Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
10903 New Hampshire Ave. Silver Spring, MD 20993-0002

Combined Clinical, Cross-Discipline Team Leader and Division Director Summary Review for Regulatory Action

Date	(Electronic stamp)
From	Christina Fang, MD, MPH, Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) Nancy Dickinson, PharmD, Clinical Team Leader, DAAP Alla Bazini, MD, Associate Director for Therapeutic Review, Anesthesiology, DAAP Leah Crisafi, MD, Division Director, DAAP
NDA Number / Supplement	206976 / Supplement-18
Applicant	Institut Biochimique SA (IBSA)
Date of Submission	June 6, 2025
PDUFA Goal Date	April 6, 2026
Established Name	Diclofenac epolamine topical system
Trade Name	LICART Topical System
Dosage Forms / Strength	Topical system (10 cm x 14 cm) contains 1.3% diclofenac epolamine
Proposed Indication	Topical treatment of acute pain due to minor strains, sprains, and contusions in adults and pediatric patients 6 years and older
Action	Approval

Material Reviewed/Consulted

Office of New Drugs (OND) Action Package, including:	
Clinical Review	Christina Fang, MD, MPH; Alla Bazini, MD
Clinical Pharmacology Review	Srikanth C. Nallani, PhD; Deep Kwatra, PhD
Division of Generic Drug Study Integrity (DGDSI) Office of Study Integrity and Surveillance (OSIS)	Makini Cobourne-Duval, Ph.D. Mei Ou, Ph.D.
Division of Medication Error Prevention and Analysis 1 (DMEPA 1) Review	Susan Hakeem, PharmD; Valerie S. Vaughan, PharmD
Office of Prescription Drug Promotion (OPDP) Labeling Review	L. Sheneé Toombs, PharmD; Sam Skariah, PharmD
Project Management Staff	Allison Meyer, PharmD; Swati Patwardhan, MS, RAC

Note: Office of Pharmaceutical Quality (OPQ)/Office of New Drug Products (ONDP) Review, Pharmacology Toxicology Review, and Statistical Review were not required for this submission.

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Regulatory Action

This NDA supplement contains findings from an open-label pediatric study in support of the proposed labeling statement for extending the use of Licart (diclofenac epolamine) topical system to pediatric patients aged 6 years and older.

The regulatory action is approval based on an acceptable benefit/risk ratio supported by the results of the pediatric study.

Benefit-Risk Assessment

The benefit of pediatric use of Licart is demonstrated through evidence showing benefit for adult use of the product in adequate and well-controlled adult studies in the original NDA and similar exposure between pediatric and adult study populations in the current study.

The current study was an open-label 14-day study of pediatric (6 to 17 years old) and adult populations with minor strains, sprains, and contusions, where the pediatric patients' pain scores improved over time. In addition, there was similar diclofenac exposure between the pediatric and adult study populations in the current study. The effectiveness is further supported by similar pain response trends and patterns from a comparison of sequential pain measurements between pediatrics and adults. Of note, the open-label study design was chosen due to ethical concerns about using a placebo arm for treatment of pain in pediatric patients.

There were few adverse events (AEs) among 101 pediatric subjects during the 14-day study. They were three individual AEs in two pediatric subjects, one AE-related dropout after 1-day exposure not considered related to Licart treatment, and no serious AEs.

The safety of Licart in the target populations is further supported by low number of AE reports and no serous AEs according to the worldwide post marketing surveillance.

In summary, the benefit/risk ratio is favorable in support of the use of the Licart topical system in pediatric population aged 6 years and older based on the review of findings submitted in the supplemental NDA.

Background

Licart is a topical system containing diclofenac epolamine 1.3%. The product differs from another topical diclofenac product, Flector (diclofenac epolamine topical system approved under NDA 021234), in its use of heparin as an enhancer for transdermal penetration. Both Flector and Licart are owned by the same Applicant.

The approval of Licart NDA 206976 for adult use on December 19, 2018, relied on the safety and efficacy findings of Flector. As a 505(b)(2) NDA application, Licart triggered the pediatric study requirements under the Pediatric Research Equity Act (PREA) because Licart had a new dosing regimen of once daily topical application in comparison to the twice daily application recommended by Flector's labeling. Under PREA, the required Post Marketing Requirement (PMR 3537-1) study was an open-label pharmacokinetics (PK) and safety study of diclofenac epolamine topical system in pediatric patients aged 6 to less than 17 years with acute pain due to minor strains, sprains, and contusions, as stated in the NDA approval letter.

