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

Date:	August 31, 2023
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Product Name:	Flector (diclofenac epolamine) topical system
Pediatric Labeling Approval Date:	March 1, 2019
Application Type/Number:	NDA 021234
Applicant:	Institut Biochimique SA
TTT Record ID:	2023-5468

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Flector (diclofenac epolamine) topical system in pediatric patients less than 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with Flector in pediatric patients.

Flector is a nonsteroidal anti-inflammatory drug (NSAID) initially approved in the United States (U.S.) on January 31, 2007. Flector is currently indicated for the topical treatment of acute pain due to minor strains, sprains, and contusions in adults and pediatric patients 6 years and older. This pediatric postmarketing safety review was prompted by the pediatric labeling on March 1, 2019, that expanded the indication to include pediatric patients. The safety and effectiveness of Flector has not been investigated in pediatric patients younger than 6 years. Flector has not been previously presented before the Pediatric Advisory Committee.

DPV reviewed all serious FAERS reports with Flector in the pediatric population aged <17 years received by FDA from January 31, 2007 – July 9, 2023, and identified one case for inclusion in our series. The case described a 15-year-old patient with type 1 diabetes mellitus who developed hypoglycemia after exposure to Flector. However, the case lacked sufficient clinical information to establish causality. An exploratory search of the FAERS data failed to identify sufficient evidence to support a signal of hypoglycemia with Flector at this time.

This review did not identify any new or unexpected pediatric safety concerns for Flector. DPV will continue to monitor all adverse events associated with the use of Flector.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Flector (diclofenac epolamine) in pediatric patients less than 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with Flector topical system in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY[1]

Flector is a nonsteroidal anti-inflammatory drug (NSAID) initially approved in the United States (U.S.) on January 31, 2007. Flector is currently indicated for the topical treatment of acute pain due to minor strains, sprains, and contusions in adults and pediatric patients 6 years and older.

This pediatric postmarketing safety review was prompted by the pediatric labeling on March 1, 2019, that expanded the indication to include pediatric patients. Support for use in pediatric patients 6 years and older derived from adequate and well-controlled studies in adults and an open-label study in pediatric patients 6 years and older. The pediatric study enrolled 104 patients aged 6 years and older with minor soft tissue injuries. Patients received one Flector topical system application to their injury site twice daily for a maximum of 14 days or until treatment was no longer required for pain management, whichever occurred first. Based on the available data from the pediatric study, the safety profile for Flector in pediatric patients was similar to that in adults. The safety and effectiveness of Flector has not been investigated in pediatric patients younger than 6 years. Flector has not been previously presented before the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION[1]

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

WARNING: RISK OF SERIOUS CARDIOVASCULAR and GASTROINTESTINAL EVENTS
See full prescribing information for complete boxed warning.

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use (5.1)**
- **FLECTOR is contraindicated in the setting of coronary artery bypass graft (CABG) surgery (4, 5.1)**
- **NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events (5.2)**

CONTRAINDICATIONS

- Known hypersensitivity to diclofenac or any components of the drug product (4)
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs (4)
- In the setting of CABG surgery (4)
- For use on non-intact or damaged skin (4)

WARNINGS AND PRECAUTIONS

- Hepatotoxicity: Inform patients of warning signs and symptoms of hepatotoxicity. Discontinue if abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop (5.3)
- Hypertension: Patients taking some antihypertensive medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure (5.4, 7)
- Heart Failure and Edema: Avoid use of FLECTOR in patients with severe heart failure unless benefits are expected to outweigh risk of worsening heart failure (5.5)
- Renal Toxicity: Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia. Avoid use of FLECTOR in patients with advanced renal disease unless benefits are expected to outweigh risk of worsening renal function (5.6)
- Anaphylactic Reactions: Seek emergency help if an anaphylactic reaction occurs (5.7)
- Exacerbation of Asthma Related to Aspirin Sensitivity: FLECTOR is contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity) (5.8)
- Serious Skin Reactions: Discontinue FLECTOR at first appearance of skin rash or other signs of hypersensitivity (5.9)
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): Discontinue and evaluate clinically (5.10).
- Fetal Toxicity: Limit use of NSAIDs, including FLECTOR, between about 20 to 30 weeks in pregnancy due to the risk of oligohydramnios/fetal renal dysfunction. Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/fetal renal dysfunction and premature closure of the fetal ductus arteriosus (5.11, 8.1)
- Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia (5.12, 7)

ADVERSE REACTIONS

The most common adverse reactions in FLECTOR and placebo-treated adult patients were pruritus (5% and 8%, respectively) and nausea (3% and 2%, respectively) (6.1). The most common adverse reactions in FLECTOR treated pediatric patients were headache (9%) and application site pruritus (7%) (6.1)

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	July 10, 2023
Time period of search	January 31, 2007[†] – July 9, 2023

Table 1. FAERS Search Strategy*	
Search type	Drug Safety Analytics Dashboard (DSAD) Quick Query
Product terms	Product name: Flector Application: NDA 021234
MedDRA search terms (Version 26.0)	All Preferred Terms
* See Appendix A for a description of the FAERS database † Flector U.S. approval date Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, NDA=New Drug Application	

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 from January 31, 2007 – July 9, 2023, with Flector.

