NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	sNDA
Application Number(s)	021234; Efficacy Supplement S-016 / S-017
Priority or Standard	Standard
Submit Date(s)	05/02/2018
Received Date(s)	05/02/2018
PDUFA Goal Date	03/02/2019 (Saturday); Anticipated action Date 03/01/2019
Division/Office	DAAAP/ OND
Review Completion Date	03/01/2019
Established/Proper Name	diclofenac epolamine topical system 1.3%
(Proposed) Trade Name	Flector® Patch 1.3%
Pharmacologic Class	nonsteroidal anti-inflammatory drugs (NSAIDs)
Applicant	IBSA Institut Biochimique SA
Dosage form	180 mg diclofenac per topical system (1.3%)
Applicant proposed Dosing Regimen	one (1) patch to the most painful area twice a day
Applicant Proposed Indication(s)/Population(s)	for the topical treatment of acute pain due to minor strains, sprains, and contusions in pediatric patients 6 to 16 years old
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	for the topical treatment of acute pain due to minor strains, sprains, and contusions in pediatric patients down to 6 years old
Recommended Dosing Regimen	one (1) topical system to the most painful area twice a day

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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat

NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

The Applicant submitted this supplemental new drug application (sNDA) 021234 -Supplement-16 as an efficacy supplement for "Flector Patch" (diclofenac epolamine topical system) 1.3%, for the topical treatment of acute pain due to minor strains, sprains, and contusions in pediatric patients 6 to 16 years old. Flector topical system contains diclofenac epolamine that is a nonsteroidal anti-inflammatory drug (NSAID). The proposed dosing regimen is one Flector topical system to the most painful area twice a day in pediatric patients ages 6 to 16 years old.

Flector was originally approved under NDA 021234 on January 31, 2007, for the topical treatment of acute pain due to minor strains, sprains, and contusions in adults. The approved dosing regimen for Flector in adults is one topical system twice per day. The proposed dosing regimen for the pediatric population is the same as the approved regimen in adults.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided substantial evidence of effectiveness to support approval of NDA 021234 for Flector topical system for the topical treatment of acute pain due to minor strains, sprains, and contusions in pediatric patients ages 6 to 16 years old. The Applicant performed one open-label study in pediatric patients to support the safety of Flector topical system in pediatric patients ages 6 to 16 years old. The available data for Flector topical system did not raise any new safety concerns for use of Flector in pediatric patients. The pharmacokinetic data of the pediatric study demonstrated comparable exposures between the pediatric population and adult population. In general, for NSAIDs, analgesic efficacy in the adult population may be extrapolated to pediatric patients down to the age of 2 years, because the underlying conditions and exposure response to NSAIDs are similar in both populations. Thus, the available pharmacokinetic data support extrapolating efficacy from adults to the pediatric population ages 6 to 16 years old, for the proposed indication.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Flector topical system is indicated for the topical treatment of acute pain due to minor strains, sprains, and contusions in adults. The Applicant proposes to use Flector for pediatric patients ages 6 to 16 years for the same indication as adults. The Division recommends approval if the Applicant and Division arrive at agreed-upon labeling.

Strains, sprains, and contusions are common among children. Pain and swelling are often associated with these injuries. The primary treatment goals are to minimize further damage and relieve pain and swelling. In general, there are limited therapeutic options available for treatment of pain of soft tissue injuries in the pediatric population and analgesic use in pediatric patients is mostly off-label. Some analgesics with pediatric labeling that may have a role in managing pain of strains, sprains, and contusions include acetaminophen, aspirin, and ibuprofen.

The most common (incidence ≥3%) adverse reactions with Flector from the controlled data in adult patients include pruritus (5% for Flector vs. 8% for placebo) and nausea (3% for Flector vs. 2% for placebo). The Applicant evaluated the safety and tolerability of Flector for the topical treatment of acute pain due to minor strains, sprains, and contusions in an open-label study in pediatric subjects ages 6 to 16 years old. The most common (incidence ≥3%) adverse reactions with Flector in this open-label pediatric study were headache (9%), pruritus (7%), nausea (3%), and stomach discomfort (3%). There were no new important potential safety concerns in the pediatric population. Review of local tolerability of Flector in this open-label pediatric study did not raise any new safety concern about use of Flector in pediatric population. Additionally, review of the available postmarket safety data for Flector topical system and diclofenac products did not raise any new safety concerns for use of Flector topical system in adult or pediatric patients.

The Applicant also evaluated the pharmacokinetic profile of Flector in their open-label study in pediatric subjects ages 6 to 16 years old. The pharmacokinetic profile of Flector in pediatric patients was similar to adult patients, with low systemic exposure to diclofenac in both patient populations.

There are no adequate and well-controlled efficacy trials to support effectiveness of Flector in the pediatric population. However, the underlying conditions and exposure response to NSAIDs is similar in both adults and pediatric populations. In general, for NSAIDs, analgesic efficacy in the adult population may be extrapolated to pediatric patients down to the age of 2 years, because the underlying conditions and

exposure response to NSAIDs are similar in both populations. The pharmacokinetic data of the pediatric study demonstrated comparable exposures between pediatric population and adult population. Thus, the available pharmacokinetic data support extrapolating efficacy from adults to the proposed pediatric population.

Approval of Flector in a pediatric population will add an alternative option for the treatment of acute of pain due to minor strains, sprains, and contusions in pediatric subjects ages 6 to 16 years old. There is currently no FDA approved topical system for treatment of pain in a pediatric population. Flector topical system will add to the existing armamentarium for pain management in the proposed indication.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Strains, sprains, and contusions are common among children. Symptoms and signs of strains, sprains, and contusions depend on the severity of the injury, but pain and swelling are often associated with these injuries.	Strains, sprains, and contusions are common among children and are associated with pain and swelling. Pain may be undertreated in pediatric patients and remains an unmet medical condition in this population.
Current Treatment Options	• Treatment of strains, sprains, and contusions depend on severity of injury, symptoms, age, and general health. The primary treatment goals are to minimize further damage and relieve pain and swelling. • Non-pharmacological treatment options include RICE approach (rest, ice, compression, and elevation), activity restrictions, splint, cast, assistive devices such as crutches, and physical therapy. • Pharmacologic treatment options for pain control include multiple classes of medications such as acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), anesthetics (such as lidocaine), anticonvulsants, antidepressants, and opioids. These medications are available in multiple formulations and can be administered through a variety of different routes such as oral, intramuscular injection, intravenous injection, and topical and transdermal systems. • In general, analgesic use in pediatric patients is mostly off-label. Some analgesics with pediatric labeling include acetaminophen [oral and	There are many different options available for pain management in adults, however, there are limited pharmacologic options for management of pain in the pediatric population. There is currently no FDA approved topical system for treatment of pain in pediatric population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	intravenous (IV)], aspirin, ibuprofen, fentanyl (transdermal and injection), buprenorphine injection, meperidine, oxycontin, codeine/APAP, and hydrocodone/APAP. Among these options, acetaminophen (oral), ibuprofen, and aspirin are appropriate for use after minor sport injuries in pediatric patients.	
Benefit	• Analgesic efficacy in the adult population may be extrapolated to the proposed target population, because the underlying conditions and exposure response to NSAIDs are similar in both populations and the pharmacokinetic profile of Flector in pediatric patients was similar to adult patients.	The available data provide substantial evidence to support safety and effectiveness of Flector for pediatric population ages 6 to 16 years old.
Risk and Risk Management	• The most common (incidence ≥3%) adverse reactions with Flector from the controlled data in adult patients include pruritus (5% for Flector vs. 8% for placebo) and nausea (3% for Flector vs. 2% for placebo). • The most common (incidence ≥3%) adverse reactions with Flector from the uncontrolled data in pediatric patients include headache (9%), pruritus (7%), nausea (3%), and stomach discomfort (3%). It is uncertain if reported cases of headache in this open-label study are related to Flector because there were no control groups for comparison. Application site reactions including application site pruritus are known adverse reactions of Flector that are reported with similar frequency in adult patients. In the absence of controlled data, the relatedness of adverse reactions to Flector cannot be assessed. • Most AEs were mild to moderate in severity. • There were no deaths, serious adverse events, dropouts/study discontinuations due to adverse events, or significant adverse events. • Postmarket safety data for Flector topical system and diclofenac products did not raise any new safety concerns for use of Flector topical system in pediatric or adult subjects.	There are no significant safety concerns regarding use of Flector in this pediatric population. There is no need for risk mitigation beyond the information in the labeling.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application

☒	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as		8.1.2. Study Results - Efficacy Results
		☒	Patient reported outcome (PRO)	8.1.2. Study Results - Efficacy Results
		☐	Observer reported outcome (ObsRO)	
		☒	Clinician reported outcome (ClinRO)	8.1.2. Study Results - Efficacy Results
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Strains, sprains, and contusions are common types of soft-tissue injuries. These injuries may occur during sports and exercise, or during simple everyday activities. Strains, sprains, and contusions are more common among children who are active and play sports, but these injuries may occur in any situation such as a simple fall. Symptoms and signs of a strain, sprain, and contusion depend on the severity of the injury, but pain and swelling are often associated with these injuries. On the other hand, pain might be underdiagnosed or undertreated in pediatric populations due to difficulty in communication between children and observers, and observers' interpretation of pain. There are limited therapeutic options available for treatment of pain of soft tissue injuries in pediatric population.

2.2. Analysis of Current Treatment Options

Treatment of strains, sprains, and contusions depend on severity of injury, symptoms, age, and general health. The primary treatment goals are to minimize further damage and relieve pain and swelling. Non-pharmacological treatment options include RICE approach (rest, ice, compression, and elevation), activity restrictions, splint, cast, assistive devices such as crutches, and physical therapy. Pharmacologic treatment options for pain control include multiple classes of medications such as acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), anesthetics (such as lidocaine), anticonvulsants, antidepressants, and opioids. These medications are available in multiple formulations and can be administered through a variety of different routes such as oral, intramuscular injection, intravenous injection, and topical and transdermal systems.

Although there are many different options available for pain management in adults, there are limited pharmacologic options for management of pain in pediatric population. In general, analgesic use in pediatric patients is mostly off-label. Some analgesics with pediatric labeling include acetaminophen [oral and intravenous (IV)], aspirin, ibuprofen, fentanyl (transdermal and injection), buprenorphine injection, meperidine, oxycontin, codeine/APAP, and hydrocodone/APAP. There is currently no FDA approved topical system for treatment of pain in pediatric population.

3 Regulatory Background

U.S. Regulatory Actions and Marketing History
The new drug application (NDA) for "Flector Patch" (diclofenac epolamine topical patch) 1.3% was submitted to the Agency on December 18, 2000, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The Agency approved NDA 021234 for Flector on January 31, 2007, for the topical treatment of acute pain due to minor strains, sprains, and contusions.

3.1. Summary of Presubmission/Submission Regulatory Activity

At the time of approval of NDA 021234 for Flector topical system on January 01, 2007, the pediatric study requirement for ages 0 through 1 year was waived and the pediatric studies for ages 2 through 16 years were deferred. The deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) for Flector as stated in the approval letter dated January 31, 2007, were as follows:

710-1 Deferred pediatric study under PREA for the treatment of acute pain due to minor strains, sprains, and contusions in pediatric patients ages 2 through 16.

