CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206976Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	206976
Supporting document/s:	SDN-46 (NDA resubmission Class 2)
Applicant's letter date:	June 25, 2018
Product:	LICART ™ (1.3% diclofenac) (b) (4)
Indication:	Topical treatment of acute pain due to minor strains, sprains, and contusions
Applicant:	Institut Biochimique SA (IBSA)
Review Division:	Division of Anesthesia, Analgesia, and Addiction Products
Reviewer:	Armaghan Emami, PhD
Team Leader:	Jay H. Chang, PhD
Supervisor	R. Daniel Mellon, PhD
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Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

Institut Biochimique SA (IBSA) resubmitted NDA 206976 for marketing approval of Licart™ (b) (4) for the treatment of pain associated with (b) (4) via the 505(b)(2) pathway referencing literature and cross-referencing all information in NDA 21234 (approved 2007) for Flector® Patch, which the Applicant owns. This NDA was originally submitted 3/4/2015, but was not filed due to deficiencies from numerous disciplines (see Refuse-to-File letter sent on 4/29/2015). This NDA was resubmitted on May 26, 2016 and was not approved during the first review cycle due to deficiencies from numerous disciplines. The complete response letter dated March 24, 2017 included one nonclinical deficiency related to their leachables evaluation. The information for leachable study was considered inadequate and several unknown compounds detected at > 5 mcg/day were not adequately qualified, see below:

Deficiencies:

1. The NDA did not include an adequate justification to support the safety of the (b) (4) leachable compounds whose structures were not fully elucidated in the leachables studies, but detected at levels exceeding the qualification threshold of 5 mcg/day. (b) (4) (b) (4) (b) (4) However, we note that the levels of difference in diclofenac released from patches subjected to leachables testing were comparable to those administered to human subjects when considering the peak levels released in clinical studies. Moreover, no evidence was provided to demonstrate that any of the leachables would be released at the same rate as diclofenac.

Information Needed to Resolve Deficiencies:

1. To address this deficiency, identify all unknown leachable compounds detected at levels that exceed 5 mcg/day and provide a toxicological risk assessment to justify the safety of these identified compounds. Alternatively, you may provide convincing evidence that none of the compounds would penetrate skin and therefore would not pose any risk to patients. If you elect to put forth an argument that the compounds (b) (4)

During a Type A Post-Action Meeting held on October of 2017, the Applicant declared their intention to generate new extractable/leachable data since they planned to use drug products manufactured at a new manufacturing site (Teikoku) with slightly different

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packaging than those used at a (b) (4)). With this resubmission, the Applicant submitted a new extractable/leachable dataset on the Teikoku manufactured drug product to address the deficiency with sufficient information for review.

Licart (b) (4), also referred to as (b) (4) during development, consists of an adhesive (b) (4) containing 1.3% diclofenac epolamine (182 mg/(b) (4), (b) (4) on a non-woven felt backing and covered with a polypropylene film as a release-liner. The size of a single patch is 10 cm x 14 cm. The difference in composition between Licart (b) (4) compared to the originally approved Flector Patch is the addition of the (b) (4) heparin (b) (4) The Applicant provided in vitro data to demonstrate that heparin is not released from the patch due to its high molecular weight (~10,000 Daltons [Da]). Therefore, the change in formulation is not expected to raise any significant safety concerns from the nonclinical perspective. Licart is intended to be applied one (b) (4) per day for 24 hours while Flector patch is applied two patches per day for 12 hours each. Human PK testing showed that the two formulations (Flector vs Licart) were bioequivalent following these dosing regimens.

1.2 Brief Discussion of Nonclinical Findings

New extractables and leachable studies with toxicology risk assessments were submitted to justify the safety of the topical delivery and container closure systems for this drug product, which will be manufactured at a new site Teikoku. Extractable and leachables evaluations were performed with appropriate study design methods and sample sets. A robust extractables study of the (b) (4) primary packaging (polyester felt backing non-woven material, polypropylene release liner and envelope) was performed and provided information about the compounds to monitor in leachable studies using drug product on stability. Subsequently, a leachables study was conducted using validated methods and artificial sweat with heat to simulate worst-case conditions of human use. (b) (4) leachables were detected above the qualification threshold of 5 mcg/day; however, they were adequately justified for safety through toxicological risk assessments employing a permissible daily exposure (PDE) approach as outlined in ICH Q3C.

1.3 Recommendations

1. 1.3.1 Approvability

From a nonclinical pharmacology toxicology perspective, NDA 207962 may be approved since adequate data were provided that justifies the safety of the container closure system and therefore addressed the nonclinical deficiency outlined in the complete response letter dated 3/24/2017.

2. 1.3.2 Additional Non Clinical Recommendations

3. 1.3.3 Labeling

This product label is the same as that approved for the Flector® Patch in 8/30/2018, since the two products are identical except for the presence of heparin in Licart. Highlighted in yellow are the parts that are unique to the Licart product label.

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Note that the Applicant performed a literature search for nonclinical and clinical data relevant to diclofenac or any diclofenac or diclofenac epolamine-containing product, as well as a review of the Flector patch pharmacovigilance databases to verify if the Pregnancy, Lactation, or Females and Males of Reproductive Potential subsections of approved Flector labeling needed to be updated. After a close examination of the study findings from the identified literature, none of the data were considered by this reviewer to warrant changes to the Flector label. Refer to nonclinical review (NDA 21234, Supplement 15) in DARRTS dated 05/24/2018.

Applicant's Proposed Labeling	**Recommended Changes to Proposed Labeling**	**Rationale for recommended changes/Comment**
INDICATIONS AND USAGE LICART is indicated for the topical treatment of acute pain due to minor strains, sprains, and contusions.	**INDICATIONS AND USAGE** LICART is indicated for the topical treatment of acute pain due to minor strains, sprains, and contusions.	No changes needed.
8.1 Pregnancy Risk Summary Published literature reports that use of NSAIDs, including LICART, after 30 weeks' gestation increases the risk of premature closure of the fetal ductus arteriosus. Data from observational studies regarding potential embryofetal risks of NSAID use, including diclofenac, in women in the first or second trimester of pregnancy are inconclusive. Avoid use of NSAIDs, including LICART, in pregnant women starting at 30 weeks of gestation (third trimester) (see *Clinical Considerations and Data*). In animal reproduction studies, diclofenac epolamine administered orally to pregnant rats and rabbits during the period of organogenesis produced embryotoxicity at approximately 3 and 7 times, respectively, the topical exposure from the maximum recommended human dose (MRHD) of LICART. In rats, increased incidences of skeletal anomalies and maternal toxicity were also observed at this dose. Diclofenac epolamine administered orally to both male and female rats prior to mating and throughout the mating period, and during gestation and lactation in females produced embryotoxicity at doses	**8.1 Pregnancy** Risk Summary Published literature reports that use of NSAIDs, including LICART, after 30 weeks' gestation increases the risk of premature closure of the fetal ductus arteriosus. Data from observational studies regarding potential embryofetal risks of NSAID use, including diclofenac, in women in the first or second trimester of pregnancy are inconclusive. Avoid use of NSAIDs, including LICART, in pregnant women starting at 30 weeks of gestation (third trimester) (see *Clinical Considerations and Data*). In animal reproduction studies, diclofenac epolamine administered orally to pregnant rats and rabbits during the period of organogenesis produced embryotoxicity at approximately 3 and 7 times, respectively, the topical exposure from the maximum recommended human dose (MRHD) of LICART. In rats, increased incidences of skeletal anomalies and maternal toxicity were also observed at this dose. Diclofenac epolamine administered orally to both male and female rats prior to mating and throughout the mating period, and during gestation and lactation in females produced embryotoxicity at doses	Pregnancy Category omitted to comply with the Pregnancy Labeling and Lactation Rule (PLLR). The language in Section 8 of the proposed Licart label is identical to the reference product Flector label language with just the tradename replaced. Note that the Flector label was recently updated with the NSAID Safety Labeling Change supplement, which included changes in accordance with PLLR, in August of 2018. In accordance with PLLR, the reference Flector patch included a comprehensive literature search for nonclinical data from the public domain that addressed the effects of diclofenac on reproduction and development. A total of nine articles were submitted. The Applicant

