– *stationary phase*: *base-deactivated octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase:

– *mobile phase A*: *acetonitrile R*;

– *mobile phase B*: 10 g/L solution of *tetrabutylammonium hydrogen sulfate R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	0 → 40	100 → 60
15 - 20	40	60
20 - 25	40 → 0	60 → 100

Flow rate: 1.5 mL/min.

Detection: spectrophotometer at 275 nm.

Injection: 10 µL; inject *dimethylformamide R* as a blank.

Retention time: benperidol = about 6.5 min; droperidol = about 7 min.

System suitability: reference solution (a):

– *resolution*: minimum 2.0 between the peaks due to benperidol and droperidol; if necessary, adjust the final concentration of acetonitrile in the mobile phase or adjust the time programme for the linear gradient.

Limits:

– *impurities A, B, C, D, E*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.25 per cent);

– *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

– *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Heavy metals (*2.4.8*): maximum 20 ppm.

1.0 g complies with test D. Prepare the reference solution using 2 mL of *lead standard solution (10 ppm Pb) R*.

Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

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

ASSAY

Dissolve 0.300 g in 50 mL of a mixture of 1 volume of *anhydrous acetic acid R* and 7 volumes of *methyl ethyl ketone R*. Using 0.2 mL of *naphtholbenzein solution R*, titrate with *0.1 M perchloric acid* until the colour changes from orange-yellow to green.

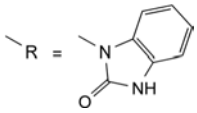
1 mL of *0.1 M perchloric acid* is equivalent to 37.94 mg of $C_{22}H_{22}FN_3O_2$.

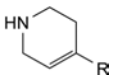
STORAGE

Protected from light.

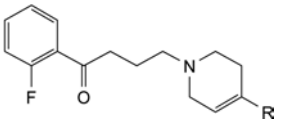
IMPURITIES

Specified impurities: A, B, C, D, E.

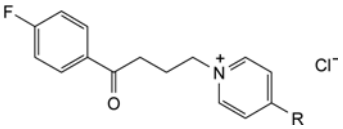




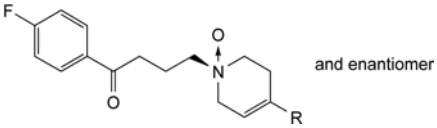
A. 1-(1,2,3,6-tetrahydropyridin-4-yl)-1,3-dihydro-2*H*-benzimidazol-2-one,



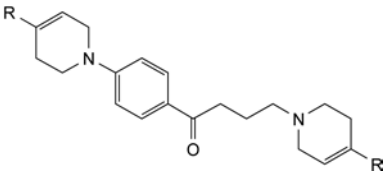
B. 1-[1-[4-(2-fluorophenyl)-4-oxobutyl]-1,2,3,6-tetrahydropyridin-4-yl]-1,3-dihydro-2*H*-benzimidazol-2-one,



C. 1-[4-(4-fluorophenyl)-4-oxobutyl]-4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)pyridinium chloride,



D. (1*RS*)-1-[4-(4-fluorophenyl)-4-oxobutyl]-4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)-1,2,3,6-tetrahydropyridine 1-oxide,

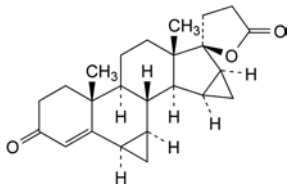


E. 1-[1-[4-[4-[4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)-3,6-dihydropyridin-1(2*H*)-yl]-1-oxobutyl]phenyl]-1,2,3,6-tetrahydropyridin-4-yl]-1,3-dihydro-2*H*-benzimidazol-2-one.

07/2009:2404

DROSPIRENONE

Drospirenonum



$C_{24}H_{30}O_3$ M_r 366.5

[67392-87-4]

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*): – 187 to – 193 (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.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;
– *stationary phase*: spherical *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) and (b).

Relative retention with reference to drospirenone (retention time = about 22 min): impurity E = about 1.1.

System suitability: reference solution (a):

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

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 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

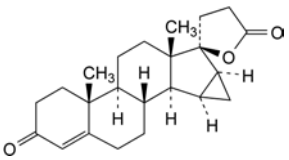
Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection: 10 µL of the test solution and reference solution (c).

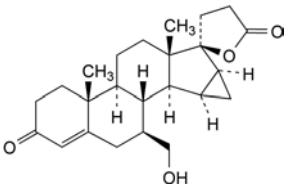
Calculate the percentage content of $C_{24}H_{30}O_3$ from the declared content of *drospirenone CRS*.

