ZIDOVUDINE INJECTION
ZIDOVUDINE INTRAVENOUS INFUSION
Draft proposal for The International Pharmacopoeia
(September 2006)

This document was provided by a contracted quality control laboratory. Comments have been provided by collaborating laboratories following discussion at an informal meeting held in Geneva on 4 May 2006, and also by the WHO Secretariat.

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*International Pharmacopoeia monograph on Zidovudine injection - Zidovudine intravenous infusion*

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ZIDOVUDINE INJECTION
ZIDOVUDINE INTRAVENOUS INFUSION:
Draft proposal for The International Pharmacopoeia
(September 2006)

Note from the Secretariat: Title to be decided.

Category. Antiretroviral drug (Nucleoside Reverse Transcriptase Inhibitor).

Description. A clear colourless solution.

Storage. Zidovudine injection should be kept in a tight, light-resistant container.

Additional information. Strengths available in the WHO Model List of Essential Medicines: 200 mg in 20ml. For intravenous administration.

Requirements

Complies with the monograph for “Parenteral preparations”.

Definition. Zidovudine injection 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 injection contains not less than 90.0% and not more than 110.0% of the amount of C10H13N5O4 stated on the label.

Identity tests

- Either test A or B 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 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 injection 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 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 method A. The retention time of principal peak in the chromatogram obtained with solution (1) corresponds to that of the principal peak in the chromatogram obtained with solution (2).

pH value. pH of the solution, 3.5 - 7.0.

Related substances. 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 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 a volume of the injection with the mobile phase to produce a solution containing 1 mg/ml of Zidovudine. Dilute 20.0 ml of the resulting solution to 200.0 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. Pipette 1.0 ml of this solution into a 100 ml volumetric flask and make up 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 each of solutions (1), (2) and (3). In the chromatogram obtained with solution (3), the following peaks are eluted at the following retention times ratio with reference to zidovudine (retention time about 12 to 13 minutes): impurity C about 0.3; impurity B about 1.2. The test is not valid unless in the chromatogram obtained with solution (3) the resolution between zidovudine and thymine (impurity C) is greater than 5.0, the resolution between zidovudine and impurity B is greater than 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 four times the area of the principal peak in the chromatogram obtained with solution (2) (2.0%). 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 areas of all peaks, other than the principal peak, is not greater than 6 times the area of the principal peak in the chromatogram obtained with solution (2) (3.0%). Disregard any peak with an

1 Waters Hypersil BDS is suitable.
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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 1.14.4 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 (5µm). 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 a volume of the injection 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. Pipette 1.0 ml of this solution into a 100 ml volumetric flask and dilute to volume with solution (2).

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 retention times ratio with reference to zidovudine (retention time about 12 to 13 minutes): impurity C about 0.3; impurity B 1.2. The assay is not valid unless the resolution between zidovudine and thymine (impurity C) is greater than 5.0, the resolution between zidovudine and impurity B is greater than 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 C10H13N5O4.

B. Dilute a volume of the injection 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 0.1 M H2SO4 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 0.1M H2SO4 VS.

Measure the absorbance 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 C10H13N5O4 using the absorptivity value of 38.0 (A 1% 1cm=380).

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