Public Assessment Report for paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended

Daivobet ointment
Calcipotriol/betamethasone

DK/W/0027/pdWS/001

Marketing Authorisation Holder: LEO Pharma A/S

Rapporteur:	Denmark
Finalisation procedure (day 120):	06-02-2013
Date of finalisation of PAR	06-03-2013

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Daivobet
INN (or common name) of the active substance(s):	Calcipotriol/betamethasone
MAH:	LEO Pharma A/S
Currently approved Indication(s)	Topical treatment of stable plaque psoriasis vulgaris amenable to topical therapy in adults.
Pharmaco-therapeutic group (ATC Code):	D05AX52
Pharmaceutical form(s) and strength(s):	Ointment 50/500 micrograms/g

I. EXECUTIVE SUMMARY

SmPC changes are proposed in sections 4.2, 4.8 and 5.1.
No PL changes are proposed.

II. RECOMMENDATION[1]

The final proposed modifications of the SmPC as suggested by the MAH after comment from CMS can be accepted with a minor correction in SPC 4.8. It is recommended that the SmPC include the following wordings:

SmPC 4.2 Posology and Method of administration (change and addition)

Paediatric population

The safety and efficacy of Daivobet ointment in children aged below 18 years have not been established.

Currently available data in children aged 12 to 17 years are described in section 4.8 and 5.1, but no recommendation on posology can be made.

SmPC 4.8 Undesirable effects (addition)

Paediatric population

In an uncontrolled open study, 33 adolescents aged 12-17 years with psoriasis vulgaris were treated with Daivobet ointment for 4 weeks to a maximum of 56 g per week. No new adverse events were observed and no concerns regarding the systemic corticosteroid effect were identified. The size of the study does not however allow firm conclusions regarding the safety profile of Daivobet ointment in children and adolescents.

SmPC 5.1 Pharmacodynamic properties (addition)

Paediatric population

The adrenal response to ACTH challenge was measured in an uncontrolled 4-week study including 33 adolescents aged 12-17 years with body psoriasis who used up to 56 g per week of Daivobet ointment. No cases of HPA axis suppression were recorded. No hypercalcaemia was reported but one patient had a possible treatment-related increase in urinary calcium.

Type IB variation to be requested from the MAH by 8 March 2013 in order to update the product information.

[1] *The recommendation from section V can be copied in this section*

III. INTRODUCTION

On 27th August 2012, the MAH submitted a completed paediatric study for Daivobet ointment, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Daivobet ointment.

The MAH proposed the following regulatory action:

SmPC 4.2 Posology and Method of administration (change and addition)

Paediatric population

The safety and efficacy of Daivobet ointment in children aged below 18 years have not been established.

Currently available data in children aged 12 to 17 years are described in section 4.8 and 5.1, but no recommendation on posology can be made.

SmPC 4.8 Undesirable effects (addition)

Paediatric population

In MAH's first proposal the following text was suggested:

In an uncontrolled study in 33 adolescents aged 12-17 years with psoriasis vulgaris treated with Daivobet ointment for 4 weeks to a maximum of 56 g per week, the safety profile was similar to that in adults.

This text was modified as follows after comments from CMS (NL):

In an uncontrolled open study, 33 adolescents aged 12-17 years with psoriasis vulgaris were treated with Daivobet ointment for 4 weeks to a maximum of 56 g per week. No new adverse events were observed and no concerns regarding the systemic corticosteroid effect were identified. The size of the study does not however allow firm conclusions regarding the safety profile of calcipotriol in children and adolescents.

Calcipotriol in the above text should be replaced by Daivobet ointment.

SmPC 5.1 Pharmacodynamic properties (addition)

Paediatric population

The adrenal response to ACTH challenge was measured in an uncontrolled 4-week study including 33 adolescents aged 12-17 years with body psoriasis who used up to 56 g per week of Daivobet ointment. No cases of HPA axis suppression were recorded. No hypercalcaemia was reported but one patient had a possible treatment-related increase in urinary calcium.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the study

Daivobet ointment is a two component product containing the D-vitamin analogue calcipotriol 50 microgram/g in combination with a potent corticosteroid betamethasone as dipropionate 0.5 mg/g.

