World Health Organization

ALBENDAZOLE (ALBENDAZOLUM)

Draft proposal for revision in *The International Pharmacopoeia*

(July 2023)

DRAFT FOR COMMENTS

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For any technical queries, please contact **Dr Herbert Schmidt**, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (schmidth@who.int), with a copy to Ms Sinéad Jones (jonessi@who.int, nsp@who.int).

Comments should be submitted through the online platform on or by **27 September 2023**. Please note that only comments received by this deadline will be considered for the preparation of this document.

Our working documents are sent out electronically and uploaded into PleaseReview™. The working documents are also placed on the WHO Medicines website (https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/pharmaceuticals/working-documents-public-consultation) under the "Working documents in public consultation". If you wish to receive all our draft guidelines during the course of the year, please send your full name, organization/ affiliation, and email address to jonessi@who.int, nsp@who.intand your name will be added to our electronic mailing list and review platform.

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SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/18.755:

ALBENDAZOLE
(ALBENDAZOLUM)

Description	Date
Revision of the monograph.	February 2018
Discussion at the informal Consultation on Screening Technology, Sampling and Specification for Medicines.	2-4 May 2018
Presentation to the Fifty-third WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP).	October 2018
Discussion at the informal Consultation on Screening Technologies, Laboratory Tools and Pharmacopoeial Specifications for Medicines.	2-4 May 2019
Draft revision sent out for public consultation.	July-August 2019
Presentation to the Fifty-fourth WHO ECSPP.	October 2019
Discussion at the informal Consultation on Screening Technologies, Laboratory Tools and Pharmacopoeial Specifications for Medicines.	May 2020
Discussion at the Consultation on Quality Control and Pharmacopoeial Specifications for Medicines.	April 2023
Draft revision sent out for public consultation	July – August 2023
Further follow-up action as required.	

*[**Note from the Secretariat.** It is proposed to revise the monograph on Albendazole as follows:*

- *addition of the information that the substance shows polymorphism (with a subsequent change in the identity test by IR (test A);*
- *addition of a test "Clarity and colour of solution";*
- *replacement of the TLC test for related substances with an HPLC method;*
- *update the style of the monograph; and*

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- *further minor changes in the tests and methods prescribed.*

The revision is based on information found in other pharmacopoeias, in particular, the European Pharmacopoeia *and on laboratory investigations.*

Changes from the current monograph are indicated in the text by <u>insert</u> or ~~delete~~.]

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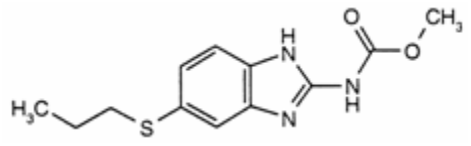
ALBENDAZOLE

(ALBENDAZOLUM)

Graphic formula



Molecular formula. $C_{12}H_{15}N_3O_2S$

Relative molecular mass. 265.3

Chemical name. ~~Methyl 5-(propylthio)-2-benzimidazolecarbamate~~Methyl *N*-[5-(propylsulfanyl)-1*H*-benzimidazol-2-yl]carbamate.

CAS Registry Number. 54965-21-8.

Description. A white or slightly yellowish powder ~~almost white powder~~.

Solubility. Practically insoluble in water R; freely soluble in anhydrous formic acid ~~glacial acetic acid~~ R; very slightly soluble in ~~acetone R and~~ dichloromethane R, ~~very slightly soluble~~ practically insoluble in ethanol (~750 g/L) TS.

Category. Anthelminthic.

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

Additional information. ~~Melting temperature, about 210°C, with decomposition~~Albendazole shows polymorphism.

Requirements

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Albendazole contains not less than 99.0~~98.0~~% and not more than 101.0% of $C_{12}H_{15}N_3O_2S$, calculated with reference to the dried substance.

Identity tests

- Either test A alone or any two of tests B, 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 albendazole RS or with the *reference spectrum* of albendazole.

