Itraconazole Capsules (Supra bioavailable formulation)

Itraconazole Capsules contain Itraconazole not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of itraconazole, $C_{35}H_{38}Cl_2N_8O_4$.

Usual strengths. 50 mg; 65 mg; 100 mg; 130 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).
Apparatus No. 2 (Paddle),
Medium. 900 ml of phosphate buffer solution prepared by dissolving 6.8 g of *potassium dihydrogen phosphate* and 0.92 g of *sodium hydroxide* in 1000 ml of *water*, adjusted to pH 6.8 with *sodium hydroxide or orthophosphoric acid*,
Speed and time. 100 rpm and30 minutes.

Withdraw a suitable volume of the medium and filter.

Determine by liquid chromatography (2.4.14).

Solution A. Dilute 4 ml of *hydrochloride acid* to 1000 ml with *methanol.*

Test solution. Dilute the filtrate with solution A to obtain a solution containing 0.0011 per cent w/v of itraconazole.

Reference solution. A 0.072 per cent w/v solution of *itraconazole IPRS* insolution A. Dilute a suitable volume of the solution to obtain a solution having similar concentration to that of test solution (Note- *Concentration of dissolution medium should be similar in final dilution of the test solution and reference solution).*

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (2.7µm)(Such as Supelco, Acentis Express),
- column temperature: 35º,
- mobile phase: a mixture of 40 volumes of a buffer solution prepared by dissolving 1.36 g of*potassium dihydrogen phosphate* in 1000 ml of *water*, adjusted to pH 3.0 with *orthophosphoric acid* and 60 volumes of *acetonitrile*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 260 nm,
- injection volume: 20 µl.

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 medium.

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

Related substances. Determine by liquid chromatography (2.4.14).

Solution A. A 0.05 per cent v/v solution of *triethyl amine* in *water.*

*Solvent mixture.*Equal volumes of *methanol* and *tetrahydrofuran.*

Test solution. Disperse a quantity of mixed contents of capsules containing 0.5 g of Itraconazole in 15 ml of solution A, sonicate for 15 minutes with intermittent shaking. Add 70 ml of the solvent mixture and further sonicate for 45 minutes with intermittent shaking, dilute to 100.0 ml with the solvent mixture, filter.

*Reference solution (a).*A 0.05 per cent w/v solution of *itraconazole IPRS* in the solvent mixture. Transfer5.0 ml of the solution to 100-ml volumetric flask, add 15 ml of solution A and dilute to volume with the solvent mixture.

*Reference solution (b).*A solution containing of 0.1 per cent w/v of *itraconazole IPRS*and0.0002 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 (3 µm) (Such as Sunniest C18),
- column temperature: 35º,
- mobile phase: A. a buffer solution prepared by dissolving 5.8 g of *monobasic ammonium phosphate* in 1000 ml of *water*, adjusted to pH 2.0 with *orthophosphoric acid*,
  B. a mixture of 90 volumes of *acetonitrile* and 10 volumes of *tetrahydrofuran*,
- a gradient programme using the conditions given below,
- flow rate: 1.2 ml per minute,
- spectrophotometer set 225nm,
- injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	60	40
15	60	40
30	50	50
40	45	55
45	20	80
50	60	40
60	60	40

Name	Relative retention time	Correction factor
Itraconazole impurity A[1]	0.21	---
Itraconazole impurity B[2]	0.60	1.03
Itraconazole impurity C[3]and D[4]	0.76	0.98
Itraconazole impurity E[5]	0.85	1.10
Itraconazole (Retention time: about 23 minutes)	1.0	---
Itraconazole impurity F[6]	1.06	1.01
Itraconazole impurity G[7]	1.32	1.14

[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 (a) and (b). 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, the relative standard deviation for replicate injections is not more than 10.0 per cent in the chromatogram obtained with reference solution (a) and 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 in the chromatogram obtained with reference solution (b).

Inject reference solution (a) and the test solution. Run the chromatogram 3 times the retention time of itraconazole peak. The area of any peak corresponding to itraconazole impurity B, the sum of the area of the peaks corresponding to itraconazole impurity C and D and itraconazole impurity G, each of, is not more than 0.6 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 0.4 times 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 twice 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 0.2timesthe 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).

Solution A. 0.01 M sodium hydroxide solution.

*Solution B.*Dilute 4 ml of *hydrochloride acid* to 1000 ml with *methanol*.

Solvent mixture.20 volumes of solution A and 80 volumes of solution B.

Test solution. Transfer an accurately weighed quantity of the mixed contents of 20 capsules containing 0.2g of Itraconazole to a 100-ml volumetric flask, add 20 ml of solution A, and stir for 30 minutes with the aid of magnetic stirrer, add 70 ml of solution B, again stir for 15 minutes, and dilute to volume with solution B. Centrifuge a portion of the solution at 4000 rpm for 10 minutes. Dilute 5.0 ml of the supernatant to 100.0 ml with the solvent mixture.

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

Chromatographic system as described under Dissolution with injection volume: 10µl.

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°.