Daivobet ointment is approved for treatment of psoriasis vulgaris in adults with a posology of once daily application for 4 weeks. There is clinical experience with repeated courses of Daivobet treatment up to 52 weeks. The maximal daily dosage of Daivobet ointment in adults is 15 g, which corresponds to a maximum weekly dose of approximatetly 100 g.

IV.2 Clinical aspects

1. Introduction

The MAH submitted a final report for a phase 2 study of Daivobet ointment in adolescents:

Safety and efficacy of Taclonex ointment in adolescent patients (aged 12 to 17 years) with psoriasis vulgaris. A national, multicentre, prospective, non-controlled, single-group, 4 week study in patients with psoriasis vulgaris on the trunk and/or limbs.

2. Clinical study

Safety and efficacy of Taclonex (Daivobet) ointment in adolescent patients (aged 12 to 17 years) with psoriasis vulgaris (MCB 0501 INT).

- **Description**

- **Methods**

  - The primary objective was to assess the safety of Daivobet ointment in adolescents with psoriasis after 4 weeks of daily application.

  - The study design was an open uncontrolled trial.

  - The study population was adolescents with moderate to severe plaque type psoriasis with a BSA of 5-30%.

  - Treatment was Daivobet ointment once daily for 4 weeks. The maximum weekly dosage was reduced to 60 g, hence a maximum dosage of 60% of the adult maximum dosage.

  - Primary endpoints were adverse drug reactions (ADR), serum cortisol concentration < 18 mcg/dl at 30 and 60 minutes after ACTH-challenge at end of treatment and change in albumin-corrected serum-calcium: creatinine ratio from baseline to end of treatment

  - Standard statistical methods were applied.

- **Results**

  - A total of 17 female and 16 male adolescents were included.

  - All patients had BSA of 5-30% and according to investigator at least moderate severity.

  - Safety results

    None of the patients had a serum cortisol concentration of < 18 meg/dl at either 30 or 60 minutes following ACTH challenge at end of treatment.

    There were no clinically significant mean changes in albumin-corrected serum calcium or urinary calcium:creatinine ratio. No albumin-corrected serum calcium values above the upper reference were reported. One patient had an increase from normal urinary calcium:creatinine ratio at baseline to a value above the upper reference limit at week 4.

    No significant abnormalities were detected in routine haematology and biochemistry.

    A total of 11 (33%) patients reported 16 ADR, most frequently infections and infestations (n =4) and CNS (n = 4).

    Two of these were ADR, headache and pruritus of mild intensity.

    There were no serious adverse events or withdrawals due to ADR in the trial.

  - Efficacy results

    At week 4, 61% of the patients obtained clear or almost clear status (controlled disease).

    The mean reduction in modified PASI from baseline at week 4 was 72.5% (95% CI: 81.1 to 63.9%).

    The proportion of patients with modified PASI 75 and PASI 50 at week 4 was 52% and 85%, respectively.

3. Discussion on clinical aspects

The submitted uncontrolled 4-week study indicates that Daivobet ointment is well-tolerated with a safety profile similar to that in adults when applied ones daily with a weekly maximal dosage of 60 g. However, due to the low sample size no firm conclusion can be drawn as to the safety of the product in children and adolescents.

No cases of HPA axis suppression were reported. No hypercalcaemia was reported but one patient had a possible treatment-related increase in urinary calcium.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The Rapporteur agrees with the revised modification of SmPC 4.2, 4.8 and 5.1 as suggested by the MAH as these modification are substantiated in the submitted clinical study in adolescents with psoriasis vulgaris.

- **Recommendation**

The final proposed modifications of the SmPC as suggested by the MAH after comment from CMS can be accepted with a minor correction in SPC 4.8. It is recommended that the SmPC include the following wordings:

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Paediatric population

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