Final Report Submission: January 31, 2011

At that time, the required studies included assessments of pharmacokinetics, safety and efficacy for pediatric patients ages 2 years and above.

On February 22, 2008, the Applicant submitted a pediatric protocol to the IND 049459 for Flector topical system intended to fulfill the pediatric study requirement. The protocol was an open-label uncontrolled study of safety and local tolerability of Flector in pediatric patients ages 8 to 16 years with minor soft tissue injuries. The protocol had the following deficiencies:

- (b) (4)
-

On March 15, 2011, the Division decided to release the product from the original PREA requirements and revise the PREA requirements to waive studies in pediatric patients less than 6 years of age, and to require conduct of pharmacokinetic, efficacy and safety studies in pediatric patients ages 6 to 16 years.

Subsequently, THE DIVISION determined that because Flector is an NSAID, efficacy findings for NSAIDs in adults may be extrapolated to pediatric patients over the age of 2 years. Therefore, the Applicant need not be required to conduct efficacy assessments for Flector topical system in pediatric patients ages 6 to 16 years of age, with the caveat that if the systemic pharmacokinetic profile for Flector in pediatric patients is markedly different than in adults, an

efficacy trial may be necessary.

On January 12, 2012, THE DIVISION sent an advice /information request (IR) letter to the Applicant that conveyed the following comment:

> "Pediatric studies for the Flector patch as required by PREA must include pharmacokinetic and safety studies in pediatric patients, ages 6 to 16 years. The Division's current thinking regarding NSAIDs is that efficacy in the adult population may be extrapolated to pediatric patients down to the age of 2 years, since the underlying conditions and exposure response to NSAIDs is similar in both populations. That being said, if the pharmacokinetic profile of Flector in pediatric patients is not similar to that in adults, an efficacy study may be required. Therefore, an open-label study that assesses the pharmacokinetics, safety and tolerability of Flector in pediatric patients ages 6 to <17 years is acceptable, with the caveat regarding pharmacokinetics, as stated above."

On March 8, 2012, the Applicant proposed a revised pediatric study plan to assess pharmacokinetics, safety, and tolerability for pediatric patient 6 to 16 years of age, under Study 08US/Fp03. The Agency reviewed the protocol and sent an IR on July 13, 2012 requesting further information. The Applicant submitted a revised pediatric protocol on October 03, 2012 to reflect the Agency's requests.

On December 21, 2012, the agency determined that the Applicant was released from the initial postmarketing requirement (PMR) 710-1 and issued a new postmarketing requirement under PREA to reflect the new agreed-upon age range and study goals. According to the Agency's letter titled "release from postmarketing requirement, new postmarketing requirement", dated December 21, 2012, the Agency waived the pediatric study requirement for ages birth to less than 6 years because the necessary studies are impossible or highly impracticable. The Agency stated that strains and sprains are uncommon in pediatric patients under the age of 6 years, and there are too few patients to study. The Agency deferred submission of pediatric study for ages 6 to 16 years for this application because the pediatric study had not been completed at that time.

The deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act was a required postmarketing study, as listed below:

1989-1	Deferred pediatric study under PREA to assess the pharmacokinetics, safety, and tolerability in pediatric patients 6 to 16 years of age with minor soft tissue injuries.	
	Final Protocol Submission:	Complete (submitted October 3, 2012)
	Study/Trial Completion:	April 1, 2015
	Final Report Submission:	April 1, 2016

The Agency had further communications with the Applicant regarding the pediatric study, including an IR dated February 14, 2013. The Applicant submitted a revised pediatric study protocol for "Study 08US/Fp03" on April 03, 2013, that served as the final pediatric study protocol to fulfill the PMR 1989-1. Study 08US/Fp03 entitled "an open-label, prospective, uncontrolled study of the safety and local tolerability of the diclofenac epolamine patch (Flector® Patch) in pediatric patients with minor soft tissue injuries".

Completion of Study 08US/Fp03 was delayed, but patient enrollment was ongoing. On October 23, 2017, the Applicant submitted a deferral extension (DE) request to NDA 021234 (Flector) for their pediatric post-marketing study completion and final report submission timelines. The original final report submission goal date was April 1, 2016. The Applicant stated that they intend to submit the final report by November 28, 2017. The DE request was submitted within a relatively short time from the date that the Applicant planned to submit the final study report. THE DIVISION and the Pediatric Research Committee (PeRC) reviewed this matter and decided that it would not be necessary to take regulatory action on the DE request given the Applicant's plans and timeline.

On December 13, 2017, the Applicant submitted the final clinical study report (CSR) for Study 08US/Fp03 to address PREA requirement for Flector topical system. Upon the Agency's review, an IR was sent to the Applicant on February 01, 2018, requesting additional information to be submitted as a supplement to their NDA to address the PREA requirements for Flector topical system. In response to the Agency's IR, the Applicant (IBSA) submitted the current supplement, S-016 to NDA 021234 for Flector topical system on May 2, 2018. This supplemental application proposes to incorporate the results of the PREA postmarketing requirement study 1989-1 entitled "An open-label, prospective, uncontrolled study of the safety and local tolerability of the diclofenac epolamine patch (Flector® Patch) in pediatric patients with minor soft tissue injuries" into the labeling for Flector.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

An OSI consult was not requested given the single completed study in this submission.

4.2. Product Quality

There was no new CMC information to review in this submission. Diclofenac topical system is a previously approved product in adults. There is no pediatric-specific formulation intended for marketing.

A smaller size of Flector topical system was used in six subjects. Flector topical system is (b) (4) intended for local delivery. Thus, there is no CMC concern about using a smaller size of Flector topical system.

4.3. Clinical Microbiology

No clinical microbiology consult was requested for this previously approved product.

4.4. Devices and Companion Diagnostic Issues

Device or companion diagnostic test was not needed in support of this product

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

No new nonclinical pharmacology/toxicology ata was provided for this previously approved product.

6 Clinical Pharmacology

6.1. Executive Summary

IBSA submitted a labeling supplement to support use of Flector topical system for the topical treatment of acute pain due to minor strains, sprains, and contusions in pediatric patients 6 to 16 years old. The supplement is supported by PREA PMR (1989-1) study 08US/Fp03. THE DIVISION indicated to the Applicant that efficacy in the adult population may be extrapolated to pediatric patients down to the age of 2 years, since the underlying conditions and exposure response to NSAIDS is similar in both populations. The open-label study, 08US/Fp03, assessed the pharmacokinetics, safety and tolerability of Flector in pediatric patients ages 6 to <17 years. The Applicant compared the observed plasma concentrations in pediatric patients with different adult data after repeated application of Flector topical system. The results indicate that systemic exposure of diclofenac with Flector is low in adults and pediatric patients. Additionally, in those subjects with detectable plasma concentrations, the plasma levels are

similar between adult and pediatric patients when used as indicated with one Flector applied to the most painful area twice a day.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Flector topical system applied to intact skin provides local analgesia by releasing diclofenac epolamine from the Flector into the skin. Plasma concentrations of diclofenac in the range of 1.3 – 8.8 ng/mL were noted after five days with twice-a-day Flector application in adults and suggest that penetration into the local tissue was achieved in the pediatric population in manner similar to the adult populations previously studied.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The recommended dose of Flector topical system in adults is one (1) Flector to the most painful area twice a day.

Therapeutic Individualization

Flector topical system may be applied to pediatric patients 6 -16 years old. (b) (4)

Outstanding Issues

None

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Flector topical system applied to intact skin provides local analgesia by releasing diclofenac epolamine from the patch into the skin. In adult patients, following a single application of the Flector on the upper inner arm, peak plasma concentrations of diclofenac (range 0.7 – 6 ng/mL) were noted between 10 – 20 hours of application. Plasma concentrations of diclofenac in the range of 1.3 – 8.8 ng/mL were noted after five days with twice-a-day Flector application in adults. The pharmacokinetics of Flector has been tested in healthy adult volunteers at rest or undergoing moderate exercise (cycling 20 min/h for 12 h at a mean HR of 100.3 bpm). No

clinically relevant differences in systemic absorption were observed, with peak plasma concentrations in the range of 2.2 – 8.1 ng/mL while resting, and 2.7 – 7.2 ng/mL during exercise in adults.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

On January 12, 2012, THE DIVISION sent an advice /information request (IR) letter to the Applicant that conveyed the following comment:

> "Pediatric studies for the Flector patch as required by PREA must include pharmacokinetic and safety studies in pediatric patients, ages 6 to 16 years. The Division's current thinking regarding NSAIDs is that efficacy in the adult population may be extrapolated to pediatric patients down to the age of 2 years, since the underlying conditions and exposure response to NSAIDS is similar in both populations. That being said, if the pharmacokinetic profile of Flector in pediatric patients is not similar to that in adults, an efficacy study may be required. Therefore, an open-label study that assesses the pharmacokinetics, safety and tolerability of Flector in pediatric patients ages 6 to <17 years is acceptable, with the caveat regarding pharmacokinetics, as stated above."

The Applicant evaluated systemic exposure of diclofenac in pediatric Study 08US/Fp03 (S-1) which was "An open-label, prospective, uncontrolled study of the safety and local tolerability of the diclofenac epolamine patch (Flector® Patch) in pediatric patients with minor soft tissue injuries". The final Clinical Study Report for study 08US/Fp03 was submitted on December 13, 2017 of the NDA.

In the adult PK studies, peak plasma levels were observed at the end of duration of Flector application or at the time of removal of Flector. In the pediatric study, plasma pharmacokinetics (PK) were based on two blood draws, one 24 hours after initial Flector application and the second at the final study visit. This limited sampling is adequate to capture the peak plasma concentrations, based on previously known experience from adults. One-hundred four subjects with a soft tissue injury, the majority male (65.4%), were enrolled in the study, with equal numbers being assigned to two age groups, 6-11 years and 12-16 years. There were six subjects out of 104 subjects that needed a smaller topical system during the study. The topical system was cut because opposing ends of the full-sized topical system were going to overlap at the site of injury. The plasma levels of diclofenac were presented for all ages 6-16 and split by age groups 6-11 years and 12-16 years (see Table 1 below). Additionally, the plasma concentrations are presented based on number of days of application. The range of plasma levels are also presented with a maximum plasma concentration noted up to 17.55 ng/mL in only four subjects out of 52 in the Age 6-11 group after 5 to 7-day application of the

topical system. The observed low plasma levels of diclofenac in pediatric patients is consistent with the observation in adults and therefore the observations may not be clinically significant.

As indicated in the Flector topical system label "No clinically relevant differences in systemic absorption were observed, with peak plasma concentrations in the range of 2.2 – 8.1 ng/mL while resting, and 2.7 – 7.2 ng/mL during exercise (b) (4)." The systemic exposure of diclofenac is low when Flector is applied in adults. Approved product label reads "Systemic exposure (AUC) and maximum plasma concentrations of diclofenac, after repeated dosing for four days with Flector (b) (4), were lower (<1%) than after a single oral 50-mg diclofenac sodium tablet."

