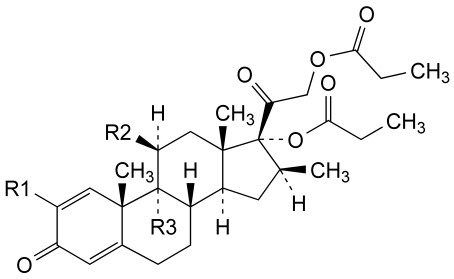
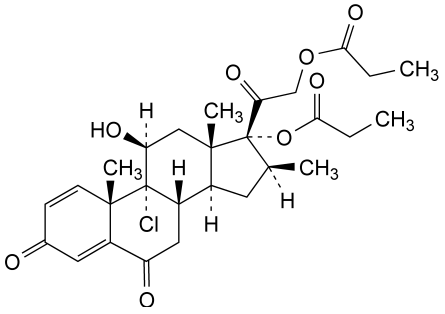


N. R1 = Br, R2 = OH, R3 = Cl: 2-bromo-9-chloro-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-diene-17,21-diyl dipropanoate,

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,

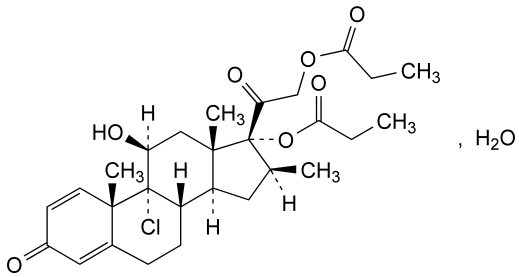


P. 9-chloro-11β-hydroxy-16β-methyl-3,6,20-trioxopregna-1,4-diene-17,21-diyl dipropanoate.

01/2008:1709
corrected 6.0

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.

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 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);
- *impurities A, C, D, M*: for each impurity, 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 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 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*): 2.8 per cent to 3.8 per cent, determined on 1.000 g by drying in an oven at 105 °C.

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 $C_{28}H_{37}ClO_7$.

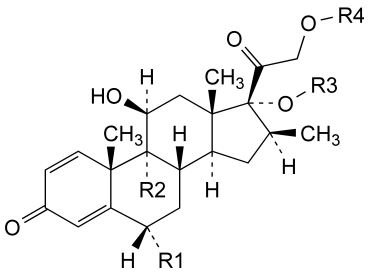
STORAGE

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),

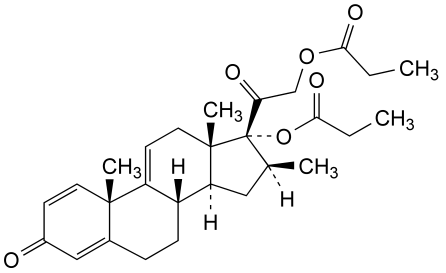
D. R1 = H, R2 = Br, R3 = R4 = CO-C_2H_5: 9-bromo-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-diene-17,21-diyl dipropanoate,

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,

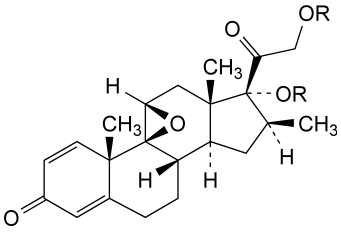
F. R1 = Br, R2 = Cl, R3 = R4 = CO-C_2H_5: 6α-bromo-9-chloro-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-diene-17,21-diyl dipropanoate,

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),

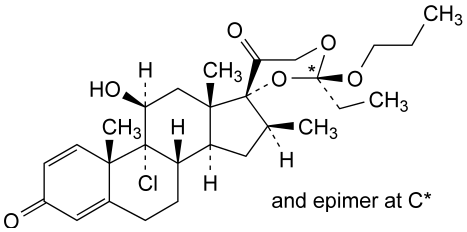


I. 16β-methyl-3,20-dioxopregna-1,4,9(11)-triene-17,21-diyl dipropanoate,

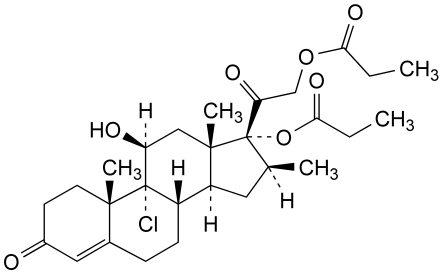


J. R = CO-C_2H_5: 9,11β-epoxy-16β-methyl-3,20-dioxo-9β-pregna-1,4-diene-17,21-diyl dipropanoate,

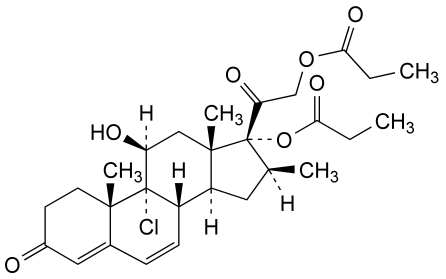
R. R = H: 9,11β-epoxy-17,21-dihydroxy-16β-methyl-9β-pregna-1,4-diene-3,20-dione,



