NORETHISTERONE ENANTAS
NORETHISTERONE ENANTATE
Draft proposal for The International Pharmacopoeia
(July 2017)

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 15 September 2017.

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.

© World Health Organization 2017

All rights reserved.

This draft is intended for a restricted audience only, i.e. the individuals and organizations having received this draft. The draft may not be reviewed, abstracted, quoted, reproduced, transmitted, distributed, translated or adapted, in part or in whole, in any form or by any means outside these individuals and organizations (including the organizations' concerned staff and member organizations) without the permission of the World Health Organization. The draft should not be displayed on any website.

Please send any request for permission to:
Dr Sabine Kopp, Manager, Medicines Quality Assurance Programme, Technologies Standards and Norms, Department of Essential Medicines and Health Products, World Health Organization, CH-1211 Geneva 27, Switzerland. Fax: (41-22) 791 4730; email: kopps@who.int.

The designations employed and the presentation of the material in this draft do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers’ products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by the World Health Organization to verify the information contained in this draft. However, the printed material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the World Health Organization be liable for damages arising from its use.

This draft does not necessarily represent the decisions or the stated policy of the World Health Organization.
### SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/17.724:

**NORETHISTERONE ENANTATE (NORETHISTERONE ENANTAS)**

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>First draft (Revision 1) received from collaborating laboratory</td>
<td>June 2017</td>
</tr>
<tr>
<td>Draft revision (Revision 2) sent out for public consultation</td>
<td>July–September 2017</td>
</tr>
<tr>
<td>Presentation to WHO Expert Committee on Specifications for Pharmaceutical Preparations</td>
<td>October 2017</td>
</tr>
<tr>
<td>Further follow-up action as required</td>
<td></td>
</tr>
</tbody>
</table>
NORETHISTERONE ENANTATE
(NORETHISTERONI ENANTAS)

Molecular formula. $\text{C}_{27}\text{H}_{38}\text{O}_3$

Relative molecular mass. 410.6

Chemical names. 17-Hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one heptanoate;
17-[(1-oxoheptyl)oxy]-19-nor-17α-pregn-4-en-20-yn-3-one; CAS Reg. No. 3836-23-5.

Other name. Norethindrone enantate

Description. A white to yellowish white, crystalline powder.

Solubility. Practically insoluble in water R; freely soluble in acetone R, methanol R,
dehydrated ethanol R and dioxan R.

Category. Contraceptive.

Storage. Norethisterone enantate should be kept in a tightly closed container, protected
from light.

Requirements

Norethisterone enantate contains not less than 98.0% and not more than 102.0% (“Assay”,
Method A) or not less than 97.0% and not more than 102.0% (“Assay”, Method B) of
$\text{C}_{27}\text{H}_{38}\text{O}_3$, calculated with reference to the dried 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 norethisterone enantate RS or with the reference spectrum of norethisterone enantate.

B. The absorption spectrum (1.6) of a solution of about 15 μg of the test substance per mL in methanol R, when observed between 210 nm and 290 nm, exhibits a maximum at about 240 nm.

C. Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given under “Assay”, Method B. The retention time of the principle peak in the chromatogram obtained with solution (1) corresponds to the retention time of the peak due to norethisterone enantate in the chromatogram obtained with solution (2).

Specific optical rotation. Use a 20 mg/mL solution in dichloromethane R; \([\alpha]_{D}^{20^\circ} = -10.0^\circ\) to \(-15.0^\circ\).

Sulfated ash. Not more than 1.0 mg/g.

Loss on drying. Dry over desiccant silica gel R at ambient temperature for 4 hours; it loses not more than 5.0 mg/g.

Related substances. Carry out the test as described under 1.14.4 High-performance liquid chromatography using the chromatographic conditions as described under “Assay”, Method B.

Prepare the following solutions in methanol R. For solution (1) dilute a suitable amount of sample to obtain a concentration of 1.0 mg of Norethisterone enantate per mL. For solution (2) dilute 1 volume of solution (1) to 100 volumes. For solution (3) prepare a solution containing 1.0 mg per mL of norethisterone enantate RS and 0.1 mg per mL of norethisterone caproate R.

Inject 20 μL of solution (3). The test is not valid unless the resolution between the peak due to norethisterone caproate (with a relative retention of about 0.95) and the peak due to norethisterone enantate (retention time about 27 minutes) is at least 4.0.

Inject alternatively 20 μL of solutions (1) and (2).

In the chromatogram obtained with solution (1):

- the area of any impurity peak is not greater than 0.3 times the area of the peak due to norethisterone enantate in the chromatogram obtained with solution (2) (0.3%);
126 the sum of the areas of all impurities is not greater than the area of the peak due to
127 norethisterone enantate in the chromatogram obtained with solution (2) (1.0%).
128 Disregard any peak with an area less than 0.05 times the area of the peak due to
129 norethisterone enantate in the chromatogram obtained with solution (2) (0.05%).
130
131 Free enantic acid. Dissolve 0.3 g in 10 mL of neutralized ethanol (~750 g/L) TS. Titrate
132 the solution quickly with sodium hydroxide (0.01 mol/L) VS to a light blue end-point
133 using bromothymol blue/ethanol TS as indicator; not more than 0.3 mL (corresponding to
134 1.3 mg/g of enantic acid).
Assay
135
136 • Either method A or B may be applied.
137
138 A. Dissolve about 15 mg, accurately weighed, in sufficient methanol R and dilute to
139 100.0 mL with the same solvent. Dilute 10.0 mL of this solution to 100.0 mL with
140 methanol R.
141 Measure the absorbance of the diluted solution in a 1 cm layer at the maximum at
142 about 240 nm and calculate the content of \( \text{C}_{27}\text{H}_{38}\text{O}_{3} \) using the absorptivity value of
143 42.8 \( (A_{1\,cm}^{1\%} = 428) \).
144
145 B. Carry out the test under 1.14.4 High-performance liquid chromatography using a
146 stainless steel column (25 cm x 4.6 mm) packed with base-deactivated particles of
147 silica gel, the surface of which has been modified with chemically-bonded
148 octadecylsilyl groups (5 μm).\(^1\)
149
150 Use the following conditions for gradient elution:
151
152 mobile phase A: water R;
153 mobile phase B: acetonitrile R.
154
155 | Time (min) | Mobile phase A (% v/v) | Mobile phase B (% v/v) | Comments |
156 | 0–17 | 40 | 60 | Isocratic |
157 | 17–20 | 40 to 10 | 60 to 90 | Linear gradient |
158 | 20–45 | 10 | 90 | Isocratic |
159 | 45–46 | 10 to 40 | 90 to 60 | Return to initial composition |
160 | 46–60 | 40 | 60 | Re-equilibration |
161
162 Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet
163 spectrophotometer set at a wavelength of 254 nm. Maintain the column temperature
164 at 40 °C.

\(^1\)BDS HYPERSIL C\(_{18}\) is suitable.
Prepare the following solutions in methanol R. For solution (1) dissolve 20.0 mg of the test substance and dilute to 100.0 mL. For solution (2) dissolve 20.0 mg of norethisterone enantate RS and dilute to 100.0 mL.

Inject alternately 20 μL each of solution (1) and (2) and record the chromatograms.

Measure the areas of the peaks corresponding to norethisterone enantate obtained in the chromatograms of solution (1) and (2) and calculate the percentage content of \( \text{C}_{27}\text{H}_{38}\text{O}_3 \) using the declared content of \( \text{C}_{27}\text{H}_{38}\text{O}_3 \) in norethisterone enantate RS.

**Additional requirement for Norethisterone enantate for parenteral use**

Complies with the monograph for *Parenteral preparations*.

**Reagent to be established**

**Norethisterone caproate R**

Norethisterone caproate of a suitable quality should be used.