Table 1: Plasma Diclofenac Concentration in pediatric patients from study 08US/Fp03

Variable	Average (ng/mL)	Geometric mean‡
All Age 6-16		
Day 1-2 + SD (Range) [N=103] *	1.65 ± 1.99 (0.00 to 14.10)	1.05
Day 3-4† + SD (Range) [N=18]	2.42 ± 3.20 (0.26 to 14.09)	1.49
Day 5-7 + SD (Range) [N=25]	2.52 ± 3.51 (0.25 to 17.55)	1.45
Day 8-11 + SD (Range) [N=25]	1.27 ± 1.03 (0.00 to 3.90)	0.78
Day 12-15 + SD (Range) [N=33]	1.39 ± 1.14 (0.00 to 4.31)	0.72
Last day + SD (Range)	1.80 ± 2.36 (0.00 to 17.55)	0.99
Maximum + SD (Range)	2.37 ± 2.77 (0.17 to 17.55)	1.59
Minimum + SD (Range)	1.08 ± 0.98 (0.00 to 5.80)	0.66

	N = 52	
Variable	Average	Geometric mean
Age 6-11		
Day 1-2 + SD (Range)	1.83 ± 2.10 (0.12 to 14.10)	1.25
Day 3-4† + SD (Range) [N=13]	3.01 ± 3.60 (0.63 to 14.09)	2.02
Day 5-7 + SD (Range) [N=15]	3.25 ± 4.20 (0.51 to 17.55)	2.09
Day 8-11 + SD (Range) [N=11]	1.56 ± 1.12 (0.05 to 3.90)	1.07
Day 12-15 + SD (Range) [N=11]	2.04 ± 1.33 (0.00 to 4.31)	1.30
Last day + SD (Range)	2.49 ± 3.01 (0.00 to 17.55)	1.58
Maximum + SD (Range)	2.93 ± 3.36 (0.51 to 17.55)	2.05
Minimum + SD (Range)	1.39 ± 1.10 (0.00 to 5.80)	0.96

	N = 52	
Variable	Average	Geometric mean
Age 12-16		
Day 1-2 + SD (Range) [N=51]	1.46 ± 1.88 (0.00 to 10.92)	0.88
Day 3-4 + SD (Range) [N=5]	0.88 ± 0.67 (0.26 to 1.78)	0.68
Day 5-7 + SD (Range) [N=10]	1.43 ± 1.78 (0.25 to 5.95)	0.84
Day 8-11 + SD (Range) [N=14]	1.05 ± 0.93 (0.00 to 3.01)	0.61
Day 12-15 + SD (Range) [N=22]	1.07 ± 0.90 (0.00 to 3.31)	0.54
Last day + SD (Range)	1.11 ± 1.09 (0.00 to 5.95)	0.62
Maximum + SD (Range)	1.81 ± 1.90 (0.17 to 10.92)	1.24
Minimum + SD (Range)	0.76 ± 0.73 (0.00 to 3.99)	0.45

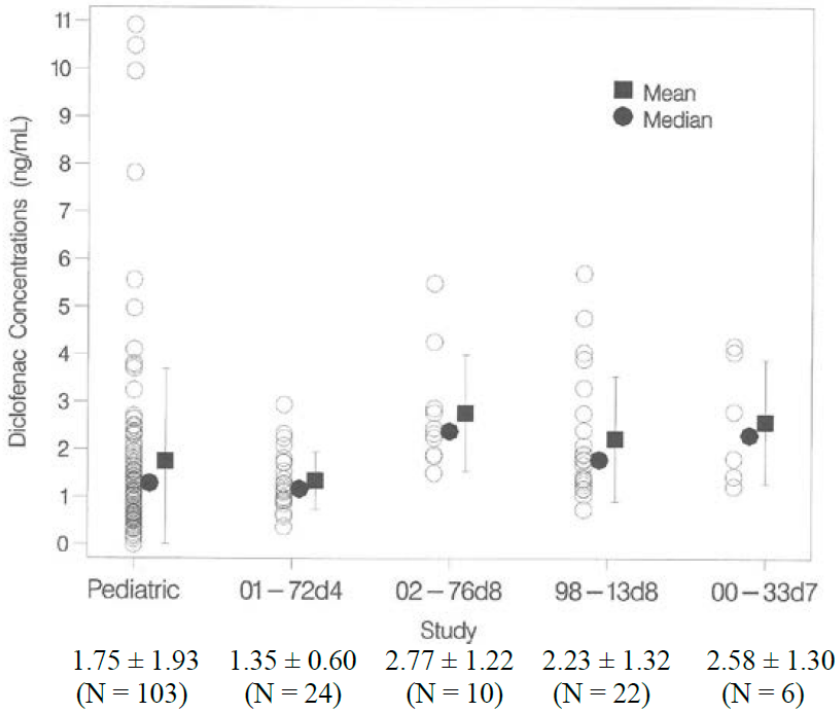
* One of the 104 subjects (b) (6) had a blood sample that was not analyzable. Unless otherwise specified, all Ns were 104 or 52.
†One patient had blood draws only on Day 1 and Day 2. The Day-2 blood draw was moved into the 2nd category.
‡ For calculation of geometric means, zero values were counted as 0.025 (half the detection limit).

(Source: Table 14.2.9 in clinical study report 08US/Fp03 submitted on 12/13/2017)

The pediatric study is an open-label study and therefore plasma concentrations cannot be correlated with any open-label assessments of efficacy.

The Applicant submitted comparison of observed pediatric plasma levels to previously noted plasma levels in adult PK studies. The blood levels of diclofenac following topical application of the Flector topical systemare low and based on only two measurements in pediatric patients and seem comparable to adult plasma levels from different studies.

Figure 1: Individual, median and mean (± SD) estimates of steady state diclofenac blood concentrations derived from the pediatric study 1-15 days after Flector application and four adult studies from Day 4 to Day 8 of Flector application.



(Source: Figure 2.7.2.1.1 in Summary of Clinical Pharmacology findings)

The Applicant compared pediatric and adult PK data in terms of arithmetic mean and variability. The arithmetic mean and standard deviation for the pediatric study was 1.75 ng/mL ± 1.93. Similar data were gathered from three other adult Flector topical system PK studies. The plasma concentrations of diclofenac were similar between pediatric patients compared to cross study diclofenac concentrations observed in adults.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Flector topical system applied to intact skin provides local analgesia by releasing diclofenac epolamine from the patch into the skin. Use the lowest effective dosage for shortest duration consist with the individual patient treatment goals. The recommended dose of Flector topical system is one (1) Flector to the most painful area twice a day.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

(b) (4)

. Overall, there were six subjects out of 104 subjects that needed a smaller patch during the study.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

None

Bioanalytical Method and Validation Summary

In the pediatric study, diclofenac was quantified using a validated High-Performance Liquid Chromatography (HPLC) method, with Tandem Mass Spectrometry Detection (MS-MS) having a quantitation range of 50 pg/mL to 50,000 pg/mL (0.05 – 50 ng/mL). Bioanalytical Report 130392 documented the bioanalytical method (SOP# ANI 10453.06.07) and validation report (125064AIPF).

Table 2: Bioanalytical method summary

Table: Bioanalytical method summary.

Method SOP No.: (b) (4) 10453.06/07
Method SOP Title: Determination of Diclofenac in Human EDTA K_2 Plasma over a Concentration Range of 50 to 50000 pg/mL using High Performance Liquid Chromatographic Method with Tandem Mass Spectrometry Detection and using Automated Extraction
Analyte: Diclofenac; Internal Standard: Diclofenac-d_4
Calibration Range: 50 to 50000 pg/mL
Biological Matrix: Human EDTA K_2 Plasma
Assay Volume Required: 0.100 mL
Sample Extraction: Automated liquid-liquid extraction with methyl tert-butyl ether
Type of Assay: LC/MS/MS (API 5000)
Column: ACE C18, 30 x 4.6 mm, 3 µm
Column Temperature: 25°C
Mobile Phase A: Milli-Q type water / methanol with ammonium formate and formic acid
Mobile Phase B: Methanol
Chromatographic Mode: Gradient; Flow Rate: 1.000 mL/min
Chromatographic Integration / Acquisition Data System: Analyst 1.6.1, AB Sciex
LIMS: Watson version 7.4.1, Thermo Fisher Scientific Corporation
Quantitation Method: Peak area ratio
Calibration Regression: Linear
Weighting Factor: $1/C^2$ [Peak area ratios (analyte/internal standard) versus the nominal concentration of the calibration standards]
Calibration equation: $y = mx + b$; Determination factor: r^2

(Source: Analytical method summary page 11 Project No. 130392 Diclofenac FDA Bioanalytical report)

Table 3: Bioanalytical method validation summary

Full Validation Report No.:	125064 (b) (4)
Full Validation Report Title:	Validation of a High Performance Liquid Chromatographic Method using Tandem Mass Spectrometry Detection and Automated Extraction for the Determination of Diclofenac (50 to 50000 pg/mL) in Human EDTA K_2 Plasma
Full Validation Report Effective Date:	21-OCT-2013
Validation Calibration Range:	50.00 to 50000.00 pg/mL (refer to the validation report in Attachment 2 including the raw numerical data)
Between-Run Accuracy and Precision:	Biases: -5.15 to 1.73% CV: 2.81 to 16.69%
Within-Run Accuracy and Precision:	Biases: -8.07 to 6.73% CV: 2.25 to 4.95%
Freeze and Thaw Stability:	4 cycles at -20°C
Short-Term Stability of Analyte in Matrix:	25h12min at room temperature
Long-Term Stability of Analyte in Matrix:	701 days at -20°C
Post-Preparative Stability:	71h08min at room temperature
Maximum Run Size	192 samples

(Source: Method Validation Summary page 12 Project No. 130392 Diclofenac FDA Bioanalytical report).

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

There was only one clinical trial relevant to this supplemental NDA. Table 4 shows the information related to this trial.

Table 4: Clinical Trial Relevant to this supplemental NDA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
-		None						
		Studies to Support Safety						
08US/Fp03	02132247	Open-label, prospective, uncontrolled study of the safety and local tolerability of the diclofenac epolamine patch (Flector® Patch) in pediatric patients with minor soft tissue injuries	1 Flector topical system to the injury site, twice daily	local tolerability and systemic safety of Flector topical system throughout the treatment period	a maximum 14 days or until treatment was no longer required for pain management, whichever occurred first	104	male and female subjects with minor soft tissue injury, with equal numbers in each age group of 6-11 years and 12-16 years	10 sites in the United States
		Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)						
-		None						

7.2. Review Strategy

The NDA submission contained one pediatric study, Study 08US/Fp03, which was a phase 4, open-label, prospective, uncontrolled study to evaluate the safety, local tolerability, and pharmacokinetics of the diclofenac epolamine topical system (Flector topical system) in a pediatric population with minor soft tissue injuries. The Applicant performed this study to fulfill the deferred pediatric study required as the postmarketing study, PMR 1989-1, for Flector topical system.

Flector topical system has been marketed since 2007 for topical treatment of acute pain due to minor strains, sprains, and contusion in adult population. Flector is an NSAID, and in general for NSAIDs, analgesic efficacy in the adult population may be extrapolated to pediatric patients over the age of 2 years. Thus, THE DIVISION had determined that the Applicant is not required to conduct efficacy assessments for Flector topical system in pediatric patients ages 6 to 16 years of age. However, THE DIVISION had noted that if the pharmacokinetic profile of Flector in pediatric patients is not similar to that in adults, an efficacy study may be required.