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approximately 3 and 7 times, respectively, the topical exposure from the MRHD *(see Data)*.	approximately 3 and 7 times, respectively, the topical exposure from the MRHD *(see Data)*.	argued that none of the findings from these published articles were appropriate for this label. This reviewer agreed.
Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as diclofenac, resulted in increased pre- and post-implantation loss.	Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as diclofenac, resulted in increased pre- and post-implantation loss.	No changes to exposure margins are recommended compared to the Flector labeling despite the change in dosing regimen. Note that exposure margins in the original Flector label were based on body surface area comparison and dose delivered from the patch in clinical studies (b) (4)
The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.	The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.	Although the MRHD of Licart (b) (4) is one half of the MRHD of Flector patch (e.g., one patch/day vs two patches/day), the upper range of the amount of diclofenac released from Licart over 24 hours during clinical use was (b) (4) Therefore, the exposure margins for the Licart label should be the same as Flector.
Clinical Considerations	Clinical Considerations	
Fetal/Neonatal Adverse Reactions	*Fetal/Neonatal Adverse Reactions*	
Avoid use of NSAIDS in pregnant women after 30 weeks' gestation because NSAIDS, including LICART, can cause premature closure of the fetal ductus arteriosus.	Avoid use of NSAIDS in pregnant women after 30 weeks' gestation because NSAIDS, including LICART, can cause premature closure of the fetal ductus arteriosus.	
Data	Data	
Human Data	*Human Data*	
Published literature reports that use of NSAIDS, including diclofenac, after 30 weeks' gestation may cause constriction of the patent ductus arteriosus and premature closure of the fetal ductus arteriosus.	Published literature reports that use of NSAIDS, including diclofenac, after 30 weeks' gestation may cause constriction of the patent ductus arteriosus and premature closure of the fetal ductus arteriosus.	Clinical sections were not altered and will be edited by Clinical and Maternal Health Teams.
Animal Data	*Animal Data*	
Pregnant Sprague Dawley rats were administered 1, 3, or 6 mg/kg diclofenac epolamine via oral gavage daily from gestation days 6 to 15. Maternal toxicity, embryotoxicity, and increased incidence of skeletal anomalies were noted with 6 mg/kg/day diclofenac epolamine, which corresponds to 3-times the maximum recommended daily exposure in humans based on a	Pregnant Sprague Dawley rats were administered 1, 3, or 6 mg/kg diclofenac epolamine via oral gavage daily from gestation days 6 to 15. Maternal toxicity, embryotoxicity, and increased incidence of skeletal anomalies were noted with 6 mg/kg/day diclofenac epolamine, which corresponds to 3-times the maximum recommended daily exposure in humans based on a	As noted above, the exposure margins from the Flector label were originally based on BSA comparison and diclofenac release from patches. Since the amount

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body surface area comparison. Pregnant New Zealand White rabbits were administered 1, 3, or 6 mg/kg diclofenac epolamine via oral gavage daily from gestation days 6 to18. No maternal toxicity was noted; however, embryotoxicity was evident at 6 mg/kg/day group which corresponds to 7-times the maximum recommended daily exposure in humans based on a body surface area comparison. Male rats were orally administered diclofenac epolamine (1, 3, 6 mg/kg) for 60 days prior to mating and throughout the mating period, and females were given the same doses 14 days prior to mating and through mating, gestation, and lactation. Embryotoxicity was observed at 6 mg/kg diclofenac epolamine (3-times the maximum recommended daily exposure in humans based on a body surface area comparison), and was manifested as an increase in early resorptions, post-implantation losses, and a decrease in live fetuses. The number of live born and total born were also reduced as was F1 postnatal survival, but the physical and behavioral development of surviving F1 pups in all groups was the same as the deionized water control, nor was reproductive performance adversely affected despite a slight treatment-related reduction in body weight.	body surface area comparison. Pregnant New Zealand White rabbits were administered 1, 3, or 6 mg/kg diclofenac epolamine via oral gavage daily from gestation days 6 to18. No maternal toxicity was noted; however, embryotoxicity was evident at 6 mg/kg/day group which corresponds to 7-times the maximum recommended daily exposure in humans based on a body surface area comparison. Male rats were orally administered diclofenac epolamine (1, 3, 6 mg/kg) for 60 days prior to mating and throughout the mating period, and females were given the same doses 14 days prior to mating and through mating, gestation, and lactation. Embryotoxicity was observed at 6 mg/kg diclofenac epolamine (3-times the maximum recommended daily exposure in humans based on a body surface area comparison), and was manifested as an increase in early resorptions, post-implantation losses, and a decrease in live fetuses. The number of live born and total born were also reduced as was F1 postnatal survival, but the physical and behavioral development of surviving F1 pups in all groups was the same as the deionized water control, nor was reproductive performance adversely affected despite a slight treatment-related reduction in body weight.	released from the two formulations (Flector vs Licart) is (b) (4) despite their different dosing regimens, exposure margins should remain the same as in the Flector Patch label.
8.3 Females and Males of Reproductive Potential Infertility Females Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including LICART may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women [see Clinical Pharmacology (12.1)]. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin- mediated follicular	**8.3 Females and Males of Reproductive Potential** Infertility Females Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including LICART may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women [see Clinical Pharmacology (12.1)]. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin- mediated follicular	No changes recommended. This section is consistent with Flector patch label, which was recently updated to include NSAID safety labeling change language.

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rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including LICART, in women who have difficulties conceiving or who are undergoing investigation of infertility.	rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including LICART, in women who have difficulties conceiving or who are undergoing investigation of infertility.	
12.1 Mechanism of Action Diclofenac has analgesic, anti-inflammatory, and antipyretic properties. The mechanism of action of diclofenac, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2). Diclofenac is a potent inhibitor of prostaglandin synthesis in vitro. Diclofenac concentrations reached during therapy have produced in vivo effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Because diclofenac is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.	**12.1 Mechanism of Action** Diclofenac has analgesic, anti-inflammatory, and antipyretic properties. The mechanism of action of diclofenac, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2). Diclofenac is a potent inhibitor of prostaglandin synthesis in vitro. Diclofenac concentrations reached during therapy have produced in vivo effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Because diclofenac is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.	No changes recommended. This section is consistent with reference product Flector patch label, which was recently updated to include NSAID safety labeling change language.
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility *Carcinogenesis* Long-term studies in animals have not been performed to evaluate the carcinogenic potential of either diclofenac epolamine or LICART. *Mutagenesis* Diclofenac epolamine is not mutagenic in Salmonella typhimurium strains, nor does it induce an increase in metabolic aberrations in cultured human lymphocytes, or the frequency of micronucleated cells in the bone marrow micronucleus test performed in rats. *Impairment of Fertility*	**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** *Carcinogenesis* Long-term studies in animals have not been performed to evaluate the carcinogenic potential of either diclofenac epolamine or LICART. *Mutagenesis* Diclofenac epolamine is not mutagenic in Salmonella typhimurium strains, nor does it induce an increase in metabolic aberrations in cultured human lymphocytes, or the frequency of micronucleated cells in the bone marrow micronucleus test performed in rats. *Impairment of Fertility*	No changes recommended. This section is consistent with Flector patch label.

Male and female Sprague Dawley rats were administered 1, 3, or 6 mg/kg/day diclofenac epolamine via oral gavage (males treated for 60 days prior to conception and during mating period, females treated for 14 days prior to mating through day 19 of gestation). Diclofenac epolamine treatment with 6 mg/kg/day resulted in increased early resorptions and post-implantation losses; however, no effects on the mating and fertility indices were found. The 6 mg/kg/day dose corresponds to 3 times the maximum recommended daily exposure in humans based on a body surface area comparison.	Male and female Sprague Dawley rats were administered 1, 3, or 6 mg/kg/day diclofenac epolamine via oral gavage (males treated for 60 days prior to conception and during mating period, females treated for 14 days prior to mating through day 19 of gestation). Diclofenac epolamine treatment with 6 mg/kg/day resulted in increased early resorptions and post-implantation losses; however, no effects on the mating and fertility indices were found. The 6 mg/kg/day dose corresponds to 3 times the maximum recommended daily exposure in humans based on a body surface area comparison.	Exposure margins remain the same as described above.

Justification for safety margin calculations:
In vivo assessments of residual content in the patch following administration to human subjects for 24 hours demonstrated that the release of active diclofenac from Licart (one patch for 24 hours) and Flector patch (two patches for 12 hours each) was 3.6% and 4.9%, respectively.

