MEBENDAZOLE
Draft proposal for revision for
The International Pharmacopoeia
(July 2016)
DRAFT FOR COMMENTS

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 16 September 2016.

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 2016
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 Programme, 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: kopps@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/16.674: MEBENDAZOLE

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revision drafted taking into consideration specifications and tests published in the monograph on Mebendazole of the European Pharmacopoeia</td>
<td>April 2016</td>
</tr>
<tr>
<td>Verification of the monograph by a WHO Collaborating Centre</td>
<td>July–September 2016</td>
</tr>
<tr>
<td>Draft revision sent out for public consultation</td>
<td>July–September 2016</td>
</tr>
<tr>
<td>Presentation to WHO Expert Committee on Specifications for Pharmaceutical Preparations</td>
<td>October 2016</td>
</tr>
<tr>
<td>Further follow-up action as required</td>
<td></td>
</tr>
</tbody>
</table>
Mebendazole

(Mebendazolum)

[Note from the Secretariat. It is proposed to revise the monograph on Mebendazole of The International Pharmacopoeia.

Changes from the current monograph are indicated in the text by *insert* or *delete.*]

![Mebendazole molecular structure]

**Relative molecular mass.** 295.3

**Chemical name.** Methyl 5-benzoyl-2-benzimidazolecarbamate; methyl (5-benzoyl-1H-benzimidazol-2-yl)carbamate; CAS Reg. No. 31431-39-7.

**Description.** A white or almost white to slightly yellow powder.

**Solubility.** Practically insoluble in water, dilute mineral acids, and ethanol (~750 g/L) TS and ether R; freely soluble in formic acid (~1080 g/L) TS.

**Category.** Anthelmintic drug.

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

**Additional information.** Mebendazole exhibits polymorphism.

**Requirements**

**Definition.** Mebendazole is polymorph C, the crystal form of mebendazole RS. Mebendazole contains not less than 998.0% and not more than 1012.0% of mebendazole (C_{16}H_{13}N_{3}O_{3}), calculated with reference to the dried substance.
Identity test

Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum obtained from the solid state is concordant with the spectrum obtained from mebendazole RS (confirmation of polymorphic form C).

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 (2.3). Not more than 1.0 mg/g.

Loss on drying. Dry at 105 °C under reduced pressure (not exceeding 0.6 kPa or about 5 mm of mercury) for 4 hours; it loses not more than 5.0 mg/g.

Related substances. 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 90 volumes of chloroform R, 5 volumes of methanol R, and 5 volumes of formic acid (~1080 g/l) TS as the mobile phase. Apply separately to the plate 10 μl of each of the following two solutions. For solution (A), dissolve 50 mg of the test substance in 1.0 mL of formic acid (~1080 g/l) TS in a 10 mL volumetric flask, dilute to volume with chloroform R, and mix. For solution (B), dilute 1.0 mL of solution A to 200 mL with a mixture of 9 volumes of chloroform R and 1 volume of formic acid (~1080 g/l) TS. After removing the plate from the chromatographic chamber, allow it to dry in air and examine the chromatogram in ultraviolet light (254 nm). Any spot obtained with solution A, other than the principal spot, is no larger or more intense than the principal spot obtained with solution B (0.5%).

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 base-deactivated particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (3 μm).¹

Use the following conditions for gradient elution:

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Mobile phase A (% v/v)</th>
<th>Mobile phase B (% v/v)</th>
<th>Comments</th>
</tr>
</thead>
</table>

¹ A HYPERSIL BDS C₁₈ column has been found suitable.
Operate with a flow rate of 1.2 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 250 nm. Maintain the column temperature at 40 °C.

Prepare the following solutions in dimethylformamide R. For solution (1) dissolve 25.0 mg of the test substance and dilute to 25.0 mL. For solution (2) dissolve 1.0 mL of solution (1) to 100.0 mL. Dilute 5.0 mL of this solution to 20.0 mL. For solution (3) dissolve 5.0 mg of mebendazole for system suitability RS (containing the impurities A, B, C, D, E, F and G) and dilute to 5.0 mL.

Inject 10 μL of solution (3). The test is not valid unless the peak-to-valley ratio (Hp/Hv) is at least 4, where Hp is the height above the baseline of the peak due to impurity D (relative retention about 1.1) and Hv is the height above the baseline of the lowest point of the curve separating this peak from the peak due to mebendazole (retention time about 12 minutes).

Inject alternately 10 μL each of solution (1) and (2).

Use the chromatogram obtained with solution (3) and the chromatogram supplied with mebendazole for system suitability RS to identify the peaks due to the impurities A, B, C, D, E, F and G. The impurities are eluted at the following relative retention with reference to mebendazole (retention time about 12 minutes): impurity A about 0.4; impurity B about 0.5; impurity C about 0.7; impurity D about 1.1; impurity E about 1.3; impurity F about 1.4 and impurity G about 1.6.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A, impurity B, impurity C, impurity D, impurity E or impurity F is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.25%).
• the area of any peak corresponding to impurity G, when multiplied by a
correction factor of 1.4, is not greater than twice the area of the principal peak
in the chromatogram obtained with solution (2) (0.5%);
• the area of any other impurity peak is not greater than 0.4 times the area of the
principal peak in the chromatogram obtained with solution (2) (0.10%);
• the sum of the areas of all impurities is not greater than 4 times the area of the
principal peak 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 in the chromatogram obtained with solution (2) (0.05%).

Assay. Dissolve about 0.2502 g, accurately weighed, in 3 mL of anhydrous formic
acid R and add 50 mL of a mixture of 1 volume of anhydrous acetic acid R and 7
volumes of methyl ethyl ketone R, 30 mL of glacial acetic acid R, and Titrate with
perchloric acid (0.1 mol/L) VS, determining the end-point potentiometrically as
described under 2.6 Non-aqueous titration, Method A.
Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 29.53 mg of \( \text{C}_{16}\text{H}_{13}\text{N}_{3}\text{O}_3 \).

Impurities

A. (2-Amino-1H-benzimidazol-5-yl)phenylmethanone

B. (2-Hydroxy-1H-benzimidazol-5-yl)phenylmethanone

C. (2-Amino-1-methyl-1H-benzimidazol-5-yl)phenylmethanone
D. Methyl (5-benzoyl-1-methyl-1H-benzimidazol-2-yl)carbamate

E. Ethyl (5-benzoyl-1H-benzimidazol-2-yl)carbamate

F. Methyl [5-(4-methylbenzoyl)-1H-benzimidazol-2-yl]carbamate

G. N,N'-bis(5-benzoyl-1H-benzimidazol-2-yl)urea