CLINDAMYCIN PALMITATE HYDROCHLORIDE

(CLINDAMYCINI PALMITAS HYDROCHLORIDUM)

Draft proposal for The International Pharmacopoeia

(Febuary 2018)

DRAFT FOR COMMENT

Should you have any comments on this draft, please send these to Dr Herbert Schmidt, Medicines Quality Assurance Programme, Technologies Standards and Norms, Department of Essential Medicines and Health Products., World Health Organization, 1211 Geneva 27, Switzerland; fax: (+41 22) 791 4730 or email: schmidt@who.int by 13 April 2018.

In order to speed up the process for receiving draft monographs and for sending comments, please let us have your email address (to bonnyw@who.int) and we will add it to our electronic mailing list. Please specify if you wish to receive monographs.

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## SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/16.654:

**CLINDAMYCIN PALMITATE HYDROCHLORIDE**

*(CLINDAMYCINI PALMITAS HYDROCHLORIDUM)*

<table>
<thead>
<tr>
<th>Activity</th>
<th>Date</th>
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<tbody>
<tr>
<td>Drafting of the monograph by a WHO Collaborating Centre</td>
<td>October 2015–January 2016</td>
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<tr>
<td>Discussion at informal consultation on quality control laboratory tools</td>
<td>9–11 May 2016</td>
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<td>and specifications for medicines</td>
<td></td>
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<tr>
<td>Draft revision sent out for public consultation</td>
<td>July–September 2016</td>
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<tr>
<td>Presentation to WHO Expert Committee on Specifications for Pharmaceutical Preparations</td>
<td>October 2016</td>
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<tr>
<td>Discussion at the informal consultation on quality control laboratory tools and specifications for medicines</td>
<td>2–4 May 2017</td>
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<tr>
<td>Further laboratory investigations in response to comments received</td>
<td>June–September 2017</td>
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<tr>
<td>Presentation of revised version (Rev.1) to WHO Expert Committee on Specifications for Pharmaceutical Preparations</td>
<td>October 2017</td>
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<tr>
<td>Revision 1 sent out for public consultation</td>
<td>February–April 2018</td>
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<tr>
<td>Further follow-up action as required</td>
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CLINDAMYCIN PALMITATE HYDROCHLORIDE
(CLINDAMYCINI PALMITAS HYDROCHLORIDUM)

Molecular formula. \( C_{34}H_{63}ClN_2O_6S \cdot HCl \)

Relative molecular mass. 699.85

Graphic formula

Chemical name. L-threo-\( \alpha \)-D-galacto-Octopyranoside, methyl 7-chloro-6,7,8-trIDEOxy-6-\([(1\text{-methyl-4-propyl-2-pyrrolidinyl})\text{-carbonyl}][\text{amino}]\text{-1-thio-2-hexadecanoate, monohydrochloride, (2S-trans)}; \text{Methyl 7-chloro-6,7,8-trIDEOxy-6-(1-methyl-trans-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-threo-\( \alpha \)-D-galacto-octopyranoside 2-palmitate monohydrochloride; CAS Reg. No. 25507-04-4.}

Description. A white or almost white powder.

Solubility. Freely soluble in ethanol and in dichloromethane; soluble in water.

Category. Antibacterial.

Storage. Clindamycin palmitate hydrochloride should be preserved in a tightly closed container.

Additional information. Clindamycin palmitate hydrochloride is a semi-synthetic product derived from a fermentation product.

Requirements

Definition. Clindamycin palmitate hydrochloride contains not less than 91.0% and not more than 102.0% of \( C_{34}H_{63}ClN_2O_6S \cdot HCl \), calculated with reference to the
anhydrous substance.

**Identity tests**

- Either test A alone or tests B and C may be applied

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

B. Carry out the test as described under *1.14.4 High-performance liquid chromatography* using the conditions given under “Assay”. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that of the principal peak in the chromatogram obtained with solution (2).

C. A 10 mg/mL solution yields reaction B described under *2.1 General identification tests* as characteristic of chlorides.

**Water.** Determine as described under *2.8 Determination of water by the Karl Fischer method*, Method A. Use 0.1 g of the test substance. The water content is not more than 30 mg/g.

**pH value (1.13).** pH of a 10 mg/mL solution in carbon-dioxide-free water R, 2.8–3.8.

**Sulfated ash (2.3).** Not more than 5 mg/g.

**Related substances.** Carry out the test as described under *1.14.4 High-performance liquid chromatography* using a column (25 cm × 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded octylsilyl groups (5 μm).¹

Use the following conditions for gradient elution:

- mobile phase A: Ammonium acetate (~0.40 g/L) TS - acetonitrile R (50:50);
- mobile phase B: Acetonitrile R.

