PROPOSAL FOR REVISION OF MONOGRAPH PUBLISHED IN THE
FOURTH EDITION OF
The International Pharmacopoeia
Artenimol
(August 2011)
PROPOSED REVISION FOR COMMENT

Should you have any comments on the attached revision, please send these to Dr S. Kopp,
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kopps@who.int with a copy to Ms Caroline Mendy (mendyc@who.int) by 26 September 2011.

We will now send out our draft monographs electronically and they will also be placed on the
Medicines web site for comment. If you do not already receive our documents please let us
have your e-mail address (to bonnyw@who.int) and we will add it to our electronic mailing
list.

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### SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/11.437

*Draft proposal for revision of a published monograph in the Fourth Edition of The International Pharmacopoeia*

**ARTENIMOL**

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[Note from Secretariat:

- the current monograph is currently under review in the context of the general revision of artemisinin derivatives. This revised draft only takes account of the changes proposed as regards to the correction of the information related to stereochemistry. Therefore, it might be subject to further changes on other aspects of the monograph.

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

**ARTENIMOLUM**

**ARTEMIMOL**

Artemimol is the International Nonproprietary Name (INN) for this substance. However, the trivial name "dihydroartemisinin" is also in common use.

C$_{15}$H$_{24}$O$_{5}$

![Chemical structure of Artemimol](image)

Relative molecular mass. 284.4


[Note from Secretariat: a systematic name following IUPAC rules has been added as an alternative for the main component.]

Other names. "Dihydroartemisinin", β-dihydroartemisinin.

Description. Colourless needles or a white or almost white, crystalline powder.

Solubility. Practically insoluble in water; slightly soluble in acetonitrile R, ethanol (~750 g/l) TS and dichloromethane R.

Category. Antimalarial drug.

Storage. Artemimol should be kept in a well-closed container, protected from light.
Additional information. In solution, Artenimol (10S-epimer) and 10-epi-artenimol (10R-epimer) are in slow equilibrium.

Requirements

Definition. Artenimol contains not less than 97.0% and not more than the equivalent of 102.0% of C_{15}H_{24}O_{5} using Assay method A, and not less than 98.0% and not more than the equivalent of 102.0% of C_{15}H_{24}O_{5} using Assay method B, both calculated with reference to the dried substance.

Identity tests

• Either test A alone or 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 artenimol RS or with the reference spectrum of artenimol.

B. See the test described below under "Related substances test B". The principal spot obtained with solution D corresponds in position, appearance, and intensity with that obtained with solution E.

C. Dissolve 5 mg in about 0.5 ml of dehydrated ethanol R, add about 0.5 ml of hydroxylamine hydrochloride TS2 and 0.25 ml of sodium hydroxide (~80 g/l) TS. Heat the mixture in a water-bath to boiling, cool, add 2 drops of hydrochloric acid (~70 g/l) TS and 2 drops of ferric chloride (50 g/l) TS; a deep violet colour is immediately produced.

D. Dissolve 5 mg in about 0.5 ml of dehydrated ethanol R, add 1.0 ml of potassium iodide (80 g/l) TS, 2.5 ml of sulfuric acid (~100 g/l) TS, and 4 drops of starch TS; a violet colour is immediately produced.

Sulfated ash. Not more than 1.0 mg/g.

Loss on drying. Dry over phosphorus pentoxide R under reduced pressure (not exceeding 2.67 kPa or 20 mm of mercury); it loses not more than 10.0 mg/g.

Related substances

• Either test A or test B may be applied.

Prepare fresh solutions and perform the tests without delay.

A. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (10 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (3
µm. As the mobile phase for gradient elution, use a mixture of 6 volumes of acetonitrile R and 4 volumes of water for the first 17 minutes; then run a gradient, which should reach 100% acetonitrile within 13 minutes.

Prepare the following solutions in methanol R with sonication. For solution (1) use 10 mg of Artenimol per ml and for solution (2) use 50 µg of Artenimol per ml.

