Relative retention with reference to ketobemidone (retention time = about 10 min): impurity A = about 0.4; impurity B = about 0.6; impurity C = about 0.7; impurity D = about 3.5; impurity E = about 4.2.

System suitability: reference solution (a):

– *resolution*: minimum 4.0 between the peaks due to impurity B and impurity C.

Limits:

– *impurities A, B, C, D*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent),

– *any other impurity*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent),

– *total*: not more than 3.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.7 per cent),

– *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (*2.5.12*): maximum 1.0 per cent, determined on 0.50 g.

Sulphated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

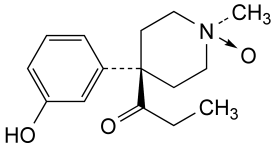
Dissolve 0.200 g in a mixture of 5.0 ml of *0.01 M hydrochloric acid* and 50 ml of *alcohol R*. Carry out a potentiometric titration (*2.2.20*) using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 ml of *0.1 M sodium hydroxide* is equivalent to 28.38 mg of $C_{15}H_{22}ClNO_2$.

IMPURITIES

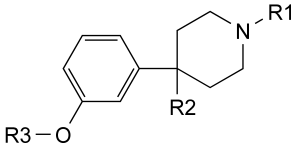
Specified impurities: *A, B, C, D.*

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*): *E.*



and *trans* isomer

A. 1-[4-(3-hydroxyphenyl)-1-methyl-1-oxidopiperidin-4-yl]propan-1-one (*cis* and *trans* isomers),



B. R1 = CH_3, R2 = CO-CH_3, R3 = H: 1-[4-(3-hydroxyphenyl)-1-methylpiperidin-4-yl]ethanone,

C. R1 = R3 = H, R2 = CO-CH_2-CH_3: 1-[4-(3-hydroxyphenyl)piperidin-4-yl]propan-1-one,

D. R1 = R3 = CH_3, R2 = CO-CH_2-CH_3: 1-[4-(3-methoxyphenyl)-1-methylpiperidin-4-yl]propan-1-one,

E. R1 = CH_3, R2 = CN, R3 = H: 4-(3-hydroxyphenyl)-1-methylpiperidin-4-carbonitrile.

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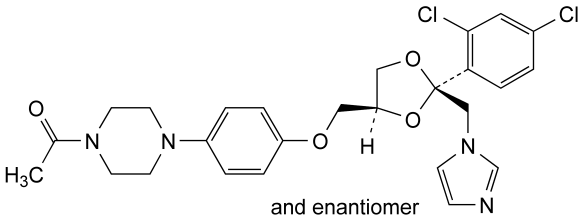
corrected 6.0

KETOCONAZOLE

Ketoconazolum



and enantiomer

$C_{26}H_{28}Cl_2N_4O_4$ M_r 531.4
[65277-42-1]

DEFINITION

1-Acetyl-4-[4-[[(2*RS*,4*SR*)-2-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-ylmethyl)1,3-dioxolan-4-yl]methoxy]phenyl]-piperazine.

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: B.

Second identification: A, C, D.

A. Melting point (*2.2.14*): 148 °C to 152 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).

Preparation: discs.

Comparison: *ketoconazole CRS*.

C. Thin-layer chromatography (*2.2.27*).

Test solution. Dissolve 30 mg of the substance to be examined in the mobile phase and dilute to 5 ml with the mobile phase.

Reference solution (a). Dissolve 30 mg of *ketoconazole CRS* in the mobile phase and dilute to 5 ml with the mobile phase.

Reference solution (b). Dissolve 30 mg of *ketoconazole CRS* and 30 mg of *econazole nitrate CRS* in the mobile phase, then dilute to 5 ml with the mobile phase.

Plate: *TLC octadecylsilyl silica gel plate R.*

Mobile phase: *ammonium acetate solution R, dioxan R, methanol R* (20:40:40 *V/V/V*).

Application: 5 µl.

Development: over a path of 15 cm.

Drying: in a current of warm air for 15 min.

Detection: expose to iodine vapour until the spots appear and examine in daylight.