The focus of this review is to assess the local tolerability, systemic safety, and pharmacokinetic profile of Flector topical system in an age 6 to 16 years pediatric population. Adverse event and local tolerability data were collected in the pediatric study. Additionally, the Applicant compared the adverse event and local tolerability data with the data obtained from four previous adult studies that were submitted in NDA 021234. The pharmacokinetic profile of diclofenac in pediatric patients was evaluated and compared with the data from adults. The pharmacovigilance reporting for Flector topical system and the safety data for diclofenac derived from the public literature were also evaluated.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. An open-label, prospective, uncontrolled study of the safety and local tolerability of the diclofenac epolamine patch (Flector® Patch) in pediatric patients with minor soft tissue injuries

Trial Design

The NDA submission did not include any adequate and well-controlled efficacy trials of Flector in the pediatric population. The only clinical trial in this NDA submission was the open-label, prospective, uncontrolled study of the safety and local tolerability of the diclofenac epolamine patch (Flector® Patch) in 100 male and female pediatric patients with minor soft tissue injuries. Equal numbers of patients were enrolled into each of two age groups of 6 to 11 years and 12 to 16 years. Patients were asked to apply one Flector to the injury site, twice daily (approximately every 12 hours, morning and evening) for a maximum of 14 days or until treatment was no longer required for pain management, whichever occurred first.

The study visits included Day 1 (baseline/ study entry), Day 2, Day 4, Day 7, and Day 14 (or the day after pain resolution). The last visit was scheduled either on Day 14 or on the day after the patient experienced pain resolution sufficient to warrant treatment discontinuation. At each study visit, vital signs were measured and adverse events (AEs) were recorded including the investigator's scoring of reactions at the application site. Blood samples were obtained at Day 2 (24 hours after initial Flector application) and at the time of study discontinuation (with topical system in place) for determination of plasma diclofenac. In addition, patients reported their pain twice daily and the investigator provided a global assessment of patient response to therapy at the end of study.

Age Groups

The study was performed in patients 6 to 16 years of age. Study subjects were equally distributed between 6 to 11 years old and 12 to 16 years old.

Eligibility Requirement

Patients with minor soft tissue injury within 96 hours of study entry who had pain of at least moderate intensity (i.e. pain of at least 3 on the 6-point Wong-Baker Faces scale as shown in Figure 2 were included in the study.

Figure 2: Wong-Baker Faces scale

Source: Applicant's submission, 08US/Fp03 Clinical Study Report (CSR), section 11.4.1.1

The subjects were excluded if they had an open skin lesion, injury to spine or digits, or major soft tissue injury (such as fractures that require a hard cast). Patients were also excluded if they concomitantly used any drugs that may have interactions with diclofenac, such as other NSAIDs, serotonin-selective reuptake inhibitors (SSRI), lithium, digoxin, anticoagulants, antidiabetic agents, cyclosporin, methotrexate, quinolone antimicrobials, steroids, and diuretics. Ancillary treatments such as cold applications (ice, cold packs), wrappings of the injured site, and supports or crutches were permitted. Use of acetaminophen was permitted up until the time of study entry.

Study Endpoints

Primary endpoints were local tolerability and systemic safety of diclofenac epolamine throughout the treatment period. Additionally, diclofenac blood levels were analyzed using a Population Pharmacokinetics approach.

Secondary endpoints were the analgesic effect of Flector topical system, assessed by the patient on an ordinal scale of 0 to 5 (Wong-Baker Faces scale), global response to therapy by the investigator, and similarity of the pediatric plasma diclofenac pharmacokinetic profile in comparison to an adult pharmacokinetic profile derived from historical data.

Statistical Analysis Plan

This was a single arm, open-label, uncontrolled study. There were no specified primary efficacy variables to form conclusions about efficacy of Flector patch in pediatric patients. Thus, a detailed evaluation of the statistical analysis plan was not required. Refer to the biometrics' team filing review in DARRTS dated July 5, 2018 under NDA 021234, for detail. Summary of the biometrics' team review is provided under section 8.1.2 Study Results – Efficacy Results.

Protocol Amendments

The initial pediatric study protocol for Study 08US/Fp03 was submitted on February 25, 2008, titled "An open-label, prospective, uncontrolled study of the safety and local tolerability of the

Flector Patch (diclofenac epolamine patch) in pediatric patients with minor sport injuries." The Applicant claimed that efficacy was established by two previously completed studies in adult patients. The proposed dosing for the pediatric protocol was once daily and the proposed age range was 8 to 16 years old. The Division noted several deficiencies in the proposed pediatric protocol including the following. For details refer to clinical review dated May 12, 2009, under IND 49459.

- (b) (4)

On January 12, 2012, THE DIVISION sent an advice /information request (IR) letter to the Applicant that conveyed the following comments:

- Pediatric studies for the Flector patch as required by PREA must include pharmacokinetic, safety and tolerability in pediatric patients, ages 6 to 16 years.
- If the pharmacokinetic profile of Flector in pediatric patients is similar to adults, an open-label study to assess safety and tolerability will be acceptable. If the pharmacokinetic profile of Flector in pediatric patients is not similar to adults, an efficacy study may be required.
- Data must be provided to support the proposed dosing regimen of one diclofenac epolamine topical system daily in children and adolescents.
- At least 100 pediatric patients must be exposed to Flector topical system, with at least 25 patients exposed for 14 days.

On March 8, 2012, the Applicant submitted a revised pediatric protocol, Study 08US/Fp03, titled "an open-label, prospective, uncontrolled study of the safety and local tolerability of the diclofenac epolamine patch (Flector Patch) in pediatric patients with minor soft tissue injuries". The revised protocol adequately addressed most of the Division's concerns including the recruitment age and the number of patients. Dosage of Flector topical system was changed to one topical system twice daily in the revised protocol.

There were clinical pharmacology deficiencies in the revised pediatric protocol of March 8, 2012. (b) (4)

(b) (4)

The pediatric study was determined not acceptable because it was not adequately designed to obtain sufficient PK data. For further detail, refer to clinical review and clinical pharmacology review dated May 31, 2012, under IND 49459.

On July 13, 2012, the Division sent an Advice/Information Request letter to the Applicant requesting the following:

- Description of how the topical system will be used in different sizes for different age groups or for smaller application sites, and
- Adequate data to demonstrate similarity of time course (profile similarity) of diclofenac concentrations between adult and pediatric subjects.

The Applicant had further communication with the clinical pharmacology team to modify the pediatric protocol to reflect the requested information. Refer to section 6. Clinical Pharmacology for further detail.

On October 3, 2012, the Applicant submitted a revised protocol for Study 08US/Fp03, that did not permit cutting the topical system (except for the cases that the opposing ends of the full-sized topical system were going to overlap at the site of injury). The revised protocol contained only one PK sampling. Thus, the Division's concerns regarding the pharmacokinetic sampling for profile similarity was not addressed.

On February 14, 2013, the Division sent another IR letter to the Applicant requesting modification of protocol to reflect collection of two blood samples, one on Day 2 and the second one at any time during the study.

On April 3, 2013, the Applicant submitted a revised pediatric protocol for Study 08US/Fp03 that reflected the changes in the PK sampling, as recommended by the Division. The pediatric protocol dated April 3, 2013 was acceptable and served as the final pediatric protocol for Study 08US/Fp03.

8.1.2. Study Results

Compliance with Good Clinical Practices

This study report states that the study was conducted in compliance with good clinical practice (GCP) guidelines, including the archival of essential documents and was conducted according to the ethical principles of human research established by the Declaration of Helsinki.

Financial Disclosure

The Applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry Financial Disclosure by Clinical Investigators.

Patient Disposition

A total of 104 subjects were enrolled at 10 participating sites in the United States; 52 in the 6 to 11 year old subgroup and 52 in the 12 to 16 year old subgroup. Two subjects per group failed to have a second blood draw. Four additional subjects were enrolled (two in each age subgroup) to account for the four subjects who failed to have a second blood draw.

Ninety-one (91) subjects completed the study with no pain reported at the end of the study, 11 subjects completed the study with continued pain (i.e. pain score > 0), and two subjects were discontinued from the study; Subject (b) (6) due to presence of a fracture, and Subject (b) (6) due to use of an excluded concomitant treatment.

Protocol Violations/Deviations

Across the 10 investigator sites that participated in the study, there were 13 important protocol deviations (IPDs) in 6 unique categories. These deviations were managed appropriately. The protocol deviations did not affect the study results.

Table of Demographic Characteristics

Table 5 shows the demographic characteristics of the study population. There was only one treatment arm in this study and there were no control groups. Thus, the table includes one treatment column only.

Table 5: Demographic characteristics

Variable	N = 104
Sex	
Males (%)	68 (65.4%)
Females (%)	36 (34.6%)
Race/Ethnicity	
White (%)	73 (70.2%)
Hispanic (%)	12 (11.5%)
Black (%)	7 (6.7%)
Pacific Islander (%)	2 (1.9%)
Asian (%)	1 (1.0%)
Mixed (%)	9 (8.7%)
Age (years) + SD (Range)	11.6 ± 3.0 (6 to 16)
Height (in) + SD (Range)	60.2 ± 7.4 (42.3 to 74.0)
Weight (lb) + SD (Range)	114.7 ± 50.2 (44.5 to 318.0)
BMI (kg/m3) + SD (Range)	21.2 ± 5.2 (11.1 to 42.2)
Age 6-11	
Sex *	
Males (%) [N=52]	38 (73.1%)
Females (%) [N=52]	14 (26.9%)
Race/Ethnicity †	
White (%) [N=52]	37 (71.2%)
Hispanic (%) [N=52]	5 (9.6%)
Black (%) [N=52]	3 (5.8%)
Pacific Islander (%) [N=52]	0 (0.0%)
Asian (%) [N=52]	0 (0.0%)
Mixed (%) [N=52]	7 (13.5%)
Age (years) + SD (Range) [N=52]	9.0 ± 1.6 (6 to 11)
Height (in) + SD (Range) [N=52]	54.1 ± 4.8 (42.3 to 66.0)
Weight (lb) + SD (Range) [N=52]	80.3 ± 28.1 (44.5 to 188.0)
BMI (kg/m3) + SD (Range) [N=52]	18.8 ± 3.9 (11.1 to 30.3)
Age 12-16	
Sex *	
Males (%) [N=52]	30 (57.7%)
Females (%) [N=52]	22 (42.3%)
Race/Ethnicity †	
White (%) [N=52]	36 (69.2%)
Hispanic (%) [N=52]	7 (13.5%)
Black (%) [N=52]	4 (7.7%)
Pacific Islander (%) [N=52]	2 (3.8%)
Asian (%) [N=52]	1 (1.9%)
Mixed (%) [N=52]	2 (3.8%)
Age (years) + SD (Range) [N=52]	14.2 ± 1.4 (12 to 16)
Height (in) + SD (Range) [N=52]	66.4 ± 3.5 (58.0 to 74.0)
Weight (lb) + SD (Range) [N=52]	149.0 ± 43.6 (93.0 to 318.0)
BMI (kg/m3) + SD (Range) [N=52]	23.5 ± 5.3 (15.3 to 42.2)

* Fisher exact test: Age x Sex p=0.149; † Age x Race p=0.284.

Source: Applicant's submission, 08US/Fp03 Clinical Study Report (CSR), 14.1.1 Demographics

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

There were no other important baseline disease-specific characteristics for this product. The baseline characteristics appear generally representative of the to-be-marketed U.S. population.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The patients applied Flector to the injury site for a maximum of 14 days or until treatment was no longer required for pain management, whichever occurred first. Treatment duration is shown in Table 6. Use of NSAIDs was not permitted during the study. Use of acetaminophen was permitted up until the time of study entry.

