EAG/Panel/Working Party	Medicinal Chemicals 1
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Notes: New monograph If limits are too restrictive, please provide batch/stability data to demonstrate that an increase is required.	

Sterile Itraconazole Concentrate

Itraconazole Preparations

Action and use
Antifungal.

DEFINITION

Sterile Itraconazole Concentrate is a sterile solution of Itraconazole in a suitable solvent.

The concentrate complies with the requirements for Concentrates for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of itraconazole, $C_{35}H_{38}Cl_2N_8O_4$
95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a volume of the concentrate containing 10 mg of Itraconazole with 5 mL of *dichloromethane*. Allow the layers to separate and use the lower layer

(2) 0.2% w/v of *itraconazole BPCRS* in *dichloromethane*.

(3) 0.2% w/v each of *itraconazole BPCRS* and *fluconazole BPCRS* in *dichloromethane*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* F_{254} (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 10 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254nm)*.

MOBILE PHASE

20 volumes of a solution containing 0.015% w/v of *ammonium acetate* and 0.0003% v/v of *glacial acetic acid* in *water*, 40 volumes of *1,4-dioxan* and 40 volumes of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances
Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A 0.1 volumes of *hydrochloric acid* and 50 volumes of mobile phase.

(1) To a volume of the concentrate containing 0.1 g of Itraconazole, add 25 mL of mobile phase and 0.2 mL of *hydrochloric acid* and shake. Dilute with mobile phase to produce 100 mL and filter through a 0.45-µm PVDF filter, discarding the first 6 mL.

(2) Dilute 1 volume of solution (1) to 100 volumes with solution A and further dilute 1 volume to 5 volumes with solution A.

(3) 0.1% w/v of *itraconazole for system suitability EPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Phenomenex Prodigy ODS-2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 254 nm.

(f) Inject 15 µL of each solution.

(g) Allow the chromatography to proceed for 3 times the retention time of itraconazole.

MOBILE PHASE

48 volumes of *acetonitrile* and 52 volumes of 0.01M *potassium dihydrogen orthophosphate*, adjusted to pH 3.0 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions, the retention times relative to itraconazole (retention time about 23 minutes) are: impurity A, about 0.3; impurity B, about 0.6; impurity C+D, about 0.7; impurity E, about 0.8; impurity F, about 1.1 and impurity G, about 1.7.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the peak to valley ratio is at least 2.0, where H_p is the height above the baseline of the peak due to itraconazole and H_v is the height above the baseline of

the lowest point of the curve separating this peak from the peak due to impurity F

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak due to impurity B, impurity C+D and impurity G is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 10 times the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%)

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A 0.1 volumes of *hydrochloric acid* and 50 volumes of mobile phase.

(1) To a quantity of the concentrate containing 0.5 g of Itraconazole, add 25 mL of mobile phase and 1 mL of *hydrochloric acid* and shake. Dilute to produce 500 mL with the mobile phase and filter through a 0.45-µm PVDF filter, discarding the first 6 mL. Dilute 1 volume of the filtrate to 10 volumes with the mobile phase.

(2) 0.01% w/v of *itraconazole BPCRS* in solution A.

(3) 0.1% w/v of *itraconazole for system suitability EPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Related substances may be used with a flow rate of 2.0 mL per minute.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the peak to valley ratio is at least 2.0, where H_p is the height above the baseline of the peak due to itraconazole and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity F.

DETERMINATION OF CONTENT

Calculate the content of itraconazole, $C_{35}H_{38}Cl_2N_8O_4$, using the declared content of $C_{35}H_{38}Cl_2N_8O_4$ in *itraconazole BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Itraconazole.