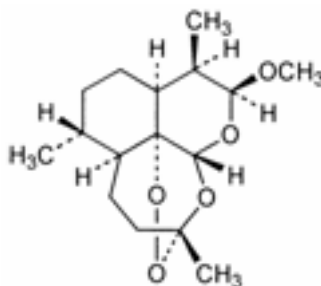
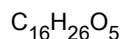


Artemether (Artemetherum)

2015-01



Relative molecular mass. 298.4

Chemical name. (3*R*,5*aS*,6*R*,8*aS*,9*R*,10*S*,12*R*,12*aR*)-Decahydro-10-methoxy-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin; CAS Reg. No. 71963-77-4.

Description. White crystals or a white, crystalline powder.

Solubility. Practically insoluble in water; very soluble in dichloromethane R and acetone R; freely soluble in ethyl acetate R and dehydrated ethanol R.

Category. Antimalarial drug.

Storage. Artemether should be kept in a tightly closed container and protected from light.

Labelling. The designation Artemether for parenteral use indicates that the substance complies with the additional requirements and may be used for parenteral administration.

Additional information. The parenteral form is normally intended for intramuscular administration.

Requirements

Artemether contains not less than 97.0% and not more than the equivalent of 102.0% of $\text{C}_{16}\text{H}_{26}\text{O}_5$ using "Assay", method A, and not less than 98.0% and not more than the equivalent of 102.0% of $\text{C}_{16}\text{H}_{26}\text{O}_5$ using "Assay", method B, both calculated with reference to the dried substance.

Identity tests

-Either tests A and B 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 artemether RS or with the *reference spectrum* of artemether.

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. To 30 mg add about 1 mL of dehydrated ethanol R and about 0.1 g of potassium iodide R. Heat the mixture on a water-bath; a yellow colour is produced.

D. Dissolve 30 mg in 6.0 mL of dehydrated ethanol R. Place a few drops of the mixture on a white porcelain dish and add 1 drop of vanillin/sulfuric acid TS1; a pink colour is produced.

Melting range. 86.0–90.0 °C.

Specific optical rotation. Use a 10 mg/mL solution in dehydrated ethanol R;

$$[\alpha]_{\text{D}}^{20} = +166^{\circ} \text{ to } +173^{\circ}.$$

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 5.0 mg/g.

Related substances

-Either test A or test B may be applied.

A. Carry out the test as described under [1.14.1 Chromatography, High-performance liquid chromatography](#) using the conditions given below under "Assay", method A.

Inject alternately 20 µL each of solutions A and C.

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

B. Carry out the test as described under [1.14.1 Chromatography, Thin-layer chromatography](#) using silica gel R1 as the coating substance and a mixture of 7 volumes of light petroleum R1 and 3 volumes of ethyl acetate R as the mobile phase. Apply separately to the plate 10 µL of each of the following 5 solutions in acetone R containing (A) 10 mg of Artemether per mL, (B) 0.05 mg of Artemether per mL, (C) 0.025 mg of Artemether per mL, (D) 0.10 mg of Artemether per mL and (E) 0.10 mg of artemether 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.

A. Determine by [1.14.1 Chromatography, High-performance liquid chromatography](#) using a stainless steel column (25 cm × 4 mm) 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 mixture of 62 volumes of acetonitrile R and 38 volumes of water.

Prepare the following solutions in the mobile phase: solution (A) 10mg of Artemether per mL; solution (B) 10 mg of artemether RS per mL; and for solution (C) dilute solution A to obtain a concentration equivalent to 0.05mg of Artemether per mL.

Operate with a flow rate of 1.5 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 216 nm.

Inject alternately 20 µL each of solutions A and B.

Measure the areas of the peak responses obtained in the chromatograms from solutions A and B and calculate the percentage content of $C_{16}H_{26}O_5$.

B. Dissolve about 0.050 g of Artemether, accurately weighed, in sufficient dehydrated ethanol R to produce 100 mL. Dilute 2 mL of this solution to 100 mL with hydrochloric acid/ethanol (1 mol/L) VS. Stopper the flask and place it in a water-bath at 55 °C for 5 hours. Allow to cool to room temperature.

Measure the absorbance of this solution in a 1 cm layer at the maximum at about 254 nm. Calculate the percentage content of $C_{16}H_{26}O_5$ using the absorptivity value of 38.5 ($A_{1\%}^{1\text{cm}} = 385$).

Additional requirement for Artemether for parenteral use

Complies with the monograph for [Parenteral preparations](#) and with [5.6 Extractable volume for parenteral preparations](#) and [5.7.2 Tests for particulate contamination, Visible particles](#).