ALBENDAZOLE TABLETS
(ALBENDAZOLI COMPRESSI)

Draft proposal for inclusion in *The International Pharmacopoeia* (July 2019)

*DRAFT FOR COMMENTS*

Please send any comments you may have on this draft working document to Dr Herbert Schmidt, Technical Officer, Medicines Quality Assurance, Technologies Standards and Norms (email: schmidt@who.int) by 31 August 2019.

Working documents are sent out electronically and they will also be placed on the WHO Medicines website (http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en/) for comments under the “Current projects” link. If you wish to receive our draft guidelines, please send your e-mail address to jonessi@who.int and your name will be added to our electronic mailing list.

© World Health Organization 2019

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, (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 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/19.812:

ALBENDAZOLE TABLETS
(ALBENDAZOLI COMPRESSI)

<table>
<thead>
<tr>
<th>Description</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revision of the monograph.</td>
<td>April 2019</td>
</tr>
<tr>
<td>Discussion at the informal Consultation on Screening Technologies, Laboratory Tools and Pharmacopoeial Specifications for Medicines.</td>
<td>2-3 May 2019</td>
</tr>
<tr>
<td>Draft revision sent out for public consultation.</td>
<td>July-August 2019</td>
</tr>
<tr>
<td>Presentation to the Fifty-fourth WHO Expert Committee on Specifications for Pharmaceutical Preparations.</td>
<td>October 2019</td>
</tr>
<tr>
<td>Further follow-up action as required.</td>
<td></td>
</tr>
</tbody>
</table>

[Note from the Secretariat. It is proposed to include a monograph on Albendazole tablets in The International Pharmacopoeia.

The draft proposal is based on information submitted by a manufacturer and on laboratory investigations. The document may be further revised inter alia based on the analysis of samples from the market. Manufacturers of Albendazole tablets are therefore invited to submit samples of their products to render the provisions also suitable for the testing of their products.

For further information regarding the submission of samples, please contact Dr Herbert Schmidt at schmidt@who.int.]
ALBENDAZOLE TABLETS
(ALBENDAZOLI COMPRESSI)

Category. Anthelminthic.

Storage. Albendazole tablets should be kept in a tightly closed container.


Requirements

Comply with the monograph for Tablets.

Definition. Albendazole tablets contain not less than 90.0% and not more than 110.0% of the amount of Albendazole (C₁₂H₁₅N₃O₂S) stated on the label.

Identity tests.

- Any two of tests A, B and C 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 6 volumes of dichloromethane R, 1 volume of ether R and 1 volume of glacial acetic acid R as the mobile phase. Apply separately to the plate 10 µL of each of the following 2 solutions in a mixture of 9 volumes of dichloromethane R and 1 volume of glacial acetic acid R. For solution (A), shake a quantity of the powdered tablets, nominally containing about 50 mg of Albendazole, with 50 mL, filter and use the filtrate. For solution (B), use a solution containing 1 mg of albendazole RS per mL. After removing the plate from the chromatographic chamber, allow the plate to dry in a current of warm air and examine the chromatogram under ultraviolet light (254 nm). The principal spot obtained with solution (A) corresponds in position, appearance and intensity with the spot due to albendazole obtained with solution (B).
B. Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given under “Assay”, Method A. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time of the peak due to albendazole in the chromatogram obtained with solution (2).

C. See the test described under “Assay”, Method B. The absorption spectrum (1.6) of the test solution, when observed between 220 and 340 nm, exhibits maxima at about 231 nm and at 308 nm.

Dissolution. For 200 mg tablets: carry out the test as described under 5.5 Dissolution test for solid oral dosage forms using 900 mL of hydrochloric acid (~3.65 g/L) TS as the dissolution medium and rotating the paddle at 50 revolutions per minute. At 30 minutes, withdraw a sample of about 10 mL of the dissolution medium through an in-line filter. Cool the filtered sample to room temperature and use it as solution (1). For solution (2), dissolve 55.0 mg of albendazole RS in 10.0 mL of sulfuric acid/methanol (1%) TS and immediately dilute to 250.0 mL with hydrochloric acid (~3.65 g/L) TS.

Measure the absorbance (1.6) of a 1.0 cm layer of the solution at about 308 nm, using hydrochloric acid (~3.65 g/L) TS as the blank. For each of the six tablets tested, calculate the total amount of albendazole (C₁₂H₁₅N₃O₂S) in the medium. The amount of albendazole released is not less than 80% (Q) of the amount declared on the label.

