Office of Clinical Pharmacology Review

NDA or BLA Number	206976 Supplement 18
Link to EDR	\\CDSESUB1\evsprod\NDA206976\0117
Submission Date	June 6, 2025
Submission Type	*Standard Review*
Brand Name	Licart
Generic Name	Diclofenac epolamine topical system
Dosage Form and Strength	Topical Patch, 182 mg of diclofenac epolamine in an aqueous base
Route of Administration	Topical
Proposed Indication	for the topical treatment of acute pain due to minor strains, sprains, and contusions.
Applicant	IBSA Institut Biochimique Sa
Associated IND	*111538*
OCP Division:	*Division of Neuropsychiatric Pharmacology*
OND Division:	*DAAP*
Clinical Pharmacology Reviewer	*Srikanth C. Nallani, Ph.D.*
Clinical Pharmacology Team Leader	*Deep Kwatra, Ph.D.*

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1. EXECUTIVE SUMMARY

1.1 Recommendations

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The low systemic exposure in pediatric patients (6-16 years old) that is similar to that observed in adults applied with Licart patch supports its safety and effectiveness in pediatric patients. The open label study 18US-FHp04 supports the safety and efficacy of Licart in pediatric patients 6 years and older.
General dosing instructions	The recommended dose is one (1) LICART topical system to the most painful area once daily.
Dosing in patient subgroups (Pediatrics)	The recommended dose is one (1) LICART topical system to the most painful area once daily in pediatric patients 6 years and older.
Labeling	Section 8.4 of the label describes the safety and effectiveness of Licart in adult and pediatric patients 6 years and older.
Bridge between the to-be-marketed and clinical trial formulations	None

1.2 Post-Marketing Requirements and Commitments

None

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

IBSA submitted NDA 206976 S-18 to fulfill the pediatric study requirements. In this submission, a final study report was submitted for Study 18US-FHp04 "A multi-center, prospective, open-label, controlled study of the pharmacokinetics and safe- ty of the Licart™ topical system in pediatric and adult participants with minor soft tissue injuries". 151 patients between 6-11 years and 12-16 years (pediatric population); and 18- 45 years (adult population) were enrolled in the study from 12 sites in the US. Among the 151 subjects enrolled in the study, 51 patients were in the pediatric subgroup (6-11 years), 50 subjects were in the pediatric subgroup (12-16 years) and 50 patients were in the adult population. Blood samples were obtained from each patient at Visit 2, 24 hours (± 1 hour) after the initial topical system application at Visit 1, and at the time of study discontinuation (with a topical system in place) for determination of plasma diclofenac concentration and plasma aPTT. At the End of Study (EOS) Visit, the PI provided an assessment of global response to therapy on a 5-point scale.

Office of Study Integrity and Surveillance (OSIS) was requested to inspect the major clinical site by clinical investigator Dr. Amid Hamidi at Ascendant Research Clinic (Site 20). The inspection identified significant protocol deviations related to the collection of blood samples for diclofenac plasma

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concentration and activated partial thromboplastin time (aPTT) measurements outside the protocol specified time windows (See OSIS review dated 11/24/2025). Given the nature and extent of these protocol violations at Site 20, the Agency required a comprehensive evaluation to determine whether similar issues exist across all clinical sites participating in Study 18US-FHp04. In an information request dated 12/17/2025, the sponsor was requested to assess the potential protocol violations, if any, where the blood samples were collected outside the specified windows at all the clinical sites enrolled in Study 18US-FHp04. The sponsor was also asked to provide a detailed listing of all subjects affected by such deviations, including the scheduled collection time, actual collection time, and the magnitude of the deviation from the protocol-specified window. Report the impact of observed plasma diclofenac concentrations and aPTT values per protocol, and any protocol violations in each age group as descriptive statistics. The sponsor submitted the reanalysis in a submission dated January 30, 2026.

