Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for calcipotriol and betamethasone (as dipropionate)

Proprietary Product Name: Daivobet 50/500

Sponsor: Leo Pharma Pty Ltd

August 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

· The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.

· The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.

· The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.

· The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.

· To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

· An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.

· AusPARs are prepared and published by the TGA.

· An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.

· An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.

· A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

AusPAR Daivobet 50/500; calcipotriol 50 µg/g and betamethasone (as dipropionate) 500 µg/g gel;
Leo Pharma Pty Ltd; PM-2011-04144-3-5; Date of Finalisation August 2013

Page 3 of 37

I. Introduction to product submission

Submission details

Type of Submission	Extension of indications
Decision:	Approved
Date of Decision:	19 March 2013
Active ingredients:	calcipotriol and betamethasone (as dipropionate)
Product Name:	Daivobet 50/500
Sponsor's Name and Address:	LEO Pharma Pty Ltd Level 3, Tower 1, 25 Montpelier Road Bowen Hills, QLD 4006
Dose form:	Gel
Strength:	50 µg/g (calcipotriol) and 500 µg/g (betamethasone, as dipropionate)
Container:	Bottle
Pack size:	4 g, 15 g, 30 g, 60 g, 2 x 60 g
Approved Therapeutic use:	Topical treatment of scalp psoriasis. Topical treatment of mild to moderate plaque psoriasis on the body in adults.
Route of administration:	Topical
Dosage (abbreviated):	Scalp psoriasis: once daily for up to 4 weeks. Body psoriasis: once daily for up to 8 weeks. When using calcipotriol containing products the maximum daily dose should not exceed 15 g and the maximum weekly dose should not exceed 100 g. The total body surface area treated should not exceed 30%.
ARTG Number:	161936

Product background

Daivobet 50/500 gel is a fixed combination gel consisting of calcipotriol 50 µg/g and betamethasone 500 µg/g (as dipropionate). Calcipotriol is a vitamin D analogue which inhibits hyperproliferation and abnormal differentiation of keratinocytes by binding to the vitamin D receptor. Betamethasone dipropionate is a topical corticosteroid which has effects on gene transcription resulting in inhibition of inflammation, proliferation and immunologic responses.

AusPAR Daivobet 50/500; calcipotriol 50 µg/g and betamethasone (as dipropionate) 500 µg/g gel; Leo Pharma Pty Ltd; PM-2011-04144-3-5; Date of Finalisation August 2013

Page 4 of 37

Daivobet 50/500 gel was registered in Australia in 2010 *for the topical treatment of scalp psoriasis*. This AusPAR described the application by Leo Pharma Pty Ltd (the sponsor) to extend the approved indications to include the following:

> *"Daivobet gel is indicated for the topical treatment of body and scalp psoriasis".*

An ointment formulation (Daivobet 50/500 ointment; sponsor, Leo Pharma) containing calcipotriol 50 µg/g and betamethasone 500 µg/g (as dipropionate) has been registered in Australia since 2004, for *the once daily topical treatment of plaque-type psoriasis vulgaris amenable to topical therapy*.

Regulatory status

The product received registration on the Australian Register of Therapeutic Goods on 22 July 2010. At the time this application was considered by TGA, a similar application (gel formulation for non-scalp areas) had been approved in several overseas countries, including the EU and USA.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Definitions used in clinical trials

Skin type

The skin type of the subjects was recorded using the following classification:

Table 1. Skin type classification system

Skin Type	Skin Colour (unexposed skin)	History -(to first 30 to 45 minutes of sun exposure after a winter season of no sun exposure)
I	White	Always burns easily; never tans

AusPAR Daivobet 50/500; calcipotriol 50 µg/g and betamethasone (as dipropionate) 500 µg/g gel; Leo Pharma Pty Ltd; PM-2011-04144-3-5; Date of Finalisation August 2013

Page 5 of 37

Skin Type	Skin Colour (unexposed skin)	History -(to first 30 to 45 minutes of sun exposure after a winter season of no sun exposure)
II	White	Always burns easily; tans minimally
III	White	Burns moderately; tans gradually (light brown)
IV	White	Burns minimally; always tans well (moderate brown)
V	Brown	Rarely burns; tans profusely (dark brown)
VI	Black	Never burns, deeply pigmented

Investigator's global assessment of disease severity (IGA)

This assessment represents the **average** lesion severity on the trunk, arm and legs. The assessment is based on the condition of the disease at the time of evaluation, and **not** in relation to the condition at the previous visit.

There was a slight difference between the scales used in the pivotal studies (Studies LEO80185-G23 and LEO80185-G21) and the supportive comparative study (MBL0202INT). For the purposes of the pooled analysis these were considered comparable.

Table 2. Investigator's Global Assessment (IGA) of disease severity

Term	Description
Clear	Plaque thickening = no elevation or thickening over normal skin Scaling = no evidence of scaling LEO80185-G23: Erythema = none (no residual red colouration but post-inflammatory hyperpigmentation may be present) LEO80185-G21: Erythema = none or hyperpigmentation or residual red colouration. MBL0202INT: Erythema = none or slight (hyperpigmentation or residual red colouration)
Almost clear	Plaque thickening = none or possible thickening but difficult to ascertain whether there is a slight elevation above normal skin level Scaling = none or residual surface dryness and scaling Erythema = light pink colouration MBL0202INT: Erythema: up to mild (up to light red or pink colouration)
Mild	Plaque thickening = slight but definite elevation Scaling = fine scales partially or mostly covering lesions

AusPAR Daivobet 50/500; calcipotriol 50 µg/g and betamethasone (as dipropionate) 500 µg/g gel; Leo Pharma Pty Ltd; PM-2011-04144-3-5; Date of Finalisation August 2013

Page 6 of 37

Term	Description
	Erythema = light red colouration
	MBL0202INT: Erythema = up to moderate (up to definite red colouration)
Moderate	Plaque thickening = moderate elevation with rounded or sloped edges
	Scaling = most lesions at least partially covered
	Erythema = definite red colouration
Severe	Plaque thickening = marked elevation typically with hard or sharp edges
	Scaling = non-tenacious scale predominates, covering most or all of the lesions
	Erythema = very bright red colouration
Very severe	Plaque thickening = very marked elevation typically with hard or sharp edges
	Scaling = thick tenacious scale covers most or all of the lesions
	Erythema = extreme red colouration; deep red colouration

'Controlled disease' = 'clear' or 'almost clear' according to IGA.

Psoriasis Area and Severity Index (PASI)

Psoriasis Area and Severity Index (PASI) is based on the investigator's assessment of extent (E) and severity of the disease locally (on trunk, arms and legs) in terms of three clinical signs: redness (R), thickness (T) and scaliness (S). The subject was scored for each of the three areas: arms, trunk and legs and calculated using the following formula:

· Arms $0.2 (R + T + S)E = X$

· Trunk $0.3 (R + T + S)E = Y$

· Legs $0.4 (R + T + S)E = Z$

The sum of X + Y + Z gives the total PASI which can range from 0 to 64.8. The PASI used in both pivotal studies was modified to exclude assessment of the head, as study treatment was not used here.

There was a minor difference between the studies in that the buttocks were to be included as part of the legs in the pivotal studies (LEO80185-G23 and LEO80185-G21) but as part of the trunk in the supportive comparative study (MBL0202INT).

Modified PASI scale (excluding scalp, face and flexures)

Table 3. Modified Psoriasis Area and Severity Index (PASI): Extent

Extent	Extent
0 = non involvement	4 = 50-69%
1 =<10%	5 = 70-89%

Extent	Extent
2 = 10-29%	6 = 90-100%
3 = 30-49%	

Table 4. Modified Psoriasis Area and Severity Index (PASI): Severity

Severity		
Redness	**Thickness**	**Scaliness**
0 = none (no erythema)	0 = none (no plaque elevation)	0 = none (no scaling)
1 = mild (faint erythema, pink to very light red)	1 = mild (slight, barely perceptible elevation)	1 = mild (sparse, fine scale lesions, only partially covered)
2 = moderate (definite light red erythema)	2 = moderate (definite elevation but not thick)	2 = moderate (coarser scales, most of lesions covered)
3 = severe (dark red erythema)	3 = severe (definite elevation, thick plaque with sharp edge)	3 = severe (entire lesion covered with coarse scales)
4 = very severe (very dark red erythema)	4 = very severe (very thick plaque with sharp edge)	4 = very severe (very thick coarse scales, possibly fissured)

In Study MBL0202INT the wording of the severity of the signs of redness, thickness and scaliness was slightly different to that used in the pivotal studies (LEO80185-G23 and LEO80185-G21) but was considered equivalent to those above:

0 = absent

1 = slight

2 = moderate

3 = severe

4 = severest possible

Investigator's assessment of body surface area (BSA) involvement of extent of disease at baseline

The total psoriatic involvement on the arms, legs and trunk was recorded as a percentage of the total body surface area (BSA), estimating that the surface of the full, flat palm (including the five digits) correlates to approximately 1% of the total BSA. The purpose was to obtain an estimate of the total area to be treated with study medication.

Patient's global assessment (PGA) of disease severity

The subject's assessment was made prior to the investigator assessments.