Average of 6.5 mg of diclofenac were recovered from Licart patches following 24 hrs of exposure in comparison to baseline mean values (3.6%). The range in values after 24 hours range is from (b) (4). At time 0 a range from (b) (4) were observed. Therefore, with the worse case scenario, diclofenac is released about (b) (4) from licart (b) (4) (b) (4)) which is about 10% (Study Report CRO-PK-12-272, See CMC review for more details which submitted in Panorama on Feb-03-2017).

Relative diclofenac release from the Flector Patch, estimated by comparing the mean values for 10 control patches to 20 patches removed from 20 volunteers each receiving one patch for 12 hours, was 9.2 mg ((b) (4) or 4.9% (NDA 21234, see Module 4.2.3.7.7 Study Report 910195/MD2). With two patches per day, the diclofenac release is (b) (4).

2 Drug Information

2.1 Drug

CAS Registry Number: 119623-66-4
Generic Name: Diclofenac epolamine
Proprietary names: Diclofenac hydroxyethyl pyrrolidine (DHEP)
Code Name: 1077

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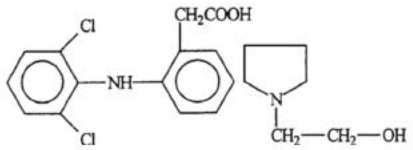
Chemical Name: 2-[(2,6-Dichlorophenyl)amino] phenylacetate 1-(2-hydroxyethyl) pyrrolidine salt

Molecular Formula: $C_{20}H_{24}Cl_2N_2O_3$

Molecular Weight: 411.3 g/mol

Structure:



Pharmacologic Class: NSAID

2.2 Relevant INDs, NDAs, BLAs and DMFs

Licart was developed under IND 111538. NDA 206976 was submitted via the 505(b)(2) pathway referencing literature and cross-referencing all of the information in the Flector® Patch NDA 21234, which the Applicant also owns.

2.3 Drug Formulation

Dosage Form Description

The topical Licart (b) (4) consists of a (b) (4) adhesive (b) (4), containing the active pharmaceutical ingredient, uniformly spread on a non-woven felt backing and covered with a polypropylene film as a release-liner. The release-liner is removed prior to application of the patch to the skin.

Composition

The size of a single (b) (4) is (b) (4), or approximately 140 cm^2. The adhesive layer is applied to the non-woven polyester felt backing in the (b) (4). The total amount of the (b) (4)

(b) (4) Schematic

(b) (4)

Drug product composition

Composition of the Adhesive (b) (4)

Ingredients	Composition (per (b) (4))		Function	Reference to Standard
	Quantity (mg)	Percent (w/w %)		
Active Substance				
Diclofenac Epolamine (DHEP)*	182	1.3	Active Ingredient	Drug Master File
Excipients				
Heparin Sodium			(b) (4)	USP/EP current ed.
(b) (4) sorbitol Solution (b) (4)				USP current ed.
(b) (4) butylene Glycol				USP current ed.
Sodium Polyacrylate				(b) (4)
Carboxymethylcellulose Sodium				USP current ed.
Kaolin				USP current ed.
Propylene Glycol				USP current ed.
Gelatin (b) (4)				USP/NF current ed.
Povidone (b) (4) (b) (4)				USP current ed.
Titanium Dioxide				USP current ed.
Tartaric Acid				USP/NF current ed.
Dihydroxyaluminum Aminoacetate				USP current ed.
Polysorbate 80				USP/NF current ed.
Edetate Disodium (EDTA)				USP current ed.
Methylparaben (b) (4)				USP/NF current ed.
Propylparaben (b) (4)				USP/NF current ed.
Fragrance (Dalin PH) †				(b) (4)
Purified Water				USP/NF current ed.
				(b) (4)

Unitary Composition of a (b) (4)

Component	Unitary Amount	Reference to Standard
(b) (4)	(b) (4)	Not Applicable
Non-Woven Polyester Felt Backing		(b) (4)
Polypropylene Film (Release Liner)		USP/ (b) (4)

2.4 Comments on Novel Excipients

No new formulation information was submitted with this NDA resubmission. Refer to the first cycle nonclinical review in DARRTS dated 2/22/2017.

2.5 Comments on Impurities/Degradants of Concern

Refer to nonclinical review in DARRTS dated 2/22/2017.

2.6 Proposed Clinical Population and Dosing Regimen

The proposed indication is the [redacted] that established for Flector® Patch (NDA 21234), the Applicant's own drug product. The proposed indication is for the relief of pain [redacted]. The maximum recommended daily dose of Licart (Diclofenac Epolamine 1.3%/[redacted] is one patch per day (QD); whereas, the currently approved Flector patch is labeled for BID dosing.

2.7 Regulatory Background

- On 3/4/2015, IBSA submitted NDA 206976 for marketing approval of [redacted] ™ via the 505(b)(2) pathway referencing literature and relying on information from the Flector® Patch NDA 21234 (approved 1/31/2007), which the Applicant owns.
- On 4/29/2015, IBSA received a refuse-to-file (RTF) letter from FDA identifying a number of deficiencies. As part of the RTF letter for the original [redacted] NDA submission, the Applicant was informed that a leachables study would be required with the resubmission.
- On 08/26/2015, IBSA had a Type A post-action meeting with the FDA (meeting minutes dated 9/16/2015). In this meeting the requirements for leachable study was discussed such as complete assessment over the course of stability and using appropriate testing condition.
- NDA 207962 was resubmitted on May 27, 2016 (SDN 10) for marketing approval of [redacted] (Licart®) for the treatment of pain [redacted]
- The Applicant received a complete response letter dated March 24, 2017 included one nonclinical deficiency related to leachable study. The information for leachable study was considered inadequate and several unknown compounds detected at > 5 mcg/day were not adequately identified or qualified.
- In Type A Post-Action Meeting on October 2017, the Applicant declared their intention to conduct new extractable/leachable studies.
- NDA 207962 was resubmitted for the second time (class 2) on June 25, 2018 (SDN 46) for marketing approval of [redacted] (Licart®) for the treatment of pain [redacted].

3 Studies Submitted

3.1 Studies Reviewed

A new extractable/leachable studies with toxicology risk assessments

3.2 Studies Not Reviewed

N/A

3.3 Previous Reviews Referenced

- NDA 21234 nonclinical reviews for Flector patch by Drs. Amouzadeh (dated 9/26/2001) and Mellon (dated 1/22/2007).

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- NDA 206976 nonclinical review by Dr. Emami for Licart (dated 2/22/2017)
  - 4-week repeat-dose (b) (4) (just the (b) (4)) dermal toxicity in rabbits
  - (b) (4) dermal hypersensitivity study in guinea pig
  - UV-Visible absorption spectrum of heparin sodium salt
  - (b) (4) packaging extraction study
  - Extractable/Leachable studies
  - Toxicology risk assessment of the leachables

4 Pharmacology

No new nonclinical pharmacology studies were conducted or required as the pharmacology of diclofenac is well established.

5 Pharmacokinetics/ADME/Toxicokinetics

Pharmacokinetic (PK) studies have not been performed with Licart in animals. However, release of heparin and diclofenac from the patch, has been investigated both in vitro and in vivo in humans (see the clinical pharmacology review for evidence of bioequivalence).

In vitro: Using a Franz Cell fitted with a synthetic membrane; heparin could not be detected in the receiving chamber of the system following Licart application and buffer sampling 24 hours later. In contrast, the concentrations of diclofenac in the receiving chamber of the Franz Cell System over 24 hours following (b) (4) application were ~2.4 fold greater than application with Flector patch.

6 General Toxicology

No new general toxicology studies were submitted with this resubmission. Refer to the first cycle nonclinical review in DARRTS dated 2/22/2017

7 Genetic Toxicology

No new genotoxicity studies were submitted with this NDA. The Licart label will include genotoxicity information for diclofenac epolamine from the Flector patch label as the Applicant also owns this NDA 21234.

8 Carcinogenicity

No new carcinogenicity studies were submitted with this NDA. No studies are required for Licart (b) (4) since the indication is for acute use.

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9 Reproductive and Developmental Toxicology

No new reproductive and developmental toxicology studies were submitted with this NDA resubmission. The reproductive, developmental, and lactation labeling language for Licart is based on information from Flector® Patch (NDA 21234), which the Applicant also owns.

