Zidovudine intravenous infusion (Zidovudini infusio intraveno)

2015-01

Category. Antiretroviral drug (Nucleoside Reverse Transcriptase Inhibitor).

Requirements

Complies with the monograph for *Parenteral preparations*.

Definition. Zidovudine intravenous infusion is a sterile solution of Zidovudine in glucose intravenous infusion. It is prepared immediately before use by diluting Zidovudine sterile concentrate with glucose intravenous infusion.

ZIDOVUDINE STERILE CONCENTRATE

Description. A clear colourless solution.

Storage. Zidovudine sterile concentrate should be kept in a tightly closed container, protected from light.

Labelling. The label indicates that the solution must be diluted with glucose intravenous infusion.

Additional information. Strength in the WHO Model list of essential medicines (EML): a solution of 10 mg per mL in a 20 mL vial. Strength in the WHO EML for children: a solution of 10 mg per mL in a 20 mL vial.

These solutions are a sterile concentrate for dilution with glucose intravenous infusion (5% w/v) immediately before intravenous administration.

Requirements

Complies with the monograph for *Parenteral preparations*.

Definition. Zidovudine sterile concentrate is a sterile solution of Zidovudine in water for injections.

The solution is sterilized by a suitable method (see *5.8 Methods of sterilization*).

Zidovudine sterile concentrate 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 concentrate with methanol R to produce a solution containing 1 mg/mL of Zidovudine. 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. Spray 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”, method A. 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 the final solution prepared for “Assay”, method B, when observed between 210 nm and 350 nm, exhibits one maximum at about 267 nm.

pH value (*1.13*). pH of the solution, 3.5–7.0.

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

Prepare the following solutions. For solution (1) dilute a volume of the concentrate with the mobile phase to produce a solution containing 1 mg/mL of Zidovudine. Dilute 5.0 mL of the resulting solution to 50.0 mL with the same solvent and mix. For solution (2) dilute 1.0 mL of solution (1) to 200.0 mL with 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 1.0 mL of this solution into a 100 mL volumetric flask and make up to volume with solution (1).

Inject separately 10 µL each of solutions (1), (2) and (3). 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 to 13 minutes): impurity C (thymine) about 0.3; impurity B about 1.2. The test is not valid unless in the chromatogram obtained with solution (3) the resolution between the peaks due to zidovudine and impurity C is at least 5.0, the resolution between the peaks due to zidovudine and impurity B is at least 2.0 and the tailing factor of zidovudine is less than 2.0.

In the chromatogram obtained with solution (1) the area of any peak corresponding to impurity C, 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%). The area of any other peak, apart from the principal peak, is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1.0%). 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 8 times the area of the principal peak in the chromatogram obtained with solution (2) (4.0%). Disregard 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

-Either method A or 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 (25 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with octadecysilyl groups (5 µm). As the mobile phase use a mixture of 20 volumes of methanol R and 80 volumes of water R.

Prepare the following solutions. For solution (1) dilute an accurately measured volume of the concentrate with the mobile phase to produce a solution containing 1 mg/mL of Zidovudine. Dilute 5.0 mL of the resulting solution to 50.0 mL with the same solvent and mix. For solution (2) prepare a 0.1 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 10.0 mL methanol R. Transfer 1.0 mL of this solution into a 100 mL volumetric flask and dilute to volume with solution (1).

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

Inject separately 10 µL of each of solutions (1), (2) and (3). 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 to 13 minutes): impurity C (thymine) about 0.3; impurity B about 1.2. The assay is not valid unless the resolution between the peaks due to zidovudine and impurity C is at least 5.0, the resolution between the peaks due to zidovudine and impurity B is at least 2.0 and the tailing factor of zidovudine is less than 2.0.

Measure the areas of the peak responses corresponding to zidovudine obtained in the chromatograms from solutions (1) and (2) and calculate the percentage content of zidovudine ($C_{10}H_{13}N_5O_4$) in the concentrate.

B. Dilute a volume of the concentrate 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.

Measure the absorbance *(1.6)* of a 1 cm layer of the final solution at the maximum at about 267 nm against a solvent cell containing the blank. Calculate the content of zidovudine ($C_{10}H_{13}N_5O_4$) in the concentrate using the absorptivity value of 38.0 ($A^{1\%}_{1cm}$ = 380).

Bacterial endotoxins. Carry out the test as described under *3.4 Test for bacterial endotoxins*; contains less than 1.0 IU of endotoxin per mg Zidovudine.

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