PROTIONAMIDUM
PROTIONAMIDE
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.

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## SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/17.722:
**PROTIONAMIDE (PROTIONAMIDUM)**

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

(PROTIONAMIDUM)

Molecular formula. C₉H₁₂N₂S

Relative molecular mass. 180.3

Graphic formula

Chemical name. 2-Propylthioisonicotinamide; 2-propyl-4-pyridinecarbothioamide; CAS Reg. No. 14222-60-7.

Description. Yellow crystals or a crystalline powder.

Solubility. Practically insoluble in water; soluble in dehydrated ethanol R and methanol R; slightly soluble in ether R.

Category. Tuberculostatic.

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

Additional information. Protionamide may exhibit polymorphism.

Requirements

Definition. Protionamide contains not less than 99.0% and not more than 101.0% of C₉H₁₂N₂S, 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 protionamide RS or with the reference spectrum of protionamide.

If the spectra thus obtained are not concordant repeat the test using the residues obtained by separately dissolving the test substance and protionamide RS in a small
amount of methanol R and evaporating to dryness. The infrared absorption spectrum
is concordant with the spectrum obtained from protonamide RS.

B. The absorption spectrum (1.6) of a 10 μg/mL solution of the test substance in ethanol
(~750 g/L) TS, when observed between 230 nm and 350 nm, exhibits a maximum at
about 291 nm and a minimum at 256 nm.

C. Carry out the test as described under 1.14.4 High-performance liquid chromatography
using the conditions given under “Related substances”. The retention time of the
principal peak in the chromatogram obtained with solution (1) corresponds to the
retention time of the peak due to protonamide in the chromatogram obtained with
solution (3).

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 20 μg/g.

Sulfated ash. Not more than 1.0 mg/g.

Loss on drying. Dry 1.000 g of the test substance to constant weight at 105 °C; it loses
not more than 5.0 mg/g.

Acidity. Dissolve 2.0 g in 20 mL of methanol R by warming. Add 20 mL of water R,
bring to a boil and cool to precipitate protonamide. Add 2 drops of cresol red/ethanol TS and
titrating with sodium hydroxide (0.1 mol/L) VS. Not more than 0.20 mL is required to
change the colour of the indicator.

Related substances. 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 for chromatography R (5 μm).¹

As the mobile phase use a mixture of 72 volumes of a buffer solution, prepared by
mixing 2.0 mL of triethylamine R with 1000 mL water and adjusting the pH to 6.0 with
phosphoric acid (~105 g/L) TS, and 28 volumes of acetonitrile R.

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet
spectrophotometer set at a wavelength of 290 nm.

Prepare the following solutions in mobile phase. For solution (1) dissolve about 50 mg of
the test substance in 100.0 mL. For solution (2) dilute 1 volume of solution (1) to 200
volumes. For solution (3) use a solution containing 0.05 mg of protonamide RS and 0.01
mg of ethionamide R per mL.

¹ Inertsil ODS was found suitable.
Inject 20 µL of solution (3). Ethionamide is eluted at a relative retention of about 0.6 with reference to protionamide (retention time about 10 minutes). The test is not valid unless the resolution between the peaks due to ethionamide and protionamide is at least 5.0.

Inject alternately 20 µL each of solution (1) and (2). Record the chromatograms for 2 times the retention time of protionamide.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A (ethionamide), is not greater than the area of the peak due to protionamide in the chromatogram obtained with solution (2) (0.5%);
- the area of any impurity peak is not greater than 0.4 times the area of the peak due to protionamide in the chromatogram obtained with solution (2) (0.2%);
- the sum of the areas of all impurity peaks is not greater than 2 times the area of the peak due to protionamide in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than 0.2 times the area of the principal peak obtained with solution (2) (0.10%).

**Assay.** Dissolve about 0.45 g, accurately weighed, in 30 mL of glacial acetic acid R1 and titrate with perchloric acid (0.1 mol/L) VS as described under 2.6 Non-aqueous titration, Method A. Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 18.03 mg of C₉H₁₂N₂S.

**Impurity**

A. 2-Ethylthioisonicotinamide; 2-ethyl-4-pyridinecarbothioamide (ethionamide).

**Reference substance to be established**

Protionamide RS

**Reagent to be established**

Ethionamide R

Ethionamide or a suitable quality should be used.