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

Daivobet
Dovobet
Xamiol
(calcipotriol/betamethasone dipropionate)

DK/W/0027/pdWS/002

Marketing Authorisation Holder: Leo Pharma A/S

Rapporteur:	Denmark
Finalisation procedure (day 120):	26-03-2014

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Daivobet, Dovobet, Xamiol
INN (or common name) of the active substance(s):	calcipotriol/betamethasone dipropionate
MAH:	Leo Pharma A/S
Currently approved Indication(s)	For DK/H/0279/002/DC (trade names Daivobet/Dovobet): Topical treatment of scalp psoriasis in adults. Topical treatment of mild to moderate “non-scalp” plaque psoriasis vulgaris in adults. For DK/H/1405/001/DC (trade name Xamiol): Topical treatment of scalp psoriasis in adults.
Pharmaco-therapeutic group (ATC Code):	D05AX52
Pharmaceutical form(s) and strength(s):	Gel, 50 microgram/g + 0.5 mg/g

I. EXECUTIVE SUMMARY

The MAH submitted safety and efficacy data from two uncontrolled studies in 109 adolescents treated once daily with application of Daivobet gel to scalp psoriasis for a total of 8 weeks:

Study MBL 0801

Effect of Calcipotriol plus Betamethasone Dipropionate Topical Suspension on the HPA Axis and Calcium Metabolism in Adolescent Subjects (Aged 12 to 17 Years) with Scalp Psoriasis

A phase 2 study evaluating the safety and efficacy of once daily use of the LEO 80185 topical suspension containing calcipotriol 50 mcg/g plus betamethasone 0.5 mg/g (as dipropionate) in adolescent subjects (aged 12 to 17 years) with scalp psoriasis.
A national, multi-centre, prospective, non-controlled, open, single-group, 8-week study in adolescent subjects (aged 12 to 17 years) with scalp psoriasis.

Study MBL 0412 INT

Safety and Efficacy of Calcipotriol plus Betamethasone Dipropionate Gel in Adolescent Subjects (Aged 12 to 17 Years) with Scalp Psoriasis

A phase 2 study evaluating the safety and efficacy of once daily use of the LEO 80185 gel containing calcipotriol 50 mcg/g plus betamethasone 0.5 mg/g (as dipropionate) in adolescent subjects (aged 12 to 17 years) with scalp psoriasis.
An international, multicentre, prospective, non-controlled, open, single-group, 8-week study in adolescent subjects (aged 12 to 17 years) with scalp psoriasis.

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

II. RECOMMENDATION[1]

A variation (C.I.3.a or z) in order to modify the approved SmPC for Daivobet/Xamiol gel with the following wording in sections 4.2, 4.8 and 5.1 to be requested from the MAH by 25 April 2014.

SmPC 4.2 Posology and method of administration
Paediatric population
The safety and efficacy of Daivobet/Xamiol gel in children 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 a posology can be made.

SmPC 4.8 Undesirable effects
Paediatric population
No new adverse events and no new adverse reactions were seen in 109 adolescents aged 12-17 years with scalp psoriasis treated with Daivobet/Xamiol gel for 8 weeks. However, due to the

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

size of the studies, no firm conclusion can be drawn as to the safety profile of Daivobet/Xamiol gel in adolescents compared to that in adults. See section 5.1.

SmPC 5.1 Pharmacodynamic properties
Paediatric population
Effects on calcium metabolism were investigated in two uncontrolled open 8-week studies including in total 109 adolescents aged 12-17 years with scalp psoriasis who used up to 69 g per week of Daivobet/Xamiol gel. No cases of hypercalcaemia and no clinically relevant changes in urinary calcium were reported. The adrenal response to ACTH challenge was measured in 30 patients; one patient showed a decrease in cortisol response to ACTH challenge after 4 weeks of treatment, which was mild, without clinical manifestations, and reversible.

