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Pediatric Postmarketing Pharmacovigilance Review

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Product Name: Caldolor (ibuprofen) IV injection

**Pediatric Labeling
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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Caldolor (ibuprofen) intravenous (IV) injection in pediatric patients through age <17 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with Caldolor IV in pediatric patients.

The FDA initially approved ibuprofen in 1974. The FDA approved Caldolor injection on June 11, 2009 and it is indicated for the management of mild to moderate pain, moderate to severe pain as an adjunct to opioid analgesics and reduction of fever. The approved pediatric labeling is for the treatment of pain and fever in ages 6 months and older.

We reviewed all serious FAERS reports with Caldolor in the pediatric population through <17 years of age during the period November 20, 2014 to July 23, 2018 and identified one serious non-fatal FAERS case. There were no new safety signals identified in this case. The case described adverse events that were likely due to concomitant medications (e.g. sevoflurane, propofol, morphine, and dexamethasone), consistent with the known adverse reactions (e.g., bradycardia, cardiac arrest) that are described in labeling of these concomitant medications. We did not identify any fatal pediatric adverse event cases.

DPV did not identify any pediatric safety concerns for Caldolor and recommends no regulatory action at this time. We will continue to monitor all adverse events associated with the use of Caldolor IV injection.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Caldolor (ibuprofen) intravenous (IV) injection in pediatric patients through age <17 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with Caldolor injection in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Caldolor, an intravenous form of the nonsteroidal anti-inflammatory drug (NSAID) ibuprofen, was approved on June 11, 2009 for the adult population and on November 20, 2015 for the pediatric population.^{1,2} Caldolor is indicated in adults and pediatric patients six months and older for the reduction of fever, for the management of mild-to-moderate pain, and the management of moderate-to-severe pain as an adjunct to opioid analgesics.

Caldolor's approval for the pediatric population was based on three pediatric studies: two fever studies and one analgesic study. Caldolor was a 505(b)(2) submission relying in part on prior findings of efficacy and safety for the Listed Drugs, Children's Motrin oral suspension (NDA 20516), Advil Liqui-gels (NDA 20402), and Motrin tablets (NDA 17463). Advil Liqui-Gels (over-the-counter) is labeled for use in adults, and Children's Motrin oral suspension, is labeled for over-the-counter use in children ages 2 to 11 years of age. At the time of initial approval for Caldolor, studies in pediatric patients, birth to <17 years of age were deferred. The specific pediatric postmarketing requirements (PMRs) under PREA at the time of Caldolor's approval are listed below:

- 205-1: A deferred study for the management of mild to moderate pain and management of moderate to severe pain as an adjunct to opioid analgesics in pediatric patients 0 to 16 years.
- 205-2: A deferred study for the treatment of reduction of fever in pediatric patients ages 0 to 16 years

The three pediatric studies³ include NCT 00225706, NCT 01002573, and NCT 01332253. Study NCT 01002573 is the key fever study of superiority design. Study NCT 00225706 is a small fever study of non-inferiority design. The study was exploratory in nature and had very few efficacy endpoints. The results of Study NCT 00225706 are mostly based on post-hoc analyses by using a similar set of endpoints as in Study NCT 01002573. Study NCT 01332253 is a single-dose study of preemptive analgesia.

The safety data from the three pediatric studies involved a total of 144 patients exposed to IV ibuprofen 10 mg/kg given by 10-minute infusion. The type of exposure to IV ibuprofen included

single-dose in 82 patients in Study 014, four doses given on a fixed dosing interval within 24 hours in 14 patients in Study 005, and multiple-dose intermittently based on need in 48 patients in Study 012. Multiple-dose experiences in the two fever studies were limited to 45 patients exposed to at least two doses, 36 patients exposed to at least four doses, and 18 patients exposed to at least six doses. The majority of exposure was in the age group of 6 to <12 years (81 of 144 patients, or 56%). The exposure to IV ibuprofen in the age group of 6 months to <2 years involved only six patients, which was less than expected.