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

~~C~~B. ~~Ignite about 0.1 g; fumes are evolved, staining lead acetate paper R black.~~ 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 and 1 volume of Acetic acid, glacial, 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 containing (A) 1.0 mg of the test substance per mL and (B) 1.0 mg of albendazole RS per mL. After removing the plate from the chromatographic chamber, allow it to dry in a current of warm air and examine the chromatogram in ultraviolet light (254 nm). The principal spot in the chromatogram obtained with solution (A) corresponds in position, appearance and intensity with the spot due to albendazole in the chromatogram obtained with solution (B).

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~~B~~C. ~~See the test described below under "Related substances". The principal spot obtained with solution (1)B corresponds in position, appearance and intensity with that obtained with solution (3)C.~~ Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography, using the conditions given under “Related substances”. Use solution (1) as described thereunder. For solution (2), transfer 25 mg of albendazole RS to a 50 mL volumetric flask. Add 5 mL of sulfuric acid/methanol (1%) TS and immediately dilute to volume with the mobile phase. Inject 5 µL of solutions (1) and (2). The retention time and the size of the principal peak in the chromatogram obtained with solution (1) correspond to the retention time and the size of the peak due to albendazole in the chromatogram obtained with solution (2).

D. Add about 0.1 g of the test substance to 3 mL of sulfuric acid (~100 g/L) TS and warm to dissolve. Add about 1 mL of potassium iodobismuthate/acetic acid TS; a reddish brown precipitate is produced.

Sulfated ash. Not more than ~~1.0~~2.0 mg/g.

Loss on drying. Dry at 105 °C for 4 hours; it loses not more than 5.0 mg/g.

Clarity and colour of solution. Dissolve 0.10 g of the test substance in a mixture of 10 volumes of anhydrous formic acid R and 90 volumes of dichloromethane R and dilute to 10 mL with the same mixture of solvents. This solution is clear and not more intensely coloured than reference solution BY_6, when compared as described under *1.11.2 Degree of coloration of liquids*, Method II.

Heavy metals. Use 1.0 g of the test substance 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 B; not more than 10 µg/g.

Related substances. Prepare the solutions immediately before use.

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Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography, using a stainless steel column (25 cm × 4.6 mm) packed with end-capped particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 µm).[1]

As the mobile phase, use a solution prepared as follows: dissolve 1.67 g of ammonium dihydrogen phosphate R in 1000 mL of water R. Mix 300 mL of this solution with 700 mL of methanol R.

Operate with a flow rate of 0.7 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 25.0 mg of the test substance to a 50 mL volumetric flask. Add 5 mL of sulfuric acid/methanol (1%) TS and immediately dilute to volume with the mobile phase. For solution (2), dilute 1.0 mL of solution (1) to 100.0 mL with the mobile phase. For solution (3), dilute 1.0 mL of solution (2) to 10.0 mL with the mobile phase. For solution (4), dissolve 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 to 10 mL with mobile phase. For solution (5), dilute 1 mL of sulfuric acid/methanol (1%) TS to 10 mL with the 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 separately 20 µL each of solutions (1), (2), (3), (4) and (5). Record the chromatogram for about twice the retention time albendazole (retention time about 11 minutes).

Use the chromatogram obtained with solution (4) and the chromatogram supplied with albendazole for system suitability RS to identify the peaks due to the impurities B and C, E, F and H. Use the chromatogram obtained with solution (5) and the chromatogram supplied with albendazole impurity mixture RS to identify the peaks

[1] A Symmetry C18 column was found suitable.

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due to the impurities A and D. The impurities are eluted at the following relative retention with reference to albendazole: impurity D about 0.35, impurities B and C about 0.40 (the impurities co-elute), impurity E about 0.45, impurity A about 0.48, impurity F about 0.57 and impurity H about 0.66.

