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

# Pediatric Postmarketing Pharmacovigilance Review

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|---|---|
| **Date:** | October 24, 2023 |
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| **Product Names:** | Taclonex (calcipotriene/betamethasone dipropionate) topical suspension<br>Enstilar (calcipotriene/betamethasone dipropionate) foam |
| **Pediatric Labeling Approval Dates:** | July 25, 2019 (Taclonex)<br>July 30, 2019 (Enstilar) |
| **Application Type/Number:** | NDA 022185 (Taclonex)<br>NDA 207589 (Enstilar) |
| **Applicant:** | LEO Pharma |
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## EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Taclonex (calcipotriene/betamethasone dipropionate) topical suspension and Enstilar (calcipotriene/betamethasone dipropionate) foam in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with calcipotriene/betamethasone dipropionate in pediatric patients.

Taclonex and Enstilar are fixed combination products that include calcipotriene, a vitamin D analog, and betamethasone dipropionate, a corticosteroid. Taclonex suspension is indicated for the topical treatment of plaque psoriasis of the scalp and body in patients ≥12 years. Enstilar foam is indicated for the topical treatment of plaque psoriasis in patients ≥12 years.

This review was prompted by approval of pediatric labeling on July 25, 2019, for Taclonex topical suspension (NDA 022185) and July 30, 2019, for Enstilar foam. Both pediatric labeling expanded the respective products' indications to include pediatric patients aged 12 years and older.

The Office of Surveillance and Epidemiology (OSE) previously evaluated postmarketing adverse event reports with calcipotriene/betamethasone dipropionate products in pediatric patients. OSE's evaluation, dated, June 28, 2017, did not identify any new safety concerns and recommended return to routine monitoring for adverse events with calcipotriene/betamethasone dipropionate.

DPV reviewed all serious FAERS reports with calcipotriene/betamethasone dipropionate in pediatric patients less than 18 years of age from March 1, 2017 – July 11, 2023, and 12 reports were identified; however, all reports were excluded from further discussion.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with calcipotriene/betamethasone dipropionate in pediatric patients less than 18 years of age. DPV will continue to conduct routine pharmacovigilance monitoring for calcipotriene/betamethasone dipropionate.

# 1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Taclonex (calcipotriene/betamethasone dipropionate) topical suspension and Enstilar (calcipotriene/betamethasone dipropionate) foam in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with calcipotriene/betamethasone dipropionate in pediatric patients.

## 1.1 PEDIATRIC REGULATORY HISTORY[1,2]

Taclonex and Enstilar are fixed combination products that include calcipotriene, a vitamin D analog, and betamethasone dipropionate, a corticosteroid. Table 1 describes the initial United States (U.S.) approval dates and current approved indications for both combination products.

**Table 1. U.S. Approval Dates and Current Indications for Taclonex and Enstilar**

| Product Name | Formulation | Application | Initial U.S. Approval Date | Current Indication |
|---|---|---|---|---|
| Taclonex[3] | Ointment | NDA 021852 | 1/9/2006 | Topical treatment of plaque psoriasis in patients ≥12 years |
| Taclonex[1] | Suspension | NDA 022185 | 5/9/2008 | Topical treatment of plaque psoriasis of the scalp and body in patients ≥12 years |
| Enstilar[2] | Foam | NDA 207589 | 10/16/2015 | Topical treatment of plaque psoriasis in patients ≥12 years |

This review was prompted by approval of pediatric labeling on July 25, 2019, for Taclonex topical suspension (NDA 022185) and July 30, 2019, for Enstilar foam. Both pediatric labeling expanded the respective products' indications to include pediatric patients aged 12 years and older. The safety and effectiveness of Taclonex and Enstilar have not been established in patients younger than 12 years.

The Office of Surveillance and Epidemiology (OSE) previously evaluated postmarketing adverse event reports with calcipotriene/betamethasone dipropionate products in pediatric patients. OSE's evaluation, dated, June 28, 2017, did not identify any new safety concerns and recommended return to routine monitoring for adverse events with calcipotriene/betamethasone dipropionate.

## 1.2 RELEVANT LABELED SAFETY INFORMATION

The Taclonex and Enstilar labeling contain the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection of the respective labeling. For additional labeling information, please refer to the full prescribing information.

**Taclonex topical suspension:[1]**

---------- WARNINGS AND PRECAUTIONS ----------

- Hypercalcemia and Hypercalciuria: Hypercalcemia and hypercalciuria have been reported. If either occurs, discontinue until parameters of calcium metabolism normalize. (5.1)
- Effects on Endocrine System: Can cause reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency during and after withdrawal of treatment. Risk factors include the use of high-potency topical corticosteroid, use over a large surface area or to areas under occlusion, prolonged use, altered skin barrier, liver failure, and use in pediatric patients. Modify use should HPA axis suppression develop. (5.2, 8.4)
- Ophthalmic Adverse Reactions: May increase the risk of cataracts and glaucoma. If visual symptoms occur, consider referral to an ophthalmologist. (5.5)