The pediatric study population consisted of mostly Caucasian patients (79%) and had slightly more females than males. The mean and median body weights of the study population were close to the mid-range weight listed for the corresponding age groups in the Motrin dosing chart. The study population included very sick pediatric patients hospitalized for serious medical conditions such as sepsis, bowel perforation, appendicitis with abscess formation, different types of pneumonia, meningitis, cellulitis, urinary tract infection, severe burn, trauma with bone fracture, toxic shock syndrome, sickle cell anemia, and febrile seizure. Some had multiple medical conditions, were on multiple concomitant medications, and were admitted to the pediatric intensive care unit (PICU).

There were no reports of deaths and seven reports of nonfatal serious adverse events in five pediatric patients, three of whom were treated with IV ibuprofen. Based on the review of narratives for all serious adverse events, the relationship of adverse events to ibuprofen could not be ruled out in case of the post tonsillectomy hemorrhage at the surgical site. The relationship of adverse events to ibuprofen could not be completely ruled out in cases of transaminitis and pancreatitis due to concurrent illness and multiple concomitant medications known for drug-induced liver enzyme elevation and pancreatitis. The cases of cardiopulmonary arrest and left pleural pneumothorax were unlikely to be related to ibuprofen treatment because of patient's serious medical conditions involving septic shock and associated respiratory failure and other unstable conditions.

Of the five cases of adverse event-related dropouts, four occurred in the IV ibuprofen group due to thrombocytopenia, hypothermia/bradycardia, headache, and urticaria, respectively. The case of urticaria was likely related to the ibuprofen treatment as the event commenced seven minutes after the start of the ibuprofen infusion.

In pediatric patients treated with IV ibuprofen, the commonly reported individual adverse events ($\geq 2\%$) were infusion site pain, vomiting, nausea, anemia, and headache. For the surgical patients treated with a single dose of ibuprofen the common adverse events were infusion site pain, nausea, vomiting, and urticaria. The commonly reported adverse events in hospitalized febrile pediatric patients were gastrointestinal symptoms and unspecified laboratory test abnormalities in both active treatment groups.

Based on the review of pediatric safety data there were no new safety signals or major issues identified. The Division of Anesthesia, Analgesia and Addiction Products (DAAAP) determined that the use of IV ibuprofen in pediatric patients is reasonably safe based on the lack of new safety signals or unexpected events in pediatric studies, the known safety profile of the ibuprofen moiety, and the anticipated short-term use and close safety monitoring in a hospital setting.

DPV has not previously evaluated postmarketing adverse event reports with a serious outcome or drug utilization data for Caldolor in pediatric patients. The FDAAA Section 915 review dated September 3, 2013 did not contain pediatric information because Caldolor was not approved for pediatric use at that time and none of the adverse event cases reported use in pediatric patients. This PREA review was triggered by approval of the pediatric indication in November 2015.

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

The following is an excerpt from the Caldolor labeling:⁴

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

See full prescribing information for complete boxed warning

- Non-steroidal 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)
- CALDOLOR 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 ibuprofen or any component of the drug product (4)
- History of asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs (4)
- In the setting of CABG surgery (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 CALDOLOR 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 CALDOLOR 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: CALDOLOR is contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity) (5.8)
- Serious Skin Reactions: Discontinue CALDOLOR at first appearance of skin rash or other signs of hypersensitivity (5.9)
- Premature Closure of Fetal Ductus Arteriosus: Avoid use in pregnant women starting at 30 weeks gestation (5.10, 8.1)
- Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia (5.11, 7)

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

The most common adverse reactions are nausea, flatulence, vomiting, headache, hemorrhage and dizziness (>5%).
 The most common adverse reactions in pediatric patients are infusion site pain, vomiting, nausea, anemia and headache (>2%). (6).

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategies described in Table 1.

	<i>Search Strategy #1</i>	<i>Search Strategy #2</i>
Date of Search	July 24, 2018	
Time Period of Search	November 20, 2014 [†] – July 23, 2018	
Search Type	<i>FBIS Quick Query, Profile Report</i>	
Product Terms	Product Name: Caldolor Active Moiety: Ibuprofen NDA # 022348	Active Moiety: Ibuprofen
Administration route	Parenteral, intramuscular, intravenous bolus, intravenous drip, intravenous (not otherwise specified) [‡]	
Age (years)	0 – 16.99	All ages
Outcome	Serious	All outcomes
* See Appendix A for a description of the FAERS database.		
[†] DPV based selected search dates on one year prior to the approval date of pediatric labeling.		
[‡] Caldolor is an injectable formulation; therefore, DPV searched only injectable administration routes.		

