Summary Review for Regulatory Action

Date	April 25, 2008
From	Stanka Kukich, M.D.
Subject	Deputy Director Summary Review
NDA #	NDA 22-185
Applicant Name	LEO Pharmaceutical Products Ltd.
Date of Submission	June 19, 2007
PDUFA Goal Date	April 28, 2008
Proprietary Name / Established (USAN) Name	Taclonex Scalp® (calcipotriene 0.005% and betamethasone dipropionate 0.064%)
Dosage Forms / Strength	Topical suspension
Proposed Indication(s)	Topical treatment of moderate to severe psoriasis vulgaris of the scalp in adults 18 years and older
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Brenda Carr, M.D.
Statistical Review	Mat Soukup, Ph.D.
Pharmacology Toxicology Review	Norman A. See, Ph.D.
CMC Review/OBP Review	Zhengfang Ge, Ph.D.
Microbiology Review	Not applicable
Clinical Pharmacology Review	Abimbola Adebowale, Ph.D.
DDMAC	Andrew Haffer
DSI	Not requested
CDTL Review	Jill Lindstrom, M.D.
OSE/DMETS	Pending
OSE/DDRE	Not requested
OSE/DSRCS	Sharon R. Mills, BSN, RN, CCRP
Other	-

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMETS=Division of Medication Errors and Technical Support
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader

1. Introduction

Taclonex Scalp® topical suspension is a combination product that contains betamethasone dipropionate 0.064%, a corticosteroid, and calcipotriene hydrate 0.005%, a vitamin D analog. Individual active substances in Taclonex topical suspension are marketed as a single component drug product; calcipotriene is indicated for the treatment of plaque psoriasis and betamethasone dipropionate is indicated for relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. Taclonex is also approved and available as an ointment for the treatment of plaque psoriasis and contains the same active ingredients in the same concentrations as in the topical suspension.

2. Background

Psoriasis is a common, chronic, relapsing skin disease. During the course of the disease spontaneous remissions may occur intermittently. Approximately fifty percent of the population with psoriasis worldwide has scalp involvement at the onset and through the course of psoriasis. The etiology of disease has not been fully elucidated, however, genetic factors play important role as well as immune system. It has been suggested that psoriasis is a T-lymphocyte mediated autoimmune disease. The pathologic features of psoriasis are abnormal cell differentiation, keratinocyte hyperproliferation, and inflammation which are manifested by demarcated erythematosquamous plaques with silver-white scaling.

The exact mechanism of action of calcipotriene, a synthetic analog of vitamin D_3, is not known, however, it may have an effect on proliferation and differentiation of a variety of cell types. Bethametasone dipropionate is a high-potency synthetic glucocorticosteroid which has anti-inflammatory, antipruritic, and vasoconstrictive properties; however, the exact mechanism of action in psoriasis is unknown.

Regulatory issues regarding the development program for this product were discussed at the Pre-IND meeting in June 2004, End-of-Phase 2 meeting in December 2004, and Pre-NDA meeting in January 2007.

The applicant has proposed in this application Taclonex as the tradename for the new topical suspension, however, in the NDA submission the applicant refers to this product as Daivobet.

3. CMC

I concur with the conclusions reached by the chemistry reviewer, Dr. Zhengfang Ge, regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable.

[redacted]

[redacted]

Stability testing supports an expiration date of 24 months. The product will be stored in the outer carton when not in use.

[redacted]

There are no outstanding CMC issues.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding issues that preclude approval.

General toxicities in the nonclinical studies pertained to calcium homeostasis, including elevated concentrations of calcium in the serum and urine, microscopic evidence of bone formation and mineralization of the kidneys.

Calcipotriene and betamethasone dipropionate did not elicit any genotoxic effects in mutagenicity assays or impairment of fertility in general reproductive studies. However, calcipotriene has been shown to be fetotoxic and betamethasone dipropionate to be teratogenic in animals.

Results of the study in albino hairless mice exposed to ultra-violet radiation and calcipotriene indicated that calcipotriene may enhance the effect of ultra-violet radiation to induce skin tumors. For that reason patients who use Taclonex should avoid excessive exposure of the treated areas to either natural or artificial sunlight.

Evaluation of the systemic carcinogenicity of calcipotriene in two year study in rats will be conducted as a postmarketing commitment. Carcinogenic potential of betamethasone dipropionate is being evaluated within postmarketing commitments for Taclonex ointment and the studies in mice and rats are ongoing.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology and biopharmaceutics information provided by the applicant was reviewed by Dr. Abimbola Adebowale and deemed acceptable. The applicant conducted a hypothalamic-pituitary-adrenal (HPA) axis and calcium metabolism study in patients with psoriasis and a vasoconstriction study in healthy volunteers. Serum calcium was also measured

in the Phase 3 studies. These parameters were used to evaluate systemic exposure and systemic and local effects of Taclonex.

In the HPA axis suppression study patients with extensive disease were enrolled; 30% scalp involvement and additional 15 to 30% of body surface area of involvement. Adrenal suppression, based on the standard parameters, was observed in 5 of 32 patients (15.6%) at 4 weeks of treatments and in 2 of 11 patients at week 8 (18.2%) of treatment. In the same study 2 patients had elevated urinary calcium levels. These changes did not lead to related clinical adverse events.

Taclonex induced less skin blanching than Diprosone ointment in a vasoconstriction study which was performed to evaluate the corticosteroid potency of betamethasone dipropionate in the proposed formulation. Therefore, it was determined that betamethasone dipropionate is a potent corticosteroid but it is not expected to exceed the potency of betamethasone dipropionate in Diprosone ointment.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical-Efficacy

The primary reviewer, Dr. Brenda Carr, and the clinical team leader, Dr. Jill Lindstrom have adequately summarized the clinical efficacy and safety data. Dr. Mat Soukup analyzed the phase 3 data from a statistical perspective.

In support of the proposed indication the applicant has submitted the safety and efficacy data from two phase 3 (MBL 0405 and MBL 0406) international, multi-center, randomized, double-blind, parallel group trials and four supportive trials. The treatment was applied once daily for up to 8 weeks. In both pivotal studies, the treatment arms included Taclonex suspension, betamethasone dipropionate, and calcipotriene. The vehicle arm was only included in the MLB 0405 study. The primary objective of these trials was to compare the efficacy of Taclonex suspension to each treatment arm.

The primary endpoint in the clinical trials was the percentage of subjects who achieve response defined as absence of disease or mild disease based on the 6-point investigator’s global assessment (IGA) scale at week 8.

The initial inclusion criteria allowed for subjects with mild disease to be enrolled into two pivotal trials. At the End-of-Phase 2 meeting it was discussed that subjects with mild disease

should achieve an IGA score of 'absence of disease' since this criterion represented clinically meaningful definition of success. Based on this discussion, the applicant has changed the enrollment criteria to include subjects with moderate to severe scalp psoriasis. At the time when enrollment criteria were changed only a small number of subjects (57) with mild disease were already enrolled into pivotal trials.

The applicant's original analysis included subjects with mild disease and subjects with one grade improvement on the IGA scale were counted as a success. In the applicant's amended analysis, base on the discussion at the End-of-Phase 2 meeting, subjects with mild disease at baseline were excluded from the efficacy analysis and only those subjects who achieved 'absence of disease' or 'very mild disease' at week 8 and had a two-grade of improvement were defined as a success.

Due to modification of inclusion criteria and the study population to be included in the efficacy analyses after trials were initiated, different efficacy analyses were conducted in the effort to explore the impact of such changes. The applicant's proposed 'amended analyses' was found to be acceptable and is consistent with the advice provided to the applicant at the End-of Phase 2 meeting.

Efficacy results for both pivotal trials are provided in the table below.

Efficacy Results for BML 0405 and BML 0406 Trials

StudyBML0405	Taclonex	Betamethasone	Calcipotriene	Vehicle
Applicant's Amended Analysis				
N	494	531	256	126
Success (%)	346 (70%)	335 (63%)	94 (37%)	25 (20%)
p-value[2]		0.0205	<.001	<.001
Study BML0406	Taclonex	Betamethasone	Calcipotriene	-
Applicant's Amended Analysis				
N	512	517	251	-
Success (%)	344 (67%)	308 (60%)	103 (41%)	
p-value[2]		0.0089	<.001	

[2]Fisher's Exact test due to small stratum in pooled sites
Source: Statistical Review and Evaluation of NDA 22-185, p.14, Mat Soukup, PhD

Taclonex was superior to each active comparator and vehicle in study MBL0405 and to each active comparator in study MBL0406 when the population with moderate to severe scalp psoriasis at baseline was included and success was defined as 'absence or very mild disease'. In both studies a treatment effect of Taclonex compared to betamethasone was smaller than that of Taclonex compared to calcipotriene.

In addition to the primary endpoint, a secondary efficacy endpoint included a proportion of patients with absent or very mild disease based on the IGA scale at week-2 of treatment. The response rates were 55.5% and 47% for study BML 0405 and 0406, respectively, for patients

treated with Taclonex. This information will be included in the Dosage and Administration Section of the labeling.

8. Safety

The safety population consisted of all randomized subjects who applied study treatment and for whom one safety evaluation was available.

The safety database for Taclonex included 2658 subjects, ages 18 years and older, who applied a study treatment during the development program. This number was slightly lower, 1953, for subjects with scalp psoriasis enrolled in controlled clinical trials. A detailed breakdown of numbers is presented below.

Number of patients presented in the summary of safety

Study Number	Taclonex Susp. Number of patients	Betamethasone Susp. Number of patients	Calcipotriene Susp. Number of patients	Vehicle Number of patients
All clinical studies(16 studies)	2658	1297	1058	213
Multiple dose studies(14 studies)	2556	1297	1058	213
Controlled scalp studies(6 studies)	1953	1214	979	173
Long term-study	419	-	413	-

Source: 2.7.4 summary of clinical safety, Table 2, page 30 of 209

Safety studies in healthy subjects included skin atrophy, photoallergy, phototoxicity, cumulative irritation, sensitization, and vasoconstriction studies.

The mean duration of exposure was 7.3 weeks in controlled studies and 44 weeks in the long-term study. A total of 281 patients received topical treatment for at least 12 months on ‘as needed’ basis and 235 patients received calcipotriene. The average weekly amount of medication used was 18.6 g of Taclonex.

There were four deaths reported, none related to study treatment. One patient randomized to calcipotriene in phase 3 study died of pneumonia. In the long- term controlled studies two patients receiving Taclonex topical suspension and one patient receiving calcipotriene died of complications of surgery, motor vehicle accident, and cardiac arrest, respectively, It appears that serious adverse events (SAEs) were evenly distributed across treatment groups; 13 (0.7%) of patients in the Taclonex group, 6 (0.5%) in the betamethasone group, 12 (1.2%) in the calcipotriene group, 1 (0.6%) in the vehicle group.

The most frequently reported local adverse events in the Taclonex treatment group were pruritus (2%), skin irritation (0.6%), and burning sensation (0.5%). In the long-term study a slightly higher number of patients reported pruritus (4.3%), skin irritation (1.2%), and burning sensation (0.7%). These adverse events were less frequent compared to calcipotriene treatment alone. Local skin infection was reported at the similar frequency across treatment groups.

Two patients in the combination group and two patients in the betamethasone group had mild hypercalcemia at week 4 of treatment. Serum calcium was not measured at the end of 8 weeks of treatment in the pivotal trials or during long-term trial.

There were no reports of skin atrophy, skin striae, or hypopigmentation during clinical trials; however, there were two reports of telangiectasia.

In the hypothalamic-pituitary-adrenal (HPA) axis study seven patients had at least one serum cortisol level of $\leq$ 18 mcg/dL 30 minutes after the ACTH test, 5 at week 4 (15.6%) and 2 at week 8 (18.2%) of treatment. The serum calcium values were within normal range in this study.

Safety analyses in this application did not reveal any unexpected findings. There were no new safety concerns given the known profile of active components of Taclonex topical suspension.

There are no postmarketing data for Taclonex topical suspension since it is not marketed in any country. Taclonex ointment has been marketed in the US since 2006 and the postmarketing safety information regarding the ointment formulation did not raise any additional safety problems.

Potential safety concerns associated with Taclonex topical suspension will be described in the Warnings and Precautions sections of the labeling and the Highlights part of the labeling.

9. Advisory Committee Meeting

None

10. Pediatrics

The applicant requested partial waiver of the requirement to study pediatric age group <12 years of age under the Pediatric Research Equity Act of 2003, section 505B (a) of the Food, Drug, and Cosmetic Act. This waiver was granted because the use of a potent corticosteroid in young children who have greater body surface-area-to-volume ratios is not desirable and should be avoided.

The applicant has requested deferral of the pediatric studies in patients $\geq$12 to 17 years of age with scalp psoriasis and proposed to conduct this study post approval. The action letter will state terms and timelines for conducting such study.

11. Other Relevant Regulatory Issues

There are no unresolved relevant regulatory issues.

12. Labeling

There are no unresolved labeling issues at this time. At this time DMETS did not indicate that there is a problem with the applicant-proposed proprietary name of Taclonex. Labeling discussion with the applicant was focused on description study results and the amount of secondary data to be included in the labeling. Carton and immediate container labels will be revised to include a correct dosage form 'topical suspension'.

13. Decision/Action/Risk Benefit Assessment

The applicant has submitted sufficient data to support the conclusion that Taclonex topical suspension is safe and effective for the treatment of moderate to severe psoriasis of the scalp in adults. Taclonex should be applied to affected areas on the scalp once daily for 2 weeks or until clear. Treatment may be continued for up to eight weeks.

Individual components of Taclonex topical suspension, calcipotriene and betamethasone dipropionate have been marketed since 1996 and 1984, respectively. Therefore safety profile of betamethasone dipropionate and calcipotriene hydrate has been well described and well-known. The HPA suppression study demonstrated that the high exposure of betamethasone was able to suppress HPA axis which is consistent with findings of other potent corticosteroids. Effects of Taclonex on calcium metabolism did not raise any specific clinical concerns. The frequency and severity of local skin reactions appears to be acceptable. No specific Postmarketing Risk Management Activities are needed.

I am in agreement with the recommendation of the review team that this application should be approved.

Based on the ICH-S1A guidelines regarding the need for long-term rodent carcinogenicity studies of pharmaceuticals, the applicant is required, pursuant to section 505(o)(3) of the Act, to evaluate the carcinogenic potential of calcipotriene in a two-year oral study in rats. The applicant should submit a protocol for this study with appropriate supporting documents for evaluation by the executive carcinogenicity assessment committee of CDER following approval of NDA 22-185. Protocol Submission: by 12/08, Study Start: by 09/09, and Final Report Submission: by 09/12

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/s/

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MEDICAL OFFICER