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<b>Notes:</b> New monograph If limits are too restrictive, please provide batch/stability data to demonstrate that an increase is required.	

## Itraconazole Capsules

### Itraconazole Preparations

**Action and use**  
Antifungal.

### **DEFINITION**

Itraconazole Capsules contain Itraconazole.

*The capsules comply with the requirements stated under Capsules and with the following requirements.*

**Content of itraconazole, C<sub>35</sub>H<sub>38</sub>Cl<sub>2</sub>N<sub>8</sub>O<sub>4</sub>**  
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 quantity of capsule contents containing 50 mg of Itraconazole with 50 mL of *water* and filter. Shake the residue with 50 mL of dichloromethane and filter through a 0.45-µm PVDF filter and use the filtrate.
- (2) 0.1% w/v of *itraconazole BPCRS* in *dichloromethane*.
- (3) 0.1% w/v of *itraconazole BPCRS* and 0.2% w/v of *fluconazole BPCRS* in *dichloromethane*.

### CHROMATOGRAPHIC CONDITIONS

- (a) Use as the coating *silica gel F<sub>254</sub>* (Merck TLC silica gel 60 F<sub>254</sub> plates are suitable).
- (b) Use the mobile phase as described below.
- (c) Apply 5 µL of each solution.
- (d) Develop the plate to 15 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**

#### **Dissolution**

Comply with the dissolution test for tablets and capsules, Appendix XII B1.

#### TEST CONDITIONS

- (a) Use Apparatus 2, and rotate the paddle at 75 revolutions per minute.
- (b) Use 900 mL of 0.5% w/v of *sodium dodecyl sulfate* in *water*, at a temperature of 37°, as the medium.

#### PROCEDURE

- (1) After 60 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with the dissolution medium if necessary, to produce a solution expected to contain 0.0055% w/v of Itraconazole.
- (2) Dissolve 27.5 mg of *itraconazole BPCRS* in 10 mL of *acetonitrile (60%)* and 1 drop of *orthophosphoric acid* and dilute to 100 mL with *acetonitrile (60%)*. Dilute 1 volume to 5 volumes with dissolution medium to produce a solution containing 0.0055% w/v of *itraconazole BPCRS*.

#### 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 2 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.

#### MOBILE PHASE

45 volumes of 0.01M *potassium dihydrogen orthophosphate*, adjusted to pH 3.0 with *orthophosphoric acid* and 55 volumes of *acetonitrile*.

#### DETERMINATION OF CONTENT

Calculate the total content of Itraconazole, C<sub>35</sub>H<sub>38</sub>Cl<sub>2</sub>N<sub>8</sub>O<sub>4</sub>, in the medium from the chromatograms obtained and using the declared content of C<sub>35</sub>H<sub>38</sub>Cl<sub>2</sub>N<sub>8</sub>O<sub>4</sub> in *itraconazole BPCRS*.

#### LIMITS

The amount of itraconazole released is not less than 70% (Q) of the stated amount.

### 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 quantity of mixed capsule contents containing 0.1 g of Itraconazole, add 5 mL of mobile phase and 0.2 mL of *hydrochloric acid* and mix with the aid of ultrasound. Add 50 mL of solution A and shake. Dilute to produce 100 mL and filter through a 0.45- $\mu$ m 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  $\times$  4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5  $\mu$ m) (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  $\mu$ L 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 1.5.

### 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% of each); 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 5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%). 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

Mix the contents of 20 capsules. 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 capsule contents containing 0.1 g of Itraconazole, add 5 mL of mobile phase and 0.2 mL of *hydrochloric acid* and mix with the aid of ultrasound. Add 50 mL of mobile phase and shake. Dilute to produce 100 mL with mobile phase and filter through a 0.45- $\mu$ m PVDF filter, discarding the first 6 mL. Dilute 1 volume of the filtrate to 10 volumes with 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  $C_{35}H_{38}Cl_2N_8O_4$  in the capsules 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 impurities A - G listed under Itraconazole.