CLINDAMYCINI HYDROCHLORIDUM –

CLINDAMYCIN HYDROCHLORIDE

Draft for The International Pharmacopoeia

(January 2015)

DRAFT FOR COMMENT

Should you have any comments on the attached text, please send these to Dr Herbert Schmidt, Medicines Quality Assurance, Technologies, Standards and Norms, World Health Organization, 1211 Geneva 27, Switzerland; email: schmidt@who.int; fax: (+41 22) 791 4730) by 21 March 2015.

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**Clindamycini hydrochloridum - Clindamycin hydrochloride**

*Draft for The International Pharmacopoeia*  
*(January 2015)*

\[
\text{C}_{18}\text{H}_{33}\text{ClN}_{2}\text{O}_{5}\text{S}, \text{HCl}
\]

**Relative molecular mass.** 461.5

**Chemical name**


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

**Solubility.** Very soluble in water, freely soluble in methanol R, and slightly soluble in ethanol (~750 g/L) TS.

**Category.** Antibacterial.

**Storage.** Clindamycin hydrochloride should be kept in a tightly closed container.

**Requirements**

**Definition.** Clindamycin hydrochloride contains not less than 91.0% and not more than 102.0% of C\textsubscript{18}H\textsubscript{33}ClN\textsubscript{2}O\textsubscript{5}S, HCl, calculated with reference to the anhydrous substance.

**Identity test**

- Either tests A and E or B, D and E or C, D and E may be applied.

  A. Carry out the examination as described under 1.7 Spectrophotometry in the
**irrelevant region. The infrared absorption spectrum is concordant with the spectrum obtained from clindamycin hydrochloride RS or with the reference spectrum of clindamycin hydrochloride.**

**B.** Carry out the test as described under 1.14.1. Thin layer chromatography using silica gel R1 as the coating substance and the upper layer of a mixture of 19 volumes of 2-propanol R, 38 volumes of a solution of ammonium acetate (~150 g/L) TS adjusted to pH 9.6 with ammonia (~260 g/L) TS and 43 volumes of ethyl acetate R as the mobile phase. Apply separately to the plate 5 µL of each of the following three solutions in methanol R. For solution (A) use 1 mg of test substance per mL. For solution (B) use 1 mg of Clindamycin hydrochloride RS per mL. For solution (C) use 1 mg of Clindamycin hydrochloride RS and 1 mg of lincomycin hydrochloride RS per mL. After removing the plate from the chromatographic chamber dry the plate in air and spray with potassium permanganate (~1 g/L) TS. Examine the chromatogram in daylight.

The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B). The test is not valid unless the chromatogram obtained with solution (C) shows 2 clearly separated spots.

**C.** See the test described under “Assay”. The principal peak in the chromatogram obtained with solution (1) is similar in retention time to the principal peak in the chromatogram obtained with solution (2).

**D.** Dissolve about 10 mg in 2 mL of hydrochloric acid (~200 g/L) TS and heat on a water-bath for 3 minutes. Add 3 mL of sodium carbonate (106 g/L) TS and 1 mL of sodium nitroprusside (20 g/L) TS. A violet-red colour develops.

**E.** A 0.01 g/mL solution yields reaction A described under 2.1 General identification tests as characteristic of chlorides.

**Specific optical rotation.** Use a 40.0 mg/mL solution and calculate with reference to the anhydrous substance: \( [\alpha]_{D}^{20^\circ} = +135^\circ \) to \( +150^\circ \).

**Sulfated ash.** Not more than 5.0 mg/g.

**Water.** Determine as described under 2.8 Determination of water by Karl Fischer Method, Method A, using 0.5 g of the substance. The water content is not less than 30 mg/g and not more than 60 mg/g.

**pH value.** pH of a 100 mg/mL solution in carbon-dioxide-free water R, 3.0–5.0.
**Related substances.** Carry out the test as described under 1.14.4 *High-performance liquid chromatography* using the conditions given below under “Assay”.