The test is not valid unless, in the chromatogram obtained with solution (4), the resolution between the peak due to impurities B and C (impurities B and C co-elute) and the peak due to impurity E 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 impurity A, when multiplied by a correction factor of 1.7, is not greater than 0.4 times the area of the peak due to albendazole in the chromatogram obtained with solution (2) (0.4%);
- 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 0.4 times the area of the peak due to albendazole in the chromatogram obtained with solution (2) (0.4%);
- the area of any peak corresponding to impurity D, when multiplied by a correction factor of 1.9, is not greater than 0.2 times the area of the peak due to albendazole in the chromatogram obtained with solution (2) (0.2%);
- the area of any peak corresponding to impurity E, when multiplied by a correction factor of 1.4, is not greater than 0.3 times the area of the peak due to albendazole in the chromatogram obtained with solution (2) (0.3%);
- the area of any peak corresponding to impurity F is not greater than 0.5 times the area of the peak due to albendazole in the chromatogram obtained with solution (2) (0.5%);

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- the area of any peak corresponding to impurity H, is not greater than 0.6 times the area of the peak due to albendazole in the chromatogram obtained with solution (2) (0.6%);
- the area of any other impurity peak is not greater than 0.1 times the area of the peak due to albendazole in the chromatogram obtained with solution (2) (0.10%).
- The sum of the areas of all impurity peaks, including the corrected areas of any peaks corresponding to impurities A, B/C, D and E, is not greater than 1.3 times the area of the peak due to albendazole in the chromatogram obtained with solution (2) (1.3%). 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%).

~~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 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 5 solutions in a mixture of 9 volumes of dichloromethane R and 1 volume of anhydrous formic acid R containing (A) 10.0 mg of Albendazole per mL, (B) 1.0 mg of Albendazole per mL, (C) 1.0mg of albendazole RS per mL, (D) 0.05 mg of albendazole RS per mL, and (E) 0.025 mg of albendazole RS per mL. After removing the plate from the chromatographic chamber, allow it to dry in a current of warm air, 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 the principal spot obtained with solution D (0.5%), and only one spot may be more intense than the principal spot obtained with solution E (0.25%).~~

Assay. In order to avoid overheating in the reaction medium, mix thoroughly throughout the titration and stop the titration immediately after the end-point has been reached.

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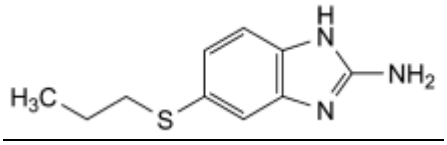
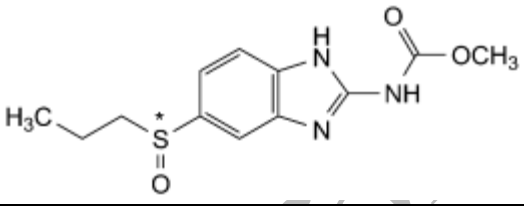
Dissolve 0.250 g in 3 mL of anhydrous formic acid R, add 40 mL of glacial acetic acid R1 ~~.Then add 0.2 mL of 1-naphtholbenzein/acetic acid TS~~and titrate with perchloric acid (0.1 mol/L) VS, ~~until a green colour is obtained~~determining the end-point potentiometrically as described under *2.6 Non-aqueous titration*, Method A. Carry out a blank determination and make any necessary correction.

Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 26.53 mg of $C_{12}H_{15}N_3O_2S$.