IMPURITIES

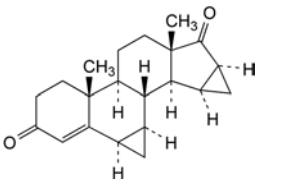
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical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



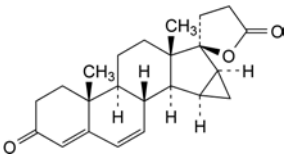
A. 3-oxo-15α,16α-dihydro-3′*H*-cyclopropa[15,16]-17α-pregn-4-ene-21,17-carbolactone (6,7-desmethylenedrospirenone),



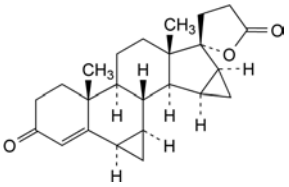
B. 7β-(hydroxymethyl)-3-oxo-15α,16α-dihydro-3′*H*-cyclopropa[15,16]-17α-pregn-4-ene-21,17-carbolactone (7β-hydroxymethyl derivative),



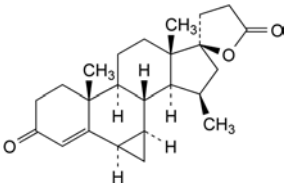
C. 6α,7α,15α,16α-tetrahydro-3′*H*,3″*H* -dicyclopropa-[6,7:15,16]androst-4-ene-3,17-dione (17-keto derivative),



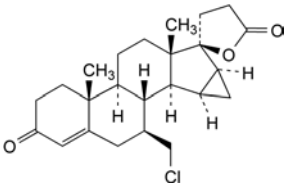
D. 3-oxo-15α,16α-dihydro-3′*H*-cyclopropa[15,16]-17α-pregna-4, 6-diene-21,17-carbolactone (Δ6-drospirenone),



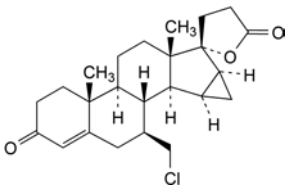
E. 3-oxo-6α,7α,15α,16α-tetrahydro-3′*H*,3″*H* -dicyclopropa[6,7:15,16]pregn-4-ene-21,17-carbolactone (17-epidrospirenone),



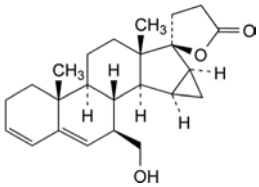
F. 15β-methyl-3-oxo-6α,7α-dihydro-3′*H*-cyclopropa[6,7]-17α-pregn-4-ene-21,17-carbolactone (3″-16-secodrospirenone),



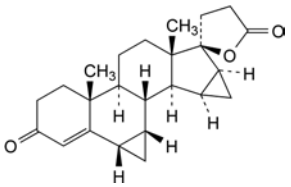
G. 7β-(chloromethyl)-3-oxo-15α,16α-dihydro-3′*H*-cyclopropa[15,16]-17α-pregn-4-ene-21,17-carbolactone (3′-chloro-3′,6-secodrospirenone),



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),

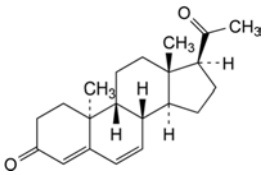


K. 3-oxo-6β,7β,15α,16α-tetrahydro-3′*H*,3″*H*-dicyclopropa-[6,7:15,16]-17α-pregn-4-ene-21,17-carbolactone (6α,7α-drospirenone).

01/2009:2357

DYDROGESTERONE

Dydrogesteronum



$C_{21}H_{28}O_2$ M_r 312.5
[152-62-5]

DEFINITION

9β,10α-Pregna-4,6-diene-3,20-dione.

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

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: practically insoluble in water, soluble in acetone, sparingly soluble in ethanol (96 per cent).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *dydrogesterone CRS*.

TESTS

Specific optical rotation (*2.2.7*): – 469 to – 485 (dried substance), measured at 25 °C.

Dissolve 0.100 g in *methylene chloride R* and dilute to 20.0 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 the mobile phase and dilute to 100.0 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 3.0 mg of *dydrogesterone impurity A CRS* in the mobile phase and dilute to 20.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (b). Dilute 1.0 mL of test solution (a) to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (c). Dissolve 10 mg of the substance to be examined in 10 mL of reference solution (a).

Reference solution (d). Dissolve 10 mg of the substance to be examined in 30 mL of *ethanol (96 per cent) R*. Add 1 mL of a 8.4 g/L solution of *sodium hydroxide R* and heat at 85 °C for 10 min. Cool to room temperature, add 1 mL of a 20.6 g/L solution of *hydrochloric acid R*, add 20 mL of *acetonitrile R*, 2 mg of *dydrogesterone impurity B CRS*, dilute to 100 mL with *water R* and mix. This solution contains dydrogesterone and impurities B and C.

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

Column:

- *size*: *l* = 0.15 m, Ø = 4.6 mm;
- *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (3 μm);
- *temperature*: 40 °C.

Mobile phase: *acetonitrile R, ethanol (96 per cent) R, water R* (21:25:54 *V/V/V*).

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 280 nm and at 385 nm.

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

Run time: twice the retention time of dydrogesterone.

Relative retention at 385 nm with reference to dydrogesterone (retention time = about 13 min): impurity A = about 0.9.

Relative retention at 280 nm with reference to dydrogesterone (retention time = about 13 min): impurity B = about 1.1; impurity C = about 1.2.

System suitability:

- *resolution at 385 nm*: minimum 1.1 between the peaks due to impurity A and dydrogesterone in the chromatogram obtained with reference solution (c);
- *resolution at 280 nm*: minimum 4.5 between the peaks due to dydrogesterone and impurity B and minimum 1.5 between the peaks due to impurity B and impurity C in the chromatogram obtained with reference solution (d).

Limits:

- *impurity A at 385 nm*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.3 per cent);
- *impurity B at 280 nm*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);
- *impurity C at 280 nm*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);
- *unspecified impurities at 280 nm*: 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 at 280 nm*: 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 at 280 nm*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).