All 151 subjects were included in the PK analysis set of the pediatric and adult population. There were 49 (98.0%) subjects in the PK analysis set and 47 (94.0%) patients in the per protocol analysis set of pediatric subgroups (12-16 years); and 46 (92.0%) subjects in the per protocol analysis set of adult population.

Of the 151 subjects enrolled, 17 had a deviation at Visit 2 (day 2), as the blood samples for diclofenac were not collected within the required 24 hours (±1 hour) window following the initial administration of the investigational product. The deviation in collection beyond the required 24 hours window was by 12 minutes to 20 hours and 17 minutes. Additionally, at Visit 5 (Day 14/End of Study), blood samples for diclofenac in 33 subjects were either not collected or were collected outside the specified time windows. The deviation in collection for Visit 5 were categorized as “Not collected” or “out of window” by 1 to 11 days.

The summary of diclofenac concentration in PK analysis set without deviations, as mean, median, SD, range and 90% CI of the mean, is presented in Table below.

On Day 2, the mean (SD) diclofenac concentrations (ng/mL) were 1.51 (1.5) in the total pediatric population [6-11 years: 1.88 (1.65) and 12-16 years: 1.16 (1.35)] and 1.79 (2.69) in the adult population.

Visit		Age group [6-11] (N = 51)	Age group [12-16] (N = 47)	Pediatric [6-16] (N = 98)	Adult (N = 46)	Overall (N = 144)
Day 2	n (missing)	46 (5)	40 (7)	86 (12)	37 (9)	123 (21)
	Mean (SD)	1.8830 (1.64573)	1.0868 (1.22269)	1.5127 (1.50976)	1.8297 (2.75610)	1.6081 (1.96236)
	90% CI	[1.4755, 2.2905]	[0.7611, 1.4125]	[1.2420, 1.7834]	[1.0647, 2.5947]	[1.3148, 1.9013]
	Median	1.6085	0.9076	1.1130	0.4580	1.0035
	Min, Max	0.000, 5.896	0.000, 6.181	0.000, 6.181	0.000, 11.511	0.000, 11.511

At the EOS, the mean (SD) diclofenac concentrations were 1.51 (3.66) in the total pediatric population [6-11 years: 1.54 (3.26) and 12-16 years: 1.48 (4.13)] and 1.48 (4.28) in the adult population.

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Visit		Age group [6-11] (N = 51)	Age group [12-16] (N = 49)	Pediatric [6-16] (N = 100)	Adult (N = 50)	Overall (N = 150)
EOS	n (missing)	40 (11)	34 (15)	74 (26)	43 (7)	117 (33)
	Mean (SD)	1.5349 (3.26028)	1.4836 (4.12974)	1.5113 (3.65911)	1.4787 (4.27613)	1.4993 (3.87900)
	90% CI	[0.6664, 2.4034]	[0.2850, 2.6822]	[0.8027, 2.2200]	[0.3819, 2.5755]	[0.9047, 2.0939]
	Median	0.1436	0.1472	0.1472	0.1424	0.1424
	Min, Max	0.000, 18.682	0.000, 23.981	0.000, 23.981	0.000, 25.345	0.000, 25.345

The resulting average concentrations across Day 2 and at EOS were 1.48 ng/mL and 1.30 ng/mL, respectively, both of which are similar to the values observed in adults.

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.

3. LABELING

The sponsor proposed labeling changes are indicated in regular font text, additions and deletions are indicated in bold and strikethrough text.

1 INDICATIONS AND USAGE

LICART is indicated for the topical treatment of acute pain due to minor strains, sprains, and contusions in adults and pediatric patients 6 years of age and older.

2.2 Recommended Dose

The recommended dose is one (1) LICART topical system to the most painful area once daily both in adults and pediatric patients 6 years and older.