From March 2019 to November 2024, IBSA requested three deferral extensions (DE) for PMR 3537-1: a 1.5-year extension of the entire timeline because of (b) (4) a 1-year extension of the timelines for study completion and final report submission due to very slow enrollment at the early stage of the COVID-19 pandemic, and a 6-month extension of the final report submission for the reason of requiring additional time

for data management and analysis. All DE requests were eventually granted upon agreement with the Pediatric Review Committee (PeRC) because the Applicant showed continuous efforts and due diligence in advancing the pediatric trial.

On June 6, 2025, IBSA submitted the current NDA supplement 18 for evaluation of pediatric use of Licart based on the results of the Study 18US-FHp04 conducted to fulfill PMR 3537-1.

Ethics and Good Clinical Practices

As stated in the study protocol, "Clinical monitors will follow written Standard Operating Procedures (SOPs) to verify that the study is being conducted in accordance with the protocol and any amendments, ICH GCP guidelines (Note: ICH here refers to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and GCP stands for Good Clinical Practice) and applicable regulatory requirements." Adult subjects and/or parent/legally authorized representatives received IRB-approved written informed consent form(s) describing the study intervention, procedures, potential benefits and risks, voluntary nature of study, and participant confidentiality and privacy.

The financial disclosure form signed by the Applicant certified that no financial arrangement with the listed clinical investigators (a complete list of all clinical investigators involved in clinical studies was attached to the form) had been made whereby study outcomes affected compensation as defined in 21 CFR 54.2(a); certified that each listed investigator was required to disclose to the Applicant whether the investigator had a proprietary interest in this product or a significant equity in the Applicant as defined in 21 CFR 54.2(b) did not disclose any such interests; and certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

The consult review by Dr. Cobourne-Duval, based on study site inspection, identified issues with deviations from scheduled blood sampling time for PK and activated partial thromboplastin time (aPTT) and recommended excluding subjects (b) (6) at Study Site #20 from analyses of diclofenac plasma concentration and aPTT. (Refer to the review by Dr. Cobourne-Duval, in the Division of Generic Drug Study Integrity (DGDSI) under the Office of Study Integrity and Surveillance (OSIS) dated November 24, 2025).

Product Quality

No new information submitted for review.

Nonclinical Pharmacology/Toxicology

No new information submitted for review.

Clinical Pharmacology

Refer to the Clinical Review section below for the protocol summary, evaluation of study conduct, and analyses of results of the Study 18US-FHp04. In response to issues about sampling time deviation for PK and aPTT blood tests identified during the site inspection, the clinical pharmacology reviewer, Dr. Nallani, commented that the extent of deviation of PK sampling involved 17 of 151 samples (11%) not collected within 24±1 hour window and 33 of 151 samples (22%) not collected within the specified time window at the end-of-study (EOS) visit. PK analysis, excluding the subsets with deviations in blood sampling time, revealed similar average diclofenac concentrations between the pediatric and adult study populations on Day 2 and at EOS, respectively.

The PK data are described in the Clinical Pharmacology Review by Drs. Srikanth Nallani and Deep Kwatra dated March 2, 2026. The clinical pharmacology team concluded the following (verbatim):

> As described in the Licart product label, systemic exposure (AUC) and maximum plasma concentrations of diclofenac, after repeated dosing for four days with LICART in healthy adult volunteers were lower (<1%) than after a single oral 50-mg diclofenac sodium tablet. As such, plasma concentrations of diclofenac following LICART application after 24 hours (Day 2) and for up to Day 14 are low in both adult and pediatric patients and similar in both the groups. The speculated reason for the protocol violations for collection of blood samples outside the specified window was probably to accommodate the pediatric patients' and parents to return for a blood sample which is often seen in pediatric studies of this scale in the proposed indication. Given that the protocol violations are limited, accounted, and did not show any untoward observations as it relates to blood levels of diclofenac, i.e. the analyses support the primary study conclusions, and the deviations do not alter the safety or efficacy assessments, the submission is acceptable from a clinical pharmacology perspective.

The clinical implication of low systemic exposure to diclofenac from the topical system is minimal risk of systemic adverse effects or changes to the time to blood clot formation due to systemic exposure to Licart which contains heparin and diclofenac, an NSAID.

The clinical pharmacology review team recommends approval of the product in the proposed pediatric age group. The Division agrees with this recommendation.

Clinical

Review strategy

Because Study 18US-FHp04 has an open-label design, the findings from the study will not allow a valid comparison for treatment difference in efficacy. The different age cohorts are not considered as control groups to each other because there is no treatment group balance at baseline. The key components of the protocol will be summarized in a table followed by presentation and discussion of major findings. The results will be evaluated for trends and general patterns across age groups.

