World Health Organization

ALBENDAZOLE CHEWABLE TABLETS

(ALBENDAZOLI COMPRESSI MANDUCABILI)

Draft proposal for revision for *The International Pharmacopoeia*

(November 2020)

DRAFT FOR COMMENTS

Please send any comments you may have on this draft working document to **Dr Herbert Schmidt**, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (schmidth@who.int), with a copy to Claire Vogel (vogelc@who.int by **15 January 2021.**

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.

SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/20.855/Rev.1:

ALBENDAZOLE CHEWABLE TABLETS

(ALBENDAZOLI COMPRESSI MANDUCABILI)

Description	**Date**
Meeting of the Working Group on Albendazole of *The International Pharmacopoeia*.	July 2020
Drafting of the revision based on information received by a manufacturer.	July 2020
Draft revision sent out for public consultation.	August-September 2020
Presentation to the Fifty-fifth WHO Expert Committee on Specifications for Pharmaceutical Preparations.	October 2020
Drafting of revision 1 based on the comments received during the first public consultation and made at the Fifty-fifth WHO Expert Committee on Specifications for Pharmaceutical Preparations	November 2020
Revision 1 sent out for public consultation.	November 2020 – January 2021
Further follow-up action as required.	

*[**Note from the Secretariat.** It is proposed to revise the Dissolution test in monograph on Albendazole chewable tablets based on information received by a manufacturer. Comments are invited on the revised section.*

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

ALBENDAZOLE CHEWABLE TABLETS
(ALBENDAZOLI COMPRESSI MANDUCABILI)

Category. Anthelminthic.

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

Labelling. The designation on the container should state that the tablets may be chewed, swallowed whole or crushed and mixed with food or liquid, and that the tablets should be crushed before being given to a young child.

Additional information. Strengths in the current WHO Model List of Essential Medicines (EML): 400 mg. Strengths in the current EML for children: 400 mg.

Requirements

Comply with the monograph for *Tablets*.

Definition. Albendazole chewable tablets contain Albendazole in a suitable basis that may contain suitable flavouring agents. They contain not less than 90.0% and not more than 110.0% of the amount of Albendazole ($C_{12}H_{15}N_3O_2S$) 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 the chromatographic conditions given under "Related substances", Test B. Apply separately to the plate 10 µL each of the following 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 containing about 2.5 mg of Albendazole with 25 mL, filter and use the filtrate. For solution (B), use 0.1 mg of albendazole RS per mL. For solution (C), use 0.1 mg of albendazole RS and 0.1 mg of oxibendazole R 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 test is not valid unless the chromatogram obtained with solution (C) shows two clearly separated spots.

The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B).

B. See the test described below under "Assay", Method A. The retention time of the principal peak in the chromatogram obtained with solution (1) is similar to the retention time of the peak due to albendazole obtained with solution (3).

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; the absorbance at 308 nm is about 0.59.

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 dilute 2.0 mL of the obtained solution to 25.0 mL with the dissolution medium.

Measure the absorbance (*1.6*) of a 1.0 cm layer of the solution at about 291 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 ($C_{12}H_{15}N_3O_2S$) in the medium using the absorptivity value of 37.6 ($A_{1\,cm}^{1\%}$ = 376). 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 dilute 2.0 mL of the obtained solution to 50.0 mL with the dissolution medium.

Measure the absorbance (*1.6*) of a 1.0 cm layer of solutions (1) and (2) at about 291 nm, using hydrochloric acid (~10 g/L) TS as the blank. For each of the six tablets tested, calculate the total amount of albendazole ($C_{12}H_{15}N_3O_2S$) in the medium using the absorptivity value of 37.6 ($A_{1\,cm}^{1\%}$ = 376). The amount of albendazole released is not less than 80% (Q) of the amount declared on the label.

~~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 75 revolutions per minute. At 30 minutes withdraw a sample of about 15 mL of the dissolution medium through an in-line filter. Cool the filtered sample to room temperature. Transfer 1.0 mL of the clear filtrate to a 50 mL volumetric flask and dilute to volume with sodium hydroxide (0.1 mol/L) VS. Measure the absorbance *(1.6)* of a 1 cm layer of the resulting solution at the maximum at about 308 nm, using sodium hydroxide (0.1 mol/L) VS as the blank.~~

~~For each of the six tablets tested calculate the total amount of albendazole ($C_{12}H_{15}N_3O_2S$) in the medium using the absorptivity value of 74.2 ($A_{1cm}^{1\%}$ = 742). The amount in solution for each tablet is not less than 80% (Q) of the amount declared on the label.~~

Related substances

- 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 the conditions given below under "Assay", Method A.

Prepare the following solutions.

