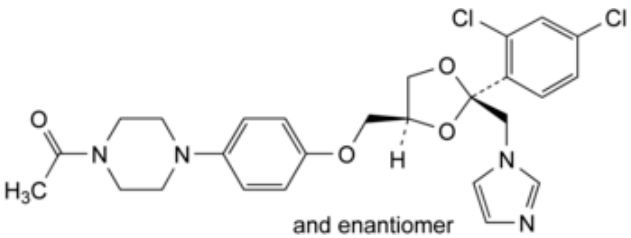
Edition: BP 2025 (Ph. Eur. 11.6 update)

Ketoconazole

General Notices

(Ph. Eur. monograph 0921)



$C_{26}H_{28}Cl_2N_4O_4$ 531.4 *65277-42-1*

Action and use

Antifungal.

Preparations

Ketoconazole Cream

Ketoconazole Shampoo

Ph Eur

DEFINITION

1-[(5^2*RS*,5^4*SR*)-5^2-(2,4-Dichlorophenyl)-3-oxa-1(1)-piperazina-7(1)-imidazola-5(2,4)-[1,3]dioxolana-2(1,4)-benzenaheptaphan-1^1-yl]ethan-1-one.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, freely soluble in methylene chloride, soluble in methanol, sparingly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A.

Second identification: B.

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *ketoconazole CRS*.

B. Melting point (*2.2.14*).

Determination A Determine the melting point of the substance to be examined.

Result A 148 °C to 152 °C.

Determination B Mix equal parts of the substance to be examined and *ketoconazole CRS*, and determine the melting point of the mixture.

Result B The absolute difference between the melting point of the mixture and the value obtained in determination A is not greater than 2 °C.

TESTS

Solution S

Dissolve 1.0 g in *methylene chloride R* and dilute to 10.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution BY_4 (*2.2.2, Method II*).

Optical rotation (*2.2.7*)

-0.10° to + 0.10°, determined on solution S.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.100 g of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve the contents of a vial of *ketoconazole impurity mixture CRS* (impurities C and D) in 1 mL of *methanol R*.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase:

— *mobile phase A*: *acetonitrile for chromatography R*, 3.4 g/L solution of *tetrabutylammonium hydrogen sulfate R* (5:95 *V/V*);

— *mobile phase B*: *acetonitrile for chromatography R*, 3.4 g/L solution of *tetrabutylammonium hydrogen sulfate R* (50:50 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	100 → 0	0 → 100
10 - 15	0	100

Flow rate 2 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 10 µL; inject *methanol R* as a blank.

Identification of impurities Use the chromatogram supplied with *ketoconazole impurity mixture CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities C and D.

Relative retention With reference to ketoconazole (retention time = about 6 min): impurity D = about 0.8; impurity C = about 0.9.

System suitability Reference solution (a):

— *resolution*: minimum 1.5 between the peaks due to impurities D and C.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity D by 1.4;

— for each impurity, use the concentration of ketoconazole in reference solution (b).

Limits:

— *impurity D*: maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 70 mL of a mixture of 1 volume of *anhydrous acetic acid R* and 7 volumes of *methyl ethyl ketone R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 26.57 mg of $C_{26}H_{28}Cl_2N_4O_4$.

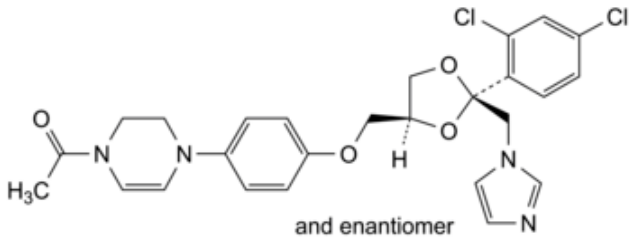
STORAGE

Protected from light.