---------- ADVERSE REACTIONS ----------

The most common adverse reactions (≥ 1%) are folliculitis and burning sensation of skin. (6.1)

**8.4 Pediatric Use**

The safety and effectiveness of Taclonex Topical Suspension for the treatment of plaque psoriasis of the scalp and body have been established in pediatric patients age 12 to 17 years. The use of Taclonex Topical Suspension for this indication is supported by evidence from adequate and well-controlled trials in adults and from three uncontrolled trials in pediatric subjects that enrolled 109 adolescents with moderate psoriasis of the scalp and 107 adolescents with psoriasis of the scalp and body. After 4 weeks of once daily treatment with Taclonex Topical Suspension, HPA axis suppression was observed in 3% of adolescents with psoriasis of the scalp and 16% of adolescents with psoriasis of the scalp and body. Calcium metabolism was evaluated in 107 adolescents with psoriasis of the scalp and body treated with Taclonex Topical Suspension and no cases of hypercalcemia or clinically relevant changes in urinary calcium were reported [see Warnings and Precautions (5.2), Adverse Reactions (6.1), and Clinical Pharmacology (12.2)].

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 corticosteroids. Pediatric patients are, therefore, also at greater risk of HPA axis suppression and adrenal insufficiency with the use of topical corticosteroids including Taclonex Topical Suspension [see Clinical Pharmacology (12.2)]. 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. Local adverse reactions including striae have also been reported with use of topical corticosteroids in pediatric patients.

The safety and effectiveness of Taclonex Topical Suspension in pediatric patients less than 12 years of age have not been established.

**Enstilar foam, for topical use:[2]**

----------WARNINGS AND PRECAUTIONS----------

- Flammability: The propellants in Enstilar Foam are flammable. Instruct the patient to avoid fire, flame, and smoking during and immediately following application. (5.1)
- Hypercalcemia and Hypercalciuria: Hypercalcemia and hypercalciuria have been observed with use of Enstilar Foam. If hypercalcemia or hypercalciuria develop, discontinue treatment until parameters of calcium metabolism have normalized. (5.2)

- Effects on Endocrine System: Topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency during and after withdrawal of treatment. Risk factors include the use of high-potency topical corticosteroids, use over a large surface area or on areas under occlusion, prolonged use, altered skin barrier, liver failure, and use in pediatric patients. Modify use should HPA axis suppression develop. (5.3, 8.4)
- Ophthalmic Adverse Reactions: Topical corticosteroid products may increase the risk of cataracts and glaucoma. If visual symptoms occur, consider referral to an ophthalmologist. (5.5)

----------ADVERSE REACTIONS----------
Adverse reactions reported in < 1% of subjects included application site irritation, application site pruritus, folliculitis, skin hypopigmentation, hypercalcemia, urticaria, and exacerbation of psoriasis. (6.1)

**8.4 Pediatric Use**
The safety and effectiveness of Enstilar Foam for the treatment of mild to severe plaque psoriasis have been established in pediatric patients age 12 to 17 years. The use of Enstilar Foam for this indication is supported by evidence from adequate and well-controlled trials in adults and from one uncontrolled trial in 106 adolescents age 12 to 17 years with psoriasis of the body and scalp. Calcium metabolism was evaluated in all pediatric subjects and no cases of hypercalcemia or clinically relevant changes in urinary calcium were reported. Hypothalamic pituitary adrenal (HPA) axis suppression was evaluated in a subset of 33 pediatric subjects with moderate plaque psoriasis of the body and scalp (mean body surface area involvement of 16% and mean scalp area involvement of 56%). After 4 weeks of once daily treatment with a mean weekly dose of 47 grams, HPA axis suppression was observed in 3 of 33 subjects (9%) [see Warnings and Precautions (5.2), Adverse Reactions(6.1) and Clinical Pharmacology (12.2)].

Because of a higher ratio of skin surface area to body mass, children under the age of 12 years are at particular risk of systemic adverse effects when they are treated with topical corticosteroids. Pediatric patients are, therefore, also at greater risk of HPA axis suppression and adrenal insufficiency with the use of topical corticosteroids including Enstilar Foam[see Warnings and Precautions (5.3) and Clinical Pharmacology (12.2)].

Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in pediatric patients treated with topical corticosteroids.

Local adverse reactions including striae have been reported with use of topical corticosteroids in pediatric patients.

The safety and effectiveness of Enstilar Foam in pediatric patients less than12 years of age have not been established.

# 2 METHODS AND MATERIALS

## 2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 2.

| Table 2. FAERS Search Strategy* | |
|---|---|
| Date of search | July 12, 2023 |
| Time period of search | March 1, 2017† – July 11, 2023 |
| Search type | RxLogix Post-Market Cases |
| Product terms | Product active ingredient: betamethasone dipropionate\calcipotriene, betamethasone dipropionate\calcipotriene hydrate, betamethasone dipropionate\calcipotriene monohydrate, betamethasone dipropionate\calcipotriene\calcipotriene hydrate, betamethasone\calcipotriene |
| MedDRA search terms (Version 26.0) | All Preferred Terms |

* See Appendix A for a description of the FAERS database.
† Datalock date from last OSE pediatric postmarketing pharmacovigilance review.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities

# 3 RESULTS

## 3.1 FAERS

### *3.1.1 Total Number of FAERS Reports by Age*

Table 3 presents the number of adult and pediatric FAERS reports from March 1, 2017 – July 11, 2023, with calcipotriene/betamethasone dipropionate.

