System suitability: reference solution (b):

– *resolution*: minimum 4.0 between the peaks due to nitrazepam and flunitrazepam.

Limits:

– *correction factor*: for the calculation of content, multiply the peak area of impurity C by 2.44,

– *any impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent),

– *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent),

– *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (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 100-105 °C.

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

ASSAY

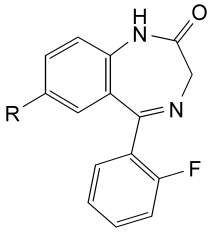
Dissolve 0.250 g in 20 ml of *anhydrous acetic acid R* and add 50 ml of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 ml of *0.1 M perchloric acid* is equivalent to 31.33 mg of $C_{16}H_{12}FN_3O_3$.

STORAGE

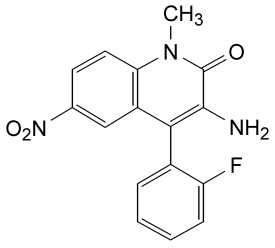
Protected from light.

IMPURITIES

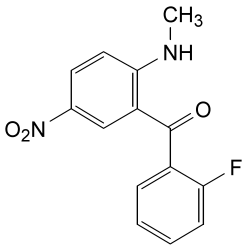


A. R = NH_2: 7-amino-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (7-aminodemethylflunitrazepam),

B. R = NO_2: 5-(2-fluorophenyl)-7-nitro-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (demethylflunitrazepam),



C. 3-amino-4-(2-fluorophenyl)-1-methyl-6-nitroquinolin-2(1*H*)-one,

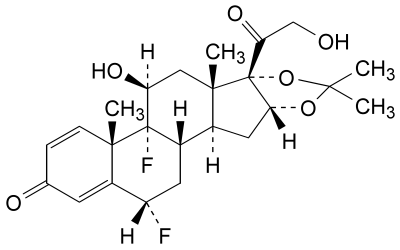


D. (2-fluorophenyl)[2-(methylamino)-5-nitrophenyl]methanone.

01/2005:0494

FLUOCINOLONE ACETONIDE

Fluocinoloni acetonidum



$C_{24}H_{30}F_2O_6$ M_r 452.5

DEFINITION

6α,9-Difluoro-11β,21-dihydroxy-16α,17-(1-methylethylidenedioxy)pregna-1,4-diene-3,20-dione.

Content: 97.0 per cent to 103.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: practically insoluble in water, soluble in acetone and in ethanol.

It shows polymorphism.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *fluocinolone acetonide CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *ethanol R*, evaporate to dryness and record new spectra using the residues.

B. Examine the chromatograms obtained in the test for related substances.

Results: the principal peak in the chromatogram obtained with the reference solution (b) is similar in retention time to the peak due to *fluocinolone acetonide CRS* in the chromatogram obtained with the reference solution (a).

TESTS

Specific optical rotation (*2.2.7*): + 100 to + 104 (dried substance).

Dissolve 0.100 g in *ethanol R* and dilute to 10.0 ml with the same solvent.

Related substances. Liquid chromatography (*2.2.29*). *Carry out the test protected from light.*

Test solution. Dissolve 25.0 mg of the substance to be examined in *acetonitrile R* and dilute to 10.0 ml with the same solvent.

Reference solution (a). Dissolve 2.5 mg of *fluocinolone acetonide CRS* and 2.5 mg of *triamcinolone acetonide R* in 45 ml of *acetonitrile R* and dilute to 100.0 ml with *water R*.

Reference solution (b). Dilute 1.0 ml of the test solution to 100.0 ml with *acetonitrile R*.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm,

– *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: mix 450 ml of *acetonitrile R* with 500 ml of *water R* and allow to equilibrate; adjust the volume to 1000.0 ml with *water R* and mix again.

Flow rate: 1 ml/min.

Detection: spectrophotometer at 238 nm.

Injection: 20 µl.

Run time: 4 times the retention time of fluocinolone acetonide.

Retention times: triamcinolone acetonide = about 8.5 min; fluocinolone acetonide = about 10 min.

