Relative retention with reference to detomidine (retention time = about 7 min): impurity A = about 0.4; impurity B = about 2.0; impurity C = about 3.0.

System suitability: reference solution (b):

– *resolution*: minimum 5 between the peaks due to detomidine and impurity B.

Limits:

– *correction factor*: multiply by 2.7 the area of any peak due to impurity C and its diastereoisomer eluting with a relative retention time of about 3;
– *impurity C*: for the sum of the areas of the peaks due to impurity C and its diastereoisomer, not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);
– *any other impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);
– *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1 per cent);
– *disregard limit*: 0.25 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 oven at 105 °C.

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

ASSAY

Dissolve 0.170 g in 50 mL of *ethanol (96 per cent) R*. Add 5.0 mL of *0.01 M hydrochloric acid*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 22.27 mg of $C_{12}H_{15}ClN_2$.

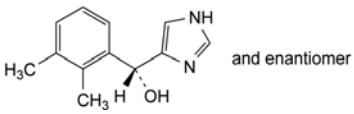
STORAGE

In an airtight container.

IMPURITIES

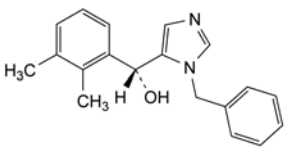
Specified impurities: *C*.

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*.



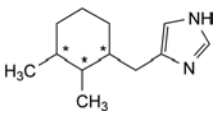
and enantiomer

A. (*RS*)-(2,3-dimethylphenyl)(1*H*-imidazol-4-yl)methanol,



and enantiomer

B. (*RS*)-(1-benzyl-1*H*-imidazol-5-yl)(2,3-dimethylphenyl)-methanol,

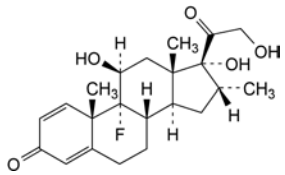


C. 4-[(2,3-dimethylcyclohexyl)methyl]-1*H*-imidazole.

04/2010:0388

DEXAMETHASONE

Dexamethasonum



$C_{22}H_{29}FO_5$ M_r 392.5

[50-02-2]

DEFINITION

9-Fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione.

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, sparingly soluble in anhydrous ethanol, slightly soluble in methylene chloride.

IDENTIFICATION

First identification: *B, C*.

Second identification: *A, C, D, E*.

A. Dissolve 10.0 mg in *anhydrous ethanol R* and dilute to 100.0 mL with the same solvent. Place 2.0 mL of this solution in a stoppered test tube, add 10.0 mL of *phenylhydrazine-sulfuric acid solution R*, mix and heat in a water-bath at 60 °C for 20 min. Cool immediately. The absorbance (*2.2.25*) measured at the absorption maximum at 419 nm is not less than 0.4.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *dexamethasone CRS*.

C. Thin-layer chromatography (*2.2.27*).

Solvent mixture: *methanol R, methylene chloride R* (1:9 *V/V*).

Test solution. Dissolve 10 mg of the substance to be examined in the solvent mixture and dilute to 10 mL with the solvent mixture.

Reference solution (a). Dissolve 20 mg of *dexamethasone CRS* in the solvent mixture and dilute to 20 mL with the solvent mixture.

Reference solution (b). Dissolve 10 mg of *betamethasone CRS* in reference solution (a) and dilute to 10 mL with reference solution (a).

Plate: *TLC silica gel F_{254} plate R*.

Mobile phase: *butanol R* saturated with *water R, toluene R, ether R* (5:10:85 *V/V/V*).

Application: 5 µL.

Development: over 2/3 of the plate.

Drying: in air.

Detection A: examine in ultraviolet light at 254 nm.

Results A: the principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

Detection B: spray with *alcoholic solution of sulfuric acid R*. Heat at 120 °C for 10 min or until the spots appear. Allow to cool. Examine in daylight and in ultraviolet light at 365 nm.

Results B: the principal spot in the chromatogram obtained with the test solution is similar in position, colour in daylight, fluorescence in ultraviolet light at 365 nm and size to the principal spot in the chromatogram obtained with reference solution (a).

System suitability: reference solution (b):

– the chromatogram shows 2 spots which may, however, not be completely separated.