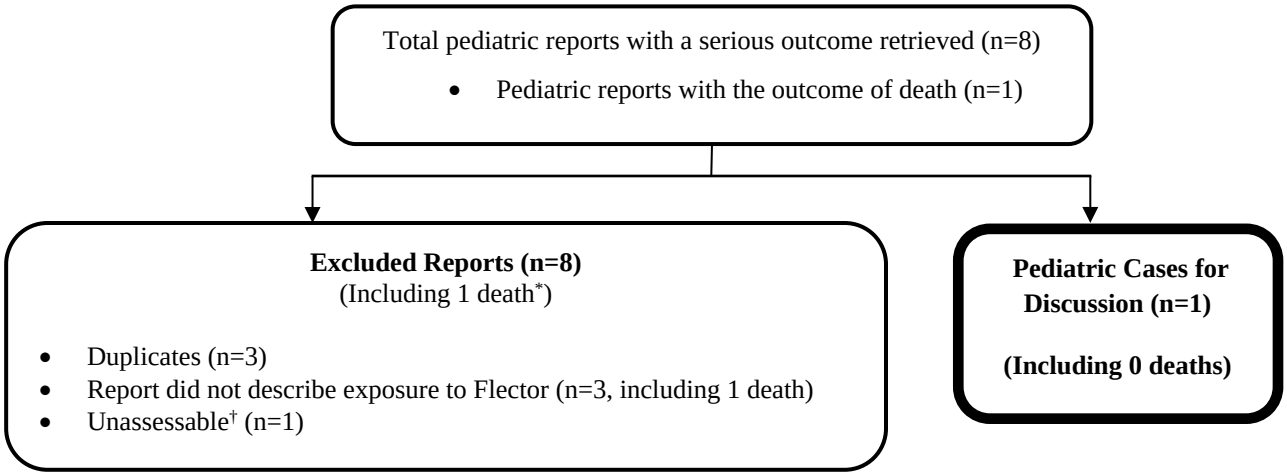
Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From January 31, 2007 – July 9, 2023, With Flector			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	1967 (1724)	527 (288)	23 (14)
Pediatrics (0 - <17 years)	16 (9)	8 (2)	1 (1)
* May include duplicates and 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 eight serious pediatric reports from January 31, 2007 – July 9, 2023. We reviewed all FAERS pediatric reports with a serious outcome. We excluded seven reports from the case series for the reasons listed in Figure 1. Figure 1 presents the selection of cases for the pediatric case series.

Appendix B contains a line listing of the pediatric case in the case series.

Figure 1. Selection of Serious Pediatric Cases with Flector



* One excluded FAERS report described a fatal outcome. The case did not describe exposure to Flector.
† 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=1)

We identified one case with Flector in the pediatric population reporting a non-fatal serious outcome. The case is summarized below.

FAERS Case #6948403, United States, Expedited Report, Other Serious:
A 15-year-old female patient with a history of Type 1 diabetes mellitus (T1DM) and arthritis received Flector topical system 1.3% for knee arthritis pain. After one dose (1 topical patch) of Flector, she experienced muscle cramping and "feeling strange" followed by a drop in blood sugar to 48 [units not reported]. The episode was "treated with eating." Blood glucose prior to Flector patch was 211 [units not reported]. Overnight, the patient experienced a second drop in blood sugar to 30 [units not reported]. She discontinued therapy with Flector. No concomitant medications were reported. Outcomes for hypoglycemic events were not reported. No further clinical information was available.

Reviewer comment: Hypoglycemia is a common complication of childhood T1DM.[2] Factors such as excessive insulin intake, timing of insulin dose, physical activity, inadequate carbohydrate consumption, and other nutritional and environmental factors may affect glycemic control in patients with T1DM.[3] The narrative lacks sufficient clinical information to assess whether any of these common risk factors contributed to the reported hypoglycemic events. NSAIDs have been associated with hypoglycemia, particularly in patients with diabetes who receive sulfonylurea products; however, the association pertains to oral NSAID exposure.[4] Recent systematic reviews examining adverse effects related to topical NSAIDs do not identify hypoglycemia as an adverse event of interest with these products.[5,6,7] An exploratory search of the FAERS data on July 10,

2023, for reports coded with the Preferred Term (PT) Hypoglycemia with Flector received by FDA from January 31, 2007 – July 9, 2023, identified two additional cases. Both cases described adult patients with a history of hypoglycemia and neither case provided sufficient clinical detail to determine baseline glucose control. Furthermore, one case described multiple co-suspect medications that may have contributed to hypoglycemia. There is insufficient data to establish a signal for hypoglycemia with Flector at this time.

4 DISCUSSION

DPV searched FAERS for all serious reports with Flector in pediatric patients less than 17 years of age from January 31, 2007 – July 9, 2023, and identified eight reports. Of the eight reports reviewed, one case was included in our series.

Overall, there were no new safety signals identified and no increased severity or frequency of any labeled adverse events associated with Flector in pediatric patients less than 17 years of age.

5 CONCLUSION

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

6 REFERENCES

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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.

7.2 APPENDIX B. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES (N=1)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	3/23/2009	6948403	1	US-KINGPHARMUSA00001-K200900282	Expedited	15	F	USA	OT

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case may have more than one serious outcome.
Abbreviations: F=female, USA=United States of America, OT=other medically significant

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CARMEN CHENG
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MONICA MUNOZ
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