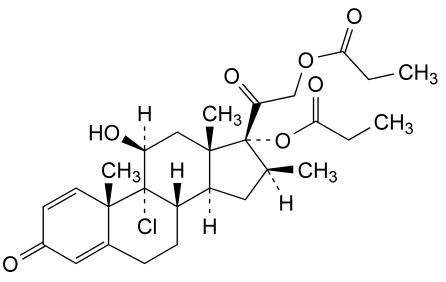
01/2008:0654
corrected 6.0

BECLOMETASONE DIPROPIONATE, ANHYDROUS

Beclometasoni dipropionas anhydricus



$C_{28}H_{37}ClO_7$ M_r 521.1
[5534-09-8]

DEFINITION

9-Chloro-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-diene-17,21-diyl dipropanoate.

Content: 96.0 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

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *anhydrous beclometasone dipropionate CRS*.

B. Treat 25 mg by the oxygen-flask method (*2.5.10*). Use a mixture of 1 ml of *1 M sodium hydroxide* and 20 ml of *water R* to absorb the combustion products. The solution gives reaction (a) of chlorides (*2.3.1*).

C. Loss on drying (see Tests).

TESTS

Specific optical rotation (*2.2.7*): + 108 to + 115 (dried substance).

Dissolve 0.100 g in *ethanol (96 per cent) R* and dilute to 10.0 ml with the same solvent.

Related substances. Liquid chromatography (*2.2.29*).

Test solution (a). Dissolve 50.0 mg of the substance to be examined in *acetonitrile R* and dilute to 50.0 ml with the same solvent.

Test solution (b). Dilute 1.0 ml of test solution (a) to 50.0 ml with *acetonitrile R*.

Reference solution (a). Dilute 5.0 ml of test solution (b) to 100.0 ml with *acetonitrile R*.

Reference solution (b). Dissolve 5 mg of *beclometasone dipropionate for system suitability CRS* (containing impurity D) in *acetonitrile R* and dilute to 5 ml with the same solvent.

Reference solution (c). Dissolve 5 mg of *beclometasone dipropionate for peak identification CRS* (containing impurities A, B, C, L and M) in *acetonitrile R* and dilute to 5 ml with the same solvent.

Reference solution (d). Dissolve 50.0 mg of *anhydrous beclometasone dipropionate CRS* in *acetonitrile R* and dilute to 50.0 ml with the same solvent. Dilute 1.0 ml to 50.0 ml with *acetonitrile R*.

Column:

– *size*: *l* = 0.25 m, Ø = 4.0 mm;
– *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);
– *temperature*: 30 °C.

Mobile phase: *acetonitrile R, water R* (45:55 *V/V*).

Flow rate: 1.5 ml/min.

Detection: spectrophotometer at 238 nm.

Injection: 20 µl of test solution (a) and reference solutions (a), (b) and (c).

Run time: 2.5 times the retention time of beclometasone dipropionate.

Identification of impurities: use the chromatogram supplied with *beclometasone dipropionate for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B, C, L and M; use the chromatogram supplied with *beclometasone dipropionate for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity D; if necessary, use the responses of impurities D and M detected at 284 nm to distinguish the 2 impurities: the response of impurity D decreases and that of impurity M increases.

Relative retention with reference to beclometasone dipropionate (retention time = about 29 min): impurity A = about 0.3; impurity B = about 0.6; impurity D = about 1.1; impurity M = about 1.1; impurity L = about 1.3; impurity C = about 1.6.

System suitability: reference solution (b):

– *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to beclometasone dipropionate.

Limits:

– *correction factor*: for the calculation of content, multiply the peak area of impurity D by 1.3;
– *impurities B, L*: for each impurity, not more than 8 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.8 per cent);
– *impurity M*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);
– *impurities A, D*: for each impurity, not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);
– *impurity C*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);
– *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);
– *total*: not more than 15 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.5 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 105 °C for 3 h.

ASSAY

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

Mobile phase: *water R, acetonitrile R* (40:60 *V/V*).

Flow rate: 1.0 ml/min.

Injection: test solution (b) and reference solution (d).

Calculate the percentage content of $C_{28}H_{37}ClO_7$.

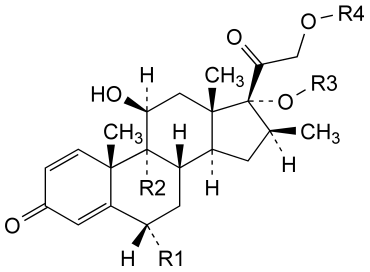
STORAGE

Protected from light.