Protocol

Protocol version 1.0 was finalized on April 26, 2021, after incorporating the Division's comments. There was also an amended protocol version 1.1 dated February 17, 2022 (not submitted for review), which involved minor revisions such as administrative changes and additional information on sample blood volume according to the current NDA supplement.

Table 1, below, summarizes key components of the protocol for pediatric Study 18US-FHp04.

Table 1 Protocol Summary for Study 18US-FHp04

Study	18US-FHp04
Title	A multi-center, prospective, open-label, controlled study of the pharmacokinetics and safety of the diclofenac epolamine topical system in pediatric and adult participants with minor soft tissue injuries
Objective	To evaluate PK and safety with 14-day use of the diclofenac epolamine topical system and analgesic effects measured by global response in both pediatric and adult patients with minor soft tissue injuries.
Design	Multi-center (12 U.S. sites), open-label, multiple-dose (14 day)
Population	Healthy pediatric patients of ages 6 to16 years and adult patients of ages 18 to 45 years who have minor soft tissue injury within 96 hours (4 days) of enrollment and spontaneous pain of at least moderate intensity (≥3 on the 6-point Wong Baker FACES scale). Refer to the list of eligibility criteria attached below this table for detail. One hundred fifty patients (50/age group) equally distributed among three age groups, 6 to 11 years old, 12 to 16 years old, and 18 to 45 years old
Baseline PI	At least moderate intensity
Treatment	One diclofenac epolamine topical system applied to the injured area once daily (at about the same time) until pain resolution, for up to a maximum of 14 days. The topical system may be cut to fit the size of the injured area and may be overlaid with a mesh netting sleeve, as needed. If a patch becomes detached due to activity, it should be replaced by a fresh patch immediately after the application surface is cleaned and dried. The maximum number of patches that can be applied (not concurrently, only if needed for replacement) per day is two.
Rescue	Not recommended; May withdraw from study for insufficient pain relief.
Prohibited Therapies	• Any systemic or topical medication with known analgesic effects other than the IP • Any topical product on the injured area • Physiotherapy (e.g., ultrasound, electrotherapy, ionization) • Alternative medical practice (e.g., acupuncture, homeopathy, mesotherapy) • Drugs which may be susceptible to interaction with diclofenac or affect safety if used concomitantly • Overlay material other than the provided elastic nets
PK data	Two plasma samples collected with the first sample at 24 hours after the initial application and the second sample on the day following pain resolution or at the end-of-study visit on Day 14, whichever comes first for PK parameters and activated partial thromboplastin time (aPTT).
Safety monitoring	Non-serious adverse events (AEs) reported during the study and followed for at least 3 days, and serious AEs (SAEs) reported during the study until 3 days after the last dose and followed until resolution or stabilization. Vital signs measured at each clinic visit. Local tolerability at the application site evaluated by PI or designee using a 7-point (0 to 6) categorical scale documenting visible changes during the vascular dilation stage and infiltration stage at each follow-up clinic visit with clinic visit 2 on Day 2 (or 24 hours), visit 3 on Day 4, visit 4 on Day 7, and visit 5 on Day 14. Activated partial thromboplastin time (aPTT), sampling at 24 hours after the start of treatment and again before removal of the last application Urine pregnancy test for females of child-bearing potential conducted at baseline.
Pain data	Pain recorded by study participants using the 6-point Wong Baker FACES Pain Rating (even numbers from 0 to 10 with descriptor and facial expression figures) at clinic visits and twice per day in the take home diary; Global response to therapy by the Investigator or designee using a 5-point categorical scale at the end-of-study visit (last scheduled visit on Day 14 or early if having pain resolution or early dropout).
Primary endpoint	PK profile Safety including AE (occurrence, frequency, nature, and severity), local tolerability, and aPTT assessments
Secondary endpoints	Effectiveness including PI reported by patients and Investigator's global assessment

