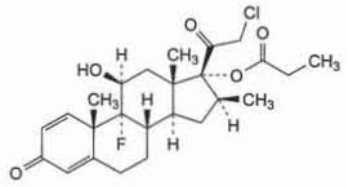
Clobetasol Propionate

(Ph. Eur. monograph 2127)



$C_{25}H_{32}ClFO_5$ 467.0 25122-46-7

Action and use
Glucocorticoid.

Preparations
Clobetasol Cutaneous Foam
Clobetasol Scalp Application
Clobetasol Shampoo

Ph Eur

DEFINITION

21-Chloro-9-fluoro-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-dien-17-yl propanoate.

Content
97.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance
White or almost white, crystalline powder.

Solubility
Practically insoluble in water, freely soluble in acetone, sparingly soluble in ethanol (96 per cent).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison clobetasol propionate CRS.

TESTS

Specific optical rotation (*2.2.7*)
+ 112 to + 118 (dried substance).

Dissolve 0.500 g in *acetone R* and dilute to 50.0 mL with the same solvent.

Related substances
Liquid chromatography (*2.2.29*).

Test solution (a) Dissolve 20.0 mg of the substance to be examined in the mobile phase and dilute to 20.0 mL with the mobile phase.

Test solution (b) Dissolve 20.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 20.0 mg of *clobetasol propionate CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve the contents of a vial of *clobetasol impurity J CRS* in 2.0 mL of the mobile phase. To 0.5 mL of this solution add 0.5 mL of test solution (b) and dilute to 20.0 mL with the mobile phase.

Reference solution (c) Dissolve the contents of a vial of *clobetasol for peak identification CRS* (containing impurities A, B, C, D, E, L and M) in 2 mL of the mobile phase.

Reference solution (d) Dilute 1.0 mL of test solution (a) to 50.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 20.0 mL with the mobile phase.

Column:
— *size*: *l* = 0.15 m, Ø = 4.6 mm;
— *stationary phase*: spherical *octadecylsilyl silica gel for chromatography R* (5 µm);
— *temperature*: 30 °C.

Mobile phase Mix 10 volumes of *methanol R*, 42.5 volumes of a 7.85 g/L solution of *sodium dihydrogen phosphate monohydrate R* adjusted to pH 5.5 with a 100 g/L solution of *sodium hydroxide R* and 47.5 volumes of *acetonitrile R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 10 µL of test solution (a) and reference solutions (b), (c) and (d).

Run time 3 times the retention time of clobetasol propionate.

Identification of impurities Use the chromatogram supplied with *clobetasol for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B, C, D, E, L and M.

Relative retention With reference to clobetasol propionate (retention time = about 10 min): impurity A = about 0.4; impurity B = about 0.6; impurity C = about 0.9; impurity J = about 1.1; impurity D = about 1.2; impurity L = about 1.3; impurity M = about 1.6; impurity E = about 2.1.

System suitability:
— *resolution*: minimum 2.0 between the peaks due to clobetasol propionate and impurity J in the chromatogram obtained with reference solution (b);
— the chromatogram obtained with reference solution (c) is similar to the chromatogram supplied with *clobetasol for peak identification CRS*.

Limits:
— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity B = 0.6; impurity C = 1.5;
— *impurity E*: not more than 1.4 times the area of the principal peak in the chromatogram obtained with reference solution (d) (0.7 per cent);
— *impurity D*: not more than the area of the principal peak in the chromatogram obtained with reference solution (d) (0.5 per cent);
— *impurities B, C*: for each impurity, not more than 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (d) (0.3 per cent);
— *impurities A, L, M*: for each impurity, not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (d) (0.2 per cent);
— *unspecified impurities*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (d) (0.10 per cent);
— *total*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (d) (2.0 per cent);
— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (d) (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 for 3 h.

Sulfated ash (*2.4.14*)
Maximum 0.1 per cent, determined on 1.0 g.

