PYRANTEL EMBONATE

Draft proposal (revision) for *The International Pharmacopoeia*

*(June 2014)*

*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 30 July 2014.

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 2014

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 web site.

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 4730; email: kopp@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 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/14.589

*Draft proposal (revision) for The International Pharmacopoeia: Pyrantel embonate*

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>First draft received from collaborating laboratory</td>
<td>January–February 2014</td>
</tr>
<tr>
<td>Discussion at consultation on specifications for medicines and quality control laboratory issues</td>
<td>April 2014</td>
</tr>
<tr>
<td>Monograph sent out for comment</td>
<td>June 2014</td>
</tr>
<tr>
<td>Collation of comments received</td>
<td>August–September 2014</td>
</tr>
<tr>
<td>Presentation to WHO Expert Committee on Specifications for Pharmaceutical Preparations for discussion</td>
<td>October 2014</td>
</tr>
<tr>
<td>Further follow-up action as required</td>
<td></td>
</tr>
</tbody>
</table>
Draft proposal (revision) for The International Pharmacopoeia

PYRANTELI EMBONAS
PYRANTEL EMBONATE

[Note from the Secretariat. It is proposed to revise the monograph on Pyrantel embonate. Changes from the current monograph are indicated in the text by insert or delete.]

Molecular formula. C₁₁H₁₄N₂S,C₂₃H₁₆O₆

Relative molecular mass. 594.7

Graphic formula.

Chemical name. (E)-1,4,5,6-Tetrahydro-1-methyl-2-[2-(2-thienyl)vinyl]pyrimidine compound with 4,4'-methylenebis[3-hydroxy-2-naphthoate] (1:1); (E)-1,4,5,6-tetrahydro-1-methyl-2-[2-(2-thienyl)ethenyl]pyrimidine 4,4'-methylene-bis[3-hydroxy-2-naphthalencarboxylate] (1:1); CAS Reg. No. 22204-24-6.

Other name. Pyrantel pamoate.

Description. A pale yellow or yellow, crystalline powder.

Solubility. Practically insoluble in water and methanol R; soluble in dimethyl sulfoxide R; slightly soluble in dimethylformamide R.

Category. Anthelmintic drug.

Storage. Pyrantel embonate should be kept in a well-closed container, protected from light.

Requirements

Definition. Pyrantel embonate contains not less than 98.097.0% and not more than 102.0103.0% of C₁₁H₁₄N₂S,C₂₃H₁₆O₆, calculated with reference to the dried substance.
Identity tests

- Either tests A alone and D or tests B and, C and D 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 pyrantel embonate RS or with the *reference spectrum* of pyrantel embonate.

B. The absorption spectrum of a 13 μg/mL solution in methanol R, when observed between 230 nm and 360 nm, exhibits 2 maxima at about 288 nm and 300 nm. The ratio of the absorbance at 288 nm to that at 300 nm is about 1.0.

C. See the test described under “Related substances”, Method A. The principal spots obtained with solution (1) correspond in position, appearance and intensity with those obtained with solution (3). Dissolve 5 mg in 1.0 ml of hydrochloric acid (~70 g/l) TS and add 1.0 ml of formaldehyde/sulfuric acid TS; a purple colour is produced.

D. Melting temperature, above 250°C with decomposition.

**Chlorides.** Dissolve 0.46 g of Pyrantel embonate in a mixture of 10 mL of nitric acid (~130 g/L) TS and 30 mL of water R. Heat on a water-bath for 5 min, allow to cool, dilute to 50 mL with water R, mix well and filter. Add 1 mL of nitric acid (~130 g/L) TS to 15 mL of the filtrate and proceed as described under 2.2.1 Limit test for chlorides; the chloride content is not more than 0.36 mg/g.

**Sulfates.** Dissolve 0.50 g of Pyrantel embonate in 2.5 mL of nitric acid (~130 g/L) TS and dilute to 30 mL with water R. Heat on a water-bath for 5 min, shake for 2 min, cool and filter and proceed as described under 2.2.2 Limit test for sulfates; the sulfate content is not more than 1 mg/g.

**Iron.** Ignite 0.66 g of Pyrantel embonate at 800 ± 50°C for 2 h. Cool and dissolve the residue in 2.5 mL of hydrochloric acid (~70 g/L) with gentle heating for 10 min. Cool and dilute to 40 mL with water R and proceed as described under 2.2.4 Limit test for iron; not more than 75 μg/g.

**Sulfated ash.** Not more than 5.0 1.0 mg/g.

**Heavy metals.** Use 1.0 g for the preparation of the test solution as described under 2.2.3 Limit test for heavy metals. Procedure 3; determine the heavy metals content according to Method A; not more than 10 μg/g.

**Loss on drying.** Dry at 60°C under reduced pressure (not exceeding 0.6 kPa or about 5 mm of mercury) for 3 hours; it loses not more than 1020 mg/g.

**Related substances**

Carry out the test as described under *1.14.1 Thin-layer chromatography*, using silica gel R2 as the coating substance and a mixture of 20 volumes of ethyl acetate R, 5 volumes of methanol R, and 1.5 volumes of diethylamine R as the mobile phase. Apply separately to the plate 100 μl of each of 2 solutions in a mixture of 5 volumes of chloroform R, 5 volumes of...
methanol R, and 0.5 volumes of ammonia (~260 g/l) TS containing (A) 20 mg of the test substance per ml and (B) 0.20 mg of the test substance per ml. After removing the plate from the chromatographic chamber, allow it to dry in a current of air for 10 minutes and examine the chromatogram in ultraviolet light (254 nm). Any spot obtained with solution A, other than the principal spot, is not more intense than that obtained with solution B.