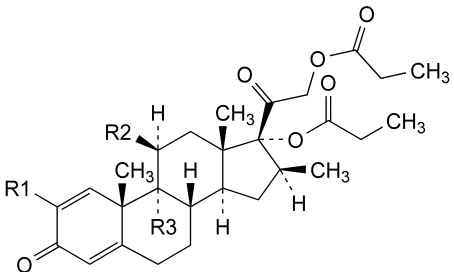
K. (2′*RS*,4′*R*)-9-chloro-2′-ethyl-11β-hydroxy-16β-methyl-2′-propoxyspiro[androsta-1,4-diene-17,4′-[1,3]dioxan]-3,5′-dione (beclometasone propyl 17,21-orthopropionate),



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



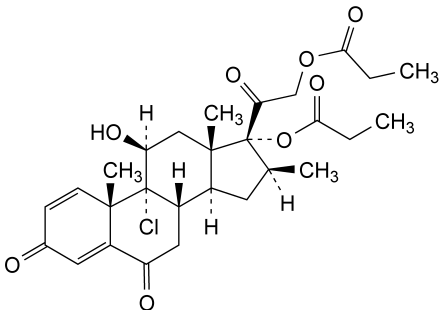
M. 9-chloro-11β-hydroxy-16β-methyl-3,20-dioxopregna-4,6-diene-17,21-diyl dipropanoate,



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.

01/2008:0069

BEESWAX, WHITE

Cera alba

DEFINITION

Wax obtained by bleaching yellow beeswax.

CHARACTERS

Appearance: white or yellowish-white pieces or plates, translucent when thin, with a fine-grained, matt and non-crystalline fracture; when warmed in the hand they become soft and malleable.

It has an odour similar to that of yellow beeswax, though fainter and never rancid. It is tasteless and does not stick to the teeth.

Solubility: practically insoluble in water, partially soluble in hot ethanol (90 per cent *V/V*) and completely soluble in fatty and essential oils.

Relative density: about 0.960.

TESTS

Drop point (*2.2.17*): 61 °C to 66 °C.

Melt the beeswax by heating on a water-bath, pour onto a glass plate and allow to cool to a semi-solid mass. Fill the metal cup by inserting the wider end into the beeswax and repeating the procedure until beeswax extrudes from the narrow opening. Remove the excess with a spatula and insert the thermometer immediately. Remove the beeswax displaced. Allow to stand at room temperature for at least 12 h before determining the drop point.

Acid value: 17.0 to 24.0.

To 2.00 g (*m* g), in a 250 ml conical flask fitted with a reflux condenser, add 40 ml of *xylene R* and a few glass beads. Heat until the substance is dissolved. Add 20 ml of *ethanol (96 per cent) R* and 0.5 ml of *phenolphthalein solution R1* and titrate the hot solution with *0.5 M alcoholic potassium hydroxide* until a red colour persists for at least 10 s (n_1 ml). Carry out a blank test (n_2 ml).

$$\text{Acid value} = \frac{28.05\,(n_1 - n_2)}{m}$$

Ester value (*2.5.2*): 70 to 80.

Saponification value: 87 to 104.

To 2.00 g (*m* g), in a 250 ml conical flask fitted with a reflux condenser, add 30 ml of a mixture of equal volumes of *ethanol (96 per cent) R* and *xylene R* and a few glass beads. Heat until the substance is dissolved. Add 25.0 ml of *0.5 M alcoholic potassium hydroxide* and heat under a reflux condenser for 3 h. Titrate the hot solution immediately with *0.5 M hydrochloric acid*, using 1 ml of *phenolphthalein solution R1* as indicator (n_1 ml). Reheat the solution to boiling several times during the course of the titration. Carry out a blank test (n_2 ml).

$$\text{Saponification value} = \frac{28.05\,(n_2 - n_1)}{m}$$

Ceresin, paraffins and certain other waxes. To 3.0 g, in a 100 ml round-bottomed flask, add 30 ml of a 40 g/l solution of *potassium hydroxide R* in *aldehyde-free alcohol R* and boil gently under a reflux condenser for 2 h. Remove the condenser and immediately insert a thermometer. Place the flask in a water-bath at 80 °C and allow to cool, swirling the solution continuously. No precipitate is formed until 65 °C, although the solution may be slightly opalescent. Beginning at 65 °C, the solution may become cloudy and precipitates may be formed. At 59 °C, the solution is cloudy.

Glycerol and other polyols: maximum 0.5 per cent *m/m*, calculated as glycerol.

To 0.20 g add 10 ml of *alcoholic potassium hydroxide solution R* and heat on a water-bath under a reflux condenser for 30 min. Add 50 ml of *dilute sulphuric acid R*, cool and filter. Rinse the flask and the filter with *dilute sulphuric acid R*. Combine the filtrate and washings and dilute to 100.0 ml with *dilute sulphuric acid R*. Place 1.0 ml of the solution in a test-tube, add 0.5 ml of a 10.7 g/l solution of *sodium periodate R*, mix and allow to stand for 5 min. Add 1.0 ml of *decolorised fuchsin solution R* and mix. Any precipitate disappears. Place the tube in a beaker containing water at 40 °C. During cooling observe for 10-15 min. Any violet-blue colour in the solution is not more intense than that in a standard prepared at the same time and in the same manner using 1.0 ml of a 10 mg/l solution of *glycerol R* in *dilute sulphuric acid R*.