8.4 Pediatric Use

The safety and effectiveness of LICART have been established in pediatric patients 6 years and older (b) (4) evidence from adequate and well-controlled studies with LICART in adults, as well as an open-label study in pediatric patients 6 years and older. (b) (4)

One LICART was applied to the injury site once a day for a maximum of 14 days or until pain (b) (4)

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resolved [redacted], whichever occurred first. Based on the available data from the pediatric study, the safety profile of LICART topical system in pediatric patients is similar to that in adults. The safety and effectiveness of LICART has not been investigated in pediatric patients less than 6 years old. [see Clinical Trials Experience (6.1), Clinical Pharmacology (12.3)].

Note: The sponsor had taken the same approach to describing pediatric safety and efficacy information in the label for their Flector Patch NDA 21234. The proposed labeling is generally acceptable.

12 Absorption – Pediatrics

Diclofenac plasma concentration was assessed in pediatric patients 6 and older at a fixed time point 24-hours after the initial patch application and at [redacted] The resulting average concentrations were 1.48 ng/mL and 1.30 ng/mL, respectively, both of which are similar to the values observed in adults.

Specific Populations

The pharmacokinetics of LICART has not been investigated in children less than 6 years old, patients with hepatic or renal impairment, or specific racial groups.

Note: The proposed labeling changes are acceptable.

14 CLINICAL STUDIES

[redacted]

Note: Observations from an open-label study are not appropriate in “Section 14 Clinical Studies” of the label. The description of pediatric experience in section 8.4 is adequate.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Analysis of plasma samples for the quantification of diclofenac was completed using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) bioanalytical method. Plasma was separated from blood collected in EDTA K2 tubes and then frozen for storage and shipment. A summary of the method parameters is provided in the Table below. The bioanalytical method demonstrated adequate performance characteristics for the intended purpose and the validation parameters meet FDA bioanalytical method validation guidance criteria and support the reliability of diclofenac concentration measurements in this pediatric study.

Table: Summary of Bioanalytical Method Validation Parameters.

Information Requested	Data
Bioanalytical method validation report location	Original validation report 125064AIPF (revision 5), Pages 1 to 125 Partial validation report 215039AZPC, Pages 1 to 35
Analyte	Diclofenac
Internal standard (IS)	Diclofenac-d_4
Method description	This method involves the extraction of diclofenac and the IS, diclofenac-d_4, from human EDTA K_2 plasma using an automated liquid-liquid extraction procedure and LC-MS/MS determination according to test method TM.3233.02. Samples were kept frozen at -20ºC prior to analysis and 0.100 mL of matrix was used for analysis.
Limit of quantitation (pg/mL)	100.00
Average recovery of drug (%)	81.77, 89.10 and 87.01%
Average recovery of IS (%)	80.73%
Standard curve concentrations (pg/mL)	100.00, 200.00, 500.00, 1000.00, 2000.00, 4000.00, 8000.00, 10000.00
QC concentrations (pg/mL)	LLQC: 100.00, QC1: 300.00, QC2: 5000.00, QC3: 7500.00
QC Intraday precision range (%)	CV: 0.75 to 4.31%
QC Intraday accuracy range (%)	Biases: 1.20 to 2.71%
QC Interday precision range (%)	CV: 2.81 to 16.69%
QC Interday accuracy range (%)	Biases: -5.15 to 1.73%
Bench-top stability (hrs) (equivalent to short-term stability of analyte in matrix)	25h12min at room temperature
Stock stability (days) (equivalent to long-term stability of analyte or internal standard in solution)	Analyte: 960 days (high concentration) and 335 days (low concentration) at -20°C IS: 265 days (high concentration) and 76 days (low concentration) at -20°C
Processed stability (hrs) (equivalent to post-preparative stability)	71h08min at room temperature
Freeze-thaw stability (cycles)	4 cycles at -20°C
Long-term storage stability (days) (equivalent to long-term stability of analyte in matrix)	26, 133, 246, 314, and 701 days at -20ºC
Dilution integrity	500000.00 pg/mL, dilution factor: 20 Bias: -3.56% CV: 3.39%
Selectivity	No significant interference observed in 8 out of 8 tested matrices for diclofenac and its IS (Including Hyperlipemic Matrix and Hemolyzed Matrix at 5%)

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