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

Calcipotriol and Betamethasone Gel

General Notices

Action and use

Vitamin D analogue + glucocorticoid; maintenance and treatment of psoriasis.

DEFINITION

Calcipotriol and Betamethasone Gel contains Calcipotriol Monohydrate and Betamethasone Dipropionate in a suitable basis.

The gel complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of calcipotriol, $C_{27}H_{40}O_3$

92.0 to 105.0% of the stated amount.

A reversible isomerisation to pre-calcipotriol takes place in solution, depending on temperature and time. The activity is due to both compounds.

Content of betamethasone, $C_{22}H_{29}FO_5$

92.0 to 105.0% of the stated amount.

IDENTIFICATION

A. *For calcipotriol* In the Assay for calcipotriol, record the UV spectrum of the principal peak in the chromatograms obtained with solutions (1) and (2) with a diode array detector in the range of 220 to 360 nm.

The UV spectrum of the first principal peak in the chromatogram obtained with solution (1) is concordant with that of the peak in the chromatogram obtained with solution (2);

the retention time of the first principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

B. *For betamethasone* In the Assay for betamethasone record the UV spectrum of the principal peak in the chromatograms obtained with solutions (3) and (4) with a diode array detector in the range 220 to 360 nm.

The UV spectrum of the second principal peak in the chromatogram obtained with solution (3) is concordant with that of the peak in the chromatogram obtained with solution (4);

the retention time of the second principal peak in the chromatogram obtained with solution (3) is similar to that of the peak in the chromatogram obtained with solution (4).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A 0.132% w/v solution of *diammonium hydrogen orthophosphate* adjusted to pH 6.4 using 1M *orthophosphoric acid*.

Solution B 40 volumes of solution A and 60 volumes of *acetonitrile*.

(1) On a water bath, melt a quantity of gel containing the equivalent of 90 µg of calcipotriol in 10 mL of n-*heptane*. Add 8 mL of solution B and shake for 15 minutes. Allow to separate and add 4 mL of the lower (aqueous) layer to 2 mL of solution A, centrifuge and use the clear lower layer.
(2) On a water bath, melt a quantity of gel containing the equivalent of 0.9 mg of betamethasone in 10 mL of n-*heptane*. Add 8 mL of solution B and shake for 15 minutes. Allow to separate and add 4 mL of the lower (aqueous) layer to 2 mL of solution A, centrifuge and use the clear lower layer.
(3) 0.00075% w/v of *calcipotriol for system suitability EPCRS* and 0.0097% w/v of *betamethasone dipropionate EPCRS* in mobile phase A.
(4) 0.0097% w/v of *betamethasone dipropionate for system suitability A EPCRS* in mobile phase A.
(5) Dilute 1 volume of solution (1) to 100 volumes with mobile phase A. Dilute 1 volume of this solution to 20 volumes with the same solvent.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 2.1 mm) packed with *octadecylsilyl silica gel for chromatography* (1.8 µm) (Zorbax Eclipse Plus RRHD is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 0.4 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a diode array detector (DAD) with a detection wavelength of 264 nm.
(f) Inject 15 µL of each solution.

MOBILE PHASE

Mobile phase A 40 volumes of *acetonitrile* and 60 volumes of solution A.

Mobile phase B 80 volumes of *acetonitrile* and 20 volumes of solution A.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	100	0	isocratic
2-38	100→10	0→90	linear gradient
38-39	10→0	90→100	linear gradient
39-43	0	100	isocratic
43-44	0→100	100→0	linear gradient
44-50	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retentions relative to calcipotriol (retention time, about 14 minutes) are about:

RRT	Impurity	RRT	Impurity
0.91	Pre-calcipotriol	1.16	Betamethasone unknown*
0.96	Calcipotriol impurity C	1.19	Betamethasone unknown*
1.12	Calcipotriol impurity D	1.23	Betamethasone impurity E
0.42	Betamethasone impurity B	1.27	Betamethasone unknown*
0.52	Betamethasone unknown*	1.43	Betamethasone unknown*
0.54	Betamethasone impurity C	1.47	Betamethasone unknown*
0.84	Betamethasone impurity D	1.51	Betamethasone unknown*
1.05	Betamethasone unknown*	1.58	Betamethasone unknown*

RRT	Impurity	RRT	Impurity

* UV scan from a DAD should be used in conjunction with the information above to attribute unknown peaks to the relevant active ingredient.
* Where betamethasone impurities are indicated, these relate to the impurities listed in the monograph for Betamethasone Dipropionate.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* is at least 1.5, where H_p is the height above the baseline of the peak due to calcipotriol impurity D and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to betamethasone dipropionate.

