

## CLINICAL REVIEW

Application Type	Supplement
Application Number(s)	NDA 21852/ S-15
Priority or Standard	Standard
Submit Date(s)	February 26, 2014
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Division / Office	DDDP/ ODE III
Reviewer Name(s)	Melinda McCord
Review Completion Date	October 6, 2014
Established Name	Calcipotriene and betamethasone dipropionate
Trade Name	Taclonex® Ointment
Therapeutic Class	Psoriasis agent
Applicant	Leo Pharmaceuticals, Ltd
Formulation(s)	Ointment
Dosing Regimen	Once daily
Indication(s)	the topical treatment of plaque psoriasis
Intended Population(s)	12 years of age and older

Template Version: [March 6, 2009](#)

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## **1 Recommendations/Risk Benefit Assessment**

### **1.1 Recommendation on Regulatory Action**

This reviewer recommends an approval action for this application. The applicant provided an adequate assessment of both systemic and local safety to support the extension of the current indication to include the treatment of plaque psoriasis in patients age 12 years and older. This recommendation is contingent upon successful completion of labeling negotiations with the applicant.

Data from Trial MCB 0501 INT was submitted to address Post Marketing Requirement #5 (Approval Letter dated January 9, 2006) under the Pediatric Research Equity Act (PREA) to conduct a trial to evaluate the effects of Taclonex® Ointment for the treatment of psoriasis vulgaris (plaque psoriasis) in pediatric patients ages 12 to 17 years. The data provided in this supplement is sufficient to establish safety of Taclonex® Ointment for the use in the pediatric population age 12 to 17 years. Taclonex® Ointment is currently approved for the topical treatment of psoriasis vulgaris (plaque psoriasis) in adults 18 years and older. Because the pathophysiology and response to treatment are similar, findings of efficacy for Taclonex® Ointment in the pediatric population age 12 to 17 years could be extrapolated from the adult population.

### **1.2 Risk Benefit Assessment**

Taclonex® Ointment (calcipotriene 0.005% and betamethasone dipropionate 0.064%) was approved on January 9, 2006 for the topical treatment of psoriasis vulgaris (plaque psoriasis) in adults 18 years of age and older. The initial assessment of efficacy in the adult population was based on one adequate and well-controlled Phase 3 trial which enrolled 1,605 subjects. The applicant submitted supportive data from 4 additional trials enrolling 1,058 subjects. The initial assessment of safety in the adult population was based on twenty-one trials which included a Phase 3 trial, a long-term safety trial and special safety studies [e.g. the evaluation of dermal safety and the effects of the product on hypothalamic-pituitary-adrenal axis (HPA axis) function and calcium metabolism.]

The risk benefit assessment in the pediatric population age 12 to 17 years was based on the analysis of data from one uncontrolled, clinical trial (MCB 0501 INT). Trial MCB 0501 INT was designed to assess the systemic safety of Taclonex® Ointment by evaluating HPA axis function and calcium metabolism in 33 pediatric subjects age 12 to 17 years with plaque psoriasis. Enrolled subjects had at least moderate psoriasis on the Investigator's Global Assessment of disease severity scale [IGA  $\geq 3$  on a 6- point scale], involvement of 5 to 30% of the total BSA (excluding the genitals and skin folds) and normal HPA axis function at Baseline. The extent and severity of psoriasis were amenable to topical treatment with a maximum of 60 g of study product per week. All

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subjects applied Taclonex® Ointment once daily to all affected areas on the body for up to 28 days.

There were no deaths, non-fatal serious adverse events (SAEs), severe adverse events or pregnancies among subjects in Trial MCB 0501 INT. Investigators did not withdraw any subject from the trial due to an adverse event.

A total of 11 subjects (33.3%) reported 16 adverse events. Among the most common adverse events occurring in  $\geq 1\%$  of subjects in Trial MCB 0501 INT were upper respiratory tract infection (6.0%), headache (6.0%), tension headache (6.0%), cough (6.0%), and rash papular (6.0%). The other adverse events which were reported by 1 subject each included the following: pyrexia (3%), body tinea (3%), gastroenteritis viral (3%), joint sprain (3%), lymphadenopathy (3%) and pruritus (3%). There were 3 subjects with adverse events which were classified as lesional/perilesional: 2 subjects with rash papular (localized to the back and leg) and one subject with pruritus. Both cases of rash were assessed as unrelated and the case of pruritus was graded as possibly related.

Two subjects (6%) reported adverse drug reactions (ADRs) [headache and pruritus] which were mild in intensity and reported by 1 subject each. There is insufficient data to support a role for Taclonex® Ointment in the etiology of headache. The only clinically relevant adverse reaction which was consistent with the mechanism of action of the product was pruritus. Pruritus was observed in trials in the adult population and is included in current labeling.

“Adverse events of clinical interest” were defined as adverse events related to exposure to the individual components of Taclonex® Ointment: topical corticosteroid or topical calcipotriene. There were no local or systemic adverse events which were potentially related to exposure to corticosteroid component of Taclonex® Ointment, betamethasone dipropionate. No subjects had elevated values for albumin-corrected serum calcium or urinary calcium at Baseline or Week 4 which were potentially related to systemic exposure to calcipotriene. However, there was one subject with an elevated urinary calcium: creatinine ratio. He had no associated symptoms and his albumin-corrected serum calcium and urinary calcium were normal at Baseline and Week 4. The clinical significance of this finding is not clear. The only local adverse event which was potentially related to calcipotriene was pruritus.

The evaluation of treatment effect was a secondary objective in Trial MCB 0501 INT. This uncontrolled trial was not designed to allow statistical conclusions related to efficacy. In the pediatric population, the proportion of subjects achieving controlled disease at Week 4 was 60.0%. In the adult population enrolled in the pivotal Phase 3 trial, the proportion of subjects achieving controlled disease at Week 4 was 48.0% in the Taclonex® Ointment arm (compared with 7.6% in the vehicle arm.)



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Trial MCB 0501 INT was adequate to inform safety and support the short-term use of Taclonex® Ointment in the pediatric population age 12 to 17 years. Based on a similar pathophysiology and response to treatment, efficacy in the pediatric population ages 12 to 17 years could be extrapolated from findings of efficacy in the adult population. Therefore, the data submitted by the applicant supports the extension of the current indication to include the treatment of plaque psoriasis in patients age 12 years and older and fulfills the post marketing requirement under PREA.

This reviewer recommends no additional risk management activities other than including the safety outcomes in product labeling.

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

None recommended.

### **1.4 Recommendations for Postmarket Requirements and Commitments**

None recommended.

## **2 Introduction and Regulatory Background**

### **2.1 Product Information**

The applicant, LEO Pharma, Inc., submitted a 505(b)(1) supplemental new drug application (sNDA) for Taclonex® (calcipotriene and betamethasone dipropionate) Ointment, 0.005%/0.64% on February 26, 2014. The objective of the current sNDA was to provide additional data regarding the effects of Taclonex® Ointment (marketed in Europe as Daivobet® Ointment) in pediatric patients age 12 years and older as required under the Pediatric Research Equity Act (PREA).

Taclonex® Ointment is a complex, multi-phased, semisolid dosage form containing two highly potent active ingredients at low concentrations. Taclonex® Ointment contains a fixed combination of calcipotriene 50 mcg/g and betamethasone 0.5 mg/g (as dipropionate). Calcipotriene is the US Adopted Name (USAN) of calcipotriol (the International Non-proprietary Name.) Calcipotriene hydrate is a synthetic vitamin D<sub>3</sub> analog and betamethasone dipropionate is a synthetic corticosteroid.

Taclonex® Ointment is an off-white to yellow paraffin ointment. Each gram of Taclonex® Ointment contains 52.18 mcg of calcipotriene hydrate (equivalent to 50 mcg of calcipotriene 0.005%) and 0.643 mg (0.64%) of betamethasone dipropionate

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(equivalent to 0.5 mg of betamethasone) in an ointment base of butylhydroxytoluene, mineral oil, PPG-11 stearyl ether, all-rac-alpha-tocopherol, and white petrolatum.

The product is distributed in a 60 gram and 100 gram collapsible tubes. Each tube has a membrane and a reclosable (b) (4) screw cap with a spike.

The current indication for Taclonex® Ointment is “the topical treatment of (b) (4) in adults 18 years of age and older.”

## 2.2 Tables of Currently Available Treatments for Proposed Indications

The FDA approved topical products indicated for the treatment of psoriasis include corticosteroids, vitamin D analogs and retinoids. Selected products are listed in Table 1.

Table 1: FDA Approved Products for the Topical Treatment of Psoriasis

Product Name	Applicant	NDA #	Approval Date	Indication/ Age in Labeling
Taclonex (calcipotriene 0.005% and betamethasone dipropionate 0.064%) Topical Suspension	Leo Pharma	022185 S-10	10/23/2012	topical treatment of plaque psoriasis of the scalp and body in patients 18 years of age and older
Sorilux (calcipotriene) Foam 0.005%	Stiefel	NDA 22563 S-2	9/27/2012	topical treatment of plaque psoriasis of the scalp and body in patients 18 years of age and older
Vectical (calcitriol) Ointment	Galderma Laboratories	022087	1/23/2009	topical treatment of mild to moderate plaque psoriasis in adults 18 years and older.
Taclonex (calcipotriene 0.005% and betamethasone dipropionate 0.064%) Ointment	Leo Pharma	021852	1/9/2006	topical treatment of psoriasis vulgaris in adults 18 years of age and older
Clobex (clobetasol propionate) 0.05% Spray	Galderma Laboratories	021835	10/27/2005	topical treatment of moderate to severe plaque psoriasis affecting up to 20% body surface area (BSA) in

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				patients 18 years of age or older
Tazorac (tazarotene) Cream 0.05%, 0.1%	Allergan	021184	9/29/2000	topical treatment of patients with plaque psoriasis. ≥18 years *
Tazorac (tazarotene) Gel 0.05%, 0.1%	Allergan	020600	6/13/1997	topical treatment of patients with stable plaque psoriasis of up to 20% body surface area involvement. ≥12 years **
Dovonex (calcipotriene) Cream 0.005%	Leo Pharma	020554	7/22/1996	treatment of plaque psoriasis ≥18 years ***

Source: Adapted from Table 1 from NDA 22-563 Updated from Drugs @FDA accessed 10/3/2014

\*The safety and efficacy of tazarotene cream have not been established in patients with psoriasis under the age of 18 years (Current labeling: Pediatric Use Section)

\*\*The safety and efficacy of tazarotene gel have not been established in pediatric patients under the age of 12 years. (Current labeling: Pediatric Use Section)

\*\*\*Safety and effectiveness (of Dovonex Cream 0.005%) in pediatric patients have not been specifically established. Because of a higher ratio of skin surface area to body mass, pediatric patients are at greater risk than adults of systemic adverse effects when they are treated with topical medication. (Current labeling: Pediatric Use Section)

### 2.3 Availability of Proposed Active Ingredient in the United States

Table 2: Availability of Proposed Active Ingredients in the United States

Generic Name and Dosage Form	Brand Name	Applicant	NDA/ANDA Number	FDA Approval Date
Calcipotriene foam, 0.005%	Sorilux	Stiefel Laboratories, Inc	22563	10/6/2010
Calcipotriene ointment, 0.005%	generic	Glenmark Generics	90633	3/24/2010
Calcipotriene cream, 0.005%	Dovonex & generics	Leo Pharma, Tolmar	20554, 200935	7/22/1996
Calcipotriene solution, 0.005%	generics	Fougera Pharms, Tolmar, G and W Labs Inc Pharma, Nycomed US	77029, 78305, 78468	3/3/1997
Calcipotriene	Taclonex	Leo Pharma	21852	1/9/2006

0.005% and Betamethasone 0.064% ointment,				
Calcipotriene 0.005% and Betamethasone 0.064% solution	Taclonex Topical Suspension	Leo Pharma	22185	5/9/2008
Betamethasone dipropionate 0.05% ointment, augmented	Diprolene & generics	Merck, Sharp Dohme, Actavis, Fougera, Taro	18741, 74304, 75373, 76753	7/27/1983
Betamethasone dipropionate 0.05% lotion, augmented	Diprolene & generics	Merck, Sharp Dohme, Fougera, Taro	19716, 77111, 77477	8/1/1988
Betamethasone dipropionate 0.05% cream, augmented	Diprolene AF & generics	Merck, Sharp Dohme, Fougera, Glenmark, Perrigo, Taro, Tolmar	19555, 76215, 78930, 76592, 76543, 76603	4/27/1987
Betamethasone dipropionate 0.05% gel, augmented	generics	Taro, Fougera,	76508, 75276	12/2/2003

Sources: NDA 22185/S-18, Table 3. Updated from Drugs @FDA accessed 7/1/2014.

## 2.4 Important Safety Issues with Consideration to Related Drugs

The adverse event profile for each of the active ingredients (calcipotriene hydrate and betamethasone dipropionate) is well characterized.

Adverse reactions associated with vitamin D analogues (e.g. calcipotriene) include both local and systemic effects. Per labeling, the most common local adverse reactions associated with calcipotriene containing products are: application site erythema, application site pain, skin irritation, burning, pruritus, rash, dermatitis, dry skin, peeling and worsening of psoriasis (Adverse Reaction Sections: SORILUX Foam, Dovonex Products). Systemic absorption of topical vitamin D analogues can produce hypercalcemia and hypercalciuria.

Topical corticosteroids may be associated with both local and systemic adverse reactions. Rare systemic adverse reactions reported with topical corticosteroids include: Cushing's syndrome, hyperglycemia, osteopathy, adrenocortical suppression, decreased growth rate, edema, hypocalcemia, hypertension, posterior subcapsular

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cataracts, and glaucoma. Children are at higher risk than adults for HPA axis suppression due to their greater body surface area to volume ratio. Common local adverse effects include atrophy, striae, rosacea, perioral dermatitis, acne, and purpura, and less frequent adverse effects include hypertrichosis, pigmentary alterations, delayed wound healing, exacerbation of skin infections, and contact sensitization reactions.

The adverse reactions observed with the fixed combination products (calcipotriene 0.005% and betamethasone dipropionate 0.064%) are similar to those reported for the active ingredients. Per current labeling, the most common adverse reactions ( $\geq 1\%$ ) reported for Taclonex® Ointment were pruritus and scaly rash and for Taclonex® Topical Suspension were folliculitis and burning sensation of skin.

Taclonex® Ointment and other products containing calcipotriene and betamethasone dipropionate are pregnancy category C drug products.

## **2.5 Summary of Presubmission Regulatory Activity Related to Submission**

On January 9, 2006 Taclonex® (calcipotriene 0.005% and betamethasone dipropionate 0.064%) Ointment (NDA 21-852) was approved for the topical treatment of psoriasis vulgaris (plaque psoriasis) in adults aged 18 years and older with the following clinical post marketing requirement under Section 2 of the Pediatric Research Equity Act (PREA):

“Deferred pediatric study under PREA for the treatment of psoriasis vulgaris in pediatric patients ages 12 to 17.”  
Final Report Submission: 01/09

The Agency waived the pediatric study requirement for ages 0 to 11 years and deferred pediatric studies for ages 12 to 17 years for this application.

After receiving a Proposed Pediatric Study Request (letter dated March 14, 2005), the Agency issued a Written Request (WR) to Leo for calcipotriene on February 20, 2007 (due date: 12/31/08). In a letter dated August 17, 2007, the applicant notified the Agency of their decision not to pursue the clinical studies outlined in the Written Request. At that time they conveyed their intent to conduct a clinical study in pediatric patients ages 12 to 17 years in order to address the postmarketing requirement attached to approval of their product.

(b) (4)



(b) (4)



(b) (4)

On November 14, 2012 the Pediatric and Maternal Health Staff (PMHS), sent the applicant a Deferral Extension Notice per the Food and Drug Administration Safety and Innovation Act (FDASIA; signed July 12, 2012). On December 6, 2012, in response to the Deferral Extension Notice, the applicant submitted the Final Study Report for protocol MCB 0501 INT. However, the applicant was notified that the Final Study Report for a trial conducted under PREA needed to be submitted to NDA 21852 as a labeling or efficacy supplement which permits the data to be included in labeling.

## **2.6 Other Relevant Background Information**

None.

## **3 Ethics and Good Clinical Practices**

The Division did not request that the Office of Scientific Investigations (OSI) conduct clinical inspections of investigational sites. In consultation with the biostatistics team, the clinical team concluded that there were no irregularities in the data requiring OSI consultation.

### **3.1 Submission Quality and Integrity**

The overall quality of the clinical information contained in this submission is adequate.

### **3.2 Compliance with Good Clinical Practices**

The applicant certifies that this trial was conducted in compliance with the requirements of the Code of Federal Regulations (21 CFR), Parts 50, 54, 56, 312, and 314, and the

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International Conference on Harmonization (ICH), and Guideline for Good Clinical Practice (E6).

### **3.3 Financial Disclosures**

The applicant completed Form FDA 3454 to document financial conflicts of interest and arrangements of clinical investigators. The applicant certified that he had not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). Refer to Appendix 9.4.

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

This submission contained no chemistry, microbiology, or pharmacology/toxicology data.

### **4.1 Chemistry Manufacturing and Controls**

The applicant proposed no changes to the drug product or drug substance in this submission. Due to the anticipated increase in use of Taclonex ® products with the revised labeling to include safety information regarding the pediatric population, the Agency requested that the applicant perform an Environmental Assessment (Filing Communication dated 4/29/2014).

In a review dated 9/30/2014, Shulin Ding, Ph.D. CMC Lead, ONDQA provided the following comments and conclusions:

“This efficacy supplement provides for an extension to pediatric population. No CMC changes are proposed for drug substance or drug product. The only things which require CMC attention are environmental assessment due to the anticipated increase in use, and minor changes in Section 11 of Package Insert and Patient Information Leaflet.

Conclusion: Adequate information is provided to support the categorical exclusion claim from the preparation of an Environmental Assessment report. The labeling changes in Section 11 of Package Insert and Patient Information leaflet have already been approved through Supplements S-014 and S- 010. This supplement is recommended for approval from CMC perspective.”

Also refer to the CMC review of the original application by Ernest Pappas, Ph.D. dated 11/30/2005.

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## 4.2 Clinical Microbiology

Not applicable to this submission.

Refer to Product Quality Microbiology Review of the original application by Anastasia G. Lolas, Ph.D. dated 8/02/2005.

## 4.3 Preclinical Pharmacology/Toxicology

Not applicable.

Refer to the Pharmacology/Toxicology review of the original application by Norman See, Ph.D. dated 1/05/2006.

## 4.4 Clinical Pharmacology

The Clinical Pharmacology Reviewer, An-Chi Lu, M.S., Pharm.D, reviewed the data from Trial MCB 0501 INT. She indicated that the study design and study population (age distribution, disease severity and extent of involvement) were acceptable for the evaluation of the pharmacodynamic effects of Taclonex ® Ointment. The mean extent of involvement of the trunk and extremities at Baseline was 14% and the number of subjects at the lower limit of the age range was adequate (5 subjects age 12 years and 5 subjects age 13 years). She identified no issues regarding the bioanalytical methods or validation of the assays. In a review dated 10/05/2014, she provided the following recommendation:

“The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 has reviewed the results of Trial MCB 0501 INT and finds NDA 21852/S015 acceptable pending agreement on recommended labeling changes.

This efficacy supplement is considered acceptable to fulfill the post marketing requirement stated in the approval letter dated 1/9/2006. ”

Refer to the Clinical Pharmacology review by An-Chi Lu, M.S., Pharm.D dated 10/05/2014 and the Clinical Pharmacology review of the original application by Abi Adebowale Ph.D. dated 1/5/2006.

### 4.4.1 Mechanism of Action

The applicant proposed no changes to labeling of Section 12.1 Mechanism of Action. Current labeling for Section 12.1 is as follows:

#### 12.1 Mechanism of Action



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Taclonex® Ointment combines the pharmacological effects of calcipotriene hydrate as a synthetic vitamin D<sub>3</sub> analogue and betamethasone dipropionate as a synthetic corticosteroid. However, while their pharmacologic and clinical effects are known, the exact mechanisms of their actions in plaque psoriasis are unknown.

### 4.2 Pharmacodynamics

The systemic pharmacodynamics of calcipotriene and betamethasone dipropionate in Taclonex® Ointment were assessed indirectly by using surrogate markers (serum and urinary calcium levels and HPA axis function) in trial MCB 0501 INT. See Clinical Pharmacology Review by An-Chi Lu, M.S., Pharm.D dated 10/05/2014.

The following changes are recommended for section 12.2 of labeling. Additions are noted as double underline and deletions are noted as ~~striketrough~~.

### 12.2 Pharmacodynamics

#### Vasoconstriction:

(b) (4)

In a vasoconstrictor trial in healthy subjects, the skin blanching response of Taclonex® Ointment was consistent with that of a potent corticosteroid when compared with other topical corticosteroids. However, similar blanching scores do not necessarily imply therapeutic equivalence.

#### Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression:

HPA axis suppression was evaluated in four trials (Trial A, B, C and D) following the application of Taclonex® Ointment.

In Trial A, Taclonex® Ointment was applied once daily for 4 weeks to adult subjects (N = 12) with plaque psoriasis (b) (4) to study its effects on the hypothalamic-pituitary-adrenal (HPA) axis. Of eleven subjects tested, none demonstrated adrenal suppression as indicated by a 30-minute post-stimulation cortisol level ≤ 18 mcg/dL.

In Trial B, (b) (4) Taclonex® Ointment was evaluated in adult subjects (N = 19), one subject (b) (4) demonstrated adrenal suppression.

In Trial C, HPA axis suppression was evaluated in adult subjects (N=32) with extensive psoriasis involving at least 30% of the scalp and, in total, 15-30% of the body surface area. Treatment consisted of once daily application of Taclonex Scalp® Topical Suspension on the scalp in combination with Taclonex® Ointment on the body. Adrenal suppression as indicated by a 30-minutes post-stimulation cortisol level less than or equal to 18 mcg/dL was observed in 5 of 32 subjects (15.6%) after

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4 weeks of treatment as per the recommended duration of use (see Dosage and Administration (2.1)).

In Trial D, HPA axis suppression was evaluated in subjects 12 to 17 years (N=32) with plaque psoriasis of the body involving 5-30% of the body surface area. Treatment consisted of once daily application of Taclonex® Ointment to the affected areas for up to 4 weeks. (Mean weekly dose was 29.6 g with a; range of 8.1-55.8 g/week) (b) (4). Adrenal suppression as indicated by a 30-minute post-stimulation cortisol level  $\leq$ 18 mcg/dL was observed in none of 32 evaluable subjects after 4 weeks of treatment.

#### *Effects on Calcium Metabolism*

In (b) (4) Trial C described above, the effects of once daily application of Taclonex® Ointment on the body in combination with Taclonex Scalp® Topical Suspension on the scalp on calcium metabolism were also examined. Elevated urinary calcium levels outside the normal range were observed in 1 of 35 subjects (2.9%) after 4 weeks of treatment.

In Trial D, calcium metabolism was evaluated in a total of 33 subjects aged 12 to 17 years with plaque psoriasis involving 5-30% of the body surface area, undergoing once daily application of Taclonex® Ointment for up to 4 weeks. No cases of hypercalcemia and no clinically relevant changes in urinary calcium were reported. However, one subject had a normal urinary calcium:creatinine ratio at Baseline (3.75 mmol/g), which increased above the normal range at week 4 (16 mmol/g). There were no relevant changes in albumin-corrected serum calcium or other markers of calcium metabolism for this subject. The clinical significance of this finding is unknown.

#### 4.4.3 Pharmacokinetics

Pharmacokinetic assessments were not performed during the conduct of trial MCB 0501 INT. The applicant proposed no changes to this section of the currently approved labeling.

See Clinical Pharmacology Review by Abimbola Adebawale Ph.D. dated 1/05/2006 for an evaluation of the pharmacokinetic data in the adult population for the review of the original application.

The following changes are recommended for section 12.3 of labeling. Additions are noted as double underline and deletions are noted as ~~strikethrough~~.

### **12.3 Pharmacokinetics**

#### **Absorption**

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In Trial C, the systemic effect of Taclonex® Ointment in extensive psoriasis was investigated in the trial described above. In this trial, the serum levels of calcipotriene and betamethasone dipropionate and their major metabolites were measured after 4 weeks (maximum recommended duration of treatment) and also after 8 weeks of once daily application of Taclonex® Ointment on the body in combination with Taclonex Scalp® Topical Suspension on the scalp.

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

Table 3: Tabulated Summary for Trial MCB 0501 INT

Type of Trial	Trial ID Trial Status, Type of Report	Trial Design	FSFV/LSLV Sites; No. & Location	No. of Subjects Treated/completed Median Age (range), Sex	Diagnosis Main Inclusion Criteria	IPs; Dose, Route, & Regimen	Duration of Treatment	Primary Endpoint(s)
Safety & efficacy	MCB 0501 INT  Completed, full CSR	Open-label, single-group, non-controlled in adolescent (aged 12 to 17 years, inclusive)	15-Jul-2009/05-Dec-2011  7 sites in US	33/33  15 years (12-17 years)  16M/17F	Psoriasis vulgaris (trunk and/or limbs) ≥ moderate 5-30% of BSA Normal HPA axis function Albumin-corrected serum calcium and urinary calcium:creatinine ratio within the reference range Aged 12 to 17 years Male or female	Calcipotriol 50 mcg/g + betamethasone 0.5 mg/g (as dipropionate) ointment  Topically, once daily	4 weeks	ADRs  Serum cortisol concentration of ≤18 mcg/dL at 30 min after ACTH-challenge and 30 and 60 min after ACTH-challenge at end of treatment.  Change in albumin-corrected serum calcium and urinary calcium:creatinine ratio from baseline to end of treatment

Source: NDA 21852 Module 5.2 page 3

ACTH = adrenocorticotrophic hormone; ADR = adverse drug reaction; CSR = Clinical Study Report; F = females; FSFV = first subject first visit; HPA = hypothalamic-pituitary-adrenal; IP = investigational product; LSLV = last subject last visit; M = males

### 5.2 Review Strategy

The review of safety was based on data from a single uncontrolled trial (MCB 0501 INT) enrolling a total of 33 subjects aged 12 to 17 years with at least moderate psoriasis according to the Investigator's Global Assessment (≥3 on a 6-point IGA scale). Enrolled subjects had involvement of 5-30% body surface area (BSA) which was amenable to topical treatment with a maximum of 60 g of study medication per week. Trial MBL 0501 INT was designed to assess the systemic safety of Taclonex® Ointment in the pediatric population with plaque psoriasis by evaluating HPA axis function and calcium

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metabolism and local safety by evaluating adverse events. All subjects applied Taclonex® Ointment once daily for 4 weeks.

The evaluation of treatment effect in Trial MCB 0501 INT was a secondary objective and was supportive of the review conclusions related to the original application. For the original NDA approval action, the applicant established the efficacy of the combination product in the adult population with one adequate and well-controlled Phase 3 trial and supportive data from 4 additional trials. See Section 6 of this review for a discussion of the findings regarding treatment effect of Taclonex® Ointment in the pediatric population with plaque psoriasis.

The other sources of safety data for Taclonex® Ointment included a review of the worldwide medical literature and the 120-Day Safety Update.

### 5.3 Discussion of Individual Studies/Clinical Trials

The applicant submitted data from Trial MCB 0501 INT which was conducted to evaluate the use of Taclonex® Ointment for the treatment of plaque psoriasis in the pediatric population age 12 to 17 years.

**Title:** “Safety and efficacy of Taclonex® Ointment in adolescent patients (aged 12 to 17 years) with psoriasis vulgaris (Protocol MCB 0501).”

#### **Study Sites**

The applicant conducted Trial MCB 0501 at 7 investigational sites in the United States. The first subject enrolled in the trial on July 15, 2009 and the last subject completed the trial assessments on December 5, 2011.

Table 4: Investigators and Study Centers (7 US Sites)

Site ID	Investigator	Site Location	# Subjects	
			Enrolled N=56	Treated N=33
US046	David Michael Pariser, MD	Pariser Dermatology Specialists, Virginia Clinical Research Inc. Norfolk, VA	3	1
US078	Amy S. Paller, MD	The Feinburg School of Medicine Chicago, IL	6	3
US080	Adelaide A. Hebert, MD	The University of Texas Health Science Center Houston, TX	16	5

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US081	Lawrence F. Eichenfield, MD	University of California San Diego, CA	16	10
US093	James A. Solomon, MD, PhD	Leavitt Management Group Inc Ormond Beach, FL	1	1
US099	Angela Yen Moore, MD	Arlington Research Center, Inc. Arlington, TX	12	11
US101	SS Dhawan	Center for Dermatology Clinical Research Inc. Freemont, CA	2	2

Source: NDA 21852 SD 209, Table 4, Main Clinical Study Report, Page 61 and Appendix 16.1.4 List of Investigators and Other Important Participants

**Objective:**

**Primary objective**

- to evaluate the safety of Taclonex® Ointment in the treatment of plaque psoriasis on the trunk and/or limbs in pediatric subjects (age 12 to 17 years).

**Secondary objective**

- to evaluate the treatment effect of Taclonex® Ointment in the treatment of plaque psoriasis on the trunk and/or limbs in pediatric subjects (age 12 to 17 years ).

**Study Population**

Investigators screened 56 subjects age 12 to 17 years with plaque psoriasis involving 5-30% BSA and at least moderate severity according to the Investigator's Global Assessment of disease severity (IGA  $\geq$  3 on a 6point scale). Investigators treated a total of 33 male and female subjects with Taclonex® Ointment for 4 weeks.

**Principle Inclusion Criteria are as follows:**

- Male and female subjects of any race or ethnicity aged 12 to 17 years
- At Visit 1
  - ✓ a clinical diagnosis of plaque psoriasis on the trunk and/or limbs which was:
    - amenable to topical treatment with a maximum of 60 g of study medication per week, and
    - of an extent of 5-30% of BSA (psoriasis localized to the genitals or skin folds was not included in the BSA calculation), and
    - of at least a moderate severity by the Investigator's Global Assessment.
- At Screening Visit 2 (SV2)
  - a serum cortisol concentration above 5 mcg/dL before ACTH-challenge and above 18 mcg/dL at 30 minutes after ACTH-challenge.
  - albumin-corrected serum calcium and urinary calcium: creatinine ratio within the reference range

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- negative urine pregnancy test and agreed to use an adequate method of contraception for an adequate period of time prior to the trial and during the trial as judged by the investigator

### **Principle Exclusion Criteria are as follows:**

- PUVA or Grenz ray therapy within 4 weeks and UVB therapy within 2 weeks prior to Visit 1 and during the study.
- Systemic treatment with biological therapies with a possible effect on plaque psoriasis within the following time period prior to Visit 1 and during the study:
  - etanercept- within 4 weeks prior to Visit 1
  - adalimumab, alefacept, efalizumab, infliximab -within 2 months prior to Visit 1
  - ustekinumab -within 4 months prior to Visit 1
  - experimental products - within 4 weeks/5 half-lives (whichever is longer) prior to enrollment
- Systemic treatment with corticosteroids within 12 weeks prior to SV2 and during the study.
- Systemic treatment with therapies with a possible effect on plaque psoriasis (e.g., vitamin D analogues, retinoids, hydroxycarbamide, azathioprine, methotrexate, cyclosporine, other immunosuppressants) within 2 weeks prior to SV2 and during the study.
- Topical treatment with Class 1 to 5 corticosteroids within 2 weeks prior to SV2, with Class 6 or 7 corticosteroids or vitamin D analogues within 1 week prior to SV2, or during the study. No other treatments were allowed within 2 weeks prior to Visit 1, except for emollients which could be used up to, but not after, Visit 1
- Calcium supplements or vitamin D supplements within 4 weeks prior to SV2 and during the study.
- Presence of systemic disease that could affect the results of the ACTH challenge test)
- Treatment with any of the following medications within 4 weeks prior to SV2 or during the study: enzymatic inductors (e.g., barbiturates, phenytoin, rifampicin, carbamazepine), systemic or topical cytochrome P450 inhibitors (e.g., ketoconazole), hypoglycemic sulfonamides, antidepressant medications, estrogen therapy or any other medication known to affect cortisol levels or HPA-axis integrity.
- Planned initiation of, or changes to, concomitant medication that could affect plaque psoriasis (e.g., beta-blockers, anti-malaria drugs, lithium, ACE inhibitors) after Visit 1.
- Clinically significant abnormality in screening laboratory assessment, physical examination or vital signs
- History of serious allergy, asthma, or allergic skin reaction or sensitivity to any medication or component of a study product

### **Study Plan:**

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This was a multicenter, uncontrolled 4- week trial designed to evaluate the safety, tolerability and pharmacokinetics of Taclonex® Ointment in 33 pediatric subjects age 12 to 17 years with moderate to severe plaque psoriasis. Subjects applied Taclonex Ointment to all plaques on the trunk and extremities once daily in the evening for 4 weeks.

The trial was conducted in 3 sequential phases:

- Washout/Screening Phase
- Treatment Phase
- Follow-up Phase (if applicable)

### 1. Washout/Screening Phase

The duration of the washout/screening phase was 3 days to 6 weeks. Investigators conducted a single screening visit (SV1/SV2) for subjects who were not using excluded treatments. Investigators scheduled a second screening visit (SV2) up to 4 weeks later for subjects who were using excluded treatments. The second screening visit (SV2) was performed 3 to 14 days before the first treatment visit.

- Treatments that required washout
  - PUVA or Grenz ray therapy (4 weeks prior to Visit 1).
  - UVB therapy (2 weeks prior to Visit 1).
  - Systemic biological therapies with a possible effect on plaque psoriasis: etanercept ( 4 weeks prior to Visit 1 ), adalimumab/alefacept/efalizumab/infliximab (2 months prior to Visit 1 ), ustekinumab ( 4 months prior to Visit 1 ), experimental products ( 4 weeks/5 half-lives, whichever is longer, prior to enrollment).
  - Systemic treatment with corticosteroids (12 weeks prior to SV2).
  - Systemic therapies with a possible effect on plaque psoriasis, e.g., vitamin D analogues, retinoids, hydroxycarbamide, azathioprine, methotrexate, cyclosporine, other immunosuppressants (2 weeks prior to SV2).
  - Treatment with Class 1 to 5 corticosteroids (2 weeks prior to SV2), or with Class 6/7 corticosteroids or vitamin D analogues (1 week prior to SV2). No other treatments (e.g. tar) were allowed on trunk/extremity plaques of psoriasis (2 weeks prior to Visit 1), except for emollients (no washout required).
  - Enzymatic inductors (e.g., barbiturates, phenytoin, rifampicin, carbamazepine), systemic or topical cytochrome P450 inhibitors (e.g., ketoconazole), hypoglycemic sulfonamides, antidepressant medications, estrogen therapy or any other medication known to affect cortisol levels/HP A axis integrity (4 weeks prior to SV2).
  - Non-marketed drug substances (4 weeks prior to enrollment, or longer if the class of substance met any of the above criteria for a longer washout, e.g. biological treatments).
  - Calcium or vitamin D supplements (4 weeks prior to SV2).

2. Treatment Phase

- The duration of the treatment phase was 4 weeks. There were 3 scheduled visits: Visit 1 (day 0), Visit 2 (day 14) and Visit 3 (day 28). Investigators recorded any visits which were not completed within  $\pm 2$  days of the scheduled time for Visits 2 and 3 on the Case Report Form (CRF). Investigators instructed subjects to apply Taclonex® Ointment once daily in the evening to all plaques of psoriasis localized to the trunk/limbs (excluding genitals, skin folds and buttocks). Subjects were instructed by the investigator regarding whether to continue treatment of plaques which cleared during the treatment phase.

3. Follow-up Phase

- If there was an ongoing adverse event (AE) which was assessed as related to the study medication (possible/probable/not assessable), the investigator could schedule two follow up visits. The first visit was scheduled 14 days after the last treatment. This first visit could be conducted as a telephone contact at the discretion of the investigator. A follow up visit was scheduled 28 days after treatment Visit 3 for any subject with a serum cortisol concentration  $\leq 18$  mcg/dL at 30 minutes after ACTH-challenge test.

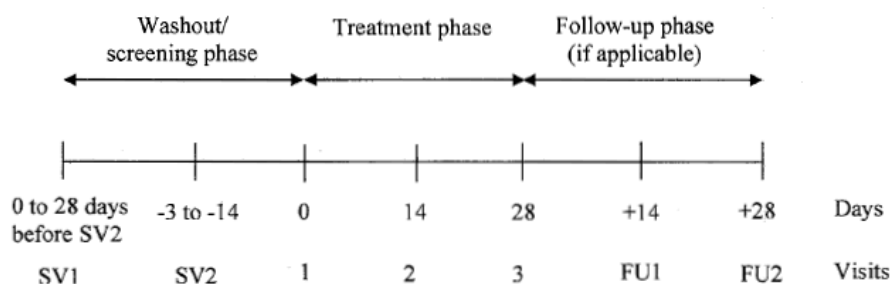


Figure 1: Trial Design

Source: NDA 21852 SD 209, Clinical Study Report, Page 27



Table 5: Trial Procedures

Phase	Washout/screening		Treatment			Follow-up	
	SV1	SV2	1	2	3	FU1 <sup>b</sup>	FU2 <sup>c</sup>
Visit							
Day	0 <sup>a</sup> to 28 days before SV2	-3 to -14	0	14	28	+14	+28
Informed Consent	X						
CRF number assigned	X						
Demographics	X						
Inclusion/exclusion criteria	X	X	X				
Concomitant medication	X	X	X	X	X		X
Physical examination/blood pressure/heart rate		X			X <sup>e</sup>		
Hematology/biochemistry/urinalysis		X			X <sup>e</sup>		
Urine pregnancy test <sup>d</sup>		X			X <sup>e</sup>		
ACTH-challenge test		X			X		X
Adverse events		X	X	X	X	X	X
Investigator assessments of psoriasis			X	X	X		
Patient assessment of psoriasis			X	X	X		
Dispensing of study medication			X	X			
Return of study medication				X	X		
Compliance check				X	X		

Source: NDA 21852 SD 209, Clinical Study Report Synopsis, Page 7

- If the necessary criteria were met, SV2 could be performed at the same time as SV1.
- FU1 was for subjects who, at the last visit during the treatment phase, had ongoing AEs of a probable/possible/not assessable relationship to study medication.
- FU2 was for subjects who, at visit 3, had a serum cortisol concentration  $\leq 18$  mcg/dL at 30 minutes after the ACTH-challenge test.
- In female subjects of child-bearing potential.
- If the subject dropped out at visit 2, these procedures were to be performed at that time

### Concomitant Medications

In addition to the treatments listed in the exclusion criteria, subjects were instructed to avoid:

- Emollients on treatment areas
- Initiation of, or changes to, concomitant medication that could affect plaque psoriasis (e.g. beta-blockers, lithium, anti-malaria drugs, ACE inhibitors).
- Excessive exposure of treated areas to either natural or artificial sunlight

Psoriasis localized to the genitals, skin folds, face and scalp could be treated with any topical medication except corticosteroids or vitamin D analogues. Subjects were permitted to use bath oils and moisturizing soaps.

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For subjects who required a repeat ACTH-challenge test during the follow-up phase, the following treatment were excluded: corticosteroid therapy (topical or systemic), enzymatic inductors, cytochrome P450 inhibitors, hypoglycemic sulfonamides, anti-depressive medications, estrogen therapy, or any other medication known to affect cortisol levels/HPA axis integrity. However, subjects of child-bearing potential were instructed to continue to use contraception.

## **Assessments**

### **Safety**

- Physical Examination, blood pressure and heart rate (Screening Visit 2 and treatment Visit 3)
- Laboratory evaluation: hematology, biochemistry and plasma parathyroid hormone (Screening Visit 2 and treatment Visit 3)
- Urine pregnancy testing in female subjects of child-bearing potential (Screening Visit 2 and treatment Visit 3)
- Adverse events: coded according to MedDRA 6.1 (all visits after Informed Consent)
  - including local adverse events (no specific scale) and pregnancy (to be followed until delivery or termination)
- ACTH-challenge test (Screening Visit 2 and treatment Visit 3)

Table 6: Laboratory Assessments

Biochemistry**	Hematology**	Urine
		Spot urine collection
Cortisol	Hemoglobin	Glucose
Urea	Hematocrit	Ketones
Creatinine	Red blood cell (RBC) count	Calcium
Albumin	Mean corpuscular volume (MCV)	Phosphate
Sodium	White blood cell (WBC) count	Creatinine
Potassium	Differential count	
Chloride	Platelet count	
Calcium		
Phosphorus		
Plasma parathyroid hormone		Urine Pregnancy Testing*

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Source: Reviewer's Table, Data from NDA 21852 SD 209, Main Clinical Study Report, Page 42

Treatment Effect: Treatment Visits 1, 2 and 3 (See scales below)

- Investigator's Global Assessment of Disease Severity (6 point IGA scale)
- Investigator's assessment of extent and severity by body region (Modified Psoriasis Area and Severity Index- mPASI-excludes psoriasis on the head)
- Total Body Surface Area (BSA) (at Visit 1 only)
- Patient's Global Assessment of Disease Severity (5 point PGA scale)

**Endpoints**

Safety

Primary

- Percent of subjects with adverse reactions (ARs)
- Percent of subjects with serum cortisol concentration of  $\leq 18$  mcg/dL at 30 minutes after ACTH-challenge at Visit 3
- Percent of subjects with serum cortisol concentration of  $\leq 18$  mcg/dL at 30 and 60 minutes after ACTH-challenge at Visit 3
- Percent of subjects with a change in albumin-corrected serum calcium from Baseline to End-of-Treatment
- Percent of subjects with a change in urinary calcium: creatinine ratio from Baseline to End-of-Treatment

Secondary

- Percent of subjects with adverse events
- Percent of subjects with changes in laboratory parameters from Baseline to End-of-Treatment
- Percent of subjects with change in blood pressure or heart rate from Baseline to End-of-Treatment

Endpoints for the Evaluation of Treatment Effect

Secondary

- Percent of subjects with 'Controlled disease' (i.e., "Clear" or "Almost clear") according to the Investigator's Global Assessment (IGA) of Disease Severity at Week 4.
- Percent of subjects with absolute and percentage change in modified PASI from Baseline (Visit 1) to Week 4.
- Percent of subjects with 'Controlled disease' (i.e., "Clear" or "Very mild") according to the Patient's Global Assessment of Disease Severity at Week 4.
- Percent of subjects with Modified PASI 75 (at least 75% reduction in modified PASI from Baseline) at Week 4.
- Percent of subjects with Modified PASI 50 (at least 50% reduction in modified PASI from Baseline) at Week 4.

Scales

1. Investigator's Global Assessment of Disease Severity

Table 7: Investigator's Global Assessment of Disease Severity

Clear	Plaque thickening = no elevation or thickening over normal skin Scaling = no evidence of scaling Erythema = none or hyperpigmentation or residual red coloration
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 coloration
Mild	Plaque thickening = slight but definite elevation Scaling = fine scales partially or mostly covering lesions Erythema = light red coloration
Moderate	Plaque thickening = moderate elevation with rounded or sloped edges Scaling = most lesions at least partially covered Erythema = definite red coloration
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 coloration
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 coloration; deep red coloration

Source: NDA 21852 SD 209, Clinical Study Report, Page 38

2. Investigator's assessment of extent and severity by body region (Modified PASI)

At Visits 1, 2 and 3, the (sub) investigator assessed the extent of psoriasis and the severity of the clinical signs (redness, thickness and scaliness) by body region (arms, legs and trunk). "Modified PASI" excludes assessment of psoriasis on the head.

Scale for extent of involvement with psoriasis by body region (e.g. arms, trunk \*and legs\*\*):

- \* includes neck
- \*\* includes buttocks and feet

- 0 =no involvement
- 1 =< 10%
- 2 =10-29%
- 3 =30-49%
- 4 =50- 69%
- 5 =70-89%
- 6 =90-100%

Table 8: Severity of Clinical Signs

Grade	Severity	Description of Clinical Sign		
		Redness	Thickness	Scaliness
0	None	No erythema	No plaque elevation	No scaling
1	Mild	Faint erythema, pink to very light red	Slight, barely perceptible elevation	Sparse, fine scale, lesions only partially covered
2	Moderate	Definite light red erythema	Definite elevation but not thick	Coarser scales, most of lesion covered
3	Severe	Dark red erythema	Definite elevation, thick plaque with sharp edges	Entire lesion covered with coarse scales
4	Very Severe	Very dark red erythema	Very thick plaque with sharp edges	Very thick scales, possibly fissured

Source: Reviewer's Table, Data from NDA 21852 SD 209, Clinical Study Report, Page 39-40

The following formula was used to calculate the modified P ASI:

Arms 0.2 (R + T + S) E =X

Trunk 0.3 (R + T + S) E = Y

Legs 0.4 (R + T + S) E = Z

R = score for redness

T = score for thickness

S = score for scaliness

E = score for extent

The sum of X+ Y + Z gave the total modified PASI, which can range from 0 to 64.8. The PASI used in this study was modified to exclude assessment of the head.

### 3. Investigator's Assessment of total BSA involvement

At Visit 1 the extent of BSA involvement with psoriasis is assessed on the arms, trunk and legs (excluding skin folds and genital) using full flat palm with 5 digits as 1% BSA. This is used to record the total area to be treated.

#### Data Analysis

The Full Analysis Set (FAS), defined as all subjects who received Taclonex® Ointment, was the primary analysis set for the evaluation of treatment effect. The Safety Analysis Set, defined as all subjects who received at least one application of the study treatment and for whom safety data was available, was the primary analysis set for safety. In this trial, both analysis groups contained 33 subjects. The Per Protocol Analysis Set which was used in the analysis of HPA axis function was the FAS excluding those subjects

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who did not apply any study medication, meet inclusion criteria #6 (normal adrenal function at Baseline) and provide data at Visit 3 after ACTH-challenge.

#### Protocol Amendments

There were no protocol amendments.

## 6 Review of Efficacy

### **Efficacy Summary**

The applicant conducted an open-label, multicenter trial (Trial MCB 0501 INT) to assess the safety of Taclonex® Ointment for the treatment of psoriasis in the pediatric population age 12-17 years. Although the trial was uncontrolled, subjects were evaluated for treatment effect.

The evaluation of treatment effect in this trial was viewed as supportive of the review conclusions related to the original application. For the original NDA approval action, the applicant established the efficacy of the combination product in the adult population with one pivotal Phase 3 trial (MCB-0003-INT) demonstrating superiority of Taclonex® Ointment to all comparators (e.g. vehicle and monads). Efficacy in the pediatric population was established by extrapolating the effectiveness results of adequate and well controlled studies in the adult population because the pathogenesis and response to treatment are essentially the same {21 CFR 201.57(f)(9)(iv).}

The study population of Trial MCB 0501 INT included 33 male and female subjects age 12 to 17 years with at least moderate plaque psoriasis on the IGA ( $\geq 3$  on a 6-point scale) and involvement of 5-30% BSA (excluding the genitals and skin folds). The extent and severity of the psoriasis were amenable to topical treatment with a maximum of 60 g of study medication per week. Trial MCB 0501 INT was designed to assess the safety of Taclonex® Ointment by evaluating HPA axis function and calcium metabolism. All subjects applied Taclonex® Ointment once daily for 4 weeks.

This uncontrolled trial (Trial MCB 0501 INT) was not designed to allow statistical conclusions related to efficacy. (b) (4)

However, the proportion of subjects achieving controlled disease at Week 4 was 60.0%. In the Phase 3 trial enrolling adult subjects, the proportion of subjects achieving controlled disease at Week 4 was 48.0% in the Taclonex® Ointment arm (compared with 7.6% in the vehicle arm.)

### 6.1 Indication

The current indication for Taclonex® Ointment is the topical treatment of (b) (4) (plaque psoriasis) in adults 18 years of age and older. The applicant provided

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an adequate assessment of both systemic and local safety to support the extension of the current indication to include the treatment of plaque psoriasis in patients age 12 years and older.

The following changes are recommended for Section 1 of labeling. Additions are noted as double underline and deletions are noted as ~~strikethrough~~.

## 1 INDICATIONS AND USAGE

Taclonex® Ointment is indicated for the topical treatment of plaque psoriasis (b) (4) in (b) (4) patients (b) (4) 12 years of age and older.

### 6.1.1 Methods

The assessment of treatment effect was a secondary objective in the following safety trial:

- Trial MCB 0501  
National, multi-center, uncontrolled 4- week trial enrolling 33 subjects aged 12 to 17 years with plaque psoriasis. The trial was designed to assess the effect of Taclonex® Ointment on HPA axis function and calcium metabolism. The trial was conducted at 7 sites in the US. Enrolled subjects had a clinical diagnosis of plaque psoriasis on the trunk and/or limbs which was at least moderate in severity according to IGA and involved 5 to 30% of the total BSA (excluding the genitals and skin folds). The extent and severity of the psoriasis were amenable to topical treatment with a maximum of 60 g of study medication per week.

### 6.1.2 Demographics

The study population was racially and ethnically diverse with a mean age of 15 years and a slight male preponderance. The majority of subjects were White with moderate disease at Baseline. The age distribution of the study population is summarized in Table 9. There are 10 subjects in the youngest age group (age 12 to 13 years). A brief summary of the demographic characteristics is provided in Table 9. The full demographic characteristics of the study population who were enrolled in Trial MCB 0501 INT are summarized in Table 13 and discussed in Section 7.2.1 of this review.

Table 9: Brief Summary of Demographic Characteristics of Subjects Treated in Trial MCB 0501 INT

Age years	12	13	14	15	16	17
	5 (15%)	5 (15%)	4 (12%)	7 (21%)	9 (27%)	3 (9%)
Gender	Female	Male				
	17 (52%)	16 (48%)				

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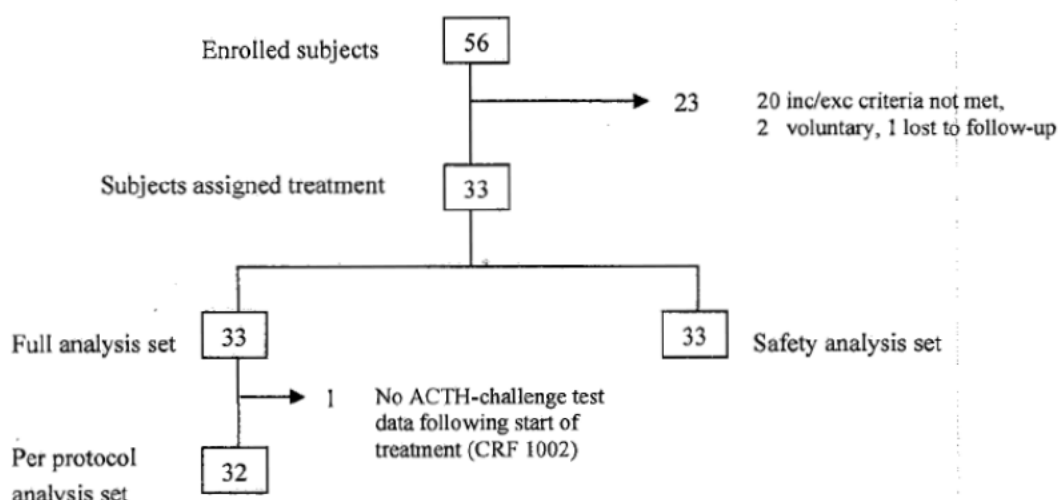
<b>Race</b>	White 22 (67%)	Asian 5 (15%)	Black 4 (12%)	Other 2 (6%)
<b>Ethnicity</b>	Not Hispanic 22 (67%)	Hispanic 11 (3%)		

Source: Modified from Statistics Filing Checklist for New NDA/BLA 4/14/2014, page 3, Kathleen Fritsch, Ph.D.

### 6.1.3 Subject Disposition

A total of 56 subjects enrolled in Trial MCB 0501 INT. During the two screening visits, investigators withdrew 23 subjects who had signed consent forms and obtained Case Report Form numbers.

Figure 2: Disposition of subjects



Source: NDA 21852 SD 209, Clinical Study Report page 60.

Most of the subjects who were withdrawn did not meet the inclusion/exclusion criteria. The reasons for withdrawal included the following:

- <5% BSA/not moderate disease (9 subjects)
- Subject did not have plaque psoriasis (e.g. wrong diagnosis/guttate psoriasis/mixed types) (3 subjects)
- Withdrew consent (2 subjects)
- No active lesions of psoriasis (1 subject)
- Abnormal laboratory parameter (3 subjects)
- Poor vascular access (1 subject)
- Other inflammatory diseases or conditions present (e.g. Pityriasis rosea) (3 subjects)



- Lost to follow up (1 subject)

All 33 subjects who attended treatment Visit 1 completed the trial. However, one subject who was treated for 4 weeks with Taclonex Ointment did not have laboratory results from the ACTH-challenge test performed at Visit 3. This subject was excluded from the per-protocol analysis set.

Investigators reported a total of 68 protocol deviations. None of these protocol violations resulted in withdrawal of the subjects from the trial. The following were assessed as major protocol violations:

- Concurrent cardiac condition (sinus arrhythmia) in violation of exclusion criterion 17.(1 subject)
- Concurrent use of topical corticosteroid (triamcinolone) on the scalp, in violation of exclusion criterion 8.(1 subject)
- Concurrent antidepressant medication (fluoxetine) in violation of exclusion criterion 9.(1 subject)
- Incomplete laboratory assessment. (e.g. no analysis of serum cortisol for HPA-challenge testing)

#### 6.1.4 Analysis of Primary Endpoint(s)

All of the primary endpoints in Trial MCB 0501 INT involved the assessment of safety parameters. Refer to Section 7 of this review for the analysis of the safety data.

#### 6.1.5 Analysis of Secondary Endpoints(s)

The key assessment of treatment effect in Trial MCB 0501 INT was the percentage of subjects with 'Controlled disease' (i.e., "Clear" or "Almost clear") according to the Investigator's Global Assessment (IGA) of Disease Severity at Week 4. Table 10 provides a summary of the percentage of pediatric subjects with controlled disease at Week 2 and Week 4.

Table 10: Percentage of Pediatric Subjects with Controlled Disease

	Clear	Almost clear	Mild	Moderate	Severe	Very Severe
Baseline				30 (91%)	3 (9%)	--
Week 2	1 (3%)	6 (18%)	17 (52%)	8 (24%)	1 (3%)	--
Week 4	6 (18%)	14 (42%)	11 (33%)	1 (3%)	0 (0%)	1 (3%)

Source: Modified from Statistics Filing Checklist for New NDA/BLA dated 4/14/2014, page 3, Kathleen Fritsch, Ph.D.

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All evaluations of treatment effect were conducted on the Full Analysis Set (FAS), defined as all subjects who received Taclonex® Ointment. There were no imputations for missing data. Although these results indicate a treatment effect in this pediatric population, the study design (e.g. uncontrolled, open label design) and size of the study population do not permit statistical conclusions related to efficacy.

Additional assessments of treatment effect were based on modified PASI 75 at Week 4, modified PASI 50 at Week 4, Patient's Global Assessment and change in modified PASI from Baseline to Week 4. Although interpretation of the data is limited by the sample size and study design, the findings support the use of Taclonex® Ointment in the population age 12 to 17 years with plaque psoriasis.

Table 11: Overview of Treatment Effect from Trials MCB 0501

N (FAS)	Baseline IGA	Treatment Effect Response Criteria (FAS)	Week 2	Week 4
N= 33	Moderate: 90.9%	Controlled disease by IGA (%)	21.2	60.0
		Change in mPASI (%)	-46.6	-72.5
	Severe: 9.1%	mPASI 75 (%)	12.1	51.5
		mPASI 50 (%)	54.5	84.8
		Controlled disease by Patient's Global (%)	36.4	69.7

Source: NDA 21852, Modified from Final Study Report Tables 62-66 page 122, (Applicant's analysis)  
 Note: The full analysis set and the safety analysis set included all 33 subjects. One subject who did not provide data for the ACTH challenge test was excluded from the per protocol analysis set.

The following changes are recommended for Section 14 of labeling. Additions are noted as double underline and deletions are noted as ~~strikethrough~~.

#### 14 CLINICAL STUDIES

##### Clinical Trials Conducted in Subjects 12 to 17 years with Psoriasis

A prospective, uncontrolled trial (N=33) was conducted in pediatric subjects age 12 to 17 years with plaque psoriasis involving 5-30% of the body surface area.

Approximately 91% of subjects had moderate disease at Baseline. Subjects were treated once daily for up to 4 weeks with Taclonex® Ointment. All subjects were evaluated for safety including calcium metabolism (N=33) and 32 subjects were evaluated for HPA axis suppression.

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#### 6.1.6 Other Endpoints

No applicable.

#### 6.1.7 Subpopulations

Given the limitations of the database (small sample size and limited enrollment of non-White subjects) and the study design (e.g. open-label), no analysis of treatment effect by age, race or sex was performed by Agency reviewers.

#### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The applicant established the safe and effective dosing regimen (concentration, duration of application and dosing interval) with data submitted to support approval of the original application for the topical treatment of psoriasis vulgaris (plaque psoriasis) in adults 18 years of age and older. In Trial MCB 9905 INT, the applicant compared once daily dosing with twice daily dosing of Taclonex® Ointment applied for up to 4 weeks. The primary efficacy endpoint was the percentage change in Psoriasis Area Severity Index score. Twice daily dosing provided significantly greater efficacy (-73.8% change compared with -68.6% change). However, the number of subjects with elevated albumin-corrected serum calcium was also greater in the group applying the study product twice daily (6.4% compared with 2.3%). Refer to Clinical Review by Brenda Carr, MD page 21.

The applicant did not investigate alternative dosing regimens for the pediatric population age 12 to 17 years. Subjects in all age groups applied Taclonex® (calcipotriene and betamethasone dipropionate) Ointment, 0.005%/0.064%, once daily up to 4 weeks.

#### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The persistence of efficacy and the development of tolerance were not assessed in the pediatric population age 12 to 17 years.

#### 6.1.10 Additional Efficacy Issues/Analyses

There were no additional efficacy issues or analyses.

## 7 Review of Safety

### Safety Summary

The applicant conducted a single, open-label, multicenter trial (Trial MCB 0501 INT) to assess the safety of Taclonex® Ointment for the treatment of psoriasis in the pediatric

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population age 12-17 years. Trial MCB 0501 INT enrolled a total of 33 subjects age 12 to 17 years with at least moderate plaque psoriasis on the Investigator Global Assessment scale of disease severity (IGA  $\geq 3$  on a 6-point scale) and involvement of 5-30% body surface area (BSA) (excluding the genitals and skin folds). The extent and severity of psoriasis must be amenable to topical treatment with a maximum of 60 g of study medication per week. Trial MCB 0501 INT was designed to assess the safety of Taclonex® Ointment by evaluating HPA axis function and calcium metabolism. The entry criteria at Screening Visit 2 (SV2) included: normal adrenal function (a serum cortisol concentration above 5 mcg/dL before ACTH-challenge and above 18 mcg/dL at 30 minutes after ACTH-challenge), albumin-corrected serum calcium and urinary calcium: creatinine ratio within the reference range and negative urine pregnancy test. All subjects applied Taclonex® Ointment once daily for 4 weeks.

Pediatric subjects enrolled in MCB 0501 INT applied a maximum weekly dose of 60 grams of Taclonex® Ointment to a maximum of 30% BSA. The labeled maximum adult dose of 100 grams was adjusted based on the expected body surface area (BSA) of pediatric subjects compared with adult subjects. The mean duration of treatment was 4.0 weeks (range 3.7-4.4 weeks). The mean amount of the drug product used per week was 29.6 grams (range 8.1-55.8 grams/week.) The mean weekly amount used in the pediatric population was similar to the mean weekly amount used in the adult population in the Phase 3 trial MCB 0003 INT (33.5 grams.) All subjects applied at least 80% of the required doses of Taclonex® Ointment during Trial MCB 0501 INT. A total of 21 subjects (63.6%) applied all the required doses of Taclonex® Ointment during the trial, 10 subjects (30.3%) applied 90% or more of the required doses and 2 subjects (6.1%) applied 80% or more of the required doses. Therefore, the overall exposure to the study product was adequate to characterize the safety profile in the intended pediatric population.

The safety evaluation included adverse events elicited by open ended questioning (summarized by severity, frequency and relationship to the study drug), vital signs, laboratory testing (e.g. chemistry, hematology and urinalysis), concomitant medication query, dietary calcium diary and pregnancy testing. Cutaneous adverse events were categorized as lesional/perilesional to the application site or distant (> 2 cm from the application site).

There were no deaths, non-fatal serious adverse events (SAEs), severe adverse events or pregnancies among subjects in Trial MCB 0501 INT. Investigators did not withdraw any subject from the trial due to an adverse event.

A total of 11 subjects (33.3%) reported 16 adverse events. The most common adverse events occurring in  $\geq 1\%$  of subjects in the safety population were: upper respiratory tract infection (6%), headache (6%), tension headache (6%), cough (6%), rash papular (6%), pyrexia (3%), body tinea (3%), gastroenteritis viral (3%), joint sprain (3%), lymphadenopathy (3%) and pruritus (3%). There were 3 subjects with adverse events

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which were classified as perilesional: 2 subjects with rash papular (localized to the back and leg) and one subject with pruritus. Both cases of rash were assessed as unrelated and the case of pruritus was graded as possibly related.

Among the subjects reporting adverse events, 2 subjects (6%) reported 2 adverse events which were categorized as adverse drug reactions (ADRs). There were 2 ADRs (headache and pruritus) which were mild in intensity and reported by 1 subject each. There is insufficient data to support a role for Taclonex® Ointment in the etiology of headache. The only clinically relevant adverse reaction which was consistent with the mechanism of action of the product was pruritus. Pruritus was observed in trials in the adult population and is included in current labeling.

“Adverse events of clinical interest” were defined as adverse events related to exposure to topical corticosteroids or topical calcipotriene. There were no adverse events potentially related to exposure to corticosteroid component of Taclonex® Ointment, betamethasone dipropionate. No subjects had elevated values for albumin-corrected serum calcium or urinary calcium at Baseline or Week 4 which were potentially related to systemic exposure to calcipotriene. However, there was one subject with an elevated urinary calcium: creatinine ratio. He had no associated symptoms and his albumin-corrected serum calcium and urinary calcium were normal at Baseline and Week 4. The clinical significance of this isolated finding is not clear. The only local adverse event which was potentially related to calcipotriene was pruritus.

Dermal safety studies were not included in the evaluation of the safety of Taclonex® Ointment for the treatment of plaque psoriasis in the pediatric population age 12-17 years. The applicant conducted dermal safety studies to support approval of the original NDA. Local safety findings in the pediatric population were consistent with local safety findings in adults.

The applicant did not evaluate the long term safety of Taclonex® Ointment in the pediatric population age 12 to 17 years. The applicant conducted two 52- week trials (MCB 0102 INT and MBL 0502 US) to evaluate long term safety in the adult population using Taclonex® Ointment. Trial MBL 0502 US also included the use of Taclonex® Topical Suspension on the scalp.

The data from Trial MCB 0501 INT is adequate to inform safety and support the short-term use of Taclonex® Ointment in the pediatric population age 12 to 17 years. Safety findings in the pediatric population are similar to safety findings in the adult population. The adverse reactions which were identified in the pediatric population were already included in current labeling. The data submitted by the applicant supports the extension of the current indication to include the treatment of plaque psoriasis in patients age 12 years and older and fulfills the post marketing requirement under PREA.

## 7.1 Methods

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Under the Pediatric Research Equity Act (PREA), the applicant was required to evaluate the safety of Taclonex® Ointment for the treatment of plaque psoriasis in pediatric patients ages 12 to 17 years. To address this requirement, the applicant evaluated the effect of their drug product on HPA axis function and calcium metabolism, the primary systemic safety issues associated with this class of products. The applicant submitted data from a single uncontrolled, prospective, multicenter trial (MCB 0501 INT) enrolling 33 pediatric subjects age 12 to 17 years with at least moderate psoriasis on the Investigator Global Assessment scale (IGA  $\geq 3$  on a 6-point scale) and amenable to topical treatment with a maximum of 60 g of study medication per week. The entry criteria included a clinical diagnosis of plaque psoriasis on the trunk and/or limbs which involved 5-30% of BSA (psoriasis localized to the genitals or skin folds was not included in the BSA calculation). In addition, the entry criteria at SV2 included: normal adrenal function (a serum cortisol concentration above 5 mcg/dL before ACTH-challenge and above 18 mcg/dL at 30 minutes after ACTH-challenge), albumin-corrected serum calcium and urinary calcium: creatinine ratio within the reference range and negative urine pregnancy test. Subjects applied Taclonex® Ointment once daily for up to 4 weeks.

The safety evaluation was conducted on the “Safety Analysis Set”, defined as all subjects who applied any study product and for whom the presence or confirmed absence of adverse events was available. The safety evaluation included adverse events elicited by open ended questioning (summarized by severity, frequency and relationship to the study drug), vital signs, laboratory testing (e.g. chemistry, hematology and urinalysis), concomitant medication query, and pregnancy testing. Cutaneous adverse events were categorized as lesional/perilesional to the application site or distant (> 2 cm from the application site). Based on data collected in the adult population, adverse events of clinical interest were identified to evaluate in the pediatric population. These adverse events were included in current labeling and related to local and systemic effects of corticosteroids and effects on calcium metabolism.

All 33 treated subjects provided data regarding the effects of Taclonex® Ointment on calcium metabolism and 32 subjects provided data regarding the effect of Taclonex® Ointment on HPA axis function.

### 7.1.2 Categorization of Adverse Events

In this safety analysis, all adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 6.1. Adverse events were presented by system organ class and preferred term.

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The assignment of verbatim terms to system organ classes and preferred terms appears to be acceptable.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The primary safety analysis was based on all randomized subjects who were dispensed Taclonex® Ointment in Trial MCB 0501 INT. No pooling was necessary since a single trial was conducted to evaluate the study product in the pediatric population age 12 to 17 years.

The applicant tabulated the number and percentage of subjects experiencing each type of adverse event (AE) (according to MedDRA preferred term within SOC) regardless of the number of times each AE was reported by each subject. The intensity of an AE was recorded as the worst intensity reported by the subject. The applicant defines adverse drug reactions (ADR) as AEs for which the investigator had not described the causal relationship to trial medication as 'not related.'

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

#### Overall Exposure

The overall exposure of pediatric subjects age 12 to 17 years to Taclonex® Ointment was assessed by the amount and the number of doses of the study product that subjects applied to the affected areas and the duration of exposure. Table 12, Table 13 and Table 14 provide summaries of the overall exposure.

The amount of drug product used by each subject was calculated by subtracting the weight of the used tubes from the mean normal weight of the full tubes. Four subjects failed to return all the used tubes at treatment Visit 2 and Visit 3 and their data was excluded. The mean total amount of the drug product used was 119.9 grams (range 30.6-223.4 g). The mean amount of the drug product used per week was 29.6 grams (range 8.1-55.8 grams/week.) The mean weekly amount used in the pediatric population was similar to the mean weekly amount used in the adult population in the Phase 3 trial MCB 0003 INT (33.5 grams.) See the Clinical Review of the original NDA submission by Brenda Carr dated 1/9/2006. The amount of study product used by subjects during the first 2 weeks (mean total amount 59.1 grams and mean weekly amount 28.8 grams/week) was similar to the amount used in the second 2 weeks (mean total amount 56.8 grams and mean weekly amount 28.5 grams/week).

Table 12: Amount of Study Product Used

<u>Parameter</u>	<u>Amount of Taclonex Ointment Used (grams)</u>
<u>Total amount used: Visit 1-3</u>	
Mean (SD)	119.9 (70.2)
Median	120.3
Range	30.6-223.4
<u>Average weekly amount used: Visit1-3</u>	
Mean (SD)	29.6 (17)
Median	29.4
Range	8.1-55.8
<u>Number of Subjects</u>	29

Source: NDA 21852 SD 209, Main Clinical Study Report, Table 36, page 89

All subjects applied at least 80% of the required doses of Taclonex® Ointment during Trial MCB 0501 INT. A total of 21 subjects (63.6%) applied all the required doses of Taclonex® Ointment during the trial, 10 subjects (30.3%) applied 90% or more of the required doses and 2 subjects (6.1%) applied 80% or more of the required doses.

Table 13: Compliance with Dosing Regimen

Doses applied	Safety Analysis Set N=33	Per Protocol Analysis Set N=32
	Number subjects (%)	Number subjects (%)
Applied all doses	21 (63.6)	21 (65.6)
Missed ≤ 10% doses	10 (30.3)	9 (28.1)
Missed > 10% to ≤ 20% doses	2 (6.1)	2 (6.3)
Total	33 (100)	32 (100)

Source: NDA 21852 SD 209 page 64, Main Clinical Study Report, Table 17, page 72

The mean duration of exposure to the study treatment was 4 weeks. The duration of exposure was assessed for all subjects in the full analysis set (safety analysis set) in the following table.

Table 14: Duration of Exposure

Parameter	Duration of Exposure to Taclonex Ointment (weeks)
Mean (SD)	4.0 (0.2)
Range	3.7 to 4.4
Number of Subjects	33

Source: NDA 21852 SD 209, Main Clinical Study Report, Table 35, page 88



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Only one subject applied more than 60 grams per week of Taclonex® Ointment for 2 or more weeks. Thus, conclusions regarding the relationship between adverse events and exposure greater than the maximal weekly dose (60 g) are limited. See Section 7.5.1 of this review for a discussion of adverse events observed in this subject.

The following changes are recommended for Section 2 of labeling. Additions are noted as double underline and deletions are noted as ~~strikethrough~~.

## 2 DOSAGE AND ADMINISTRATION

Apply an adequate layer of Taclonex® Ointment to the affected area(s) once daily for up to 4 weeks. (b) (4)

- Taclonex® Ointment should be rubbed in gently and completely. Patients should wash their hands after applying Taclonex® Ointment. Therapy should be discontinued when control is achieved.

Patients 18 years and older should not use more than 100 g per week and patients 12 to 17 years should not use more than 60 g per week. Treatment of more than 30% body surface area is not recommended.

Taclonex® Ointment should not be used with occlusive dressings unless directed by a physician. Taclonex® Ointment is not for oral, ophthalmic, or intravaginal use. Avoid use on the face, groin, or axillae, or if skin atrophy is present at the treatment site.

### Baseline Characteristics of the Study Population

The majority of subjects in the study population were White and male with a mean age of 15 years. The study population was racially and ethnically diverse including 12.1% Black and 15.2% Asian subjects. Subjects reported a mean duration of psoriasis of 4.5 years. At Baseline, the mean % BSA was 14 and the mean modified PASI Score was 8.

Table 15: Demographic Data

Baseline Parameter	Safety Analysis Set N=33	Per Protocol Analysis Set N=32
<b>Age (years)</b>		
Mean (SD)	14.6 (1.6)	14.7 (1.6)
Median	15	15
Range	12-17	12-17
<b>Sex n (%)</b>		
Female	16 (48.5)	15 (46.9)
Male	17 (51.5)	17 (51.3)
<b>Race n (%)</b>		
White	22 (66.7)	21 (65.6)

Black	4 (12.1)	4 (12.5)
Asian	5 (15.2)	5 (15.6)
Other*	2 (6.1)	2 (6.3)
<b>Ethnicity n (%)</b>		
Hispanic	11 (33.3)	10 (31.3)
Not Hispanic	22 (66.7)	22 (68.8)
<b>Duration of Disease (years)</b>		
Mean (SD)	4.5 (3.5)	4.6 (3.5)
Median	3.0	3.5
Range	0-11	0-11
<b>Extent of Psoriasis % BSA</b>		
Mean (SD)	14.2 (8.3)	13.8 (8.0)
Median	11.0	10.5
Range	5-30	5-30
<b>Modified PASI</b>		
Mean (SD)	8.1 (4.1)	8.1 (4.1)
Median	6.7	6.7
Range	3-18	3-18
<b>IGA n (%)</b>		
Moderate	30 (90.9)	29 (90.6)
Severe	3 (9.1)	3 (9.4)
<b>Patient's GA</b>		
Very Mild	2 (6.1)	1 (3.1)
Mild	3 (9.1)	3 (9.4)
Moderate	28 (84.8)	28 (87.5)
<b>Serum Cortisol (time 0)</b>		
Mean (SD)	12.6 (4.25)	12.7 (4.28)
Median	11.8	11.9
Range	5.2-20.5	5.2-20.5

Source: Compiled from data included in Tables 5-13 and 16, NDA 21852 SD 209 page 64, Main Clinical Study Report

### 7.2.2 Explorations for Dose Response

The applicant did not conduct an evaluation of dose response in submission.

### 7.2.3 Special Animal and/or In Vitro Testing

Special animal and/or in vitro testing was not included in the current submission.

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#### 7.2.4 Routine Clinical Testing

The routine clinical testing was designed to assess safety including effects on HPA axis function and calcium metabolism following daily application of Taclonex® Ointment in pediatric subjects for 4 weeks.

#### 7.2.5 Metabolic, Clearance, and Interaction Workup

The applicant did not perform an analysis of metabolic parameters or drug clearance for this submission.

An evaluation of potential drug interactions was not included in this submission. Current approved labeling does not contain data regarding drug interactions.

#### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Taclonex® Ointment is a combination product containing a corticosteroid and a vitamin D analog. The primary systemic safety assessment for topical corticosteroids is ACTH challenge testing to evaluate HPA suppression as discussed in Section 7.4.5 of this review. Hypercalcemia is a known adverse event observed with vitamin D analogs. The applicant assessed the effect of Taclonex® Ointment on calcium metabolism in all subjects in Trial MBL 0501 INT. Investigators evaluated calcium metabolism at Screening Visit 2 and after 4 weeks of treatment (Day 28). The evaluation included measurements of serum calcium, albumin, phosphorus, plasma parathyroid hormone (PTH) level and calculation of the albumin-corrected serum calcium concentration. In addition, subjects provided urine collections for measurement of urinary calcium, phosphorus, and creatinine excretion and calculation of the calcium: creatinine ratio and phosphorus: creatinine ratio. The results of the evaluation of the effect of Taclonex® Ointment on calcium metabolism are discussed in Section 7.4.2.

The safety evaluation which was conducted by the applicant to assess the potential adverse events associated with exposure to corticosteroids and vitamin D analogs in the pediatric population age 12 to 17 years was acceptable.

### 7.3 Major Safety Results

#### 7.3.1 Deaths

There were no deaths among the pediatric subjects age 12 to 17 years enrolled in Trial MCB 0501 INT.

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### 7.3.2 Nonfatal Serious Adverse Events

There were no nonfatal serious adverse events among the pediatric subjects age 12 to 17 years enrolled in Trial MCB 0501 INT.

### 7.3.3 Dropouts and/or Discontinuations

No subjects withdrew from Trial MCB 0501 INT. All 33 subjects who attended treatment Visit 1 completed the trial. However, one subject who was treated for 4 weeks with Taclonex® Ointment did not have laboratory results from the ACTH-challenge test performed at Visit 3. This subject was excluded from the per-protocol analysis set.

### 7.3.4 Significant Adverse Events

In the category of significant adverse events, the applicant included serious adverse events (SAEs), pregnancies (not recorded as SAEs), “adverse events of clinical interest” and adverse events that were clinically significant or led to a substantial intervention (e.g. discontinuation of study product).

There were no deaths, SAEs, severe adverse events, pregnancies or withdrawals reported during Trial MCB 0501 INT. “Adverse events of clinical interest” were systemic and local adverse events known to be related to exposure to corticosteroids or systemic effects known to be related to calcipotriene. These included the following:

1. Events potentially related to corticosteroid use: skin atrophy, skin striae, telangiectasia, tachyphylaxis or rebound (including lesional/perilesional or treatment related psoriasis), skin hypopigmentation, hypertrichosis, acne, rosacea, dermatitis, suppression of the HPA axis, pustular psoriasis, and lesional/perilesional or treatment related skin infections (folliculitis, rash pustular, herpes simplex, otitis externa, ear infection, eye infection, furuncle), ocular hypertension, intraocular pressure increased, glaucoma, hypertension, diabetes mellitus, increased blood glucose.
2. Events potentially related to calcipotriol absorption: hypercalcemia, blood calcium increased and urine calcium increased.

There were no reports of local or systemic adverse events related to exposure to the corticosteroid component of Taclonex® Ointment (i.e. betamethasone dipropionate). Investigators observed no signs of cutaneous atrophy (e.g. telangiectasia, loss of elasticity, purpura, or striae) or hyper/ hypopigmentation during the 4 week treatment period. There was no clinical or laboratory evidence of adrenal suppression at the End-of-Treatment.

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No subjects had elevated values for albumin-corrected serum calcium or urinary calcium at Baseline or Week 4 which were potentially related to systemic exposure to calcipotriene. However, there was one subject with an elevated urinary calcium: creatinine ratio. He had no associated symptoms and his albumin-corrected serum calcium and urinary calcium were normal at Baseline and Week 4. The clinical significance of this finding is not clear. The only local adverse event which was potentially related to calcipotriene was pruritus.

### 7.3.5 Submission Specific Primary Safety Concerns

There were no new specific safety concerns regarding the pediatric population which were identified or addressed in this submission. The safety profile of Taclonex ® Ointment for the treatment of psoriasis in the pediatric population age 12 to 17 years is similar to the safety profile in the adult population. Common adverse reactions ( $\geq 1\%$ ) included in current labeling are pruritus and scaly rash. All relevant adverse reactions identified by the applicant in the pediatric population are already included in Section 6.1 of current labeling. HPA axis suppression and the effects on calcium metabolism are the primary systemic safety concerns with the use of Taclonex ® Ointment in the pediatric population and are addressed in this review in Section 7.2.6 and Section 7.4.2.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

Investigators collected data regarding adverse events in Trial MCB 0501 INT by posing non-leading questions and recording their own observations regarding changes in subject status. In addition, investigators categorized cutaneous events as lesional/peri-lesional (located less than or equal to 2 cm from the border of the treated lesion) or distant from the treatment site. Investigators documented the location of the cutaneous adverse event and the intensity of an adverse event as the most severe intensity rating.

A total of 11 subjects (33.3%) reported 16 adverse events. As summarized in Table 16, among the most common adverse events occurring in  $\geq 1\%$  of subjects in the safety population were: upper respiratory tract infection (6%), headache (6%), tension headache (6%), cough (6%), and rash papular (6%). The other adverse events which were reported by 1 subject each included the following: pyrexia (3%), body tinea (3%), gastroenteritis viral (3%), joint sprain (3%), lymphadenopathy (3%) and pruritus(3%).

Table 16: Adverse Events and Adverse Reactions in Trial MCB 0501 INT

MedDRA System Organ Class MedDRA Preferred Term	Total AEs N (%)	Related AEs (Adverse Reactions)* N (%)
Total Number of Subjects with Any Adverse Event	11 (33)	2 (6)
Blood and lymphatic system disorders		
Lymphadenopathy	1 (3.0)	
General disorders and administration site conditions		
Pyrexia	1(3.0)	
Infections and infestations		
Body tinea	1 (3.0)	
Gastroenteritis viral	1 (3.0)	
Upper respiratory tract infection	2 (6.1)	
Injury, poisoning and procedural complications		
Joint sprain	1(3.0)	
Nervous system disorders		
Headache	2 (6.1)	1 (3.0)
Tension headache	2 (6.1)	
Respiratory, thoracic and mediastinal disorders		
Cough	2 (6.1)	
Skin and subcutaneous tissue disorders		
Pruritus	1 (3.0)	1 (3.0)
Rash papular	2 (6.1)	
Total Number of Adverse Events	16	2

\*Adverse reactions were adverse events assessed as “possibly” related by investigators. It should be noted that no adverse events were assessed as probably related.

Source: Modified from Table 40, NDA 21852 SD 209 Main Clinical Study Report page 93

The adverse events graded as moderate in intensity included: viral gastroenteritis (1 case), ankle sprain (1 case) and upper respiratory tract infection (2 cases.)

There were 3 subjects with adverse events which were classified as lesional/perilesional: 2 subjects with rash papular (localized to the back and leg) and one subject with pruritus. Both cases of rash were assessed as unrelated and the case of pruritus was graded as possibly related.

Adverse drug reactions (ADRs) were defined as adverse events for which the investigator had not described the causal relationship to study product as ‘not related’. There were 2 ADRs (headache and pruritus) which were mild in intensity and reported by 1 subject each. There is insufficient data to support a role for Taclonex® Ointment in the etiology of headache. The only clinically relevant adverse reaction which was

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consistent with the mechanism of action of the product was pruritus. Pruritus was observed in trials in the adult population and is included in current labeling.

#### 7.4.2 Laboratory Findings

The following laboratory testing was performed as part of the safety evaluation of pediatric subjects in Trial MCB 0501:

Serum Biochemistry: calcium, albumin, albumin-corrected serum calcium, potassium, sodium, chloride, creatinine, blood urea nitrogen, phosphorus, cortisol, and plasma PTH.

Urinalysis (spot urine): glucose, ketones, calcium, phosphorus, creatinine, urinary calcium: creatinine ratio, and urinary phosphorus: creatinine ratio.

Hematology: hemoglobin, hematocrit, RBC count/erythrocytes, mean corpuscular volume (MCV), WBC count/leukocytes including differential count (neutrophils, lymphocytes, monocytes, eosinophils, basophils), and platelet count.

#### HPA axis evaluation

In Trial MCB 0501 INT, investigators conducted ACTH challenge testing to evaluate the effect of Taclonex® Ointment used once daily for up to 4 weeks on the HPA axis. None of the 32 subjects showed clinical evidence (laboratory abnormalities or symptomatology) of adrenal suppression (serum cortisol concentration  $\leq 18$  mcg/dL) 30 minutes after ACTH challenge testing at Week 4. One subject (CFR 1002) did not provide data from ACTH challenge testing at Week 4. At Baseline, the mean serum cortisol concentration after 30 minutes was 24.68 mcg/dL (range 18.5-30.6 mcg/dL) while at Week 4 the mean serum cortisol concentration after 30 minutes was 24.74 mcg/dL (range 19.2 to 32.1 mcg/dL). See the Clinical Pharmacology Review by An-Chi Lu, Ph.D. dated 10/5/2014.

#### Calcium metabolism

The key parameters that should be evaluated in pediatric subjects receiving vitamin D analogs include calcium, phosphorus, alkaline phosphatase, parathyroid hormone (PTH) and urinary calcium/creatinine ratio (Ali Mohamadi, MD, Division of Metabolism and Endocrinology Products, IND 71198 Consultation dated 1/20/2012). An evaluation of calcium metabolism was performed at Screening Visit 2 (SV2) and after 4 weeks of treatment. Alkaline phosphatase was not evaluated in these trials. No meaningful changes in calcium metabolism were detected in the pediatric population age 12 to 17 years under the conditions of these trials. However, it should be noted that hypervitaminosis D, which results in elevated serum calcium levels, does not tend to occur until after several months of excessive absorption of vitamin D.

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The following is a summary of the key findings in the evaluation of the effect of Taclonex® Ointment on calcium metabolism:

Albumin-corrected serum calcium:

Per protocol all subjects had normal albumin-corrected serum calcium at Baseline. At Week 4, 29 subjects had normal albumin-corrected serum calcium while 3 subjects had values below the reference range. The 3 subjects with low albumin-corrected serum calcium levels (2.05 mmol/L, 1.95 mmol/L, 2.10 mmol/L) had values close to the lower limit of the normal reference range (e.g. 2.15 mmol/L). One subject did not provide data. None of the subjects had an elevated value at Week 4.

At Baseline, the mean albumin-corrected serum calcium was 2.27 mmol/L (range 2.13 to 2.48 mmol/L). The mean change in albumin-corrected serum calcium from Baseline to Week 4 was 0.005 mmol/L (range -0.30 to 0.13 mmol/L) as summarized in Table 17.

Table 17: Change in albumin-corrected serum calcium and urinary calcium: creatinine ratio from Baseline to Week 4

Number of Subjects Exposed to Taclonex® Ointment (n=33)		
	Albumin-corrected Serum Calcium	Urinary calcium: creatinine ratio
	mmol/L	mmol/g
Baseline Visit		
Mean	2.268	2.383
SD	0.084	1.300
Medium	2.250	1.875
Minimum	2.13	0.50
Maximum	2.48	5.00
Number	33	32
Change at Week 4		
Mean	0.005	0.717
SD	0.094	2.877
Medium	0.025	-0.125
Minimum	-0.30	-3.50
Maximum	0.13	12.25
Number	32	30
95% Confidence Interval (mean)	-0.0285-0.0395	-0.357-1.791

Source: NDA 21852, SD 209 Table 20, page 76

Urinary Calcium: Creatinine Ratio:



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The applicant provided data regarding the urinary calcium: creatinine ratio for 31 subjects. A total of 29 subjects had normal urinary calcium: creatinine ratios at Baseline and Week 4. At Baseline, one subject had a value above the reference range and one subject had an unknown value. At Week 4, 30 subjects had normal values.

One subject with normal urinary calcium: creatinine ratio at Baseline developed an elevated value at Week 4. The subject (CRF1311) was a 13 year old Hispanic male with moderate plaque psoriasis at Baseline involving 7% BSA. He applied a total of 219.8 grams of Taclonex ® Ointment during the 4 week trial which exceeded the mean for the group (119.9 grams). His urinary calcium: creatinine ratio increased from 3.75 mmol/g at Screening Visit 2 to 16.00 mmol/g at Visit 3. However, he had no associated symptoms and his albumin-corrected serum calcium and urinary calcium were normal at Baseline and Week 4. In addition, his serum cortisol concentration 30 minutes after ACTH challenge testing was normal (20 mcg/dl). The clinical significance of this isolated finding of urinary calcium: creatinine ratio above the reference range is not clear.

The mean change in urinary calcium: creatinine ratios from Baseline to Week 4 is summarized in Table 17. The changes in the key parameters of calcium metabolism are summarized in the following shift table (Table 18). No meaningful trends are evident from the data.

Table 18: Effects on Calcium Metabolism

Shift Table				
Laboratory parameters categorized as low, normal, high or unknown at Week 4 compared with the Baseline category				
Laboratory Parameter	Baseline Category	Low	Normal	High
Albumin-corrected serum calcium	Normal	3	29	0
Urinary calcium: creatinine ratio	Normal	0	29	1
	Unknown	0	1	0
Serum Phosphorus	Normal	1	25	1
	High	0	2	3
	Low	0	2	1
Urinary phosphorus: creatinine ratio	Normal	0	17	6
	High	0	4	0
	Unknown	0	1	0
PTH intact	Normal	1	30	0

Source: NDA 21852, MCB INT Clinical Study Report Table 21, 23, 25, 2, 29; page 79-82

No meaningful changes in the other biochemistry or hematologic parameters were detected in the pediatric population age 12 to 17 years under the conditions of these

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trials. The changes in the key parameters are summarized in the following shift table (Table 19).

Table 19: Effects of Taclonex Ointment on Other Laboratory Parameters

Shift Table				
Laboratory parameters categorized as low, normal, high or unknown at Week 4 compared with the Baseline category				
Laboratory Parameter	Baseline Category	Low	Normal	High
Hemoglobin	Low	1	0	0
	Normal	0	29	0
	High	0	1	0
Hematocrit	Low	2	1	0
	Normal	0	28	0
	High	0	0	1
Leukocytes	Low	3	0	0
	Normal	2	25	0
	High	0	0	1
Neutrophils	Low	0	2	1
	Normal	0	17	6
	High	0	4	0
Lymphocytes	Unknown	0	1	0
	Low	0	1	0
	Normal	0	30	0
Monocyte	Normal	0	28	1
	High	0	2	0
	Normal	0	29	1
Eosinophils	High	0	1	0
	Low	0	1	0
	Normal	1	25	0
Platelet Count	High	0	1	2
	Unknown	0	1	0
	Normal	1	30	0
Blood Urea Nitrogen	High	0	1	0
	Normal	0	30	0
	High	0	1	1
Creatinine	Normal	0	32	0
	Normal	0	32	0
	Normal	0	31	1
Albumin	Normal	0	29	2
	High	0	1	0
	Normal	1	30	1
Sodium	Normal	0	32	0
	Normal	0	31	1
	Normal	0	29	2
Potassium	Normal	0	29	2
	High	0	1	0
	Normal	1	30	1
Chloride	Normal	1	30	1
	Normal	1	30	1
	Normal	1	30	1

Source: NDA 21852, MCB INT Clinical Study Report Table 46, 47 page 106

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#### 7.4.3 Vital Signs

Vital signs including blood pressure and heart rate were assessed at Screening Visit 2 (SV2), and Day 28 as part of the safety evaluation of Taclonex® Ointment in the pediatric population age 12-17 years. Changes from Baseline to the End- of- Treatment were generally small and not clinically relevant.

No clinically relevant changes in blood pressure or heart rate were found by the clinical reviewer in the assessment of the data collected in the adult population (Review by Brenda Carr, MD dated 1/9/2006, page 72).

#### 7.4.4 Electrocardiograms (ECGs)

The applicant did not conduct cardiac safety monitoring in Trial MCB 0501.

To support approval of Taclonex® Ointment for the treatment of plaque psoriasis in the adult population, the applicant collected ECGs as part of the safety monitoring during Trial MCB 0201 FR (HPA Axis Trial). However, only 12 subjects were exposed to Taclonex® Ointment during that trial.

Both calcipotriene and betamethasone were evaluated for cardiovascular effects in nonclinical studies. No effects were seen on cardiac parameters including ECGs, arterial blood pressure, heart rate or conduction times (e.g. QT interval) following oral dosing to conscious telemetered dogs. However, it is not clear that similar testing was conducted with the combination product. See the Clinical Review by Brenda Carr, M.D. dated 1/9/2006 page 72.

#### 7.4.5 Special Safety Studies/Clinical Trials

The applicant conducted Trial MBL 0501 INT to assess the effect of Taclonex® Ointment on the HPA axis function and calcium metabolism in the pediatric population age 12-17 years. The primary systemic safety assessment was the response to the ACTH-challenge testing. ACTH-challenge testing was performed at Baseline and the final visit (i.e. Week 4) to evaluate HPA axis suppression. An abnormal HPA response was defined as a 30-minute post-stimulation serum cortisol level < 18 micrograms/dL at the End- of- Treatment. No subjects demonstrated an abnormal ACTH-challenge test result.

Per current labeling (Section 12.2), the applicant conducted three trials to assess the effect of Taclonex® Ointment on HPA Axis function in the adult population (Trial MCB 0201 FR, Trial MBL 0404 FR and MCB 0102 INT). In Trial MBL 0404 FR, HPA axis suppression was evaluated in adult subjects (N=32) with extensive psoriasis involving at least 30% of the scalp and 15-30% of the total body surface area. Treatment consisted of once daily application of Taclonex® Topical Suspension on the scalp in combination

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with Taclonex® Ointment on the body for 4 to 8 weeks. Adrenal suppression as indicated by a 30-minute post-stimulation cortisol level  $\leq 18$  mcg/dL was observed in 5 of 32 subjects (15.6%) after 4 weeks of treatment and in 2 of 11 subjects (18.2%) who continued treatment for 8 weeks.

In Trial MCB 0201 FR, HPA axis suppression was evaluated in adult subjects (N=24) with extensive psoriasis involving 15-30% of the total body surface area who were randomized to treatment with Taclonex® Ointment or Diprosone® Ointment. Of eleven subjects who applied Taclonex® Ointment, none demonstrated adrenal suppression as indicated by a 30-minute post-stimulation cortisol level  $\leq 18$  mcg/dL.

Trial MCB 0102 INT was an international (Europe and Canada), multi-center, prospective randomized, double-blind, 3-arm, parallel group 52-week safety trial. A subset of 19 subjects was evaluated for HPA Axis suppression. Among 7 subjects exposed to Taclonex® Ointment and evaluated with ACTH-challenge testing, one subject demonstrated adrenal suppression as indicated by a 30-minute post-stimulation cortisol level  $\leq 18$  mcg/dL. The 60-minute post-stimulation cortisol level was normal.

The results of the assessment of the effect of Taclonex® Ointment on calcium metabolism in the pediatric population age 12-17 years are discussed in Section 7.4.2.

The following changes are recommended for Section 5 of labeling for Taclonex® Ointment. Additions are noted as double underline and deletions are noted as ~~strikethrough~~.

## 5 WARNINGS AND PRECAUTIONS

### (b) (4) Hypercalcemia and Hypercalciuria

#### 5.1

Hypercalcemia and hypercalciuria have been (b) (4) observed with use of Taclonex® Ointment. If hypercalcemia or hypercalciuria develops, treatment should be discontinued until parameters of calcium metabolism have normalized. In the trials that included assessment of the effects of Taclonex® Ointment on calcium metabolism, such testing was done after 4 weeks of treatment. The effects of Taclonex® Ointment on calcium metabolism following treatment durations of longer than 4 weeks have not been evaluated.

#### (b) (4) 5.2 Effects on Endocrine System

(b) (4) Taclonex® Ointment can (b) (4) cause reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for clinical glucocorticosteroid insufficiency. [See Clinical Pharmacology (12.2)] This may occur during treatment or upon withdrawal of (b) (4) treatment. Factors that predispose a patient to HPA axis suppression include the use of high-potency corticosteroids, large treatment surface

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areas, after prolonged use, concomitant use of more than one corticosteroid-containing product, use of occlusive dressings, altered skin barrier, liver failure, and young age. Evaluation for HPA axis suppression may be done by using the adrenocorticotrophic hormone (ACTH) stimulation test.

(b) (4)

In a trial evaluating the effects of Taclonex® Topical Suspension and Taclonex® Ointment on the HPA axis (b) (4)-32 adult subjects (b) (4) were treated with Taclonex® Scalp Topical Suspension on the scalp and Taclonex® Ointment on the body (b) (4). Adrenal suppression was identified in 5 of 32 subjects (15.616%) after 4 weeks of treatment [see Clinical Pharmacology(12.2)]. The effects of Taclonex® Ointment on the HPA axis following treatment durations of longer than 4 weeks have not been adequately studied.

(b) (4)

(b) (4)

If HPA axis suppression is documented, gradually withdraw the drug, reduce the frequency of application, or substitute with a less potent corticosteroid.

Cushing's syndrome and hyperglycemia may, (b) (4) also (b) (4) occur due to systemic (b) (4) effects of topical corticosteroids. These complications are rare and generally occur after prolonged exposure to excessively large doses, especially of high-potency topical corticosteroids. Use of more than one corticosteroid-containing product at the same time may increase the total systemic corticosteroid exposure.

Use of more than one corticosteroid-containing product at the same time may increase the total systemic corticosteroid exposure.

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Pediatric patients may be more susceptible to systemic toxicity from use of topical corticosteroids due to their larger skin surface to body mass ratios [see *Use in Specific Populations (8.4)*].

(b) (4)

### 5.3 Allergic Contact Dermatitis with Topical Corticosteroids

Allergic contact dermatitis to any component of topical corticosteroids is usually diagnosed by a failure to heal rather than a clinical exacerbation. Clinical diagnosis of allergic contact dermatitis can be confirmed by patch testing.

### 5.4 Allergic Contact Dermatitis with Topical Calcipotriene

Allergic contact dermatitis has been observed with use of topical calcipotriene. Clinical diagnosis of allergic contact dermatitis can be confirmed by patch testing.

(b) (4)

### (b) (4) 5.5 Skin Irritation

If irritation develops, treatment with Taclonex® Ointment should be discontinued and appropriate therapy instituted.

(b) (4)

### 5.6 Risks of Ultraviolet Light Exposure

Patients who apply Taclonex® Ointment to exposed skin should avoid excessive exposure to either natural or artificial sunlight, including tanning booths, sun lamps, etc. Physicians may wish to limit or avoid use of phototherapy in patients who use Taclonex® Ointment.

## 7.4.6 Immunogenicity

Immunogenicity was not anticipated in this drug class or evaluated.

## 7.5 Other Safety Explorations

### 7.5.1 Dose Dependency for Adverse Events

In Trial MCB 0501 INT, subjects used the marketed product with the approved dosing regimen. The maximum weekly dose in the pediatric population was 60% of the labeled dose for the adult population. One subject (CRF 1311) applied an average weekly dose greater than 60 g (66.10 g) during the trial (Week 2 to Week 4.) He developed a urinary calcium: creatinine ratio above the normal range at Week 4. See Section 7.4.2. Based on the limited data from subjects exceeding the maximum dose, no analysis of the dose dependency of adverse events is possible.

### 7.5.2 Time Dependency for Adverse Events

The applicant did not design this trial to evaluate time dependency of adverse events.

### 7.5.3 Drug-Demographic Interactions

There were no reports of HPA axis suppression or elevation in albumin- corrected serum calcium to evaluate for drug-demographic interactions. The number of subjects reporting other adverse events ( $\leq 2$  subjects each) and the size of the overall database were insufficient for a meaningful analysis of the frequency of adverse events by age, sex or race.

### 7.5.4 Drug-Disease Interactions

The study population included subjects with a clinical diagnosis of plaque psoriasis which was at least moderate in severity according to Investigator's Global Assessment of disease severity [i.e. IGA  $\geq 3$  on a 6 point scale.] The majority of subjects had moderate disease at Baseline (moderate: 30/33; severe: 3/33). Due to the limited numbers of subjects in the severe group, identification of trends in adverse events by Baseline disease severity is not meaningful.

### 7.5.5 Drug-Drug Interactions

The applicant did not conduct an assessment of drug-drug interactions.

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

The applicant did not evaluate human carcinogenicity as part of the clinical development program in pediatric subjects aged 12 to 17 years. The trials were open label and the duration was insufficient to provide meaningful data.

Nonclinical data regarding carcinogenicity in rats and mice is included in Section 13.1 of labeling. Data from the oral carcinogenicity study with calcipotriene in rats was recently included in current labeling for Taclonex® Ointment (S-016, approved 7/28/2014 with additions noted as double underline) as follows:

#### 13.1 Carcinogenesis, mutagenesis, impairment of fertility

When calcipotriene was applied topically to mice for up to 24 months at dosages of 3, 10, and 30 mcg/kg/day (corresponding to 9, 30, and 90 mcg/m<sup>2</sup>/day), no significant changes in tumor incidence were observed when compared to control.

In a study in which albino hairless mice were exposed to both ultra-violet radiation (UVR) and topically applied calcipotriene, a reduction in the time required for UVR to induce the formation of skin tumors was observed (statistically significant in males only), suggesting that calcipotriene may enhance the effect of UVR to induce skin tumors.

A 104-week oral carcinogenicity study was conducted with calcipotriene in male and female rats at doses of 1, 5 and 15 mcg/kg/day (corresponding to dosages of approximately 6, 30, and 90 mcg/m<sup>2</sup>/day). Beginning week 71, the dosage for high-dose animals of both genders was reduced to 10 mcg/kg/day (corresponding to a dosage of approximately 60 mcg/m<sup>2</sup>/day). A treatment-related increase in benign C-cell adenomas was observed in the thyroid of females that received 15 mcg/kg/day. A treatment-related increase in benign pheochromocytomas was observed in the adrenal glands of males that received 15 mcg/kg/day. No other statistically significant differences in tumor incidence were observed when compared to control. The relevance of these findings to patients is unknown.

When betamethasone dipropionate was applied topically to CD-1 mice for up to 24 months at dosages approximating 1.3, 4.2, and 8.5 mcg/kg/day in females, and 1.3, 4.2, and 12.9 mcg/kg/day in males (corresponding to dosages of up to approximately 26 mcg/m<sup>2</sup>/day and 39 mcg/m<sup>2</sup>/day, in females and males, respectively), no significant changes in tumor incidence were observed when compared to control.



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When betamethasone dipropionate was administered via oral gavage to male and female Sprague Dawley rats for up to 24 months at dosages of 20, 60, and 200 mcg/kg/day (corresponding to dosages of approximately 3, 10, and 30 [REDACTED] (b) (4) mcg/m<sup>2</sup>/day), no significant changes in tumor incidence were observed when compared to control.

### 7.6.2 Human Reproduction and Pregnancy Data

Investigators performed urine pregnancy testing in all female subjects of child bearing potential at Screening (SV2) and Week 4. There were no reports of pregnancies during the conduct of Trial MCB 0501 INT. The post marketing database included a 13-year-old female who experienced a spontaneous abortion. She applied Taclonex® Ointment for one week while pregnant. A causal relationship between the spontaneous abortion and treatment with Taclonex® Ointment is unlikely due to the limited exposure and greater risk of spontaneous abortion in this age group.<sup>1</sup>

Per current labeling, Taclonex® Ointment is Pregnancy Category C. Pregnant and lactating females were excluded from all clinical trials in the adult population. However, the Clinical Reviewer described 5 pregnancies in the development program conducted for approval of the original application. Two pregnancies occurred in the Taclonex® Ointment group, two pregnancies occurred in the calcipotriene group and one pregnancy occurred in the betamethasone group. One subject in the calcipotriene group experienced a spontaneous abortion (outcome considered unrelated) and one subject in the betamethasone group developed polyhydramnios and delivered 3 weeks prematurely. The premature neonate developed jaundice which was considered by the investigator to be unrelated. Two subjects discontinued treatment with and gave birth to healthy babies. The applicant did not provide outcome information for one pregnancy. (Clinical Review by Brenda Carr dated 1/9/2006, page 92).

### 7.6.3 Pediatrics and Assessment of Effects on Growth

The Pediatric Review Committee (PeRC) met on September 10, 2014 to discuss the data submitted by the applicant to fulfill the Postmarketing Requirement (PMR) under PREA attached to the original approval of Taclonex® Ointment (dated January 9, 2006).

The applicant provided an adequate assessment of both local and systemic safety (e.g. HPA axis suppression and changes in calcium metabolism) in the population age 12 to 17 years. In addition, there is an extensive safety database for Taclonex® Ointment in the adult population as well as safety data in the pediatric population age 12 to 17 years for the moiety from the Taclonex® Topical Suspension pediatric trials. Review of the safety data indicates no differences in safety profiles for Taclonex® Ointment in the pediatric and adult populations.

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<sup>1</sup> Andersen, AN et al. Maternal age and fetal loss: population based register linkage study. BMJ

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The findings from Trial MCB 0501 INT were presented to PeRC on September 10, 2014. PeRC concurred with the review team that the assessment of subjects age 12 to 17 years was adequate and supported the revision of the indication to include the pediatric population. The PREA PMR for the topical treatment of plaque psoriasis in pediatric patients age 12 to 17 was fulfilled for this product.

The following changes are recommended for Section 8.4 of labeling. Additions are noted as double underline and deletions are noted as ~~strike through~~.

#### 8.4 Pediatric Use

Safety and effectiveness of the use of Taclonex® Ointment in pediatric patients under the age of 12 years have not been <sup>(b) (4)</sup> established. <sup>(b) (4)</sup>

The safety and effectiveness of Taclonex® Ointment for the treatment of plaque psoriasis have been established in the age group 12 to 17 years. In a prospective, uncontrolled trial, 33 pediatric subjects aged 12-17 years with plaque psoriasis on the body were treated with Taclonex® Ointment for 4 weeks up to a maximum of <sup>(b) (4)</sup> g per week. Subjects were assessed for HPA axis suppression and effects on calcium metabolism. <sup>(b) (4)</sup> No adverse effects on adrenal suppression <sup>(b) (4)</sup> were observed. <sup>(b) (4)</sup>

Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of systemic toxicity when treated with topical drugs. They are, therefore, also at greater risk of HPA axis suppression and adrenal insufficiency upon the use of topical corticosteroids. [See Warnings and Precautions (5.2)]

Rare systemic toxicities such as Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in pediatric patients, especially those with prolonged exposure to large doses of high potency topical corticosteroids.

<sup>(b) (4)</sup>



#### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

##### Overdose

The applicant stated that “no data are available regarding overdose in the adolescent population”. Overdose has been observed in the adult population. See Clinical Review by Brenda Carr dated 1/9/2006, page 93.

##### Drug Abuse Potential

No reports of drug abuse are included in this submission. The applicant stated that “no data are available regarding drug abuse in the adolescent population”.

##### Withdrawal and Rebound

The applicant did not evaluate the potential for withdrawal or rebound in pediatric subjects who use Taclonex® Ointment. The applicant stated that “no data are available regarding withdrawal or rebound in the adolescent population”.

### **7.7 Additional Submissions / Safety Issues**

The applicant submitted a 120-Day Safety Update [June 26, 2014, SD 232 in accordance with 21 CFR 314.50(d) (5)(vi)(b)]. This submission included all the safety data in the global safety database received by the applicant regarding the use of Taclonex® Ointment in the pediatric population (age 0-17 years) from October 1, 2013 to May 31, 2014. These cases include both spontaneous reports and reports from market research programs.

Taclonex® Ointment is currently approved for the topical treatment of psoriasis vulgaris (plaque psoriasis) in adults 18 years of age and older. Thus, all cases of exposure to the product in the pediatric population represent off-label use. A total of 10 patients reported 12 adverse events during the reporting period. All adverse events were characterized as non-serious. Among the 10 cases, eight concerned pediatric patients age 12 to 17 years and the remainder concerned pediatric patients younger than age 12 years.

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In nine cases, the only adverse event included in the report was off-label use. In one case, the report included incorrect drug administration. Table 20 provides a summary of adverse events by MedDRA Preferred Term (PT).

Table 20: Adverse events reported worldwide in the Pediatric Population

SOC	Adverse event (PT)	No. of events
General disorders and administration site conditions	No adverse event	1
Injury, poisoning and procedural complications	Incorrect drug administration duration	1
Surgical and medical procedures	Off label use	10
<b>Total</b>		<b>12</b>

Source: NDA 21852, SD- 232 submitted 6/26/2014, page 2

The data from the 120-Day Safety Update Report regarding exposure to Taclonex® Ointment in the pediatric population (age 0-17 years) is too limited to allow conclusions regarding the safety profile.

## 8 Postmarket Experience

In this submission, the applicant included a summary of safety information in the pediatric population compiled from the global safety database. There were 71 spontaneous post-marketing reports regarding off-label use of Taclonex® Ointment in the pediatric population. Among these 71 cases, 36 cases concerned pediatric patients age 12 to 17 years and the remainder concerned pediatric patients younger than age 12 years. In 41 cases, there were no adverse events except off-label use. The remaining 30 cases included 51 adverse events.

The adverse events experienced by pediatric patients were categorized under 10 different Organ System Classes (SOCs). The majority of adverse events occurred in 3 different SOC. The largest number of adverse events was in the category of "Skin and subcutaneous tissue disorders" (18 events). The 13 events in the SOC of "Injury, poisoning and procedural complications" included drug administered at inappropriate site, drug administration error, incorrect drug administration duration, and inappropriate schedule of drug administration. In the majority of these cases, the patient applied the product for longer than the labelled duration of treatment (i.e. 4 weeks), applied to sites not indicated in labeling (e.g. face, skin folds or palms), or used an unapproved dosing regimen (i.e. twice daily.) The third most common class of adverse events was "General disorders and administration site conditions" (10 events).

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Among the 71 cases, the following four cases included serious adverse events:

1. An 11-year-old patient experienced rebound effect (manifested as pustular psoriasis) when her mother administered an overdose of Taclonex® Ointment without medical supervision.
2. A 13-year-old experienced an abortion. She applied Taclonex® Ointment for one week while pregnant. A causal relationship between the spontaneous abortion and Taclonex® Ointment treatment was unlikely.
3. A 17-year-old male attempted suicide during treatment with Taclonex® Ointment. He had a history of depression. A causal relationship between the attempted suicide and Taclonex® Ointment treatment was unlikely.
4. A 13-year-old experienced hypopigmentation at the Taclonex® Ointment application site. Hypopigmentation is a known adverse event associated with Taclonex® Ointment.

A total of 13 case reports were submitted from sources in the United States. In 3 cases, there were no adverse events except off-label use. In the 10 remaining cases, patients experienced 17 adverse events as follows:

4. Case # 108769: abdominal pain, fatigue and headache
5. Case # 218057: drug administered at inappropriate site, vitiligo, incorrect drug administration duration
6. Case # 216530: drug administration error
7. Case # 216432: incorrect drug administration duration
8. Case # 108474: suicide attempt
9. Case # 106597: nail disorder, nail pitting
10. Case # 223643: rash
11. Case # 106187: rash generalized, swelling face
12. Case # 217378: skin irritation
13. Case # 106602: foot deformity, limb deformity. (A 6 year old pediatric patient was diagnosed with bowed legs and flat feet which the pediatrician assessed as unrelated to exposure to Taclonex® Ointment.

Table 21 includes a summary of the adverse events reported in the pediatric population after initial marketing approval in 2006.

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Table 21: Adverse Events Reported Post-Marketing World-wide in the Pediatric Population

SOC Name	Adverse event (PT)	No.
Gastrointestinal disorders	Abdominal pain	1
General disorders and administration site conditions	Application site discolouration	1
	Drug ineffective	4
	Fatigue	1
	Medication residue (greasy hair)	1
	Pyrexia	1
	Rebound effect	1
	Therapeutic response unexpected	1
Injury, poisoning and procedural complications	Drug administered at inappropriate site	2
	Drug administration error	2
	Inappropriate schedule of drug administration	1
	Incorrect drug administration duration	6
	Maternal exposure during pregnancy	1
	Overdose	1
Investigations	Hepatic enzyme increased	1
Musculoskeletal and connective tissue disorders	Arthralgia	1
	Foot deformity	1
	Limb deformity	1
Nervous system disorders	Headache	1
Pregnancy, puerperium and perinatal conditions	Abortion spontaneous	1
Psychiatric disorders	Intentional drug misuse	1
	Suicide attempt	1
Skin and subcutaneous tissue disorders	Hair texture abnormal	2
	Leukoderma	1
	Nail disorder	1
	Nail pitting	1
	Pain of skin	1
	Psoriasis	2
	Pustular psoriasis	1
	Rash	1

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SOC Name	Adverse event (PT)	No.
	Rash generalised	1
	Skin depigmentation	2
	Skin irritation	2
	Skin striae	1
	Swelling face	1
	Vitiligo	1
Surgical and medical procedures	Product used for unknown indication	1
Total		51

Source: NDA 21852, SD 219, Module 5.3.6, page 4

The post marketing data in the pediatric population is limited. The adverse event profile in the pediatric population appears to be similar to the adult population.

The following changes are recommended for section 6.2 of labeling. Additions are noted as double underline and deletions are noted as ~~strikethrough~~.

#### 6.2 Postmarketing Experience

The following adverse reactions associated with the use of Taclonex® Ointment have been identified post-approval: pustular psoriasis and rebound effect.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Postmarketing reports for local adverse reactions to topical corticosteroids may also include: dryness, acneiform eruptions, perioral dermatitis, secondary infection and miliaria.

## **9 Appendices**

### **9.1 Literature Review/References**

Literature references are included as footnotes within the review document.

### **9.2 Labeling Recommendations**

The applicant submitted labeling which was reviewed and modified to be consistent with current recommendations regarding the content and format of labeling for corticosteroid products. The following sections of the revised draft labeling include significant changes:

The following sections of the revised draft labeling include significant changes:

- 1 INDICATIONS AND USAGE (See Section 6.1 of this review)
- 2 DOSAGE AND ADMINISTRATION (See Section 7.2.1 of this review)
- 5 WARNINGS AND PRECAUTIONS (See Section 7.4.5 of this review)
- 6 ADVERSE REACTIONS (See Section 8 of this review)
- 8 USE IN SPECIFIC POPULATIONS (See Section 7.6.3 of this review)
- 12 CLINICAL PHARMACOLOGY (See Section 4.4.2 of this review)
- 14 CLINICAL STUDIES (See Section 6.1.5 of this review)

### **9.3 Advisory Committee Meeting**

The Agency conducted no Advisory Committee Meetings regarding this sNDA application.



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## 9.4 Financial Disclosure

### Clinical Investigator Financial Disclosure Review Template

Application Number: NDA 21852

Submission Date(s): 2/26/2014

Applicant: LEO Pharmaceuticals

Product: Taclonex® Ointment

Reviewer: Melinda McCord

Date of Review: 10/6/2014

Covered Clinical Study: MCB 0501 INT

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: The applicant provided data from 7 study sites in the US and provided the names of the investigators.		
Number of investigators who are applicant employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in applicant of covered study: _____</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information

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minimize potential bias provided:		from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

The applicant completed FDA Form 3454 and certified that they have not entered into any financial arrangements with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The applicant provides a list of investigators who have completed the financial disclosure forms and certified that they have no financial interests/arrangements with the applicant. The applicant adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MELINDA L MCCORD  
10/06/2014

GORDANA DIGLISIC  
10/06/2014