D. Add about 2 mg to 2 mL of *sulfuric acid R* and shake to dissolve. Within 5 min, a faint reddish-brown colour develops. Add this solution to 10 mL of *water R* and mix; the colour is discharged.

E. Mix about 5 mg with 45 mg of *heavy magnesium oxide R* and ignite in a crucible until an almost white residue is obtained (usually less than 5 min). Allow to cool, add 1 mL of *water R*, 0.05 mL of *phenolphthalein solution R1* and about 1 mL of *dilute hydrochloric acid R* to render the solution colourless. Filter. To a freshly prepared mixture of 0.1 mL of *alizarin S solution R* and 0.1 mL of *zirconyl nitrate solution R*, add 1.0 mL of the filtrate. Mix, allow to stand for 5 min and compare the colour of the solution with that of a blank prepared in the same manner. The test solution is yellow and the blank solution is red.

TESTS

Specific optical rotation (*2.2.7*): + 86 to + 92 (dried substance).

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

Related substances. Liquid chromatography (*2.2.29*). *Carry out the test protected from light.*

Test solution. Dissolve 25 mg of the substance to be examined in 1.5 mL of *acetonitrile R* and add 5 mL of mobile phase A. Mix with the aid of an ultrasonic bath until complete dissolution, and dilute to 10.0 mL with mobile phase A.

Reference solution (a). Dissolve 5 mg of *dexamethasone for system suitability CRS* (containing impurities B, F and G) in 0.5 mL of *acetonitrile R* and add 1 mL of mobile phase A. Mix with the aid of an ultrasonic bath until complete dissolution and dilute to 2.0 mL with mobile phase A.

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

Column:

– *size*: *l* = 0.15 m, Ø = 4.6 mm;

– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);

– *temperature*: 45 °C.

Mobile phase:

– *mobile phase A*: mix 250 mL of *acetonitrile R* with 700 mL of *water R* and allow to equilibrate; dilute to 1000.0 mL with *water R* and mix again;

– *mobile phase B*: *acetonitrile R*;

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

Flow rate: 1.2 mL/min.

Detection: spectrophotometer at 254 nm.

Injection: 20 µL; inject mobile phase A as a blank.

Identification of impurities: use the chromatogram supplied with *dexamethasone for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities B, F and G.

Relative retention with reference to dexamethasone (retention time = about 15 min): impurity B = about 0.94; impurity F = about 1.5; impurity G = about 1.7.

System suitability: reference solution (a):

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

Limits:

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

– *impurities B, F*: for each impurity, 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 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 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 0.500 g by drying in an oven at 105 °C.

ASSAY

Dissolve 0.100 g in *ethanol (96 per cent) R* and dilute to 100.0 mL with the same solvent. Dilute 2.0 mL of this solution to 100.0 mL with *ethanol (96 per cent) R*. Measure the absorbance (*2.2.25*) at the absorption maximum at 238.5 nm.

Calculate the content of $C_{22}H_{29}FO_5$ taking the specific absorbance to be 394.

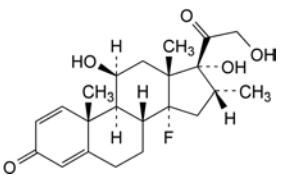
STORAGE

Protected from light.

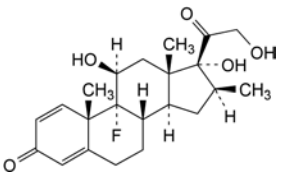
IMPURITIES

Specified impurities: *B, F, G.*

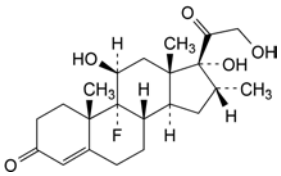
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical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



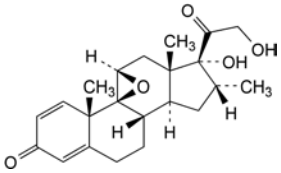
A. 14-fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione,



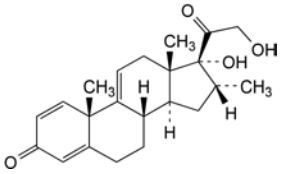
B. 9-fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione (betamethasone),



