Oseltamivir capsules (Oseltamiviri capsulae)

Category. Antiviral.

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

Labelling. The designation of the container of Oseltamivir capsules should state that the active ingredient is in the phosphate form and the quantity should be indicated in terms of equivalent amount of oseltamivir.

Additional information. Strengths in the current WHO Model list of essential medicines: 30 mg, 45 mg, 75 mg. Strengths in the current WHO Model list of essential medicines for children: 30 mg, 45 mg, 75 mg of oseltamivir.

1 mg of oseltamivir is equivalent to approximately 1.3 mg of oseltamivir phosphate.

Requirements

Comply with the monograph for "Capsules".

Definition. Oseltamivir capsules contain Oseltamivir phosphate. They contain not less than 90.0% and not more than 110.0% of the amount of oseltamivir ($C_{16}H_{28}N_2O_4$) stated on the label.

Identity tests

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

A. To a quantity of the contents of the capsules containing the equivalent of 20 mg of oseltamivir, add 10 mL of methanol R, shake to dissolve and filter. Evaporate the filtrate to dryness.

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 oseltamivir phosphate RS or with the reference spectrum of oseltamivir phosphate.

B. Carry out the test as described under *1.14.1 Chromatography*, Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 8 volumes of methanol R, 6 volumes of ethyl acetate R, 4 volumes of toluene R and 2 volumes of ammonia (~ 260 g/l) TS as the mobile phase. Apply separately to the plate 10 µl of each of the following two solutions in methanol R. For solution (A) shake a quantity of the contents of the capsules containing the equivalent of 7.5 mg of oseltamivir with 5 mL, filter and use the clear filtrate. For solution (B) use 2 mg of oseltamivir phosphate RS per mL. After removing the plate from the chromatographic chamber allow it to dry exhaustively in air or in a current of cool air. Examine the chromatogram in ultraviolet light (254 nm).

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

C. See the test described under Assay method A. The retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that in the chromatogram obtained with solution (2).

D. Dissolve a quantity of the contents of the capsules to obtain a solution containing the equivalent of 4 mg of oseltamivir per mL. Neutralize this solution with a few mL of sodium hydroxide (0.1 mol/l) VS. Use 5 mL of the resulting solution; it yields reaction B described under 2.1 General identification tests as characteristic of orthophosphates.

Related substances

Carry out the test as described under 1.14.4 High performance liquid chromatography, using the same conditions as under Assay, method A using solutions (1), (3) and (4).

Inject separately 15 µl each of solutions (1), (3) and (4).

Use the chromatogram obtained with solution (4) to identify the peaks due to impurities A, B, C and D. The impurity peaks are eluted at the following relative retention with reference to oseltamivir phosphate (retention time about 19 minutes): impurity A about 0.16, impurity B about 0.17, impurity C about 0.51, impurity D about 0.55 and impurity F about 1.5. The test is not valid unless the resolution between the peaks due to impurities A and B and that between the peaks due to impurities C and D is at least 1.3.

In the chromatogram obtained with solution (1) the area of any peak corresponding to impurity B, when multiplied by a correction factor of 1.4, is not greater than 20 times the area of the peak in the chromatogram obtained with solution (3) (2.0%), the area of any peak corresponding to impurity C, when multiplied by a correction factor of 0.6, is not greater than 3 times the area of the peak in the chromatogram obtained with solution (3) (0.3%), the area of any peak corresponding to impurity F is not greater than 5 times the area of the peak in the chromatogram obtained with solution (3) (0.5%), the area of any other peak, apart from the principal peak, is not greater than the area of the peak in the chromatogram obtained with solution (3) (0.1%). The sum of the

corrected areas of any peaks corresponding to impurities B or C and of the areas of all other peaks, apart from the principal peak, is not greater than 30 times the area of the peak obtained with solution (3) (3.0%). Disregard any peak with an area less than 0.5 times the area of the principal peak obtained with solution (3) (0.05%).

Assay

Carry out the test as described under 1.14.4 High performance liquid chromatography , using a stainless steel column (25 cm x 4.6 mm) packed with octylsilyl silica gel for chromatography (5 µm).

The mobile phase consists of a mixture of 620 volumes of 0.05 M potassium dihydrogen phosphate (adjusted to pH 6 with potassium hydroxide (~110 g/l) TS), 245 volumes of methanol R and 135 volumes of acetonitrile R.

Operate with a flow rate of 1.2 mL per minute and the column oven temperature at 50 °C. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 207 nm.

Prepare the following solutions in a mixture of 620 volumes of water R, 245 volumes of methanol R and 135 volumes of acetonitrile R (dissolution solvent).

For solution (1) weigh and mix the contents of 20 capsules and transfer a quantity containing the equivalent of 40 mg of oseltamivir, accurately weighed, into a 50 mL volumetric flask. Add about 20 mL of the dissolution solvent, sonicate for about 15 minutes and make up to volume using the dissolution solvent. Filter a portion of this solution through a 0.45 µm filter, discarding the first few mL of the filtrate. For solution (2) dissolve 50 mg of oseltamivir phosphate RS in the dissolution solvent and dilute to 50.0 mL with the same solvent. For solution (3) dilute 1.0 mL of solution (1) to 100 mL with the dissolution solvent and then dilute 1.0 mL of this solution to 10 mL with the same solvent. For solution (4) dissolve about 2 mg of oseltamivir for system suitability RS in the dissolution solvent and dilute to 2 mL with the same solvent.

Inject separately 15 µl each of solutions (1), (2) and (4).

Use the chromatogram obtained with solution (4) to identify the peaks due to impurities A, B, C and D. The impurity peaks are eluted at the following relative retention with reference to oseltamivir phosphate (retention time about 19 minutes): impurity A about 0.16; impurity B about 0.17; impurity C about 0.51, impurity D about 0.55; and impurity F about 1.5. The assay is not valid unless the resolution between the peaks due to impurities A and B and that between the peaks due to impurities C and D is at least 1.3.

Measure the areas of the peak responses in the chromatograms obtained with solutions (1) and (2). Calculate the content of oseltamivir ($C_{16}H_{28}N_2O_4$) in the capsules.

Impurities

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