Artemether injection (Artemetheri injectio)

2016-01

Description. A clear, colourless or almost colourless, oily solution.

Category. Antimalarial drug.

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

Labelling. The oil used in the formulation should be indicated.

Additional information. Strength in the current WHO Model List of Essential Medicines (EML): 80 mg/mL in 1 mL ampoule; other available strengths: 40 mg/mL (paediatric formulation), 60 mg/mL, 100 mg/mL (adult formulation).

Artemether injection is normally intended for intramuscular administration.

Requirements

Comply with the monograph for *Parenteral preparations* and with *5.6 Extractable volume for parenteral preparations*, *3.4 Test for bacterial endotoxins* and *5.7.2 Tests for particulate contamination, Visible particles*.

Definition. Artemether injection is a sterile solution of artemether in a suitable oil for injection. The solution is sterilized by a suitable method (see *5.8 Methods of sterilization*).

Artemether injection contains not less than 90.0% and not more than 110.0% of the amount of $C_{16}H_{26}O_5$ stated on the label.

Identity tests

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

A. To a volume of the injection equivalent to 0.050 g of Artemether add 25 mL of acetone R, mix and filter. Evaporate the filtrate at low temperature and dry overnight over desiccant silica gel R. 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 a volume of Artemether injection equivalent to about 30 mg of Artemether add 6 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.

Related substances

-Either test A or test B may be applied.

A. *Note*: This test cannot be performed if arachis oil is present in the formulation.

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 the area 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. For solution (A) dilute a volume of the injection with acetone R to obtain a concentration equivalent to 10 mg of Artemether per mL. Prepare similarly solution (B) with the equivalent of about 0.05 mg of Artemether per mL, solution (C) with the equivalent of about 0.025 mg of Artemether per mL and solution (D) with the equivalent of about 0.10 mg of Artemether per mL. For solution (E) use 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. For solution (A) dilute a volume of the injection to obtain a concentration equivalent to 10 mg of Artemether per mL, for solution (B) use 10 mg of artemether RS per mL and for solution (C) dilute a suitable volume of solution A to obtain a concentration equivalent to 0.05 mg 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. Dilute an accurately measured volume of the injection equivalent to about 0.08 g with sufficient ethanol R to produce 100 mL. Dilute 5 mL of this solution with the same solvent to 50 mL and mix. Transfer a further 5 mL of the diluted solution to a 50 mL volumetric flask and dilute to volume with hydrochloric acid/ethanol (1 mol/L) VS. Stopper the flask and place it in a water-bath at 55 ± 1 °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. (*Note*: If arachis oil is used in the formulation of Artemether injection subtract the value of 0.025 from the absorbance value determined; the correction in absorbance value for other oils would have to be established.) Calculate the percentage content of $C_{16}H_{26}O_5$ in the formulation being examined, using the absorptivity value of 38.5 ($A^{1\%}_{1cm}$ = 385).

Bacterial endotoxins. Carry out the test as described under *3.4 Test for bacterial endotoxins*; contains less than 1.56 IU of endotoxin per mg Artemether.