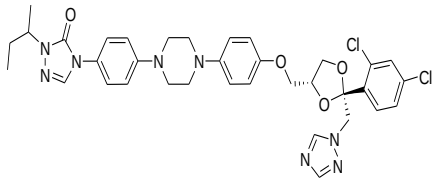
Itraconazole



$C_{35}H_{38}Cl_2N_8O_4$ Mol. Wt. 706.0

Itraconazole is 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-[(1*RS*)-1-methylpropyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one.

Itraconazole contains not less than 99.0 per cent and not more than 101.0 per cent of $C_{35}H_{38}Cl_2N_8O_4$, calculated on the dried basis.

Category. Antifungal

Description. A white or almost white powder.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *itraconazole IPRS* or with the reference spectrum of itraconazole.

B. 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

Appearance of solution. A 10.0 per cent w/v solution in *dichloromethane* is clear (2.4.1) and not more intensely coloured than reference solution RS6 or BS6 (2.4.1).

Related substances. Determine by liquid chromatography (2.4.14).

NOTE — Prepare the solutions immediately before use.

Test solution. Dissolve 0.1 g of the substance under examination in *methanolic hydrochloric acid* and dilute to 10.0 ml with *methanolic hydrochloric acid*.

Reference solution (a). A 0.001 per cent w/v solution of *itraconazole IPRS* in *methanolic hydrochloric acid*.

Reference solution (b). Dissolve 10 mg of *itraconazole system suitability IPRS* (containing impurities B, C, D, E, F and G) in 1.0 ml of *methanolic hydrochloric acid*.

Chromatographic system

- a stainless steel column 10 cm x 4.6 mm, packed with base deactivated end-capped octadecylsilane bonded to porous silica (3 µm),
- mobile phase: A. a 2.72 per cent w/v solution of *tetrabutylammonium hydrogen sulphate* in *water*,
  B. *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 225 nm,
- injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	80	20
2	80	20
22	50	50
27	50	50
30	80	20

Name	Relative retention time
Itraconazole impurity B[1]	0.7
Itraconazole impurity C[2] and D[3]	0.8
Itraconazole impurity E[4]	0.9
Itraconazole (retention time: about 14 minutes)	1.0
Itraconazole impurity F[5]	1.05
Itraconazole impurity G[6]	1.3

[1]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,
[2]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,
[3]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,
[4]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,
[5]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,
[6]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 1.5, 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 area of any peak corresponding to itraconazole impurity E is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 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 the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent) and the sum of areas of all the secondary peaks is not more than 8 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.8 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) (0.05 per cent).

Heavy metals (2.3.13). 1.0 g complies with the limit test for heavy metals, method B (20 ppm).

Sulphated ash (2.3.18). Not more than 0.1 per cent.

Loss on drying (2.4.19). Not more than 0.5 per cent, determined on 1g by drying in an oven at 105° for 4 hours.

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 0.1 g of substance under examination in 50 ml of *methanolic hydrochloric acid* and dilute to 100.0 ml with the same solvent. Dilute 1.0 ml of the solution to 10.0 ml with *methanolic hydrochloric acid.*

Reference solution. A 0.01 per cent w/v solution of *itraconazole IPRS* in *methanolic hydrochloric acid*.

Use Chromatographic system as described under Related substances.

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 $C_{35}H_{38}Cl_2N_8O_4$.

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

Solubility. Freely soluble in *dichloromethane*; very slightly soluble in *ethanol (95 per cent)* and practically insoluble in *water*.