Carry out the operations in subdued light and without any prolonged interruptions, preferably using low-actinic glassware.

- Either method A or B may be applied.

A. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R6 as the coating substance and a mixture of 3 volumes of ethyl acetate R, 1 volume of water R and 1 volume of glacial acetic acid R as the mobile phase.

Prepare the following solutions. For solution (1) dissolve about 100 mg of Pyrantel embonate in 10.0 mL dimethylformamide R (1). For solution (2) dilute 1.0 mL of solution (1) to 100 mL with dimethylformamide R. For solution (3) use 10 mg of pyrantel embonate RS per mL dimethylformamide R. For solution (4) expose a quantity of solution (3) under 2000 lx illumination for 24 hours. In case a suitable device to provide the requested illuminance is not available use 10 mg of pyrantel embonate impurity A RS and 2 mg pyrantel embonate RS per mL dimethylformamide R for solution (4).

Apply separately to the plate 5 μL of each of the solutions (1), (2), (3) and (4).

After application allow the spots to dry for 15 minutes in a current of air. Develop over a path of 12 cm. After removing the plate from the chromatographic chamber allow it to dry for 10 minutes in a current of air. Examine the chromatogram in ultraviolet light (254 nm).

Pyrantel and related substances have the following Rf values: impurity A about 0.2; pyrantel about 0.3; embonic acid about 0.9. The test is not valid unless the chromatogram obtained with solution (4) exhibits three well separated spots.

In the chromatogram obtained with solution (1) any spot, other than the two principal spots, is not more intense than the pyrantel spot in the chromatogram obtained with solution (2) (1.0%). Disregard any spot remaining at the point of application.

B. 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 high purity base particles of silica gel for chromatography R (5 μm).\(^{1}\)

As the mobile phase use a mixture of 92.8 volumes of acetonitrile R and 7.2 volumes of a solvent mixture composed of 5 volumes of glacial acetic R, 5 volumes of water R and 2 volumes of diethylamine R.

---

\(^{1}\) Shim-pack HRS-SIL column (25 cm × 4.6 mm, 5 μm) has been found suitable.
Prepare the following solutions. For solution (1) transfer about 72 mg of Pyrantel embonate, accurately weighed, to a 100 mL volumetric flask. Add 7 mL of a mixture composed of 5 volumes of glacial acetic R, 5 volumes of water R and 2 volumes of diethylamine R. Shake and dilute to volume with acetonitrile R, mix and filter. For solution (2), dilute 1.0 mL of the solution (1) to 100.0 mL with mobile phase. For solution (3) expose 10 mL of solution (1) under 2000 lx illumination for 24 hours. In case a suitable device to provide the requested illuminance is not available transfer 10 mg of pyrantel embonate impurity A RS to a 10.0 mL flask, add 8 mL of solution (1) and make up to volume with dimethylformamide R to obtain solution (3).

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 288 nm.

Inject separately 20 μL each of solution (1), (2) and (3) and record the chromatograms for 4 times the retention time of pyrantel.

In the chromatogram obtained with solution (3) the following peaks are eluted at the following relative retention with reference to pyrantel (retention time about 14 minutes): embonic acid about 0.5; impurity A about 1.3. The test is not valid unless the resolution factor between the pyrantel peak and the impurity A peak is at least 4.0.

In the chromatogram obtained with solution (1) the area of any impurity peak is not greater than the area of the pyrantel peak 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%).

Assay

Perform the assay in subdued light and without any prolonged interruptions, preferably using low-actinic glassware.

Transfer about 0.10 g, accurately weighed, to a 200 mL volumetric flask, dissolve in a mixture of 10 mL of dioxan R and 10 mL of ammonia (~100 g/l) TS, and dilute to volume with perchloric acid (~140 g/l) TS. Filter, discard the first 10 mL of the filtrate, and transfer 5 mL of the subsequent filtrate to a 50 mL volumetric flask. Dilute to volume with perchloric acid (~140 g/l) TS and mix. Transfer 25 mL to a 250 mL separating funnel, add 100 mL of chloroform R, and shake well. Drain off the chloroform layer into a second separating funnel. Repeat the extraction of the aqueous phase with a second 100 mL portion of chloroform R, and combine the chloroform extracts into the same separating funnel. Add 40 mL of hydrochloric acid (0.05 mol/l) VS to the combined chloroform extracts and shake well. Drain off the chloroform phase into a third separating funnel and extract with a further 40 mL portion of hydrochloric acid (0.05 mol/l) VS, discarding the chloroform phase. Combine the aqueous phases in a 100 mL volumetric flask, rinse the separating funnel, draining into the volumetric flask, and dilute to volume with hydrochloric acid (0.05 mol/l) VS. Measure the absorbance of a 1 cm layer of this solution at the maximum at about 311 nm against a solvent cell containing hydrochloric acid (0.05 mol/l) VS. Calculate the amount of \( C_{11}H_{14}N_2S,C_{23}H_{16}O_6 \) in the substance being tested by comparison with pyrantel embonate RS, similarly and concurrently examined.
Dissolve about 0.450 g of Pyrantel embonate, accurately weighed, in 10 mL of acetic anhydride R and 50 mL of glacial acetic acid R. Heat at 50 °C and stir for 10 minutes. Allow to cool and titrate the suspension with perchloric acid (0.1 mol/L) VS as described under 2.6 Nonaqueous titration, Method A, determining the end-point potentiometrically. Carry out a blank titration. Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 59.47 mg of pyrantel embonate C_{11}H_{14}N_S.C_{23}H_{16}O_6.

**Impurities**

A. 1-methyl-2-[(1E)-2-(thiophen-2-yl)ethenyl]-1,4,5,6-tetrahydropyrimidine.

***