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 strength. 100 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 reference solution (a).

Tests

Dissolution (2.5.2).
Apparatus No. 2 (Paddle),
Medium. 900 ml of 0.5 per cent w/v of *sodium lauryl sulphate* in *water,*
Speed and time. 75 rpm and 60 minutes.

Withdraw a suitable volume of the medium and filter.

Determine by liquid chromatography (2.4.14).

Test solution. Use the filtrate, dilute if necessary, with the dissolution medium.

Reference solution. Dissolve 27.5 mg of *itraconazole IPRS* in 10 ml of *acetonitrile* (60 per cent) and 1 drop of *orthophosphoric acid*, and dilute to 100.0 ml with *acetonitrile* (60 per cent). Dilute a suitable volume of the solution with the dissolution medium to obtain a solution containing 0.0055per cent w/v of *itraconazole.*

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm)(Such as Phenomwnex Prodigy ODS-2),
- column temperature: 40°,
- mobile phase: a mixture of 45 volumes of *0.01 M potassium dihydrogen orthophosphate*, adjusted to pH 3.0 with *orthophosphoric acid* and 55 volumes of *acetonitrile,*
- flow rate: 2 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 15 µl.

Inject the reference solution and the test solution.

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

Q. Not less than 70 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. A 0.2 per cent v/v solution of *hydrochloric acid* in the mobile phase.

Test solution. Disperse a quantity of mixed contents of capsules containing 0.1 g of Itraconazolein 5 ml of the mobile phase and 0.2 ml of *hydrochloric acid*, with the aid of ultrasound. Add 50 ml of the solvent mixture, shake and dilute to 100.0 ml with the mobile phase, filter.

*Reference solution (a).*A 0.02 per cent w/v solutionof *itraconazole IPRS* in the solvent mixture. Dilute 1.0 ml of the solution to 100.0 ml with the solvent mixture.

*Reference solution (b).*A solution containing of 0.1 per cent w/v of *itraconazole IPRS* and 0.0002 per cent w/v of *itraconazole impurity F IPRS* 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 *0.01Mpotassium dihydrogen orthophosphate*, adjusted to pH 3.0 with *orthophosphoric acid* and 48 volumes of *acetonitrile*,
- flow rate: 1.5 ml per minute,
- spectrophotometer set 254nm,
- 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) to identify the peaks due to itraconazole impurity A, B, C and D, E, G and F.

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. Run the chromatogram 3 times the retention time of itraconazole. The area of any peak corresponding to itraconazole impurity B, sum of impurity C and D and impurity G, each of, is not more than 1.5 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 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 5 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 0.5 times 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 0.2 per cent v/v solution of *hydrochloric acid* in 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 and filter. Dilute 1.0 ml of the filtrate solution to 10.0 ml with the mobile phase.

*Reference solution (a).*A 0.01 per cent w/v solution of *itraconazole IPRS* in the solvent mixture.

*Reference solution (b).*A solution containing of 0.1 per cent w/v of *itraconazole IPRS* and 0.0002 per cent w/v of *itraconazole impurity F IPRS* in the solvent mixture.

Use chromatographic systemas described under Related substances using flow rate of 2 ml per minute.

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.

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°.