ASSAY
Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

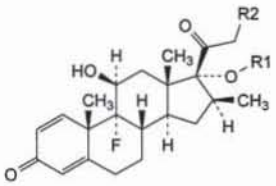
Injection Test solution (b) and reference solution (a).

Calculate the percentage content of $C_{25}H_{32}ClFO_5$ using the chromatogram obtained with reference solution (a) and the declared content of *clobetasol propionate CRS*.

STORAGE
Protected from light.

IMPURITIES
Specified impurities A, B, C, D, E, L, M

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*): *F, G, H, I, J, K.*



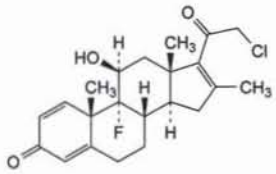
A. R1 = CO-C_2H_5, R2 = OH: 9-fluoro-11β,21-dihydroxy-16β-methyl-3,20-dioxopregna-1,4-dien-17-yl propanoate (betamethasone 17-propionate),

G. R1 = H, R2 = Cl: 21-chloro-9-fluoro-11β,17-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione (clobetasol),

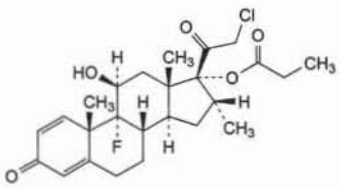
H. R1 = CO-C_2H_5, R2 = H: 9-fluoro-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-dien-17-yl propanoate,

I. R1 = CO-C_2H_5, R2 = O-SO_2-CH_3: 9-fluoro-11β-hydroxy-16β-methyl-21-[(methylsulfonyl)oxy]-3,20-dioxopregna-1,4-dien-17-yl propanoate,

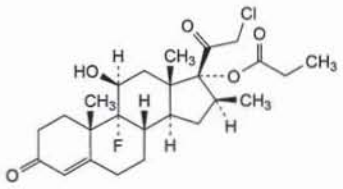
K. R1 = H, R2 = O-CO-C_2H_5: 9-fluoro-11β,17-dihydroxy-16β-methyl-3,20-dioxopregna-1,4-dien-21-yl propanoate (betamethasone 21-propionate),



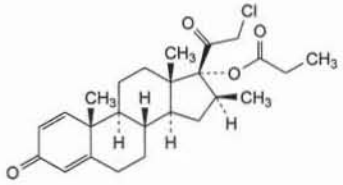
B. 21-chloro-9-fluoro-11β-hydroxy-16-methylpregna-1,4,16-triene-3,20-dione,



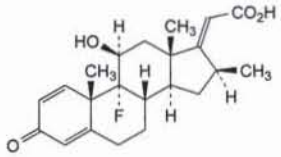
C. 21-chloro-9-fluoro-11β-hydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-17-yl propanoate,



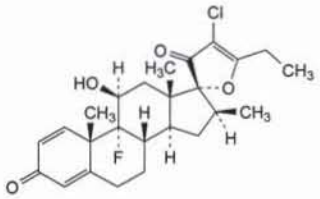
D. 21-chloro-9-fluoro-11β-hydroxy-16β-methyl-3,20-dioxopregn-4-en-17-yl propanoate (1,2-dihydroclobetasol 17-propionate),



E. 21-chloro-16β-methyl-3,20-dioxopregna-1,4-dien-17-yl propanoate,



F. 9-fluoro-11β-hydroxy-16β-methyl-3-oxopregna-1,4,17(20)-trien-21-oic acid,



J. (17*R*)-4′-chloro-5′-ethyl-9-fluoro-11β-hydroxy-16β-methylspiro[androsta-1,4-diene-17,2′(3′*H*)-furan]-3,3′-dione (17α-spiro compound),

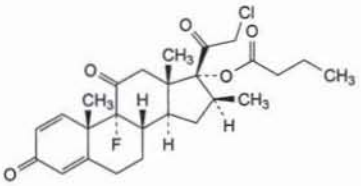
L. unknown structure,

M. unknown structure.

Ph Eur

Clobetasone Butyrate

(Ph. Eur. monograph 1090)



$C_{26}H_{32}ClFO_5$ 479.0 *25122-57-0*

Action and use
Glucocorticoid.

