Ketoconazole Shampoo

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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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Ketoconazole Shampoo

Ketoconazole Shampoo contains not less than 90.0 per cent and not more than 110.0 per cent of stated amount of Ketoconazole, $C_{26}H_{28}Cl_2N_4O_4$. ~~It contains ketoconazole~~ in a suitable base~~is~~.

Usual strengths. 1 per cent w/v; 2 per cent w/v.

Identification

A. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel*. (Such as merck silica gel 60 HPTLC plates).

Mobile phase. A mixture of 20 volumes of *ammonium acetate solution*, 40 volumes of a *dioxan*, 40 volumes of *methanol*.

Test solution. Mix a quantity of the shampoo containing 30 mg of Ketoconazole, in ~~16~~ 14 ml of *methanol*, with the aid of ultrasound, add 2 ml of *wate*r and dilute to 20.0 ml with *methanol.*

Reference solution (a). A 0.15 per cent w/v solution of *ketoconazole IPRS* in *methanol*.

Reference solution (b). A solution containing 0.15 per cent w/v each of *ketoconazole IPRS* and *econazole nitrate IPRS* in *methanol.*

Apply to the plate 20 µl of each solution. Allow the mobile phase to rise 15 cm. Dry the plate in air and expose to *iodine* vapour until spots appear and examine in daylight. The test is not valid unless the chromatogram obtained with reference solution (b) shows two clearly separated spots. The principal spot in the chromatogram obtained with the test solution corresponds to the principal spot in the chromatogram obtained with the reference solution (a).

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 (a).

Tests

Related substances. Determine by liquid chromatography (2.4.14).

NOTE — Protect the solutions from light, using low-actinic glassware.

Test solution. Shake a quantity of the shampoo containing 50 mg of Ketoconazole with 50.0 ml of *methanol* for 15 minutes, add 15 ml of mobile phase A, shake for another 15 minutes, allow to cool and dilute to 100.0 ml with *methanol.*

Reference solution (a). A 0.00025 per cent w/v solution of *ketoconazole IPRS* in mobile phase A.

Reference solution (b). Dilute 1.0 ml of the reference solution (a) to 5.0 ml with mobile phase A.

Reference solution (c). A solution containing 0.05 per cent w/v of *ketoconazole IPRS*, 0.00035 per cent w/v of *ketoconazole impurity D IPRS* and 0.00025 per cent w/v, each of *ketoconazole impurity 1 IPRS* and *ketoconazole impurity 2 IPRS* in mobile phase A.

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, packed with end-capped polar-embedded octadecylsilane bonded to amorphous organosilica polymer (5 µm), (Such as Waters XBridge).
- column temperature: 35º,
- mobile phase: A. a buffer solution prepared by dissolving 1.42 g of anhydrous *disodium hydrogen orthophosphate* and 3.1 g of *sodium dihydrogen orthophosphate* in 1000 ml of *water*.
  B. *acetonitrile.*
  C. *propan-2-ol*.
- flow rate: 0.6 ml per minute,
- spectrophotometer set at 230 nm,
- injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)	Mobile phase C (per cent v/v)
0	55	35	10

3	55	35	10
13	37	53	10
18	37	53	10
20	55	35	10
23	55	35	10

Name	Relative retention time	correction factor
Ketoconazole Impurity 1[1]	-	-
Ketoconazole Impurity 2[2]	-	-
Ketoconazole Impurity D[3]	0.78	1.5
Ketoconazole	1.0	-

[1] rac-4-acetyl-1-[4-({(2R,4S)-2-(2,4-dichlorophenyl)-2-[(1H-imidazol-1-yl)methyl]-1,3-dioxolan-4-yl}methoxy)phenyl]piperazine N1-oxide.
[2] rac-{(2R,4S)-2-(2,4-dichlorophenyl)-2-[(1H-imidazol-1-yl)methyl]-1,3-dioxolan-4-yl}methanol.
[3] 1-[4-[[(2*RS*,4*SR*)-2-(2,4-dichlorophenyl)-2-[(1*H*-imidazol-1-yl)methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine,

Inject reference solution (c) to identify any peaks due to ketoconazole impurity 1, 2 and D.
Inject reference solution (c). The test is not valid unless the resolution between the peaks due to ketoconazole impurity 1 and ketoconazole impurity D is not less than 3.0.

Inject reference solution (a), (b) and the test solution. In the chromatogram obtained with the test solution, the area of the any peak corresponding to ketoconazole impurities D is not more than 1.4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.7 per cent), the area of the any peak corresponding to ketoconazole impurity 2 is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent), the area of any other secondary peak 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) and the sum of areas of all the secondary peaks is not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (2.0 per cent). Ignore any peak with an area less than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent).

Other tests. Complies with the tests stated under liquid for cutaneous application.

Assay. Determine by liquid chromatography (2.4.14).

NOTE — Protect the solutions from light, using low-actinic glassware.

Test solution. Weigh a quantity of the shampoo containing 50 mg of ketoconazole, add 50.0 ml of *methanol*, shake for 15 minutes, and add 15 ml of mobile phase A, shake for another 15 minutes, allow to cool and dilute to 100.0 ml with *methanol*. Dilute 5.0 ml of the solution to 50.0 ml with mobile phase A.

Reference solution (a). A 0.05 per cent w/v solution of *ketoconazole IPRS* in *methanol*. Dilute 1.0 ml of the solution to 10.0 ml with mobile phase A.

Reference solution (b). A solution containing 0.05 per cent w/v *ketoconazole IPRS*, 0.00035 per cent w/v of *ketoconazole impurity D IPRS* and 0.00025 per cent w/v, each of *ketoconazole impurity 1 IPRS* and *ketoconazole impurity 2 IPRS* in mobile phase A.

Use chromatographic system as described under Related substances.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to ketoconazole impurity 1 and ketoconazole impurity D is not less than 3.0.

Inject reference solution (a) and the test solution.

Determine the weight per ml of the shampoo and calculate the content of $C_{26}H_{28}Cl_2N_4O_4$ in the shampoo.

Storage. Store protected from light, and in a temper evident container.