NORETHISTERONI ENANTAS INJECTIO
NORETHISTERONE ENANTATE INJECTION
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.

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## SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/17.725:
### NORETHISTERONE ENANTATE INJECTION

*(NORETHISTERONI ENANTAS INJECTIO)*

<table>
<thead>
<tr>
<th>Event Description</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–August 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 INJECTION

*(NORETHISTERONI ENANTAS INJECTIO)*

**Description.** A clear, colourless or almost colourless, oily solution.

**Category.** Contraceptive.

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

**Labelling.** The oil used in the formulation should be indicated.

**Additional information.** Strength in the current WHO Model List of Essential Medicines (EML): 200 mg/mL in 1 mL ampoule.

**Requirements**

Complies with the monograph for *Parenteral preparations*.

**Definition.** Norethisterone enantate injection contains not less than 90.0% and not more than 110.0% of the amount of Norethisterone enantate (C<sub>27</sub>H<sub>38</sub>O<sub>3</sub>) stated on the label.

**Identity tests**

- Either test A or test B may be applied.

**A.** Carry out the test as described under *1.14.4 High-performance liquid chromatography* using the conditions as given under “Assay”. 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).

**B.** Carry out the test as described under *1.14.1 Thin-layer chromatography* using silica gel R<sub>6</sub> as the coating substance and a mixture of 2 volumes of cyclohexane R and 1 volume of ethyl acetate R as the mobile phase. Apply separately to the plate 10 µL of each of the following two solutions in dichloromethane R. For solution (A) use a dilution of the test solution containing the equivalent of 1.0 mg of Norethisterone enantate per mL. For solution (B) use a solution containing 1.0 mg of norethisterone enantate RS per mL. After removing the plate from the chromatographic chamber allow it to dry in air and examine the chromatogram in ultraviolet light (254 nm). Spray the plate with antimony trichloride TS, heat at 110 °C for 15 minutes and examine the chromatogram in ultraviolet light (365 nm). The principal spot obtained with solution (A) corresponds in position, appearance and intensity to that obtained with solution (B).
**Bacterial endotoxins.** Carry out the test as described under 3.4 Test for bacterial endotoxins; contains not more than 1.5 IU of endotoxin RS per mg.

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

Prepare the following solutions in methanol R. For solution (1) dilute a suitable volume of the 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) use a solution containing 0.1 mg of benzyl benzoate R per mL. For solution (4) use 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 (4). 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), (2) and (3) and record the chromatograms. Use the chromatogram obtained with solution (3) to identify any peak due to benzyl benzoate, if present.

In the chromatogram obtained with solution (1):

- the area of any impurity peak is not greater than 0.5 times the area of the peak due to norethisterone enantate in the chromatogram obtained with solution (2) (0.5%);
- the sum of the areas of all impurities is not greater than the area of the peak due to norethisterone enantate in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than 0.1 times the area of the principal peak obtained with solution (2) (0.1%) and disregard any peak due to benzyl benzoate.

**Assay.** Carry out the test under 1.14.4 High-performance liquid chromatography using a stainless steel column (25 cm x 4.6 mm) packed with base-deactivated particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 μm).¹

Use the following conditions for gradient elution:

- mobile phase A: water;
- mobile phase B: acetonitrile R.

¹ BDS HYPERSIL C18 is suitable
<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Mobile phase A (% v/v)</th>
<th>Mobile phase B (% v/v)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–17</td>
<td>40</td>
<td>60</td>
<td>Isocratic</td>
</tr>
<tr>
<td>17–20</td>
<td>40 to 10</td>
<td>60 to 90</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>20–45</td>
<td>10</td>
<td>90</td>
<td>Isocratic</td>
</tr>
<tr>
<td>45–46</td>
<td>10 to 40</td>
<td>90 to 60</td>
<td>Return to initial composition</td>
</tr>
<tr>
<td>46–60</td>
<td>40</td>
<td>60</td>
<td>Re-equilibration</td>
</tr>
</tbody>
</table>

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 254 nm. Maintain the column temperature at 40 °C.

Prepare the following solution in methanol R. For solution (1) dilute 1.0 mL of the injection to 100.0 mL. Dilute 10.0 mL of this solution to 100.0 mL. For solution (2) dissolve 20.0 mg of norethisterone enantate RS and dilute to 100.0 mL.

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

Measure the areas of the peaks corresponding to norethisterone enantate obtained in the chromatograms from solutions (1) and (2) and calculate the percentage content of C27H38O3 using the declared content of C27H38O3 in norethisterone enantate RS.

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