Clear   No psoriasis symptoms at all

Very mild   Very slight psoriasis symptoms, does not interfere with daily life

Mild   Slight psoriasis symptoms, interferes with daily life only occasionally

Moderate   Definite psoriasis symptoms, interferes with daily life frequently

Severe   Intense psoriasis symptoms, interferes or restricts daily life very frequently

Patient's assessment of plaque discomfort

This assessment was based on the condition of the disease at the time of evaluation and used a visual analogue scale. This assessment was made prior to the IGA and used the subject's mark on an arbitrary scale of 0=100 graduated in 10 unit intervals.

Quality of life assessment

The scale used for this assessment was the Dermatology Life Quality Index (DLQI) which is a validated dermatology specific questionnaire.

Total clinical score (Study PLQ-001)

All assessments for a subject were to be made by the same investigator. The severity of the symptoms was rated on Day 1 (baseline), 4, 8, 11, 15, 18, and 22 (end of treatment) according to the following 0-3 with half point grading scale.

Table 5. Total Clinical Score (Study PLQ-001)

Score	Intensity	Erythema Description	Scaling Description	Infiltration Description
0	No evidence	Normal skin colour	No scaling	
0.5	Doubtful or very mild			
1.0	Mild	Pink or light red	Slight roughness, mainly fine scales	Slight definite infiltration
1.5	Mild to moderate			
2.0	Moderate	Red	Coarse scaling	Moderate infiltration
2.5	Moderate to severe			
3.0	Severe	Intense red	Coarse, thick scales	Very marked Infiltration

The Total Clinical Score was defined as the sum of erythema plus scaling plus thickness scores and therefore ranges from 0 (all symptoms absent) to 9 (all symptoms severe).

Clinical rationale

Calcipotriol and betamethasone have been used by dermatologists in combination for the treatment of psoriasis vulgaris. The development of the Daivobet ointment provided a fixed dose combination which has been approved for the treatment of non-scalp psoriasis vulgaris. It has been shown that the betamethasone dipropionate counteracts the local

skin irritation that calcipotriol exhibits in some subjects, thereby allowing calcipotriol to exert its beneficial effects. Calcipotriol may also reduce the amount of corticosteroid required due to a positive additive effect and thus reduce the risk of steroid-related adverse effects. The previous clinical development program for Daivobet ointment is said to have demonstrated an additive/synergistic effect on the trunk and limbs, while the safety profile is similar or better than the single constituents given alone.

The cosmetic properties of a formulation are important for patient acceptability and greasy ointments can be a barrier to patient compliance leading to a disappointing clinical effect. Since compliance remains a critical factor in achieving effective treatment of psoriasis, patient preferences regarding agents and vehicles are an integral part of therapy selection. Daivobet gel was developed to complement Daivobet ointment. Daivobet gel contains the same active components as Daivobet ointment but in a gel vehicle that has the advantages of the combination treatment while allowing once daily application with a cosmetically acceptable formation. The gel formulation was originally developed for use on the scalp but its physical properties also make it a suitable alternative treatment for psoriasis lesions on non-scalp areas of the body. The favourable cosmetic properties of a non-greasy gel may improve patient compliance. Thus the objective of the clinical development program was to demonstrate sufficient evidence to include the treatment of psoriasis vulgaris on non-scalp areas of the body.

Guidance

The TGA has adopted the following EU Guideline with amendment: "Guideline on Clinical Investigation of Medicinal Products Indicated for the Treatment of Psoriasis. (CHMP/EWP/2454/02)". This guideline became effective in Europe in June2004 and in Australia in July 2005.

The key points of this guideline are:

· There are no validated diagnostic criteria for psoriasis, the diagnosis being clinical and histological confirmation not necessary.

· In previously treated patients a washout period is necessary to avoid unnecessary rebound of psoriasis.

· Inter-individual comparison with parallel groups is the recommended study design.

· A duration of 8 to 12 weeks is generally sufficient to show short term efficacy with specified assessments at a minimum of 0, 4, 8 and 12 weeks.

· A least one confirmatory trial should include an observation period of at least 2 months in order to explore the duration of remission/response, rebound and time to relapse.

· Psoriasis is a seasonal, chronic relapsing disease and so one year intermittent or prolonged use is recommended.

· Body surface area (BSA) affected by psoriasis and Psoriasis Area and Severity Index (PASI) scores are recommended methods to assess psoriasis severity. Physician global assessment (PGA) of psoriasis severity is also used. Training of investigators prior to study start may decrease inter-observer variability.

· PASI alone is not sufficient to evaluate psoriasis severity at baseline and on treatment. It is recommended to use at least 2 endpoints to assess efficacy: a validated, standardised global scale (for example, PGA) in conjunction with PASI.

· The best evidence of efficacy is the percentage of patients who achieve the result of "clear or almost clear" (PASI >90%) on treatment.

AusPAR Daivobet 50/500; calcipotriol 50 µg/g and betamethasone (as dipropionate) 500 µg/g gel; Leo Pharma Pty Ltd; PM-2011-04144-3-5; Date of Finalisation August 2013

Page 10 of 37

- >50% and >75% improvements compared to baseline have been considered as clinically meaningful. Clear or almost clear has been defined as an improvement of PASI >90%.

- A reduction in the PASI score <50% is currently not considered as an acceptable demonstration of treatment response.

Contents of the clinical dossier

Scope of the clinical dossier

The clinical dossier documented a development program of pharmacodynamic, pivotal and other clinical trials relating to the proposed extension of indication.

The submission contained the following clinical information:

Module 5:

- 1 x clinical pharmacology study (LEO80185-G24), which aimed to provide pharmacodynamic and pharmacokinetic data

- 2 x pivotal comparative efficacy/safety studies (LEO80185-G23 and LEO80185-G21)

- 2 x other efficacy/safety studies (MBL0202INT and PLQ-001)

- 3 x periodic safety update reports (PSURs), Integrated Summary of Efficacy (which was identical to the Module 2 Summary of Clinical Efficacy), Integrated Summary of Safety (which was identical to the Module 2 Summary of Clinical Safety)

Module 1:

Application letter, application form, draft Australian PI and consumer medicine information (CMI), FDA-proposed product label, European Summary of Product Characteristics (SmPC) as approved in the Netherlands, Sweden and the UK, and Pre-Submission Details. No Risk Management Plan (RMP) was included.

Module 2:

Clinical Overview, Summary of Clinical Pharmacology, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.

Paediatric data

The submission did not include paediatric data.

Good clinical practice

The clinical studies were conducted in the USA, European Union (EU) and Canada. All studies were conducted in accordance with Good Clinical Practice and with the principles of the Declaration of Helsinki as adopted in 1964 and subsequent amendments and with national regulatory requirements. The protocols were reviewed by institutional or independent ethics committees and all patients signed written informed consent prior to study participation.

Pharmacokinetics

Studies providing pharmacokinetic data

No pharmacokinetic (PK) data was provided in the submission.

One study (LEO80185-G24) aimed to collect PK data but none of the PK parameters could be calculated because only a minority of patients had values above the lower detection limit. This study also collected pharmacodynamics (PD) data.

Evaluator's overall conclusions on pharmacokinetics

No information is provided on the dose selection or how the gel is applied to the skin (for example, thickness). No information is provided on drug interactions; reference is made to the previously approved ointment formulation.

No information is provided in the study reports on how or when the patients applied the cream. The study protocols only provided the information "To be applied once daily on psoriasis vulgaris lesions on the trunk, arms and legs". There were no specific instructions as to time of day for dosing.

The instructions to the patients outlined in the protocols are similar for the clinical trials.

Pharmacodynamics

Studies providing pharmacodynamic data

The table below shows the studies relating to each PD topic. Only one new PD study was included in this submission.

Table 6. Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID	Primary Aim of Study
Primary Pharmacology	Effect on hypothalamic-pituitary-adrenal (HPA) axis and calcium metabolism	LEO80185-G24	HPA suppression
Secondary Pharmacology		No Study	
Gender, other genetic and age-related differences in PD response	Effect of gender	No Study	
	Effect of age	No Study	
PD Interactions		No Study	
Population PD and PK-PD analyses	Healthy subjects	No Study	
	Target§ population	No Study	

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

The PD study did not have deficiencies that excluded its results from consideration.

Evaluator's overall conclusions on pharmacodynamics

No new data is presented on the PD of the product. No summary of the PD is provided in the submission.

AusPAR Daivobet 50/500; calcipotriol 50 μg/g and betamethasone (as dipropionate) 500 μg/g gel; Leo Pharma Pty Ltd; PM-2011-04144-3-5; Date of Finalisation August 2013

Page 12 of 37

Study LEO80185-G24 was a small study which assessed the effect of Daivobet gel on HPA axis suppression and calcium metabolism in patients with moderate to severe psoriasis. HPA axis suppression was seen in approx 3/43 (7%) of subjects. Another study (MBL0404FR, evaluated in a previous submission) in which patients used Daivobet gel on the scalp and Daivobet ointment on the body showed that 5 of 32 (15.6%) patients had serum cortisol ≤18 µg/dL (all five had values >17 µg/dL) 30 minutes after ACTH challenge at Week 4. Two of the 11 (18.2%) patients who continued to Week 8 had serum cortisol ≤18 µg/dL at 30 minutes. All patients had serum cortisol >18 µg/dL at 60 minutes both at Weeks 4 and 8. The results of the new study appear consistent with the previous study.

Dosage selection for the pivotal studies

No explanation is provided as to the dose selection for the clinical studies.

The justification for the dose given in the protocols is: "A once daily treatment regimen has been chosen as this is considered more convenient for the subject and has been shown to be effective in previous studies. It decreases drug exposure and time spent on application and thus, probably enhances subject compliance."

