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

Ketoconazole Cream

General Notices

Action and use

Antifungal.

DEFINITION

Ketoconazole Cream contains Ketoconazole in a suitable basis.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

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

95.0 to 105.0% 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: 2 volumes of *water* and 98 volumes of *methanol*.

(1) Mix with the aid of ultrasound a quantity of the cream containing 30 mg of Ketoconazole with 50 mL of *methanol*, add 2 mL of *water*, allow to cool and dilute to 100 mL with *methanol*. Cool the solution in an ice-bath for 1 hour and filter.
(2) Dilute 1 volume of solution (1) to 500 volumes with solution A.
(3) 0.03% w/v of *ketoconazole impurity standard BPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer* (5 µm) (Waters XBridge BEH C18 is suitable).

(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.2 mL per minute.
(d) Use a column temperature of 40°.
(e) Use an autosampler temperature of 4°.
(f) Use a detection wavelength of 230 nm.
(g) Inject 25 µL of each solution.

MOBILE PHASE

Mobile phase A 25 volumes of *acetonitrile* and 75 volumes of 0.05M *ammonium acetate*, adjusted to pH 6.0 with *glacial acetic acid*.

Mobile phase B 20 volumes of 0.05M *ammonium acetate*, adjusted to pH 6.0 with *glacial acetic acid* and 80 volumes of *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	85	15	isocratic
5-10	85→76	15→24	linear gradient
10-20	76→52	24→48	linear gradient
20-21	52→0	48→100	linear gradient
21-22	0	100	isocratic
22-23	0→85	100→15	linear gradient
23-28	85	15	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 0.35; impurity 1, about 0.40; impurity D, about 0.6.

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 1.5;

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 1 is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak due to impurity D is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (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: 2 volumes of *water* and 98 volumes of *methanol*.

(1) To a weighed quantity of the cream containing 30 mg of Ketoconazole add 50 mL of *methanol* and shake for 45 minutes, mix with the aid of ultrasound for 10 minutes, add 2 mL of *water,* allow to cool and dilute to 100 mL with *methanol*. Cool the solution at 5° for 1 hour, filter and dilute 1 volume of the resulting solution to 10 volumes with solution A.
(2) 0.003% w/v of *ketoconazole BPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

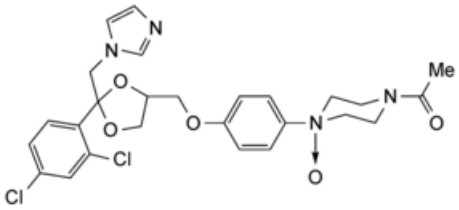
DETERMINATION OF CONTENT

Calculate the content of ketoconazole, $C_{26}H_{28}Cl_2N_4O_4$, in the cream 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.