World Health Organization

ETHAMBUTOL DIHYDROCHLORIDE DISPERIBLE TABLETS

(ETHAMBUTOLI DIHYDROCHLORIDI COMPRESSI DISPERSIBILI)

Draft proposal for inclusion in *The International Pharmacopoeia*

(August 2023)

DRAFT FOR COMMENTS

Please submit your comments through the online platform, PleaseReview™ (https://who.pleasereview.net/Main/Default.aspx?action=loaddocument&reviewid=200). If not registered or included in our mailing list, kindly submit your request with your full name, email address and organization/affiliation to jonessi@who.int, nsp@who.int.

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 **9 October 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.

SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/23.935:

ETHAMBUTOL DIHYDROCHLORIDE DISPERIBLE TABLETS

(ETHAMBUTOLI DIHYDROCHLORIDI COMPRESSI DISPERSIBILI)

Description	**Date**
Drafting of the text.	Jan – Sept 2023
Draft monograph sent out for public consultation	Aug – October 2023
Presentation at the 57th meeting of the Expert Committee on Specifications for Pharmaceutical Preparations	October 2023
Further follow-up action as required.	

ETHAMBUTOL DIHYDROCHLORIDE DISPERIBLE TABLETS

(ETHAMBUTOLI DIHYDROCHLORIDI COMPRESSI DISPERSIBILI)

Category. Antibacterial (antituberculosis).

Storage. Ethambutol hydrochloride dispersible tablets should be kept in a tightly closed container.

Additional information. Strengths in the current WHO Model list of essential medicines: 100 mg. Strengths in the current WHO Model list of essential medicines for children: 100 mg.

Requirements

Comply with the monograph for *Tablets*.

Definition. Ethambutol dihydrochloride dispersible tablets contain Ethambutol dihydrochloride in a suitable dispersible basis. They contain not less than 90.0% and not more than 110.0% of the amount of Ethambutol dihydrochloride ($C_{10}H_{24}N_2O_2$, 2HCl) stated on the label.

Manufacture. The manufacturing process is validated to demonstrate that the tablets, if tested, would comply with the following test for impurity B.

Impurity B. Prepare the solutions immediately before use. Carry out the test under *1.14.1 Chromatography*, High-performance liquid chromatography, using a stainless steel column (10 cm x 4.6 mm) packed with end-capped particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (3 µm)[1].

[1] A Luna C18(2) column has been found suitable.

Using the following conditions for gradient elution:

Mobile phase A: 50 volumes of methanol for chromatography R and 50 volumes of water R.

Mobile phase B: methanol for chromatography R.

Time (minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0–30	71	29	Isocratic
30–35	71 to 0	29 to 100	Linear gradient
35-37	0	100	Isocratic
37–38	0 to 71	100 to 29	Return to initial composition
38-48	71	29	Re-equilibration

Operate with a flow rate of 1.0 mL per minute. Maintain the column temperature at 40 °C. As a detector, use an ultraviolet spectrophotometer set at a wavelength of 215 nm.

Prepare the following solutions:

For solution (1), transfer a quantity of the powder tablets, nominally containing 200.0 mg of ethambutol dihydrochloride, to a 20 mL volumetric flask, add about 14 mL of water R, sonicate for about 15 minutes, and dilute with water R to volume, mix and filter. Dilute 2.0 mL of the filtrate to 20.0 mL with acetonitrile R. Transfer 4.0 mL of this solution to a test tube, add 100 µL of triethylamin R and 15 µL of (*R*)-(+)-α-methylbenzyl isocyanate R, insert a stopper, mix and heat at 70 °C for 20 minutes.

For solution (2), dilute 2.0 mL of solution (1) to 200.0 mL with acetonitrile.

For solution (3), transfer 4 mg of ethambutol for system suitability RS (containing ethambutol and impurity B) to a test tube, add 4 mL of mixture containing 9 volumes of acetonitrile R and 1 volume of water and 100 µL of triethylamine. Sonicate for 5 minutes to dissolve, add 15 µL of (*R*)-(+)-α-methylbenzyl isocyanate R, insert a stopper, mix and heat at 70 °C for 20 minutes.