Efficacy

Studies providing evaluable efficacy data in the indication psoriasis of the body (non-scalp)

Pivotal efficacy studies

Study LEO80185-G23

- Calpitotriol plus betamethasone dipropionate topical suspension compared to betamethasone dipropionate in the topical suspension vehicle, calcipotriol in the topical suspension vehicle and the topical suspension vehicle alone in psoriasis vulgaris.

Primary objective: to compare the efficacy of once daily treatment for up to 8 weeks of Daivobet gel with betamethasone gel, calcipotriol gel and the gel vehicle alone in subjects with psoriasis vulgaris on the non-scalp regions of the body (trunk and/or limbs).

Secondary objective: to compare the safety of Daivobet gel with betamethasone gel, calcipotriol gel and gel vehicle alone in subjects with psoriasis vulgaris on the non-scalp regions of the body (trunk and/or limbs).

Study design: The study was a multicentre, prospective, randomised, double-blind, 4-arm, parallel group, 8 week study conducted in 59 centres in the USA from September 2010 to March 2011.

Treatments: Subjects were randomised to receive one the following treatments:

- Daivobet gel (calcipotriol 50 µg/g plus betamethasone 0.5 mg/g as dipropionate)
- Betamethasone 0.5 mg/g (as dipropionate) in the gel vehicle
- Calcipotriol 50 µg/g in the gel vehicle
- The gel vehicle alone

No details of dosing are provided other than the treatments were applied topically once daily for 8 weeks.

The following concomitant therapies were allowed during the study:

· Inhaled steroids, bath oils and moisturising soaps

· Unlimited use of emollients for face, flexures (skin folds) and scalp

· All topical medications for face, flexures and scalp except Class 1 to 5 corticosteroids, vitamin D analogues and prescription shampoos for the scalp.

No information is provided in the study report on how treatment is to be applied. The study protocol contains directions on use for the patient. This states that the patient should not use more than 100 g (2 bottles) per week.

Study LEO80185-G21

· Efficacy and safety of calcipotriol plus betamethasone gel compared with tacalcitol ointment and the gel vehicle alone in patients with psoriasis vulgaris.

Comment: Tacalcitol is a vitamin D3 derivative, which inhibits keratinocyte hyper-proliferation and induces differentiation of these cells. Tacalcitol ointment was approved in the EU in 2006 but does not appear to have been approved in Australia.

Primary objective: was to compare the efficacy of once daily treatment for up to 8 weeks of Daivobet gel with tacalcitol ointment and the gel vehicle alone in subjects with psoriasis vulgaris on the body.

Secondary objectives were:

· Compare safety of once daily treatment for up to 8 weeks of Daivobet gel with tacalcitol ointment and the gel vehicle alone in subjects with psoriasis of the body

· To investigate the occurrence of and the time to relapse and occurrence of rebound after the end of treatment in subjects with 'controlled disease'

· To obtain data on the quality of life of subjects treated with Daivobet gel, tacalcitol ointment and the gel vehicle alone, using quality of life questionnaires.

Study design: This was a multicentre, prospective, randomised, investigator blind, active and vehicle controlled, 3 arm, parallel group, 8 week Phase III clinical study conducted in 18 centres in Canada. The study was conducted from April 2008 to February 2009.

Treatments: Subjects were randomised in a 2:2:1 ratio to one of the following treatments:

· Daivobet gel (calcipotriol 50 µg/g as hydrate plus betamethasone 0.5 mg/g as dipropionate)

· Curaderm ointment (tacalcitol 4 µg/g as monohydrate)

· Gel vehicle

Subjects were instructed to apply the treatment once daily on affected areas on the trunk and/or limbs.

The following concomitant therapies were allowed during the study:

· Treatments for conditions other than psoriasis vulgaris (with no potential effect on psoriasis vulgaris) without change in dosage whenever possible

· Unlimited use of emollients for face, flexures (skin folds) and scalp

· All topical medications for face, skin folds/flexures and scalp except very potent World Health Organization (WHO) group IV corticosteroids and vitamin D analogues

AusPAR Daivobet 50/500; calcipotriol 50 µg/g and betamethasone (as dipropionate) 500 µg/g gel; Leo Pharma Pty Ltd; PM-2011-04144-3-5; Date of Finalisation August 2013

Page 14 of 37

Other efficacy studies

Study MBL0202INT

· Calcipotriol plus betamethasone dipropionate gel compared to betamethasone diproprionate in the gel vehicle, calcipotriol in the gel vehicle alone in psoriasis vulgaris.

Objectives: To compare the efficacy and safety of once daily treatment for up to 8 weeks of Daivobet gel (calcipotriol plus betamethasone dipropionate) with betamethasone dipropionate in the gel vehicle, calcipotriol in the gel vehicle and the gel vehicle alone in patients with psoriasis vulgaris on the trunk and/or limbs.

Study design: an international, multicentre, prospective, randomised, double blind, 4 arm, parallel group, 8 week study conducted at 19 centres (Canada 6; Germany 4; Ireland 1; Sweden 3; UK 5) between December 2005 and May 2006.

Treatments: Patients were randomised in a 4:2:2:1 ratio to receive once daily treatment for up to 8 weeks to one of the following four treatment groups:

· Daivobet gel (calcipotriol 50 µg/g plus betamethasone dipropionate 0.5 mg/g)

· Betamethasone dipropionate 0.50 mg/g in the gel vehicle

· Calcipotriol 50 µg/g in the gel vehicle

· Gel vehicle

Treatment was applied once daily to the affected area on the trunk and/or limbs for 8 weeks.

Study PLQ-001

· A plaque test comparing three marketed products and two investigational products and a vehicle control for the treatment of psoriasis vulgaris.

Objectives: To evaluate the psoriasis plaque test using two investigational products:

· LEO 80185 gel (calcipotriol 50 µg/g as hydrate plus betamethasone 0.5 mg/g as dipropionate)

· LEO 80190 ointment (calcipotriol 25 µg/g as hydrate plus hydrocortisone 10 mg/g)

Three active marketed reference products:

· Daivonex ointment - (calcipotriol 50 µg/g as hydrate)

· Daivonex cream - (calcipotriol 50 µg/g as hydrate)

· Daivobet ointment (calcipotriol 50 µg/g as hydrate plus betamethasone 0.5 mg/g as dipropionate)

One reference product as control:

· Daivobet ointment vehicle

Secondary objectives were to validate the use of immunohistochemical scoring of biopsy material in conjunction with clinical scoring of the treated areas in the evaluation of treatment effects in psoriatic skin in the subjects and to obtain safety information for each of the treatments.

Study design: single centre, investigator blinded, within subject randomised, active and vehicle controlled, repeat dose, translational study at one centre in France between February 2008 and March 2009.

AusPAR Daivobet 50/500; calcipotriol 50 µg/g and betamethasone (as dipropionate) 500 µg/g gel; Leo Pharma Pty Ltd; PM-2011-04144-3-5; Date of Finalisation August 2013

Page 15 of 37

Treatments: Six test sites of 2 cm diameter were selected on predetermined lesions, marked with a disposable circular device and mapped on a drawn figure. The investigational products were applied once daily (50 µL per application) 6 days a week (not Sundays) for three weeks (21 days), for a total of 18 application days per patient.

Evaluator's conclusions on clinical efficacy for extension of indication to include psoriasis of the body

No study was conducted in which there was a direct comparison between Daivobet ointment and Daivobet gel. This is surprising as the company development plan stated that the Daivobet gel was developed as a formulation expected to have similar efficacy and safety but greater patient acceptability. This has not been tested. One of the supportive studies (PLQ001) does compare gel with ointment but no direct analysis of results is given.

Instead the company provided studies in which the primary efficacy outcome was the percentage of patients with 'controlled disease' ('clear' or 'almost clear'):

· one comparative study against the individual components (in the gel vehicle) which found superiority to betamethasone alone only at 8 weeks (not at 4 weeks). It was superior to calcipotriol and gel vehicle at both 4 and 8 weeks

· one comparative study against tacalcitol (which is not approved for sale in Australia) and the gel vehicle which found that the combination was superior to the tacalcitol and gel vehicle at both 4 and 8 weeks

· one supportive study which also found that Daivobet gel was superior to calcipotriol gel and the gel vehicle at 4 and 8 weeks but was only superior to betamethasone at 8 weeks

· one supportive study which suggests similar effectiveness absolute change in Total Clinical Score (TCS) between Daivobet gel and ointment

Efficacy beyond 8 weeks was not tested. Only approx 30% of all patients achieved 'clear' disease at 8 weeks and so it is disappointing that a longer term trial was not conducted as there is likely to be pressure to continue treatment beyond 8 weeks if some improvement is achieved but not clearing of all lesions. The results are consistent in the studies presented.

The studies presented are not strictly in compliance with the approved guideline[1]. Only one primary efficacy parameter was included in each study. Secondary outcomes did include other scoring systems. No long term study is presented (required in guideline).

It is risky and difficult to compare results across different trials but comparing the results presented in this submission versus that presented in the original ointment submission the impression is that the gel formulation is slightly less effective than the ointment formulation.

