Public Assessment Report

Decentralised Procedure

Dalbecal 50 microgram/g + 0.5mg/ g Ointment
Calcipotriol/Betamethasone 50 micrograms per g / 500 micrograms per g ointment

Calcipotriol, anhydrous and betamethasone dipropionate

Procedure No: UK/H/2269 and 5269-5270/001/DC

UK Licence No: PL 00289/1216 and 1781-1782

Teva UK Limited
LAY SUMMARY
Dalbecal 50 microgram/g + 0.5mg/g Ointment
Calcipotriol/Betamethasone 50 micrograms per g / 500 micrograms per g ointment
(calcipotriol (anhydrous) 50 micrograms/g and betamethasone 0.5mg [as 0.643 mg betamethasone dipropionate]/g, ointment)

This is a summary of the Public Assessment Report (PAR) for Dalbecal 50 microgram/g + 0.5mg/g Ointment (PL 00289/1216; UK/H/2269/001/DC) and Calcipotriol/Betamethasone 50 micrograms per g / 500 micrograms per g ointment (PL 00289/1781-2; UK/H/5269-5270/001/DC). It explains how Dalbecal 50 microgram/g + 0.5mg/g Ointment or Calcipotriol/Betamethasone 50 micrograms per g / 500 micrograms per g ointment were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Dalbecal 50 microgram/g + 0.5mg/g Ointment or Calcipotriol/Betamethasone 50 micrograms per g / 500 micrograms per g ointment.

For practical information about using Dalbecal 50 microgram/g + 0.5mg/g Ointment or Calcipotriol/Betamethasone 50 micrograms per g / 500 micrograms per g ointment, patients should read the package leaflet(s) or contact their doctor or pharmacist.

The products may be referred to as Dalbecal Ointment and Calcipotriol/Betamethasone ointment in this report.

What are Dalbecal Ointment and Calcipotriol/Betamethasone ointment and what are they used for?
Dalbecal Ointment and Calcipotriol/Betamethasone ointment are used on the skin to treat plaque psoriasis (psoriasis vulgaris) in adults. Psoriasis is caused by the skin cells being produced too quickly. This causes redness, scaling and thickness of the skin.

Dalbecal Ointment and Calcipotriol/Betamethasone ointment are ‘hybrid’ medicines. This means that Dalbecal Ointment and Calcipotriol/Betamethasone ointment contain the same active substances and are similar to a reference medicine already authorised in the European Union (EU) called Dovobet 50 microgram/g + 0.5 mg/g ointment (Leo Pharma A/S, Denmark).

How are Dalbecal Ointment and Calcipotriol/Betamethasone ointment used?
Dalbecal Ointment and Calcipotriol/Betamethasone ointment can only be obtained on prescription.

How do Dalbecal Ointment and Calcipotriol/Betamethasone ointment work?
Dalbecal Ointment and Calcipotriol/Betamethasone ointment contain the active substances calcipotriol (anhydrous) and betamethasone (as betamethasone dipropionate). Calcipotriol helps to bring the rate of skin cell growth back to normal and betamethasone acts to reduce inflammation.

How have Dalbecal Ointment and Calcipotriol/Betamethasone ointment been studied?
Because Dalbecal Ointment and Calcipotriol/Betamethasone ointment are hybrid medicines, studies in patients have been limited to tests to determine that they are therapeutically equivalent to the reference medicine, Dovobet 50 microgram/g + 0.5 mg/g ointment (Leo Pharma A/S, Denmark). Two medicines are therapeutically equivalent when they produce the same measure of the therapeutic effect in the body.

In addition the company provided data from the published literature on calcipotriol (anhydrous) and betamethasone dipropionate, individually and in combination.
What are the benefits and risks of Dalbecal Ointment and Calcipotriol/Betamethasone ointment?
Because Dalbecal Ointment and Calcipotriol/Betamethasone ointment are hybrid medicines and are therapeutically equivalent to the reference medicine, Dovobet 50 microgram/g + 0.5 mg/g ointment (Leo Pharma A/S, Denmark), their benefits and risks are taken as being the same as the reference medicine.

Why are Dalbecal Ointment and Calcipotriol/Betamethasone ointment approved?
It was concluded that, in accordance with EU requirements, Dalbecal Ointment and Calcipotriol/Betamethasone ointment have been shown to have comparable quality and to be comparable to Dovobet 50 microgram/g + 0.5 mg/g ointment (Leo Pharma A/S, Denmark). Therefore, the view was that, as for Dovobet 50 microgram/g + 0.5 mg/g ointment (Leo Pharma A/S, Denmark), the benefit outweighs the identified risk.

