Artesunate tablets (Artesunati compressi)

Category. Antimalarial.

Storage. Artesunate tablets should be kept in a well-closed container.

Additional information. Strength in the current WHO Model list of essential medicines: 50 mg. Strength in the current WHO Model list of essential medicines for children: 50 mg.

Requirements

Comply with the monograph for *Tablets*.

Definition. Artesunate tablets contain Artesunate. They contain not less than **90.0%** and not more than **110.0%** of the amount ofartesunate ($C_{19}H_{28}O_8$) stated on the label.

Identity tests

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

A. To a quantity of the powdered tablets containing 0.050 g of Artesunate add 25 mL of acetone R, shake and filter. Evaporate the filtrate at low temperature and dry overnight over desiccant silica gel R. Carry out the examination with the residue as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum isconcordant with the spectrum obtained from artesunate RS or with the *reference spectrum* of artesunate.

B. Carry out the test as described under *1.14.1 Chromatography*, Thin-layer chromatography, usingsilica gel R5 as the coating substance and a mixture of 70 volumes of ethanol R, 30 volumes of toluene R and 1.5 volumes of ammonia (~260 g/l) TS as themobile phase. Apply separately to the plate 1 µl of the following two solutions in methanol R. For solution (A) shake a quantity of the powdered tabletscontaining about 5.0 mg of Artesunate with 5 mL, filter and use the clear filtrate. For solution (B) use 1.0 mg of artesunate RS per mL. After removing theplate from the chromatographic chamber allow it to dry in air or in a current of cool air. Spray with anisaldehyde/methanol TS and heat the plate to 120 °Cfor 5 minutes. Examine the chromatogram in daylight.

The principal spot obtained with solution A corresponds in position, appearance and intensity with that obtained with solution B.

C. To a quantity of the powdered tablets containing 0.1 g of Artesunate add 40 mL of dehydrated ethanol R, shake for a few minutes and filter. To half ofthe filtrate (keep the remaining filtrate for test D) 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 5 drops of hydrochloric acid (~70 g/l) TS and 2 drops of ferric chloride (50 g/l) TS; areddish-brown colour is produced.

D. Evaporate the remaining filtrate from test C on a water-bath to a volume of about 5 mL. Place a few drops of the mixture on a white porcelain dish, add1 drop of vanillin/sulfuric acid TS1; a red colour is produced.

Dissolution. Analyse the dissolution samples without delay.

Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms, using as thedissolution medium, 900 mL of dissolution buffer, pH 6.8, TS and rotating the paddle at 75 revolutions per minute. At 45 minutes withdraw a sample of 10 mlof the medium through an inline filter. Allow the filtered sample to cool to room temperature (solution (1)).

Determine the concentration in solution (1) by carrying out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography, using a stainless steel column (25cm × 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (5 µm). As the mobilephase use a mixture of equal volumes of acetonitrile R and buffer pH 3.0 (prepare the buffer as described under Assay method A).

For solution (2) dissolve 25 mg of artesunate RS, accurately weighed, in acetonitrile R and dilute to 20 mL with the same solvent. Dilute 2 mL of theresulting solution to 50 mL with mobile phase.

Operate with a flow rate of 1.5 mL per minute. Maintain the column temperature at 30 °C and use as detector an ultraviolet spectrophotometer set at awavelength of about 210 nm.

Inject alternately 100 µl each of solutions (1) and (2).

For each of the six tablets tested calculate the total amount of artesunate ($C_{19}H_{28}O_8$) in the medium from the resultsobtained. The amount in solution for each tablet is not less than 80% of the amount stated on the label. If the amount obtained for one of the six tabletsis less than 80%, repeat the test using a further six tablets; the average amount for all 12 tablets tested is not less than 75% and the amount obtainedfor no tablet is less than 60%.

Related substances

Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography, using the conditions given below under Assay method A.

Use solutions (1) and (3) as described below under Assay method A. For solution (4) dilute 1 mL of solution (1) to 100 mL with acetonitrile R.

Operate with a flow rate of 1.0 mL per minute. Maintain the column temperature at 30 °C and use as detector an ultraviolet spectrophotometer set at awavelength of about 216 nm.

Inject separately 20 µl each of solutions (1), (3) and (4). Record the chromatograms for about 4 times the retention time of artesunate.

