in the chromatogram obtained with reference solution (b) (1.0 per cent);

- **impurities B, C:** any spot due to impurity B or C is not more intense than the principal spot in the chromatogram obtained with reference solution (c) (0.5 per cent).

**Related substances.** Liquid chromatography (2.2.29).

Test solution. Dissolve 25 mg of the substance to be examined in methanol R and dilute to 10.0 ml with the same solvent.

Reference solution (a). Dilute 1.0 ml of the test solution to 100.0 ml with methanol R. Dilute 1.0 ml of this solution to 10.0 ml with methanol R.