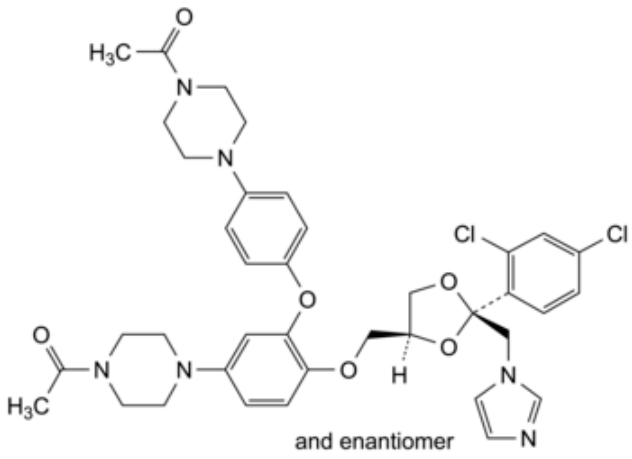
IMPURITIES

Specified impurities D.

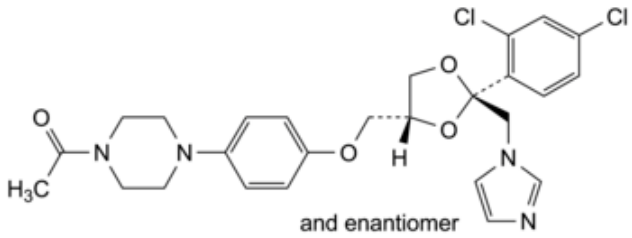
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, E.



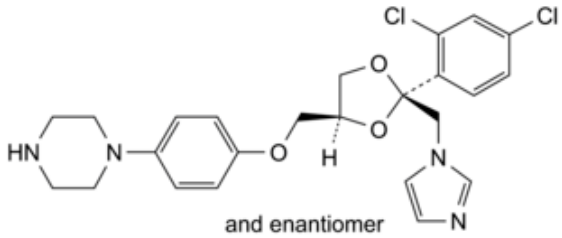
A. 1-[(5[2]*RS*,5[4]*SR*)-5[2]-(2,4-dichlorophenyl)-1[2],1[3]-dihydro-1[1]*H*-3-oxa-1(1)-pyrazina-7(1)-imidazola-5(2,4)-[1,3]dioxolana-2(1,4)-benzenaheptaphan-1[1]-yl]ethan-1-one,



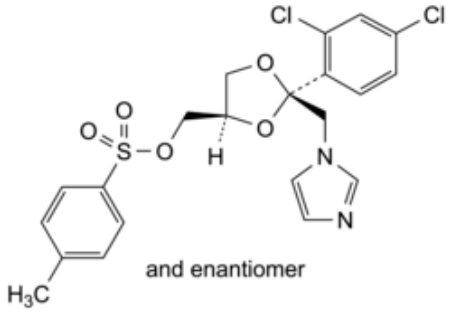
B. 1-[4-[(7[2]*RS*,7[4]*SR*)-1[1]-acetyl-7[2]-(2,4-dichlorophenyl)-3,5-dioxa-1(1)-piperazina-9(1)-imidazola-7(2,4)-[1,3]dioxolana-2(1,4),4(1,2)-dibenzenanonaphan-4[5]-yl]piperazin-1-yl]ethan-1-one,



C. 1-[(5^2*RS*,5^4*RS*)-5^2-(2,4-dichlorophenyl)-3-oxa-1(1)-piperazina-7(1)-imidazola-5(2,4)-[1,3]dioxolana-2(1,4)-benzenaheptaphan-1^1-yl]ethan-1-one,



D. (5^2*RS*,5^4*SR*)-5^2-(2,4-dichlorophenyl)-3-oxa-1(1)-piperazina-7(1)-imidazola-5(2,4)-[1,3]dioxolana-2(1,4)-benzenaheptaphane,



E. [(2*RS*,4*SR*)-2-(2,4-dichlorophenyl)-2-[(1*H*-imidazol-1-yl)methyl]-1,3-dioxolan-4-yl]methyl 4-methylbenzene-1-sulfonate.

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