Table 6: Treatment duration

Variable	N = 104
Data from Final Evaluation	
Days to final visit* + SD (Range)	9.7 ± 3.9 (2 to 16)
Days to last patch application* + SD (Range)	9.5 ± 3.9 (2 to 16)
Data from Investigational Patch Log	
Patches returned + SD (Range)	10.9 ± 7.7 (0 to 26)
Patches not dispensed + SD (Range)	11.3 ± 1.5 (0 to 14)
Total Patches unused + SD (Range)	22.2 ± 8.5 (7 to 40)
Total Patches used + SD (Range)	19.8 ± 8.5 (2 to 35)
Patches used per day + SD (Range)	2.1 ± 0.3 (1.0 to 2.8)
Data from Diary	
Patches used + SD (Range)	17.9 ± 8.0 (2 to 31)
Patches used per day + SD (Range)	1.8 ± 0.3 (1.0 to 2.4)
Age 6-11	
Data from Final Evaluation	
Days to final visit* + SD (Range) [N=52]	8.6 ± 3.9 (2 to 16)
Days to last patch application* + SD (Range) [N=52]	8.5 ± 3.9 (2 to 16)
Data from Investigational Patch Log	
Patches returned + SD (Range) [N=52]	13.1 ± 7.4 (0 to 26)
Patches not dispensed + SD (Range) [N=52]	11.3 ± 1.9 (0 to 14)
Total Patches unused + SD (Range) [N=52]	24.4 ± 8.6 (7 to 40)
Total Patches used + SD (Range) [N=52]	17.6 ± 8.6 (2 to 35)
Patches used per day + SD (Range) [N=52]	2.0 ± 0.3 (1.0 to 2.4)
Data from Diary	
Patches used + SD (Range) [N=52]	15.9 ± 8.0 (2 to 31)
Patches used per day + SD (Range) [N=52]	1.8 ± 0.3 (1.0 to 2.4)
Age 12-16	
Data from Final Evaluation	
Days on final visit* + SD (Range) [N=52]	10.8 ± 3.6 (2 to 15)
Days to last patch application* + SD (Range) [N=52]	10.5 ± 3.6 (2 to 15)
Data from Investigational Patch Log	
Patches returned + SD (Range) [N=52]	8.6 ± 7.4 (0 to 26)
Patches not dispensed + SD (Range) [N=52]	11.3 ± 0.9 (10 to 14)
Total Patches unused + SD (Range) [N=52]	19.9 ± 7.8 (10 to 40)
Total Patches used + SD (Range) [N=52]	22.1 ± 7.8 (2 to 32)
Patches used per day + SD (Range) [N=52]	2.1 ± 0.3 (1.0 to 2.8)
Data from Diary	
Patches used + SD (Range) [N=52]	19.9 ± 7.7 (2 to 31)
Patches used per day + SD (Range) [N=52]	1.9 ± 0.3 (1.0 to 2.3)

* Includes Day 0.

Source: Applicant's submission, 08US/Fp03 Clinical Study Report (CSR), Table 14.1.3

Efficacy Results – Primary Endpoint

Study 08US/Fp03 was not intended to evaluate efficacy. Thus, there were no primary efficacy endpoints.

Data Quality and Integrity

A senior applicant team member and the clinical monitor(s) trained the study site personnel on all aspects of the conduct of the studies prior to enrolling patients.

Efficacy Results – Secondary and other relevant endpoints

The Flector topical system was not compared to a placebo or any active comparator in this study. To establish efficacy in pediatric subjects, the Applicant evaluated the similarity between the pharmacokinetic profile of Flector topical system in this study and a historical adult population, to determine whether there was a foundation for extrapolating efficacy from adults to children. The pharmacokinetic data of the pediatric study showed that the systemic exposure to diclofenac with Flector was low and plasma levels of diclofenac were similar between adult and pediatric patients. Of note, Flector topical system is believed to provide analgesia primarily by delivering diclofenac to the local tissue at the site of injury rather than by its systemic exposure. Therefore, the small amount of diclofenac that is absorbed systemically is an indirect measure of the product's penetration and exposure of the local tissue at the site of injury. The available pharmacokinetic data support extrapolating efficacy from adults to the proposed pediatric population.

The Applicant also gathered data on pain reduction as secondary endpoints in Study 08US/Fp03. The secondary efficacy parameters assessed during the study were pain score by the patient and global response to therapy by the investigator. Table 7Table 7: Clinic visit pain scores shows the reported pain scores during the study. Figure 3 shows the reported pain score at different times for pediatric population and adult population. The data for the adult population is based on historical data in a previously completed study for Flector topical system (Study 00GB/Fp05).

Table 7: Clinic visit pain scores

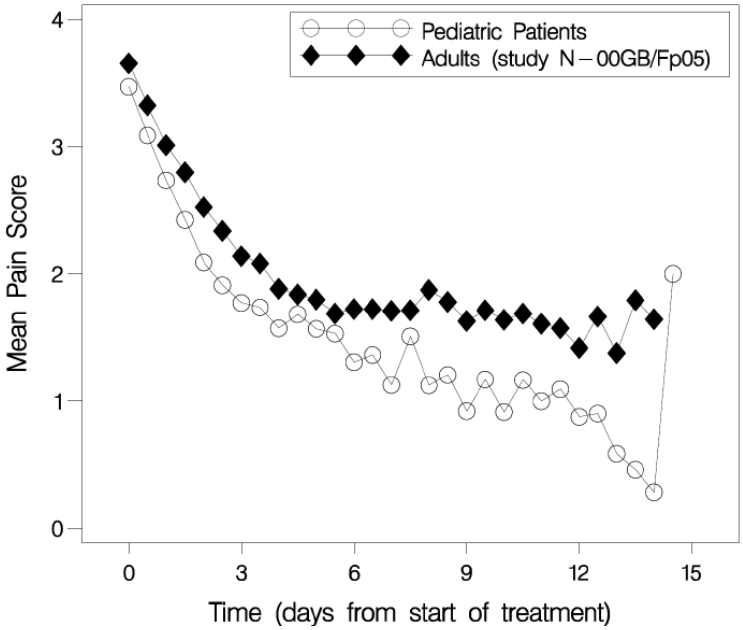
Variable	N	All Patients Mean+SD (range)	N	Age 6-11 Mean+SD (range)	N	Age 12-16 Mean+SD (range)	P*
Absolute Levels							
Screening	104	3.47 ± 0.61 (2 to 5)	52	3.37 ± 0.56 (2 to 5)	52	3.58 ± 0.64 (2 to 5)	0.075
Day 1-2	104	2.52 ± 0.96 (0 to 5)	52	2.25 ± 0.97 (0 to 4)	52	2.79 ± 0.87 (1 to 5)	0.004
Day 3-4	98	1.60 ± 1.18 (0 to 5)	49	1.33 ± 1.13 (0 to 4)	49	1.88 ± 1.18 (0 to 5)	0.020
Day 5-7	80	1.10 ± 1.07 (0 to 4)	36	0.75 ± 0.81 (0 to 3)	44	1.39 ± 1.19 (0 to 4)	0.008
Day 8-11	29	0.24 ± 0.64 (0 to 2)	12	0.17 ± 0.58 (0 to 2)	17	0.29 ± 0.69 (0 to 2)	0.604
Day 12-15	33	0.42 ± 0.66 (0 to 3)	11	0.27 ± 0.47 (0 to 1)	22	0.50 ± 0.74 (0 to 3)	0.361
Last Visit	104	0.19 ± 0.58 (0 to 3)	52	0.12 ± 0.47 (0 to 3)	52	0.27 ± 0.66 (0 to 3)	0.174
Change from Baseline							
Day 1-2	104	0.95 ± 0.83 (-1 to 3)	52	1.12 ± 0.88 (0 to 3)	52	0.79 ± 0.75 (-1 to 3)	0.044
Day 3-4	98	1.85 ± 1.16 (0 to 4)	49	2.02 ± 1.11 (0 to 4)	49	1.67 ± 1.20 (0 to 4)	0.140
Day 5-7	80	2.39 ± 1.07 (-1 to 4)	36	2.67 ± 0.86 (1 to 4)	44	2.16 ± 1.18 (-1 to 4)	0.034
Day 8-11	29	3.34 ± 0.81 (1 to 5)	12	3.17 ± 0.83 (1 to 4)	17	3.47 ± 0.80 (2 to 5)	0.331
Day 12-15	33	3.09 ± 0.84 (1 to 5)	11	3.18 ± 0.75 (2 to 4)	22	3.05 ± 0.90 (1 to 5)	0.668
Last Visit	104	3.28 ± 0.73 (1 to 5)	52	3.25 ± 0.59 (2 to 4)	52	3.31 ± 0.85 (1 to 5)	0.689
Percentage with Pain>0							
Day 1-2	104	103 (99.04%)	52	51 (98.08%)	52	52 (100.0%)	1.000
Day 3-4	98	77 (78.57%)	49	35 (71.43%)	49	42 (85.71%)	0.139
Day 5-7	80	53 (66.25%)	36	20 (55.56%)	44	33 (75.00%)	0.096
Day 8-11	29	4 (13.79%)	12	1 (8.33%)	17	3 (17.65%)	0.622
Day 12-15	33	12 (36.36%)	11	3 (27.27%)	22	9 (40.91%)	0.703
Last Visit	104	14 (13.46%)	52	4 (7.69%)	52	10 (19.23%)	0.149

Screening is defined as Day 0. Thus, Day 1-2 is 1-2 days after the start of treatment, etc.

* P derived from ANOVA comparing the two age groups.

Source: Applicant's submission, 08US/Fp03 Clinical Study Report (CSR), Table 14.2.1

Figure 3: Clinic visit pain score vs. time: pediatric population and historical adult population



Source: Applicant's submission, 08US/Fp03 Clinical Study Report (CSR), Section 14.2.6

The biometrics team provided a brief review dated July 5, 2018, under NDA 021234, including the following comments.

"Given that this was a single arm, OL study, there were not any specified primary efficacy variables that were used to form conclusions about efficacy of Flector patch in pediatric patients. The secondary variables included pain scores assessed at clinical visits, pain scores collected in the patient diary, global response to the therapy and plasma diclofenac concentration.

The analysis set included all patients who received at least one Flector patch application. Analysis of variance (ANOVA) were performed for both the clinic visit and patient diary pain scores. Longitudinal Generalized Estimating Equation (GEE) models (adjusting for multiple assessments per patient) with an independent covariance matrix were used to analyze the data. The models contained the following factors: baseline pain score, gender, center (with the 4 centers with the fewest patients combined), age category (6-11 vs 12-16), day (as a categorical variable including morning and evening times for the diary analyses), age by center interaction, and age by day interaction. A second analysis was performed in which both interaction terms were removed regardless of their level of statistical significance.

For global response to the therapy, the two age groups (6-11 years and 12-16 years) were compared using the Wilcoxon rank-sum test. In addition, they were compared using an ANOVA model that treated the global improvement score as a continuous variable. Factors in the

model included gender, center, age category and the age category-by-center interaction. In an additional model, the interaction term was removed.

