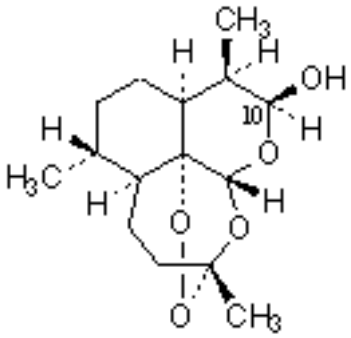
Artenimol (Artenimolum)

2022-01

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

Graphic formula



Molecular formula. $C_{15}H_{24}O_5$

Relative molecular mass. 284.3.

Chemical names. (3*R*,5a*S*,6*R*,8a*S*,9*R*,10*S*,12*R*,12a*R*)-3,6,9-trimethyldecahydro-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10-ol; 3*R*,5a*S*,6*R*,8a*S*,9*R*,10*S*,12*R*,12a*R*)-decahydro-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10-ol; CAS Reg. No. 71939-50-9.

Additional information. In solution, artenimol (10*S*-epimer) and 10-*epi*-artenimol (10*R*-epimer) equilibrate slowly.

Other names. "Dihydroartemisinin", ß-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.

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

Requirements

Definition. Artenimol contains not less than 97.0% and not more than 102.0% of $C_{15}H_{24}O_5$, calculated with reference to the dried substance.

Identity tests

Either test A alone or tests B, C, and D may be applied.

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.

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.

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.

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.

Carry out the test as described under *1.14.1 Chromatography*, 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).

Use the following conditions for gradient elution:

Mobile phase A: water R;

Mobile phase B: acetonitrile for chromatography R

Time (minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0–17	40	60	Isocratic
17–30	40 to 0	60 to 100	Linear gradient
30–31	0 to 40	100 to 60	Return to initial composition
31–40	40	100	Re-equilibration

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 artenimol 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 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 responses for 10-epi-artenimol and artenimol, eluting in this order, 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 two principal peaks, is not greater than the sum of the areas of the two principal peaks obtained with solution (2) (0.5%). Not more than one peak is greater than half the sum of the areas 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 sum of the areas of the two principal peaks obtained with solution (2) (1.0%). Disregard any peak with an area less than 0.1 times the sum of the areas of the two principal peaks in the chromatogram obtained with solution (2).

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 equal volumes of light petroleum R1 and ether R as the mobile phase. Apply separately to the plate 10 µl 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 artenimol 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

Determine by *1.14.1 Chromatography*, 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.

Perform the test without delay.

Prepare freshly the following solutions in the mobile phase: solution (1) 1.0 mg of Artenimol per mL and solution (2) 1.0 mg of artenimol 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 artenimol 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 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 responses for artenimol and 10-*epi* -artenimol obtained in the chromatograms from solutions (1) and (2) and calculate the percentage content of $C_{15}H_{22}O_5$ with reference to the dried substance.