Itraconazole Oral Solution

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Manufacturers, regulatory authorities, health authorities, researchers, and other stakeholders are invited to provide their feedback and comments on this draft proposal. Manufacturers are also invited to submit samples of their products to the IPC to ensure that the proposed monograph adequately controls the quality of the product(s) they manufacture. Comments and samples received after the last date will not be considered by the IPC before finalizing the monograph.

Please send any comments you may have on this draft document to lab.ipc@gov.in, with a copy to Dr. Gaurav Pratap Singh (email: gpsingh.ipc@gov.in) before the last date for comments.

Document History and Schedule for the Adoption Process

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Itraconazole Oral Solution

Itraconazole Oral Solution contains 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. 10 mg per ml.

Identification

A. Determine by thin-layer chromatography (2.4.17), coating the plate with silica gel $60F_{254}$.

Mobile phase. A mixture of 20 volumes of a solution containing 0.015 per cent w/v of *ammonium acetate* and 0.0003 per cent v/v of *glacial acetic acid* in *water*, 40 volumes of *1,4-dioxan* and 40 volumes of *methanol*.

Test solution. Shake a volume of oral solution containing 10 mg of Itraconazole with 5 ml of *dichloromethane.* Allow the layers to separate and use the lower layer.

Reference solution (a). A 0.2 per cent w/v solution of *itraconazole IPRS* in *dichloromethane*.

Reference solution (b). A solution containing 0.2 per cent w/v each of, *itraconazole IPRS* and *fluconazole IPRS* in *dichloromethane*.

Apply to the plate 5 µl each of the reference solution and the test solution. Allow the mobile phase to rise 10 cm. Dry the plate under air and examine the plate under ultraviolet light at 254 nm. The principal spot in the chromatogram obtained with the test solution corresponds to the spot in the chromatogram obtained with reference solution (a). The test is not valid unless the chromatogram obtained with reference solution (b) shows two clearly separated spots.

B. In the Assay, the principal peak in the chromatogram obtained with test solution (b) corresponds to the peak in the chromatogram obtained with reference solution (a).

Tests

Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. 0.2 volumes of *hydrochloric acid* and 100 volumes of the mobile phase.

Test solution (a). Shake a volume of oral solution containing 0.1 g of Itraconazole with 25 ml of the mobile phase, add 0.2 ml of *hydrochloric acid* and dilute to 100.0 ml with the mobile phase.

Test solution (b). Dilute 5.0 ml of test solution (a) to 50.0 ml with the solvent mixture

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

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 50.0 ml with the solvent mixture

Reference solution (c). A solution containing 1.0 per cent w/v solution of *itraconazole IPRS* and 0.001 per cent w/v of *itraconazole impurity F IPRS* in 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: 40°,
- mobile phase: a mixture of 52 volumes of *0.01 M potassium dihydrogen orthophosphate*, adjusted to pH 3.0 with *dilute orthophosphoric acid* and 48 volumes of *acetonitrile*,
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 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]+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-l-yl]phenyl]-2-[(1*RS*)-1-methylpropyl]-2,4-dihydro-3*H*-l,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*-l,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-(1*H*-1,2,4-triazol-1-ylmethyl)-I,3-dioxolan-4-yl)methoxy]phenyl]piperazin-l-yl]phenyl)-2-(1-methylethyl)-2,4-dihydro-3*H*-l,2,4-triazol-3-one,
[5]4-[4-[4-[4-[[*trans*-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-3H-1,2,4-triazol-3-one,
[6]2-butyl-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]-2,4-dihydro-3*H*-1,2,4-triazol-3-one,
[7]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-[[*cis*-2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one.

Inject reference solution (c). The test is not valid unless the peak-to-valley ratio (Hp/Hv) is not less than 2.0, where Hp is the height above the baseline of the peak due to itraconazole impurity F and Hv 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 (b) and test solution (a). Run the chromatogram 3 times the retention time of the principal peak. In the chromatogram obtained with test solution (a), the area of any peak corresponding to itraconazole impurity B, itraconazole impurity C+D and itraconazole impurity G, each of, is not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (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 (b) (0.2 per cent) and the sum of areas of all the secondary peaks is not more than 10 times of the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 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 (b) (0.1 per cent).

Other tests. Comply with the tests stated under Oral Liquids.

Assay. Determine by liquid chromatography (2.4.14), as described under Related substances with the following modifications.

– flow rate: 2 ml per minute,

Inject reference solution (c). The test is not valid unless the peak-to-valley ratio (Hp/Hv) is not less than 2.0, where Hp is the height above the baseline of the peak due to itraconazole impurity F and Hv 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 test solution (b).

Determine the weight per ml of the oral solution (2.4.29) and calculate the content of $C_{35}H_{38}Cl_2N_8O_4$ in the solution.

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