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 November 20, 2014 through July 23, 2018 with Ibuprofen IV using our FAERS search strategy.

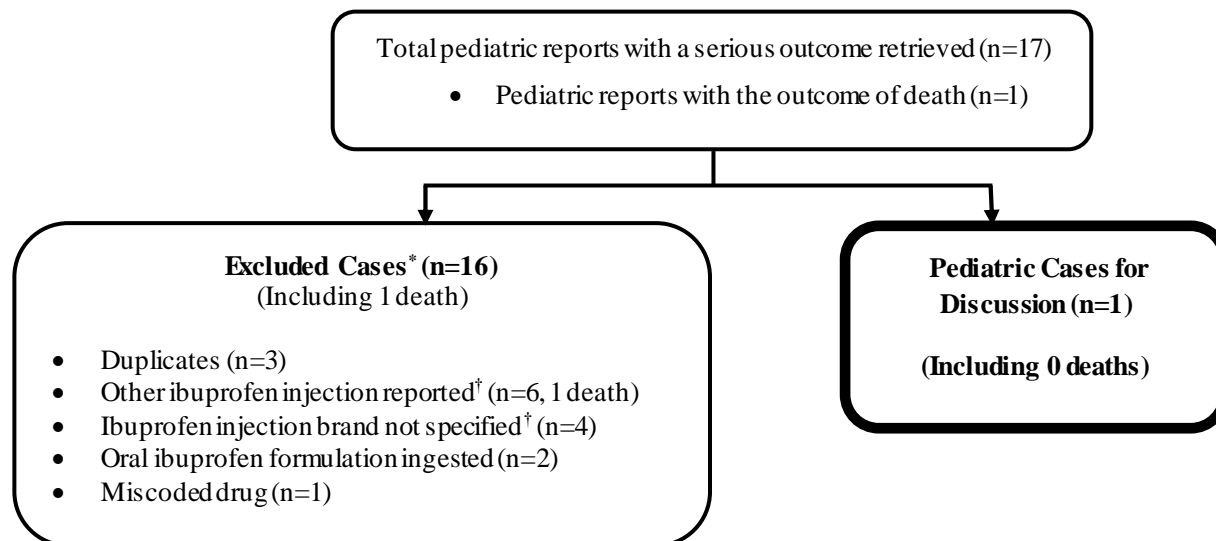
	All reports (U.S.)	Serious[†] (U.S.)	Death (U.S.)
Adults (≥17 years)	25 (13)	19 (7)	0 (0)
Pediatrics (0 - <17 years)	17 (2)	17 (2)	1 (0)
* May include duplicates and other ibuprofen products (not Caldolor) and have not been assessed for causality.			
[†] For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.			

3.1.2 Selection of Serious Pediatric Cases in FAERS

Our FAERS search retrieved 17 serious pediatric reports from November 20, 2014 through July 23, 2018. Figure 1 represents the selection of cases for discussion.

We summarize the remaining case in the section 3.1.4 below.

Figure 1. Selection of Serious Pediatric Cases with Caldolor



* DPV reviewed these cases but excluded them from further discussion for the reasons listed above.

† The focus of this pediatric review is on Caldolor. We excluded 10 cases where another ibuprofen injection was reported, six of which specifically stated NeoProfen, and four which described patients in the neonatal age range who received ibuprofen injection for the indication of PDA closure, thus, suggesting that the product was another ibuprofen injection that has the indication for PDA. Caldolor is not approved for the indication of PDA, so we suspect Caldolor was not the product used in these cases. The cases described neonates with adverse events such as renal injury, necrotizing enterocolitis (NEC) with and without complications, pneumothorax, sepsis, hypoxia in the setting of pulmonary hypertension, and hemorrhage in the setting of thrombocytopenia. The cause of death in the one fatal case was NEC in a premature neonate. The adverse events in all 10 cases were plausibly explained by underlying conditions (e.g. prematurity) or concomitant medications. Additionally, various ibuprofen products are labeled for renal injury (NeoProfen, Caldolor, others) which is a class effect, and for NEC (NeoProfen). We did not identify any new safety signals from these excluded cases.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

We did not identify any fatal pediatric adverse event cases.