System suitability: reference solution (b):

– the chromatogram shows 2 clearly separated spots.

Results: the principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

D. To about 30 mg in a porcelain crucible add 0.3 g of *anhydrous sodium carbonate R*. Heat over an open flame for 10 min. Allow to cool. Take up the residue with 5 ml of *dilute nitric acid R* and filter. To 1 ml of the filtrate add 1 ml of *water R*. The solution gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S. Dissolve 1.0 g in *methylene chloride R* and dilute to 10 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 2.5 mg of *ketoconazole CRS* and 2.5 mg of *loperamide hydrochloride CRS* in *methanol R*, then dilute to 50.0 ml with the same solvent.

Reference solution (b). Dilute 5.0 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*: *octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase:

– *mobile phase A*: *acetonitrile R1*, 3.4 g/l solution of *tetrabutylammonium hydrogen sulphate R* (5:95 *V/V*);

– *mobile phase B*: *acetonitrile R1*, 3.4 g/l solution of *tetrabutylammonium hydrogen sulphate 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.

Equilibration: with *acetonitrile R* for at least 30 min and then with mobile phase A for at least 5 min.

Injection: 10 µl; inject *methanol R* as a blank.

Retention time: ketoconazole = about 6 min; loperamide = about 8 min.

System suitability: reference solution (a):

– *resolution*: minimum 15 between the peaks due to ketoconazole and loperamide; if necessary, adjust the final concentration of acetonitrile in the mobile phase or adjust the time programme for the linear gradient elution.

Limits:

– *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

– *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Heavy metals (*2.4.8*): maximum 20 ppm.

1.0 g complies with test D. Prepare the reference solution using 2 ml of *lead standard solution (10 ppm Pb) R*.

Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulphated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

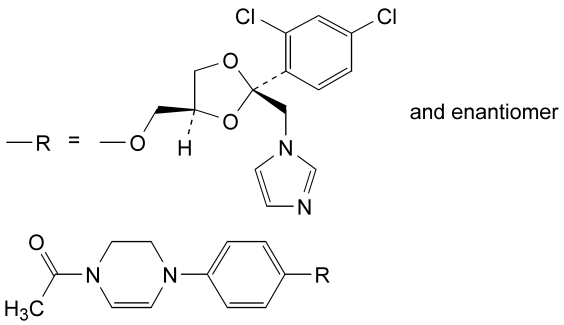
Dissolve 0.200 g in 70 ml of a mixture of 1 volume of *anhydrous acetic acid R* and 7 volumes of *methyl ethyl ketone R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

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

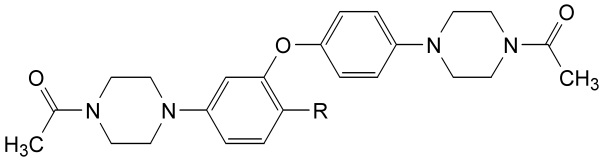
STORAGE

Protected from light.

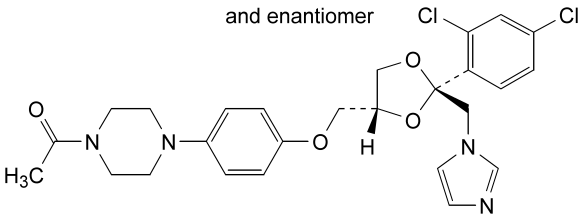
IMPURITIES



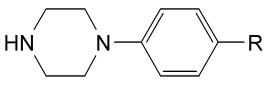
A. 1-acetyl-4-[4-[[(2*RS*,4*SR*)-2-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]1,2,3,4-tetrahydropyrazine,



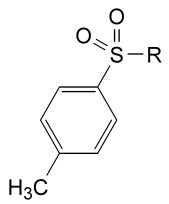
B. 1-acetyl-4-[4-[[(2*RS*,4*SR*)-2-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]-3-[4-(4-acetylpiperazin-1-yl)phenoxy]phenyl]piperazine,



C. 1-acetyl-4-[4-[[(2*RS*,4*RS*)-2-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine,



D. 1-[4-[[(2*RS*,4*SR*)-2-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine,



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

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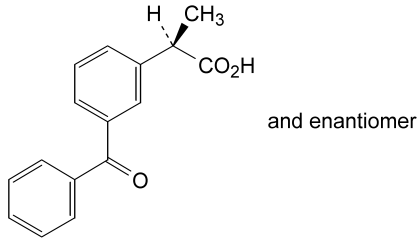
KETOPROFEN

Ketoprofenum



$C_{16}H_{14}O_3$ M_r 254.3
[22071-15-4]

DEFINITION

(2*RS*)-2-(3-Benzoylphenyl)propanoic acid.