What measures are being taken to ensure the safe and effective use of Dalbecal Ointment and Calcipotriol/Betamethasone ointment?
Safety information has been included in the Summary of Product Characteristics and the package leaflets for Dalbecal Ointment and Calcipotriol/Betamethasone ointment, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Dalbecal Ointment and Calcipotriol/Betamethasone ointment.
Marketing Authorisations were granted in the UK on 18 September 2013.

For more information about treatment with Dalbecal Ointment and Calcipotriol/Betamethasone ointment, read the package leaflet(s), or contact your doctor or pharmacist.

This summary was last updated in November 2013.

The full PAR for Dalbecal 50 microgram/g + 0.5mg/g Ointment and Calcipotriol/Betamethasone 50 micrograms per g / 500 micrograms per g ointment follows this summary.
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</table>
Module 1
Information about the initial procedure

| Product Name | UK/H/2269/001/DC: Dalbecal 50 microgram/g + 0.5mg/g Ointment
|              | UK/H/5269/001/DC: Calcipotriol/Betamethasone 50 micrograms per g / 500 micrograms per g ointment
|              | UK/H/5270/001/DC: Calcipotriol/Betamethasone 50 micrograms per g / 500 micrograms per g ointment
| Type of Application(s) | Hybrid, 10(3)
| Active Substance(s) | (1) Calcipotriol anhydrous
|                     | (2) Betamethasone dipropionate
| Form(s) | Ointment
| Strength(s) | 50 micrograms calcipotriol and 500 micrograms betamethasone (as 0.643 mg betamethasone dipropionate) per g ointment
| MA Holder | Teva UK Limited, Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG, United Kingdom
| Reference Member State (RMS) | UK
| Concerned Member States (CMS) | UK/H/2269/001/DC:
|                              | Belgium, Germany, Denmark, Spain, Finland, France, Ireland, Iceland, Italy, the Netherlands, Norway, Poland, Portugal, Sweden and Slovenia
|                              | UK/H/5269/001/DC:
|                              | Germany, Spain, France, Luxembourg, and Portugal
|                              | UK/H/5270/001/DC:
|                              | Germany
| Procedure Numbers | UK/H/2269 and 5269-5270/001/DC
| Timetable | Day 210 – 05 August 2013
Module 2  
Summary of Product Characteristics

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU, the Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4
Labelling
Dalbecal 50 mcg/g and 0.5mg/g Ointment & Calcipotriol/Betamethasone 50 mcg per g / 500 mcg per g ointment

The Marketing Authorisation Holder has submitted the text versions only for Calcipotriol/Betamethasone 50 micrograms per g / 500 micrograms per g ointment (PL 00289/1781-2; UK/H/5269-5270/001/DC) and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed.

<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON &lt;THE OUTER PACKAGING&gt; &lt;AND&gt; &lt;THE IMMEDIATE PACKAGING&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>TUBE LABEL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcipotriol/Betamethasone 50 micrograms per g / 500 micrograms per g ointment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>One gram of ointment contains 50 micrograms of calcipotriol (anhydrous) and 0.5 mg of betamethasone (as 0.643 mg betamethasone dipropionate).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. LIST OF EXCIPIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liquid paraffin, polyoxypropylene-15 stearyl ether, white soft paraffin and butylhydroxytoluene (E321).</td>
</tr>
<tr>
<td>Please see the enclosed leaflet for further information</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ointment</td>
</tr>
<tr>
<td>30g</td>
</tr>
<tr>
<td>60g</td>
</tr>
<tr>
<td>120g</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>For cutaneous use only.</td>
</tr>
<tr>
<td>Please read the package leaflet before use</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep out of the sight and reach of children.</td>
</tr>
</tbody>
</table>

| 7. OTHER SPECIAL WARNING(S), IF NECESSARY |
8. **EXPIRY DATE**

EXP

After first opening: 1 year

9. **SPECIAL STORAGE CONDITIONS**

Do not store above 25°C.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Discard the tube 1 year after the date of first opening.

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Teva UK Ltd, Eastbourne, BN22 9AG

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 00289/1781

13. **BATCH NUMBER**

LOT

14. **GENERAL CLASSIFICATION FOR SUPPLY**

POM

15. **INSTRUCTIONS ON USE**

Use as directed by the doctor

16. **INFORMATION IN BRAILLE**
** PARTICULARS TO APPEAR ON <THE OUTER PACKAGING> <AND> <THE IMMEDIATE PACKAGING>**

**CARTON**

1. **NAME OF THE MEDICINAL PRODUCT**

Calcipotriol/Betamethasone 50 micrograms per g / 500 micrograms per g ointment

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

One gram of ointment contains 50 micrograms of calcipotriol (anhydrous) and 0.5 mg of betamethasone (as 0.643 mg betamethasone dipropionate).

3. **LIST OF EXCIPIENTS**

Liquid paraffin, polyoxypropylene-15 stearyl ether, white soft paraffin and butylhydroxytoluene (E321).

Please see the enclosed leaflet for further information

4. **PHARMACEUTICAL FORM AND CONTENTS**

Ointment

30g
60g
120g

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

For cutaneous use only.

Please read the package leaflet before use

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**
8. EXPIRY DATE

EXP

After first opening: 1 year

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard the tube 1 year after the date of first opening.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva UK Ltd, Eastbourne, BN22 9AG

12. MARKETING AUTHORISATION NUMBER(S)

PL 00289/1781

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Use as directed by the doctor

16. INFORMATION IN BRAILLE

Calcipotriol/Betamethasone 50 micrograms per g / 500 micrograms per g ointment
PARTICULARS TO APPEAR ON <THE OUTER PACKAGING> <AND> <THE IMMEDIATE PACKAGING>

TUBE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Calcipotriol/Betamethasone 50 micrograms per g / 500 micrograms per g ointment

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One gram of ointment contains 50 micrograms of calcipotriol (anhydrous) and 0.5 mg of betamethasone (as 0.643 mg betamethasone dipropionate).

3. LIST OF EXCIPIENTS

Liquid paraffin, polyoxypropylene-15 stearyl ether, white soft paraffin and butylhydroxytoluene (E321).

Please see the enclosed leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Ointment

30g
60g
120g

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For cutaneous use only.

Please read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY
8. EXPIRY DATE

EXP

After first opening: 1 year

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard the tube 1 year after the date of first opening.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva UK Ltd, Eastbourne, BN22 9AG

12. MARKETING AUTHORISATION NUMBER(S)

PL 00289/1782

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Use as directed by the doctor

16. INFORMATION IN BRAILLE
PARTICULARS TO APPEAR ON <THE OUTER PACKAGING> <AND> <THE IMMEDIATE PACKAGING>

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Calcipotriol/Betamethasone 50 micrograms per g / 500 micrograms per g ointment

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One gram of ointment contains 50 micrograms of calcipotriol (anhydrous) and 0.5 mg of betamethasone (as 0.643 mg betamethasone dipropionate).

3. LIST OF EXCIPIENTS

Liquid paraffin, polyoxypropylene-15 stearyl ether, white soft paraffin and butylhydroxytoluene (E321).

Please see the enclosed leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Ointment

30g

60g

120g

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For cutaneous use only.

Please read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY
8. **EXPIRY DATE**

EXP

After first opening: 1 year

9. **SPECIAL STORAGE CONDITIONS**

Do not store above 25°C.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Discard the tube 1 year after the date of first opening.

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Teva UK Ltd, Eastbourne, BN22 9AG

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 00289/1782

13. **BATCH NUMBER**

LOT

14. **GENERAL CLASSIFICATION FOR SUPPLY**

POM

15. **INSTRUCTIONS ON USE**

Use as directed by the doctor

16. **INFORMATION IN BRAILLE**

Calcipotriol/Betamethasone 50 micrograms per g / 500 micrograms per g ointment
Module 5

Scientific discussion during initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Dalbecal 50 microgram per g / 50 micrograms per g ointment (PL 00289/1216; UK/H/2269/001/DC) and Calcipotriol/Betamethasone 50 micrograms per g / 500 micrograms per g ointment (PL 00289/1781-2; UK/H/5269-5270/001/DC) could be approved. The products are prescription-only medicines (POM) and are indicated for the topical treatment of stable plaque psoriasis vulgaris amenable to topical therapy in adults.

The applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Belgium, Germany, Denmark, Spain, Finland, France, Ireland, Iceland, Italy, Luxembourg, the Netherlands, Norway, Poland, Portugal, Sweden and Slovenia as Concerned Member States (CMS). The applications were submitted under Article 10(3) of Directive 2001/83/EC, as hybrid applications. The reference medicinal product for these applications is Dovobet 50 microgram/g + 0.5 mg/g ointment (Leo Pharma A/S, Denmark), which was first authorised in the UK on 18 December 2001.

Dalbecal 50 microgram per g / 50 micrograms per g ointment and Calcipotriol/Betamethasone 50 micrograms per g / 500 micrograms per g ointment contain the active ingredients, calcipotriol (anhydrous), a vitamin D analogue, and betamethasone dipropionate. Calcipotriol is a synthetic derivative of calcitriol (1,25-dihydroxyvitamin D), an active form of vitamin D₃. Betamethasone is a synthetic corticosteroid with a chemical structure similar to dexamethasone. Like other topical corticosteroids, betamethasone dipropionate has anti-inflammatory, antipruritic, vasoconstrictive and immunosuppressive properties.

No new non-clinical data have been submitted and none are required for these applications, given that these are hybrid applications based on an originator product that has been in clinical use for over 10 years. The non-clinical dossier consists of published literature and this is acceptable.

One therapeutic equivalence study was submitted to support these applications, comparing the applicant’s test product (a calcipotriol + betamethasone 50 µg/g + 0.5 mg/g ointment) versus the reference product Dovobet (Leo Pharma A/S, Denmark) and vehicle. The study was conducted in accordance with the European Medicines Agency’s Guideline on Clinical Investigation of Medicinal Products Indicated for the Treatment of Psoriasis (CHMP/EWP/2454/02 corr, 204).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of these products. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites. For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates issued by the inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS and CMS considered that the applications could be approved at the end of procedure (Day 210) on 05 August 2013. After a subsequent national phase, licences were granted in the UK on 18 September 2013.
II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name(s) of the product(s) in the Reference Member State</th>
<th>UK/H/2269/001/DC: Dalbecal 50 microgram/g + 0.5mg/g Ointment UK/H/5269/001/DC: Calcipotriol/Betamethasone 50 micrograms per g / 500 micrograms per g ointment UK/H/5270/001/DC: Calcipotriol/Betamethasone 50 micrograms per g / 500 micrograms per g ointment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>(1) Calcipotriol anhydrous (2) Betamethasone dipropionate</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Other antipsoriatics for topical use, Calcipotriol, combinations. (ATC code: D05AX52)</td>
</tr>
<tr>
<td>Pharmaceutical form(s) and strength(s)</td>
<td>Ointment; 50 micrograms calcipotriol (anhydrous) and 500 micrograms betamethasone (as 0.643 mg betamethasone dipropionate) per g ointment</td>
</tr>
<tr>
<td>Reference number(s) for the Decentralised Procedure</td>
<td>UK/H/2269/001/DC UK/H/5269/001/DC UK/H/5270/001/DC</td>
</tr>
<tr>
<td>Reference Member State (RMS)</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Concerned Member State(s) (CMS)</td>
<td>UK/H/2269/001/DC: Belgium, Germany, Denmark, Spain, Finland, France, Ireland, Iceland, Italy, the Netherlands, Norway, Poland, Portugal, Sweden and Slovenia UK/H/5269/001/DC: Germany, Spain, France, Luxembourg, and Portugal UK/H/5270/001/DC: Germany</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 00289/1216 PL 00289/1781-2</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Teva UK Limited, Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG, United Kingdom</td>
</tr>
</tbody>
</table>

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE - CALCIPOTRIOL, ANHYDROUS

Chemical Name: (5Z,7E,22E,24S)-24-Cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-1α,3β,24-triol

Molecular formula: C_{27}H_{40}O_{3}

Structure:

Molecular mass: 412.6

Appearance: White or almost white, crystalline powder

Solubility: Practically insoluble in water, freely soluble in ethanol (96 per cent), slightly soluble in methylene chloride.

Calcipotriol, anhydrous is the subject of a European Pharmacopoeia monograph.
All aspects of the manufacture and control of the active substance, calcipotriol, anhydrous, are covered by European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability.

ACTIVE SUBSTANCE - BETAMETHASONE DIPROPIONATE
Chemical Name: 9-Fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione17,21-dipropionate.
Molecular formula: C$_{28}$H$_{37}$FO$_7$
Structure: 

Molecular mass: 504.6
Appearance: White or almost white, crystalline powder
Solubility: Practically insoluble in water, freely soluble in acetone and in methylene chloride, sparingly soluble in ethanol (96 per cent).

Betamethasone dipropionate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, betamethasone dipropionate, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

MEDICINAL PRODUCT
Other Ingredients
Other ingredients consist of the pharmaceutical excipients liquid paraffin, polyoxypropylene-15 stearyl ether, white soft paraffin and butylhydroxytoluene (E321). Appropriate justification for the inclusion of each excipient has been provided.

All the excipients comply with their respective European Pharmacopoeia monographs with the exception of polyoxypropylene-15 stearyl ether, which is controlled to a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Pharmaceutical Development
The objective of the development programme was to develop a robust safe, efficacious ointment formulation consisting of (calcipotriol + betamethasone; 50 μg/g + 0.5 mg/g) comparable in performance to the reference product, Dovobet/Daivobet (calcipotriol + betamethasone; 50 μg/g + 0.5 mg/g) Ointment (Leo Laboratories).

Suitable pharmaceutical development data have been provided for these applications.

A comparison of various physico-chemical properties has been provided for the proposed and reference products.

Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated.
with full production-scale batches and has shown satisfactory results.

**Control of Finished Product**
The finished product specifications are acceptable. Test methods have been described and adequately validated, as appropriate. Batch data have been provided, which comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

**Container-Closure System**
The products are packaged in aluminium tubes with high density polyethylene (HDPE) closures. The inner surfaces of the tubes are coated with epoxy phenolic resin. The tubes are packed with the Patient Information Leaflet into cardboard cartons, in pack sizes of 30 g, 60 g and 120 g.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for the primary packaging material have been provided. All primary packaging is controlled to European Pharmacopoeia standards and complies with guidance concerning materials in contact with foodstuff.

**Stability of the Product**
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf life of 3 years for the unopened product and 1 year for the opened product, with the storage instructions ‘Do not store above 25°C.’ have been accepted.

**Therapeutic Equivalence**
The applicant has submitted a therapeutic equivalence study which is appropriate for these topical products as standard bioequivalence studies are not applicable for applications of this type. The therapeutic equivalence study is discussed in Section III.3, Clinical Aspects.

**Summaries of Product Characteristics (SmPCs), Product Information Leaflets (PILs) and Labels**
The SmPCs, PILs and labels are satisfactory from a pharmaceutical perspective. Mock-ups of the labelling and PIL have been provided for Dalbecal 50 microgram per g / 50 micrograms per g Ointment. Final text versions of the labelling and PIL for Calcipotriol/Betamethasone 50 micrograms per g / 500 micrograms per g ointment have been provided. The Marketing Authorisation Holder has committed to submitting mock-ups to the relevant competent authorities for approval before marketing any pack size.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that the leaflet contains.

**Marketing Authorisation Application (MAA) Forms**
The MAA forms are satisfactory from a pharmaceutical perspective.

**Expert Report (Quality Overall Summary)**
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

**Conclusion**
The grant of Marketing Authorisations is recommended.
III.2 NON-CLINICAL ASPECTS
The pharmacodynamic, pharmacokinetic and toxicological properties of calcipotriol and betamethasone, individually and in combination, are well-known. No new non-clinical data have been submitted and none are required.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

The MAH has provided adequate justification for non-submission of an Environmental Risk Assessment (ERA). As these products are intended to replace a currently marketed medicinal product, no increase in environmental exposure to calcipotriol and betamethasone is anticipated.

The grant of Marketing Authorisations is recommended.

III.3 CLINICAL ASPECTS
Clinical Pharmacology
The clinical pharmacology of calcipotriol and betamethasone is well-known. With the exception of data from the therapeutic equivalence study detailed below, no new pharmacodynamic or pharmacokinetic data are provided or required for these applications.

In support of the applications, the Marketing Authorisation Holder submitted the following therapeutic equivalence study:

A multicentre, randomised, double-blind, parallel-group study comparing the efficacy and safety of a Teva ointment (calcipotriol + betamethasone 50 µg/g + 0.5 mg/g ointment) versus vehicle (Teva) and Dovobet (Leo Laboratories Limited, UK) in the treatment of mild to severe plaque-type psoriasis.

Patients with the clinical diagnosis of mild to severe plaque psoriasis were randomised in a 3:3:1 fashion to the treatment arms: the proposed product, Dovobet or vehicle, respectively.

Before start of the study a (medication) washout period of 2-4 weeks was applied to patients that were treated with local treatments for psoriasis or systemic corticosteroids.

The study required 4 or 5 visits: Screening Visit, Baseline (may be identical to Screening Visit) and Weeks 3, 5 and 9. The maximum total time that a subject could be in the study was (4+) 8 weeks: (possible 4 weeks washout), 4 weeks under study treatment and 4 weeks without study treatment but without breaking the blind to assess relapse and rebound effects.

Patients were required to have:
• mild to severe psoriasis, as defined by an Investigator’s Static Global Assessment (ISGA) of at least 2 at Baseline Visit greater than or equal to 10% of one body segment (arms, or legs, or trunk) and less than or equal to 30% of total body surface area (BSA) affected , excluding the face and scalp.
• a target lesion (greater than 2 cm²) on the trunk or extremities (excluding palms/soles) with a score of at least 2 (on a 0-5 scale) for each of erythema, scaling and plaque thickness) at Baseline Visit. Whenever possible, knees or elbows were not to be used as a target lesion.

If new psoriatic lesions appeared during the treatment period, they were to be treated as well. A representative number of subjects with each level of severity of psoriasis (mild, moderate and severe) were included.

The dose used was the smallest amount of medication necessary to cover all lesions (excluding the face and
scalp); the maximum daily dose not exceeding 15g, the maximum weekly dose not exceeding 100 g and the treated area not more than 30% of BSA. All study treatments were administered once daily.