For the system suitability test prepare solution (3) by dissolving 1.0 mg of artemisinin RS per ml and 1.0 mg of artemimol RS per ml in methanol R with sonication.

Operate with a flow rate of 0.6 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 216 nm.

Inject separately 20 µl each of solutions (1), (2) and (3).

The test is not valid unless the relative retention of artemimol α-artenimol compared with artemisinin is about 0.6, and the resolution between the peaks is not less than 2.0.

Measure the areas of the peak (twin peak) responses for artemimol and 10-epi-artenimol obtained in the chromatograms from solutions (1) and (2), and calculate the content of the related substances as a percentage. In the chromatogram obtained with solution (1), the area of any peak, other than the twin peaks, is not greater than that obtained with solution (2) (0.5%). Not more than one peak is greater than half the area of the two principal peaks obtained with solution (2) (0.25%). The sum of the areas of all the peaks, other than the two principal peaks, is not greater than twice the area of the two principal peaks obtained with solution (2) (1.0%). Disregard any peak with an area less than 0.1 times the area of the two principal peaks in the chromatogram obtained with solution (2).

B. Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R1 as the coating substance and a mixture of equal volumes of light petroleum R1 and ether R as the mobile phase. Apply separately to the plate 10 ml of each of the following 5 solutions in toluene R containing (A) 10 mg of Artenimol per ml, (B) 0.05 mg of Artenimol per ml, (C) 0.025 mg of Artenimol per ml, (D) 0.10 mg of Artenimol per ml, and (E) 0.10 mg of artemimol RS per ml. After removing the plate from the chromatographic chamber, allow it to dry in air, and spray with vanillin/sulfuric acid TS1. Examine the chromatogram in daylight.

Any spot obtained with solution A, other than the principal spot, is not more intense than that obtained with solution B (0.5%). Furthermore, not more than one such spot is more intense than that obtained with solution C (0.25%).

Assay

• Either method A or method B may be applied.
Prepare fresh solutions and perform the tests without delay.

A. Determine by 1.14.4 High-performance liquid chromatography, using a stainless steel column (10 cm × 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (3 µm). As the mobile phase, use a mixture of 6 volumes of acetonitrile R and 4 volumes of water R.

Prepare the following solutions in the mobile phase: solution (1) 1.0 mg of Artenimol per ml, and solution (2) 1.0 mg of arteminol RS per ml.

For the system suitability test prepare solution (3) containing 1.0 mg of artemisinin RS per ml and 1.0 mg of artemimol RS per ml in a mixture of 8 volumes of acetonitrile R and 2 volumes of water R.

Operate with a flow rate of 0.6 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 216 nm.

Inject separately 20 µl each of solutions (1), (2), and (3).

The test is not valid unless the relative retention of α-artenimol:artemimol compared with artemisinin is about 0.6, and the resolution between the peaks is not less than 2.0.

Measure the areas of the peak (twin-peak) responses for artemimol and 10-epi-artemimol obtained in the chromatograms from solutions (1) and (2), and calculate the percentage content of C₁₅H₂₂O₅ with reference to the dried substance.

B. Dissolve about 0.05 g of Artenimol, accurately weighed, in sufficient ethanol (~750 g/l) TS to produce 100 ml and dilute 10 ml to 100 ml with the same solvent. Accurately transfer 10 ml to a 50-ml volumetric flask, dilute to volume with sodium hydroxide (0.05 mol/l) VS, mix thoroughly, and warm to 50 °C in a water-bath for 30 minutes. Cool to room temperature.

Measure the absorbance of a 1-cm layer at the maximum at about 292 nm against a solvent cell containing a blank prepared with 10 ml of ethanol (~750 g/l) TS diluted with sufficient sodium hydroxide (0.05 mol/l) VS to produce 50 ml. Calculate the percentage content of C₁₅H₂₂O₅ in the substance being tested by comparison with artemimol RS, similarly and concurrently examined, and with reference to the dried substance.

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