**Table 3. Total Adult and Pediatric FAERS Reports* Received by FDA From March 1, 2017 – July 11, 2023, With Calcipotriene/Betamethasone Dipropionate**

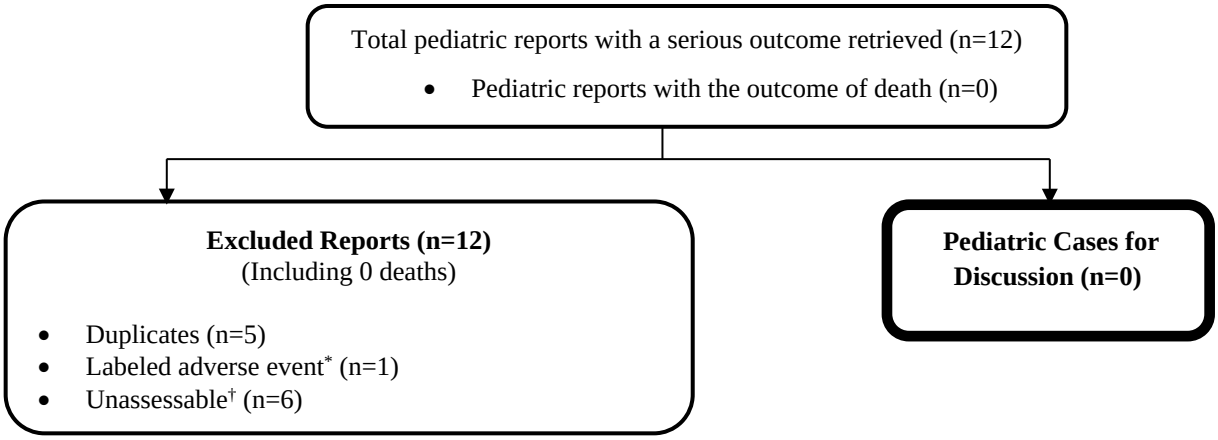
| | All reports (U.S.) | Serious† (U.S.) | Death (U.S.) |
|---|---|---|---|
| Adults (≥ 18 years) | 267 (71) | 211 (20) | 4 (0) |
| Pediatrics (0 - < 18 years) | 19 (5) | 12 (0) | 0 (0) |

* May include duplicates and transplacental exposures, and 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, or other serious important medical events.

### *3.1.2 Selection of Serious Pediatric Cases in FAERS*

The FAERS search retrieved 12 serious pediatric reports from March 1, 2017 – July 11, 2023. DPV reviewed all FAERS pediatric reports with a serious outcome. DPV excluded all reports from the case series for the reasons listed in Figure 1. Figure 1 presents the selection of cases for the pediatric case series.

**Figure 1. Selection of Serious Pediatric Cases with Calcipotriene/Betamethasone Dipropionate**




* Labeled adverse event does not represent increased severity or frequency.
† Unassessable: The report cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome), the information is contradictory, or information provided in the report cannot be supplemented or verified.

### *3.1.3 Summary of Fatal Pediatric Cases (N=0)*

There are no fatal pediatric adverse event cases for discussion.

### *3.1.4 Summary of Serious Non-Fatal Pediatric Cases (N=0)*

There are no non-fatal pediatric adverse event cases for discussion.

## 4 DISCUSSION

DPV reviewed all serious FAERS reports with calcipotriene/betamethasone dipropionate in pediatric patients less than 18 years of age from March 1, 2017 – July 11, 2023, and identified 12 reports; however, all reports were excluded from further discussion.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with calcipotriene/betamethasone dipropionate in pediatric patients less than 18 years of age.

## *5* CONCLUSION

DPV did not identify any new pediatric safety concerns for calcipotriene/betamethasone dipropionate at this time and will continue to conduct routine pharmacovigilance monitoring for calcipotriene/betamethasone dipropionate.

# 6 REFERENCES


1. Taclonex (calcipotriene and betamethasone dipropionate) topical suspension [Prescribing information]. Madison, NJ; LEO Laboratories Ltd.: July, 2019.
2. Enstilar (calcipotriene and betamethasone dipropionate) foam, for topical use [Prescribing information]. Madison, NJ; LEO Laboratories Ltd.: August, 2021.
3. Taclonex (calcipotriene and betamethasone dipropionate) ointment, for topical use [Prescribing information]. Madison, NJ; LEO Laboratories Ltd.: December, 2018.


# 7 APPENDICES

## 7.1 APPENDIX A. 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 FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council 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 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.

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