Safety

Studies providing evaluable safety data

Comment: The Summary of Clinical Safety presents data on the 'safety analysis set' comprising only the 3 comparative studies (LEO80185-G23, LEO80185-G21 and

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[1] *Guideline on Clinical Investigation of Medicinal Products Indicated for the Treatment of Psoriasis.* (CHMP/EWP/2454/02). November 2004

MBL0202INT). The PD study (LEO80185-G24) and the other efficacy study PLQ-001 is included only in some sections of the summary but not in all the tabulations of adverse events (AEs). Where possible the data from the additional studies is taken from the individual study reports in addition to the data presented by the applicant in the summary.

The following studies provided evaluable safety data:

Comparative efficacy studies

In the comparative efficacy studies, the following safety data were collected:

· General adverse events (AEs) were assessed by means of non-leading questioning of the subjects and by recording changes not reported by the subjects but observed by the investigator.

· AEs of particular interest, including cutaneous events, were assessed in Studies MBL0202INT and LEO80185-G21 as lesional/perilesional AE or distant from the treated lesions. A lesional/perilesional AE was defined as an AE located less than or equal to 2 cm from the lesional border of areas treated with the investigational product. Study LEO80185-G23 did not record cutaneous AEs in the same manner as the other two studies (although this was planned in the protocol) but it was recorded whether AEs were 'in the treatment area' or not. The AEs recorded 'in the treatment area' in Study LEO80185-G23 have been pooled together with the lesional/perilesional AEs in Study MBL0202INT and LEO80185-G21. This is a conservative approach as any non-cutaneous AEs and AEs distant from the treated lesions but in the treatment area would be included.

· Laboratory tests were only conducted in the comparative Studies LEO80185-G23 and PLQ-001. No clinical laboratory evaluations were performed in Studies LEO80185-G21 or MBL0202INT. Study LEO80185-G23 included measurement of serum calcium, albumin, alkaline phosphatase (ALP), and phosphate, plasma parathyroid hormone (PTH), and urinary calcium, phosphate and creatinine from a spot test. Albumin corrected serum calcium, and urinary calcium:creatinine and phosphate:creatinine ratios were calculated.

Patient exposure

Table 7. Exposure to Daivobet and comparators in clinical studies

Study type/ Indication	Controlled studies					Un-controlled studies	Total Daivobet gel
	Daivobet gel	Gel vehicle	Betametha-sone gel	Calcipo-triol gel	Tacalcitol ointment	Daivobet gel	
Clinical pharmacology LEO80185-G24						43	43
Pivotal: LEO80185-G23 LEO80185-G21	482 182	95 91	479 0	96 0	184		482 182
Other MBL0202INT PLQ-001*	160 24	40	83	79			160 24

AusPAR Daivobet 50/500; calcipotriol 50 μg/g and betamethasone (as dipropionate) 500 μg/g gel; Leo Pharma Pty Ltd; PM-2011-04144-3-5; Date of Finalisation August 2013

Page 17 of 37

Study type/ Indication	Controlled studies					Un-controlled studies	Total Daivobet gel
	Daivobet gel	Gel vehicle	Betametha-sone gel	Calcipo-triol gel	Tacalcitol ointment	Daivobet gel	
TOTAL	848	226	562	175	184	43	891

* in study PLQ-001 each patient served as own control for comparison with calcipotriol cream and ointment

Table 8. Duration of exposure to Daivobet gel in clinical studies: Duration of exposure to study treatment in 'controlled non-scalp studies': safety analysis set

Length of drug exposure	Daivobet gel (n=824)	Betametha-sone gel (n=562)	Calcipotriol gel (n=175)	Gel vehicle (n=226)	Tacalcitol (n=184)
Exposure <4 weeks. No (%)	43 (5.2)	47 (8.4)	15 (8.6)	30 (13.3)	11 (6.0)
Exposure ≥4 weeks. No (%)	781 (94.8)	515 (91.6)	160 (91.4)	196 (86.7)	173 (94.0)
Exposure ≥8 weeks. No (%)	615 (74.6)	400 (71.2)	123 (70.3)	143 (63.3)	123 (66.8)
Mean exposure (weeks)	7.7	7.4	7.4	7.0	7.6
Number of exposed subjects	824	562	175	226	184
Subject-treatment-weeks	6323	4176	1290	1581	1391

For study LEO80185-G24: the 43 subjects in the study had a mean duration of exposure of 7.5 weeks (SD 1.1; range 4.3 to 8.3 weeks).

In Study PLQ-001: 24 subjects were treated with 18 applications over 3 weeks.

In each of the 'controlled non-scalp studies', subjects were instructed to treat all psoriasis vulgaris lesions on the trunk and/or arms and/or legs (genitals and skin folds were excluded) with a maximum of 100 g of topical gel per week. The amount of study drug used in the 'controlled non-scalp studies' was calculated by subtracting the weight of the used bottles from the mean weight of full bottles. An average weekly amount of study drug used was calculated by dividing the total amount of study drug used by the number of days of exposure then multiplying by 7 and is shown in Table below.

Table 9. Average weekly amount of study drug used for the 'controlled non-scalp studies': safety analysis set

Average study drug used[1] (g/week)	Daivobet gel (n=824)	Betametha-sone gel (n=562)	Calcipotriol gel (n=175)	Gel vehicle (n=226)	Tacalcitol (n=184)
Mean	29.0	27.4	29.8	28.3	33.2
SD	23.2	22.1	22.2	23.3	23.2
Median	22.6	21.1	25.5	19.6	27.3
Minimum	0	0	0	0	0
Maximum	102	91	94	92	95
Number[2]	706	454	146	171	150

1) Calculated by subtracting the weight of the used bottles from the mean normal weight of full bottles. Negative weights have been set to zero.

2) Only subjects who returned all dispensed bottles provide data.

The mean amount of Daivobet gel used was 29.0 g/week with approximately 46 % of subjects using <20 g/week and 73% using <40 g/week.

In Study LEO80185-G24 the average weekly amount of Daivobet gel used was 52 g (range 7.6 to 93 g).

Evaluator's overall conclusions on clinical safety

Safety in the clinical trials and post marketing data has not indicated any new or significant safety issues beyond the risk of HPA axis suppression. This (worst case scenario) was found in approximately 7% (3/43) in a small trial, but was only assessed following 4-8 weeks of therapy. No long term study was conducted and so if the product is approved there should be very clear indication of risk and statement that safety beyond 8 weeks has not been studied.

The company claim that a long term study is not required as the long term safety is "well known" from the Daivobet ointment submission.

The wording of the *Precautions* section of the proposed PI is different from that in the Daivobet ointment PI which appears to be more strongly worded.

The results for safety were consistent in the clinical studies and appear to be consistent with that previously presented in the ointment submissions.

First round benefit-risk assessment

First round assessment of benefits

The benefits of Daivobet gel in the proposed usage are:

AusPAR Daivobet 50/500; calcipotriol 50 µg/g and betamethasone (as dipropionate) 500 µg/g gel; Leo Pharma Pty Ltd; PM-2011-04144-3-5; Date of Finalisation August 2013

Page 19 of 37

- Product is statistically significantly superior to betamethasone alone in improving symptoms of psoriasis after 8 weeks of therapy and superior to calcipotriol alone in the gel vehicle after 4 and 8 weeks. Daivobet gel was not superior to betamethasone alone in the gel vehicle at 4 weeks.

- The results are consistent in the studies provided.

First round assessment of risks

The risks of Daivobet gel in the proposed usage are:

- Studies conducted are very short: only 8 weeks. No study longer than 8 weeks was provided despite the EU guideline requiring at least one long term study of 12 months

- Studies conducted in a very homogeneous population, predominantly white populations from US, Canada and northern Europe (Germany, Ireland, Sweden, UK and France)

- Studies conducted mostly over the Northern winters, in patients selected to be avoiding sunlight. Unsure of relevance and applicability to Australian conditions but the same comments appear to have been made about the previous ointment dossier

- HPA suppression seen in 7% of patients after 8 weeks, consistent with previous studies on the ointment formulation

- Pivotal studies only included patients with mild–moderate disease. This is not included in the proposed indication

First round assessment of benefit-risk balance

The benefit-risk balance of Daivobet gel, given the proposed usage, is favourable.

First round recommendation regarding authorisation

Based on the clinical data presented in the submission approval is recommended.

Clinical questions and evaluation of responses

Question 1. Dosage and administration instructions

Please explain why the [proposed] indication say, "Body Psoriasis: Daivobet gel should be applied to the affected areas of skin once daily for up to 8 weeks or until cleared", when no data beyond 8 weeks of treatment were submitted?

Sponsor response was to agree to amend the 'Dosage and Administration' section of the PI to: remove the treatment beyond eight weeks. The wording would be: "Body Psoriasis: Daivobet gel should be applied to the affected skin once daily until cleared for up to 8 weeks."

The wording suggested by company is clumsy and may be misinterpreted to imply treatment until cleared (which may be longer than eight weeks) and remains cleared for eight weeks.

It is suggested that more accurate wording which reflects what was done in the clinical trials would be: "Body Psoriasis: Daivobet should be applied once daily for up to eight weeks."

AusPAR Daivobet 50/500; calcipotriol 50 µg/g and betamethasone (as dipropionate) 500 µg/g gel; Leo Pharma Pty Ltd; PM-2011-04144-3-5; Date of Finalisation August 2013

Page 20 of 37

Question 2. Studies presented and product information

How do the doses applied in Studies LEO80185-G24 and MBL0404FR relate to those proposed in the draft PI?

Study MBL040FR was not included as part of this evaluation (it was not available to the evaluator) and LEO80815-G24 was a supporting (other) study. The company response cannot be verified for Study MBL040FR but is correct for Study LEO80815-G24.

The company response stated:

"The Studies LEO80185-G24 and MBL0404FR included subjects with psoriasis vulgaris involving 15-30% of the body surface area. The weekly amount of medication supplied was 100 g and 110 g in LEO-G24 and MBL0404FR respectively. The mean weekly amounts applied were 52.27 g (range 7.64 to 92.95 g) in Study LEO80185-G24 (gel) and 62.5 g (range 29.7 to 105.8 g) in Study MBL0404FR (gel and ointment). The maximum dosages applied in these studies were at the level of the maximum proposed dose. Overall, in these studies there were no reports of hypercalcaemia and no correlation between amount of drug used and the ACTH stimulated serum cortisol levels."

The dose proposed in the PI is consistent with that seen in the clinical trials: "When using calciprotriol containing products, the maximum daily dose should not exceed 15 grams and the maximum weekly dose should not exceed 100 grams. The total body surface area treated with calcipotriol should not exceed 30%."

Question 3. Statistical testing in LEO80815-G23

In Study LEO80185-G23, please clarify the pre-determined sequence of statistical testing and the sequence of testing. It is noted that there was no difference at Week 4 for the first test in the sequence, betamethasone gel. Statistical significance has been reported for secondary endpoints.

The sponsor's response states that there was no pre-determined sequence of testing. The reason for this was to avoid prioritisation of the two endpoints. The sponsor states that the Hochberg procedure allows this, because the p values are calculated for each of the co-primary endpoints and only the actual values determines the conclusions, as described by the method. The explanation given in the Statistical Analysis Plan Update states:

"For each comparison the Hochberg correction for the p-values for the two endpoints means that the largest of the two p-values must be <5% for both to be statistically significant. If the largest p-value is ≥5% then the corresponding hypothesis cannot be rejected. If the smaller p-value is <2.5%, then it is statistically significant and the corresponding hypothesis is rejected, otherwise it cannot be rejected. This means that both p-values must be <5% for LEO80125 [Daivobet] to be superior to that comparator at both week 4 and week 8. If LEO80185 is superior to all three comparators at weeks 4 and 8, then superiority can be claimed for both endpoints. If statistical significance is obtained at week 8 for all three comparators, then superiority of LEO80185 can be claimed at week 8. The conclusion is similar for week 4."

The company conducted the statistical analysis in line with the statistical plan. They acknowledge that this method does not control strongly the type 1 error. However, they state that the method of evaluating p-values set out in the submission, which was the intended application of the Hochberg method for adjusting for multiplicity controls the type 1 error strongly. This appears an adequate response.

Question 4 Formulation of daivobet 50/500 gel in clinical trials

No detailed formulation details are provided in the application form or other parts of the clinical module of the submission. Please confirm that the formulation is unchanged from that currently approved and the formulation was the same in all clinical trials in the submission.

The sponsor has confirmed that the formulation is unchanged from the current approved and the formulation was the same in all the clinical trials in the submission.

Second round benefit-risk assessment

Second round assessment of benefits

No new clinical information was submitted in response to questions. Accordingly, the risks of Daivobet gel are unchanged from those identified in the first round assessment of benefits.

Second round assessment of risks

No new clinical information was submitted in response to questions. Accordingly, the risks of Daivobet are unchanged from those identified in the first round assessment of risks.

Second round assessment of benefit-risk balance

The benefit-risk balance of Daivobet, given the proposed usage, is favourable.

Second round recommendation regarding authorisation

Based on the clinical data presented in the submission approval is recommended.

The proposed indication should be changed to be the same as that approved in Europe. The indication should be:

> *"Topical treatment of scalp psoriasis in adults. Topical treatment of mild to moderate 'non-scalp' plaque psoriasis in adults."*

V. Pharmacovigilance findings

No risk management plan (RMP) was submitted. This was considered acceptable by the TGA Office of Product Review.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

AusPAR Daivobet 50/500; calcipotriol 50 μg/g and betamethasone (as dipropionate) 500 μg/g gel; Leo Pharma Pty Ltd; PM-2011-04144-3-5; Date of Finalisation August 2013

Page 22 of 37

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

Daivobet 50/500 gel formulation was initially approved in 2010. At present, the registered indication is topical treatment of scalp psoriasis. This application proposes to extend the indications to include topical treatment of body psoriasis.

Only Module 5 data are submitted. The clinical evaluator states that the following data are submitted:

· 1 x clinical pharmacology study (LEO80185-G24), which aimed to provide PD and PK data;

· 2 x pivotal comparative efficacy/safety studies (LEO80185-G23 and LEO80185-G21);

· 2 x other efficacy/safety studies (MBL0202INT and PLQ-001).

Pharmacology

Study LEO80155-G24 is a PD study. This is a multicentre open, 8 week study in subjects with extensive psoriasis involving 15-30% of total BSA. The primary objective was to assess the effect of once daily Daivobet gel on HPA and calcium metabolism.

The clinical evaluator mentions that, "adrenal function was determined by measuring serum cortisol before and at 30 and 60 minutes after stimulation by a rapid standard dose adrenocortiotrophic hormone (ACTH) (Cortrosyn) challenge test. The ACTH tests were performed within 7 days of baseline and after 4 and 8 weeks of treatment (Days 28 and 56). If the cortisol level at 30 days after ACTH stimulation was ≤18 μg/dL, the subject was withdrawn from treatment and the test was repeated 28 days after treatment was stopped. Evaluation of calcium metabolism was performed after 3 days of an individual standardised calcium diet at baseline and at Day 28 and 56".

A total of 43 subjects received treatment. The mean weekly use of Daivobet gel was 52.27 g. 3 subjects (7%) had serum cortisol ≤ 18μg/dL, 30 minutes after ACTH stimulation tests at Day 28. Of these, 2 showed signs of adrenal suppression (one was borderline suppression and the other was overt suppression). There were no abnormal results at 8 weeks.

The calcium metabolism was not changed.

The evaluator compares the results with a previously submitted Study MBL0404FR, where cortisol levels ≤ 18 μg/dL were observed in 5/32 (15.6%) patients after 4 weeks and in 2/11 (18.2%) patients who continued for 8 weeks. It is stated that the values were close to the defined cut-off level at 30 minutes.

The evaluator was of the opinion that the results of the current study were consistent with the previous study.

Dose selection studies

None were submitted. The evaluator states that, the sponsor's justification for the dosing is, "a once daily treatment regimen has been chosen as this is considered more convenient for the subject and has been shown to be effective in previous studies. It decreases drug exposure and time spent on application and thus, probably enhances subject compliance."

AusPAR Daivobet 50/500; calcipotriol 50 μg/g and betamethasone (as dipropionate) 500 μg/g gel; Leo Pharma Pty Ltd; PM-2011-04144-3-5; Date of Finalisation August 2013

Page 23 of 37

Efficacy studies

The evaluator mentions three studies (LEO80185-G23, LEO80185-G21 and MBL0202INT), of which the former two are considered pivotal by the evaluator.

LEO 80185-G23

This was a randomised double blind 4 arm study. The treatment arms were: Daivobet gel (calcipotriol 50 µg/g plus betamethasone 0.5 mg/g as dipropionate), betamethasone gel (0.5 mg/g as dipropionate), calcipotriol gel (50 µg/g) and gel vehicle. The treatment was applied once daily for 8 weeks in those with stable psoriasis vulgaris of the body. The washout and treatment details are included in the CER (see Attachment 2 of this AusPAR). Those over the age of 18 years with stable plaque psoriasis of at least 6 months were eligible to participate. Other inclusion criteria were: an IGA of mild or moderate on the body (trunk and/or limbs) at Day 0 (Visit 1); a minimum modified PASI score for extent of 2 in at least one body region (that is, psoriasis affecting at least 10% of arms, and/or 10% of trunk, and/or 10% of legs).

Primary efficacy outcome: the percentage of patients with 'controlled disease' according to the IGA at Weeks 4 and 8 (both Last observation carried forward; LOCF). Details of the scoring scales are provided in the Definitions section in the CER (Attachment 2 of this AusPAR).

'Controlled disease' is defined as 'clear' or 'almost clear' for subjects with moderate disease at baseline and 'clear' for subjects with mild disease at baseline.

The primary analysis was to test for superiority of Daivobet gel versus betamethasone gel, calcipotriol gel and the gel vehicle using the full analysis set (intent to treat; ITT). To be considered superior, all three tests had to be statistically significant.

The other efficacy outcomes included the percentage change in PASI from baseline, those achieving controlled disease at various time points, those achieving 75% and 50% reduction in PASI score.

It is stated that all randomised patients were included in the ITT analysis. Sample size calculations are adequate.

The demographics are included in the CER (Attachment 2). Of note: the mean duration of psoriasis was 16.8 (13.1) years. IGA at baseline was 78% moderate and 22 % mild. The mean PASI score was 7.9 (3.5); the BSA involved was 12.2 % (10.8).

The primary efficacy results extracted from the evaluation report is as follows:

Table 10. Study LEO80185-G23 Percentage of patients with 'controlled disease' at Week 4 and 8

	Daivobet gel (n=482)	Betamethasone gel (n=479)	Calcipotriol gel (n=96)	Vehicle (n=95)
Week 4				
Controlled Disease	Number of subjects (%)	Number of subjects (%)	Number of subjects (%)	Number of subjects (%)
Controlled	64 (13.3)	60 (12.5)	5 (5.2)	2 (2.1)
Non-controlled	418 (86.7)	419 (87.5)	91 (94.8)	93 (97.9)
Total	482 (100.0)	479 (100.0)	96 (100.0)	95 (100.0)

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Page 24 of 37

	Daivobet gel (n=482)	Betamethasone gel (n=479)	Calcipotriol gel (n=96)	Vehicle (n=95)
Statistical analysis				
Difference (%)		0.8	8.1	11.2
95% confidence interval (CI)		-3.5 to 5.0	2.7 to 13.4	7.0 to 15.4
Odds ratio[1]		1.0	3.0	8.4
95% CI		0.7 to 1.5	1.1 to 7.6	1.9 to 37.1
CMH test p-value[2]		0.82	0.019	0.001
Breslow-Day test p-value[3]		0.65	0.43	0.96
Week 8				
Controlled	140 (29.0)	103 (21.5)	14 (14.6)	6 (6.3)
Non-controlled	342 (71.0)	376 (78.5)	82 (85.4)	89 (93.7)
Total	482 (100.0)	479 (100.0)	96 (100.0)	95 (100.0)
Statistical analysis				
Difference (%)		7.5	14.5	22.7
95% CI		2.1 to 13.0	6.3 to 22.6	16.4 to 29.1
Odds ratio[1]		1.5	2.8	7.5
95% CI		1.1 to 2.0	1.5 to 5.3	3.0 to 18.8
CMH test p-value[2]		0.008	0.002	<0.001
Breslow-Day test p-value[3]		0.56	0.94	0.98

1) Cochran-Mantel-Haenszel odds ratio for Controlled disease (Daivobet gel relative to Betamethasone gel /Calcipotriol gel/Vehicle) adjusted for pooled centre

2) Cochran-Mantel-Haenszel test for the hypothesis of odds ratio equal to 1

3) Breslow-Day test for homogeneity of odds ratios across pooled centres

The evaluator mentions that "At Week 4 Daivobet gel was statistically significantly more effective than calcipotriol gel and the gel vehicle. Because of the lack of statistical significance in the comparison with betamethasone, a formal claim of superiority could not be made at Week 4 for any of the three pair-wise comparisons.

At Week 8 Daivobet gel was statistically significantly more effective than betamethasone gel, calcipotriol gel and the gel vehicle".

The percentage change in PASI at 4 weeks was statistically significant compared with vehicle -28.9 (95% confidence interval (CI): -35.4 to -22.5) and compared with calcipotriol -16.3 (95% CI: -22.7 to -9.8). It was not statistically significantly different regarding betamethasone gel -3.9 (95% CI: -7.6 to -0.2). At 8 weeks all comparisons were statistically significant, that is, versus vehicle -34.2 (95% CI:-42.0 to -26.4); versus calcipotril -14.9 (95% CI:-22.7 to -7.0) and betamethasone gel -7.6 (95% CI:-12.1 to -3.1).

The other endpoints did not include statistical testing; the descriptive analyses are presented on pages 28 and 29. They tended to reflect the changes seen with the primary endpoint.

Study LEO80185-G21 (see 29 to 40, CER).

Here Daivobet gel (calcipotriol 50 µg/g as hydrate plus betamethasone 0.5 mg/g as dipropionate was) was compared with tacalcitol ointment (tacalcitol 4 µg/g as monohydrate) and gel vehicle alone. Tacalcitol is a vitamin D3 analogue and is not registered in Australia and thus, this study cannot be considered a pivotal study. This was a multicentre randomised (2:2:1) investigator blinded 8 week study conducted in several centres in Canada.

This included a washout phase and a treatment phase; (the latter was of 8 weeks duration); this was followed by an observation phase of a further 8 weeks where subjects were evaluated at Weeks 10, 12 and 16 to investigate occurrence and time to relapse. There was a follow up phase of 2 weeks in those who experienced AEs on treatment.

Those over the ages of 18 years with IGA of moderate, severe or very severe psoriasis were eligible to participate. Exclusion criteria were similar to the previous study.

The treatment was administered once daily.

The primary efficacy outcome was those with controlled disease according to IGA at Week 8. Other efficacy outcomes also included endpoints that assessed relapse and rebound.

The evaluator mentions that, "the sample size calculation assumed that 28% of subjects in the Daivobet gel treatment group, 15% of the subjects in the tacalcitol ointment treatment group and 5% of the subjects in the gel vehicle treatment group had 'controlled disease' and that a two-tailed significance level, α of 0.05 was used. With 180 subjects in the Daivobet gel and tacalcitol treatment groups a chi-square test would have 82% power to reject the null hypothesis of no difference between the two groups regarding the primary response criterion. Likewise, with 90 subjects in the gel vehicle treatment group a chi-square test would have 99% power to reject the null hypothesis of no difference between the Daivobet gel treatment group and the gel vehicle treatment group. Thus the overall power was approximately 81%."

The study was designed to show superiority of Daivobet gel over vehicle; and superiority over tacalcitol ointment, for the proportion of subjects with 'controlled disease' at Week 8 according to the IGA.
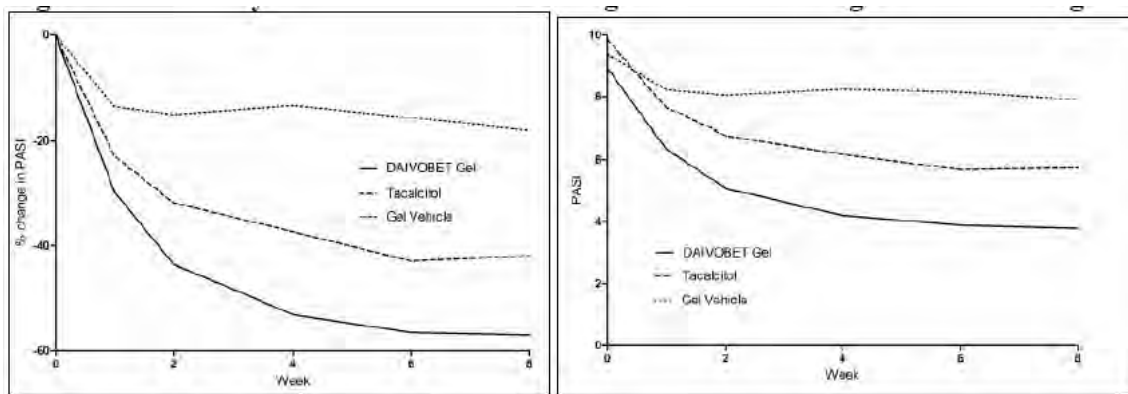
The subject number randomised was 458; Daivobet gel group n=183; tacalcitol group n=184 and in the gel vehicle group n= 91. 60 subjects withdrew.

The mean age of the subjects was 51.6 (standard deviation (SD) 14.0) years; duration of psoriasis was 19.8 years (SD 13.3); IGA status: moderate 68.3%; severe 29.5%; very severe 2.2%.

The primary efficacy outcome was subjects with 'controlled disease' according to IGA at Week 8.

The proportion of subjects who achieved 'controlled disease' at Week 8 (LOCF) in the Daivobet gel group was 39.9% compared with 5.5% in the gel vehicle group and 17.9% in the tacalcitol group. Daivobet gel was statistically significantly more effective than the gel vehicle (odds ratio (OR) 13.9, 95% CI 4.99 to 38.7; $p<0.001$) and the sequential test versus tacalcitol also showed that Daivobet gel was statistically significantly more effective (OR 3.42, 95% CI 2.05 to 5.70; $p<0.001$). There was no treatment by centre interaction ($p>0.10$).

The secondary efficacy outcomes showed similar changes. Of note, the changes in the PASI is given below.

AusPAR Daivobet 50/500; calcipotriol 50 µg/g and betamethasone (as dipropionate) 500 µg/g gel; Leo Pharma Pty Ltd; PM-2011-04144-3-5; Date of Finalisation August 2013

Page 27 of 37

Figure 1. Study LEO80185-G21 Percentage and actual change in PASI during study

Relapse: The evaluator mentions that 'relapse' is defined as a reduction in PASI improvement from baseline by at least 50% among subjects with 'controlled disease' at Week 8.

It is stated that, "at the end of the treatment phase 67 subjects in the Daivobet gel group, 31 in the tacalcitol group and 5 subjects in the gel vehicle group had 'controlled disease' and entered the observation phase". The following results are extracted from the CER.

Table 11. Study LEO80185-G21 Development of relapse during observation period

Relapse[1]	Daivobet Gel (n=67)	Tacalcitol (n=31)	Gel Vehicle (n=5)
	Number of Subjects (%)	Number of Subjects (%)	Number of Subjects (%)
Relapse	28 (41.8)	7 (22.6)	3 (60.0)
No Relapse	39 (58.2)	24 (77.4)	2 (40.0)
Kaplan-Meier estimates[2]			
Median time to relapse (days)	63	61	61
Lower quartile (days)	28	56	56
Upper quartile (days)[2]		63	61

1) 7 patients had controlled disease but withdrew after week 8; these patients were not included in this table

2) Upper quartile in the Daivobet group cannot be estimated due to the large number of censored patients (ie patients who had not relapsed when leaving the study)

It appears that 41% in the Daivobet gel relapsed; this figure is higher than that observed in tacalcitol (22.6%). However, the numbers are small to be meaningful.

Change in quality of life from baseline to Week 4 and Week 8 were assessed using SF-36 (a survey that measures general health-related quality of life) and Skindex-16 (Skindex-16 (a 16-item survey that measures skin specific quality of life) questionnaires. The Skindex questionnaire is a skin disease specific questionnaire that showed statistically significant difference favouring Daivobet gel over tacalcitol and vehicle gel at Week 4 and Week 8.

AusPAR Daivobet 50/500; calcipotriol 50 μg/g and betamethasone (as dipropionate) 500 μg/g gel; Leo Pharma Pty Ltd; PM-2011-04144-3-5; Date of Finalisation August 2013

Page 28 of 37

Other efficacy studies:

Study MBL0202INT is a Phase II "proof of concept" study submitted previously which compared Daivobet gel versus its individual components and the vehicle gel in subjects with psoriasis vulgaris in non-scalp areas. It was a randomised (4:2:2:1) double blind study of the following treatments: Daivobet gel (calcipotriol 50 µg/g plus betamethasone dipropionate 0.5 mg/g); betamethasone dipropionate 0.50 mg/g in the gel vehicle; calcipotriol 50 µg/g in the gel vehicle and gel vehicle.

Percentage of patients with controlled disease according to IGA at Week 4 and Week 8 was the primary efficacy endpoint. Changes in PASI scores at various time points were secondary endpoints. The evaluator mentions that there was no pre-set margin for superiority.

364 subjects were randomised. Daivobet gel: n=162; betamethasone gel: n=83; calcipotriol gel: n=79 and the Gel vehicle: n=40.

The evaluator mentions that the mean age of the study recruits was 52.6 years. 98.1% were Caucasians. The mean duration of disease ranged from 18.5 to 19.5 years in the study groups; mean PASI score was 7.7 to 7.9 between groups and > 50% had moderate disease (according to IGA and PGA).

The results on 'controlled disease' are shown below:

Table 12. Study MBL0202INT Patients with 'controlled disease' according to IGA at week 4 and 8 and results of statistical analysis: full analysis set

Controlled disease	Daivobet Gel (n=162) No. (%)	Betamethasone (n=83) No. (%)	Calcipotriol (n=79) No. (%)	Gel Vehicle (n=40) No. (%)
Week 4 (LOCF)				
Controlled disease	26 (16.0)	8 (9.6)	3 (3.8)	1 (2.5)
Non-controlled disease	136 (84.0)	75 (90.4)	76 (96.2)	39 (97.5)
Odds ratio		2.02	5.98	10.83
95% CI		0.84 to 4.82	1.53 to 23.34	1.04 to 112.73
CMH test[1] (p value)		0.11	0.006	0.027
Breslow-Day test[2]		0.39	0.92	1.00
Week 8 (LOCF)				
Controlled disease	44 (27.2)	14 (16.9)	9 (11.4)	0 (0)
Non-controlled disease	118 (72.8)	69 (83.1)	70 (88.6)	40 (100.0)
Odds ratio		2.40	2.89	

Controlled disease	Daivobet Gel	Betamethasone	Calcipotriol	Gel Vehicle
	(n=162) No. (%)	(n=83) No. (%)	(n=79) No. (%)	(n=40) No. (%)
95% CI		1.11 to 5.20	1.31 to 6.38	
CMH test[1] (p value)		0.027	0.006	< 0.001
Breslow-Day test[2]		0.88	0.29	

1. Cochran-Mantel-Haenszel test for the hypothesis of odds ratio equal to 1

2. Test for homogeneity of odds ratios across centres

Daivobet gel was statistically significantly more effective than betamethasone dipropionate gel, calcipotriol gel and the vehicle at Week 8; but at Week 4, the comparison with betamethasone dipropionate gel did not reach statistical significance.

Percentage change in PASI showed similar results i.e greater change with Daivobet gel than the individual components.

The evaluator mentions that in relation to the PGA, at Week 4 and 8, Daivobet gel was statistically significantly more effective than calcipotriol gel and vehicle but not compared to betamethasone dipropionate gel.

Study PLQ001 is a Phase II study conducted to evaluate the psoriasis plaque test comparing three marketed products and two investigational products (LEO 80185 and LEO 80190) and a vehicle control in the treatment of psoriasis vulgaris. LEO 80185 gel contained calcipotriol 50 μg/g as hydrate plus betamethasone 0.5 mg/g as dipropionate; LEO 80190 ointment contained calcipotriol 25 μg/g as hydrate plus hydrocortisone 10 mg/g. The marketed products contained calcipotriol 50 μg/g as hydrate as cream or ointment; and Daivobet ointment. There were two investigational products: calcipotriol 50 μg/g as hydrate plus betamethasone 0.5 mg/g as dipropionate as gel and ointment. There was also a vehicle gel included as treatment. The aim of the study was to evaluate the use of the psoriasis plaque test and specific selected biomarkers in predicting treatment efficacy of psoriasis vulgaris. (This study is generally used early in development to identify the optimal formulation that can be selected for further development).

27 subjects were analysed; 24 completed the study. Total clinical score was the primary outcome. The results showed that the treatment effect separated into three pairs: 1) Daivobet ointment and LEO 80185 (Daivobet gel); 2) Calcipotriol ointment and LEO 80190 3) Daivobet ointment vehicle and calcipotriol cream.

The evaluator states that there was a good correlation with the TCS and selected biomarkers (that is, epidermal thickness, morphology and infiltration of inflammatory cells).

Pooled analysis

The evaluator discusses a pooled analysis of the 3 efficacy studies, LEO80185-G23, LEO80185-G21 and MBL0202INT. It is noted that LEO80185-G21 had no 'mild disease' and LEO80185-G23 had no 'severe' and 'very severe' disease. Baseline PASI was also higher in LEO80185-G21.

The pooled 'controlled disease' results are given below. These data suggest that 8 Week treatment duration was required to show significant benefit.

Table 13. Pooled data - 'Controlled disease' (IGA) at Weeks 4 and 8 by study, treatment group and pooled treatment group: full analysis set

Week Controlled disease	Daivobet gel Number of subjects (%)	Betametha-sone gel Number of subjects (%)	Calcipotriol gel Number of subjects (%)	Gel vehicle Number of subjects (%)	Tacalcitol Number of subjects (%)
Week 4					
Controlled Disease	124 (15.0)	68 (12.1)	8 (4.6)	4 (1.8)	12 (6.5)
Non-Controlled Disease	703 (85.0)	494 (87.9)	167 (95.4)	222 (98.2)	172 (93.5)
Total	**827 (100.0)**	**562 (100.0)**	**175 (100.0)**	**226 (100.0)**	**184 (100.0)**
Lower 95% CL (controlled)	12.6	9.5	2.0	0.5	3.4
Upper 95% CL (controlled)	17.6	15.1	8.8	4.5	11.1
Week 8					
Controlled Disease	257 (31.1)	117 (20.8)	23 (13.1)	11 (4.9)	33 (17.9)
Non-Controlled Disease	570 (68.9)	445 (79.2)	152 (86.9)	215 (95.1)	151 (82.1)
Total	**827 (100.0)**	**562 (100.0)**	**175 (100.0)**	**226 (100.0)**	**184 (100.0)**
Lower 95% CL (controlled)	27.9	17.5	8.5	2.5	12.7
Upper 95% CL (controlled)	34.4	24.4	19.1	8.5	24.3

CL = confidence limits

AusPAR Daivobet 50/500; calcipotriol 50 μg/g and betamethasone (as dipropionate) 500 μg/g gel; Leo Pharma Pty Ltd; PM-2011-04144-3-5; Date of Finalisation August 2013

Page 31 of 37

The change in PASI scores are also discussed in the pooled dataset. The pattern is similar to the previous outcome.

Overall efficacy conclusions:

The evaluator's conclusions on efficacy identified a deficiency in that there is no direct comparison of Daivobet gel versus ointment, especially as the gel formulation is expected to have better patient acceptability. This has not been verified with data. The pivotal study showed superiority of the combination product versus betamethasone only at 8 Weeks. Thus, another significant deficiency identified is that there are no studies conducted beyond 8 weeks. It is noted that the adopted EU Guideline CHMP/EWP/2454/02 recommends that studies of 12 month duration, to assess safety and efficacy of intermittent or prolonged use (as appropriate) are to be done.

The evaluator also states that, 'the studies presented are not strictly in compliance with the approved guideline. Only one primary efficacy parameter was included in each study. Secondary outcomes did include other scoring systems.'

Safety:

A total of 891 patients have been exposed to Daivobet gel. The mean exposure of treatment is 7.7 weeks. Average weekly use of Daivobet gel is 29.0 g/week.

