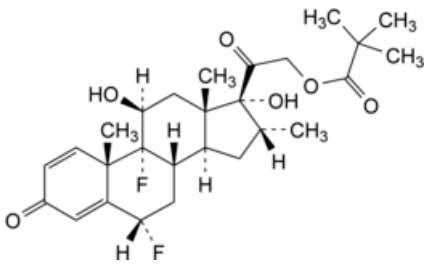
Edition: BP 2025 (Ph. Eur. 11.6 update)

Flumetasone Pivalate

General Notices

(Ph. Eur. monograph 1327)



$C_{27}H_{36}F_2O_6$ 494.6 *2002-29-1*

Action and use

Glucocorticoid.

Preparation

Flumetasone and Clioquinol Ear Drops

Ph Eur

DEFINITION

6α,9-Difluoro-11β,17-dihydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-yl 2,2-dimethylpropanoate.

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, sparingly soluble in acetone, slightly soluble in ethanol (96 per cent) and in methylene chloride.

It shows polymorphism (*5.9*).

IDENTIFICATION

First identification: A, B.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *flumetasone pivalate CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *acetone R*, evaporate to dryness on a water-bath and record new spectra using the residues.

B. 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 *flumetasone pivalate CRS* in *acetone R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of *desoxycortone acetate CRS* in *acetone R* and dilute to 10 mL with the same solvent. Dilute 5 mL of this solution to 10 mL with reference solution (a).

Plate *TLC silica gel F_{254} plate R*.

Mobile phase Add a mixture of 1.2 volumes of *water R* and 8 volumes of *methanol R* to a mixture of 15 volumes of *ether R* and 77 volumes of *methylene chloride R*.

Application 5 µL.

Development Over a path of 15 cm.

Drying In air.

Detection A Examine in ultraviolet light at 254 nm.

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

Detection B Spray with *alcoholic solution of sulfuric acid R*. Heat at 120 °C for 10 min or until the spots appear. Allow to cool. Examine in daylight and in ultraviolet light at 365 nm.

Results B The principal spot in the chromatogram obtained with the test solution is similar in position, colour in daylight, fluorescence in ultraviolet light at 365 nm and size to the principal spot in the chromatogram obtained with reference solution (a).

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

C. Add about 2 mg to 2 mL of a mixture of 0.5 mL of *water R* and 1.5 mL of *sulfuric acid R* and shake to dissolve. Within 5 min, a pink colour develops. Add this solution to 10 mL of *water R* and mix. The colour fades and a clear solution remains.

D. Mix about 5 mg with 45 mg of *heavy magnesium oxide R* and ignite in a crucible until an almost white residue is obtained (usually less than 5 min). Allow to cool, add 1 mL of *water R*, 0.05 mL of *phenolphthalein solution R1* and about 1 mL of *dilute hydrochloric acid R* to render the solution colourless. Filter. To a freshly prepared mixture of 0.1 mL of *alizarin S solution R* and 0.1 mL of *zirconyl nitrate solution R* add 1.0 mL of the filtrate. Mix, allow to stand for 5 min and compare the colour of the solution with that of a blank prepared in the same manner. The test solution is yellow and the blank is red.

TESTS

Solution S

Dissolve 0.50 g in *acetone R* and dilute to 25.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution BY_6 (2.2.2, Method II).

Specific optical rotation (2.2.7)

+ 69 to + 77 (dried substance), determined on solution S.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 10 mg of *dexamethasone pivalate CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase. To 5.0 mL of this solution, add 5.0 mL of the test solution, mix and dilute to 50.0 mL with the mobile phase.

Reference solution (b) Dilute 2.0 mL of the test solution to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *tetrahydrofuran R*, *acetonitrile R*, *water R*, *methanol R* (5:30:30:35 *V/V/V/V*).

Flow rate 0.6 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

Run time 1.5 times the retention time of flumetasone pivalate.

Relative retention With reference to flumetasone pivalate: impurity C = about 1.1.

System suitability Reference solution (a):

— *resolution*: minimum 2.8 between the peaks due to flumetasone pivalate and impurity C; if necessary, adjust the concentration of tetrahydrofuran in the mobile phase.

Limits:

— *impurities A, B, C, D*: for each impurity, not more than 0.75 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.5 per cent);

— *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (2 per cent);

— *disregard limit*: 0.025 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 0.500 g by drying in an oven at 105 °C for 4 h.

ASSAY

Dissolve 50.0 mg in *ethanol (96 per cent) R* and dilute to 100.0 mL with the same solvent. Dilute 2.0 mL of this solution to 100.0 mL with *ethanol (96 per cent) R*. Measure the absorbance (2.2.25) at the absorption maximum at 239 nm.

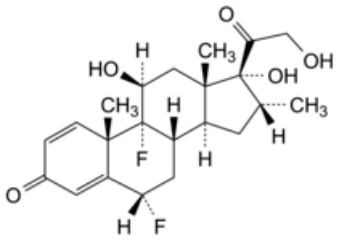
Calculate the content of $C_{27}H_{36}F_2O_6$ taking the specific absorbance to be 336.

STORAGE

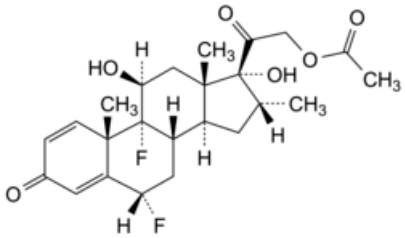
Protected from light.

IMPURITIES

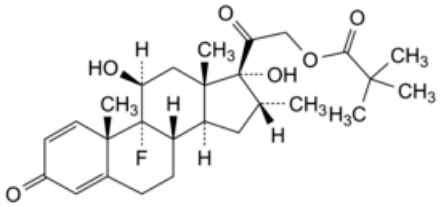
Specified impurities *A, B, C, D*.



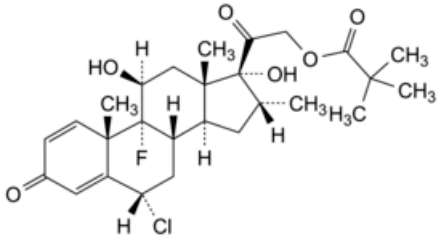
A. 6α,9-difluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione (flumetasone),



B. 6α,9-difluoro-11β,17-dihydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-yl acetate (flumetasone acetate),



C. 9-fluoro-11β,17-dihydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-yl 2,2-dimethylpropanoate (dexamethasone pivalate),



D. 6α-chloro-9-fluoro-11β,17-dihydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-yl 2,2-dimethylpropanoate (chlordexamethasone pivalate).