Calcipotriol and Betamethasone Cutaneous Foam

Details for the public consultation of this monograph are as follows:

EAG/Panel/Working Party	**Medicinal Chemicals 3**
Contact Details	adrian.evans@mhra.gov.uk
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Target Publication Date (subject to change)	BP 2020
Notes:	New monograph If limits are too restrictive, please provide batch/stability data to demonstrate that an increase is required.

Action and use

Vitamin D analogue + glucocorticoid.

DEFINITION

Calcipotriol and Betamethasone Cutaneous Foam contains Calcipotriol Monohydrate and Betamethasone Dipropionate in a suitable basis.

The cutaneous foam 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 forms.

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

92.0 to 105.0% of the stated amount.

IDENTIFICATION

A. In the Assay, the ultraviolet absorption spectrum, Appendix II B, of solution (1) in the range 220 to 360 nm is similar to the spectrum obtained with solution (2).

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

C. In the Assay, the ultraviolet absorption spectrum, Appendix II B, of solution (3) in the range 220 to 360 nm is similar to the spectrum obtained with solution (4).

D. In the Assay, the retention time of the 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 60 volumes of acetonitrile and 40 volumes of solution A.

(1) On a water bath, heat a quantity of cutaneous foam 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.
(2) On a water bath, melt a quantity of cutaneous foam containing the equivalent of 90 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 BPCRS* and 0.097% w/v of *betamethasone dipropionate BPCRS* in mobile phase A
(4) 0.00075% w/v of *calcipotriol BPCRS* in mobile phase A.
(5) 0.097% w/v of betamethasone dipropionate for system suitability A CRS in mobile phase A.
(6) Dilute 1 volume of solution (1) to 100 volumes with mobile phase A, further dilute 5 volumes of this solution to 100 volumes with the same solvent.

CHROMATOGRAPHIC CONDITIONS

(a) Use a column (150 mm × 2.1 mm) packed with octadecylsilyl silica gel for UHPLC (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 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

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
44-50	100	0	re-equilibration

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

RRT	Impurity	RRT	Impurity
0.91	Pre-calcipotriol	1.16	Betamethasone unknown*
0.96	Caclipotriol impurity C	1.19	Betamethasone unknown*
1.12	Caclipotriol 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*

* UV scan from a PDA detector, or response ratios from a dual wavelength detector, should be used in conjunction with the information above to attribute unknown peaks to the relevant active ingredient.

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 correct API using solutions (4) and (5) 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):

calcipotriol impurity C is not more than 1.50%;

calcipotriol impurity D is not more than 1.0%.

any other *secondary peak* is not greater than 0.50%;

the sum of all secondary peaks is not greater than 1.50%.

Disregard any peak less than 0.050% and any peak due to betamethasone dipropionate.

For betamethsone dipropionate

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

In the chromatogram obtained with solution (2):

betamethasone impurity B is not more than 0.80%;

betamethasone impurity C is not more than 0.80%;

any other *secondary peak* is not greater than 0.50%;

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

Disregard any peak less than 0.10% and any peak attributed to calcipotriol.

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 60 volumes of acetonitrile and 40 volumes of solution A.

(1) On a water bath, melt a quantity of cutaneous foam 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.
(2) 0.00075% w/v of *calcipotriol BPCRS* in mobile phase A.
(3) On a water bath, melt a quantity of cutaneous foam containing the equivalent of 90 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) 0.097% w/v of *betamethasone propionate BPCRS* in mobile phase A.
(5) 0.00075% w/v of *calcipotriol BPCRS* and 0.097% w/v of *betamethasone dipropionate BPCRS* in mobile phase A

CHROMATOGRAPHIC CONDITIONS

The chromatography described under Related substances may be used.

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.

DETERMINATION OF CONTENT

For calcipotriol

combine the peaks due to calcipotriol and pre-calcipotriol. Calculate the content of $C_{27}H_{40}O_3$ in the cutaneous foam using the declared content of $C_{27}H_{40}O_3$ in *calcipotriol BPCRS*.

For betamethasone

Calculate the content of betamethasone ($C_{22}H_{29}FO_5$) in the cutaneous foam 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 1.2857 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 betamethasone.

IMPURITIES

The impurities limited by the requirements of this monograph include the following impurities from the monographs for Calcipotriol Monohydrate and Betamethasone Dipropionate:

calcipotriol impurity C
calcipotriol impurity D
betamethasone impurity B
betamethasone impurity C