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¹ Agilent® Zorbax Elipse XDB-C8 has been found suitable.
<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Mobile phase A (%) v/v</th>
<th>Mobile phase B (%) v/v</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–30</td>
<td>100 to 0</td>
<td>0 to 100</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>30–80</td>
<td>0</td>
<td>100</td>
<td>Isocratic</td>
</tr>
<tr>
<td>80–81</td>
<td>0 to 100</td>
<td>100 to 0</td>
<td>Return to initial composition</td>
</tr>
<tr>
<td>81–90</td>
<td>100</td>
<td>0</td>
<td>Re-equilibration</td>
</tr>
</tbody>
</table>

Prepare the following solutions in methanol R. For solution (1) dissolve about 100 mg of clindamycin palmitate hydrochloride and dilute to 10.0 mL. For solution (2) dilute 2.0 mL of solution (1) to 100 mL. For solution (3) dissolve about 75 mg clindamycin palmitate hydrochloride RS (containing clindamycin palmitate hydrochloride and impurity A) and dilute to 10.0 mL.

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 230 nm.

Inject alternately 20 μL each of solution (1), (2) and (3).

In the chromatogram obtained with solution (3) the retention time of clindamycin palmitate is about 37 minutes. The test is not valid unless the resolution between the peaks due to clindamycin palmitate and impurity A (relative retention about 0.9) is at least 3.0.

In the chromatogram obtained with solution (1) the following impurities, if present, are eluted at the following relative retention with reference to clindamycin palmitate: impurity B about 0.8 and impurity A about 0.9.

In the chromatogram obtained with solution (1):

- the area of any impurity peak is not more than the area of the principal peak in the chromatogram obtained with solution (2) (2.0%);
- the sum of the areas of all impurity peaks is not more than 3.5 times the area of the principal peak in the chromatogram obtained with solution (2) (7.0%). 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 octylsilyl groups (5 μm).²

² Waters Symmetry C8 column has been found suitable.
As the mobile phase, use a mixture of 10 volumes of ammonium acetate (~0.40 g/L) TS and 90 volumes of acetonitrile R.

Prepare the following solutions in mobile phase. For solution (1) transfer about 50 mg of the test substance, accurately weighed, into a 50 mL volumetric flask, dissolve and dilute to volume. For solution (2) dissolve about 50 mg of clindamycin palmitate hydrochloride RS and dilute to 50.0 mL.

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 230 nm.

Inject alternately 20 μL each of solutions (1) and (2) and record the chromatograms for about 40 minutes.

Measure the areas of the peak responses corresponding to clindamycin palmitate obtained in the chromatograms from solutions (1) and (2) and calculate the percentage content of clindamycin palmitate hydrochloride (C_{34}H_{63}ClN_{2}O_{6}S.HCl), using the declared content of clindamycin palmitate hydrochloride (C_{34}H_{63}ClN_{2}O_{6}S.HCl) in clindamycin palmitate hydrochloride RS.

**Impurities**

A. L-threo-α-D-galacto-Octopyranoside, methyl 7-chloro-6,7,8-trideoxy-6-[[1-methyl-4-ethyl-2-pyrrolidinyl]-carbonyl]amino]-1-thio-2-hexadecanoate, (2S-trans); Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-trans-4-ethyl-L-2-pyrrolidine carboxamido)-1-thio-L-threo-α-D-galacto-octopyranoside 2-palmitate (clindamycin B palmitate) (synthesis-related impurity)
B. L-threo-α-D-galacto-Octopyranoside, methyl-epimer-7-chloro-6,7,8-trideoxy-6-[[1-methyl-4-propyl-2-pyrrolidinyl]-carbonylamino]-1-thio-2-hexadecanoate, (2S-trans); Methyl-epimer-7-chloro-6,7,8-trideoxy-6-(1-methyl-trans-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-threo-α-D-galacto-octopyranoside 2-palmitate; (7-epiclindamycin 2-palmitate) (synthesis-related impurity)

Reagents to be established

Ammonium acetate (~0.40 g/L) TS

A solution of ammonium acetate R containing about 0.385 g of C₂H₇NO₂ per litre (approximately 0.005 mol/L).

Docusate sodium R

C₂₀H₃₇NaO₇S

A commercially available reagent of suitable grade.

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