Content: 99.0 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: practically insoluble in water, freely soluble in acetone, in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

First identification: C.

Second identification: A, B, D.

A. Melting point (*2.2.14*): 94 °C to 97 °C.

B. Ultraviolet and visible absorption spectrophotometry (*2.2.25*).

Test solution. Dissolve 50.0 mg in *ethanol (96 per cent) R* and dilute to 100.0 ml with the same solvent. Dilute 1.0 ml of this solution to 50.0 ml with *ethanol (96 per cent) R*.

Spectral range: 230-350 nm.

Absorption maximum: at 255 nm.

Specific absorbance at the absorption maximum: 615 to 680.

C. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *ketoprofen CRS*.

D. Thin-layer chromatography (*2.2.27*).

Test solution. Dissolve 10 mg of the substance to be examined in *acetone R* and dilute to 10 ml with the same solvent.

Reference solution (a). Dissolve 10 mg of *ketoprofen CRS* in *acetone R* and dilute to 10 ml with the same solvent.

Reference solution (b). Dissolve 10 mg of *indometacin CRS* in *acetone R* and dilute to 10 ml with the same solvent. To 1 ml of this solution add 1 ml of reference solution (a).

Plate: *TLC silica gel GF_{254} plate R.*

Mobile phase: *glacial acetic acid R, methylene chloride R, acetone R* (1:49:50 *V/V/V*).

Application: 10 µl.

Development: over a path of 15 cm.

Drying: in air.

Detection: examine in ultraviolet light at 254 nm.

System suitability: reference solution (b):

– the chromatogram shows 2 clearly separated principal spots.

Results: the principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in obtained with reference solution (a).

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

Dissolve 1.0 g in *acetone R* and dilute to 10 ml with the same solvent.

Related substances. Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution. Dissolve 20.0 mg of the substance to be examined in the mobile phase and dilute to 20.0 ml with the mobile phase.

Reference solution (a). Dilute 1.0 ml of the test solution to 50.0 ml with the mobile phase. Dilute 1.0 ml of this solution to 10.0 ml with the mobile phase.

Reference solution (b). Dissolve 5.0 mg of *ketoprofen impurity A CRS* in the mobile phase and dilute to 50.0 ml with the mobile phase. Dilute 1.0 ml of this solution to 50.0 ml with the mobile phase.

Reference solution (c). Dissolve 5.0 mg of *ketoprofen impurity C CRS* in the mobile phase and dilute to 50.0 ml with the mobile phase. Dilute 1.0 ml of this solution to 50.0 ml with the mobile phase.

Reference solution (d). Dilute 1.0 ml of the test solution to 100.0 ml with the mobile phase. To 1.0 ml of this solution add 1.0 ml of reference solution (b).

Column:

– *size*: *l* = 0.15 m, Ø = 4.6 mm;

– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm) with a specific surface area of 350 m^2/g and a pore size of 10 nm.

Mobile phase: mix 2 volumes of freshly prepared *phosphate buffer solution pH 3.5 R*, 43 volumes of *acetonitrile R* and 55 volumes of *water R*.

Flow rate: 1 ml/min.

Detection: spectrophotometer at 233 nm.

Injection: 20 µl.

Run time: 7 times the retention time of ketoprofen.

Relative retention with reference to ketoprofen (retention time = about 7 min): impurity C = about 0.34; impurity H = about 0.39; impurity G = about 0.46; impurity E = about 0.69; impurity B = about 0.73; impurity D = about 1.35; impurity I = about 1.43;