Fluconazole injection (Fluconazoli injectio)

2015-01

Description. A clear, colourless solution.

Category. Antifungal.

Storage. Fluconazole injection should be kept in a tightly closed container, protected from light.

Additional information. Strength in the current WHO Model list of essential medicines (EML) and in the current WHO EML for Children:

2 mg/mL in vial.

Requirements

Complies with the monograph for *Parenteral preparations*.

Definition. Fluconazole injection is a sterile solution of Fluconazole in Water for injections. The solution is sterilized by a suitable method (see *5.8 Methods of sterilization*). Fluconazole injection contains not less than 90.0% and not more than 110.0% of the amount of fluconazole ($C_{13}H_{12}F_2N_6O$) stated on the label.

Identity tests

· Either test A and C or test B and C may be applied.

A. 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 80 volumes of dichloromethane R, 20 volumes of methanol R and 1 volume of ammonia (~260 g/L) TS solution as the mobile phase. Apply separately to the plate 20 µL of each of the following three solutions. For solution (A) use the injection to be examined. For solution (B) use 2 mg of fluconazole RS per mL in methanol R. For solution (C) use a mixture of 2 mg of fluconazole RS per mL and 1 mg of ketoconazole RS per mL in methanol R. After application allow the spots to dry in a current of air. Develop the plate. After removing the plate from the chromatographic chamber allow it to dry in a current of air and examine the chromatogram in ultraviolet light (254 nm).

The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B). The test is not valid unless the chromatogram obtained with solution (C) shows two clearly separated spots.

B. Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography using the conditions given 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. Dilute a volume of the injection containing 2 mg of Fluconazole to 10 mL with water R. The absorption spectrum (*1.6*) of the resulting solution, when observed between 230 nm and 300 nm, exhibits maxima at 261 nm and 267 nm and a minimum at about 264 nm. The ratio of the absorbance of a 1 cm layer at the maximum at about 261 nm to that at the minimum at about 264 is about 1.4.

pH value (1.3). pH of the injection, 4.0–6.0.

Related substances

Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography using the conditions given below under “Assay”. Prepare the following solutions in the mobile phase. For solution (1) use the injection to be examined. For solution (2) dilute 5 volumes of solution (1) to 100 volumes, then dilute l volume of this solution to 10 volumes. For solution (3) use 0.02 mg of fluconazole impurity C RS per mL. For solution (4) mix 1 volume of solution (3) with 1 volume of solution (1).

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 261 nm.

Maintain the column at 40 °C.

Inject separately 20 µL each of solutions (1), (2), (3) and (4). Record the chromatograms for about 3.5 times the retention time of fluconazole.

The peaks are eluted at the following relative retentions with reference to fluconazole (retention time about 11 minutes): impurity B about 0.4; impurity A about 0.5; impurity C about 0.8.

The test is not valid unless in the chromatogram obtained with solution (4) the resolution between the peaks due to impurity C and due to fluconazole is at least 3.0

In the chromatogram obtained with solution (1):

- -the area of any peak corresponding to impurity A is not greater than 0.8 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);
- -the area of any peak corresponding to impurity B, when multiplied by a correction factor of 1.5, is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (3) (0.3%);
- -the area of any peak corresponding to impurity C is not greater than 0.2 times the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);
- -the area of any other impurity peak, other than the principal peak, is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);
- -the sum of the areas of all peaks, other than the peak due to fluconazole, is not greater than 2 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0 %). 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

Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography using a stainless steel column (25 cm × 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 mobile phase use a mixture of 86 volumes of a 0.63 g/L solution of ammonium formate R and 14 volumes of acetonitrile R.

Prepare the following solutions in the mobile phase. For solution (1) dilute 5.0 mL of the injection to be examined to 20.0 mL. For solution (2) use 0.5 mg of fluconazole RS per mL. For solution (3) use a solution containing 0.01 mg of fluconazole impurity C RS per mL and 1 mg of fluconazole RS per mL.

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 261 nm.

Maintain the column at 40 °C.

Inject separately 20 µL of each of solutions (1), (2) and (3). The test is not valid unless in the chromatogram obtained with solution (3) the resolution between the peaks due to impurity C and due to fluconazole is at least 3.0.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2) and calculate the percentage content of fluconazole ($C_{13}H_{12}F_2N_6O$) in the injection using the declared content of $C_{13}H_{12}F_2N_6O$ in fluconazole RS.

Bacterial endotoxins. Carry out the test as described under *3.4 Test for bacterial endotoxins*; contains not more than 0.416 IU of endotoxin RS per mg of Fluconazole.