For comparative purposes, pain score data from a prior adult study (N-00GB/Fp05) were compared with data from the current pediatric cohort. The effects included in the model were baseline pain score, study (Pediatric vs Adult), assessment (generally but not exactly comparable to day because of slight differences in the protocol) and the study by assessment number interaction. Because in the adult study, pain was scored on a scale of 0 to 10, while in the present pediatric study, pain was scored on a scale of 0 to 5, pain scores from the prior adult study were divided by 2. A second analysis was performed in which the interaction term was removed. In addition, analyses were performed on the first 14 patch assessments and on the last 14 patch assessments.

There were 104 patients included in the study, with equal numbers in two age groups (6-11 years and 12-16 years). In the total study population, the baseline pain score averaged 3.47 and declined to 0.19 (in-clinic) and 0.28 (Diary) at the final assessment, with 14 patients (13.5%) still experiencing a pain score greater than 0. Interestingly, pain scores declined more rapidly in the 6-11 year old subgroup when compared to the 12-16 year old subgroup over the first seven days of the study. The ANOVA models for all changes from baseline pain scores for the in-clinic visits and diary revealed an overall difference between the age-based subgroups ($p = 0.004$ and $p = 0.011$ respectively). The diary data were further analyzed to compare the total pediatric population with a historical adult population, and the results revealed that the reduction in pain following Flector patch usage was somewhat greater in the younger cohort during the first 7 days of treatment when relatively few patients in either study had exited (1.66 vs 1.44), although not quite reaching statistical significance. For global response to the therapy, 87 patients (83.7%) experienced restoration of normal function and 2 (1.9%) experienced no clinical improvement, with the remaining 15 falling somewhere in between. Consistent with the aforementioned pain score data, more patients in the 6-11 year old subgroup experienced restoration of normal function than their older counterparts, although the comparison did not quite reach statistical significance ($p < 0.084$)."

In general, the results demonstrated improvement in pain level in all pediatric patients in Study 08US/Fp03, with a more rapid improvement in the younger age group (6 to 11 years old) that is an expected pattern after soft tissue injuries in pediatric patients. However, no conclusion can be made about the efficacy of Flector topical system in pediatric patients based on pain assessment in this open-label uncontrolled study.

Dose/Dose Response

Only one dose of Flector topical system, 180 mg diclofenac (1.3%) every 12 hours, was used in this open-label study. This is the same as the approved dose for Flector in the adult population and is reasonable in the context of current NDA submission as a pediatric supplement.

Durability of Response

The study subjects were followed for up to 14 days or until resolution of symptoms. No conclusion can be made regarding the effect of the drug over time for this individual study.

Persistence of Effect

The study subjects were not followed after discontinuation of Flector. No conclusion can be made regarding the effect of Flector over time after treatment was stopped or withheld for this individual study.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The analgesic effect of Flector topical system assessed by the patient on an ordinal scale of 0 to 5 (Wong-Baker Faces scale) and global response to therapy by the investigator were the secondary efficacy endpoints. However, Study 08US/Fp03 was an open-label study and no conclusion on efficacy can be made in the absence of a placebo group. Refer to Efficacy Results – Secondary and other relevant endpoints for details.

Additional Analyses Conducted on the Individual Trial

Refer to Efficacy Results – Secondary and other relevant endpoints for details.

8.1.3. Assessment of Efficacy Across Trials

There were no controlled trials in this submission to evaluate efficacy.

8.1.4. Integrated Assessment of Effectiveness

There are no adequate and well-controlled efficacy trials to support effectiveness of Flector in the pediatric population. The Applicant evaluated the pharmacokinetic profile of Flector in their open-label pediatric study (Study 08US/Fp03). The plasma diclofenac concentration results from this study were analyzed and compared with data from historical studies for Flector topical system in adult population. The data from Study 08US/Fp03 demonstrated that the pharmacokinetic profile of Flector in pediatric patients ages 6 to 16 years old is similar to that in adults. In general, for NSAIDs, analgesic efficacy in the adult population may be extrapolated to pediatric patients over the age of 2 years because the underlying conditions and exposure response to NSAIDs are similar in both populations. Thus, the available pharmacokinetic data support extrapolating efficacy from adults to the pediatric population ages 6 to 16 years old.

The Applicant also collected data on pain scores as secondary efficacy endpoints in their open-label study. (b) (4)

8.2. Review of Safety

8.2.1. Safety Review Approach

Pursuant to the PREA post-marketing commitment for NDA 021234, the Applicant performed one pediatric study (Study 08US/Fp03), that was a phase 4, open-label, prospective, uncontrolled study to assess the local tolerability, systemic safety, analgesic effect, and pharmacokinetic profile of Flector topical system in pediatric population ages 6 to 16 years old with minor soft tissue injuries.

The following were reviewed to assess safety of Flector topical system in pediatric patients:

- Adverse events and local tolerability data from the open-label pediatric study
- Comparison of the adverse event data from the pediatric study with those obtained from previous four phase 3 adult studies reported in NDA 021234
- Pharmacokinetic profile and systemic exposure of diclofenac from the open-label pediatric study
- Pharmacovigilance reporting and safety data for diclofenac as derived from literature

8.2.2. Review of the Safety Database

Overall Exposure

A total of 104 subjects were enrolled at 10 sites in the United States, 52 subjects in the 6 to 11 years old subgroup and 52 subjects in the 12 to 16 years old subgroup..

The average duration of treatment with Flector topical system application was 9.5 days, as shown in Table 6. Twenty-eight (28) subjects (26.9%) applied the Flector topical system for at least 13 days and 7 subjects (6.7%) for at least 14 days. The treatment duration for the 6 to 11 years old subgroup was shorter than the 12 to 16 years old subgroup, and fewer patients in the younger subgroup were treated for 13 days or longer (9 vs. 19). The younger subgroup of 6 to

11 years old had a more rapid pain reduction, which is expected in younger patients. Ninety-one (91) subjects completed the protocol with complete pain resolution and 11 subjects completed the protocol without pain resolution (i.e. pain score > 0). Two subjects were discontinued from the study due to exclusionary criteria, one subject was diagnosed with a fracture and one subject received Tylenol as concomitant treatment.

In the Advice Letter dated January 12, 2012, the Division had provided the following advice: "At least 100 pediatric patients must be exposed to the patch, with at least 25 exposed for 14 days." The overall exposure and the number of subjects who were exposed to Flector for 14 days are acceptable, given that natural course of recovery from minor injuries is shorter in the younger population.

Adequacy of the safety database

The Applicant followed the requirement to evaluate the safety of Flector topical system in 100 pediatric patients ages 6 to 16 years old. Patients were distributed evenly between the two age groups. Flector topical system was applied every 12 hours for a total of maximum 14 days or until pain resolution, whichever came first. The pediatric study was performed in 10 locations in the United States.

The pediatric patients in this open-label study were exposed to the appropriate dose and duration of treatment with Flector topical system. Patient demographic characteristics represent the U.S. target population. The safety database included a sufficiently diverse population of patients in the U.S. to represent the expected target population of pediatric patients age 6 to 16 years old.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The submission was poorly organized. The Applicant submitted data from previously completed adult studies in addition to the data from the pediatric study (Study 08US/Fp03). These datasets were not organized by clinical study and were not labeled by study number, which made it laborious and time-consuming to assess the consistency of the data with the study report for Study 08US/Fp03.

For Study 08US/Fp03, the Applicant submitted the datasets intended to support the critical safety analyses, including the preferred terms and verbatim terms for adverse events to allow an analysis of how verbatim terms were mapped to preferred terms in the study. The submitted datasets were not compliant with the clinical data interchange standards consortium

(CDISC) standards because the study was initiated prior to December 17, 2016. No case report forms or narratives were submitted because there were no deaths, serious adverse events (SAEs), or discontinuations due to adverse events.

Categorization of Adverse Events

The Applicant's definitions of treatment-emergent adverse events and serious adverse events were acceptable. For the purposes of pooling, the Applicant coded adverse events using Medical Dictionary for Regulatory Activities (MedDRA) version 18.1.

Routine Clinical Tests

Following the recommendations from the Division, two blood samples were collected from each subject for assessment of plasma diclofenac concentrations. Blood samples were obtained at Day 2 (24 hours after initial Flector application) and at the time of study discontinuation (with topical system in place) for determination of plasma diclofenac levels. The were no other clinical laboratory evaluations performed during this study.

There were no signals from the pediatric clinical study or from prior experience with Flector that would warrant additional laboratory testing beyond the routine testing that the Applicant conducted. The pediatric clinical study had a short duration (maximum 14 days) and testing at 24 hours after initial Flector application and at the time of study discontinuation (with topical system in place) were therefore adequate.

Local Tolerability

Local tolerability at the application site was assessed by the Investigator according to the application site scoring schema as shown in Table 8. This evaluation was performed on Day 3, Day 7, and Day 14 (or the day after pain resolution).

Table 8: Application site scoring schema

Response	Visible Change	Grade
Absent	None	0
Inflammation Present		
Vascular Dilation Stage	Faint redness (not considered clinically relevant)	1
	Moderate redness	2
	Intense redness	3
Infiltration Stage	Redness with edema or papules	4
	Redness with weeping vesicles, blisters or bullae	5
	Redness with extension of effect beyond margin of contact site	6

Source: Applicant's submission, Study 08US/Fp03, Table 1, submitted 04/03/2013 under IND 49459

The local tolerability assessment methods and time points were reasonable for the evaluation of pharmacokinetic and systemic safety of Flector topical system in pediatric population.

8.2.4. Safety Results

Deaths

There were no deaths during the study.

Serious Adverse Events

There were no serious adverse events (SAEs) during the study.

Dropouts and/or Discontinuations Due to Adverse Effects

There were no dropouts or discontinuations due to adverse effects. Two subjects discontinued during the study, one due to a fracture after enrollment, and one due to using an excluded medication. Both subjects were included in the efficacy and safety evaluations.

Significant Adverse Events

There were no significant adverse events during this study.

Treatment Emergent Adverse Events and Adverse Reactions

- Adverse events in the open-label pediatric study

In the total pediatric study population (104), 32 patients (30.8%) experienced 54 adverse events (AEs); 26 AEs were in the 6 to 11 years old subgroup and 28 AEs were in the 12 to 16 years old subgroup. Table 9 shows the adverse events in pediatric study.

Table 9: Adverse events – all Patients (N=104)

Adverse event	AEs*	Patients*
Ear and labyrinth disorders		
Motion sickness	1	1 (1.0%)
Gastrointestinal disorders		
Abdominal pain	1	1 (1.0%)
Abdominal pain upper	2	2 (1.9%)
Loose stools	1	1 (1.0%)
Nausea	3	3 (2.9%)
Stomach discomfort	3	3 (2.9%)
Vomiting	1	1 (1.0%)
Total	11	10 (9.6%)
General disorders and administration site		
Fatigue	2	2 (1.9%)
Infections and infestations		
Lice infestation	1	1 (1.0%)
Injury, poisoning and procedural complications		
Concussion	1	1 (1.0%)
Excoriation	1	1 (1.0%)
Scratch	1	1 (1.0%)
Total	3	3 (2.9%)
Musculoskeletal and connective tissue disorders		
Muscle spasms	1	1 (1.0%)
Myalgia	1	1 (1.0%)
Total	2	2 (1.9%)
Nervous system disorders		
Dizziness	3	2 (1.9%)
Headache	10	9 (8.7%)
Total	13	10 (9.6%)
Psychiatric disorders		
Enuresis	1	1 (1.0%)
Respiratory, thoracic and mediastinal disorders		
Cough	1	1 (1.0%)
Nasopharyngitis	1	1 (1.0%)
Total	2	2 (1.9%)
Skin and subcutaneous tissue disorders		
Dermatitis exfoliative	1	1 (1.0%)
Dry skin	1	1 (1.0%)
Erythema	2	2 (1.9%)
Pruritus	10	7 (6.7%)
Total	14	8 (7.7%)
Vascular disorders		
Epistaxis	2	2 (1.9%)
Flushing	1	1 (1.0%)
Syncope vasovagal	1	1 (1.0%)
Total	4	4 (3.8%)
All Adverse Events	54	32 (30.8%)

*AEs: Number of Adverse Events; Patients: Number of Patients with an Adverse Event.