3.1.4 Summary of Non-Fatal Pediatric Serious Cases (N=1)

We identified one serious non-fatal FAERS case with Caldolor in the pediatric population. The narrative summary is described below.

Case 13522795, USA, Life-threatening, Expedited, FDA Received Date 5/8/2017

A 3-year-old, 15.8 kg male developed pulselessness after receiving Caldolor. The patient had a history of adenotonsillar and inferior turbinate hypertrophy and nasal dyspnea; he was seen in an out-patient surgery center for a bilateral tympanostomy tube procedure to be followed by tonsillectomy and adenoidectomy with submucosal resection of inferior turbinate. He was given ondansetron and midazolam 20 minutes before surgery. At induction of anesthesia, he received sevoflurane, propofol, morphine, and dexamethasone. He was intubated and Caldolor 150 mg was infused over 12 minutes. The tympanostomy procedure lasted 10 minutes and the anesthetist noted the child's pulse rate decreased and became undetectable. The remainder of the surgeries were cancelled; anesthetics were discontinued and the patient received a fluid bolus. The patient was pulseless for two minutes. Atropine was administered with reported little to no effect on the heart rate. However, the case reports the child recovered after this incident. He underwent a cardiac evaluation 4 days later and the results were normal. Laboratory evaluation performed at an unspecified time was reportedly normal and notable for hemoglobin of 10.8 g/dL (reference lower limit normal 10.9 g/dL) and calcium 8.6 mg/dL (reference lower limit 9.0mg/dL).

Reviewer's comments: Ibuprofen is not labeled for an absence of pulse or bradycardia; however, sevoflurane, propofol, morphine, and dexamethasone are potential cardiac depressants labeled for bradycardia and cardiac arrest. The case does not contain sufficient information to discern the extent to which each drug product contributed to the child's bradycardia and pulselessness. Additionally, the case lacks details about the patient's medical history and his condition prior to the procedure that potentially contributed to the adverse events. The laboratory results reported deviate minimally from the reference ranges and lack clinical significance in the absence of more detailed clinical context.

4 DISCUSSION

We reviewed all serious FAERS reports with Caldolor in the pediatric population through <17 years of age during the period November 20, 2014 to July 23, 2018, and identified one serious non-fatal FAERS case for discussion. There were no new safety signals identified in this case. The case described adverse events that were likely due to concomitant medications used in anesthetic induction (e.g. sevoflurane, propofol, morphine, and dexamethasone), consistent with the known adverse reactions (e.g. bradycardia, cardiac arrest) described in labeling of these concomitant medications. We did not identify any fatal pediatric adverse event cases for our case series.

5 CONCLUSION

DPV did not identify any pediatric safety concerns for Caldolor at this time.

6 RECOMMENDATION

DPV recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of Caldolor (ibuprofen) IV injection.

7 REFERENCES

1. Fields, E. Summary Review for Regulatory Action. Deputy Division Director Summary Review. NDA 22348 Supplement 005. Caldolor pediatric indication. November 19, 2015.
2. Fang, C. Clinical Review sNDA 22348. Caldolor (ibuprofen) IV Injection. November 9, 2015.
3. NIH. U.S. National Library of Medicine. <https://clinicaltrials.gov>. Accessed August 20, 2018.
4. Caldolor (ibuprofen) Injection, for intravenous use [package insert]. Nashville, TN: Cumberland Pharmaceuticals Inc.: April 2016.

8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM

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.

8.2 APPENDIX B. FAERSLINE 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 Outcome*
1	5/8/2017	13522795	1	US-CUMBERLAND PHARMACEUTICALS INC.- 2020392	Expedited	3	Male	USA	LT
<p>*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, or a congenital anomaly/birth defect, and 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: LT= Life-threatening</p>									

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