System suitability:

– *resolution*: minimum of 3.0 between the peaks due to triamcinolone acetonide and fluocinolone acetonide in the chromatogram obtained with reference solution (a).

Limits:

– *any impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1 per cent) and not more than 1 such peak has an area greater than half the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent),

– *total*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (2.5 per cent),

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

Loss on drying (*2.2.32*): maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 100-105 °C for 3 h.

ASSAY

Protect the solutions from light throughout the assay.

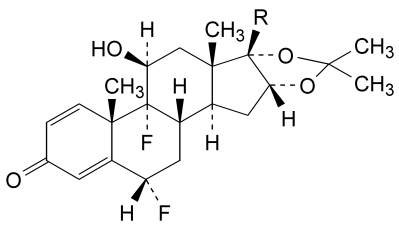
Dissolve 50.0 mg in *alcohol R* and dilute to 50.0 ml with the same solvent. Dilute 2.0 ml of this solution to 100.0 ml with *alcohol R*. Measure the absorbance (*2.2.25*) at the maximum at 238 nm.

Calculate the content of $C_{24}H_{30}F_2O_6$ taking the specific absorbance to be 355.

STORAGE

Protected from light.

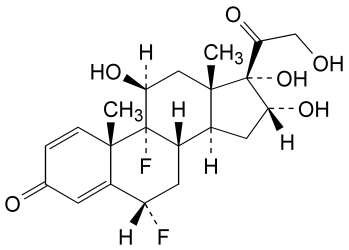
IMPURITIES



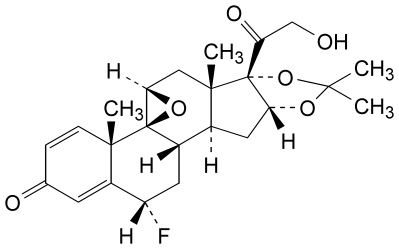
A. R = $CO\text{-}CO_2H$: 6α,9-difluoro-11β-hydroxy-16α,17-(1-methylethylidenedioxy)-3,20-dioxopregna-1,4-dien-21-oic acid,

B. R = CO_2H: 6α,9-difluoro-11β-hydroxy-16α,17-(1-methylethylidenedioxy)-3-oxoandrosta-1,4-diene-17β-carboxylic acid,

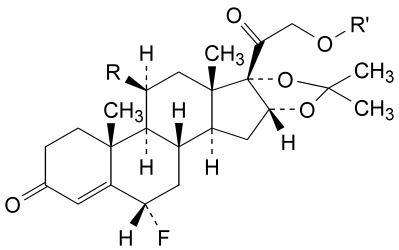
D. R = CO-CH=O: 6α,9-difluoro-11β-hydroxy-16α,17-(1-methylethylidenedioxy)-3,20-dioxopregna-1,4-dien-21-al,



C. 6α,9-difluoro-11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione (fluocinolone),



E. 9,11β-epoxy-6α-fluoro-21-hydroxy-16α,17-(1-methylethylidenedioxy)-9β-pregna-1,4-diene-3,20-dione,



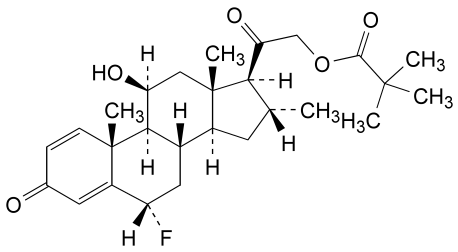
F. R = R′ = H: 6α-fluoro-21-hydroxy-16α,17-(1-methylethylidenedioxy)pregn-4-ene-3,20-dione,

G. R = OH, R′ = $CO\text{-}CH_3$: 6α-fluoro-11β-hydroxy-16α,17-(1-methylethylidenedioxy)-3,20-dioxopregn-4-en-21-yl acetate.

01/2005:1212

FLUOCORTOLONE PIVALATE

Fluocortoloni pivalas



$C_{27}H_{37}FO_5$ M_r 460.6

DEFINITION

Fluocortolone pivalate contains not less than 97.0 per cent and not more than the equivalent of 103.0 per cent of 6α-fluoro-11β-hydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-yl 2,2-dimethylpropanoate calculated with reference to the dried substance.