Source: Adapted from study protocol 18US-FHp04 Version 1.0

Inclusion Criteria

1. Willing to provide written informed consent
2. Male or female, 6 to 11 years old; 12 to 16 years old; or 18 to 45 years old
3. BMI <32kg/m^2
4. Minor soft tissue injury within 96 hours of enrollment
5. Spontaneous pain of at least moderate intensity (i.e. pain of at least three on the 6-point Wong Baker FACES® scale) according to the participant)
6. Clinically significant injury according to the principal investigator
7. Willing and able to accommodate study requirements for data collection, including visits on Days 2, 4, 7 and 14
8. Negative urine pregnancy test at inclusion for females of reproductive potential (started the menstrual cycle)
9. For adult females of reproductive potential: use of highly effective contraception for at least 30 days prior to screening, and agreement to use such a method during study participation and for 3 days following the final topical system application
10. For pediatric female participants of reproductive potential (started the menstrual cycle): abstinence from sexual intercourse for at least 30 days prior to screening and agreement to use such a method during study participation and for 3 days following the final topical system application
11. For pediatric and adult males of reproductive potential: abstinence from sexual intercourse, or use of condoms or other methods to ensure effective contraception with partner during study participation and for 3 days following the final topical system application
12. Able to read and speak English

Exclusion Criteria

1. Major soft tissue injury (fractures are only exclusionary if the injury is stabilized with a device, e.g. a hard cast, that cannot be removed to allow a topical system to be applied to the injured area)
2. Open skin lesion or any dermatological condition (e.g. skin infection, eczema) within the injured area
3. Injury involves the spine, digits, hands, or bottom of foot
4. Prior injury to the same site within the past 90 days
5. Three or more other prior injuries (minor or major) to the region in the past
6. Injury occurred more than 96 hours prior to study entry
7. Prior use of topical medication to involved area within 48 hours of study entry
8. Allergic disorders, including asthma or urticaria, but only if associated with exposure to aspirin or non-steroidal anti-inflammatory drugs (NSAIDs)
9. Coagulation defects
10. Prior use of over-the-counter (OTC) analgesics or short-acting NSAIDs (ibuprofen, ketoprofen) within 6 hours of study entry (acetaminophen permitted up until the time of study entry)
11. Prior use of narcotic analgesics within 7 days of study entry
12. Prior use of systemic anti-inflammatory steroidal drugs within 60 days of study entry
13. Prior use of long-acting NSAIDs such as piroxicam or naproxen since injury
14. Concomitant use of drugs which may be susceptible to interactions with diclofenac, or affect safety if used concomitantly (e.g. serotonin-selective reuptake inhibitors, lithium, digoxin, anticoagulants, antidiabetic agents, cyclosporin, methotrexate, quinolone antimicrobials, other NSAIDs, steroids and diuretics)
15. Participants with mental, behavioral or neurodevelopmental disorders for which the relevant disorder(s) prevent compliance with the protocol
16. Documented alcohol or drug abuse within 365 days of study entry
17. Documented nicotine dependence within 365 days of study entry
18. Severe cardiac, renal or hepatic impairment
19. Severe systemic diseases (e.g. cancer, severe acute infection)
20. Any underlying disease or medication that severely compromises the participant's immune system
21. Prior history of any chronic pain disorder
22. Prior history of GI bleeds, ulcers, liver or kidney disease
23. Hypersensitivity to diclofenac or other NSAIDs, including aspirin
24. Females who are pregnant or breast feeding
25. Participation in another clinical trial within 90 days of enrollment

Results

Demographic and other baseline characteristics

The data summarized in Table 2 below presents the demographic and other baseline characteristics of the enrolled population.

The demographic data demonstrate an acceptable age distribution across 6 to 11 and 12- to 16-year-old age ranges. The pediatric age groups here have more racial and ethnic diversity than that of the adult group. Pediatric subjects are roughly evenly distributed by sex. Mean and median BMIs for the pediatric study subjects were similar within each age group.

Table 2 Demographic and Other Baseline Characteristics

	Age group	**Pediatric**		Adult
	Age range (years)	**6 to 11**	**12 to 16**	18 to 45
	Number of subjects	N = 51	N = 50	N = 50
Age (years)	Mean (SD)	8.3 (1.5)	14.4 (1.5)	30.1 (7.6)
	Median	8	15	30
	Min, Max	6, 11	12, 16	18, 45
Race, n (%)	White	22 (43.1)	28 (56.0)	34 (68.0)
	Black or African American	23 (45.1)	19 (38.0)	7 (14.0)
	Asian	2 (3.9)	—	8 (16.0)
	Other	4 (7.8)	3 (6.0)	1 (2.0)
Ethnicity, n (%)	Hispanic or Latino	19 (37.3)	20 (40.0)	23 (46.0)
	Not Hispanic or Latino	30 (58.8)	27 (54.0)	25 (50.0)
	Unknown	2 (3.9)	3 (6.0)	2 (4.0)
Sex, n (%)	Male	30 (58.8)	25 (50.0)	18 (36.0)
	Female	21 (41.2)	25 (50.0)	32 (64.0)
Height (cm)	n (missing)	51 (0)	50 (0)	50 (0)
	Mean (SD)	134.6 (11.3)	163.8 (12.1)	167.6 (10.2)
	Median	133.0	165.1	166.1
	Min, Max	116.0, 160.0	122.0, 183.0	149.0, 188.0
Weight (kg)	n (missing)	51 (0)	50 (0)	50 (0)
	Mean (SD)	37.0 (14.3)	64.5 (14.4)	76.5 (14.4)
	Median	34.0	62.3	77.0
	Min, Max	19.3, 79.5	36.2, 103.8	49.9, 111.1
BMI (kg/m^2)	n (missing)	51 (0)	50 (0)	50 (0)
	Mean (SD)	19.8 (4.6)	24.0 (4.10)	27.19 (3.89)
	Median	18.7	23.4	27.3
	Min, Max	13.6, 31.8	15.4, 31.4	18.8, 31.8