Solvent mixture: dilute 1 volume of sulfuric acid R with 99 volumes of methanol R.

For solution (1), transfer a quantity of the powdered tablets containing about 25 mg of Albendazole to a 50 mL volumetric flask. Add 5 mL of the solvent mixture and 20 mL of methanol R and shake to dissolve for about 15 minutes. Dilute to volume with methanol R. For solution (2), dilute 1.0 mL of solution (1) to 100.0 mL with methanol R. For solution (3), dissolve about 20 mg of albendazole RS and about 20 mg of oxibendazole R in 5 mL of solvent mixture and dilute to 100.0 mL with methanol R.

Inject separately 20 µL each of solutions (1), (2) and (3). Record the chromatogram for about 25 minutes.

In the chromatogram obtained with solution (3), the peak due to oxibendazole is eluted at a retention time of about 9.9 min and the peak due to albendazole at a retention time of about 13.6 minutes. The test is not valid unless the resolution factor between the peak due to oxibendazole and the peak due to albendazole is at least 3.0.

In the chromatogram obtained with solution (1):

- the area of any peak, other than the principal peak, is not greater than the area of the peak due to albendazole in the chromatogram obtained with solution (2) (1.0%); and
- the area of not more than one such peak is greater than 0.75 times the area of the peak due to albendazole in the chromatogram obtained with solution (2) (0.75%).

B. Carry out the test as described under *1.14.1 Thin-layer chromatography* using silica gel R5 as the coating substance and a mixture of dichloromethane R, glacial acetic acid R and ether R (30:7:3 v/v) as the mobile phase. Apply separately to the plate 10 µL each of the following 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 containing about 250 mg of Albendazole with 25 mL, filter and use the filtrate. For solution (B), use 0.1 mg of albendazole RS per mL. For solution (C), use 0.075 mg of albendazole RS per mL. For solution (D), use 0.1 mg albendazole RS and 0.1 mg oxibendazole R per mL. After removing the plate from the chromatographic chamber, allow the plate to dry in a current of warm air. Examine the chromatogram in ultraviolet light (254 nm). The test is not valid unless the chromatogram obtained with solution (D) shows two clearly separated spots.

In the chromatogram obtained with solution (A), any spot, other than the principal spot, is not more intense than the principal spot obtained with solution (B) (1.0%) and not more than one spot is more intense than the principal spot obtained with solution (C) (0.75%).

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 (25 cm × 4.6 mm) packed with octadecylsilyl base-deactivated silica gel for chromatography R (5 µm).

As the mobile phase, use a solution prepared as follows: dissolve 1.67 g of monobasic ammonium phosphate R in 1000 mL of water R, mix and filter. Mix 300 mL of this solution with 700 mL of methanol R. Make adjustments if necessary.

Prepare the following solutions.

Solvent mixture: dilute 1 volume of sulfuric acid R with 99 volumes of methanol R.

For solution (1), weigh and powder 20 tablets. Transfer a quantity of the powdered tablets containing ~~about~~ 100.0 mg of Albendazole~~, accurately weighed,~~ to a 50 mL volumetric flask. Add 5 mL of the solvent mixture and 20 mL of methanol R and shake for about 15 minutes. Dilute to volume with methanol R, mix and filter, discarding the first 15 mL of the filtrate. Dilute 5.0 mL of this solution to 50.0 mL with methanol R. For solution (2), transfer 25.0 mg of Albendazole RS to a 25 mL volumetric flask, add 5 mL of the solvent mixture and 15 mL of methanol R and shake to dissolve. Dilute to volume with methanol R. For solution (3), dilute 2.0 mL of solution (2) to 10.0 mL with methanol R. For solution (4), dissolve about 20 mg of oxibendazole R in 5 mL of solvent mixture in a 100 mL volumetric flask, add 20 mL of solution (2), mix and dilute to volume with 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.

Inject separately 20 µL each of solutions (1), (3) and (4). The test is not valid unless, in the chromatogram obtained with solution (4), the resolution factor between the peaks due to albendazole and due to oxibendazole is at least 3.0.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (3) and calculate the content of Albendazole ($C_{12}H_{15}N_3O_2S$) in the tablets using the declared content of $C_{12}H_{15}N_3O_2S$ in albendazole RS.

B. Weigh and powder 20 tablets. Transfer a quantity of the powdered tablets containing ~~about~~ 20.0 mg of Albendazole~~, accurately weighed,~~ 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. Transfer 1.0 mL of the subsequent filtrate to a 50 mL volumetric flask and dilute to volume 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 ($C_{12}H_{15}N_3O_2S$), using the absorptivity value of 74.2 ($A_{1\,cm}^{1\%}$ = 742).

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