Department of Health and Human Services
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review

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Product Name:	Taclonex (betamethasone dipropionate/calcipotriene hydrate) 0.064%/0.005%
Pediatric Labeling Approval Date:	August 29, 2014 (topical suspension) December 23, 2014 (topical ointment)
Application Type/Number:	NDA 021852 (topical ointment) NDA 022185 (topical suspension)
Applicant/Sponsor:	LEO Pharma AS
OSE RCM #:	2017-62

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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) and the Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports and drug utilization data for Taclonex (betamethasone dipropionate/calcipotriene hydrate) 0.064%/0.005% topical ointment and topical suspension in pediatric patients.

Taclonex topical ointment was approved on January 9, 2006 for the treatment of psoriasis vulgaris in adults aged 18 years and older. The approved pediatric indication is for plaque psoriasis in ages 12 and older.

Taclonex topical suspension was approved on May 9, 2008 for the topical treatment of moderate to severe psoriasis vulgaris of the scalp in adults aged 18 years and above. On October 17, 2012, the FDA approved Taclonex suspension for the treatment of plaque psoriasis of the body in adults. The approved pediatric indication is for plaque psoriasis of the scalp in patients 12 and older.

Drug utilization for Taclonex ointment (brand and generic) and suspension was assessed in the U.S. outpatient retail pharmacy setting from August 1, 2014 through February 28, 2017. Approximately 227,000 patients received a dispensed prescription for Taclonex ointment (brand or generic) or suspension for the review period. The pediatric population aged 0-17 years accounted for 3% of patients (7,879 patients) with a dispensed prescription for Taclonex ointment or suspension. Patients aged 12-17 years accounted for 75% of pediatric patients (5,959 patients) and patients aged 0-11 years accounted for the remaining 25% of pediatric patients (1,976 patients). Although the data showed off-label use of Taclonex ointment and suspension in pediatric patients under 12 years of age, this use cannot be validated due to the lack of access to medical records.

The Division of Pharmacovigilance (DPV) did not identify new safety signals or evidence of increased severity or unexpected frequency of labeled adverse events in the pediatric population in the FDA Adverse Event Reporting System (FAERS) cases. We searched FAERS from the initial approval of betamethasone dipropionate/calcipotriene hydrate in adults and identified eight pediatric cases. No deaths in the patients using betamethasone dipropionate/calcipotriene hydrate were reported.

Seven cases reported serious outcomes. However, in all of these cases the adverse events are either captured in the Taclonex labeling, or there was limited evidence of an association of the events with Taclonex use. Two cases reported dermatologic events, and the remaining five cases reported events related to other organ systems. None of the cases reporting unlabeled events provided information suggesting the need for additional evaluation or changes to labeling.

We did not identify evidence of pediatric safety concerns with betamethasone dipropionate/calcipotriene hydrate at this time. DPV will continue pharmacovigilance monitoring for betamethasone dipropionate/calcipotriene hydrate.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Taclonex ointment (NDA 021852) is a combination of betamethasone dipropionate 0.064%, a corticosteroid, and calcipotriene hydrate 0.005%, a vitamin D analog. The FDA approved Taclonex ointment on January 9, 2006 for the treatment of psoriasis vulgaris in adults aged 18 years and older for up to four weeks. It is marketed in 60 and 100 gram (g) tubes.

On December 23, 2014, the FDA approved Taclonex ointment for use in patients 12 to 17 years of age with plaque psoriasis. The risk benefit assessment in the pediatric patient population was based on adequate and well-controlled trials in adults, and supported by the analysis from 1 uncontrolled clinical trial designed to assess systemic safety by evaluating hypothalamic-pituitary-adrenal (HPA) axis function and calcium metabolism in pediatric subjects with plaque psoriasis. Efficacy was extrapolated from the adult population, because the pathophysiology and response to treatment are similar between the two populations. In the pediatric trial, 33 subjects from 12 to 17 years of age with at least moderate psoriasis, and involvement of 5 to 30% of body surface area (BSA), applied a maximum of 60 g of Taclonex ointment per week for up to 28 days.[1] The subjects all had normal HPA axis function at baseline. There were no deaths, serious adverse events, pregnancies, withdrawal of any subject from the trial due to an adverse event, or subjects that experienced HPA axis suppression. There were no cases of hypercalcemia or clinically relevant changes in urinary calcium, although in 1 subject with a normal baseline urinary calcium:creatinine ratio, the ratio increased above the normal range. The clinical significance of this finding was unknown.