In the chromatogram obtained with solution (3) the following peaks are eluted at the following relative retention with reference to artesunate (retentiontime about 9 minutes): 10-*epi*-artenimol about 0.58; artenimol about 0.91; and impurity B (artemisinin) about 1.30. The test is not validunless the peak-to-valley ratio (Hp/Hv) is at least 5.0, where Hp is the height above the extrapolated baseline of the peak due to artenimol and Hvis the height above the extrapolated baseline at the lowest point of the curve separating the peak due to artenimol from the peak due to artesunate. Thechromatogram obtained with solution (1) may show a peak due to impurity C eluting at a relative retention of about 2.7 with reference to artesunate.

In the chromatogram obtained with solution (1):

- -the combined areas of any peaks corresponding to 10-*epi*-artenimol and artenimol (impurity A) are not greater than 2.5 times the area of theprincipal peak obtained with solution (4) (2.5%);
- -the area of any peak corresponding to impurity B (artemisinin) is not greater than 0.5 times the area of the principal peak obtained with solution (4)(0.5%);
- -the area of any peak corresponding to impurity C, when multiplied by a correction factor of 0.07, is not greater than 0.3 times the area of the principalpeak obtained with solution (4) (0.3%);
- -the area of any other peak, other than the principal peak, is not greater than 0.3 times the area of the principal peak in the chromatogram obtained withsolution (4) (0.3%);
- -the sum of the corrected area of any peak corresponding to impurity C and the areas of all other peaks, other than the principal peak, is not greater than3.5 times the area of the principal peak obtained with solution (4) (3.5%). Disregard any peak with an area less than 0.1 times the area of the principalpeak in the chromatogram obtained with solution (4) (0.1%), and any peak eluting before acetonitrile.

Assay

-Either method A or method B may be applied.

A. Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography, using a stainless steel column (10cm × 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 mobilephase, use a mixture of 44 volumes of acetonitrile R and 56 volumes of buffer pH 3.0.

Prepare the buffer pH 3.0 by dissolving 1.36 g of potassium dihydrogen phosphate R in 900 mL of water R, adjust the pH to 3.0 with phosphoric acid (~1440g/l) TS and dilute to 1000 mL with water R.

Prepare the following solutions in acetonitrile R. For solution (1) weigh and powder 20 tablets. Shake or sonicate a quantity of the powder containingabout 40 mg of Artesunate, accurately weighed, for 15 minutes with 10 mL of acetonitrile R. Filter the resulting solution through a 0.45 µm filter,discarding the first few mL of the filtrate. For solution (2) dissolve 40 mg of artesunate RS, accurately weighed, and dilute to 10 mL. For solution (3)dissolve about 1 mg of artenimol RS, about 1 mg of artemisinin RS and about 10 mg of artesunate RS in 10 mL.

Operate with a flow rate of 1.0 mL per minute. Maintain the column temperature at 30 °C and use as detector an ultraviolet spectrophotometer set at awavelength of about 216 nm.

Inject separately 20 µl each of solutions (1), (2) and (3). Record the chromatograms for about 4 times the retention time of artesunate. In thechromatogram obtained with solution (3) the following peaks are eluted at the following relative retention with reference to artesunate (retention timeabout 9 minutes): 10-*epi*-artenimol about 0.58; artenimol about 0.91; and impurity B (artemisinin) about 1.30. The test is not valid unless thepeak-to-valley ratio (Hp/Hv) is at least 5.0, where Hp is the height above the extrapolated baseline of the peak due to artenimol and Hv is the heightabove the extrapolated baseline at the lowest point of the curve separating the peak due to artenimol from the peak due to artesunate. The chromatogramobtained with solution (1) may show a peak due to impurity C eluting at a relative retention of about 2.7 with reference to artesunate.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2) and calculate the content of artesunate ($C_{19}H_{28}O_8$) in the tablets, using the declared content of $C_{19}H_{28}O_8$ in artesunate RS.

B. Weigh and powder 20 tablets. To a quantity of the powder containing about 0.5 g of Artesunate, accurately weighed, add 50 mL of neutralized ethanol TS,shake thoroughly, filter and discard about 10 mL of the initial filtrate. Titrate 25 mL of the filtrate with sodium hydroxide (0.05 mol/l) VS, using 2drops of phenolphthalein/ethanol TS as indicator.

Each mL of sodium hydroxide (0.05 mol/l) VS is equivalent to 19.22 mg of $C_{19}H_{28}O_8$.

Impurities

The impurities limited by the requirements of this monograph include those listed in the monograph for Artesunate.