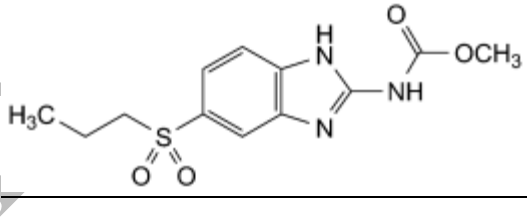
Impurities



A. 5-(Propylsulfanyl)-1*H*-benzimidazol-2-amine (degradation product).



B. Methyl *N*-[5-(propylsulfinyl)-1*H*-benzimidazol-2-yl]carbamate (degradation product).



C. Methyl *N*-[5-(propylsulfonyl)-1*H*-benzimidazol-2-yl]carbamate (degradation product).

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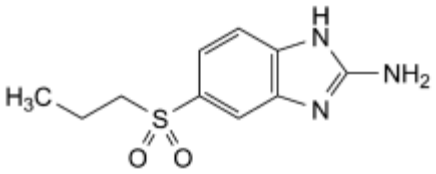
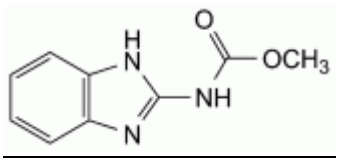
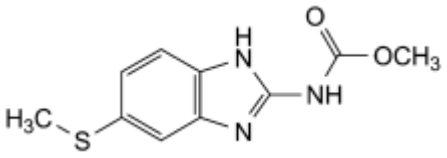


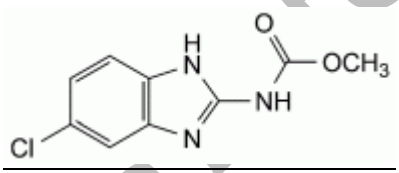
D. (2-Amino-1*H*-benzimidazol-5-yl)propyl-λ^6-sulfanedione (degradation product).



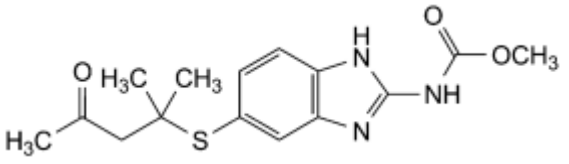
E. Methyl *N*-(1*H*-benzimidazol-2-yl)carbamate (degradation product , synthesis related impurity).



F. Methyl *N*-[5-(methylsulfanyl)-1*H*-benzimidazol-2-yl]carbamate (degradation product , synthesis related impurity).



G. Methyl *N*-(5-chloro-1*H*-benzimidazol-2-yl)carbamate.



H. Methyl *N*-[5-[(2-methyl-4-oxopentan-2-yl)sulfanyl]-1*H*-benzimidazol-2-yl]carbamate (degradation product).

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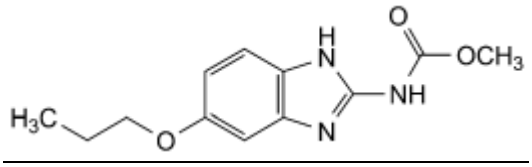
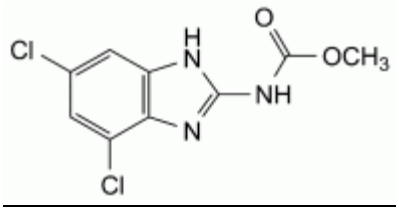
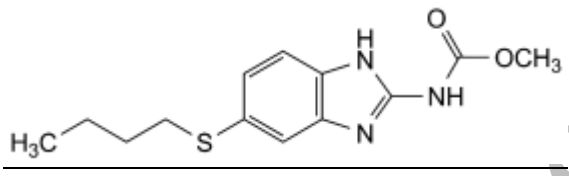


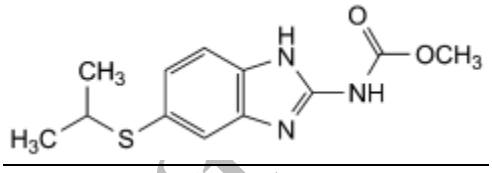
I. Methyl *N*-(5-propoxy-1*H*-benzimidazol-2-yl)carbamate.



J. Methyl *N*-(4,6-dichloro-1*H*-benzimidazol-2-yl)carbamate.



K. Methyl *N*-[5-(butylsulfanyl)-1*H*-benzimidazol-2-yl]carbamate.



L. Methyl *N*-[5-[(propan-2-yl)sulfanyl]-1*H*-benzimidazol-2-yl]carbamate.

Reagents to be added

Sulfuric acid/methanol (1%) TS

Procedure: cool separately 10 mL of sulfuric acid (~1760 g/L) TS and 990 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

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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.

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Draft for comments