For 400 mg tablets: carry out the test as described under 5.5 Dissolution test for solid oral dosage forms using 900 mL of hydrochloric acid (~10 g/L) TS as the dissolution medium and rotating the paddle at 50 revolutions per minute. At 30 minutes, withdraw a sample of about 10 mL of the dissolution medium through an in-line filter. Cool the filtered sample to room temperature and use it as solution (1). For solution (2), dissolve 44.0 mg of albendazole RS in 10.0 mL of sulfuric acid/methanol (1%) TS and immediately dilute to 100.0 mL with hydrochloric acid (~10 g/L) TS.

Measure the absorbance (1.6) of a 1.0 cm layer of the solution at about 308 nm, using hydrochloric acid (~10 g/L) TS as the blank. For each of the six tablets tested, calculate the total amount of albendazole (C₁₂H₁₅N₃O₂S) in the medium. The amount of albendazole released is not less than 80% (Q) of the amount declared on the label.
[Note from the Secretariat. It is intended to determine the absorptivity value of albendazole in the described solvents during the re-establishment of albendazole RS and to use this value for the calculation of the test result.]

Related substances. Prepare the solutions immediately before use.

Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (15 cm × 3.9 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (4 µm).¹

Use the following conditions for gradient elution:

- mobile phase A: a solution of 1.15 g of ammonium dihydrogen phosphate R in 1000 mL of water R; and
- mobile phase B: methanol R.

<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>
<tbody>
<tr>
<td>0–3</td>
<td>70 to 66</td>
<td>30 to 34</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>3–13</td>
<td>66 to 50</td>
<td>34 to 50</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>13–43</td>
<td>50</td>
<td>50</td>
<td>Isocratic</td>
</tr>
<tr>
<td>43–45</td>
<td>50 to 70</td>
<td>50 to 30</td>
<td>Return to initial composition</td>
</tr>
<tr>
<td>45–55</td>
<td>70</td>
<td>30</td>
<td>Re-equilibration</td>
</tr>
</tbody>
</table>

Operate with a flow rate of 0.8 mL per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of 254 nm.

Prepare the following solutions. For solution (1), transfer a quantity of the powdered tablets, nominally containing 200.0 mg of Albendazole, to a 100 mL volumetric flask. Add 10 mL of sulfuric acid/methanol (1%) TS and 25 mL of methanol R and sonicate for 15 minutes. Shake to dissolve for a further 15 minutes. Dilute to volume with methanol R, mix and allow the insoluble to settle. Dilute 5.0 mL of the supernatant liquid to 50.0 mL with methanol R and

¹ A Nova-Pak C18 column was found suitable.
filter the solution. For solution (2), dilute 1.0 mL of solution (1) to 100.0 mL with methanol R. For solution (3), dilute 1.0 mL of solution (2) to 10.0 mL with methanol R. For solution (4), dissolve about 5 mg of albendazole for system suitability RS (containing albendazole and the impurities B, C, E, F and H) in 1 mL of sulfuric acid/methanol (1%) TS and dilute with 10 mL with the mobile phase. For solution (5), dilute 1 mL of sulfuric acid/methanol (1%) TS to 10 mL with mobile phase. Use 1 mL of this solution to dissolve the content of a vial of albendazole impurity mixture RS (containing the impurities A and D).

Inject alternately 20 µL each of solutions (1), (2), (3), (4) and (5).

Use the chromatogram obtained with solution (4) to identify the peaks due to the impurities B, C, E and F. Use the chromatogram obtained with solution (5) to identify the peaks due to the impurities A and D. The impurities are eluted at the following relative retention with reference to albendazole (retention time 32 minutes): impurity D about 0.13, impurity E about 0.25, impurity B and impurity C about 0.28, impurity F about 0.48, impurity A about 0.56 and impurity H about 0.69.

The test is not valid unless in the chromatogram obtained with solution (4) the resolution factor between the peak due to impurity E and the peak due to impurities B and C (impurities B and C co-elute) is at least 1.5. Also, the test is not valid unless in the chromatogram obtained with solution (3) the peak due to albendazole is detected with a signal-to-noise ratio of at least 20.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to either impurity A, when multiplied by a correction factor of 1.4, is not greater than the area of the peak due to albendazole in the chromatogram obtained with solution (2) (1.0%);
- the sum of the areas of any peaks corresponding to impurities B and C (impurities B and C co-elute), when multiplied by a correction factor of 1.4, is not greater than the area of the peak due to albendazole in the chromatogram obtained with solution (2) (1.0%);
- the area of any peak corresponding to either impurity D, when multiplied by a correction factor of 1.9, is not greater than the area of the peak due to albendazole in the chromatogram obtained with solution (2) (1.0%);
the area of any peak corresponding to impurity E, when multiplied by a correction factor
of 1.4, is not greater than the area of the peak due to albendazole in the chromatogram
obtained with solution (2) (1.0%);