Preparations
Clobetasone Cream
Clobetasone Ointment

Ph Eur

DEFINITION

21-Chloro-9-fluoro-16β-methyl-3,11,20-trioxopregna-1,4-dien-17-yl butanoate.

Content

97.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, freely soluble in acetone and in methylene chloride, slightly soluble in ethanol (96 per cent).

mp

About 178 °C.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison clobetasone butyrate CRS.

TESTS

Specific optical rotation (*2.2.7*)

+ 131 to + 138 (dried substance).

Dissolve 0.250 g in *ethanol R1* and dilute to 25.0 mL with the same solvent.

Related substances

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

Solvent mixture anhydrous formic acid R, acetonitrile R, water R (0.1:43:57 *V/V/V*).

Test solution Dissolve 65 mg of the substance to be examined in 5.0 mL of *acetonitrile R* and dilute to 25.0 mL with the solvent mixture.

Reference solution (a) Dissolve 13 mg of *clobetasone butyrate for system suitability CRS* (containing impurity F) in 1 mL of *acetonitrile R* and dilute to 5.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Column:

- *size*: *l* = 0.15 m, Ø = 4.6 mm;
- *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3.5 µm);
- *temperature*: 40 °C.

Mobile phase:

- *mobile phase A*: *anhydrous formic acid R, water R* (0.1:99.9 *V/V*);
- *mobile phase B*: *anhydrous formic acid R, acetonitrile R* (0.1:99.9 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	57	43
3 - 26	57 → 43	43 → 57

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 241 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *clobetasone butyrate for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peak due to impurity F.

Relative retention With reference to clobetasone butyrate (retention time = about 14 min): impurity F = about 0.9.

System suitability:

- *resolution*: minimum 3.5 between the peaks due to impurity F and clobetasone butyrate in the chromatogram obtained with reference solution (a);
- *signal-to-noise ratio*: minimum 10 for the principal peak in the chromatogram obtained with reference solution (b).

Limits:

- *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);
- *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);
- *disregard limit*: 0.5 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 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

Dissolve 20.0 mg in *ethanol (96 per cent) R* and dilute to 100.0 mL with the same solvent. Dilute 5.0 mL of the solution to 50.0 mL with *ethanol (96 per cent) R*. Measure the absorbance (*2.2.25*) at the absorption maximum at 235 nm.

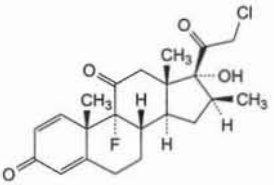
Calculate the content of $C_{26}H_{32}ClFO_5$, taking the specific absorbance to be 327.

STORAGE

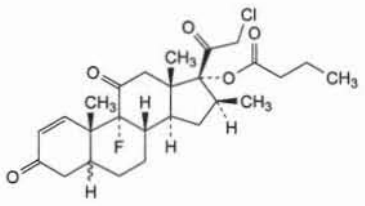
Protected from light.

IMPURITIES

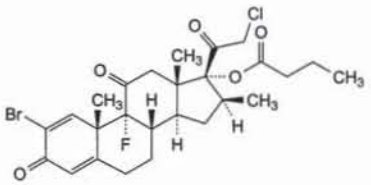
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical 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, C, D, E, F, G, H, I.*



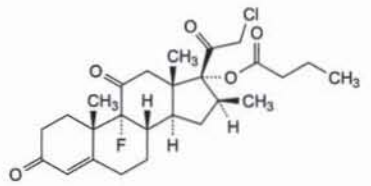
A. 21-chloro-9-fluoro-17-hydroxy-16β-methylpregna-1,4-diene-3,11,20-trione (clobetasone),