IMPURITIES

Specified impurities: A, B, C, D, 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*): *E, F, G, H, I, J, K, N, O, P, Q, R.*



A. R1 = R3 = H, R2 = Cl, R4 = CO-C_2H_5: 9-chloro-11β,17-dihydroxy-16β-methyl-3,20-dioxopregna-1,4-dien-21-yl propanoate (beclometasone 21-propionate),

B. R1 = H, R2 = Cl, R3 = CO-C_2H_5, R4 = CO-CH_3: 21-(acetyloxy)-9-chloro-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-dien-17-yl propanoate (beclometasone 21-acetate 17-propionate),

C. R1 = H, R2 = Cl, R3 = CO-C_2H_5, R4 = CO-CH_2-CH_2-CH_3: 9-chloro-11β-hydroxy-16β-methyl-3,20-dioxo-17-(propanoyloxy)-pregna-1,4-dien-21-yl butanoate (beclometasone 21-butyrate 17-propionate),

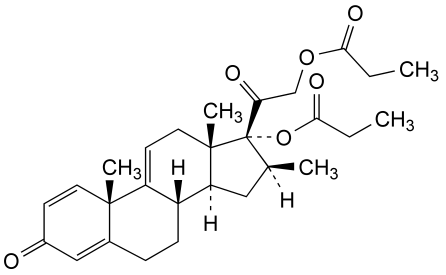
D. R1 = H, R2 = Br, R3 = R4 = CO-C_2H_5: 9-bromo-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-diene-17,21-diyl dipropanoate,

E. R1 = R2 = Cl, R3 = R4 = CO-C_2H_5: 6α,9-dichloro-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-diene-17,21-diyl dipropanoate,

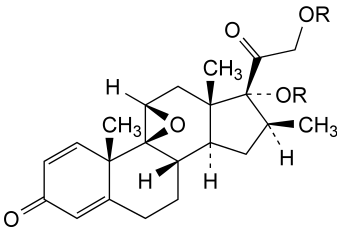
F. R1 = Br, R2 = Cl, R3 = R4 = CO-C_2H_5: 6α-bromo-9-chloro-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-diene-17,21-diyl dipropanoate,

G. R1 = R3 = R4 = H, R2 = Cl: 9-chloro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione (beclometasone),

H. R1 = R4 = H, R2 = Cl, R3 = CO-C_2H_5: 9-chloro-11β,21-dihydroxy-16β-methyl-3,20-dioxopregna-1,4-dien-17-yl propanoate (beclometasone 17-propionate),

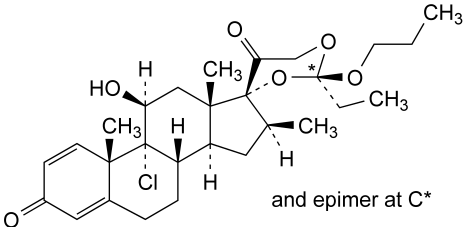


I. 16β-methyl-3,20-dioxopregna-1,4,9(11)-triene-17,21-diyl dipropanoate,

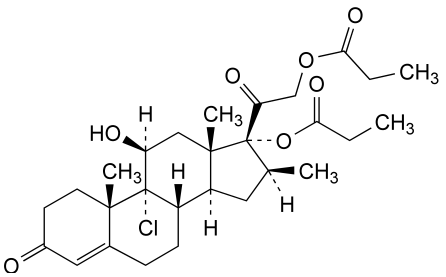


J. R = CO-C_2H_5: 9,11β-epoxy-16β-methyl-3,20-dioxo-9β-pregna-1,4-diene-17,21-diyl dipropanoate,

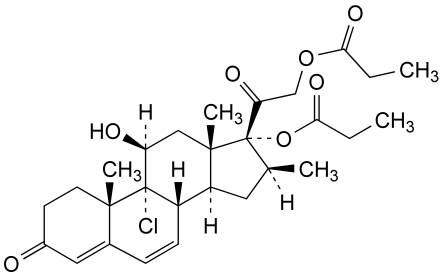
R. R = H: 9,11β-epoxy-17,21-dihydroxy-16β-methyl-9β-pregna-1,4-diene-3,20-dione,



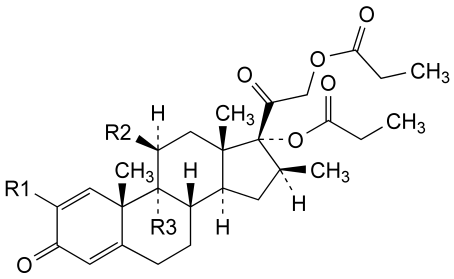
K. (2′*RS*,4′*R*)-9-chloro-2′-ethyl-11β-hydroxy-16β-methyl-2′-propoxyspiro[androsta-1,4-diene-17,4′-[1,3]dioxan]-3,5′-dione (beclometasone propyl 17,21-orthopropionate),



