Edition: BP 2025 (Ph. Eur. 11.6 update)

Ketoconazole Shampoo

General Notices

Action and use

Antifungal.

DEFINITION

Ketoconazole Shampoo contains Ketoconazole in a suitable basis.

The shampoo complies with the requirements stated under Liquids for Cutaneous Application and with the following requirements.

Content of ketoconazole, $C_{26}H_{28}Cl_2N_4O_4$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

In the Assay, record the UV spectrum of the principal peak in the chromatograms obtained with solutions (1) and (2) with a diode array detector in the range 220 to 400 nm.

The UV spectrum of the principal peak in the chromatogram obtained with solution (1) is concordant with that of the peak in the chromatogram obtained with solution (2);

the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in low-actinic glassware. Store the solutions at 4°.

Solution A: 15 volumes of mobile phase A and 85 volumes of *methanol*.

(1) Shake a quantity of the shampoo containing 50 mg of Ketoconazole with 50 mL of *methanol*, add 15 mL of mobile phase A, allow to cool and dilute to 100 mL with *methanol*.
(2) Dilute 1 volume of solution (1) to 100 volumes with solution A.
(3) 0.03% w/v of *ketoconazole impurity standard BPCRS* in solution A.
(4) Dilute 1 volume of solution (2) to 10 volumes with solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 3.0 mm) packed with *end-capped phenylsilyl silica gel for chromatography* (5 µm) (Waters XBridge BEH Phenyl is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 0.6 mL per minute.
(d) Use a column temperature of 45°.
(e) Use an autosampler temperature of 4°.
(f) Use a detection wavelength of 230 nm.
(g) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A Dissolve 1.42 g of *anhydrous disodium hydrogen orthophosphate* and 3.1 g of *anhydrous sodium dihydrogen orthophosphate* in 1000 mL of *water*.

Mobile phase B *acetonitrile*.

Mobile phase C *propan-2-ol R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Mobile phase C (% v/v)	Comment
0-5	70	24	6	isocratic
5-35	70→30	24→64	6	linear gradient
35-40	30	64	6	isocratic
40-45	30→70	64→24	6	linear gradient
45-55	70	24	6	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to ketoconazole (retention time about 17 minutes) are: impurity 2, about 0.5; impurity 1, about 0.6; impurity D, about 0.7; impurity 3, about 0.78.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to impurity 2 and impurity 1 is at least 5.0;

the *signal-to-noise ratio* of the peak due to impurity 2 is at least 40.

LIMITS

Identify any peak in solution (1) corresponding to impurity 2 using the chromatogram obtained with solution (3) and the chromatogram supplied with *ketoconazole impurity standard BPCRS* and multiply the area of this peak by a correction factor of 1.5.

In the chromatogram obtained with solution (1):

the area of any peak due to impurity D is not greater than 0.7 times the area of the principal peak in the chromatogram obtained with solution (2) (0.7%);

the area of any peak due to impurity 2 is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak due to impurity 3 is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the sum of the areas of the *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in low-actinic glassware. Store the solutions at 4°.

Solution A: 15 volumes of mobile phase A and 85 volumes of *methanol*.

(1) Shake a weighed quantity of the shampoo containing 50 mg of Ketoconazole with 50 mL of *methanol*, add 15 mL of mobile phase A, allow to cool and dilute to 100 mL with *methanol*. Dilute 1 volume of the resulting solution to 10 volumes solution A.
(2) Dissolve 50 mg of *ketoconazole BPCRS* in 100 mL of *methanol* and dilute 1 volume of the resulting solution to 10 volumes with solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 3.0 mm) packed with *end-capped phenylsilyl silica gel for chromatography* (5 µm) (Waters XBridge BEH Phenyl is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 0.6 mL per minute.
(d) Use a column temperature of 35°.
(e) Use an autosampler temperature of 4°.
(f) Use a detection wavelength of 230 nm.
(g) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A Dissolve 1.42 g of *anhydrous disodium hydrogen orthophosphate* and 3.1 g of *anhydrous sodium dihydrogen orthophosphate* in 1000 mL of *water*.

Mobile phase B *acetonitrile*.

Mobile phase C *propan-2-ol R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Mobile phase C (% v/v)	Comment
0-3	55	35	10	isocratic
3-13	55→37	35→53	10	linear gradient
13-18	37	53	10	isocratic
18-20	37→55	53→35	10	linear gradient
20-23	55	35	10	re-equilibration

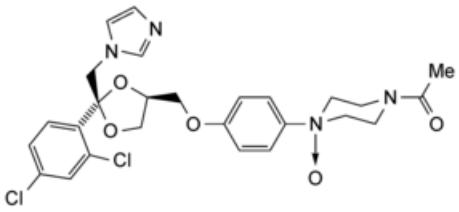
DETERMINATION OF CONTENT

Calculate the content of ketoconazole, $C_{26}H_{28}Cl_2N_4O_4$, in the shampoo from the chromatograms obtained and using the declared content of $C_{26}H_{28}Cl_2N_4O_4$ in *ketoconazole BPCRS*.

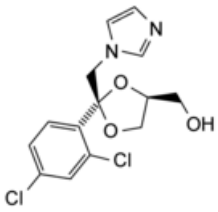
IMPURITIES

The impurities limited by the requirements of this monograph include impurity D listed under Ketoconazole and the following:

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



2. *rac*-{(2*R*,4*S*)-2-(2,4-dichlorophenyl)-2-[(1*H*-imidazol-1-yl)methyl]-1,3-dioxolan-4-yl}methanol.



3. Unknown structure