III. INTRODUCTION

On June 21st, 2013, the MAH submitted completed paediatric studies for Daivobet/Dovobet/Xamiol, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

The two trials, trials MBL 0801 and MBL 0412 INT, were conducted as Required Post Marketing study under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), in connection with the approval of the product in USA (Taclonex® Topical Suspension NDA 22- 185) for topical treatment of moderate to severe psoriasis vulgaris of the scalp in adults aged 18 years and above.

These two trials are currently the only paediatric trials conducted for Daivobet gel, containing calcipotriol 50 mcg/g plus betamethasone 0.5 mg/g (as dipropionate).

A short critical expert overview has also been provided.

Study MBL 0801 investigated safety and efficacy of calcipotriol + betamethasone dipropionate in adolescents with psoriasis vulgaris on the scalp. It was a 8-week national (US, only), multicentre, prospective, noncontrolled, single-group phase 2 trial in adolescent patients (aged 12 to 17 years, inclusive) with psoriasis vulgaris on scalp using calcipotriol + betamethasone dipropionate once daily. In total, 31 patients (12 boys and 19 girls) were treated in the trial; 29 patients completed the trial according to the protocol.

Study MBL 0412 INT investigated safety and efficacy of calcipotriol + betamethasone dipropionate in adolescents with psoriasis vulgaris on the scalp. It was an 8-week multinational, multi-centre, prospective, noncontrolled, single-group phase 2 trial in adolescent patients (aged 12 to 17 years, inclusive) with psoriasis vulgaris on scalp using calcipotriol + betamethasone dipropionate once daily. In total, 78 patients (35 boys and 43 girls) were treated in the trial; 74 patients completed the trial according to the protocol.
Both trials were 8-week trials with visits at Baseline, Week 2, Week 4, Week 6, and Week 8 as well as follow-up visits if required by the protocol. Efficacy (by the investigator and patient) was assessed at all visits. Safety was assessed by adverse events at all visits and by vital signs and clinical laboratory tests at Baseline, Week 4 and Week 8.

In these 2 phase 2 trials no cases of hypercalcaemia were reported and there were no clinically relevant changes in urinary calcium or other parameters of calcium metabolism.

In general the Daivobet/Xamiol gel treatment of scalp psoriasis in adolescents was well-tolerated with an efficacy comparable to that observed in adults. However, the study population is not sufficiently large to recommend the use of the products in adolescents with scalp psoriasis.

No changes for use in adolescents were proposed to the currently approved SmPC section 4.1.

Based on the results of these studies the MAH proposed the following changes in sections 4.2, 4.8 and 5.1 of the SmPC:

SmPC 4.2 Posology and method of administration (change and addition)
Paediatric population
The safety and efficacy of Daivobet gel in children 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 a posology can be made.

SmPC 4.8 Undesirable effects (addition)
Paediatric population
In two uncontrolled open studies, a total of 109 adolescents aged 12-17 years with scalp psoriasis were treated with Daivobet gel for 8 weeks to a maximum of 69 g per week. No new adverse events or clinically relevant effects on calcium metabolism were observed. One patient showed a decrease in cortisol response to ACTH challenge after 4 weeks of treatment, which was mild, without clinical manifestations and reversible.

SmPC 5.1 Pharmacodynamic properties (addition)
Paediatric population
Effects on calcium metabolism were investigated in two uncontrolled open 8-week studies including in total 109 adolescents aged 12-17 years with scalp psoriasis who used up to 69 g per week of Daivobet gel. No cases of hypercalcaemia and no clinically relevant changes in urinary calcium were reported. The adrenal response to ACTH challenge was measured in 30 patients; one patient showed a decrease in cortisol response to ACTH challenge after 4 weeks of treatment, which was mild, without clinical manifestations, and reversible.

IV. SCIENTIFIC DISCUSSION

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

Daivobet gel is approved for treatment of mild to moderate psoriasis vulgaris in adults, including treatment of scalp psoriasis.

