PROTIONAMIDIDI COMPRESSI
PROTIONAMIDE TABLETS
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/17.723:
PROTIONAMIDE TABLETS (*PROTIONAMIDI COMPRESSI*)

<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–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>
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</tbody>
</table>
PROTIONAMIDE TABLETS

(PROTIONAMIDI COMPRESSIONI)

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Category. Tuberculostatic.

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

Additional information. Strength in the current WHO Model List of Essential Medicines (EML): 125 mg; 250 mg. Strength in the current WHO EML for children: 125 mg; 250 mg.

Requirements

Comply with the monograph for Tablets.

Definition. Protonamide tablets contain not less than 90.0% and not more than 110.0% of the amount of protonamide (C₉H₁₂N₂S) stated on the label.

Identity tests

Either test A alone or tests B and C may be applied.

A. Extract a quantity of the powered tablets containing about 25 mg of protonamide with 5 mL of methanol R, filtrate and evaporate the filtrate to dryness. 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 protonamide RS or with the reference spectrum of protonamide.

If the spectra thus obtained are not concordant repeat the test using the residues obtained by separately dissolving the test substance and protonamide 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. To a quantity of powdered tablets containing the equivalent of about 2.5 mg of protonamide add 25 mL ethanol (~750 g/L) TS, shake and filter. Dilute 1 mL of the filtrate to 10 mL with the same solvent. The absorption spectrum (1.6) of the resulting solution, 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 “Assay”. The retention time of the principle peak in the chromatogram obtained from solution (1) corresponds to the
Retention time of the peak due to protonamide in the chromatogram obtained with solution (2).

**Dissolution.** Carry out the test as described under 5.5 *Dissolution test for solid oral dosage forms*, using as the dissolution medium 900 mL of hydrochloric acid (~4 g/L) TS and rotating the paddle at 100 revolutions per minute. At 30 minutes withdraw a sample of 10 mL of the medium through an in-line filter and allow the filtered sample to cool to room temperature. Measure the absorbance (1.6) of a 1 cm layer of the resulting solution, suitably diluted if necessary, at a wavelength of 277 nm using the dissolution medium as the blank. Measure at the same time and under the same conditions the absorbance of a suitable solution of protonamide RS in the dissolution medium.

For each of the tablets tested, calculate the total amount of protonamide ($C_9H_{12}N_2S$) in the dissolution medium from the absorbances obtained. Evaluate the results as described under 5.5 *Dissolution test for solid dosage forms*. The amount of protonamide in solution for each tablet is not less than 75% (Q) of the amount stated on the label.

*[Note from the Secretariat. It is intended to determine the absorptivity value of protonamide during the establishment of protonamide RS. The value will then be included in the test description.]*

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

For solution (1) transfer a quantity of the powdered tablets equivalent to about 250 mg of protonamide, accurately weighed, into a 250 mL volumetric flask, disperse in 100 mL, shake vigorously and dilute to volume. Filter the resulting solution and dilute 25.0 mL of this solution to 50.0 mL. For solution (2) dilute 1 volume of solution (1) to 100 volumes with mobile phase. For solution (3) use a solution containing 0.05 mg of protonamide RS and 0.01 mg of ethionamide R per mL mobile phase.

Inject 20 µL of solution (3). Ethionamide is eluted at a relative retention of about 0.6 with reference to protonamide (retention time about 10 minutes). The test is not valid unless the resolution between the peaks due to ethionamide and protonamide 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 protonamide.

In the chromatogram obtained with solution (1):

- the area of any impurity peak is not greater than the area of the peak due to protonamide in the chromatogram obtained with solution (2) (0.5%).
Assay. 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).  

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 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 290 nm.

Prepare the following solutions in mobile phase. For solution (1) weigh and powder 20 tablets. Transfer a quantity of the powdered tablets containing about 250 mg of protonamid, accurately weighed, into a 250 mL volumetric flask, disperse in 100 mL, shake vigorously and dilute to volume. Filter the resulting solution and dilute 10.0 mL of this solution to 200.0 mL. For solution (2) dilute 50.0 mg of protonamide RS and 10.0 mg of ethionamide R in 100.0 mL. Dilute 10.0 mL of this solution to 100.0 mL.

Inject 20 μL of solution (2). Ethionamide is eluted at a relative retention of about 0.6 with reference to protonamide (retention time about 10 minutes). The test is not valid unless the resolution between the peaks due to ethionamide and protonamide is at least 5.0.

Inject alternately 20 μL each of solution (1) and (2). Record the chromatogram.

Measure the areas of the peaks corresponding to protonamide obtained in the chromatograms of solutions (1) and (2) and calculate the percentage content of protonamide (C9H12N2S) in the tablets, using the declared content of protonamide (C9H12N2S) in protonamide RS.

Impurities

The impurities limited by the requirements of this monograph include the impurity listed in the monograph on Protonamide.

Reference substance to be established

Protonamide RS

Reagent to be established

Ethionamide R

Ethionamide or a suitable quality should be used.

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1 Inertsil ODS was found suitable.