PUBLIC SUMMARY DOCUMENT
Product: Calcipotriol with betamethasone dipropionate, ointment, 50 micrograms-500 micrograms (base) per g, Daivobet®
Sponsor: CSL Biotherapies Limited
Date of PBAC Consideration: July 2009

1. Purpose of Application
To request a restricted benefit listing for chronic stable plaque type psoriasis vulgaris patients in whom treatment with either calcipotriol or a potent topical corticosteroid alone is inadequate.

2. Background
The combined presentation of calcipotriol and betamethasone dipropionate had not previously been considered by the PBAC.

3. Registration Status
Daivobet® 50/500 has been registered by the TGA since 20 August 2004 for the once daily topical treatment of plaque type psoriasis vulgaris amenable to topical therapy.

4. Listing Requested and PBAC’s View
Restricted Benefit
Chronic stable plaque type psoriasis vulgaris patients in whom treatment with either calcipotriol or a potent topical corticosteroid alone is inadequate.

See Recommendation and Reasons for PBAC’s view.

5. Clinical place for the proposed therapy
The ability to apply calcipotriol and a potent corticosteroid at the same time, rather than at different times of the day, leads to a less complicated treatment regimen and thereby potentially improved compliance.

6. Comparator
The submission nominated the individual constituents given as single agents, and the two constituent agents given in combination as the main comparators. The PBAC considered the comparators appropriate.

7. Clinical Trials
The submission presented nine randomised trials comparing calcipotriol/betamethasone combination ointment with calcipotriol or/plus potent corticosteroids in patients with psoriasis vulgaris. Details of the trials are presented in the following table. Each of the trials utilised various dosing regimens for each of the medications not all of which were within their TGA approved dosage regimens.

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Publication title</th>
<th>Publication citation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial 9904 Douglas</td>
<td>A new calcipotriol/betamethasone formulation with rapid onset of action was superior to monotherapy with betamethasone dipropionate or</td>
<td>Acta Derm Veneral 2002; 82: 131-135.</td>
</tr>
</tbody>
</table>

Trial 0003
Kaufmann R, et al.
Calcipotriol/betamethasone dipropionate once daily in psoriasis vulgaris. A new calcipotriol/betamethasone dipropionate formulation (Daivobet™) is an effective once-daily treatment for psoriasis vulgaris. 

Dermatology 2002; 205: 389-393.

Trial 9905
Guenther L, et al.
Efficacy and safety of a new combination of calcipotriol and betamethasone dipropionate (once or twice daily) compared to calcipotriol (twice daily) in the treatment of psoriasis vulgaris: a randomized, double-blind, vehicle-controlled clinical trial.


Van de Kerkhof PC.


Trial 0002
Kragballe K, et al.
Efficacy of once-daily treatment regimens with calcipotriol/betamethasone dipropionate ointment and calcipotriol ointment in psoriasis vulgaris.


Trial 9904
Saraceno R, et al
Efficacy, safety and quality of life of calcipotriol/betamethasone dipropionate (Dovobet) versus calcipotriol (Daivonex) in the treatment of psoriasis vulgaris: A randomised, multicentre, clinical trial.


Kragballe K et al Calcipotriol cream with or without concurrent topical corticosteroid in psoriasis: tolerability and efficacy. 


Ruzicka T et al
Comparison of calcipotriol monotherapy and a combination of calcipotriol and betamethasone valerate after 2 weeks' treatment with calcipotriol in the topical therapy of psoriasis vulgaris: a multicentre, double-blind, randomised study.