Source: Table 12 on pages 64-65 of the study report for Study 18US-FHp04.

Subject disposition

Most subjects completed the 14-day treatment. Six of 150 (4%) subjects discontinued early, one in the age group of 6 to 11 years, two in the age group of 12 to 16 years, and three in the adult group.

The reasons for early discontinuation in the pediatric group included one case of lost to follow-up in the age group of 6 to 11 years, and one case of AE-related dropout and one case of withdrawal by parent/guardian in the age group of 12 to16 years. Refer to Table 3.

Table 3 Disposition Summary

Age group	**Pediatric**		Adult
Age range (years)	**6 to 11**	**12 to 16**	18 to 45
Number of subjects	N = 51	N = 50	N = 50
Number discontinued	1	2	3
Reason for discontinuation			
AE		1	2
Lost to Follow-Up	1		
Study Terminated by Sponsor			1
Withdrawal by Parent/Guardian		1	
Withdrawal by Participant			1

Source: Table 10 on pages 60-61 of the study report for Study 18US-FHp04.

Protocol deviations

Major protocol deviations

Three pediatric subjects in the age group of 12 to16 years had major protocol deviations: one case of deviation of "administer/dispense investigational product" for having topical treatment beyond the specified maximum time interval, and two cases of deviation of "biological specimen sample procedures" for having blood samples collected after the end of study.

Four adult subjects had major protocol deviations, two for taking prohibited medication, one for treatment beyond the maximum time interval, and one for applying an excessive number of patches. Refer to Table 4.

Table 4 Major Protocol Deviations

Age group	**Pediatric**		Adult
Age range (years)	**6 to 11**	**12 to 16**	18 to 45
Number of subjects	N = 51	N = 50	N = 50
Number with ≥one major protocol deviation	-	3	4
Deviation Category			
Administer/Dispense Investigational Product	-	1	2
Biological Specimen Sample Procedures	-	2	-
Prohibited Medication	-	-	2

Source: Table 11 on pages 61-62 and Listing 16.2.7-1.2 of the study report Study 18US-FHp04.

Minor protocol deviations

As shown in Table 5, a high proportion (around 90%) of overall study subjects had minor protocol deviations, mostly in the categories of deviation from assessment procedure (around 68%) and administer/dispense study drug (around 63%).

Table 5 Minor Protocol Deviations

Age group	**Pediatric**				Adult	
Age range (years)	**6 to 11**		**12 to 16**		18 to 45	
Number of subjects	N = 51		N = 50		N = 50	
	# of event	Subject, n (%)	# of event	Subject, n (%)	# of event	Subject, n (%)
Total	115	49 (96.1)	126	43 (86.0)	150	44 (88.0)
Assessment procedure	40	37 (72.5)	36	35 (70.0)	39	31 (62.0)
Administer/dispense study drug	38	31 (60.8)	38	32 (64.0)	52	33 (66.0)
Supply procedure	1	1 (2.0)	6	6 (12.0)	23	22 (44.0)
Blood sample procedures	22	9 (17.6)	27	10 (20.0)	19	9 (18.0)
Visit schedule	8	6 (11.8)	13	11 (22.0)	13	10 (20.0)
Consent	0	0 (0.0)	1	1 (2.0)	4	4 (8.0)
Eligibility	1	1 (2.0)	0	0 (0.0)	0	0 (0.0)
Other	5	5 (9.8)	5	4 (8.0)	0	0 (0.0)

Source: Table 1.11.3.1 in the submission dated September 9, 2025, and Listing 16.2.7-1.3 of the study report.

Treatment compliance

The Investigator reported treatment compliance by evaluating days of exposure at each clinical visit. As shown in Table 6 below, mean compliance was above 90%, and higher for pediatric groups than for the adult group.