Inject 10 µL each of solutions (1), (2) and (3) and record the chromatograms.

Use the chromatogram obtained with solution (3), and the chromatogram supplied with ethambutol for system suitability RS, to identify the peaks due to the impurity B. The impurities are eluted, if present, at the following relative retention with reference to ethambutol (retention time about 14 minutes): impurity C about 0.9 and impurity B about 1.3.

The test is not valid unless in the chromatogram obtained with solution (3) the resolution between the peak due to ethambutol and impurity B is at least 4.0.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity B is not greater than twice the area of the peak due to ethambutol in the chromatogram obtained with solution (2) (1.0%).

Identity tests

- Either tests A or tests B and C may be applied.

A. Carry out the test as described under *1.7 Spectrophotometry in the infrared region*. To a quantity of the powdered tablets, nominally containing 0.1 g of Ethambutol dihydrochloride, add 10 mL of methanol R and shake. Filter and evaporate the filtrate to dryness. The infrared absorption spectrum of the residue is concordant with the spectrum obtained from ethambutol hydrochloride RS or with the *reference spectrum* of ethambutol hydrochloride.

B. Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography using the conditions given under "Assay". The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time of the peak due to ethambutol in the chromatogram obtained with solution (2).

C. Carry out the test as described under *1.14.1 Chromatography*, Thin layer chromatography, using the conditions given under "Impurity A (2-Aminobutanol)".

Apply separately to the plate 5 µL of each of the following two solutions in methanol R. For solution (A), transfer a quantity of the powdered tablets, nominally containing 20 mg of Ethambutol dihydrochloride, to a 10 mL volumetric flask, add 8 mL of methanol R, sonicate for 5 minutes, and fill up to volume. Filter the solution and use the filtrate. For solution (B), use a solution containing 2 mg of ethambutol dihydrochloride RS per mL. After removing the plate from the chromatographic chamber, allow it to dry in air or in a current of air.

Spray the plate with anisaldehyde/methanol TS and heat it to 105 °C for 10 minutes. Allow the plate to cool and examine the chromatogram in daylight.

The principal spot in the chromatogram obtained with solution (A) corresponds in position, appearance, and intensity with the spot due to ethambutol in the chromatogram obtained with solution (B).

Impurity A (2-Aminobutanol). Carry out the test as described under *1.14.1 Chromatography*, Thin-layer chromatography, using silica gel R5 as the coating substance and a mixture of 10 volumes of ammonia (~260 g/L) TS, 15 volumes of water R and 75 volumes of methanol R as the mobile phase. Apply separately to the plate 2 µL of each of the following 3 solutions:

For solution (A), transfer a quantity of the powdered tablets, nominally containing 500.0 mg of Ethambutol dihydrochloride, to a 100 mL flask with a stopper, add 10.0 mL of methanol R and shake for 5 minutes. Filter the suspension and use the filtrate.

For solution (B), dissolve 50.0 mg of 2-aminobutanol R (impurity A) in 100.0 mL of methanol.

For solution (C), prepare a solution containing 5 mg of ethambutol dihydrochloride RS and 0.5 mg of 2-aminobutanol R per mL.

Develop the plate for 2/3 of its height. After removing the plate from the chromatographic chamber, allow it to dry in air, heat it at 110 °C for 10 minutes, and allow it to cool. Spray the plate with ninhydrin/ethanol (1 g/ 60 mL) TS, heat it at 110 °C for 5 minutes, and examine the chromatogram in daylight. The test is not valid unless the chromatogram obtained with solution (B) shows two clearly separated spots.

Any spot due to impurity A in the chromatogram obtained with solution (A) is not more intense than the spot in the chromatogram obtained with solution (B) (1.0%).

