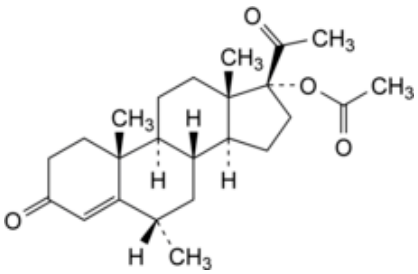
Edition: BP 2025 (Ph. Eur. 11.6 update)

Medroxyprogesterone Acetate

General Notices

(Ph. Eur. monograph 0673)



$C_{24}H_{34}O_4$ 386.5 *71-58-9*

Action and use

Progestogen.

Preparations

Medroxyprogesterone Injection

Medroxyprogesterone Tablets

Ph Eur

DEFINITION

6α-Methyl-3,20-dioxopregn-4-en-17-yl acetate.

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

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *medroxyprogesterone acetate CRS*.

TESTS

Specific optical rotation (*2.2.7*)

+ 47 to + 53 (dried substance).

Dissolve 0.250 g in *acetone R* and dilute to 25.0 mL with the same solvent.

Impurity F

Liquid chromatography (*2.2.29*).

Test solution Dissolve 20 mg of the substance to be examined in 5.0 mL of *acetonitrile R1* and dilute to 10.0 mL with *water for chromatography R*.

Reference solution (a) Dilute 1.0 mL of the test solution to 20.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 10 mg of *medroxyprogesterone acetate for peak identification CRS* (containing impurity F) in 3.0 mL of *acetonitrile R1* and dilute to 5.0 mL with *water for chromatography R*.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase *water for chromatography R*, *acetonitrile R1* (44:56 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 200 nm.

Injection 25 µL.

Identification of impurities Use the chromatogram supplied with *medroxyprogesterone acetate for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity F.

Relative retention With reference to medroxyprogesterone acetate (retention time = about 8 min): impurity F = about 1.8.

Limit:

— *correction factor*: for the calculation of content, multiply the peak area of impurity F by 1.8;

— *impurity F*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent).

Related substances

Liquid chromatography (2.2.29).

Solvent mixture acetonitrile R, water R (50:50 *V/V*).

Test solution Dissolve 20 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dissolve 4 mg of medroxyprogesterone acetate for system suitability CRS (containing impurities A, B, C, D, E, G and I) in the solvent mixture and dilute to 2.0 mL with the solvent mixture.

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

Reference solution (c) Dilute 1.0 mL of reference solution (b) to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 3.0 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 60 °C.

Mobile phase tetrahydrofuran R, acetonitrile R, water R (12:23:65 *V/V/V*).

Flow rate 0.9 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

Run time Twice the retention time of medroxyprogesterone acetate.

Identification of impurities Use the chromatogram supplied with medroxyprogesterone acetate for system suitability CRS and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, C, D, E, G and I.

Relative retention With reference to medroxyprogesterone acetate (retention time = about 20 min): impurity A = about 0.3; impurity I = about 0.5; impurity H = about 0.65; impurity B = about 0.7; impurity C = about 0.8; impurity G = about 0.85; impurity D = about 0.9; impurity E = about 0.95.

System suitability Reference solution (a):

— peak-to-valley ratio: minimum 2.5, where H_p = height above the baseline of the peak due to impurity E and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to medroxyprogesterone acetate.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 1.5; impurity G = 2.6;

— *impurity D*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *impurity B*: not more than 0.7 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.7 per cent);

— *impurity A*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.3 per cent);

— *impurities C, E, G, I*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent);

— *total*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (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 3 h.

ASSAY

Dissolve 50.0 mg in *ethanol (96 per cent) R* and dilute to 50.0 mL with the same solvent. Dilute 2.0 mL of the solution to 100.0 mL with *ethanol (96 per cent) R*. Measure the absorbance (*2.2.25*) at the absorption maximum at 241 nm.

Calculate the content of $C_{24}H_{34}O_4$ taking the specific absorbance to be 420.

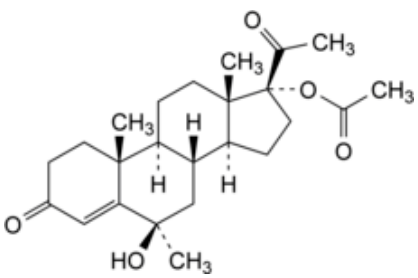
STORAGE

Protected from light.

