Itraconazole Capsules

Itraconazole Capsules contain Itraconazole not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of itraconazole, $C_{35}H_{38}Cl_2N_8O_4$.

Usual strengths. 100 mg; 200 mg.

Identification

In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

Tests

Dissolution (2.5.2).
NOTE —Perform the determination under subdued light and use amber autosampler vials and low-actinic glassware.
Apparatus No. 1,
Medium. 900 ml of *gastric juice, artificial* (without enzyme),
Speed and time. 100 rpm and 60 minutes.

Withdraw a suitable volume of the medium and filter.

Withdraw a suitable volume of the medium and filter. Measure the absorbance of the filtered solution, suitably diluted with the medium if necessary, at the maximum at about 255 nm (2.4.7). Calculate the content of itraconazole, $C_{35}H_{38}Cl_2N_8O_4$ in the medium from the absorbance obtained from a solution of 0.0022 per cent w/v solution of *itraconazole RS* prepared by dissolving 55 mg of *itraconazole RS* in 80 ml of *methanol*, heat the solution at 65° in the water-bath until dissolved and dilute to 100.0 ml with *methanol*. Dilute 2.0 ml of the solution to 50.0 ml with the dissolution medium.

D. Not less than 80 per cent of the stated amounts of $C_{35}H_{38}Cl_2N_8O_4$.

Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. 0.1 volume of *hydrochloric acid* and 50 volumes of the mobile phase.

Test solution. Disperse a quantity of mixed contents of capsules containing 0.1 g of Itraconazole in 5 ml of the mobile phase and 0.2 ml of *hydrochloric acid*, with the aid of ultrasound and dilute to 100.0 ml with the solvent mixture.

Reference solution (a). Dilute 1.0 ml of the test solution to 100.0 ml with the solvent mixture. Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.
Reference solution (b). A 0.1 per cent w/v solution of *itraconazole system suitability RS* (containing impurities A, B, C, D, E, F and G) in the solvent mixture.
Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as Phenomenex Prodigy ODS-2),
- column temperature: 40º,
- mobile phase: a mixture of 52 volumes of *0.01M potassium dihydrogen orthophosphate*, adjusted to pH 3.0 with *orthophosphoric acid* and 48 volumes of *acetonitrile*,
- flow rate: 1.5 ml per minute,
- spectrophotometer set 254 nm,
- injection volume: 15 µl.

Name	Relative retention time
Itraconazole impurity A[1]	0.3
Itraconazole impurity B[2]	0.6
Itraconazole impurity C[3] and D[4]	0.7
Itraconazole impurity E[5]	0.8
Itraconazole (retention time: about 23 minutes)	1.0
Itraconazole impurity F[6]	1.1
Itraconazole impurity G[7]	1.5

[1]4-[4-[4-(4-methoxyphenyl)piperazin-1-yl]phenyl]-2-[(1*RS*)-1-methylpropyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one,
[2]4-[4-[4-[4-[[*cis*-2-(2,4-dichlorophenyl)-2-(4*H*-1,2,4-triazol-4-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazin-1-yl]phenyl]-2-[(1*RS*)-1-methylpropyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one,
[3]4-[4-[4-[4-[[*cis*-2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazin-1-yl]phenyl]-2-propyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one,
[4]4-[4-[4-[4-[[cis-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazin-1-yl]phenyl]-2-(1-methylethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one,
[5]4-[4-[4-[4-[[trans-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazin-1-yl]phenyl]-2-[(1RS)-1-methylpropyl]-2,4-dihydro-3H-1,2,4-triazol- 3-one,
[6]2-butyl-4-[4-[4-[4-[[cis-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazin-1-yl]phenyl]-2,4-dihydro-3H-1,2,4-triazol-3-one,
[7]4-[4-[4-[4-[[cis-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazin-1-yl]phenyl]-2-[[cis-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methyl]-2,4-dihydro-3H-1,2,4-triazol-3-one.

Inject reference solution (b). The test is not valid unless the peak to valley ratio is not less than 2.0, where H_p is the height above the baseline of the peak due to itraconazole impurity F and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to itraconazole.

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to itraconazole impurity B and impurity G, each of, is not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent), the sum of areas of the peaks corresponding to itraconazole impurity C and impurity D is not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent), the area of any other secondary peak is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent) and the sum of areas of all the secondary peaks is not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent). Ignore any peak with an area less than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent).

Other tests. Comply with the tests stated under Capsules.

Assay. Determine by liquid chromatography (2.4.14).

Solvent mixture. A 0.1 volume of *hydrochloric acid* and 50 volumes of the mobile phase.

Test solution. Disperse a quantity of the mixed contents of 20 capsules containing 0.1 g of Itraconazole in 5 ml of the mobile phase and 0.2 ml of *hydrochloric acid*, with the aid of ultrasound and dilute to 100.0 ml with the mobile phase. Dilute 1.0 ml of the solution to 10.0 ml with the mobile phase.

Reference solution. A 0.01 per cent w/v solution of *itraconazole RS* in the solvent mixture.

Chromatographic system as described under Related substances using flow rate of 2 ml per minute.

Inject the reference solution. The test is not valid unless the column efficiency is not less than 2000 theoretical plates, the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{35}H_{38}Cl_2N_8O_4$ in the capsules.

Storage. Store protected from light and moisture, at a temperature not exceeding 30°.