Disintegration. Carry out the test as described under *5.3 Disintegration test for tablets and capsules*, but using water at 15 to 25 °C. The dispersible tablets disintegrate within 3 minutes.

Dissolution. Carry out the test as described under *5.5 Dissolution test for oral dosage forms*, using as the dissolution medium, 900 mL of dissolution buffer, pH 6.8, TS and rotating the paddle at 50 revolutions per minute. At 30 minutes, withdraw a sample of 10 mL of the medium through an in-line filter. Allow the filtered sample to cool to room temperature and use it as solution (1). For solution (2), dissolve 56.0 mg of ethambutol dihydrochloride in the dissolution buffer.

Analyse solutions (1) and (2) as described under *1.14.1 Chromatography*, High-performance liquid chromatography, using the chromatographic conditions as described under "Assay".

For each of the six tablets tested, calculate the total amount of ethambutol dihydrochloride ($C_{10}H_{24}N_2O_2$, 2HCl) in the medium from the results obtained.

Evaluate the results as described under *5.5 Dissolution test for oral dosage forms*, Acceptance criteria. The amount of ethambutol dihydrochloride released is not less than 75% (Q) of the amount declared on the label.

Assay. Carry out the test as under *1.14.1 Chromatography*, High-performance liquid chromatography, using as the stationary phase a stainless steel column packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (5 µm).

As the mobile phase, use a solution prepared as follows: transfer 50 g of ammonium acetate R and 0.2 g of copper (II) acetate R to a 1000 mL volumetric flask, add 800 mL water R, shake to dissolve, adjust to pH 5.0 with glacial acetic acid R and fill up to volume with water R. Mix 800 mL of this solution with 200 mL of methanol R.

As the diluent, use a solution prepared as follows: transfer 7.7 g of ammonium acetate R to a 1000 mL volumetric flask, add 800 mL water R, shake to dissolve, adjust to pH 2.0 with phosphoric acid (~1440 g/L) TS and fill up to volume with water R.

Prepare the following solutions in diluent. For solution (1) weigh and powder 20 tablets. Transfer a quantity of the powder, nominally containing 100.0 mg of Ethambutol dihydrochloride, to a 500-mL volumetric flask. Add 400 mL and shake for about 15 minutes to dissolve. Dilute to volume, mix and filter. For solution (2), dissolve 50.0 mg of ethambutol dihydrochloride RS in 250.0 mL.

Operate with a flow rate of 1.0 mL per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of about 270 nm.

Inject 20 µl each of solutions (1) and (2) and record the chromatogram for 15 minutes.

Measure the areas of the peaks corresponding to ethambutol obtained in the chromatograms from solutions (1) and (2) and calculate the percentage content of ethambutol dihydrochloride ($C_{10}H_{24}N_2O_2$, 2HCl) in the tablets using the declared content of $C_{10}H_{24}N_2O_2$, 2HCl in ethambutol dihydrochloride RS.

Impurities

The impurities limited by the requirements of this monograph include those listed in the monograph on Ethambutol dihydrochloride.

Reference substance invoked

Ethambutol dihydrochloride ICRS

Already established ICRS. Intended uses to be adapted.

Ethambutol for system suitability RS (containing ethambutol and the impurity B)

It is intended to refer to the corresponding reference substances established for the European Pharmacopeia.

Reagent to be added

(*R*)-(+)-α-methylbenzyl isocyanate R

C_9H_9NO.

Content. minimum 99.0%.

Description. A colourless liquid.

Relative density. d_{20}^{20} is about 1.045.

Refractive index. n_D^{20} is about 1.513.

Boiling point. 55 °C to 56°C at 2.5 mm Hg.

Enantiomeric purity. minimum 99.5.

Storage. At a temperature of 2 °C to 8 °C.

Ninhydrin/ethanol (1 g/ 60 mL) TS

Dissolve 1.0 g of ninhydrin R in 50 mL of dehydrated ethanol R and add 10 mL of glacial acetic acid R.

***