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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Product Name	Application Type/Number	Pediatric Labeling Approval Date	Applicant
Ultravate (halobetasol propionate) lotion	NDA 208183	August 27, 2020	Sun Pharmaceutical Industries, Inc.
Lexette (halobetasol propionate) topical foam	NDA 210566	August 18, 2021	Mayne Pharma

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Ultravate (halobetasol propionate) lotion and Lexette (halobetasol propionate) topical foam in pediatric patients less than 17 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 halobetasol in pediatric patients.

Ultravate (halobetasol propionate) lotion (NDA 208183) is a corticosteroid initially approved in the United States on November 6, 2015. Lexette (halobetasol propionate) topical foam (NDA 210566) is another topical corticosteroid initially approved in the United States on May 24, 2018. At initial FDA approval, both products were indicated for the topical treatment of plaque psoriasis in patients aged 18 years and older.

On August 27, 2020, FDA approved expanding the indication for Ultravate (NDA 208183) to include use in pediatric patients aged 12 years and older. On August 18, 2021, FDA also expanded the indication for Lexette (NDA 210566) to include pediatric patients aged 12 years and older. Ultravate and Lexette are the only halobetasol products indicated for use in pediatric patients.

This pediatric postmarketing safety review was prompted by pediatric labeling on August 27, 2020, for Ultravate, and the pediatric labeling on August 18, 2021, for Lexette, which expanded the indication from use in patients aged 18 years and older to use in pediatric patients 12 years and older.

A pediatric postmarketing pharmacovigilance review for halobetasol propionate has not been previously presented to the Pediatric Advisory Committee.

DPV reviewed all serious FAERS reports with halobetasol in pediatric patients less than 17 years of age through February 22, 2024, and identified four 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 halobetasol in pediatric patients less than 17 years of age.

DPV did not identify any new pediatric safety concerns for halobetasol at this time and will continue routine pharmacovigilance monitoring for halobetasol.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Ultravate (halobetasol propionate) lotion and Lexette (halobetasol propionate) topical foam in pediatric patients less than 17 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 halobetasol in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Ultravate (halobetasol propionate) lotion (NDA 208183) is a corticosteroid initially approved in the United States on November 6, 2015.[1] Lexette (halobetasol propionate) topical foam (NDA 210566) is another topical corticosteroid initially approved in the United States on May 24, 2018.[2] At initial FDA approval, both products were indicated for the topical treatment of plaque psoriasis in patients aged 18 years and older.[3,4]

On August 27, 2020, FDA approved expanding the indication for Ultravate (NDA 208183) to include use in pediatric patients aged 12 years and older.[5] On August 18, 2021, FDA also expanded the indication for Lexette (NDA 210566) to include pediatric patients aged 12 years and older.[6] Ultravate and Lexette are the only halobetasol products indicated for use in pediatric patients.[7,8] **Appendix A** provides a description of all halobetasol propionate products.

This pediatric postmarketing safety review was prompted by pediatric labeling on August 27, 2020, for Ultravate, and the pediatric labeling on August 18, 2021, for Lexette, which expanded the indication from use in patients aged 18 years and older to use in pediatric patients 12 years and older for the respective products.[7,8]

A pediatric postmarketing pharmacovigilance review for halobetasol propionate has not been previously presented to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

The Ultravate (halobetasol propionate) lotion and the Lexette (halobetasol propionate) topical foam labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional halobetasol labeling information, please refer to the full prescribing information.[7,8]

Ultravate (halobetasol propionate) lotion:

----------CONTRAINDICATIONS----------
None.

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

- Reversible hypothalamic-pituitary-adrenal (HPA) axis suppression may occur, with the potential for glucocorticosteroid insufficiency during or after treatment. Systemic absorption may require evaluation for HPA axis suppression. (5.1)
- Systemic effects of topical corticosteroids may also include Cushing's syndrome, hyperglycemia, and glucosuria. Use of potent corticosteroids on large areas, for prolonged durations, under occlusive dressings, or on an altered skin barrier may increase systemic exposure. (5.1)

- Children may be more susceptible to systemic toxicity when treated with topical corticosteroids. (5.1, 8.4)
- Local adverse reactions with topical steroids may include atrophy, striae, irritation, acneiform eruptions, hypopigmentation, and allergic contact dermatitis. Adverse reactions may be more likely to occur with occlusive use or more potent corticosteroids. (5.2, 5.5)
- Topical corticosteroids may increase the risk of cataract and glaucoma formation. If visual symptoms occur, consider referral to an ophthalmologist for evaluation. (5.3)
- Initiate appropriate therapy if concomitant skin infections develop. (5.4)

----------ADVERSE REACTIONS----------
The most commonly reported adverse reactions (≥1%) are telangiectasia, application site atrophy, and headache. (6.1)