Taclonex topical suspension (betamethasone dipropionate 0.064%/calcipotriene hydrate 0.005%; NDA 022185) was approved on May 9, 2008 for the treatment of moderate to severe psoriasis vulgaris of the scalp in adults aged 18 years and above. On October 17, 2012, the FDA approved Taclonex suspension for the treatment of plaque psoriasis of the body in adults. It is marketed in bottles containing 60 g, in packages containing 1 or 2 bottles.

On August 29, 2014, the FDA approved the use of Taclonex suspension for the treatment of plaque psoriasis of the scalp in patients 12 to 17 years of age. The risk benefit assessment in the pediatric population was based on efficacy and safety data extrapolated from adult trials, and two uncontrolled clinical trials in pediatric subjects that assessed safety by evaluating HPA axis function and calcium metabolism. Efficacy was extrapolated from the adult trials. In the pediatric trials, 31 subjects from 12 to 17 years of age with at least moderate plaque psoriasis of the scalp and at least 20% involvement of the scalp area applied Taclonex suspension once daily for up to 8 weeks. There were no deaths, serious adverse events, pregnancies, or specific safety concerns regarding the pediatric population identified in the trial. Of the 30 subjects who completed adrenocorticotropic hormone (ACTH) challenge, 1 subject showed laboratory evidence of adrenal suppression at Week 4. The subject was asymptomatic, treatment was discontinued, and at Week 8, a repeat ACTH was normal.[2]

The combination of betamethasone dipropionate 0.064% and calcipotriene 0.005% is also marketed as Enstilar aerosol foam under NDA 207589. The FDA approved Enstilar on October 16, 2015 for the topical treatment of plaque psoriasis in patients 18 years of age and older. An

open-label pediatric study of Enstilar in subjects 12 years to 16 years and 11 months with plaque psoriasis of the scalp and body is ongoing.

Betamethasone dipropionate and calcipotriene are also marketed separately in various formulations.

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

The following is excerpted from the Taclonex ointment labeling.[3] The language for the Taclonex suspension labeling is similar, except that it includes a subheading for eye irritation, rather than skin irritation, in WARNINGS AND PRECAUTIONS.[4]

> CONTRAINDICATIONS
> None.
>
> WARNINGS AND PRECAUTIONS
> *Hypercalcemia and Hypercalciuria*
> Hypercalcemia and hypercalciuria have been observed with use of Taclonex® Ointment. If hypercalcemia or hypercalciuria develops, treatment should be discontinued until parameters of calcium metabolism have normalized.
>
> *Effects on Endocrine System*
> Taclonex® Ointment can cause reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for clinical glucocorticosteroid insufficiency. This may occur during treatment or upon withdrawal of treatment. Factors that predispose a patient to HPA axis suppression include the use of high-potency corticosteroids, large treatment surface areas, prolonged use, concomitant use of more than one corticosteroid-containing product, use of occlusive dressings, altered skin barrier, liver failure, and young age.
>
> In a trial evaluating the effects of Taclonex® Topical Suspension and Taclonex® Ointment on the HPA axis, 32 adult subjects were treated with Taclonex® Topical Suspension on the scalp and Taclonex® Ointment on the body. Adrenal suppression was identified in 5 of 32 subjects (15.6%) after 4 weeks of treatment.
>
> 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 also occur due to the systemic effects of topical corticosteroids. These complications are rare and generally occur after prolonged exposure to excessively large doses, especially of high-potency topical corticosteroids.
>
> Pediatric patients may be more susceptible to systemic toxicity due to their higher skin surface to body mass ratios.
>
> *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.

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.

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

Risk 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.

USE IN SPECIFIC POPULATIONS
Pregnancy

- Teratogenic Effects: Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Taclonex® Ointment should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus. Animal reproduction studies have not been conducted with Taclonex® Ointment. Taclonex® Ointment contains calcipotriene that has been shown to be fetotoxic and betamethasone dipropionate that has been shown to be teratogenic in animals when given systemically.

Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels.

Nursing Mothers
Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects.

It is not known whether topically administered calcipotriene or corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk.

Because many drugs are excreted in human milk, caution should be exercised when Taclonex® Ointment is administered to a nursing woman.

2 DRUG UTILIZATION DATA

2.1 METHODS AND MATERIALS

Proprietary databases available to the Agency were used to conduct the drug utilization analyses in this review (see **Appendix A** for full database descriptions and limitations).

2.1.1 Determining Settings of Care

The QuintilesIMS National Sales Perspectives™ database was used to determine the various retail and non-retail channels of distribution for Taclonex ointment (brand and generic) and suspension. Sales data for the period of August 2014 through February 2017 indicated that approximately 88% of packages were distributed to U.S. outpatient retail pharmacies; 8% were to non-retail settings; and 4% were to mail-order/specialty pharmacies.[5] As a result, only U.S. outpatient retail pharmacy utilization patterns were examined. Data from mail-order/specialty and non-retail settings were not included in this analysis.

2.1.2 Data Sources Used

The QuintilesIMS Total Patient Tracker™ (TPT) database was used to provide national estimates of patients with a Taclonex ointment (brand and generic) or suspension prescription dispensed from U.S. outpatient retail pharmacies from August 1, 2014 through February 28, 2017, cumulative.

2.2 RESULTS

2.2.1 Number of Patients

Table 2.2.1

Nationally estimated number of patients who received a dispensed prescription for Taclonex from U.S. outpatient retail pharmacies, stratified by patient age*, August 2014 - Feb 2017

	Aug 2014 - Feb 2017	
	Patient Count	***Share***
	N	***%***
Taclonex topical ointment† and suspension	**226,866**	***100.0%***
Age 0-17 years	**7,879**	***3.5%***
Age 0-11 years	1,976	*25.1%*
Age 12-17 years	5,959	*75.6%*
Age 18+ years	218,908	*96.5%*
Unknown Age	2,355	*1.0%*

*Source: QuintilesIMS Total Patient Tracker. Aug 2014 - Feb 2017. Extracted May 2017. File: TPT 2017-62 Taclonex by age 5-23-17.xlsx *Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients 0-17 years of age include patients less than 18 years of age (17 years and 11 months).*

Subtotals may not sum exactly, due to rounding. Patients may have received multiple administrations of a drug during the study period and due to aging of patients during the study period, patients may be counted more than once across age groups. For this reason, summing is not advisable and will result in overestimates of patient counts.

† Includes brand and generic products

3 POSTMARKET ADVERSE EVENT REPORTS

3.1 METHODS AND MATERIALS

3.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

The Division of Pharmacovigilance (DPV) searched the FAERS database with the strategy described in Table 3.1.1. See Appendix B for a description of the FAERS database.

Table 3.1.1 FAERS Search Strategy

Date of Search	May 16, 2017
Time Period of Search	January 9, 2006* - February 28, 2017
Search Type	FBIS Quick Query
Product Terms	Product Active Ingredient: Betamethasone dipropionate\calcipotriene, Betamethasone dipropionate\calcipotriene hydrate, Betamethasone dipropionate\calcipotriene\calcipotriene hydrate, Betamethasone\calcipotriene
Search Parameters	All ages, all outcomes, worldwide

* *U.S. Approval date for Taclonex ointment*

3.2 RESULTS

3.2.1 Total number of FAERS reports by Age

Table 3.2.1 Total adult and pediatric FAERS reports* from January 9, 2006 to February 28, 2017 with Taclonex (betamethasone dipropionate/calcipotriene hydrate) 0.064%/0.005% topical suspension and topical ointment

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥18 years)	309 (109)	235 (41)	4 (0)
Pediatrics (0 to <18 years)	**12 (5)**	10 (3)	2 (0) ‡

* *May include duplicates and transplacental exposures; reports have not been assessed for causality.*

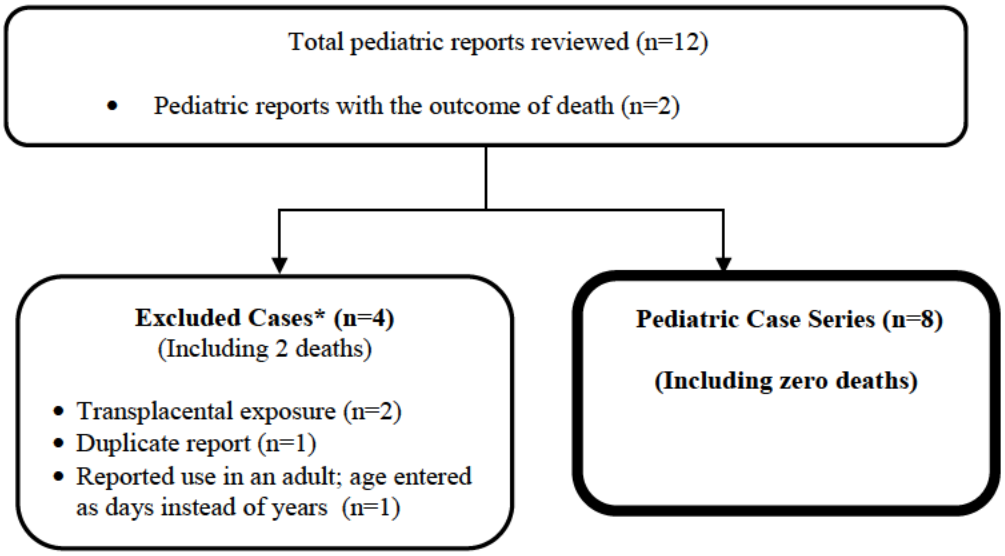
† *For the purposes of this review, the following outcomes qualify as serious:* ***death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.***

‡ ***The two reports of pediatric deaths were transplacental exposures identified from reports not reporting an age.***

3.2.2 Selection of Pediatric Cases in FAERS

We identified 12 pediatric reports (See Table 3.2.1). See **Figure 3.2.2** below for the specific selection of cases to be summarized in **Sections 3.3 and 3.4.**

Figure 3.2.2 Selection of Pediatric Cases with Taclonex (betamethasone dipropionate/calcipotriene hydrate) topical ointment and topical suspension.



* DPV reviewed these cases, but they were excluded from the case series for the reasons listed above

3.3 Summary of Fatal Pediatric Adverse Event Cases (N=0)

There were no cases reporting death in patients using betamethasone/calcipotriene in this case series.

3.4 Summary of Non-Fatal Pediatric Adverse Event Cases (N=8)

One case was not coded with a serious outcome. It reported the use of Enstilar foam in a 17-year-old, and did not report an adverse event. This was the only case reporting the use of Enstilar. A summary of the remaining seven cases, including the FAERS case and version numbers, the year initially received by FDA, source of the report (U.S. or foreign), type of report, and coded outcome, is provided below. Appendix C lists all FAERS case and version numbers, Manufacturer Control Numbers, and duplicate case numbers.

3.4.1 *Cases with serious outcomes reporting dermatologic adverse events (N=2)*

We identified two cases reporting dermatologic events in association with the use of betamethasone/calcipotriene.

FAERS Case #6069069 Version 2, 2006, Foreign, Expedited, Hospitalized
An 11-year-old male experienced biopsy-confirmed *generalized pustular psoriasis* after discontinuing betamethasone/calcipotriene (formulation not specified) for treatment-resistant plaque psoriasis involving between 30 and 40% of BSA. His medical history also included gastroesophageal reflux. Concomitant medication included diflucortolone/salicylic acid cream for use on the scalp. One tube (size not specified) of betamethasone/calcipotriene per month was

prescribed, but the patient used four to five tubes in one month, without medical supervision. His symptoms, which also included *arthralgia*, *fever*, and *cutaneous pain*, began an unspecified time, described as "quickly," after the betamethasone/calcipotriene was discontinued. His *white blood cell count and C-reactive protein were increased*. Other laboratory values, including *Mycoplasma* serology, anti-streptodornase antibodies, and anti-streptolysin antibodies, were within normal limits. He was hospitalized and treated with potassium permanganate baths, cold cream, acetaminophen, antihistamines, and oral antibiotics. His symptoms improved, and treatment with acitretin was started.

Reviewer's comment: Betamethasone/calcipotriene ointment and suspension are not indicated for use in patients less than 12 years of age, or in doses exceeding 60 g per week in patients 12 to 17 years of age. The suspension is indicated only for use on the scalp in patients 12 to 17 years of age. The dose used was 4 to 5 times the prescribed dose, and may have been higher than the recommended pediatric dose. Pustular psoriasis and rebound effect are included in the Postmarketing Experience section of the ointment labeling. Pustular rash is included in the Clinical Trials Experience section of the suspension labeling. Although this case describes a close temporal association to the discontinuation of betamethasone/calcipotriene, and pustular psoriasis has been reported with both the use and withdrawal of some topical and systemic drugs, including corticosteroids, other potential precipitating factors, including infection, have also been reported.[6] The patient's associated symptoms, including arthralgia, fever, and skin pain, are consistent with the clinical manifestations of generalized pustular psoriasis.[6]

FAERS Case # 10915871 Version 3, 2015, Foreign, Expedited, Other serious
A 14-year-old female developed a *pustular and pruritic rash* on the face, and *erythema* and *edema* of the eyelid 5 months after starting betamethasone/calcipotriene for psoriasis. The report did not specify the formulation used or the area of application. She had no adenopathy or mucus membrane involvement, and her general condition was good. Her medical history included psoriatic arthritis. Concomitant medication included methotrexate 15 mg weekly. Previous medication included cyclosporine, which was discontinued 5 months earlier, when methotrexate and betamethasone/calcipotriene were started. Laboratory results, including polymerase chain reaction for herpes simplex virus and herpes zoster virus, were negative. Methotrexate and betamethasone/calcipotriene were discontinued, and she was treated with acyclovir and pristinamycin. She recovered. Methotrexate was reintroduced two months later, with no recurrence of pustular rash or edema.

Reviewer's comment: The labeling for Taclonex ointment includes local reactions such as allergic contact dermatitis, pustular rash, erythema, skin irritation, pustular psoriasis, pruritus and secondary infection. The labeling for Taclonex suspension includes allergic contact dermatitis, pustular rash, exacerbation of psoriasis, skin irritation, application site pruritus, and secondary infection. We consider the events described in this case to be adequately labeled.

3.4.2 *Cases with serious outcomes reporting other adverse events (N=5)*

The remaining cases reported events related to other organ systems.

FAERS Case # 6714223 Version 2, 2008, Foreign, Expedited, Other serious

A neonate born at 33 weeks gestation with *mild growth retardation* experienced *hypercalcemia* approximately two weeks after birth, and ten days after starting to breastfeed. He was *receiving nasal continuous positive airway pressure ventilation*, and his weight was 3.4 pounds. His mother started using betamethasone/calcipotriene ointment sparingly six months before his birth for extensive psoriasis of the trunk; it was unknown if her breasts were affected. The mother, who had severe psoriasis with arthropathy, was also taking codeine, labetalol, tramadol, and prednisolone, which were reported as starting on the day of the baby's delivery. Either the mother or the neonate was taking a multivitamin supplement that included ergocalciferol, Phosphate Sandoz (potassium bicarbonate, sodium bicarbonate, sodium phosphate monobasic), and cefotaxime. The mother was reported to be normocalcemic. Ten days after starting to breastfeed, the baby's calcium level (reported as a corrected calcium with no albumin concentration provided; normal range reported as 2.14-2.52 mmol/L) was 2.55 mmol/L, and one week later was 2.9 mmol/L. His *phosphate concentration* (normal range 0.84-1.45 mmol/L) was normal for the first week after breastfeeding started, then *increased* to 2.07 on Day 8 of breastfeeding. The mother's betamethasone/calcipotriene was changed to clobetasol, and the multivitamin was discontinued. Breastfeeding was stopped one month after it started, when the mother started an unspecified medication. The baby was discharged. Two weeks after breastfeeding was stopped, the *baby's calcium (2.59 mmol/L) and phosphate (2.18 mmol/L) continued to be elevated*. The baby was later readmitted for a possible *seizure* and *apnea*, and was discharged on an anticonvulsant. Calcium and phosphate concentrations during that admission were not provided.

Reviewer's comment: The labeling for Taclonex states that it should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus, and advises caution if used in nursing mothers (see Section 1.2). The labeling also includes a Warning for hypercalcemia. Hyperphosphatemia is not labeled. The role of betamethasone/calcipotriene is difficult to assess in this case, because of the concomitant use of oral ergocalciferol and sodium phosphate, lack of information on the nutrition provided before and after breastfeeding, and the continued increased calcium and phosphate concentrations after the breastfeeding and the mother's betamethasone/calcipotriene were stopped.

FAERS Case # 6870202 Version 1, U.S., Expedited, Other serious

A 17-year-old male attempted suicide by taking 7 acitretrin capsules (strength not specified) and an unspecified amount of an over-the-counter product containing acetaminophen, aspirin, and caffeine. He weighed 53 kg, and used betamethasone/calcipotriene ointment and acitretin for the previous 4 months for the treatment of psoriasis. He received an unspecified treatment in the emergency room, but was not admitted. Acitretin was discontinued, and the action taken for betamethasone/calcipotriene was not reported. According to the patient's mother, the patient experienced depression and threatened suicide during a previous course of acitretin therapy. No additional follow-up was provided.

Reviewer's comment: The labeling for the Taclonex products does not include depression or suicidal ideation and behavior (SIB). The labeling for acitretin, which is approved for use in adults, includes depression, suicidal thoughts, suicidal behavior, and self-injurious behavior.[7] *Psoriasis may be a risk factor for depression and suicidality.*[8] *Based on other potential risk factors for SIB in this case, the role of betamethasone/calcipotriene is difficult to assess.*

FAERS Case # 8478860 Version 1, Foreign, Expedited, Other serious
A 13-year-old female was started on betamethasone/calcipotriene ointment approximately two months after becoming pregnant. One week later, the *fetus was noted to be dead* at a pregnancy follow-up visit. Her medical history included psoriasis for approximately one year. No other concomitant medication was reported. An abortion was performed.

Reviewer's comment: The labeling for Taclonex ointment states that it should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus. The labeling states that betamethasone dipropionate was shown to be teratogenic in animals when administered systemically at relatively low doses, and that calcipotriene was shown to be fetotoxic in animals when given systemically. A partial listing of this information is included above in Section 1.2; the labeling also includes information from animal studies.[3] *The case report does not state when the status of the fetus was last assessed relative to the start of betamethasone/calcipotriene, or if the patient received any treatment for her psoriasis prior to the start of betamethasone/calcipotriene. The incidence of miscarriage in clinically recognized pregnancies up to 20 gestational weeks is 8-20%.*[9]

FAERS Case # 10412253 Version 2, 2014, Foreign, Expedited, Hospitalized
A 10-year-old female woke up during the night with *tremor, myoclonus, and fasciculations* of the lower limbs, which "oscillated around a position" 19 months after starting betamethasone/calcipotriene ointment for psoriasis. No other medical history or information about concomitant medication use was provided. She was hospitalized, and neurological examination did not reveal any abnormalities. Laboratory evaluation, including complete blood count, 15-hydroxyvitamin D_3, parathyroid hormone levels, and electrolytes including phosphorus and magnesium, were reported as normal. The symptoms resolved after 12 hours and the patient was discharged. Betamethasone/calcipotriene was discontinued. No additional follow-up was provided.

Reviewer's comment: Taclonex ointment is not approved for use in patients less than 12 years of age. It is not labeled for tremor, myoclonus, fasciculations, or related events. The association between the event and betamethasone/calcipotriene use is difficult to assess, because of the delayed time to onset and lack of follow-up information.

FAERS Case # 10518720 Version 2, 2014, U.S., Expedited, Other serious
A 15-year-old female experienced *hematuria* an unspecified time after starting Taclonex suspension to the scalp for an unspecified indication. Medical history, concomitant medication, and the frequency and duration of betamethasone/calcipotriene use were not provided. The report did not describe the severity or duration of the hematuria, or provide information on diagnostic evaluation of the event. The action taken for betamethasone/calcipotriene was not reported, and no additional follow-up was provided.

Reviewer's comment: Hematuria is not a labeled event for the Taclonex products. This case does not provide sufficient information to assess the event and its association with betamethasone/calcipotriene use.

4 DISCUSSION

Drug utilization for Taclonex ointment and suspension was assessed in the U.S. outpatient retail pharmacy setting. The pediatric population aged 0-17 years accounted for 3% of patients with a dispensed prescription for Taclonex ointment (brand or generic) or suspension from August 2014 through February 2017, the majority of whom were aged 12-17 years. Although the data showed off-label use of Taclonex ointment and suspension in pediatric patients under 12 years of age, this use cannot be validated due to the lack of access to medical records.

DPV did not identify new safety signals or evidence of increased severity or unexpected frequency of labeled adverse events in the pediatric population in the FAERS cases. We searched FAERS from the initial approval of betamethasone dipropionate/calcipotriene hydrate in adults and identified eight pediatric cases. No deaths in the patients using betamethasone dipropionate/calcipotriene hydrate were reported. Three of the cases were reported from the U.S. Two of the five foreign cases reported use in children younger than 12 years of age.

Seven of the eight cases reported serious outcomes, and were reported during the use of Taclonex products. However, in all of these cases, the adverse events are either captured in the Taclonex labeling, or there was limited evidence of an association of the events with Taclonex use. Of the two cases reporting dermatologic events, one reported use in a patient below the approved pediatric age, at a dose in excess of the prescribed dose. Although we could not determine which formulation was used in either of these two cases, the events appear to be adequately captured in the product labeling.

The betamethasone/calcipotriene labeling includes information on the risks of use in pregnancy and lactation. In the case reporting possible transplacental exposure followed by possible exposure from breastmilk or secondary skin to skin transfer, the concurrent hypercalcemia and hyperphosphatemia are difficult to assess, and could potentially be related to other iatrogenic causes, including the multivitamin, a phosphate-containing product, or nutrition. This case and the case reporting a miscarriage in a 13-year-old do not suggest the need for labeling changes.

Three of the remaining four cases reported events for which there is no related labeling for betamethasone/calcipotriene. The three cases reported a suicide attempt, hematuria, and tremor, myoclonus, and fasciculations, and did not provide follow-up information or strong evidence of an association between the event and the use of betamethasone/calcipotriene. The last case reported a non-serious outcome, did not report an adverse event, and described the use of Enstilar foam in a 17-year-old. At this time, Enstilar foam is approved for use in patients 18 years of age and older in the U.S.

5 CONCLUSION

We did not identify evidence of pediatric safety concerns with betamethasone dipropionate/calcipotriene hydrate at this time.

6 RECOMMENDATIONS

DPV will continue pharmacovigilance monitoring for betamethasone dipropionate/calcipotriene hydrate.

7 REFERENCES

1 McCord M. NDA 21852 Clinical Review: Taclonex Ointment Supplement 15. October 6, 2014.

2 McCord M. NDA 22185 Clinical Review: Taclonex Topical Suspension Supplement 18. July 7, 2014.

3 Taclonex Ointment Prescribing Information. LEO Pharma Inc. Madison, NJ. January 2017.

4 Taclonex Suspension Prescribing Information. LEO Pharma Inc. Parsippany, NJ. January 2017.

5 QuintilesIMS, National Sales Perspectives™. August 2014-February 2017. Extracted May 2017. NSP 2017-62 Taclonex channels 5-4-17.xlsx

6 Kalb RE. Pustular psoriasis: pathogenesis, clinical manifestations, and diagnosis. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Accessed May 9, 2017.

7 Soriatane Capsule Prescribing Information. Stiefel Laboratories, Inc. Research Triangle Park, NC. May 2015.

8 Takeshita J, Grewal S, Langan SM, Mehta NN, Ogdie A, Van Voorhees AS, Gelfand JM. Psoriasis and comorbid diseases. J Am Acad Dermatol. 2017; 76:393-403.

9 Tulandi T. Spontaneous abortion: risk factors, etiology, clinical manifestations, and diagnostic evaluation. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Accessed April 21, 2017.

8 APPENDICES

8.1 APPENDIX A. DRUG UTILIZATION DATABASE DESCRIPTIONS/LIMITATIONS

QuintilesIMS, National Sales Perspectives™: Retail and Non-Retail

The QuintilesIMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

QuintilesIMS, Total Patient Tracker™ (TPT)

Total Patient Tracker (TPT) is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 2.1 billion prescription claims per year.

Subtotals may not sum exactly, due to rounding. Patients may have received multiple administrations of a drug during the study period and due to aging of patients during the study period, patients may be counted more than once across age groups. For this reason, summing is not advisable and will result in overestimates of patient counts.

8.2 APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

8.3 APPENDIX C. FAERS CASE NUMBERS, FAERS VERSION NUMBERS, AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASE SERIES WITH TACLONEX (N=8)

FAERS Case Number	FAERS Version Number	Manufacturer Control Number
Enstilar foam non-serious case (n=1)		
12849515	1	US-LEO PHARMA-244296
Taclonex cases coded with serious outcomes (n=7)		
6069069	2	105292
6714223	2	08-001114
6870212 (Duplicate: 6945092)	1 (Duplicate: 1)	2008S1000544 (Duplicate: 09-000293)
8478860	1	216975
10412253	2	FR-LEO PHARMA-229411
10518720	2	US-LEO PHARMA-224566
10915871	3	FR-LEO PHARMA-233015

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/s/

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