Revision of the Monograph on Estradiol Valerate

(ESTRADIOLI VALERAS)

Draft Proposal for The International Pharmacopoeia

(July 2018)

DRAFT FOR COMMENTS

Should you have any comments on the attached text, please send these to Dr Herbert Schmidt, Technical Officer, Medicines Quality Assurance, Technologies Standards and Norms (schmidt@who.int) with a copy to Mrs Xenia Finnerty (finnertyk@who.int) by 31 August 2018.

Working documents are sent out electronically and they will also be placed on the Medicines website (http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en/) for comments under the “Current projects” link. If you have not already received our draft guidelines, please send your e-mail address to jonesi@who.int and we will add you to our electronic mailing list.

© World Health Organization 2018

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, Group Lead, Medicines Quality Assurance, Technologies Standards and Norms, Department of Essential Medicines and Health Products, World Health Organization, CH-1211 Geneva 27, Switzerland, fax: (41-22) 791 4856, e-mail: koppss@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/18.77:

ESTRADIOL VALERATE

(ESTRADIOLI VALERAS)

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>First draft received from collaborating laboratory.</td>
<td>June 2018</td>
</tr>
<tr>
<td>Draft revision sent out for public consultation.</td>
<td>July – August 2018</td>
</tr>
<tr>
<td>Presentation to WHO Expert Committee on Specifications for Pharmaceutical Preparations.</td>
<td>October 2018</td>
</tr>
<tr>
<td>Further follow-up action as required.</td>
<td></td>
</tr>
</tbody>
</table>

[Note from the Secretariat: The draft monograph on estradiol valerate is proposed for inclusion in The International Pharmacopoeia. The proposed methods and specifications are based on information found in the Chinese, European and the United States Pharmacopoeia scientific literature and upon laboratory investigations.]
DRAFT PROPOSAL FOR INCLUSION IN
THE INTERNATIONAL PHARMACOPOEIA
ESTRADIOL VALERATE
(ESTRADIOLI VALERAS)

Molecular formula. $\text{C}_{23}\text{H}_{32}\text{O}_3$
Relative molecular mass. 356.5

Graphic formula.

Chemical name. 3-Hydroxyestra-1,3,5(10)-trien-17β-yl pentanoate; CAS Reg. No. 979-32-8.

Description. A white, or almost white, crystalline powder or colourless crystals.

Solubility. Practically insoluble in water R; soluble in methanol R; freely soluble in ethanol R, acetone R and methylene chloride R.

Category. Estrogen.

Storage. Estradiol valerate should be kept in a tight container, protected from light.

REQUIREMENTS

Definition. Estradiol valerate contains not less than 97.5% and not more than 102.0% of $\text{C}_{23}\text{H}_{32}\text{O}_3$, calculated with reference to the dried substance.
Identity tests.

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

A. Carry out the test as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from estradiol valerate RS or with the reference spectrum of estradiol valerate.

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

C. Determine the specific optical rotation (1.4) using a 25 mg per mL solution of the test substance in methanol R. Calculate with reference to the dried substance: $[\alpha]_{0}^{D} = +41$ to $+47$.

Clarity and colour of solution. A solution of 0.500 g of the test substance in 20 mL of methanol R is clear and colourless when analysed, as described under 1.11.2 Degree of coloration of liquids, method II.

Loss on drying. Dry 0.500 g of the test substance to a constant weight at 105 °C; it does not lose more than 5.0 mg/g.

Related substances. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (10 cm × 4.6 mm) packed with end-capped particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsyl gel groups (2.6 μm).

Use the following conditions for gradient elution:

---

1 Inertsil ODS2, Spherisorb ODS2, Hypersil ODS, and Kinetex C18 columns have been found suitable.
mobile phase A: water R; and
mobile phase B: acetonitrile R1.

<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>0–1</td>
<td>48</td>
<td>52</td>
<td>Isocratic</td>
</tr>
<tr>
<td>1–10</td>
<td>48 to 35</td>
<td>52 to 65</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>10–17.5</td>
<td>35 to 0</td>
<td>65 to 100</td>
<td>Isocratic</td>
</tr>
<tr>
<td>17.5–26</td>
<td>0</td>
<td>100</td>
<td>Return to initial composition</td>
</tr>
<tr>
<td>26–31</td>
<td>0</td>
<td>100</td>
<td>Re-equilibration</td>
</tr>
</tbody>
</table>

Operate with a flow rate of 2.0 mL per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of 220 nm.