The primary variable (efficacy end-point) in the study was the percentage reduction in the Modified Psoriasis Area and Severity Index (PASI) score from Baseline to Week 5 (Visit 3). The Modified PASI grading system uses a mathematical formula that yields a single number (0 to 64.8) to communicate disease severity and to monitor a subject’s response to therapy over time. The higher the Modified PASI score, the more severe psoriasis.

An ISGA, the severity of the signs of psoriasis of the target lesion (erythema, scaling and plaque thickness) and Subject’s Global Assessment were performed at all visits.

Equivalence between the two active arms was assumed if the 95% confidence intervals for the difference between the mean percentage reductions in Modified PASI score from baseline to week 4 were within ±10%.

The results for the primary variable in the intent-to-treat population (ITT) and per protocol set (PPS) are presented below:

**Percentage Reduction in Modified PASI Score from Baseline – ITT Analysis Set**

<table>
<thead>
<tr>
<th>Reduction in Modified PASI score at Visit 2</th>
<th>TREATMENT GROUP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>Teva</td>
</tr>
<tr>
<td>Mean</td>
<td>21.2%</td>
</tr>
<tr>
<td>SD 1)</td>
<td>24.5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reduction in Modified PASI score at Visit 3</th>
<th>TREATMENT GROUP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>24.7%</td>
</tr>
<tr>
<td>Mean</td>
<td>25.2%</td>
</tr>
<tr>
<td>SD 1)</td>
<td>29.8%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reduction in Modified PASI score at Visit 4</th>
<th>TREATMENT GROUP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>30.0%</td>
</tr>
<tr>
<td>Mean</td>
<td>32.2%</td>
</tr>
<tr>
<td>SD 1)</td>
<td>33.6%</td>
</tr>
</tbody>
</table>

*SD = Standard Deviation
Source: section 14.2, Table 14-28
Dalbeal 50 mcg/g and 0.5mg/g Ointment & Calcipotriol/Betamethasone 50 mcg per g / 500 mcg per g ointment

The mean percentage change in Modified PASI from baseline to the end of treatment (Visit 3) was -65.4% (SD=24.7%) in the Teva ointment group, -67.6% (SD=25.2%) in the Dovobet group and -25.0% (SD=32.5%) in the vehicle group.

Results were similar for the per protocol set. In particular, the difference between Teva and Dovobet was 1.96% with 95% confidence interval -2.21% to 6.12%.

Thus the primary endpoint supports the claim that the test and reference product are equivalent.

In response to objections raised by the member states, the applicant presented further analysis of the data to support the applications. The further analysis of the data included the proportion of patients in each treatment group with treatment success on (i) the ISGA and (ii) the PASI at Visit 3. The data is presented below:

### Treatment Differences in Percentage Reduction in Modified PASI Score from Baseline to Visit 3 – ITT Analysis Set

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>SE 1)</th>
<th>95% Confidence Interval 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teva – Dovobet</td>
<td>2.09%</td>
<td>2.12%</td>
<td>-2.08% to 6.26%</td>
</tr>
<tr>
<td>Teva – Vehicle</td>
<td>-40.73%</td>
<td>3.03%</td>
<td>-46.68% to -34.79%</td>
</tr>
<tr>
<td>Dovobet – Vehicle</td>
<td>-42.82%</td>
<td>3.04%</td>
<td>-48.79% to -36.86%</td>
</tr>
</tbody>
</table>

1) SE = Standard Error
2) Comparison-wise two-sided 95% confidence intervals

### Summary Statistics for Responder Analysis – ITT Analysis Set

<table>
<thead>
<tr>
<th></th>
<th>Treat</th>
<th>TREATMENT GROUP</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ISGA at Visit 3, (%)</td>
<td>Teva</td>
<td>Dovobet</td>
</tr>
<tr>
<td>Clear or Almost Clear</td>
<td>59.4%</td>
<td>59.8%</td>
<td>13.2%</td>
</tr>
<tr>
<td>Total</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Modified PASI at Visit 3, (%)</td>
<td>Teva</td>
<td>Dovobet</td>
</tr>
<tr>
<td>Improvement &gt; 90% 1)</td>
<td>15.5%</td>
<td>15.6%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Total</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Modified PASI at Visit 3, (%)</td>
<td>Teva</td>
<td>Dovobet</td>
</tr>
<tr>
<td>Improvement &gt; 75% 1)</td>
<td>39.9%</td>
<td>43.1%</td>
<td>4.4%</td>
</tr>
<tr>
<td>Total</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Modified PASI at Visit 3, (%)</td>
<td>Teva</td>
<td>Dovobet</td>
</tr>
<tr>
<td>Improvement &gt; 50% 1)</td>
<td>74.6%</td>
<td>80.8%</td>
<td>24.2%</td>
</tr>
<tr>
<td>Total</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