8.4 Pediatric Use

Safety and effectiveness of ULTRAVATE lotion for the treatment of moderate to severe plaque psoriasis have been established in patients 12 years of age and older. It is supported by evidence from adequate and well-controlled trials in adults and from one uncontrolled safety trial in 16 adolescents (12 to less than 17 years of age). Adolescent patients with moderate to severe plaque psoriasis covering a minimum of 10% of the total body surface area were treated twice daily for 2 weeks with ULTRAVATE lotion. Hypothalamic-pituitary adrenal (HPA) axis function (ACTH stimulation test) was evaluated in a subset of 14 patients. After 2 weeks of treatment, 1 of 14 patients (7%) experienced laboratory evidence of adrenal suppression (i.e., cortisol serum level of ≤18 µg/dL) that recovered upon retest. No other adverse reactions were reported in the study.

Because of higher skin surface area to body mass ratios, pediatric patients are at a greater risk than adults of HPA axis suppression and Cushing's syndrome when they are treated with topical corticosteroids. They are therefore also at greater risk of adrenal insufficiency during or after withdrawal of treatment. Adverse reactions including striae have been reported with use of topical corticosteroids in infants and children.

HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels and an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Lexette (halobetasol propionate) topical foam:

_____CONTRAINDICATIONS _____
None.

_____ WARNINGS AND PRECAUTIONS _____
- Reversible hypothalamic-pituitary-adrenal (HPA) axis suppression may occur, with the potential for glucocorticosteroid insufficiency during or after treatment. (5.1)
- Systemic effects following prolonged exposure of topical corticosteroids may also include Cushing's syndrome, hyperglycemia, and glucosuria. (5.1)
- Use of potent corticosteroids on large areas, for prolonged durations, under occlusive dressings, or on an altered skin barrier may increase systemic exposure. (5.1)
- Children may be more susceptible to systemic toxicity when treated with topical corticosteroids. (5.1, 8.4)
- Local adverse reactions with topical steroids may include atrophy, striae, irritation, acneiform eruptions, hypopigmentation, and allergic contact dermatitis. Adverse reactions may be more likely to occur with occlusive use or more potent corticosteroids. (5.2)
- Topical corticosteroids may increase the risk of cataract and glaucoma formation. If visual symptoms occur, consider referral to an ophthalmologist for evaluation. (5.3)
- Initiate appropriate therapy if concomitant skin infections develop. (5.4)
- Flammable contents. Avoid heat, flame, or smoking during and immediately following application. (5.6)

_____ADVERSE REACTIONS_____

The most commonly reported adverse reactions (≥1%) are application site pain and headache. (6.1)

8.4 Pediatric Use

Safety and effectiveness of LEXETTE in patients younger than 12 years of age have not been established; therefore, use in children younger than 12 years is not recommended.

The safety and effectiveness of LEXETTE for the treatment of stable plaque psoriasis in subjects 12 to less than 18 years of age is supported by evidence from adequate and well-controlled studies in adults and from one open-label safety study in 24 subjects aged 12 to less than 18 years. Subjects 12 to less than 18 years with stable plaque psoriasis covering a minimum of 10% of the total body surface area at baseline were treated twice daily for 2 weeks with LEXETTE. Hypothalamic-pituitary adrenal (HPA) axis function (ACTH stimulation test) was evaluated in a subset of 23 subjects. After 2 weeks of treatment, 6 of 23 subjects (26.1%) experienced laboratory evidence of adrenal suppression (i.e., cortisol serum level of ≤18 μg/dL) that recovered upon retesting after at least 4 weeks of stopping the treatment [see Clinical Pharmacology (12.2)].

Because of higher skin surface area to body mass ratios, pediatric patients are at a greater risk than adults of HPA axis suppression and Cushing's syndrome when they are treated with topical corticosteroids. They are therefore also at greater risk of adrenal insufficiency during or after withdrawal of treatment. Adverse reactions including striae have been reported with use of topical corticosteroids in infants and children [see Warnings and Precautions (5.1)].

HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels and an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema [see Warnings and Precautions (5.1)].

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in **Table** 1.

Table 1. FAERS Search Strategy*	
Date of search	February 23, 2024
Time period of search	All dates through February 22, 2024
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Product active ingredient: Halobetasol, halobetasol propionate
MedDRA search terms (Version 26.1)	All Preferred Terms
* See Appendix A for a description of the FAERS database. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 2 presents the number of adult and pediatric FAERS reports through February 22, 2024, with halobetasol.