Source: Applicant's submission, 08US/Fp03 Clinical Study Report (CSR), Table 14.3.1.2

The most common system-level categories of AEs were Nervous System Disorders (10 patients/ 9.6% experienced 13 AEs), Gastrointestinal Disorders (10 patients/ 9.6% experienced 11 AEs), and Skin and Subcutaneous Tissue Disorders (8 patients/ 7.7% experienced 14 AEs).

From the total of 54 AEs, the Applicant assessed 14 AEs as unexpected and 40 AEs as expected based on the current Investigator Brochure and approved prescription drug labeling on DailyMed. The unexpected AEs included mild flushing, common cold symptoms, cough, concussion, nocturnal enuresis episode, scratch marks on leg, knee abrasion, muscle spasm in ankle, soreness, vomiting, and mild vasovagal response. These AEs were mild to moderate in severity and did not require discontinuation of Flector. The unexpected AEs do not reveal any specific new signals or safety concerns.

Forty-four (44) AEs were of mild severity and 10 AEs were of at least moderate severity. There were no severe AEs reported during the study. The AEs were similarly distributed in two age groups.

The Applicant reported 14 AEs in nine patients that the investigator assessed as at least possibly related to treatment, including 12 Skin and Subcutaneous Tissue Disorders at the application site, one nausea, and one headache. The pediatric case with headache [subject (b) (6)] reported a worsening headache after the initial application of Flector topical system, however, the headache resolved without treatment prior to conclusion of the study. Application site reactions including application site pruritus are known adverse reactions of Flector that are reported with similar frequency in adult patients. There were no control groups for comparison. In the absence of controlled data, the relatedness of the adverse reactions to Flector cannot be assessed.

Among the AEs that the investigator assessed as possibly related to treatment, there were slightly more AEs in the 12 to 16 years old subgroup compared with 6 to 11 years old subgroup [8 AEs in 6 patients (11.5%) in older subgroup vs. 6 AEs in 3 patients (5.8%) in younger subgroup].

Review of adverse events in this open-label pediatric study did not raise any new safety concern about use of Flector in pediatric population.

- Local tolerability of Flector in the open-label pediatric study

Local tolerability of Flector topical system at the application site was evaluated based on "Application site scoring" as shown in Table 8. Absence of any visible changes at the application site correlated with a score of 0. Presence of inflammation was defined as a score of 1 (faint redness) to a score of 6 (redness with extension of effect beyond margin of contact site). The results of local tolerability of Flector based on application site scoring are shown in Table 10. Most patients (93%) had application site score of 0 at any time point, which correlates with absence of visible skin changes. Seven percent (7%) of patients had application site score of 1

at 1-2 days after the start of treatment, which correlates with faint redness. There were no patients with application site score of more than 1 at any time point during the study. The percentage of patients with application site score of 1 decreased with continuation of treatment. The total number of patients decreased with continuation of treatment, which correlates with improvement in pain level and not requiring further treatment with topical system.

Table 10: Local tolerability based on application site scoring in Table 8

Variable	N = 104			
All Patients Age 6-16				
Day 01-02 Tolerability Score + SD (Range)*	0.07 ± 0.25 (0 to 1)			
Day 03-04 Tolerability Score + SD (Range) [N=99]	0.05 ± 0.22 (0 to 1)			
Day 05-07 Tolerability Score + SD (Range) [N=80]	0.05 ± 0.22 (0 to 1)			
Day 08-11 Tolerability Score + SD (Range) [N=29]	0.03 ± 0.19 (0 to 1)			
Day 12-15 Tolerability Score + SD (Range) [N=33]	0.00 ± 0.00 (0 to 0)			
	0	1	2	3
Day 01-02 Tolerability Score Frequencies	97 (93%)	7 (7%)		
Day 03-04 Tolerability Score Frequencies [N=99]	94 (95%)	5 (5%)		
Day 05-07 Tolerability Score Frequencies [N=80]	76 (95%)	4 (5%)		
Day 08-11 Tolerability Score Frequencies [N=29]	28 (97%)	1 (3%)		
Day 12-15 Tolerability Score Frequencies [N=33]	33 (100%)			

* Screening is defined as Day 0. Thus, Day 01-02 is 1-2 days after the start of treatment, etc.
Source: Applicant's submission, 08US/Fp03 Clinical Study Report (CSR), Table 14.3.1.5

Review of local tolerability of Flector in this open-label pediatric study did not raise any new safety concern about use of Flector in the pediatric population.

- Adverse Events in Children/Adolescents vs. Adults

The adverse events in the open-label pediatric study (N=104) were compared with the adverse events in adults from four phase 3 clinical trials that served as the basis for the approval of NDA 021234. The data for pediatric patients included 104 subjects and the data for adult patients included 568 subjects who used Flector and 562 patients who used placebo topical system. Table 11 shows the adverse events in pediatric and adults patients. All study subjects were exposed to Flector topical system over a similar treatment duration of up to 14 days. Adverse events were recorded according to their SOC/Preferred Term classification.

Table 11: Adverse events in pediatric and adult patients

	Pediatric Flector N=104		Adult Flector N=568		Adult Placebo N=562		
Adverse event	AE*	Pct.**	AE	Pct.	AE	Pct.	p***
Any Adverse Event	32	30.8%	116	20.4%	134	23.8%	0.028
Application site conditions	8	7.7%	54	9.5%	66	11.7%	0.712

	Pediatric Flector N=104		Adult Flector N=568		Adult Placebo N=562		
Adverse event	AE*	Pct.**	AE	Pct.	AE	Pct.	p***
Cardiac disorders					2	0.4%	
Ear and labyrinth disorders	1	1.0%					0.155
Eye disorders			1	0.2%	2	0.4%	1.000
Gastrointestinal disorders	10	9.6%	34	6.0%	27	4.8%	0.193
General disorders	2	1.9%	7	1.2%	7	1.2%	0.636
Immune system disorders			2	0.4%			1.000
Infections and infestations	1	1.0%	4	0.7%	2	0.4%	0.570
Injury, poisoning and procedural complications	3	2.9%			2	0.4%	0.004
Metabolism and nutrition disorders					1	0.2%	
Musculoskeletal and connective tissue disorders	2	1.9%	7	1.2%	9	1.6%	0.636
Nervous system disorders	10	9.6%	19	3.3%	21	3.7%	0.008
Psychiatric disorders	1	1.0%	6	1.1%	3	0.5%	1.000
Renal and urinary disorders			1	0.2%			1.000
Respiratory, thoracic and mediastinal disorders	2	1.9%	3	0.5%	3	0.5%	0.173
Skin and subcutaneous tissue disorders			7	1.2%	8	1.4%	0.603
Vascular disorders	4	3.8%			4	0.7%	0.001

* Number of patients with AEs. ** Pct. Percentage of patients with AEs. *** Pediatric Flector vs. Adult Flector
Source: Applicant's submission, Supplement 16, summary-clin-safety, Table 2.7.4.2.1

Headache was reported in 8.7% of pediatric patients vs. 1.2% of adult patients who used Flector and 1.4% of adults who used placebo topical system. Application site pruritus was reported in 6.7% of pediatric patients vs. 5.1% of adult patients used Flector and 6.9% of adults who used placebo topical system. Nausea was reported in 2.9% of pediatric patients vs. 2.3% of adult patients who used Flector and 2.0% of adults who used placebo topical system. Stomach discomfort was reported in 2.9% of pediatric patients vs. none in adult patients who used either Flector or placebo topical system. Epistaxis was reported in 1.9% of pediatric patients vs. none in adult patients who used either Flector or placebo topical system.

In general, data from this open-label pediatric study did not raise any new safety concern about use of Flector in the pediatric population.

Local tolerability scoring was not compared between pediatric and adult patients, because the grading schemes for the two cohorts in the respective studies were different. For the adult population, local tolerability was evaluated by "patient assessment of local tolerability (5-point verbal scale)" and "investigator assessment of local tolerability (5-point verbal scale)". For the pediatric population, local tolerability was assessed based on visible skin changes at the

application site (0 – 6 scoring). Application site conditions are listed as the most common adverse reactions with Flector in adults. The current label for Flector states the following under ADVERSE REACTION section of the highlights: "Most common adverse reactions are application site conditions, occurring in 11% and 12%, respectively, of FLECTOR PATCH and Placebo Patch-treated patients (6.1)".

Laboratory Findings

Two blood samples were collected from each subject for assessment of plasma diclofenac concentrations. The Applicant compared the observed plasma concentrations in pediatric patients with different adult data after repeated application of Flector patch. The results indicate that systemic exposure of diclofenac with Flector patch is low in adults and pediatric patients. The data suggested that administration of Flector topical system per current approved labeling in pediatric patients ages 6 to 16 years old is not expected to expose children to higher blood levels of diclofenac compared with adults. Therefore, it is unlikely for the pediatric population to experience safety issues related to blood levels of diclofenac that are not previously reported in the older subjects. Refer to section 6. Clinical Pharmacology for details pf pharmacokinetic profile of Flector.

The were no other clinical laboratory evaluations performed during this study.

Vital Signs

Vital signs were recorded prior to treatment with Flector topical system and at all subsequent study visits. There were no vital signs outside the normal range for children 6-16 years old.

Electrocardiograms (ECGs)

There were no ECG assessments in this study.

QT

There were no QT clinical trials in this submission.

Immunogenicity

There were no immunogenicity safety issues related to this product.

8.2.5. Analysis of Submission-Specific Safety Issues

There were no significant safety issues with this product that warranted a more thorough or specific evaluation.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

N/A

8.2.7. Safety Analyses by Demographic Subgroups

There were equal number of subjects in each age subgroup of 6 to 11 years old and 12 to 16 years old. Twenty-six (26) AEs occurred in the 6 to 11 years old subgroup and 28 AEs occurred in the 12 to 16 years old group. Patients in the 6 to 11 years old subgroup experienced more Gastrointestinal Disorders compared to 12 to 16 years old sub group (6 patients/11.5% vs. 4 patients/7.7% respectively), but fewer Nervous System Disorders (4 patients/7.7% vs. 6 patients/11.5% respectively) and Skin and Subcutaneous Tissue Disorders (2 patients/3.8% vs. 6 patients/11.5% respectively). The available data did not raise any new safety concern in either of the age subgroups.

There were no other safety analysis data available for other subgroups in this pediatric study.

8.2.8. Specific Safety Studies/Clinical Trials

N/A

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

There were no signals for carcinogenicity in the available data for Flector topical system.

Human Reproduction and Pregnancy

Female subjects were excluded from the study if they were pregnant or breast feeding. Thus, there were no exposures in pregnancies and in lactating women in this pediatric study.