Table 6 Treatment Compliance

Age group	**Pediatric**		Adult
Age range (years)	**6 to 11**	**12 to 16**	18 to 45
Number of subjects	N = 51	N = 50	N = 50
Mean (SD) compliance	97.6% (6.51%)	95.0% (11.82%)	92.8% (10.51%)

Source: Table 11 on pages 61-62 and Listing 16.2.7-1.2 of the study report.

Pharmacokinetic findings

Refer to the Clinical Pharmacology Review section above.

Findings based on pain scores

Due to open-label design and lack of placebo control the results of pain measurements serve as basis for a general comparison of trends and patterns.

As shown in Table 7 below, the trends for pain reduction over time were similar across age groups based on subject reported pain scores at five study visits.

Table 7 Summary of Subject Reported Pain Scores at Study Visits

Age group	**Pediatric**		Adult
Age range (years)	**6 to 11**	**12 to 16**	18 to 45
Number of subjects	N = 51	N = 50	N = 50
Data collection	Score mean (SD) (scale of 0-10)		
Day 1 screening (baseline)	7.2 (1.45)	7.0 (1.23)	7.8 (1.70)
Day 2, visit 2	5.8 (2.16)	5.8 (1.79)	6.2 (2.19)
Day 4, visit 3	4.7 (2.22)	4.4 (1.93)	5.0 (1.86)
Day 7, visit 4	3.2 (2.15)	3.4 (1.92)	3.4 (2.12)
End of study, visit 5	0.3 (0.70)	0.8 (1.73)	0.7 (1.51)

Source: Table 22 on pages 82-83 of the study report.

Pain scores recorded twice a day by the take-home diary until EOS (last scheduled visit on Day 14 or early if having pain resolution or early dropout) also showed similar trends across age groups based on data summarized in Table 8 below. Group mean scores reduced to the range of mild pain (less than 4 on a scale of 0 to 10) by Day 5 in the age group of 6 to 11 years, by Day 6 in the age group of 12 to 16 years, and by Day 7 in the adult group. By Day 7 at least 50% of subjects in each of the three treatment groups were still recording pain scores. After 7 days of treatment, group mean scores were fluctuating within a fixed range for each age group, suggesting that pain measurements beyond 1 week were no longer contributing to meaningful evaluation of efficacy in the clinical reviewer's opinion.

Table 8 Summary of Subject Recorded Pain Scores by Daily Diary, Day 1 to EOS

Age group		**Pediatric**		Adult
Age range (years)		**6 to 11**	**12 to 16**	18 to 45
Number of subjects		N = 51	N = 50	N = 50
Data collection		Score mean (SD) (scale of 0-10)		
Day 1	AM	——	6.0	——
	PM	5.9 (2.00)	6.3 (2.09)	7.0 (2.34)
Day 2	AM	5.3 (2.34)	5.8 (2.20)	6.3 (2.27)
	PM	5.4 (2.37)	5.9 (2.25)	5.9 (2.49)
Day 3	AM	4.7 (2.41)	5.6 (2.33)	5.7 (2.09)
	PM	4.5 (2.55)	5.3 (2.26)	5.4 (2.21)
Day 4	AM	4.3 (2.35)	4.9 (2.19)	5.0 (1.96)
	PM	4.2 (2.69)	4.7 (2.38)	5.1 (1.96)
Day 5	AM	**3.6** (2.53)	4.7 (2.46)	4.7 (2.22)
	PM	3.6 (2.42)	4.8 (2.09)	4.5 (2.06)
Day 6	AM	3.4 (2.28)	**3.8** (2.05)	4.2 (2.10)
	PM	3.1 (2.27)	4.1 (2.23)	4.4 (2.29)
Day 7	AM	2.9 (2.30)	3.9 (2.40)	**3.3** (2.21)
	PM	2.5 (2.49)	4.1 (2.85)	3.3 (2.10)
Day 8	AM	2.6 (2.26)	**3.7** (2.79)	3.0 (2.24)
	PM	2.2 (2.30)	3.5 (2.39)	2.1 (2.15)
Day 9	AM	2.2 (2.60)	3.1 (3.06)	2.7 (2.34)
	PM	2.4 (1.90)	3.2 (3.07)	3.0 (2.25)
Day 10	AM	2.4 (2.96)	3.4 (2.87)	2.7 (2.22)
	PM	2.4 (2.57)	3.3 (2.99)	2.5 (2.45)
Day 11	AM	2.4 (2.48)	3.6 (3.24)	2.2 (2.04)
	PM	2.6 (2.62)	3.6 (3.28)	2.7 (1.99)
Day 12	AM	2.0 (2.39)	3.1 (2.75)	2.0 (2.19)
	PM	2.1 (2.36)	4.0 (2.49)	2.3 (2.31)
Day 13	AM	2.3 (2.68)	3.8 (2.89)	2.3 (2.36)
	PM	3.2 (2.89)	3.6 (2.75)	3.3 (3.00)
Day 14	AM	2.0 (2.55)	4.0 (3.37)	2.5 (2.67)
	PM	1.3 (2.12)	0.0	2.5 (3.16)