Overall incidence of AEs was similar across treatment groups in the comparative studies. Treatment related events are included in the Table below on treatment-related AEs (adverse drug reactions) from the comparative studies

Table 14. Adverse drug reactions occurring in ≥1% of subjects in the Daivobet gel, betamethasone gel, calcipotriol gel or gel vehicle group by MedDRA primary system organ class and preferred term for the 'controlled non-scalp studies': safety analysis set

System Organ Class Preferred Term[1]	Daivobet gel (n=824) No (%)	Betameth-asone gel (n=562) No (%)	Calcipotriol gel (n=175) No (%)	Gel vehicle (n=226) No (%)	Tacalcitol (n=184) No (%)
Nervous system disorders					
Burning sensation	2 (0.2)	0 (0.0)	0 (0.0)	5 (2.2)	2 (1.1)
Skin and subcutaneous tissue disorders					
Pruritus	12 (1.5)	2 (0.4)	5 (2.9)	15 (6.6)	11 (6.0)
Erythema	1 (0.1)	0 (0.0)	2 (1.1)	0 (0.0)	1 (0.5)
Skin burning sensation	0 (0.0)	0 (0.0)	2 (1.1)	2 (0.9)	1 (0.5)
General disorders and administration site conditions					
Application site pain	3 (0.4)	1 (0.2)	0 (0)	0 (1.3)	2 (1.1)
Pain	2 (0.2)	1 (0.2)	2 (1.1)	0 (0.0)	0 (0.0)

System Organ Class Preferred Term[1]	Daivobet gel (n=824) No (%)	Betameth-asone gel (n=562) No (%)	Calcipotriol gel (n=175) No (%)	Gel vehicle (n=226) No (%)	Tacalcitol (n=184) No (%)
Investigations					
Blood parathyroid hormone increased	7 (0.9)	6 (1.1)	0 (0.0)	1 (0.4)	0 (0.0)

1) Classification according to Medical Dictionary for Regulatory Activities (MedDRA) version 14.1.

The numbers were small to detect any significant trends. Of note, were three subjects reporting adrenal suppression.

The evaluator also mentions that Study LEO 80185-G24 evaluated once daily use of Daivobet gel on HPA and calcium metabolism. There were no significant trends seen in relation to albumin corrected serum calcium, urinary calcium: creatinine ratio, serum PTH. There were two subjects with possible clinically significant increases in 24 hour urinary calcium excretion. The average weekly use of Daivobet gel in these subjects ranged from 73- 87g. One subject was withdrawn at day 28 as there was an abnormal ACTH suppression test.

Overall the evaluator concludes that the AE profile was in line with previously reported AEs.

Clinical evaluator's overall conclusions and recommendation

The evaluator recommends that the indication be amended from 'topical treatment of body psoriasis' to,

> *'topical treatment of mild to moderate 'non-scalp plaque psoriasis in adults'.*

This is to be in line with the indication in Europe, based on a similar data set.

The evaluator also recommends that the statement in the proposed PI on HPA effects based on study LEO80185-G24, 'These results demonstrated that Daivobet gel may have effects on the HPA axis but the incidence is low and did not increase over time even in a maximum use setting,' should be removed as the study was small and of a short duration. This should be replaced with the statement that is similar to that in the Daivobet ointment PI.

In line with the studies submitted, the sponsor has amended the dosing, that is, "Body psoriasis: Daivobet should be applied once daily for up to 8 weeks."

The dose proposed in PI is consistent with the dose used in the clinical trial.

The formulation of Daivobet gel used in the clinical trials is that which is proposed for marketing.

Overall, the evaluator recommends registration.

Risk management plan

No RMP was submitted. This was considered acceptable by the Office of Product Review.

Risk-benefit analysis

Delegate considerations

The pivotal study is LEO 80185-G23 and in this study Daivobet gel shows superiority versus the individual components in those with mild to moderate disease as per the IGA. Thus, the Delegate agreed with the clinical evaluator's comment that the indication should include treatment of those with mild to moderate psoriasis, only, in relation to severity. Statistical superiority of Daivobet gel (over the comparators) was seen, as specified in the protocol, only at 8 Weeks. This should be included in the PI.

The second study, LEO 80185-G21 includes tacalcitol as a comparator which is not registered in Australia. Thus, it is a supportive study. There are data in a small group on relapse and rebound; this is inadequate. Thus the PI document should state that there are inadequate data on relapse and rebound with this product.

The PD study LEO 80185-G24 examined HPA suppression. 3/43 subjects showed suppression. The number included in this study is too small to yield conclusive results. There should be a precautionary statement that there are no long term data with this product and body psoriasis. Also, that data on HPA is lacking.

The PI should also include a statement that treatment should not be continued beyond 8 Weeks.

There also should be a statement in the PI that those who are non-responders at 4 weeks should discontinue treatment without continuing for a further 4 weeks.

All other PI amendments recommended by the evaluator should be incorporated[2].

There is a statement in the PI that the maximum weekly dose should not exceed 100 g. The average weekly use, in the clinical trials is 29 g (23.2). The presentation section of the PI states that it comes in bottles of 30 g. Thus, it would appear that the patient would need up to 8 bottles for up to 8 weeks. The sponsor should justify the presentation of 30 g in their response to this overview.

Proposed action

The Delegate proposed to approve Daivobet 50/500 gel (calcipotriol 50 ㎎/g betamethasone as dipropionate 500 ㎎/g) for the treatment of body psoriasis.

Advice requested from ACPM

General advice on this application was sought from the Advisory Committee on Prescription Medicines (ACPM).

Response from sponsor

Indication

The original indication proposed by the applicant was, *"Topical treatment of body and scalp psoriasis"*.

The clinical evaluator stated that the proposed indication should be changed to be the same as that approved in Europe, *"Topical treatment of scalp psoriasis in adults. Topical treatment of mild to moderate, non-scalp plaque psoriasis in adults"*.

The applicant proposes a modified indication statement for Australia which is more in line with the European indication statement compared to that originally proposed,

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[2] Details of recommended revisions to the PI are generally beyond the scope of the AusPAR.

AusPAR Daivobet 50/500; calcipotriol 50 μg/g and betamethasone (as dipropionate) 500 μg/g gel; Leo Pharma Pty Ltd; PM-2011-04144-3-5; Date of Finalisation August 2013

Page 34 of 37

> *"Topical treatment of scalp psoriasis. Topical treatment of mild to moderate plaque psoriasis on the body".*

The first statement, "Topical treatment of scalp psoriasis", is the same as that approved in the original Daivobet gel application. The second statement, "Topical treatment of mild to moderate plaque psoriasis on the body", provides the restriction of "mild to moderate" and the type of psoriasis, "plaque psoriasis". The term "non-scalp" is replaced by equivalent term "body" as this is the convention throughout the PI, CMI, labelling and packaging and will be the Australian convention used for all medical professional and patient directed information for this product. The term, "in adults", has not been included in the Australian indication statement as it refers to the treatment population which is stated in the relevant section in the PI. Moreover, "in adults" was not included in the originally approved indication statement for Daivobet gel for scalp psoriasis.

Other revisions to the PI recommended by the clinical evaluator

Details of these are beyond the scope of the AusPAR.

Comments from the delegate's summary and proposed action

The Delegate requested that the statement, "there are inadequate data on relapse and rebound", is incorporated into the PI. This statement has been added under the Adverse Effects heading in the revised draft PI.

The Delegate requested that the statement, "there are no long term data with this product and body psoriasis". The balanced statement, "While there are no long-term safety data available beyond 8 weeks in patients treated with Daivobet gel on the body, there are safety data on intermittent courses of Daivobet gel used for up to 52 weeks for scalp psoriasis." has been added to the *Precautions* section.

The Delegate also adds, "Also, that data on HPA are lacking". As there are data on HPA axis suppression, although limited, which the applicant considers useful information for medical professionals, the applicant proposes the following addition to the proposed text (new text underlined), "The results **from this limited number of subjects** demonstrated that Daivobet gel may have effects on the HPA axis but the incidence is low and did not increase over time even in a maximum use setting."

The Delegate requests that the statements, "treatment should not be continued beyond 8 weeks" and "those who are non-responders at 4 weeks should discontinue treatment without continuing for an additional 4 weeks", are included in the PI. To address these comments the applicant proposes the following text in the *Dosage and Administration* section, "Body psoriasis: Daivobet gel should be applied once daily for up to 8 weeks. If there is no response after 4 weeks, treatment options should be reassessed by a medical practitioner". Whether to discontinue or continue Daivobet gel treatment is a clinical issue that should really be decided and assessed by the medical practitioner on a case by case basis.

Other issue

To address the issue raised by the Delegate regarding the 30g pack size of Daivobet gel, the company will provide a larger 60g pack size in addition to the 30g immediately after approval of the extension of the indication to include the body. This new larger pack is stated in the updated PI

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered this product to have an overall positive benefit–risk profile for the following indication:

> *For the topical treatment of mild to moderate body psoriasis in adults*

In making this recommendation, the ACPM expressed concern with the quality of the overall data package, the lack of specificity in end points and absence of long term data in support of the safe and efficacious use of this product.

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following;

· a statement in the *Dosage and Administration* and *Precautions* sections of the PI and relevant sections of the CMI to strengthen the detail of the overall and dose-dependent risk and management to prevent the development of HPA axis suppression. For example, patients may not fully understand the "30% body surface" description. In addition, the clarity in description of this adverse event in the EU and FDA PI's should be considered

· a much greater emphasis on the risk to paediatric populations due to the lower body mass to body surface area ratio

· a statement in the *Dosage and Administration / Clinical Trials / Precautions* sections to require treatment to be ceased if no response is observed after 4 weeks and ceased after 8 weeks.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the use of Daivobet 50/500 gel, containing calcipotriol 50 µg/g and betamethasone (as dipropionate) 500 µg/g gel, for the new indication:

> *Topical treatment of mild to moderate plaque psoriasis on the body in adults.*

The full indications are now:

> *Topical treatment of scalp psoriasis.*

> *Topical treatment of mild to moderate plaque psoriasis on the body in adults.*

The usual conditions of registration were applied.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration