Zidovudine oral solution (Zidovudini solutio peroralum)

Category. Antiretroviral drug (Nucleoside Reverse Transcriptase Inhibitor).

Storage. Zidovudine oral solution should be kept in a tightly closed container, protected from light.

Additional information. Strength in the current WHO Model list of essential medicines: 50 mg per 5 mL (10 mg per mL). Strength in the current WHO Model list of essential medicines for children: 50 mg per 5 mL (10 mg per mL).

Requirements

Complies with the monograph for "Liquid preparations for oral use".

Definition. Zidovudine oral solution is a solution of Zidovudine in a suitable vehicle, which may be flavoured. It contains not less than 90.0% and not more than 110.0% of the amount of zidovudine ($C_{10}H_{13}N_5O_4$) stated on the label.

Identity tests

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

A. Carry out test A.1 or, where UV detection is not available, test A.2.

A.1 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 90 volumes of dichloromethane R, 10 volumes of methanol R, and 3 volumes of glacial acetic acid R as the mobile phase. Apply separately to the plate 5 µl of each of the following two solutions. For solution (A) dilute a volume of the oral solution containing 50 mg of Zidovudine to 50 mL with methanol R. Filter if necessary. For solution (B) prepare a 1 mg/mL solution of zidovudine RS in methanol R. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or in a current of cool air and 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.

A.2 Carry out the test as described under *1.14.1 Chromatography*, Thin-layer chromatography, using the conditions described above under test A.1 but using silica gel R5 as the coating substance. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or in a current of cool air. Dip the plate in basic potassium permanganate (~1 g/l) TS. Examine the chromatogram in daylight.

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

B. See the test described under Assay. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that of the principal peak in the chromatogram obtained with solution (2).

C. The absorption spectrum (1.6) of a solution prepared as described below, when observed between 210 nm and 300 nm, exhibits one maximum at about 267 nm.

Dilute a volume of the oral solution with a mixture consisting of 20 volumes of methanol R and 80 volumes of water R to give a solution containing 1 mg per mL of Zidovudine. Dilute 5.0 mL of the resulting solution to 25.0 mL with the same solvent and mix. Further dilute 5.0 mL of the diluted solution to 50.0 mL with sulfuric acid (0.1 mol/l) VS and mix. For the blank, use 5.0 mL of the mixture consisting of 20 volumes of methanol R and 80 volumes of water R diluted to 50.0 mL with sulfuric acid (0.1 mol/l)VS.

pH value (*1.13*). pH of the oral solution, 3.0 - 4.0.

Related substances

- Apply criterion A in all cases and criteria B, whenever possible.

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

Prepare the following solutions. For solution (1) dilute a quantity of the oral solution with the mobile phase to give a solution containing 0.2 mg of Zidovudine per mL. For solution (2) dilute 1 mL of solution (1) to 200 mL with the mobile phase. For solution (3) dissolve about 5 mg of zidovudine RS in solution (TSB), prepared as described below, and dilute to 10 mL with the same solution. For solution (TSB) dissolve 1 mg of each of thymine R (impurity C), stavudine RS (impurity A) and zidovudine impurity B RS in the mobile phase and dilute to 10 mL with the mobile phase; dilute 1 mL of the resulting solution to 10 mL with the same solvent. For solution (4) dissolve a suitable amount of each of the excipients (other than any parahydroxybenzoates) stated on

the label in 10 mL of a suitable solvent and dilute to 100 mL with the mobile phase.

Inject separately 10 µl each of solutions (1), (2), (3) and (4). Record the chromatograms for about 4 times the retention time of the principal peak in the chromatogram obtained with solution (2). For preparations containing parahydroxybenzoates, continue the chromatography for solution (1) for about 8 times the retention time of the principal peak in the chromatogram obtained with solution (2) in order to wash these excipients from the column.

In the chromatogram obtained with solution (3), the following peaks are eluted at the following relative retention with reference to zidovudine (retention time about 12 minutes): impurity C (thymine) about 0.3; impurity A (stavudine) about 0.4; impurity B about 1.2. The test is not valid unless the resolution between zidovudine and impurity C is at least 5.0, the resolution between zidovudine and impurity B is at least 2.0 and the tailing factor of zidovudine is less than 2.0.

If information concerning the excipients used in manufacturing the oral solution is not available or, if any of the peaks in the chromatogram obtained with solution (4) corresponds to any of the peaks in the chromatogram obtained with solution (3) or, if interference by excipients has been demonstrated by any other means, apply only criterion A.

A. In the chromatogram obtained with solution (1), the area of any peak corresponding to impurity C (thymine), when multiplied by a correction factor of 0.6, is not greater than 6 times the area of the principal peak in the chromatogram obtained with solution (2) (3.0%).

B. In the chromatogram obtained with solution (1), the area of any other peak, apart from the principal peak, is not greater than twice the area of the principal peak obtained with solution (2) (1.0%) and the area of not more than one such peak is greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).The sum of the corrected area of any peak corresponding to impurity C and of the areas of all other peaks, apart from the principal peak, is not greater than 12 times the area of the peak obtained in the chromatogram with solution (2) (6.0%). Disregard any peak with the same retention time as that of any of the peaks in the chromatogram obtained with solution (4), any peak with a relative retention with reference to zidovudine greater than 2.0 (corresponding to parahydroxybenzoates) and any peak with an area less than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

Assay. Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography, using a stainless steel column (25 cm x 4.6 mm) packed with particles of silica gel the surface of which has been modified by chemically bonded octadecylsilyl groups (5µm). As the mobile phase, use a mixture of 20 volumes of methanol R and 80 volumes of buffer pH 5.3 (a 0.045M solution of sodium acetate R, previously adjusted to pH 5.3 with glacial acetic acid R).

Prepare the following solutions. For solution (1) dilute an accurately weighed quantity of the oral solution containing 10 mg of Zidovudine to 50 mL with the mobile phase. For solution (2) prepare a 0.2 mg/mL solution of zidovudine RS in the mobile phase. For solution (3) dissolve a small amount (about 2 mg) each of thymine R (impurity C) and zidovudine impurity B RS in 10 mL of methanol R. Transfer 1 mL of this solution into a 50-mL volumetric flask and make up to volume with solution (1). For solution (4) dissolve a suitable amount of each of the excipients (other than any parahydroxybenzoates) stated on the label in 10 mL of a suitable solvent and dilute to 100 mL with the mobile phase.

Operate with a flow rate of 1.2 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 265nm.

Inject separately 10 µl of solutions (3) and (4). In the chromatogram obtained with solution (3), the following peaks are eluted at the following relative retention with reference to zidovudine (retention time about 12 minutes): impurity C (thymine) about 0.3; impurity B about 1.2. The assay is not valid unless the resolution between zidovudine and impurity C is at least 5.0, the resolution between zidovudine and impurity B is at least 2.0 and the tailing factor of zidovudine is less than 2.0. The assay is also not valid if any of the peaks in the chromatogram obtained with solution (4) corresponds to the peak due to zidovudine in the chromatogram obtained with solution (3).

Inject separately 10 µl of each of solutions (1) and (2).

Measure the areas of the peak responses corresponding to zidovudine obtained in the chromatograms from solutions (1) and (2). Determine the weight per mL (1.3.1) of the oral solution and calculate the percentage content of zidovudine ($C_{10}H_{13}N_5O_4$) weight in volume.

Impurities. The impurities limited by the requirements of this monograph include impurities A to C listed in the monograph for Zidovudine.