LIMITS

Identify any secondary peaks and attribute to the relevant active ingredient using solutions (3) and (4) and the information included in the above table.

For calcipotriol

Calculate the results by *normalisation*, using all peaks attributed to calcipotriol. Any secondary peak that cannot be attributed to an impurity of betamethasone dipropionate should be calculated with respect to calcipotriol.

In the chromatogram obtained with solution (1):

the area of any peak due to calcipotriol impurity C is not more than 1.5%;

the area of any peak due to calcipotriol impurity D is not more than 1.0%;

the area of any other *secondary peak* is not greater than 0.5%;

the sum of the areas of all secondary peaks is not greater than 3.0%.

Disregard any peak with an area less than 0.05%, and any peak due to betamethasone dipropionate and betamethasone dipropionate related impurities.

For betamethasone dipropionate

Calculate the results by *normalisation*, using all peaks attributed to betamethasone dipropionate.

In the chromatogram obtained with solution (2):

the area of any peak due to betamethasone impurity B is not more than 0.8%;

the area of any peak due to betamethasone impurity C is not more than 0.8%;

the area of any other *secondary peak* is not greater than 0.5%;

the sum of the areas of all *secondary peaks*, excluding impurities B and C, is not greater than 1.0%.

Disregard any peak with an area less than 0.1%, any peak attributed to calcipotriol, pre-calcipotriol and calcipotriol related impurities, and any unattributed secondary peaks.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A 0.132% w/v solution of *diammonium hydrogen orthophosphate* adjusted to pH 6.4 using 1M *orthophosphoric acid*

Solution B 40 volumes of solution A and 60 volumes of *acetonitrile*.

(1) On a water bath, melt a quantity of gel containing the equivalent of 90 µg mg of calcipotriol in 10 mL of *n-heptane*. Add 8 mL of solution B and shake for 15 minutes. Allow to separate and add 4 mL of the lower (aqueous) layer to 2 mL of solution A, centrifuge and use the clear lower layer.
(2) 0.0008% w/v of *calcipotriol monohydrate EPCRS* in mobile phase A.

(3) On a water batch melt a quantity of gel containing the equivalent of 0.9 mg of betamethasone in 10 mL of n-*heptane*. Add 8 mL of solution B and shake for 15 minutes. Allow to separate and add 4 mL of the lower (aqueous) layer to 2 mL of solution A, centrifuge and use the clear lower layer.
(4) 0.0097% w/v of *betamethasone dipropionate EPCRS* in mobile phase A.
(5) 0.0008% w/v of *calcipotriol for system suitability EPCRS* and 0.0097% w/v of *betamethasone dipropionate EPCRS* in mobile phase A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5), the *peak-to-valley ratio* is at least 1.5, where H_p is the height above the baseline of the peak due to calcipotriol impurity D and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to betamethasone dipropionate.

DETERMINATION OF CONTENT

For calcipotriol

Combine the areas of the peaks due to calcipotriol and pre-calcipotriol. Calculate the content of $C_{27}H_{40}O_3$ in the gel using the declared content of $C_{27}H_{40}O_3$ in *calcipotriol monohydrate EPCRS*.

For betamethasone

Calculate the content of betamethasone $C_{22}H_{29}FO_5$ in the gel using the declared content of betamethasone dipropionate $C_{28}H_{37}FO_7$ in *betamethasone dipropionate EPCRS*. Each mg of $C_{28}H_{37}FO_7$ is equivalent to 0.7778 mg of $C_{22}H_{29}FO_5$.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of calcipotriol and the equivalent amount of betamethasone.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities C and D listed under Calcipotriol Monohydrate and impurities B, C, D and E listed under Betamethasone Dipropionate:

calcipotriol impurity C
calcipotriol impurity D
betamethasone dipropionate impurity B
betamethasone dipropionate impurity C
betamethasone dipropionate impurity D
betamethasone dipropionate impurity E