• the area of any peak corresponding to impurity F is not greater than the area of the peak
due to albendazole in the chromatogram obtained with solution (2) (1.0%);

• the area of any peak corresponding to impurity H, when multiplied by a correction factor
of 1.7, is not greater than the area of the peak due to albendazole in the chromatogram
obtained with solution (2) (1.0%);

• the area of any other impurity peak is not greater than twice the area of the peak due to
albendazole in the chromatogram obtained with solution (3) (0.2%);

• the sum of the area of any peak corresponding to impurity F, the corrected areas of any
peaks corresponding to impurities A, B/C, D, E and H and the areas of all other impurity
peaks is not greater than three times the area of the peak due to albendazole in the
chromatogram obtained with solution (2) (3.0%). Disregard any peak with an area less
than 0.5 times the area of the peak due to albendazole in the chromatogram obtained with
solution (3) (0.05%).

Assay

• Either method A or method B may be applied.

A. Carry out the test as described under 1.14.4 High-performance liquid chromatography
using a stainless steel column (15 cm × 3.9 mm) packed with particles of silica gel, the
surface of which has been modified with chemically-bonded octadecylsilyl groups (4
µm).\(^2\)

As the mobile phase, use a solution prepared as follows: dissolve 1.15 g of ammonium
dihydrogen phosphate R in 1000 mL of water R. Mix 400 mL of this solution with 600
mL of methanol R.

For solution (1), weigh and powder 20 tablets. Transfer a quantity of the powdered
tablets, nominally containing 100.0 mg of Albendazole, to a 50 mL volumetric flask.
Add 10 mL of sulfuric acid/methanol (1%) TS and 25 mL of methanol R and sonicate

\(^2\) A Nova-Pak C18 column was found suitable.
for 15 minutes. Shake to dissolve for further 15 minutes. Dilute to volume with methanol R, mix and allow the insoluble to settle. Dilute 5.0 mL of the supernatant liquid to 50.0 mL with methanol R and filter the solution. For solution (2), transfer 50.0 mg of albendazole RS to a 250 mL volumetric flask, add 10 mL of sulfuric acid/methanol (1%) TS and 25 mL of methanol R and sonicate for 15 minutes. Dilute to volume with methanol R and mix.

Operate with a flow rate of 0.8 mL per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of 254 nm.

Inject alternately 20 µL each of solutions (1) and (2). Record the chromatograms for about 1.5 times the retention time of albendazole.

Measure the areas of the peaks corresponding to albendazole obtained in the chromatograms from solutions (1) and (2) and calculate the percentage content of Albendazole (C₁₂H₁₅N₃O₂S) in the tablets using the declared content of C₁₂H₁₅N₃O₂S in albendazole RS.

B. Weigh and powder 20 tablets. Transfer a quantity of the powdered tablets, nominally containing about 20.0 mg of Albendazole, to a 50 mL volumetric flask, add 30 mL of hydrochloric acid/methanol (0.01 mol/L) VS, shake for 15 minutes and dilute to volume with the same solvent. Mix and filter, discarding the first 10 mL of the filtrate. Dilute 2.0 mL of the filtrate to 100.0 mL with sodium hydroxide (0.1 mol/L) VS. Measure the absorbance of the resulting solution at the maximum at about 308 nm, using sodium hydroxide (0.1 mol/L) VS as the blank. Calculate the content of Albendazole (C₁₂H₁₅N₃O₂S), using the absorptivity value of 74.2 (A₁%₁cm=742).

Impurities. The impurities limited by the requirements of this monograph include those listed in the monograph on Albendazole.

Reagents to be added

Sulfuric acid/methanol (1%) TS
Procedure: cool separately 10 mL of sulfuric acid (~1760 g/L) TS and 900 mL of methanol R to about -5 °C. Very carefully add the acid to the methanol keeping the solution as cool as possible and mix gently.

**Reference substances to be established**

**Albendazole for system suitability RS** (containing albendazole and the impurities B, C, E, F and H)

*It is intended to refer to the corresponding reference substance established for the European Pharmacopoeia.*

**Albendazole impurity mixture RS** (containing the impurities A and D).

*It is intended to refer to the corresponding reference substance established for the European Pharmacopoeia.*