Prepare the following solutions in the mobile phase. For solution (1) dissolve 100 mg of the test substance and dilute to 25.0 mL. For solution (2) dilute 2.0 mL of solution (1) to 100.0 mL. For solution (3) dissolve 100 mg of clindamycin hydrochloride RS in a 25 mL volumetric flask.

Inject alternately 20 µL each of solution (1), (2) and (3). Record the chromatograms for about 2 times the retention time of clindamycin (retention time about 10 minutes).

In the chromatogram obtained with solution (3) the peaks are eluted at the following relative retention with reference to clindamycin (retention time about 10 minutes): impurity A (lincomycin) about 0.4; impurity B (clindamycin B) about 0.65; impurity C (7-epiclindamycin) about 0.8. The test is not valid unless the resolutions between the peaks due to impurities B and C and impurity C and clindamycin are at least 3.0.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to either impurity B or impurity C is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (2.0%);
- the area of any other peak, other than the principal peak, is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);
- the sum of the areas of all peaks, other than the principal peak, is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (6.0%). Disregard any peak with an area less than 0.025 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

**Assay.** Carry out the test as described under 1.14.4 *High-performance liquid chromatography* using a stainless steel column (25 cm × 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 µm).\(^1\) As the mobile phase use a mixture of 45 volumes of acetonitrile R and 55 volumes of potassium dihydrogen phosphate (6.8 g/L) TS adjusted to pH 7.5 with potassium hydroxide (~400 g/L) TS.

Prepare the following solutions in mobile phase. For solution (1) use a solution containing 1.0 mg of the test substance per mL. For solution (2) use a solution containing 1.0 mg of clindamycin hydrochloride RS per mL.

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet

\(^1\) Hypersil BDS 5 µm was found to be suitable.
spectrophotometer set at a wavelength of 210 nm. Inject alternately 20 µL each of solutions (1) and (2).

Measure the areas of the peaks corresponding to clindamycin obtained in the chromatograms from solution (1) and (2) and calculate the percentage content of clindamycin hydrochloride (C$_{18}$H$_{33}$ClN$_2$O$_5$S.HCl) using the declared content of C$_{18}$H$_{33}$ClN$_2$O$_5$S.HCl in clindamycin hydrochloride RS.

**Impurities**

A. R$_1$=CH$_2$-CH$_2$-CH$_3$, R$_2$=OH, R$_3$=H: methyl 6,8-dideoxy-6-[[[(2S,4R)-1-methyl-4-propylpyrrolidin-2-yl]carbonyl]amino]-1-thio-d-erythro-α-d-galacto-octopyranoside (lincomycin)

B. R$_1$=C$_2$H$_5$, R$_2$=H, R$_3$=Cl: methyl 7-chloro-6,7,8-trideoxy-6-[[[(2S,4R)-4-ethyl-1-methylpyrrolidin-2-yl]carbonyl]amino]-1-thio-l-threo-α-d-galacto-octopyranoside (clindamycin B)

C. R$_1$=CH$_2$-CH$_2$-CH$_3$, R$_2$=Cl, R$_3$=H: methyl 7-chloro-6,7,8-trideoxy-6-[[[(2S,4R)-1-methyl-4-propylpyrrolidin-2-yl]carbonyl]amino]-1-thio-d-erythro-α-d-galacto-octopyranoside (7-epiclindamycin)

**Reagents to be established**

Hydrochloric acid (~200 g/L) TS

Procedure. Dilute hydrochloric acid (~250 g/L) TS with water to contain approximately 200 g of HCl in 1000 mL (approximately 5.5 mol/L).

Sodium carbonate (106 g/L) TS

A solution of sodium carbonate R containing about 106 g of Na$_2$CO$_3$ per litre (approximately 1 mol/L).
Sodium nitroprusside (20 g/L) TS
A solution of sodium nitroprusside R containing about 20 g of Na2Fe(NO)(CN)5 per litre.
Note: Sodium nitroprusside (20 g/L) TS must be freshly prepared.

Potassium dihydrogen phosphate (6.8 g/L) TS
A solution of potassium dihydrogen phosphate R containing 6.8 g of KH₂PO₄ per litre (0.1 mol/L).

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