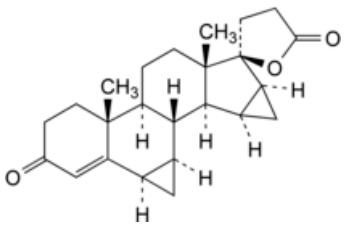
Edition: BP 2025 (Ph. Eur. 11.6 update)

Drospirenone

General Notices

(Ph. Eur. monograph 2404)



$C_{24}H_{30}O_3$ 366.5 *67392-87-4*

Action and use

Aldosterone receptor antagonist.

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DEFINITION

3-Oxo-6α,7α,15α,16α-tetrahydro-3′*H*,3″*H*-dicyclopropa[6,7:15,16]-17α-pregn-4-en-21,17-carbolactone.

Content

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

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, freely soluble in methylene chloride, soluble in methanol, sparingly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Specific optical rotation (see Tests).
B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *drospirenone CRS*.

TESTS

Specific optical rotation (*2.2.7*)

-193 to -187 (dried substance).

Dissolve 0.100 g in *methanol R* and dilute to 10.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

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

Test solution Dissolve 30.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 10.0 mL with the solvent mixture. Use 1.0 mL of this solution to dissolve the contents of a vial of *drospirenone impurity E CRS*.

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.

Reference solution (c) Dissolve 30.0 mg of *drospirenone CRS* in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (d) Dissolve 3 mg of *drospirenone for peak identification CRS* (containing impurity A) in the solvent mixture and dilute to 5.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

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

— *temperature*: 35 °C.

Mobile phase:

— *mobile phase A*: *water R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	63	37
2 - 16	63 → 52	37 → 48
16 - 23	52	48
23 - 31	52 → 20	48 → 80
31 - 39	20	80

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 245 nm.

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

Identification of impurities Use the chromatogram supplied with *drospirenone for peak identification CRS* and the chromatogram obtained with reference solution (d) to identify the peak due to impurity A; use the chromatogram obtained with reference solution (a) to identify the peak due to impurity E.

Relative retention With reference to drospirenone (retention time = about 22 min): impurity E = about 1.1; impurity A = about 1.2.

System suitability Reference solution (a):

— *resolution*: minimum 5.0 between the peaks due to drospirenone and impurity E.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity A by 0.5;

— *impurity A*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *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 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 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 for 3 h.

ASSAY

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

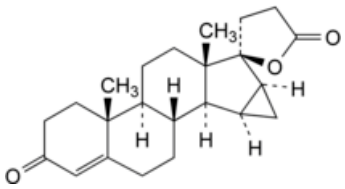
Injection Test solution and reference solution (c).

Calculate the percentage content of $C_{24}H_{30}O_3$ taking into account the assigned content of *drospirenone CRS*.

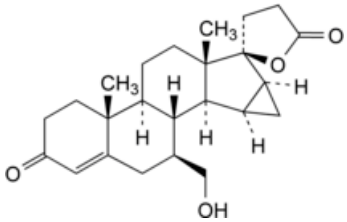
IMPURITIES

Specified impurities *A.*

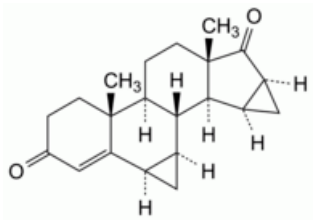
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical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



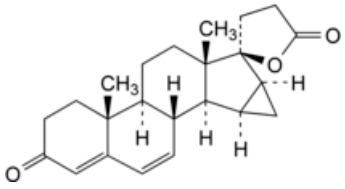
A. 3-oxo-15α,16α-dihydro-3′*H*-cyclopropa[15,16]-17α-pregn-4-ene-21,17-carbolactone (6,7-desmethylenedrospirenone),



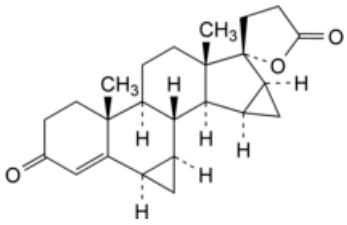
B. 7β-(hydroxymethyl)-3-oxo-15α,16α-dihydro-3′*H*-cyclopropa[15,16]-17α-pregn-4-ene-21,17-carbolactone (7β-hydroxymethyl derivative),



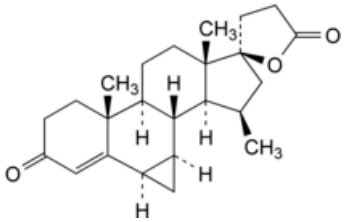
C. 6α,7α,15α,16α-tetrahydro-3′*H*,3″*H* -dicyclopropa[6,7:15,16]androst-4-ene-3,17-dione (17-keto derivative),



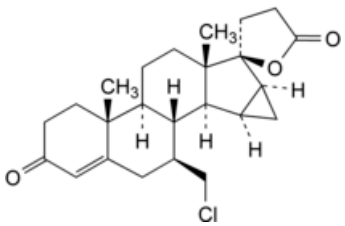
D. 3-oxo-15α,16α-dihydro-3′*H*-cyclopropa[15,16]-17α-pregna-4,6-diene-21,17-carbolactone (Δ6-drospirenone),



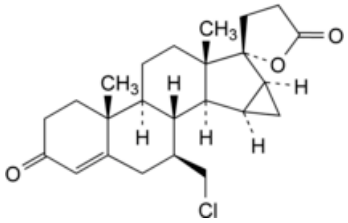
E. 3-oxo-6α,7α,15α,16α-tetrahydro-3′*H*,3″*H* dicyclopropa[6,7:15,16]pregn-4-ene-21,17-carbolactone (17-epidrospirenone),



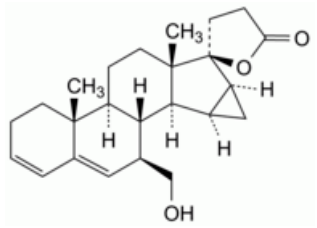
F. 15β-methyl-3-oxo-6α,7α-dihydro-3′*H*-cyclopropa[6,7]-17α-pregn-4-ene-21,17-carbolactone (3″-16-secodrospirenone),



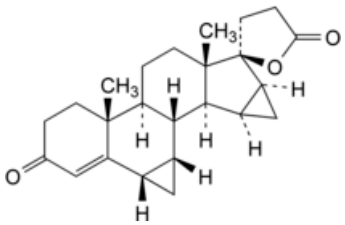
G. 7β-(chloromethyl)-3-oxo-15α,16α-dihydro-3′*H*-cyclopropa[15,16]-17α-pregn-4-ene-21,17-carbolactone (3′-chloro-3′,6-secodrospirenone),



H. 7β-(chloromethyl)-3-oxo-15α,16α-dihydro-3′*H*-cyclopropa[15,16]pregn-4-ene-21,17-carbolactone (3′-chloro-3′,6-seco-17-epidrospirenone),



I. 7β-(hydroxymethyl)-15α,16α-dihydro-3′*H*-cyclopropa[15,16]-17α-pregna-3,5-diene-21,17-carbolactone (7β-hydroxymethyldiene derivative),



K. 3-oxo-6β,7β,15α,16α-tetrahydro-3′*H*,3″*H*-dicyclopropa[6,7:15,16]-17α-pregn-4-ene-21,17-carbolactone (6α,7α-drospirenone).

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