Prepare the following solutions in acetonitrile R1: For solution (1), dissolve 50 mg of the test substance and dilute to 10.0 mL. For solution (2), dilute 1.0 mL of solution (1) to 100.0 mL. Dilute 1.0 mL of this solution to 10.0 mL. For solution (3), dissolve 3 mg of estradiol valerate for system suitability RS (containing estradiol valerate and the impurities A, C, D and E) and dilute to 1.0 mL.

Inject alternately 5 μL each of solution (1), (2) and (3) and record the chromatograms.

Use the chromatogram obtained with solution (3) and the chromatogram supplied with estradiol valerate for system suitability RS, to identify the peaks due to estradiol valerate and the impurities A, C, D and E in the chromatogram obtained with solution (1). The impurities, if present, are eluted at the following relative retentions with reference to estradiol valerate (retention time about 9 minutes): impurity A about 0.1; impurity C about 0.9; impurity D about 1.3; and impurity E about 1.7.

The test is not valid unless the resolution between the peaks due to estradiol valerate and the peak due to impurity C is at least 2.5 in the chromatogram obtained with solution (1).
In the chromatograms obtained with test solution (1):

- the area of any peak corresponding to impurity A is not greater than 5 times the area of the peak due to estradiol valerate obtained with solution (2) (0.5%);
- the area of any peak corresponding to impurity C, when multiplied by a correction factor of 0.5, is not greater than 5 times the area of the peak due to estradiol valerate obtained with solution (2) (0.5%);
- the area of any peak corresponding to impurity D is not greater than 5 times the area of the peak due to estradiol valerate obtained with solution (2) (0.5%);
- the area of any peak corresponding to impurity E is not greater than 1.5 times the area of the peak due to estradiol valerate obtained with solution (2) (0.15%);
- the area of any other impurity peak is not greater than the area of the peak due to estradiol valerate obtained with solution (2) (0.10%); and
- the sum of the corrected area of any peak corresponding to impurity C and the areas of all other impurity peaks, is not greater than 10 times the area of the peak due to estradiol valerate obtained with the solution (2) (1.0 %). Disregard any peak with an area less than 0.5 times the area of the peak due to estradiol valerate obtained with solution (2) (0.05%).

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

Prepare the following solutions in acetonitrile R1. For solution (1), dissolve 60.0 mg of the test substance and dilute to 50.0 mL. For solution (2), dissolve 60.0 mg of estradiol valerate RS and dilute to 50.0 mL.

Inject alternately 5 μL each of solution (1) and (2) and record the chromatograms.

Measure the areas of the peaks corresponding to estradiol valerate obtained in the chromatograms of solutions (1) and (2) and calculate the percentage content of C_{23}H_{32}O_{3}, using the declared content of C_{23}H_{32}O_{3} in estradiol valerate RS.
Impurities.

A. 1,3,5(10)-triene-3,17β-diol (estradiol) [synthesis-related impurity, degradation product].

B. 17β-hydroxyestra-1,3,5(10)-trien-3-yl pentanoate.

C. 3-hydroxyestra-1,3,5(10),9(11)-tetraen-17β-yl pentanoate.

D. 3-hydroxy-4-methylene-1,3,5(10)-trien-17β-yl pentanoate [synthesis-related impurity].
E. 198 estr-1,3,5(10)-tri-en-3,17β-diyl dipentanoate [synthesis-related impurity].

F. 201 3-hydroxyestr-1,3,5(10)-tri-en-17β-yl butanoate [synthesis-related impurity].

G. 204 3-hydroxyestr-1,3,5(10),6-tetra-en-17β-yl pentanoate.


I. (1S,3aS,3bR,10aR,10bS,13S,13aS,15aS,18bS,20aS)-13a,17,17,20a-tetramethyl-

2,3,3a,3b,4,5,9,10,10a,10b,11,12,13,13a,14,15,15a,17,18b,19,20,20a-docosahydro-

1H-bis(cyclopenta[5,6]naphtho)[1,2-b:2',1'-i]xanthene-1,13-diyl dipentanoate.
J. 3-methoxyestra-1,3,5(10)-trien-17β-yl pentanoate.