1) Change at Visit 3 from baseline;
Summary Statistics for Responder Analysis – PPS Analysis Set

<table>
<thead>
<tr>
<th>ISGA at Visit 3, (%)</th>
<th>TEVA</th>
<th>TREATMENT GROUP</th>
<th>Vehicle</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear or Almost Clear</td>
<td>59.9%</td>
<td>61.0%</td>
<td>13.5%</td>
<td>53.9%</td>
</tr>
<tr>
<td>Total</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Modified PASI at Visit 3, (%)</th>
<th>TEVA</th>
<th>TREATMENT GROUP</th>
<th>Vehicle</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement &gt; 90% 1)</td>
<td>15.4%</td>
<td>15.7%</td>
<td>0.0%</td>
<td>13.4%</td>
</tr>
<tr>
<td>Total</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Modified PASI at Visit 3, (%)</th>
<th>TEVA</th>
<th>TREATMENT GROUP</th>
<th>Vehicle</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement &gt; 75% 1)</td>
<td>40.1%</td>
<td>43.4%</td>
<td>4.5%</td>
<td>36.5%</td>
</tr>
<tr>
<td>Total</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Modified PASI at Visit 3, (%)</th>
<th>TEVA</th>
<th>TREATMENT GROUP</th>
<th>Vehicle</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement &gt; 50% 1)</td>
<td>75.3%</td>
<td>81.6%</td>
<td>23.6%</td>
<td>70.7%</td>
</tr>
<tr>
<td>Total</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

1) Change at Visit 3 from baseline;

Treatment Differences for Responders - ITT Analysis Set

<table>
<thead>
<tr>
<th>ISGA ≤ 1 at Visit 3 1)</th>
<th>Teva - Dovobet</th>
<th>Teva - Vehicle</th>
<th>Dovobet - Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weighted mean 2)</td>
<td>-0.04%</td>
<td>47.14%</td>
<td>46.97%</td>
</tr>
<tr>
<td>95% CI 3)</td>
<td>-7.71% to 7.63%</td>
<td>38.39% to 55.89%</td>
<td>38.09% to 55.84%</td>
</tr>
</tbody>
</table>

Modified PASI Improvement at Visit 3 > 90% from Baseline

<table>
<thead>
<tr>
<th>Weighted mean 2)</th>
<th>Teva - Dovobet</th>
<th>Teva - Vehicle</th>
<th>Dovobet - Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weighted mean 2)</td>
<td>-0.01%</td>
<td>15.77%</td>
<td>15.83%</td>
</tr>
<tr>
<td>95% CI 3)</td>
<td>-5.53% to 5.51%</td>
<td>11.66% to 19.89%</td>
<td>12.02% to 19.63%</td>
</tr>
</tbody>
</table>

Modified PASI Improvement at Visit 3 > 75% from Baseline

<table>
<thead>
<tr>
<th>Weighted mean 2)</th>
<th>Teva - Dovobet</th>
<th>Teva - Vehicle</th>
<th>Dovobet - Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weighted mean 2)</td>
<td>-3.10%</td>
<td>36.42%</td>
<td>39.13%</td>
</tr>
<tr>
<td>95% CI 3)</td>
<td>-10.67% to 4.46%</td>
<td>29.63% to 43.21%</td>
<td>32.31% to 45.94%</td>
</tr>
</tbody>
</table>

Modified PASI Improvement at Visit 3 > 50% from Baseline

<table>
<thead>
<tr>
<th>Weighted mean 2)</th>
<th>Teva - Dovobet</th>
<th>Teva - Vehicle</th>
<th>Dovobet - Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weighted mean 2)</td>
<td>-6.01%</td>
<td>50.07%</td>
<td>56.34%</td>
</tr>
<tr>
<td>95% CI 3)</td>
<td>-12.86% to 0.83%</td>
<td>40.64% to 61.10%</td>
<td>46.21% to 66.47%</td>
</tr>
</tbody>
</table>

1) Investigator’s Static Global Assessment = Clear or Almost Clear;
2) Mantel Haenszel weights are used;
3) The 95% confidence interval (two-sided).
Treatment Differences for Responders - PPS Analysis Set

<table>
<thead>
<tr>
<th></th>
<th>Teva - Dovobet</th>
<th>Teva - Vehicle</th>
<th>Dovobet - Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISGA ≤ 1 at Visit 3 1)</td>
<td>-0.71%</td>
<td>47.51%</td>
<td>48.04%</td>
</tr>
<tr>
<td>Weighted mean 2)</td>
<td>-8.45% to 7.03%</td>
<td>38.65% to 56.36%</td>
<td>39.04% to 57.05%</td>
</tr>
<tr>
<td>95% CI 3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modified PASI Improvement at Visit 3 &gt; 90% from Baseline</td>
<td>-0.29%</td>
<td>15.46%</td>
<td>15.75%</td>
</tr>
<tr>
<td>Weighted mean 2)</td>
<td>-5.90% to 5.31%</td>
<td>11.36% to 19.56%</td>
<td>11.90% to 19.61%</td>
</tr>
<tr>
<td>95% CI 3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modified PASI Improvement at Visit 3 &gt; 75% from Baseline</td>
<td>-3.27%</td>
<td>36.35%</td>
<td>39.23%</td>
</tr>
<tr>
<td>Weighted mean 2)</td>
<td>-10.96% to 4.42%</td>
<td>29.45% to 43.24%</td>
<td>32.26% to 46.20%</td>
</tr>
<tr>
<td>95% CI 3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modified PASI Improvement at Visit 3 &gt; 50% from Baseline</td>
<td>-6.05%</td>
<td>52.23%</td>
<td>57.51%</td>
</tr>
<tr>
<td>Weighted mean 2)</td>
<td>-12.93% to 0.82%</td>
<td>41.91% to 62.56%</td>
<td>47.22% to 67.80%</td>
</tr>
<tr>
<td>95% CI 3)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1) Investigator’s Static Global Assessment = Clear or Almost Clear;
2) Mantel Haenszel weights are used;
3) The 95% confidence interval (two-sided).

Conclusion
1. The percentages in the Teva ointment group were similar to the percentages in the Dovobet group.
2. The percentages in the vehicle group differed greatly from the percentages in both the active treatment groups.
3. The differences between the active treatment were not statistically significant at the α=0.05 level of significance as the corresponding 95% confidence intervals did not exclude zero. These results support the primary conclusion of equivalence.
4. The differences between Teva ointment and vehicle were statistically significant at the α=0.05 level of significance as the corresponding 95% confidence intervals excluded zero. These results support the primary conclusion of efficacy of Teva ointment.
5. The differences between Dovobet and vehicle were statistically significant at the α=0.05 level of significance as the corresponding 95% confidence intervals excluded zero. These results demonstrate assay sensitivity.
6. All the conclusions above could be drawn for both the ITT analysis population and the PPS analysis population. This is a demonstration of robustness – i.e. a lack of sensitivity of the results to alternative choices of the set of subjects analysed.

Safety
With the exception of the safety data generated during the therapeutic equivalence study, no new safety data were submitted and none are required for applications of this type. The safety data collected during the therapeutic equivalence study showed that the test and reference products had a comparable tolerability. No new or unexpected safety issues arose during the therapeutic equivalence study.

Summaries of Product Characteristics (SmPCs), Patient Information Leaflets (PILs) and Labels
The SmPCs, PILs and labels are acceptable from a clinical perspective. The PILs are consistent with the details in the SmPCs and in line with the current guidance. The labelling is in line with the current guidance.
Clinical Expert Report (Clinical Overview)
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the MAH, fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for non-submission of a Risk Management Plan (RMP) for these applications which were received prior to the date (July 2012) when the pharmacovigilance regulations in accordance with Directive 2010/84/EU came into force.

Conclusion
The grant of Marketing Authorisations is recommended.

IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT
QUALITY
The important quality characteristics of Dalbecal 50 microgram per g / 50 micrograms per g Ointment and Calcipotriol/Betamethasone 50 micrograms per g / 500 micrograms per g ointment are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type. A non-clinical overview has been provided by an appropriately qualified person and consists of a review of the published literature.

EFFICACY
The applicant’s products, Dalbecal 50 mcg/g and 0.5mg/g Ointment and Calcipotriol/Betamethasone 50 mcg per g / 500 mcg per g ointment, have been shown to be therapeutically equivalent to the reference product Dovobet (Leo Laboratories Limited, UK).

SAFETY
With the exception of the safety data from the therapeutic equivalence study, no new data were submitted and none are required for applications of this type. As the safety profiles of calcipotriol and betamethasone are well-known, no additional data were required. No new or unexpected safety concerns arose from the therapeutic equivalence study.

PRODUCT LITERATURE
The SmPCs, PILs and labelling are satisfactory and in line with current guidance.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Calcipotriol and betamethasone are well-known active substances. Extensive clinical experience with calcipotriol and betamethasone is considered to have demonstrated the therapeutic value of the compounds. The benefit/risk balance is therefore considered to be positive.
## Module 6

### STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</table>