8. Results of Trials
The results of the primary outcome of all trials (percent change PASI- Psoriasis Area and Severity Index) are presented in the table below.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Tx, weeks</th>
<th>Mean difference percent change PASI (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Combination ointment od v Calcipotriol bd: -9.8 (-15.2, -4.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Combination ointment od v Vehicle bd: -42.0 (-47.5, -36.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Combination ointment bd v Vehicle bd: -47.3 (-52.3, -42.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Combination ointment bd v Combination ointment od: -5.4 (-10.8, 0.1)</td>
</tr>
<tr>
<td>Trial 9905</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Combination ointment bd v Calcipotriol bd: -24.4 (-28.9, -20.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Combination ointment bd v Betamethasone dipropionate bd: -10.3 (-14.7, -5.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Combination ointment bd v Vehicle bd: -44.6 (-50.8, -38.4)</td>
</tr>
<tr>
<td>Trial 9802</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Combination ointment od v Calcipotriol bd: -19.0 (-22.8, -15.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Combination ointment bd v Betamethasone dipropionate bd: -13.1 (-16.9, -9.3)</td>
</tr>
<tr>
<td>Trial 9904</td>
<td>4 (8b)</td>
<td>Combination ointment od v Calcipotriol bd: -25.3 (-28.7, -21.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Combination ointment od v Betamethasone dipropionate od: -14.2 (-17.6, -10.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Combination ointment od v Vehicle od: -48.3 (-53.2, -43.4)</td>
</tr>
<tr>
<td>Trial 0003</td>
<td>4</td>
<td>Combination ointment od 8/4 v Calcipotriol bd after 8 weeks: -9.2 (-13.7, -4.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Combination ointment 4/8 v Calcipotriol bd after 8 weeks: -4.4 (-8.9, 0.1)</td>
</tr>
<tr>
<td>Trial 0002</td>
<td>8 (12c)</td>
<td>Calciopotriol bd less effective than other treatments</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Calcipotriol bd as effective as Calcipotriol + Clobetasone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Calcipotriol + Betamethasone valerate 0.1% more effective than Calcipotriol bd</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Calcipotriol + Clobetasone no different to Calcipotriol + Betamethasone valerate 0.1%</td>
</tr>
<tr>
<td>Kragbelle (1998)</td>
<td>8 (10i)</td>
<td></td>
</tr>
<tr>
<td>Saraceno (2007)</td>
<td>12</td>
<td>No difference between combination ointment once daily for 4 weeks and calcipotriol twice daily for 8 weeks compared with calcipotriol twice daily for 12 weeks</td>
</tr>
<tr>
<td>Ruzicka (1998)</td>
<td>4 (16)</td>
<td>Statistically significant difference between calcipotriol + betamethasone valerate 0.1% concomitant treatment and calcipotriol twice daily treatment following 2 and 4 weeks of randomised treatment (P&lt;0.001). No difference between groups 8 weeks after cessation of treatment.</td>
</tr>
</tbody>
</table>

Bolded typography indicates statistically significant differences
Tx=treatment duration, od=once daily, bd=twice daily,
b double-blind treatment period of 4 weeks, then all patients switch to calcipotriol twice daily for 4 weeks, results for 4 week double-blind period

c 12 weeks total treatment: see footnotes “d” and “e” – results reported here at the treatment effect at 8 weeks

d Calcipotriol with betamethasone dipropionate combination ointment once daily for 8 weeks then calcipotriol once daily for 4 weeks

e Calcipotriol with betamethasone dipropionate combination ointment once daily for 4 weeks then for 8 weeks, used calcipotriol once daily on weekdays and calcipotriol with betamethasone dipropionate combination ointment once daily on weekends

f 10 weeks total: 2 weeks wash-out, 8 weeks randomised treatment

g values for % mean change calculated from mean change provided in publication

h Calcipotriol with betamethasone dipropionate combination ointment once daily for 4 weeks then calcipotriol twice daily for 8 weeks

i 2 week wash-out (ointment base applied), 2 weeks calcipotriol twice daily, then patients randomised to concomitant calcipotriol and betamethasone valerate or calcipotriol twice daily for 4 weeks, then follow-up to 8 weeks after cessation of treatment (applied ointment only)

The PBAC noted the heterogeneity of the clinical data submitted in support of listing; each of the trials utilised various dosing regimens for each of the medications not all of which are within their TGA approved dosage regimens. However, the PBAC noted the trend across the trials was for an improvement in psoriasis as measured by a change in PASI score when comparing the combination product to the monotherapies.

The submission also presented an indirect comparison of the results (mean percent change in PASI) from Trial 9904 and Kragbelle (1998) in order to demonstrate non-inferiority of combination ointment compared with its individual components used concomitantly. The results of this indirect comparison are presented below.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Combination ointment twice daily</th>
<th>Calcipotriol twice daily</th>
<th>Concomitant calcipotriol and betamethasone valerate 0.1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial 9904</td>
<td>-74.4 (22.3)</td>
<td>-55.3 (29.1)</td>
<td>NA</td>
</tr>
<tr>
<td>Kragbelle 1998</td>
<td>NA</td>
<td>-53.3 (NR)</td>
<td>-59.5 (NR)</td>
</tr>
</tbody>
</table>

With respect to toxicity, statistically significantly fewer total adverse events were reported for the combination ointment compared with calcipotriol monotherapy in trials 9802, 9904, 0003 and 0002 (the 8 week combination/4 week calcipotriol arm v calcipotriol). No differences in this outcome were observed in Trial 9905, Saraceno (2007), Ruzicka (1998) or Trial MCB 0102 INT, and the outcome was not reported in Kragbelle (1998). Statistically significantly fewer lesional/perilesional adverse events were reported for the combination ointment compared with calcipotriol monotherapy in trials 9802, 0003, 9905, 0002, Kragbelle (1998) and Trial MCB 0102 INT. No differences in this outcome were observed in Trial 9904 or Ruzicka (1998), and the outcome was not reported in Saraceno (2007).

9. Clinical Claim

The submission claimed that calcipotriol/betamethasone dipropionate combination ointment was equivalent in terms of comparative effectiveness to calcipotriol and betamethasone topical products given concomitantly, and that the combination product may have safety advantages over the two agents given concomitantly.
The submission claimed that the combination product was superior in terms of comparative effectiveness over calcipotriol and betamethasone monotherapies.

For PBAC’s views, see Recommendation and Reasons.

10. Economic Analysis
The submission presented a cost minimisation analysis.

Given the data from the direct randomised trials indicated that the use of medication was similar when the combination ointment was used and when the individual components were used, the equi-effective doses were estimated as combination ointment 30 g was equi-effective with calcipotriol 30 g and potent corticosteroid 2 x 15 g. These estimates were derived from an indirect comparison of Trial 9904 and Kragbelle (1998), based on the effectiveness observed and the amount of medication used in the respective trials.

11. Estimated PBS Usage and Financial Implications
The submission estimated the likely number of packs dispensed per year (accounting for market share as necessary) would be up to 100,000 in Year 5 of listing, with the financial cost per year to the PBS of less than $1 million in Year 5.

12. Recommendation and Reasons
The PBAC recommended the listing of calcipotriol with betamethasone ointment (50 micrograms-500 micrograms (base) per g) as a restricted benefit on a cost minimisation basis compared with the individual components for use in the treatment of chronic stable plaque type psoriasis in a patient not adequately controlled with either calcipotriol or potent topical corticosteroid monotherapy. One 30 g tube of the combination product was considered to be of equivalent comparative effectiveness to one 30 g tube of calcipotriol ointment 50 micrograms per g and two 15 g tubes of betamethasone dipropionate ointment 500 micrograms (base) per g. The PBAC noted the product met the requirements of the Guidelines for the listing of fixed combination products. However, there was concern that the combination product could result in continuous use of a steroid, which is not recommended by the TGA, and thus would not represent quality use of medicine.

The PBAC noted the heterogeneity of the clinical data submitted in support of listing; each of the trials utilised various dosing regimens for each of the medications not all of which were within their TGA approved dosage regimens. However, the PBAC noted the trend across the trials was for an improvement in psoriasis as measured by a change in PASI score when comparing the combination product to the monotherapies and accepted the claim that the combination product was superior in terms of comparative effectiveness over calcipotriol and betamethasone monotherapies. The Committee considered that Trial 9905 presented the most relevant comparison in terms of TGA approved dosages of combination ointment and calcipotriol monotherapy.

The PBAC noted that the Therapeutic Guidelines Dermatology 2009 listed methylprednisolone aceponate as being a corticosteroid of ‘moderate’ potency, and given the heterogeneity of the clinical data, considered the requested listing on a cost-minimisation basis of one 30 g tube of the combination ointment being equivalent to one 30 g tube of calcipotriol ointment plus twice the weighted average price of 15 g potent topical corticosteroid product was not adequately demonstrated.
**Recommendation**

CALCIPOTRIOL with BETAMETHASONE DIPROPIONATE, ointment, 50 micrograms – 500 micrograms (base) per g (0.005 % - 0.05 %), 30 g

**Restriction:** Restricted Benefit  
Chronic stable plaque type psoriasis vulgaris in a patient who is not adequately controlled with either calcipotriol or potent topical corticosteroid monotherapy.

Max qty: 1  
Repeats: 1

13. **Context for Decision**  
The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. **Sponsor’s Comment**  
The sponsor has no comment.