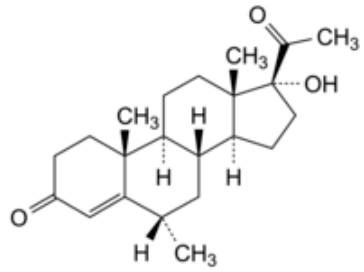
IMPURITIES

Specified impurities *A, B, C, D, E, F, G, I.*

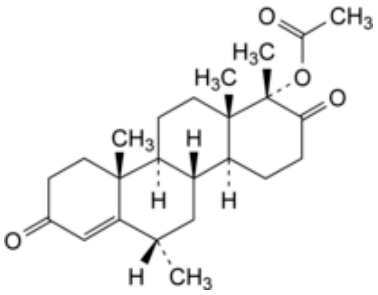
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical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



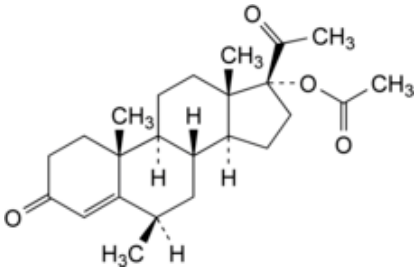
A. 6β-hydroxy-6-methyl-3,20-dioxopregn-4-en-17-yl acetate (6-hydroxymedroxyprogesterone acetate),



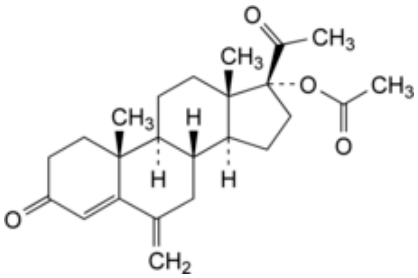
B. 17-hydroxy-6α-methylpregn-4-ene-3,20-dione (medroxyprogesterone),



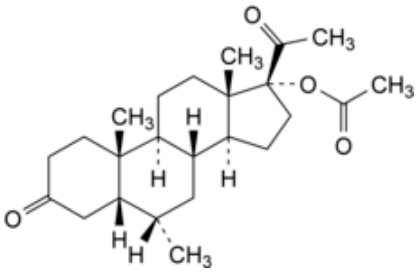
C. 6α,17a-dimethyl-3,17-dioxo-*D*-homoandrost-4-en-17aα-yl acetate,



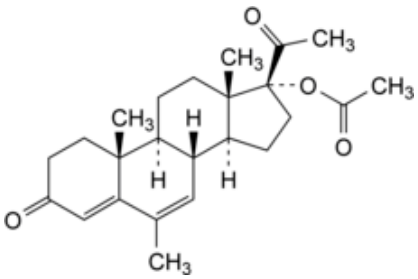
D. 6β-methyl-3,20-dioxopregn-4-en-17-yl acetate (6-epimedroxyprogesterone acetate),



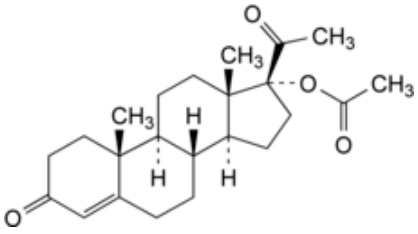
E. 6-methylidene-3,20-dioxopregn-4-en-17-yl acetate (6-methylenehydroxyprogesterone acetate),



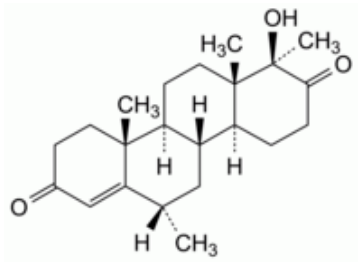
F. 6α-methyl-3,20-dioxo-5β-pregnan-17-yl acetate (4,5-dihydromedroxyprogesterone acetate),



G. 6-methyl-3,20-dioxopregna-4,6-dien-17-yl acetate (megestrol acetate),



H. 3,20-dioxopregn-4-en-17-yl acetate (hydroxyprogesterone acetate),



I. 17aβ-hydroxy-6,17a-dimethyl-*D*-homoandrost-4-ene-3,17-dione.

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