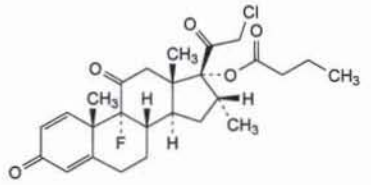
C. 21-chloro-9-fluoro-16β-methyl-3,11,20-trioxopregn-1-en-17-yl butanoate (4,5-dihydroclobetasone butyrate),



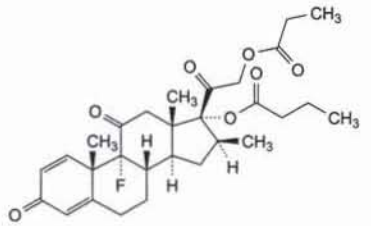
D. 2-bromo-21-chloro-9-fluoro-16β-methyl-3,11,20-trioxopregna-1,4-dien-17-yl butanoate (2-bromoclobetasone butyrate),



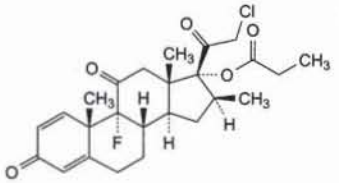
E. 21-chloro-9-fluoro-16β-methyl-3,11,20-trioxopregn-4-en-17-yl butanoate (1,2-dihydroclobetasone butyrate),



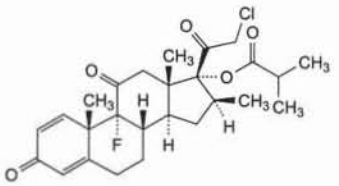
F. 21-chloro-9-fluoro-16α-methyl-3,11,20-trioxopregna-1,4-dien-17-yl butanoate (16α-methyl clobetasone butyrate),



G. 9-fluoro-16β-methyl-3,11,20-trioxo-21-(propanoyloxy)pregna-1,4-dien-17-yl butanoate,



H. 21-chloro-9-fluoro-16β-methyl-3,11,20-trioxopregna-1,4-dien-17-yl propanoate (17-*O*-propionyl clobetasone),

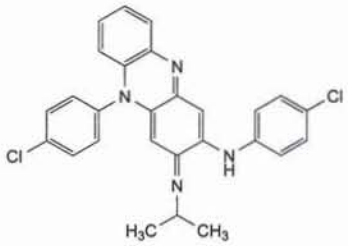


I. 21-chloro-9-fluoro-16β-methyl-3,11,20-trioxopregna-1,4-dien-17-yl 2-methylpropanoate (17-*O*-isobutyryl clobetasone).

Ph Eur

Clofazimine

(Ph. Eur. monograph 2054)



$C_{27}H_{22}Cl_2N_4$ 473.4 2030-63-9

Action and use
Antileprosy drug.

Preparation
Clofazimine Capsules

Ph Eur

DEFINITION

N,5-Bis(4-chlorophenyl)-3-[(1-methylethyl)imino]-3,5-dihydrophenazin-2-amine.

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

CHARACTERS

Appearance
Reddish-brown, fine powder.

Solubility
Practically insoluble in water, soluble in methylene chloride, very slightly soluble in ethanol (96 per cent).

It shows polymorphism (*5.9*).

IDENTIFICATION

First identification: A.

Second identification: B, C.

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison clofazimine CRS.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methylene chloride R*, evaporate to dryness 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 *methylene chloride R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 10 mg of *clofazimine CRS* in *methylene chloride R* and dilute to 10 mL with the same solvent.

Plate TLC silica gel GF_{254} plate R.

Mobile phase propanol R, methylene chloride R (6:85 *V/V*).

Application 5 µL.

First development Over 2/3 of the plate.

Drying Horizontally in air for 5 min.

Second development Over 2/3 of the plate.

Drying In air for 5 min.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal