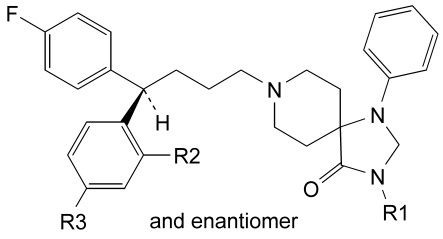
IMPURITIES

Specified impurities: A, B, C.



A. R1 = R2 = R3 = H: 8-[(4*RS*)-4-(4-fluorophenyl)-4-phenylbutyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one,

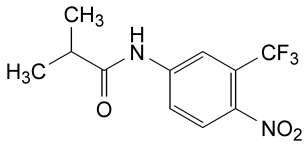
B. R1 = R3 = H, R2 = F: 8-[(4*RS*)-4-(2-fluorophenyl)-4-(4-fluorophenyl)butyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one,

C. R1 = CH_2OH, R2 = H, R3 = F: 8-[4,4-bis(4-fluorophenyl)butyl]-3-(hydroxymethyl)-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one.

01/2005:1423

FLUTAMIDE

Flutamidum



$C_{11}H_{11}F_3N_2O_3$ M_r 276.2

DEFINITION

Flutamide contains not less than 97.0 per cent and not more than the equivalent of 103.0 per cent of 2-methyl-*N*-[4-nitro-3-(trifluoromethyl)phenyl]propanamide, calculated with reference to the dried substance.

CHARACTERS

A pale yellow, crystalline powder, practically insoluble in water, freely soluble in acetone and in alcohol.

It melts at about 112 °C.

IDENTIFICATION

Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *flutamide CRS*.

TESTS

Related substances. Examine by liquid chromatography (*2.2.29*).

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). Dissolve 2 mg of *flutamide CRS* and 2 mg of *flutamide 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 20.0 ml with the mobile phase.

Reference solution (b). Dilute 1.0 ml of the test solution to 50.0 ml with the mobile phase. Dilute 2.0 ml of this solution to 20.0 ml with the mobile phase.

The chromatographic procedure may be carried out using:

– a stainless steel column 0.25 m long and 4.0 mm in internal diameter packed with *octadecylsilyl silica gel for chromatography R* (5 µm),

– as mobile phase at a flow rate of 0.5 ml/min a mixture of equal volumes of *acetonitrile R* and *water R*,

– as detector a spectrophotometer set at 240 nm.

Inject 20 µl of reference solution (b). Adjust the sensitivity of the system so that the height of the principal peak in the chromatogram obtained is not less than 50 per cent of the full scale of the recorder.

Inject 20 µl of reference solution (a). When the chromatogram is recorded in the prescribed conditions, the retention times are: flutamide about 19 min and impurity C about 14 min. The test is not valid unless the resolution between the peaks corresponding to impurity C and flutamide is at least 10.5.

Inject 20 µl of the test solution and 20 µl of reference solution (b). Continue the chromatography for 1.5 times the retention time of the principal peak. In the chromatogram obtained with the test solution: the area of the peak corresponding to impurity C, with a retention time of about 0.72 relative to flutamide, is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent); the area of any other peak apart from the principal peak and the peak corresponding to impurity C is not greater than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent); the sum of the areas of the peaks apart from the principal peak is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent). Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b).

Heavy metals (*2.4.8*). 1.0 g complies with limit test C for heavy metals (20 ppm). Prepare the standard using 2 ml of *lead standard solution (10 ppm Pb) R*.

Loss on drying (*2.2.32*). Not more than 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C for 3 h.

Sulphated ash (*2.4.14*). Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

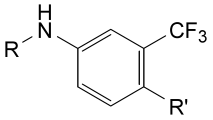
Dissolve 25.0 mg in *methanol R* and dilute to 25.0 ml with the same solvent. Dilute 2.0 ml of this solution to 100.0 ml with *methanol R*. Measure the absorbance (*2.2.25*) at the maximum at 295 nm.

Calculate the content of $C_{11}H_{11}F_3N_2O_3$ taking the specific absorbance to be 295.

STORAGE

Store protected from light.

IMPURITIES

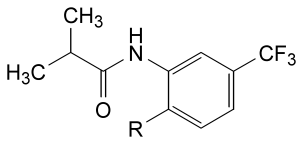


A. R = H, R′ = NO_2: 4-nitro-3-(trifluoromethyl)aniline,

B. R = CO-CH_3, R′ = NO_2: *N*-[4-nitro-3-(trifluoromethyl)phenyl]acetamide,

C. R = CO-CH_2-CH_3, R′ = NO_2: *N*-[4-nitro-3-(trifluoromethyl)phenyl]propanamide,

D. R = R′ = H: 3-(trifluoromethyl)aniline,



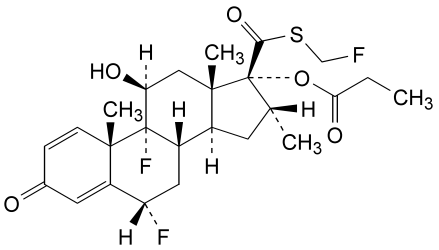
E. R = H: 2-methyl-*N*-[3-(trifluoromethyl)phenyl]propanamide,

F. R = NO_2: 2-methyl-*N*-[2-nitro-5-(trifluoromethyl)phenyl]propanamide.

01/2005:1750

FLUTICASONE PROPIONATE

Fluticasoni propionas



$C_{25}H_{31}F_3O_5S$ M_r 500.6

DEFINITION

6α,9-Difluoro-17-[[(fluoromethyl)sulphanyl]carbonyl]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl propanoate.

Content: 97.0 per cent to 102.0 per cent (anhydrous and solvent-free substance).

CHARACTERS

Appearance: white or almost white powder.

Solubility: practically insoluble in water, sparingly soluble in methylene chloride, slightly soluble in alcohol.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *fluticasone propionate CRS*.

B. Examine the chromatograms obtained in the assay.
Results: the principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with reference solution (b).

TESTS

Specific optical rotation (*2.2.7*): + 32 to + 36 (anhydrous and solvent-free substance).

Dissolve 0.25 g in *methylene chloride R* and dilute to 50.0 ml with the same solvent.

Related substances. Liquid chromatography (*2.2.29*): use the normalisation procedure.

Test solution. Dissolve 20 mg of the substance to be examined in a mixture of equal volumes of mobile phase A and mobile phase B and dilute to 100.0 ml with the same mixture of mobile phases.

Reference solution (a). Dissolve 4 mg of *fluticasone impurity D CRS* in a mixture of equal volumes of mobile phase A and mobile phase B and dilute to 100.0 ml with the same mixture of mobile phases.

Reference solution (b). Dissolve 20 mg of *fluticasone propionate CRS* in a mixture of equal volumes of mobile phase A and mobile phase B, add 1.0 ml of reference solution (a) and dilute to 100.0 ml with a mixture of equal volumes of mobile phase A and mobile phase B.

Column:
- *size*: *l* = 0.25 m, Ø = 4.6 mm,
- *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 μm),
- *temperature*: 40 °C.

Mobile phase:
- *mobile phase A*: a solution containing 0.05 per cent *V/V* of *phosphoric acid R* and 3.0 per cent *V/V* of *methanol R* in *acetonitrile R*,
- *mobile phase B*: a solution containing 0.05 per cent *V/V* of *phosphoric acid R* and 3.0 per cent *V/V* of *methanol R* in *water R*,

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 40	43 → 55	57 → 45
40 - 60	55 → 90	45 → 10
60 - 70	90	10
70 - 75	90 → 43	10 → 57

Flow rate: 1 ml/min.

Detection: spectrophotometer at 239 nm.

Injection: 50 μl; inject the test solution and reference solution (b).

Relative retention with reference to fluticasone propionate (retention time = about 30 min): impurity A = about 0.38; impurity B = about 0.46; impurity C = about 0.76; impurity D = about 0.95; impurity E = about 1.12; impurity F = about 1.18; impurity G = about 1.33; impurity H = about 1.93; impurity I = about 2.01.

System suitability: reference solution (b):
- *resolution*: minimum 1.5 between the peaks due to impurity D and to fluticasone propionate.

Limits:
- *impurities D, G*: for each impurity, maximum 0.3 per cent,
- *impurities A, B, C, E, F, H, I*: for each impurity, maximum 0.2 per cent,
- *impurity with relative retention at about 1.23*: maximum 0.2 per cent,
- *any other impurity*: maximum 0.1 per cent,
- *total*: maximum 1.2 per cent,
- *disregard limit*: 0.05 per cent.

Acetone. Gas chromatography (*2.2.28*).

Internal standard solution. Dilute 0.5 ml of *tetrahydrofuran R* to 1000 ml with *dimethylformamide R*.

Test solution. Dissolve 0.50 g of the substance to be examined in the internal standard solution and dilute to 10.0 ml with the same solution.

Reference solution. Dilute 0.40 g of *acetone R* to 100.0 ml with the internal standard solution. Dilute 1.0 ml to 10.0 ml with the internal standard solution.

Column:
- *material*: fused silica,
- *size*: *l* = 25 m, Ø = 0.53 mm,
- *stationary phase*: cross-linked *macrogol 20 000 R* (film thickness 2 μm).

Carrier gas: *nitrogen for chromatography R*.

Flow rate: 5.5 ml/min.