Pediatrics and Assessment of Effects on Growth

Flector topical system was used for a maximum of 14 days during this pediatric study and systemic exposure of diclofenac was low. Effect of diclofenac on growth was not assessed during this study.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Flector is an NSAID and systemic exposure to diclofenac was low in the pediatric study. There are no concerns related to overdose, drug abuse potential, withdrawal, and rebound related to

NSAIDs. Thus, there was no need for controlled substance staff (CSS) consultation and abuse potential assessment for this submission.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant reported that since January 31, 2007 up to the time of their report in 2017, approximately 708 million topical systems were sold throughout the world. The pharmacovigilance unit at IBSA recorded 3242 adverse events in 1470 patients since January 31, 2007. Forty-three (43) events were recorded in 16 subjects under 18 years of age and the remaining 3199 were recorded in 1454 subjects 18 years of age or older. The most common system organ class (SOC) adverse event in both cohorts was General Disorders and Administration Site Conditions, as shown in Table 12. Headache was reported in 46 cases (1.4% of total) in subjects ≥ 18 years, and there was no reported case of headache in subjects under 18 years of age.

Table 12: Flector Patch Adverse Events from Pharmacovigilance Reporting

Adverse Events (AEs) by System Organ Class (SOC)	Number of AEs in patients 18 years old and older	Number of AEs in patients 17 years old and younger
Blood and lymphatic system disorders	13	0
Cardiac Disorders	41	1
Ear and labyrinth disorders	22	0
Endocrine disorders	1	0
Eye disorders	38	0
Gastrointestinal disorders	398	5
General disorders and administration site conditions	992	13
Hepatobiliary disorders	5	0
Immune system disorders	60	2
Infections and infestations	26	
Injury, poisoning and procedural complications	391	10
Investigations	104	0
Metabolism and nutrition disorders	15	1
Musculoskeletal and connective tissue disorders	113	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6	0

Adverse Events (AEs) by System Organ Class (SOC)	Number of AEs in patients 18 years old and older	Number of AEs in patients 17 years old and younger
Nervous system disorders	291	2
Pregnancy, puerperium and perinatal conditions	1	0
Product issues	87	2
Psychiatric disorders	60	0
Renal and urinary disorders	41	0
Reproductive system and breast disorders	15	0
Respiratory, thoracic and mediastinal disorders	108	1
Skin and subcutaneous tissue disorders	326	5
Social circumstances	10	0
Surgical and medical procedures	3	0
Vascular disorders	32	1
Total	3199	43
Number of Patients	1454	16

Source: Applicant's submission, Supplement 16, summary-clin-safety, Table 2.7.4.4.1

The Applicant also provided adverse event data for two other diclofenac drug products, a topical gel (Voltaren) and an oral capsule (Zipsor). In the Voltaren group [(16 grams/day of exposure for 8 to 12 weeks (N=913)], the only adverse events with an incidence of >1% in Voltaren versus placebo were application site reactions (7% vs. 2%) and application site dermatitis (4% vs. <1%).

In Zipsor group [25 mg or higher, three or four times a day, for 4 to 5 days (N=345)], the most common adverse reactions with an incidence of ≥ 1% in Zipsor were gastrointestinal adverse events including abdominal pain, constipation, diarrhea, dyspepsia, nausea, vomiting, dizziness, headache, somnolence, pruritus, and increased sweating, as shown in Table 13.

Table 13: Incidence of Treatment Emergent Adverse Reactions with Incidence ≥ 1% of Zipsor Treated Patients in Multiple-Dose Studies

MedDRA System Organ Class and Preferred Term	Zipsor* 25 mg n=345 n (%)	Placebo* n=327 n (%)
Any Adverse Events	144 (41.7)	181 (55.4)
Abdominal Pain	24 (7.0)	11 (3.4)
Constipation	11 (3.2)	9 (2.8)
Diarrhea	8 (2.3)	9 (2.8)
Dyspepsia	4 (1.2)	8 (2.4)
Nausea	57 (16.5)	66 (20.2)
Vomiting	20 (5.8)	26 (8.0)
Dizziness	12 (3.5)	17 (5.2)
Headache	43 (12.5)	56 (17.1)
Somnolence	9 (2.6)	6 (1.8)
Pruritus	5 (1.4)	6 (1.8)
Sweating Increase	4 (1.2)	2 (0.6)

*There was greater use of concomitant opioid rescue medication in placebo treated patients than in Zipsor treated patients.

Source: Applicant's submission, Supplement 16, summary-clin-safety, Table 2.7.4.5.2

In general, the postmarket safety data for Flector topical system and diclofenac products do not raise any new safety concerns for use of Flector topical system in pediatric or adult subjects.

Expectations on Safety in the Postmarket Setting

There are no potential safety concerns regarding pediatric subpopulations in the safety database. There are no important differences in the administration and use of Flector in the pediatric study versus its expected use in the postmarket setting. There are no specific safety concerns that could be expected from anticipated off-label use.

Headache was noted as an adverse reaction in the uncontrolled pediatric population. The Division will continue to monitor adverse events with Flector in pediatric population in the postmarket data.

8.2.11. Integrated Assessment of Safety

The most common (incidence ≥3%) adverse reactions with Flector from the controlled data in adult patients include pruritus (5% for Flector vs. 8% for placebo) and nausea (3% for Flector vs. 2% for placebo). The most common (incidence ≥3%) adverse reactions with Flector from the uncontrolled data in pediatric patients include headache (9%), pruritus (7%), nausea (3%), and stomach discomfort (3%). Review of local tolerability of Flector from the uncontrolled pediatric study did not raise any new safety concern about topical use of Flector in pediatric population. In the absence of controlled data, the relatedness of adverse reactions to Flector cannot be assessed in the pediatric study.

Review of the available postmarket safety data for Flector topical system and other diclofenac products did not raise any new safety concerns for use of Flector topical system in adult or pediatric patients.

The pharmacokinetic assessment of Flector topical system indicated that systemic exposure of diclofenac was low in pediatric patients. In the subjects with detectable plasma concentrations, the plasma levels were similar between adult and pediatric patients when used as indicated with one patch applied to the most painful area twice a day.

The available data did not raise any new safety concern about use of Flector in pediatric population. Based on review of available data, the safety profile of Flector topical system in pediatric patients is similar to that in adults.

8.3. Statistical Issues

This submission included one open-label pediatric study that did not require a detailed statistical review. There were no other statistical issues that impact the overall conclusions.

8.4. Conclusions and Recommendations

Flector topical system is indicated for the topical treatment of acute pain due to minor strains, sprains, and contusions in adults. The Applicant proposes to use Flector for pediatric patients ages 6 to 16 years for the same indication as adults. The Division recommends approval if the Applicant and Division arrive at agreed-upon labeling.

The Applicant's development program included one open-label to assess the local tolerability, systemic safety, and pharmacokinetic profile of Flector topical system in pediatric patients 6 to 16 years old with minor soft tissue injuries.

There are no adequate and well-controlled efficacy trials to support effectiveness of Flector in the pediatric population. However, the underlying conditions and exposure response to NSAIDs is similar in both adults and pediatric populations. For NSAIDs, analgesic efficacy in the adult population may be extrapolated to pediatric patients down to the age of 2 years, because the underlying conditions and exposure response to NSAIDs are similar in both populations. The pharmacokinetic data of the pediatric study demonstrated comparable exposures between pediatric population and adult population. Thus, the available pharmacokinetic data support extrapolating efficacy from adults to the proposed pediatric population.

The safety data that were reviewed for this application included data from the uncontrolled pediatric study (Study 08US/Fp03), comparison of safety results from uncontrolled pediatric study with previously completed controlled studies for Flector in adult, and postmarketing data for diclofenac products. Review of available safety data do not raise any new safety concerns about use of Flector in pediatric population.

Approval of Flector in a pediatric population will add an alternative option for the treatment of acute of pain due to minor strains, sprains, and contusions in pediatric subjects ages 6 to 16 years old. There is currently no FDA approved topical system for treatment of pain in a pediatric population. Flector topical system will add to the existing armamentarium for pain management in the proposed indication.

9 Advisory Committee Meeting and Other External Consultations

An Advisory Committee (AC) meeting was not required for Flector as an NSAID product.

10 Pediatrics

This supplemental application (S-016) was submitted to fulfill the PREA postmarketing requirement study 1989-1 entitled "An open-label, prospective, uncontrolled study of the safety and local tolerability of the diclofenac epolamine patch (Flector® Patch) in pediatric patients with minor soft tissue injuries". The PMR 1989-1 was adequately addressed in this submission.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information
The following major changes were made to the Applicant's proposed prescribing information.

- Section 1 Indication
  - The indication is best articulated as pediatric patients down to 6 years old rather than 6 to 16 years old

- Section 8.4 Pediatric Use

The Applicant's language under section "8.4 Pediatric use" included the following.

"8.4 Pediatric Use

(b) (4)

The Applicant's language was revised (b) (4) the PK data are described in section 12.3

of the label. The Division proposed the following language for better description of safety and effectiveness of Flector in pediatric population.

> "8.4 Pediatric Use
> The safety and effectiveness of FLECTOR have been established in pediatric patients ages 6 to 16 years old. Use of FLECTOR is supported by evidence from adequate and well controlled studies with FLECTOR in adults, as well as an open-label study in 104 pediatric patients ages 6 to 16 years. The safety and effectiveness of FLECTOR has not been investigated in pediatric patients less than 6 years old."

(b) (4)

Other Prescription Drug Labeling

On July 24, 2018, the Division sent a "PRIOR APPROVAL SUPPLEMENT REQUEST" to the Applicant, stating that the term (b) (4) should be removed from the product title in all labeling components and replaced with "topical system." On November 13, 2018, the Applicant submitted a new labeling supplement to NDA 021234 (S-017) to reflect the Division's request. The changes from labeling supplement 017 were combined with the efficacy supplement 016 (current application) and were reviewed together.

12 Risk Evaluation and Mitigation Strategies (REMS)

Flector is an NSAID and no risk evaluation and mitigation strategies are recommended for this product.

13 Postmarketing Requirements and Commitment

The PMR 1989-1 is the only postmarketing requirement (PMRs) / postmarketing commitment (PMCs) for Flector, which is the focus of this review. The final study report for PMR 1989-1 was submitted on December 13, 2017. The Division followed up with a request to the Applicant to submit an efficacy supplement to fully address the PREA requirements. The Applicant submitted this supplement on May 2nd, 2018. The PMR 1989-1 was adequately addressed in this submission. Refer to section 3 Regulatory Background for further detail.

14 Division Director Comments

I concur with the review findings and conclusions, that the application be approved for use in children age 6 and older.

15 Appendices

15.1. References

N/A

15.2. Financial Disclosure

The Applicant's compliance with the Final Rule on Financial Disclosure by Clinical Investigators is attested to in Module 1.3.4 of this NDA application. Details of the financial disclosure are outlined below.

Clinical Study (08US/Fp03):

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 10		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Applicant of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		

Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

• The applicant submitted FDA Form 3454 certifying that investigators were in compliance with 21 CFR Part 54.

• No potentially conflicting financial interests were identified.

15.3. Nonclinical Pharmacology/Toxicology

N/A

15.4. OCP Appendices (Technical documents supporting OCP recommendations)

N/A

15.5. Additional Clinical Outcome Assessment Analyses

N/A

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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03/01/2019 06:47:49 PM

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