L. 9-chloro-11β-hydroxy-16β-methyl-3,20-dioxopregn-4-ene-17,21-diyl dipropanoate,



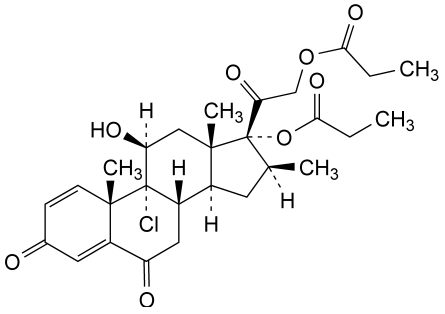
M. 9-chloro-11β-hydroxy-16β-methyl-3,20-dioxopregna-4,6-diene-17,21-diyl dipropanoate,



N. R1 = Br, R2 = OH, R3 = Cl: 2-bromo-9-chloro-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-diene-17,21-diyl dipropanoate,

O. R1 = H, R2 = R3 = Cl: 9,11β-dichloro-16β-methyl-3,20-dioxopregna-1,4-diene-17,21-diyl dipropanoate,

Q. R1 = R2 = R3 = H: 16β-methyl-3,20-dioxopregna-1,4-diene-17,21-diyl dipropanoate,



P. 9-chloro-11β-hydroxy-16β-methyl-3,6,20-trioxopregna-1,4-diene-17,21-diyl dipropanoate.

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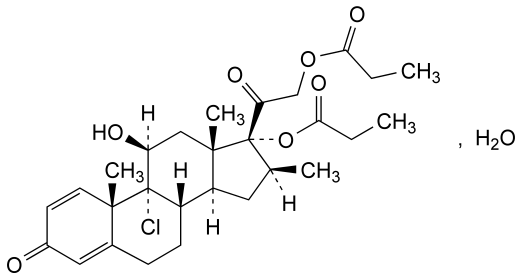
BECLOMETASONE DIPROPIONATE MONOHYDRATE

Beclometasoni dipropionas monohydricus



$C_{28}H_{37}ClO_7,H_2O$ M_r 539.1

DEFINITION

9-Chloro-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-diene-17,21-diyl dipropanoate monohydrate.

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, sparingly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *beclometasone dipropionate monohydrate CRS*.

B. Treat 25 mg by the oxygen-flask method (*2.5.10*). Use a mixture of 1 ml of *1 M sodium hydroxide* and 20 ml of *water R* to absorb the combustion products. The solution gives reaction (a) of chlorides (*2.3.1*).

C. Loss on drying (see Tests).

TESTS

Specific optical rotation (*2.2.7*): + 108 to + 115 (dried substance).

Dissolve 0.100 g in *ethanol (96 per cent) R* and dilute to 10.0 ml with the same solvent.

Related substances. Liquid chromatography (*2.2.29*).

Test solution (a). Dissolve 50.0 mg of the substance to be examined in *acetonitrile R* and dilute to 50.0 ml with the same solvent.

Test solution (b). Dilute 1.0 ml of test solution (a) to 50.0 ml with *acetonitrile R*.

Reference solution (a). Dilute 5.0 ml of test solution (b) to 100.0 ml with *acetonitrile R*.

Reference solution (b). Dissolve 5 mg of *beclometasone dipropionate for system suitability CRS* (containing impurity D) in *acetonitrile R* and dilute to 5 ml with the same solvent.

Reference solution (c). Dissolve 5 mg of *beclometasone dipropionate for peak identification CRS* (containing impurities A, B, C, L and M) in *acetonitrile R* and dilute to 5 ml with the same solvent.

Reference solution (d). Dissolve 50.0 mg of *beclometasone dipropionate anhydrous CRS* in *acetonitrile R* and dilute to 50.0 ml with the same solvent. Dilute 1.0 ml to 50.0 ml with *acetonitrile R*.

Column:
- *size*: *l* = 0.25 m, Ø = 4.0 mm;
- *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);
- *temperature*: 30 °C.

Mobile phase: *acetonitrile R, water R* (45:55 *V/V*).

Flow rate: 1.5 ml/min.

Detection: spectrophotometer at 238 nm.

Injection: 20 µl of test solution (a) and reference solutions (a), (b) and (c).

Run time: 2.5 times the retention time of beclometasone dipropionate.

Identification of impurities: use the chromatogram supplied with *beclometasone dipropionate for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B, C, L and M; use the chromatogram supplied with *beclometasone dipropionate for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity D; if necessary, use the responses of impurities D and M detected at 284 nm to distinguish the 2 impurities: the response of impurity D decreases and that of impurity M increases.

Relative retention with reference to beclometasone dipropionate (retention time = about 29 min): impurity A = about 0.3; impurity B = about 0.6; impurity D = about 1.1; impurity M = about 1.1; impurity L = about 1.3; impurity C = about 1.6.

System suitability: reference solution (b):
- *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to beclometasone dipropionate.