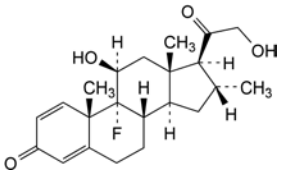
C. 9-fluoro-11β,17,21-trihydroxy-16α-methylpregn-4-ene-3,20-dione,



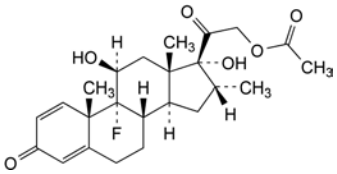
D. 17,21-dihydroxy-16α-methyl-9β,11β-epoxypregna-1,4-diene-3,20-dione,



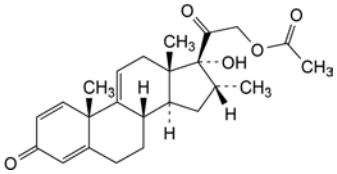
E. 17,21-dihydroxy-16α-methylpregna-1,4,9(11)-triene-3,20-dione,



F. 9-fluoro-11β,21-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione,



G. 9-fluoro-11β,17-dihydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-yl acetate (dexamethasone acetate),

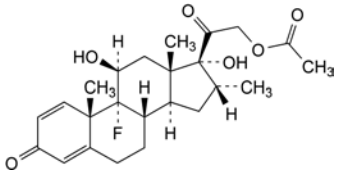


H. 17-hydroxy-16α-methyl-3,20-dioxopregna-1,4,9(11)-trien-21-yl acetate.

04/2010:0548

DEXAMETHASONE ACETATE

Dexamethasoni acetas



$C_{24}H_{31}FO_6$ M_r 434.5
[1177-87-3]

DEFINITION

9-Fluoro-11β,17-dihydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-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 ethanol (96 per cent), slightly soluble in methylene chloride.

It shows polymorphism (*5.9*).

IDENTIFICATION

First identification: B, C.

Second identification: A, C, D, E, F.

A. Dissolve 10.0 mg in *anhydrous ethanol R* and dilute to 100.0 mL with the same solvent. Place 2.0 mL of this solution in a ground-glass-stoppered tube, add 10.0 mL of *phenylhydrazine-sulfuric acid solution R*, mix and heat in a water-bath at 60 °C for 20 min. Cool immediately. The absorbance (*2.2.25*) measured at the absorption maximum at 419 nm is not less than 0.35.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *dexamethasone acetate CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methylene chloride R*, evaporate to dryness and record new spectra using the residues.

C. Thin-layer chromatography (*2.2.27*).

Solvent mixture: *methanol R, methylene chloride R* (1:9 *V/V*).

Test solution. Dissolve 10 mg of the substance to be examined in the solvent mixture and dilute to 10 mL with the solvent mixture.

Reference solution (a). Dissolve 20 mg of *dexamethasone acetate CRS* in the solvent mixture and dilute to 20 mL with the solvent mixture.

Reference solution (b). Dissolve 10 mg of *cortisone acetate R* in reference solution (a) and dilute to 10 mL with reference solution (a).

Plate: *TLC silica gel F_{254} plate R*.

Mobile phase: add a mixture of 1.2 volumes of *water R* and 8 volumes of *methanol R* to a mixture of 15 volumes of *ether R* and 77 volumes of *methylene chloride R*.

Application: 5 µL.

Development: over 3/4 of the plate.

Drying: in air.

Detection A: examine in ultraviolet light at 254 nm.

Results A: the principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

Detection B: spray with *alcoholic solution of sulfuric acid R*, heat at 120 °C for 10 min or until the spots appear, and allow to cool; examine in daylight and in ultraviolet light at 365 nm.

Results B: the principal spot in the chromatogram obtained with the test solution is similar in position, colour in daylight, fluorescence in ultraviolet light at 365 nm and size to the principal spot in the chromatogram obtained with reference solution (a).

System suitability: reference solution (b):

– the chromatogram shows 2 clearly separated spots.

D. Add about 2 mg to 2 mL of *sulfuric acid R* and shake to dissolve. Within 5 min, a faint reddish-brown colour develops. Add this solution to 10 mL of *water R* and mix. The colour is discharged and a clear solution remains.

E. Mix about 5 mg with 45 mg of *heavy magnesium oxide R* and ignite in a crucible until an almost white residue is obtained (usually less than 5 min). Allow to cool, add 1 mL of