IV.2 Clinical aspects

1. Introduction

The MAH submitted final study reports for:

MBL 0801

and

MBL 0401 INT

2. Clinical studies

Study MBL 0801

Effect of Calcipotriol plus Betamethasone Dipropionate Topical Suspension on the HPA Axis and Calcium Metabolism in Adolescent Subjects (Aged 12 to 17 Years) with Scalp Psoriasis.

Design

Open-label, non-controlled, single-group study.

Objectives

Primary objective
The primary objective was to evaluate the safety of once daily use of calcipotriol (50 mcg/g) + betamethasone (0.5 mg/g) (as dipropionate) gel in adolescent subjects (aged 12 to 17 years) with scalp psoriasis.

Secondary objective
The secondary objective was to evaluate the efficacy of once daily use of calcipotriol (50 mcg/g) plus betamethasone (0.5 mg/g) (as dipropionate) gel in adolescent subjects (aged 12 to 17 years) with scalp psoriasis.

Study population

A sufficient number of subjects were enrolled to ensure 30 subjects were evaluable for HPA (hypothalamic-pituitaryadrenal) axis suppression and calcium metabolism.

In total, 31 subjects were treated with at least 1 application of investigational product and 29 subjects completed the trial.

Treatments

The subjects were treated with Daivobet gel once daily for up to 8 weeks.

Outcomes/endpoints

The primary endpoints/response criteria were:

- Adverse drug reactions (ADRs).
- Subjects with serum cortisol concentration of ≤18 mcg/dl at 30 minutes after ACTH-challenge at Week 4, and Week 8.
- Subjects with serum cortisol concentration of ≤18 mcg/dl at 30 and 60 minutes after ACTH-challenge at Week 4, and Week 8.
- Change in albumin-corrected serum calcium from Baseline (SV2) to Week 4, Week 8, and end of treatment.
- Change in 24-hour urinary calcium excretion from Baseline (SV2) to Week 4, Week 8, and end of treatment.
- Change in urinary calcium:creatinine ratio from Baseline (SV2) to Week 4, Week 8 and, end of treatment.

Secondary Response Criteria – Safety
The secondary safety endpoints/response criteria were:

- Adverse events (AEs)
- Change in serum phosphate from Baseline (SV2) to Week 4 and Week 8
- Change in 24-hour urinary phosphate excretion from Baseline (SV2) to Week 4 and Week 8
- Change in urinary phosphate:creatinine ratio from Baseline (SV2) to Week 4 and Week 8
- Change in 24-hour urinary hydroxyproline excretion from Baseline (SV2) to Week 4 and Week 8
- Change in urinary hydroxyproline:creatinine ratio from Baseline (SV2) to Week 4 and Week 8
- Change in plasma PTH from Baseline (SV2) to Week 4 and Week 8
- Change in other laboratory parameters from Baseline (SV2) to Week 4 and Week 8
- Reasons for withdrawal
- Change in blood pressure and heart rate from Baseline (SV2) to Week 4 and Week 8

Secondary Response Criteria – Efficacy
The secondary endpoints/response criteria were:

- Subjects with controlled disease (i.e., clear or almost clear) according to the investigator's global assessment of disease severity at Weeks 2, 4, 8, and end of treatment.
- Percentage change in Total Sign Score (TSS; sum of severity scores for each individual clinical sign, redness, thickness, and scaliness) from Baseline to Weeks 2, 4, 8, and end of treatment.
- Subjects with success (Total Sign Score ≤ 1) at Weeks 2, 4, 8, and end of treatment.
- Subjects with controlled disease (defined as clear or very mild) according to the patient's global assessment of disease severity at Weeks 2, 4, 8, and end of treatment.

Statistical methods

Results were assessed by the use of descriptive statistics.

Results

Number analysed

A total of 31 subjects (mean age 14.8 years) were treated (in 5 centres) with at least one application of investigational product and 29 subjects completed the trial; one subject left the trial at Visit 3 (Week 4)
as due to signs of adrenal suppression (serum cortisol concentration ≤18 mcg/dl) at 30 minutes after the ACTH-challenge and one subject was withdrawn at Visit 2 (Week 2) when it was discovered that the inclusion criterion regarding the HPA axis function was not fulfilled. Three subjects had cleared scalp psoriasis after 4-weeks treatment and left the trial at Visit 3 (Week 4) according to the study protocol.