Source: Table 24 on pages 86-88 of the study report.
Note: By Day 8 or 9, less than 50% of subjects were recording pain data in the take-home diary.

Safety findings

Exposure

Calculated by age group, the mean exposure ranged from 11.3 to 11.8 days, and the longest exposure was 16, 17, or 25 days as shown in Table 9 below. The combined pediatric groups had a mean exposure of 12 days, median exposure of 13 days, and longest exposure of 25 days. Subjects with at least 14 days of exposure included 25 of 51 (49%) subjects in the age group of 6 to 11 years and 22 of 50 (44%) subjects in the age group of 12 to 16 years, or 47 of 101 (47%) for the combined pediatric groups, and 21 of 50 (42%) subjects in the adult group.

Table 9 Exposure by Number of Days

Age group	**Pediatric**		Adult
Age range (years)	**6 to 11**	**12 to 16**	18 to 45
Number of subjects	N = 51	N = 50	N = 51
Number of days			
Mean (SD)	11.6 (3.1)	11.8 (4.2)	11.3 (2.9)
Median	13.0	12.5	11.5
Min, Max	5, 17	2, 25	5, 16

Source: Response to IR received March 11, 2026.

The average number of topical systems used per subject during the treatment period, including the topical systems used as replacements during the 24-hour usage period, was 14 to 16, as shown in Table 10.

Table 10 Exposure by Number of Topical Systems

Age group	Pediatric		Adult
Age range (years)	**6 to 11**	**12 to 16**	18 to 45
Number of subjects	N = 51	N = 50	N = 51
Number of topical systems			
Applied, mean (SD)	14.6 ± 6.1	15.5 ± 6.9	13.8 ± 4.2
Substituted, mean (SD)	1.5 ± 2.4	1.5 ± 2.2	1.7 ± 1.9
Patch exposure*	13.2 ± 5.9	14.1 ± 6.6	12.1 ± 4.3

Note: Patch exposure = Mean number of patched applied – mean number of patches substituted
Source: Table 5.3.5.3.35 on page 86 of the Integrated Summary of Safety and Effectiveness (ISSE).

Deaths and nonfatal serious AEs
There were no reports of deaths or nonfatal serious AEs in the study.

Adverse event-related dropouts
There were three cases of AE-related early discontinuation. One case in the pediatric study population was a subject 12 years of age who reported symptoms of excessive hunger and frequent urination after 1 day of drug application for contusion of his right knee. The AEs appeared unlikely to be related to 1-day topical treatment.

Two cases of AE-related dropouts in the adult group did not appear to be related to the study drug; one AE was leg muscle spasm in a subject treated for neck pain, and the second was headache in a subject treated for contusion in left elbow.

Adverse events (AEs)
Few subjects reported AEs, including none in the age group of 6 to 11 years, two (4%) in the age group of 12 to 16 years, and three (6%) in the adult group.

As shown in Table 11, the reported individual AEs included application site erythema in one subject and appetite disorder and pollakiuria (benign idiopathic urinary frequency) in another subject in the age group of 12 to 16 years and one case of each of the following: nasopharyngitis, muscle spasms, and headache in adults. None of the AEs were graded as severe.

Table 11 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

Age group		Pediatric		Adult
Age range (years)		**6 to 11**	**12 to 16**	18 to 45
Number of subjects		N = 51	N = 50	N = 50
Number with ≥one TEAE		-	2	3
Organ system	**Preferred Term**			
General disorders and administration site conditions	Application site erythema	-	1	-
Infections and infestations	Nasopharyngitis	-	-	1
Metabolism and nutritional disorders	Appetite disorder	-	1	-
Musculoskeletal and connective tissue disorders	Muscle spasms	-	-	1
Nervous system disorders	Headache	-	-	1
Renal and urinary disorders	Pollakiuria	-	1	-

Source: Table 27 on pages 98-99 of the study report.

Local tolerability

Based on the Investigator's local tolerability assessment of the application site at each follow-up clinic visit, there were no visible skin changes in most subjects, except faint redness observed in one pediatric subject at Day-4 visit, who had AE reported as application site erythema, and in one adult at Day-2 visit.

Table 12 Local Tolerability

Age group	**Pediatric**		Adult
Age range (years)	**6 to 11**	**12 to 16**	18 to 45
Number of subjects	N = 51	N = 50	N = 50
Faint redness	-	1 case (only on Day-4 visit)	1 case (only on Day-2 visit)

Source: Table 14.7-10.1 of the study report.

Laboratory findings

In reporting results indicating changes in the activated partial thromboplastin time (aPTT) the Applicant used adjusted aPTT, or aPTT1 to adapt to inter-laboratory variability and variation in reagent sensitivity to heparin for more precise monitoring.

The mean and median adjusted activated partial thromboplastin time (aPTT1) values were within the expected normal range for each age group based on individual lab reference range per age group on Day 2 and at end-of-study (EOS) as shown in Table 13 below.

A major limitation to the interpretation of aPTT findings was the lack of baseline lab values that the study only collected Day 2 (24-hour exposure) and EOS aPTT data.

Table 13 Summary of Adjusted Activated Partial Thromboplastin Time - aPTT1

Age group		**Pediatric**		Adult
Age range (years)		**6 to 11**	**12-16**	
Number of subjects		N = 51	N = 50	N = 50
Day 2	*n (missing)*	*36 (15)*	*43 (7)*	*47 (3)*
	Mean (SD)	33.8 (6.97)	30.6 (6.00)	36.8 (6.05)
	Median	31.9	29.5	36.0
End of study	*n (missing)*	*41 (10)*	*36 (14)*	*48 (2)*
	Mean (SD)	33.5 (7.07)	30.0 (4.98)	36.9 (5.69)
	Median	32.4	29.3	36.9
Expected aPTT range per age group		*31.8-**43.7***	*33.9-**46.1***	*28.6-**38.2***

Source: Source: Table 28 on pages 102-103 of the study report.

The Applicant did not submit analysis of changes from Day 2 to EOS in individual aPTT or aPTT1 laboratory values. Nevertheless, it is a challenge to interpret the individual findings without baseline aPTT values available for comparison. However, the absence of any cases of bleeding reported from the study supports the safety of this heparin-containing product in the 6- to 17-year-old population.

Postmarketing Experience

The Applicant summarized post marketing safety reports for Licart approved in the United States and for similar products approved in the countries of the European Union (EU). During the time from December 2018 to February 2025, there were about 100 adverse reactions over an estimated exposure in more than one million patients, and none was reported as a serious AE. Representative drug reactions included mainly application site reactions such as erythema/rash and dermatological conditions resulting from local irritation or allergy. Other adverse reactions included drug ineffective, off-label use, and intentional and nonintentional misuse due to cutting the patch.

Advisory Committee Meeting

The review identified no issues that warranted discussions at an advisory committee meeting**.**

Pediatrics

For the age group of 6 to less the 17 years, the Post-Marketing Study PMR 3537-1, issued under PREA, follows:

> "An open-label pharmacokinetics and safety study of diclofenac epolamine topical system in pediatric patients aged 6 to less than 17 years with acute pain due to minor strains, sprains, and contusions."

PMR 3537-1 requirement is considered fulfilled upon approval of the current supplemental NDA.

For pediatric patients less than 6 years of age, a partial waiver of pediatric study was granted on the basis that necessary studies are impossible or highly impracticable because less than 5% of patients present with minor soft tissue injuries according to literature reports. The regulatory decision on granting the partial waiver for the youngest age group was supported by the Pediatric Review Committee (PeRC) at the most recent PeRC meeting dated February 24, 2026.

Other Relevant Regulatory Issues

None.

Labeling Review

The Division of Medication Error Prevention and Analysis 1 (DMEPA 1) recommended adding caregivers to receive dosing instructions. Refer to the Consult Review by Dr. Hakeem dated November 14, 2025.

The Applicant and the Division agreed on final labeling. Changes in labeling are in Indications and Usage (1), Dosage and Administration (2.2), Clinical Trials Experience (6.1), Pediatric Use (8.4), pediatric experience with heparin (12.1), and Pharmacokinetics (12.3).

Postmarketing Recommendations

None.

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/s/

CHRISTINA L FANG
03/27/2026 09:24:44 AM

NANCY C DICKINSON
03/27/2026 09:28:55 AM

NANCY C DICKINSON on behalf of ALLA T BAZINI
03/27/2026 09:29:28 AM

LEAH H CRISAFI
03/27/2026 11:35:48 AM