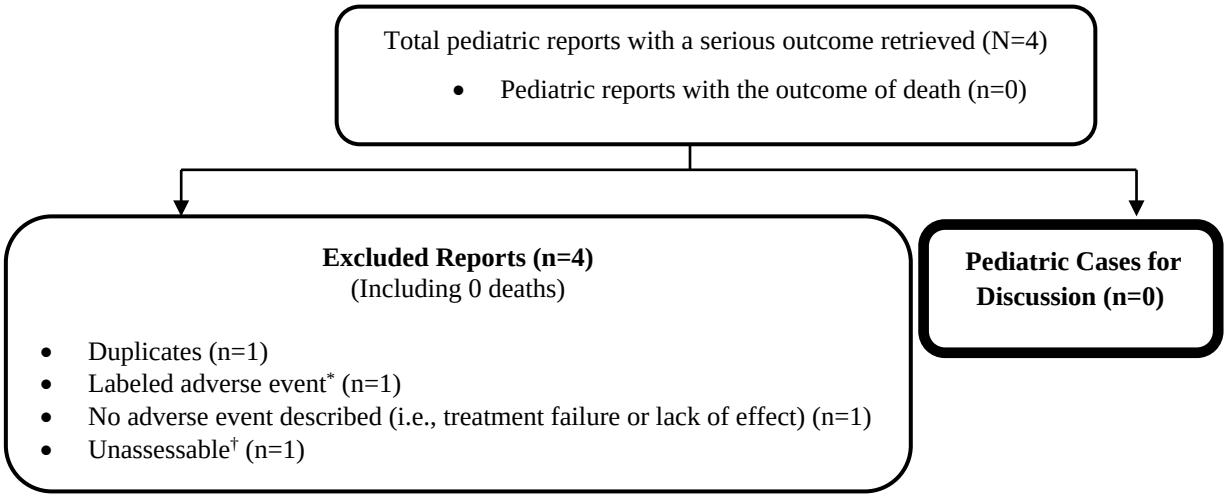
Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA Through February 22, 2024, With Halobetasol			
	All Reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	154 (122)	65 (33)	0 (0)
Pediatrics (0 - < 17 years)	6 (4)	4 (2)	0 (0)

* 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

Our FAERS search retrieved four serious pediatric reports through February 22, 2024. We reviewed all FAERS pediatric reports with a serious outcome. We 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 a Serious Pediatric Cases With Halobetasol



* 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 halobetasol in pediatric patients less than 17 years of age through February 22, 2024, and identified four 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 halobetasol in pediatric patients less than 17 years of age.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for halobetasol at this time and will continue routine pharmacovigilance monitoring for halobetasol.

6 REFERENCES

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7. Ultravate (halobetasol propionate) lotion. [Prescribing information]. Cranbury, NJ; Sun Pharmaceutical Industries, Inc.: August, 2020.
8. Lexette (halobetasol propionate) foam. [Prescribing information]. Greenville, NC; Mayne Pharma: May 2021. Approval letter. NDA 208183. August 27, 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/208183Orig1s002ltr.pdf

7 APPENDICES

7.1 APPENDIX A. DESCRIPTION OF AVAILABLE PROPIONATE PRODUCTS

Table A. Halobetasol Propionate Products

Product Name	Application Type/Number	Initial FDA Approval Date	Applicant	Indication	Pediatric Indication
Ultravate (halobetasol propionate) cream*	NDA 019967	12/27/1990	Sun Pharmaceutical Industries, Inc.	Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses	Yes; ≥ 12 years old
Ultravate (halobetasol	NDA 019968	12/17/1990	Sun Pharmaceutical Industries, Inc	Relief of the inflammatory and pruritic	Yes; ≥ 12 years old

Table A. Halobetasol Propionate Products					
Product Name	**Application Type/Number**	**Initial FDA Approval Date**	**Applicant**	**Indication**	**Pediatric Indication**
propionate) ointment*				manifestations of corticosteroid-responsive dermatoses	
Ultravate (halobetasol propionate) lotion	NDA 208183	11/6/2015	Sun Pharmaceutical Industries, Inc	Topical treatment of plaque psoriasis in patients 12 years of age and older	Yes; ≥ 12 years old
Lexette (halobetasol propionate) topical foam	NDA 210566	5/24/2018	Mayne Pharma	Topical treatment of plaque psoriasis in patients 12 years of age and older	Yes; ≥ 12 years old
Bryhali (halobetasol propionate) lotion	NDA 209355	11/6/2018	Bausch	Topical treatment of plaque psoriasis in adults	None
Duobrii (halobetasol propionate, tazarotene) lotion	NDA 209354	4/25/2019	Bausch	Topical treatment of plaque psoriasis in adults	None
* Discontinued Halobetasol propionate is also available in generic formulations under abbreviated new drug applications (ANDAs) 076872, 076903*, 076994, 077001, 077109, 077123, 077227, 077721*, 078162, 209978*, 211464*, 213560, 214285, 215266 and halobetasol propionate/tazarotene is available in a generic formulation under ANDA 217190.					

7.2 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 terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

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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