Efficacy

Investigator's Global Assessment (IGA) of Disease Severity
Overall, the majority of subjects had improved during the trial. At end of treatment 54.8% (17 subjects) had controlled disease. There were no clinical relevant differences between males and females or between the age groups.

Investigator's Assessment of Clinical Signs – Total Sign Score (TSS) of Redness, Thickness, and Scaliness
The mean TSS decreased (improved) over time, from 6.9 at Baseline to 2.9 at end of treatment; a 59.2% improvement.
The percentage of subjects with TSS success (TSS ≤1) improved over time and was 38.7% at the end of treatment.

Patient's Global Assessment of Disease Severity and Patient Assessment of Itching
Overall, the majority of subjects experienced an improvement during the trial as assessed by the Patient's Global Assessment of disease severity. The percentage of subjects with controlled disease improved over time and 58.1% of the subjects had controlled disease the end of the treatment.

Overall, there was an improvement in itching over time as assessed by the patients; at the end of treatment 90.3% (28 subjects) reported to have mild or none itching.

Safety

Daivobet gel was well tolerated in this adolescent population; there were no SAEs, few adverse events (none of them lesional/perilesional), and one adverse drug reaction that also lead to withdrawal.

Table 20: Adverse events by MedDRA primary system organ class and preferred term: safety analysis set

System Organ Class Preferred Term[1]	LEO 80185 (n=31) Number of subjects	%
Endocrine disorders		
Hypothalamo-pituitary disorder	1	3.2
Gastrointestinal disorders		
Abdominal pain	1	3.2
General disorders and administration site conditions		
Pain	1	3.2
Infections and infestations		
Hand-foot-and-mouth disease	1	3.2
Nasopharyngitis	2	6.5
Upper respiratory tract infection	2	6.5
Injury, poisoning and procedural complications		
Joint dislocation	1	3.2
Nervous system disorders		
Headache	1	3.2
Psychiatric disorders		
Anxiety	1	3.2
Respiratory, thoracic and mediastinal disorders		
Cough	3	9.7
Nasal congestion	1	3.2
Oropharyngeal pain	3	9.7
Wheezing	1	3.2
Skin and subcutaneous tissue disorders		
Acne	1	3.2
Total number of adverse events[2]	20	
Total number of subjects	16	51.6

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1) Classification according to MedDRA version 14.1.
2) Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.

One subject (3.3%) showed signs of possible adrenal suppression (serum cortisol concentration ≤18 mcg/dl) at 30 minutes after ACTH challenge at Week 4 (>18 mcg/dl at 60 minutes after ACTH challenge). The suppression was reversible as evidenced by a normal challenge test at follow-up 4 weeks after end of treatment.

No cases of hypercalcaemia were reported and there were no clinically relevant increases in urinary calcium or other parameters of calcium metabolism.

There were no clinically relevant changes in the clinical laboratory assessment or in vital signs.

Study MBL 0412 INT

Safety and Efficacy of Calcipotriol plus Betamethasone Dipropionate Gel in Adolescent Subjects (Aged 12 to 17 Years) with Scalp Psoriasis

Design

Open-label, non-controlled, single-group study.

Objectives

Primary objective
The primary objective was to evaluate the safety of once daily use of calcipotriol (50 mcg/g) plus betamethasone (0.5 mg/g) (as dipropionate) gel in adolescent subjects (aged 12 to 17 years) with scalp psoriasis.

Secondary objective
The secondary objective was to evaluate the efficacy of once daily use of calcipotriol (50 mcg/g) plus betamethasone (0.5 mg/g) (as dipropionate) gel in adolescent subjects (aged 12 to 17 years) with scalp psoriasis.

Study population

A sufficient number of subjects were enrolled to ensure 70 subjects were evaluable for evaluation of calcium metabolism. In total, 78 subjects were treated with at least 1 application of investigational product and 74 subjects completed the trial.

Treatments

The patients received Davobet gel ones daily for up to 8 weeks.

Outcomes/endpoints

The primary response criteria were:

- Adverse drug reactions (ADRs).
- Change in albumin-corrected serum calcium from Baseline (SV2) to Week 4, Week 8, and end of treatment.
- Change in 24-hour urinary calcium excretion from Baseline (SV2) to Week 4, Week 8, and end of treatment.
- Change in urinary calcium:creatinine ratio from Baseline (SV2) to Week 4, Week 8 and, end of treatment.

The secondary safety response criteria were:

- Adverse events (AEs)
- Change in serum phosphate from Baseline (SV2) to Week 4 and Week 8
- Change in 24-hour urinary phosphate excretion from Baseline (SV2) to Week 4 and
- Week 8
- Change in urinary phosphate:creatinine ratio from Baseline (SV2) to Week 4 and Week 8
- Change in 24-hour urinary hydroxyproline excretion from Baseline (SV2) to Week 4 and Week 8
- Change in urinary hydroxyproline:creatinine ratio from Baseline (SV2) to Week 4 and Week 8
- Change in plasma PTH from Baseline (SV2) to Week 4 and Week 8
- Change in other laboratory parameters from Baseline (SV2) to Week 4 and Week 8
- Reasons for withdrawal
- Change in blood pressure and heart rate from Baseline (SV2) to Week 4 and Week 8

The secondary efficacy response criteria were:

- Subjects with controlled disease (i.e., clear or almost clear) according to the investigator's global assessment of disease severity at Weeks 2, 4, 8, and end of treatment.
- Percentage change in Total Sign Score (TSS; sum of severity scores for each individual clinical sign, redness, thickness, and scaliness) from Baseline to Weeks 2, 4, 8, and end of treatment.
- Subjects with success (Total Sign Score ≤ 1) at Weeks 2, 4, 8, and end of treatment.
- Subjects with controlled disease (i.e., clear or very mild) according to the patient's global assessment of disease severity at Weeks 2, 4, 8, and end of treatment.

Statistical methods

The data were summarised using descriptive statistics.

Results

Number analysed

A total of 78 subjects (mean age 14.6 years) were treated (in 17 centres) with at least one application of investigational product and 74 subjects completed the trial; 2 subjects had emerging exclusion criteria, 1 subject withdrew due to unacceptable adverse events and 1 subject due to other reason(s). Thirteen subjects had controlled disease at Visit 3 or 4 and left the trial as per the specifications in the Clinical Study Protocol.

Efficacy

Investigator's Global Assessment (IGA) of Disease Severity
Overall, the majority of subjects had improved during the trial. At end of treatment 84.6% (66 subjects) had controlled disease. There were no clinically relevant differences between males and females or between the age groups.

Investigator's Assessment of Clinical Signs – Total Sign Score (TSS)
The mean TSS decreased (improved) over time, from 7.1 at Baseline to 1.4 at end of treatment; a 80.4% improvement. The percentage of subjects with success (TSS≤1) improved over time and was 62.8% at the end of treatment.

Patient's Global Assessment of Disease Severity and Patient Assessment of Itching
Overall, the majority of subjects experienced an improvement during the trial as assessed by the Patient's Global Assessment of disease severity. The percentage of subjects with controlled disease improved over time and 87.2% (68 subjects) had controlled disease at end of treatment. Overall, there was an improvement in itching over time as assessed by the patients; at the end of treatment 96.2% (75 subjects) reported to have none or mild itching.

Safety

Daivobet gel was well tolerated in this adolescent population; there were no SAEs, few adverse events. Two subjects had lesional/perilesional adverse events on the scalp, 5 subjects had adverse drug reactions, and two subjects withdrew from trial due to adverse events.

No cases of hypercalcaemia were reported and there were no clinically relevant increases in urinary calcium or other parameters of calcium metabolism.

Table 19: Adverse events by MedDRA preferred term: safety analysis set

Preferred Term[1]	LEO 80185 (n=78) Number of subjects	%
Headache	4	5.1
Pharyngitis	4	5.1
Upper respiratory tract infection	4	5.1
Urine calcium decreased	3	3.8
Acne	2	2.6
Blood parathyroid hormone increased	2	2.6
Diarrhoea	2	2.6
Gastroenteritis	2	2.6
Psoriasis	2	2.6
Pyrexia	2	2.6
Seasonal allergy	2	2.6
Abdominal pain	1	1.3
Alopecia	1	1.3
Application site pruritus	1	1.3
Arthritis	1	1.3
Asthenia	1	1.3
Asthma	1	1.3
Blood calcium decreased	1	1.3
Cardiac flutter	1	1.3
Conjunctivitis allergic	1	1.3
Cough	1	1.3
Dermatitis acneiform	1	1.3
Dyspnoea	1	1.3
Fatigue	1	1.3
Gastroenteritis viral	1	1.3
Jaw disorder	1	1.3
Ligament sprain	1	1.3
Malaise	1	1.3
Myalgia	1	1.3
Nausea	1	1.3
Nystagmus	1	1.3
Oropharyngeal pain	1	1.3
Otitis externa	1	1.3
Oxygen saturation decreased	1	1.3
Sinus headache	1	1.3
Skeletal injury	1	1.3
Skin striae	1	1.3
Speech disorder	1	1.3
Staphylococcal infection	1	1.3
Tendonitis	1	1.3
Tooth extraction	1	1.3
Toothache	1	1.3
Urinary tract infection	1	1.3
Urine phosphorus decreased	1	1.3
Vomiting	1	1.3
Wheezing	1	1.3
Total number of adverse events[2]	64	
Total number of subjects	27	34.6

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1) Classification according to MedDRA version 14.1.
2) Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.

There were no clinically relevant changes in the clinical laboratory values

3. Discussion on clinical aspects

In conclusion, in these two trials with a total of 109 adolescent patients with psoriasis of the scalp, Daivobet gel applied once daily for up to 8 weeks had a safety profile similar to that in adults.
However, due to the limited number of patients treated with Daivobet gel in uncontrolled trials no firm conclusion can be drawn as to the efficacy or safety of Daivobet gel in adolescents with scalp psoriasis.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

Overall, these two small non-controlled trials do not provide firm efficacy data to conclude that Daivobet gel is effective in treating scalp psoriasis in adolescents. At the moment no posology in this group of patients is recommended as larger controlled trials are missing. Similarly the safely profile of Daivobet gel in adolescents with scalp psoriasis have not yet been clearly defined.

- **Recommendation**

A variation (C.I.3.a or z) in order to modify the approved SmPC for Daivobet/Xamiol gel with the following wording in sections 4.2, 4.8 and 5.1 to be requested from the MAH by 25 April 2014.

SmPC 4.2 Posology and method of administration
Paediatric population
The safety and efficacy of Daivobet/Xamiol gel in children 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 a posology can be made.

SmPC 4.8 Undesirable effects
Paediatric population
No new adverse events and no new adverse reactions were seen in 109 adolescents aged 12-17 years with scalp psoriasis treated with Daivobet/Xamiol gel for 8 weeks. However, due to the size of the studies, no firm conclusion can be drawn as to the safety profile of Daivobet/Xamiol gel in adolescents compared to that in adults. See section 5.1.

SmPC 5.1 Pharmacodynamic properties
Paediatric population
Effects on calcium metabolism were investigated in two uncontrolled open 8-week studies including in total 109 adolescents aged 12-17 years with scalp psoriasis who used up to 69 g per week of Daivobet/Xamiol gel. No cases of hypercalcaemia and no clinically relevant changes in urinary calcium were reported. The adrenal response to ACTH challenge was measured in 30 patients; one patient showed a decrease in cortisol response to ACTH challenge after 4 weeks of treatment, which was mild, without clinical manifestations, and reversible.