Notably, the Flector label was recently updated in accordance with PLLR. For this, the Applicant performed a literature review for the effects of diclofenac on reproduction, development, lactation, and fertility. Refer to nonclinical review (NDA 21234, Supplement 15) in DARRTS dated 05/24/2018. These updates are incorporated in the proposed Licart label.

10 Special Toxicology Studies

10.1 [redacted] dermal hypersensitivity study in guinea pig

Refer to the first cycle nonclinical review in DARRTS dated 2/22/2017.

10.2 UV-Visible absorption spectrum of heparin sodium salt

Refer to the first cycle nonclinical review in DARRTS dated 2/22/2017.

10.3 Extractable study

With this resubmission, the Applicant submitted new extractables and leachables studies to justify the safety of the container closure system and delivery system manufactured at the new manufacturing site at Teikoku. The extractable study of the primary packaging materials and plastic components of the drug product was executed under exaggerated conditions in order to characterize potential extractables and leachables, with the materials subjected to extraction and extract characterization listed below. Note that the CMC review team has verified that the extraction study was performed appropriately under adequately robust conditions.

Components tested:

- Polypropylene Film (Release Liner)
- Non-Woven Polyester Felt Backing
- Primary Packaging: Envelope ([redacted]).

The sealing closure of the envelope, which is made from [redacted], and was also included in the study even though the contact

20 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

ARMAGHAN EMAMI
11/16/2018

JAY H CHANG
11/16/2018

RICHARD D MELLON
11/16/2018
I concur.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	206976
Supporting document/s:	SDN-10 (NDA resubmission) SDN-18 (labeling) SDN-29 (leachable study) SDN-32 (nonclinical request)
Applicant's letter date:	May 27, 2016
Product:	LICART ™ (1.3% diclofenac) (b) (4)
Indication:	Topical treatment of acute pain due to minor strains, sprains, and contusions
Applicant:	Institut Biochimique SA (IBSA)
Review Division:	Division of Anesthesia, Analgesia, and Addiction Products
Reviewer:	Armaghan Emami, PhD
Team Leader:	Jay H. Chang, PhD
Supervisor	R. Daniel Mellon, PhD
Division Director:	Sharon Hertz, MD
Project Manager:	Spiros Nicols, PharmD

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 206976 are owned by IBSA or are data for which IBSA has obtained a written right of reference.
Any information or data necessary for approval of NDA 206976 that IBSA does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 206976.

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1 Executive Summary

1.1 Introduction

Institut Biochimique SA (IBSA), the Applicant, has submitted NDA 206976 for marketing approval of Licart™ (b) (4) for the treatment of pain (b) (4) via the 505(b)(2) pathway referencing literature and cross-referencing all information in NDA 21234 (approved 2007) for Flector® Patch, which the Applicant also owns. This NDA was originally submitted 3/4/2015, but was not filed due to deficiencies from numerous disciplines (see Refuse-to-File letter sent on 4/29/2015). From the nonclinical perspective, the NDA lacked an adequate leachables evaluation to support the safety of the product. Note that this NDA resubmission included a leachables study that was considered adequate for review.

Licart (b) (4), also referred to as (b) (4) during development, consists of an adhesive (b) (4) containing 1.3% diclofenac epolamine (182 mg (b) (4)), (b) (4) on a non-woven felt backing and covered with a polypropylene film as a release-liner. The size of a single (b) (4) is 10 cm x 14 cm. (b) (4) between Licart (b) (4) compared to the originally approved Flector Patch is the addition of the (b) (4) heparin (b) (4). The Applicant provided in vitro data to demonstrate that heparin is not released from the patch due to its high molecular weight (~10,000 Daltons [Da]). Therefore, the change in formulation is not expected to raise any significant safety concerns from the nonclinical perspective. According to the Applicant, the rationale for the inclusion of heparin in the Flector formulation is that (b) (4) (b) (4) Based on results from clinical studies, the Applicant contends that inclusion of heparin in the Flector formulation (Licart) was significantly more effective in reducing pain than Flector patch. Another notable difference is that Licart is intended to be applied one patch per day for 24 hours while Flector patch is applied two patches per day for 12 hours each. Human PK testing showed that the two formulations (Flector vs Licart) were bioequivalent following these dosing regimens.

1.2 Brief Discussion of Nonclinical Findings

An extensive nonclinical pharmacology/toxicology program was undertaken with the Flector Patch and data submitted to NDA 21234, which the Applicant owns and is cross-referencing. Given the indication, history of clinical use with the approved Flector product, and predicted lack of absorption of heparin from the patch, local toxicology studies were not required for the Licart (b) (4) program. Nevertheless, the Applicant had previously conducted a 4-week rabbit dermal toxicology study with the new diclofenac and heparin formulation and a dermal hypersensitivity study in guinea pigs, and submitted these studies to the NDA. In addition, a heparin in vitro release study and extractables/leachables studies with a toxicity risk assessment were also submitted.

The 4-week repeat-dose dermal rabbit toxicity study showed no evidence of local toxicity at the application sites except for mild, transient erythema in some of the study animals. No histology was performed in this study, but this is not an issue as the study was not required. The dermal guinea pig hypersensitivity study showed no toxic symptoms in treated animals and it was concluded that Licart was non-sensitizing in

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guinea pigs. In vitro data (Franz cell testing) showed that heparin is not released from the patch presumably due to its high molecular weight. This in vitro data also demonstrated that the release of diclofenac from Licart was ~2.4 fold greater than release from Flector. In contrast, an in vivo assessment of residual content in the patch following administration to human subjects for 24 hours demonstrated that the release of active diclofenac from Licart (one patch for 24 hours) and Flector patch (two patches for 12 hours each) was 3.6% and 4.9%, respectively. Nevertheless, human PK testing showed that the two formulations were bioequivalent following administration based on their respective dosing regimens.

Extractable and leachables evaluations were performed with appropriate study design methods and sample sets. The studies employed analytical evaluation thresholds to be able to detect nearly all compounds that exceed the qualification threshold of 5 mcg/day (b) (4) (b) (4). The compounds identified in the extraction studies were appropriately monitored in the leachables studies. The leachables study design simulated worst-case use (e.g., exercise) by subjecting patch components from batches on stability testing to a solvent that mimicked sweat for 24 hours under heated conditions. (b) (4) compounds were detected at peak levels exceeding 5 mcg/day, (b) (4) (b) (4), from drug matrix poultice extracts from one or more of the various age categories of finished product tested. In addition, (b) (4) compounds that were not fully characterized, but referred to (b) (4) (b) (4) (b) (4). Notably, all compounds, known or unknown, were well below the acceptable daily limit for mutagenic compounds per ICH M7; therefore, the levels of leachables that would likely be exposed to patients from the Licart (b) (4) product are considered safe from a genotoxicity perspective. From a general toxicity perspective, all known (identified) leachables detected at levels exceeding 5 mcg/day were adequately justified through toxicological risk assessments employing a permitted daily exposure (PDE) approach as outlined in the ICH Q3D guidance.

Attempting to justify the safety of the unknown leachables posed a challenge as a traditional toxicology risk assessment could not be performed on compounds that were not fully characterized. In our 74-day letter to the Applicant, we informed the Applicant that the assessment originally submitted to the NDA for the unknown leachables did not appear adequate based on our preliminary review and that they should submit as much information as possible to support a weight-of-evidence argument to justify their safety. The Applicant conducted additional leachable studies to demonstrate (b) (4) (b) (4) not warranted. However, this reviewer does not believe that the Applicant provided adequate information to draw the conclusion that these (b) (4) (b) (4) (b) (4). Further, regardless of the source of the leachable, a safety assessment is required for any compound patients could be exposed to that exceeds

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the recommended qualification threshold. The Applicant also performed additional studies to demonstrate that the [redacted]

simulated-use leachables studies was approximately 4-fold higher than the average amount of diclofenac released from Licart patches worn for 24 hours by human subjects in Clinical Study CRO-PK-12-272. However, when considering the peak levels of diclofenac released from patches worn by human subjects, the difference compared to amount released in the simulated-use leachables study was only 1.4-fold. Adjusting the levels of unknown leachables by a factor of 1.4 may lower two of the compounds so they are less than 5 mcg/day. However, it's important to note that it is unclear if the unknown leachables would leach from the patch at a similar rate as diclofenac as supporting information in this regard was not provided. As there are many questions unanswered, this reviewer can only conclude at this time that there are inadequate data to justify the safety of those unknown leachables that were not fully characterized.

1.3 Recommendations

1.3.1 Approvability

From the pharmacology and toxicology perspective, there are inadequate nonclinical data to support approval of NDA 206976 at this time and a complete response is recommended. Specifically, the NDA did not include an adequate justification to support the safety of [redacted] leachable compounds that could be exposed to patients through administration of the Licart [redacted]. Specifically, [redacted] compounds whose structures were not fully elucidated were detected in leachables studies at levels exceeding the recommended qualification threshold for general toxicity. An adequate risk assessment taking into consideration available toxicology information could not be performed on these compounds since they were not fully characterized. Rather than fully characterize these compounds, the Applicant pursued a weight-of-evidence approach to demonstrate that the compounds [redacted] and that the leachables study represented a worst-case scenario that overestimated leachable levels based on the contention that a higher level of diclofenac was demonstrated to be released from patches subjected to the leachables study than observed in clinical studies where the patch was administered to human subjects for 24 hours. The Applicant's justification was not considered adequate for the following reasons. Adequate supporting information was not provided to describe precisely how any of the compounds could have been derived from excipients in the drug product. [redacted]. Additionally, the Applicant did not provide references to support that that compounds

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(b) (4) Lastly, the difference in diclofenac release from patches subjected to leachables testing compared to those administered to human subjects was not significant, and no evidence to demonstrate that any of the leachables would be released at the same rate as diclofenac was provided. Taken together, the information submitted was not considered adequate by this reviewer to justify the safety of these uncharacterized leachables.

Deficiencies:

1. (b) (4)

Information Needed to Resolve Deficiencies:

1. To address this deficiency, identify all unknown leachable compounds detected at levels that exceed 5 mcg/day and provide a toxicological risk assessment to justify the safety of these identified compounds. The approach for toxicological evaluation of the safety of leachables must be based on good scientific principles and take into account the drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). The safety assessment should be specifically discussed in Module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. The risk assessment should be based on the maximum level of each leachable detected in long-term stability samples that include any intended secondary container closure system(s) unless otherwise justified. Include copies of all referenced studies upon which a safety assessment is based.

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- If you employ a Permissible Daily Exposure (PDE) assessment as described in ICH Q3C, provide justification for all safety factors employed.

- Published literature to support the safety of any compound rarely provides adequate detail of the study design and study results to permit a thorough independent evaluation of the data. Summary reviews, (e.g., BIBRA, CIR, HERA), although potentially useful to identify original source material, are not acceptable as the source material is not provided and the conclusions cannot be independently verified. Submission of any published study reports must be accompanied by a detailed comparison to modern toxicology study endpoints and any shortcomings of the study must be discussed and justification must be provided to support your assertion that these data are adequate to support the safety of your drug product formulation.

- Safety justifications based on analogous compounds are also not acceptable unless you can provide adequate data to support your conclusions that a risk assessment based on one compound can be logically interpolated to represent an adequate safety evaluation for your leachable/extractable. This should include a detailed understanding of the absorption, distribution, metabolism, and elimination of the compounds and an adequate scientific bridge to interpolate a NOAEL for the novel leachable.

Alternatively, you may provide convincing evidence that none of the compounds would penetrate skin and therefore would not pose any risk to patients. If you elect to put forth an argument that the compounds are too large to penetrate skin, employ an accurate and reliable method to demonstrate compound size and submit the articles that demonstrate and/or support the argument that specific size compounds do not penetrate skin.

1.3.2 Additional Non Clinical Recommendations: None

1.3.3 Labeling

The Applicant's proposed label language is shown in the left column of the table below. The right columns summarize this reviewer's recommended changes, rationale for this reviewer's recommended changes and general comments. Recommended additions to the label language are indicated with bold underlined text. The final label, which will be based on further internal discussion and negotiations with the Applicant, can be found in the Action letter.

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Applicant's Proposed Labeling	Recommended Changes to Proposed Labeling	Rationale for recommended changes/Comment
HIGHLIGHTS OF PRESCRIBING INFORMATION **INDICATIONS AND USAGE** LICART (b) (4) is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the topical treatment of acute pain due to minor strains, sprains, and contusions. (1)	**HIGHLIGHTS OF PRESCRIBING INFORMATION** **INDICATIONS AND USAGE** LICART (b) (4) is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the topical treatment of acute pain due to minor strains, sprains, and contusions. (1)	No changes needed.
8.1 Pregnancy Pregnancy Category C prior to 30 weeks gestation; Category D starting 30 weeks gestation. <u>Risk Summary</u> Use of NSAIDs, including LICART (b) (4), during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including LICART (b) (4), in pregnant women starting at 30 weeks of gestation (third trimester). (b) (4) In animal reproduction studies, diclofenac epolamine administered orally to pregnant rats and rabbits during the period of organogenesis produced embryotoxicity at approximately 3 and 7 times, respectively, the topical exposure from the maximum recommended human dose (MRHD) of LICART (b) (4). In rats, increased incidences of skeletal anomalies and	<u>Risk Summary</u> Use of NSAIDs, including LICART (b) (4), during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including LICART (b) (4), in pregnant women starting at 30 weeks of gestation (third trimester). (b) (4) In animal reproduction studies, diclofenac epolamine administered orally to pregnant rats and rabbits during the period of organogenesis produced embryotoxicity at approximately 3 and 7 times, respectively, the topical exposure from the maximum recommended human dose (MRHD) of LICART (b) (4) In rats, increased incidences of skeletal anomalies and maternal toxicity were also observed	Pregnancy Category omitted to comply with the Pregnancy Labeling and Lactation Rule (PLLR). The language in Section 8 of the proposed Licart label is identical to the reference product Flector label language with just the tradename replaced. Note that the Flector label was recently updated with the NSAID Safety Labeling Change supplement, which included PLLR formatting changes. In accordance with PLLR, this new NDA submission further included a comprehensive literature search for nonclinical data from the public domain that addressed the effects of diclofenac on reproduction and development. A total of nine articles were submitted. The Applicant argued that none of the findings from these published articles were appropriate for this label. This reviewer agrees. No changes to exposure margins are recommended. Note that exposure margins

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maternal toxicity were also observed at this dose. Diclofenac epolamine administered orally to both male and female rats prior to mating and throughout the mating period, and during gestation and lactation in females produced embryotoxicity at doses approximately 3 and 7 times, respectively, the topical exposure from the MRHD [see Data]. Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as diclofenac, resulted in increased pre- and post-implantation loss. Clinical Considerations (b) (4) Data Animal Data Pregnant Sprague Dawley rats were administered 1, 3, or 6 mg/kg diclofenac epolamine via oral gavage daily from gestation days 6 to 15. Maternal toxicity, embryotoxicity, and increased incidence of skeletal anomalies were noted with 6 mg/kg/day diclofenac epolamine, which corresponds to 3-times the maximum recommended daily exposure in humans based on a body surface area comparison. Pregnant New Zealand White rabbits were administered 1, 3, or 6 mg/kg diclofenac epolamine via oral gavage daily from gestation days 6 to 18. No maternal toxicity was noted; however, embryotoxicity was evident at 6 mg/kg/day group which corresponds to 7-times the maximum recommended daily exposure in	at this dose. Diclofenac epolamine administered orally to both male and female rats prior to mating and throughout the mating period, and during gestation and lactation in females produced embryotoxicity at doses approximately 3 and 7 times, respectively, the topical exposure from the MRHD [see Data]. Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as diclofenac, resulted in increased pre- and post-implantation loss. Clinical Considerations (b) (4) Data Animal Data Pregnant Sprague Dawley rats were administered 1, 3, or 6 mg/kg diclofenac epolamine via oral gavage daily from Gestation Days (GD) 6 to 15. Maternal toxicity, embryotoxicity, and increased incidence of skeletal anomalies were noted with 6 mg/kg/day diclofenac epolamine, which corresponds to 3-times the maximum recommended daily (b) (4) (b) (4) in humans based on a body surface area comparison. Pregnant New Zealand White rabbits were administered 1, 3, or 6 mg/kg diclofenac epolamine via oral gavage daily from GD 6 to 18. No maternal toxicity was noted; however, embryotoxicity was evident at 6 mg/kg/day group which corresponds to 7-times the maximum recommended daily (b) (4) in humans based on a body surface	in the original Flector label were based on body surface area comparison and dose delivered from the patch in clinical studies (e.g., amount released from patch). Although the MRHD of Licart (b) (4) is one half of the MRHD of Flector patch (e.g., one (b) (4) /day vs two patches/day), the two products were demonstrated to be bioequivalent despite the differing dosing regimens. Clinical sections were not altered and will be edited by Clinical and Maternal Health Teams. As noted above, the exposure margins from the Flector label were originally based on BSA comparison and diclofenac release from patches. Since human PK testing demonstrated the two formulations (Flector vs Licart) are bioequivalent despite their different dosing regimens, exposure margins should remain the same as in the Flector Patch label.

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humans based on a body surface area comparison. Male rats were orally administered diclofenac epolamine (1, 3, 6 mg/kg) for 60 days prior to mating and throughout the mating period, and females were given the same doses 14 days prior to mating and through mating, gestation, and lactation. Embryotoxicity was observed at 6 mg/kg diclofenac epolamine (3-times the maximum recommended daily exposure in humans based on a body surface area comparison), and was manifested as an increase in early resorptions, post-implantation losses, and a decrease in live fetuses. The number of live born and total born were also reduced as was F1 postnatal survival, but the physical and behavioral development of surviving F1 pups in all groups was the same as the deionized water control, nor was reproductive performance adversely affected despite a slight treatment-related reduction in body weight.	area comparison. Male rats were orally administered diclofenac epolamine (1, 3, 6 mg/kg) for 60 days prior to mating and throughout the mating period, and females were given the same doses 14 days prior to mating and through mating, gestation, and lactation. Embryotoxicity was observed at 6 mg/kg diclofenac epolamine (3-times the maximum recommended daily (b) (4) in humans based on a body surface area comparison), and was manifested as an increase in early resorptions, post-implantation losses, and a decrease in live fetuses. The number of live born and total born were also reduced as was F1 postnatal survival, but the physical and behavioral development of surviving F1 pups in all groups was the same as the deionized water control, nor was reproductive performance adversely affected despite a slight treatment-related reduction in body weight.	
8.3 Females and Males of Reproductive Potential **Infertility** Females Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including LICART (b) (4) may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin- mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including LICART (b) (4), in women who have difficulties conceiving or who are undergoing investigation of infertility.	**8.3 Females and Males of Reproductive Potential** **Infertility** Females Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including LICART (b) (4) may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin- mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including LICART (b) (4), in women who have difficulties conceiving or who are undergoing investigation of infertility	No changes recommended. This section is consistent with reference product Flector patch label, which was recently updated to include NSAID safety labeling change language.
12.1 Mechanism of Action	**12.1 Mechanism of Action**	

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Diclofenac has analgesic, anti-inflammatory, and antipyretic properties. The mechanism of action of diclofenac, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2). Diclofenac is a potent inhibitor of prostaglandin synthesis in vitro. Diclofenac concentrations reached during therapy have produced in vivo effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Because diclofenac is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.	Diclofenac has analgesic, anti-inflammatory, and antipyretic properties. The mechanism of action of diclofenac, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2). Diclofenac is a potent inhibitor of prostaglandin synthesis in vitro. Diclofenac concentrations reached during therapy have produced in vivo effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Because diclofenac is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.	No changes recommended. This section is consistent with reference product Flector patch label, which was recently updated to include NSAID safety labeling change language.
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenesis Long-term studies in animals have not been performed to evaluate the carcinogenic potential of either diclofenac epolamine or LICART (b) (4). Mutagenesis Diclofenac epolamine is not mutagenic in Salmonella typhimurium strains, nor does it induce an increase in metabolic aberrations in cultured human lymphocytes, or the frequency of micronucleated cells in the bone marrow micronucleus test performed in rats. Impairment of Fertility Male and female Sprague Dawley rats were administered 1, 3, or 6 mg/kg/day diclofenac epolamine via oral gavage (males treated for 60 days prior to conception and during mating period, females treated for 14 days prior to mating through day 19 of gestation). Diclofenac epolamine treatment with 6 mg/kg/day resulted in increased early resorptions and	**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** Carcinogenesis Long-term studies in animals have not been performed to evaluate the carcinogenic potential of either diclofenac epolamine or LICART (b) (4). Mutagenesis Diclofenac epolamine is not mutagenic in Salmonella typhimurium strains, nor does it induce an increase in metabolic aberrations in cultured human lymphocytes, or the frequency of micronucleated cells in the bone marrow micronucleus test performed in rats. Impairment of Fertility Male and female Sprague Dawley rats were administered 1, 3, or 6 mg/kg/day diclofenac epolamine via oral gavage (males treated for 60 days prior to conception and during mating period, females treated for 14 days prior to mating through day 19 of gestation). Diclofenac epolamine treatment with 6 mg/kg/day resulted in increased early resorptions and	No changes recommended. This section is consistent with reference product Flector patch label. As noted above, the exposure margins from the Flector label were originally based on BSA comparison and diclofenac release from patches. Since human PK testing demonstrated the two formulations (Flector vs Licart) are bioequivalent despite their different

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post-implantation losses; however, no effects on the mating and fertility indices were found. The 6 mg/kg/day dose corresponds to 3 times the maximum recommended daily exposure in humans based on a body surface area comparison.	post-implantation losses; however, no effects on the mating and fertility indices were found. The 6 mg/kg/day dose corresponds to 3 times the maximum recommended daily (b) (4) (b) (4) in humans based on a body surface area comparison.	dosing regimens, exposure margins should remain the same as in the Flector Patch label.

2 Drug Information

2.1 Drug

CAS Registry Number: 119623-66-4

Generic Name: Diclofenac epolamine

Proprietary names: Diclofenac hydroxyethyl pyrrolidine (DHEP)

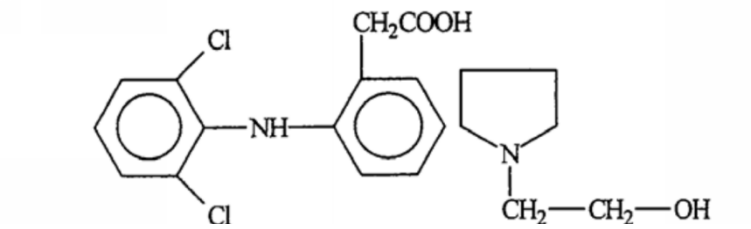
Code Name: 1077

Chemical Name: 2-[(2,6-Dichlorophenyl)amino] phenylacetate 1-(2-hydroxyethyl) pyrrolidine salt

Molecular Formula: $C_{20}H_{24}Cl_2N_2O_3$

Molecular Weight: 411.3 g/mol

Structure:



Pharmacologic Class: NSAIDs

2.2 Relevant INDs, NDAs, BLAs and DMFs

Licart was developed under IND 111538. NDA 206976 was submitted via the 505(b)(2) pathway referencing literature and cross-referencing all of the information in the Flector® Patch NDA 21234, which the Applicant also owns.

2.3 Drug Formulation

Dosage Form Description

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The topical Licart (b) (4) consists of a (b) (4) adhesive (b) (4), containing the active pharmaceutical ingredient, (b) (4) on a non-woven felt backing and covered with a polypropylene film as a release-liner. The release-liner is removed prior to application of the (b) (4) to the skin.

Composition

The size of a single (b) (4) is (b) (4) or approximately 140 cm^2. The adhesive layer is applied to the non-woven polyester felt backing in the (b) (4). The total amount of the (b) (4) per (b) (4) (b) (4)

Schematic

(b) (4)

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Drug product composition

Composition of the Adhesive (b) (4)

Ingredients	Composition (per (b) (4))		Function	Reference to Standard
	Quantity (mg)	Percent (w/w %)		
Active Substance				
Diclofenac Epolamine (DHEP)*	182	1.3	Active Ingredient	Drug Master File
Excipients				
Heparin Sodium				USP/EP current ed.
(b) (4) sorbitol Solution (b) (4)				USP current ed.
(b) (4) butylene Glycol				USP current ed.
Sodium Polyacrylate				(b) (4)
Carboxymethylcellulose Sodium				USP current ed.
Kaolin				USP current ed.
Propylene Glycol				USP current ed.
Gelatin (b) (4)				USP/NF current ed.
Povidone (b) (4) (b) (4)				USP current ed.
Titanium Dioxide				USP current ed.
Tartaric Acid				USP/NF current ed.
Dihydroxyaluminum Aminoacetate				USP current ed.
Polysorbate 80				USP/NF current ed.
Edetate Disodium (EDTA)				USP current ed.
Methylparaben (b) (4)				USP/NF current ed.
Propylparaben (b) (4)				USP/NF current ed.
Fragrance (Dalin PH) †				(b) (4)
Purified Water				USP/NF current ed.
(b) (4)				

Unitary Composition of a (b) (4)

Component	Unitary Amount	Reference to Standard
(b) (4)	(b) (4)	Not Applicable
Non-Woven Polyester Felt Backing		(b) (4)
Polypropylene Film (Release Liner)		USP/ (b) (4)

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2.4 Comments on Novel Excipients

Note that the [(b) (4)] in composition between Licart [(b) (4)] compared to the original Flector Patch (NDA 21234) is the addition of heparin, [(b) (4)] molecule. The Applicant's table below shows a comparison of the compositions of the Licart vs Flector patches.

[(b) (4)] and Flector Patch Formulations

Components	[(b) (4)] % (w/w)	Flector % (w/w)
Drug Substance		
Diclofenac Epolamine	1.3	1.3
Excipients	[(b) (4)]	
Heparin Sodium		
Gelatin		
Povidone [(b) (4)]		
[(b) (4)] Sorbitol solution		
Kaolin		
Titanium Dioxide		
Propylene Glycol		
Methyl Parahydroxybenzoate		
Propyl Parahydroxybenzoate		
Edetate Disodium		
Tartaric Acid		
Carboxymethylcellulose Sodium		
Polyacrylate Sodium		
[(b) (4)]		
[(b) (4)] Butylene Glycol		
Polysorbate 80		
Fragrance (Dalin PH)		
Water, Purified q.s. to		

On 12/05/2016, the Applicant submitted the composition of the Dalin PH fragrance (table below) used in the drug product. The composition of this fragrance was described in Dr. Mellon's review of NDA 21234 dated 01/22/2007. According to Dr. Mellon's review there are no safety concerns with the use of this fragrance in the drug product for the proposed indication. However, [(b) (4)], shown below, of the fragrance were not provided at that time and therefore were not evaluated in Dr. Mellon's review.

[(b) (4)]

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Reference ID: 4369106

Table 1.11.1.1.2.1: CFR References for Dalin PH Fragrance

CAS Registry Number for the Substance (as per Formula Disclosure)	Amount (%)	The name of the substance as recognized by FDA	Regulation numbers in Title 21 of the CFR where the chemical appears
(b) (4)			

(b) (4)

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The to-be-marketed formulation was not used in the 4-week toxicity study. Note that a leachable study was conducted with new and aged placebo Licart patches to determine if any of the components of the patch are released in simulated conditions of use.

2.5 Comments on Impurities/Degradants of Concern

The impurity/degradant specifications for (b) (4) correspond to those approved for Flector Patch (NDA 21234).

Drug substance (DS)

(b) (4)

Drug product (DP)

(b) (4)

Impurities/Degradation Products Specifications

Impurities/Degradation Products	Release Acceptance Criteria	Shelf Life Acceptance Criteria
(b) (4)		

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Residual Solvents

(b) (4)

[redacted]

2.6 Proposed Clinical Population and Dosing Regimen

The proposed indication (b) (4) as that established for Flector® Patch (NDA 21234), the Applicant's own drug. The proposed indication is for the relief of pain (b) (4). The maximum recommended daily dose of Licart (Diclofenac Epolamine 1.3%/ (b) (4) is one patch per day (QD); whereas, the currently approved Flector patch is labeled for BID dosing.

2.7 Regulatory Background

- (b) (4) Diclofenac Epolamine 1.3%/ (b) (4), was the subject of a pre-IND meeting under IND 111538 held on May 10, 2011 (meeting minutes dated June 6, 2011) and a pre-NDA meeting held on November 15, 2012 (meeting minutes dated December 13, 2012).
- At the PreIND meeting held 5/10/2011, we informed the Applicant that we would waive the requirement the dermal toxicology requirement for this product given the (b) (4) of the topical patch formulations, the extensive history of clinical use with the approved Flector product, and predicted lack of absorption of heparin from the patch. Nevertheless, the Applicant had previously conducted a 4-week rabbit dermal toxicology study and submitted it to this NDA. It did not employ the to-be-marketed patch, but rather a product containing diclofenac epolamine and heparin that was plastered on to the animal skin. From the nonclinical perspective, there do not appear to be any safety concerns with the to-be-marketed drug product formulation.
- On 3/4/2015, IBSA submitted NDA 206976 for marketing approval of (b) (4) ™ via the 505(b)(2) pathway referencing literature and relying on information from the Flector® Patch NDA 21234 (approved 1/31/2007), which the Applicant owns.
- On 4/29/2015, IBSA received a refuse-to-file (RTF) letter from FDA identifying a number of deficiencies. As part of the RTF letter for the original (b) (4) NDA submission, the Applicant was informed that a leachables study would be required with the resubmission.
- On 08/26/2015, IBSA had a Type A post-action meeting with the FDA (meeting minutes dated 9/16/2015). In this meeting the requirements for leachable study was discussed such as complete assessment over the course of stability and using appropriate testing condition.
- On October 7, 2015, IBSA submitted a leachable protocol for review. Below are the FDA comments on the protocol:

  Your proposed protocol for the leachable assessment appears to be adequately designed with acceptable study conditions and time-points.

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However, your justification to only evaluate those extractables that were associated with high and medium risk is unacceptable. As part of your safety assessment of the patch, you must provide adequate justification for the selection of the potential leachables that you will be monitoring over stability. This justification should be based on results of the extraction studies and good scientific principles that take into account the whole patch. As communicated to your earlier, you have not conducted an extractables assessment of the drug adhesive matrix and you must conduct this extraction study to ensure your leachable assessment will evaluate all relevant potential leachables.

For your overall risk assessment, submit a toxicological risk assessment for any leachable that exceeds 5 mcg/day. From a genetic toxicology perspective, any leachable that contains a structural alert for mutagenicity must not exceed 120 mcg/day for an acute indication, or must be adequately qualified for safety. The risk assessment should be based on the maximum level of each leachable detected in long-term stability samples.

- NDA 207962 was resubmitted on May 27, 2016 (SDN 10) for marketing approval of (b) (4) (Licart®) for the treatment of pain (b) (4)
- On July 29, 2016, FDA issued a Filing Communication 74-day Letter with the following nonclinical comments:

1. Based upon a preliminary review of your leachable study evaluation, we have the following comments:

    a. Your toxicological risk assessment employs a safety threshold of 150 mcg/day for compounds exceeding daily exposures of 5 mcg/day with some additional safety factors included for some of these compounds. Note that a safety justification based on categories of compounds described via the Cramer Method alone is not adequate as it is not clear how these designations were made for the compounds in question and if the bases of those assessments are also applicable to the dermal route of administration. We also note that the PQRI documents cited in your toxicological risk assessment acknowledge that the safety thresholds based on the Cramer approach are preliminary and need to be further reviewed and validated prior to final recommendation. As such, provide a revised toxicological risk assessment that adequately justifies the safety of leachable compounds exceeding daily exposures of 5 mcg/day. You may consider employing a permitted daily exposure (PDE) approach as outlined in the ICH guidance for industry: *Q3D Elemental Impurities*, which is available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm371025.pdf. Submit copies of all referenced studies.

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b. It appears that you were unable to specifically identify several compounds, including compounds indicated as [redacted] (b) (4), [redacted] (b) (4), that resulted in daily exposures exceeding 5 mcg/day. As we noted in the Refuse To File letter sent to you on 4/29/2015, your NDA submission must include a full leachable profile for your product, including identification of and justification for the safety of those compounds that may transfer from the patch to the skin. We acknowledge that your toxicological risk assessment includes a safety rationale for these unidentified compounds, but they do not appear sufficient based on our preliminary review. To aid in our review of such compounds, provide as much additional information as possible so that we can determine if there is an adequate weight of evidence to justify the safety of these compounds. [redacted] (b) (4)

2. We note that all NDA applications filed after June 30, 2015 must submit labeling consistent with the Final Pregnancy Labeling and Lactation Rule (PLLR). Per PLLR, you must conduct a thorough review of the existing clinical and nonclinical literature for each drug substance in your drug product and propose a risk summary statement and text for Section 8 of the labeling that includes relevant information from the literature if appropriate. Information on the final rule and links to the FDA draft guidance document are available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm.

- On September 6, 2016, a review and summary of the available clinical and nonclinical literature to support the PLLR format was submitted (SDN 18)
- On November 21, 2016 (SDN 29) and December 14, 2016 (SDN 32) the revised toxicological risk assessment including safety rationale for unidentified compounds was submitted.
- SDN 18 (9/6/2016) Request for Pregnancy and Lactation Labeling Rule (PLLR) Information.

3 Studies Submitted

3.1 Studies Reviewed

1. 4-week repeat-dose [redacted] (b) (4) (just the [redacted] (b) (4)) dermal toxicity in rabbits
2. [redacted] (b) (4) dermal hypersensitivity study in guinea pig
3. UV-Visible absorption spectrum of Heparin Sodium Salt
4. [redacted] (b) (4) packaging extraction study
5. Leachable study
6. Toxicology risk assessment of the leachables

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3.2 Studies Not Reviewed

N/A

3.3 Previous Reviews Referenced

NDA 21234 nonclinical reviews for Flector patch by Drs. Amouzadeh (dated 9/26/2001) and Mellon (dated 1/22/2007).

4 Pharmacology

No new nonclinical pharmacology studies were conducted or required as the pharmacology of diclofenac is well established.

5 Pharmacokinetics/ADME/Toxicokinetics

Pharmacokinetic (PK) studies have not been performed with (b) (4) in animals. However, release of heparin and diclofenac from the patch, has been investigated both in vitro and in vivo in humans (see the clinical pharmacology review for evidence of bioequivalence).

In vitro: Using a Franz Cell fitted with a synthetic membrane; heparin could not be detected in the receiving chamber of the system following (b) (4) application and buffer sampling 24 hours later. In contrast, the concentrations of diclofenac in the receiving chamber of the Franz Cell System over 24 hours following (b) (4) application were ~2.4 fold greater than application with Flector patch.

6 General Toxicology

6.1 Single-dose toxicity

No single-dose toxicity studies were submitted with this NDA.

6.2 Repeat-dose toxicity

Study title: DHEP/HEPARIN TISSUGEL: 4-Week Repeated Dose Dermal Toxicity Study in the Rabbit (Semi-Occlusive Application)	
Study no.:	851832
Conducting laboratory and location:	(b) (4)
Date of study initiation:	January 6, 2004
GLP compliance:	Yes
QA statement:	Yes
Drug (test article), lot #:	DHEP/HEPARIN TISSUGEL *Diclofenac epolamine and heparin containing medicated plaster (180 mg DHEP + 5600 I.U. Sodium Heparin/plaster)* Batch Number 0210122

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Key findings
Once daily, 12-hour applications of diclofenac epolamine and heparin containing medicated plaster (not the to-be-marketed product) or the placebo patch under occlusion for 28 consecutive days to New Zealand white rabbits was well tolerated, and only produced mild, transient erythema in some of the study animals.

Methods	
Doses:	5 cm x 7 cm patches One adhesive plaster/flank on the skin
Frequency of dosing:	12 hours once daily, 28 days
Route of administration:	Dermal (skin of clipped area on the flank)
Formulation/Vehicle:	Adhesive plaster (note: the to-be-marketed product was not used) Diclofenac epolamine and heparin containing medicated plaster (180 mg DHEP + 5600 I.U. Sodium Heparin/plaster)
Species/Strain:	New Zealand White rabbits
Number/Sex/Group:	5/sex/group (treatment) 5/sex/group (placebo)
Age:	11-14 weeks (males) 10-12 weeks (females)
Weight:	Not provided
Satellite groups (TK):	N/A
Unique study design:	N/A
Deviation from study protocol:	N/A

The animals were examined daily for clinical signs and mortality. Local dermal signs were recorded daily from the start of treatment to the end of the study. Each day when the patch was removed, the underlying skin was examined for erythema (0 = no erythema to 4 = severe erythema (beet redness) to slight eschar formation), and edema (0 = no edema to 4 = severe edema (raised more than 1 mm and extending beyond the area of exposure). Body weights were recorded at start of acclimatization, on the day of application, then weekly and on Test Day 29. The treated and untreated skin sites were collected for possible histopathological examinations. Due to the very slight transient local findings noted, histopathology was not performed. Though this study is not an adequate justification to exclude histopathology, it is not considered a pivotal safety study to support approval of the product and therefore, no additional studies are warranted.

Observations and Results

Mortality
No deaths were observed during the treatment period.

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Clinical signs:
No adverse clinical signs were observed.

Clinical observations on application sites:
Edema was not observed in any of the animals in either group over the entire 29-day observation period, while erythema scored as 1 (very slight) was recorded sporadically for four of the five females exposed to the plaster, but no males at any time point. Similarly, for the placebo patch control group, Grade 1 erythema was observed in two males and two females.

Skin reactions after 12-hour application

GROUP 1: DHEP/HEPARIN TISSUGEL

	MALES										FEMALES									
Animal No.	1		2		3		4		5		6		7		8		9		10	
Day	E	Oe	E	Oe	E	Oe	E	Oe	E	Oe	E	Oe	E	Oe	E	Oe	E	Oe	E	Oe
1	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

GROUP 1: DHEP/HEPARIN TISSUGEL (continued)

	MALES										FEMALES									
Animal No.	1		2		3		4		5		6		7		8		9		10	
Day	E	Oe	E	Oe	E	Oe	E	Oe	E	Oe	E	Oe	E	Oe	E	Oe	E	Oe	E	Oe
16	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**1**	0
17	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**1**	0
18	0	0	0	0	0	0	0	0	0	0	0	0	**1**	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**1**	0	**1**	0	**1**	0
20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**1**	0	**1**	0	**1**	0
21	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**1**	0	**1**	0	**1**	0
22	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**1**	0	**1**	0	**1**	0
23	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**1**	0	**1**	0	0	0
24	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**1**	0	**1**	0	0	0
25	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**1**	0	**1**	0	0	0
26	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**1**	0	0	0	0	0
27	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
28	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
29	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

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PLACEBO TISSUGEL

	MALES										FEMALES									
Animal No.	11		12		13		14		15		16		17		18		19		20	
Day	E	Oe	E	Oe	E	Oe	E	Oe	E	Oe	E	Oe	E	Oe	E	Oe	E	Oe	E	Oe
1	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0	0	**1**	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0	**1**	0	0	0	0	0	**1**	0
11	0	0	0	0	0	0	0	0	0	0	0	0	**1**	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0	0	**1**	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	**0**	0	0	0	0	**1**	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

PLACEBO TISSUGEL (continued)

	MALES										FEMALES									
Animal No.	11		12		13		14		15		16		17		18		19		20	
Day	E	Oe	E	Oe	E	Oe	E	Oe	E	Oe	E	Oe	E	Oe	E	Oe	E	Oe	E	Oe
16	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	**1**	0	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	**1**	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	**1**	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	**1**	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	**1**	0	0	0	0	0	0	0	**1**	0	0	0	0	0	0	0
24	0	0	0	0	**1**	0	0	0	0	0	0	0	**1**	0	0	0	0	0	0	0
25	0	0	0	0	**1**	0	0	0	0	0	0	0	**1**	0	0	0	0	0	0	0
26	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
27	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
28	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
29	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

A = first application; s = scaling

Grading scale according to Draize:

ERYTHEMA (E)
0 = no erythema
1 = very slight erythema (barely perceptible)
2 = well-defined erythema
3 = moderate to severe erythema
4 = severe erythema (beet redness) to slight eschar formation (injuries in depth)

OEDEMA (Oe)
0 = no oedema
1 = very slight oedema (barely perceptible)
2 = well-defined oedema (area well defined by definite raising)
3 = moderate oedema (raised approximately 1 mm)
4 = severe oedema (raised more than 1 mm and extending beyond the area of exposure)

Body Weight: No treatment related findings of body weight were observed.

Food consumption: Not evaluated

Ophthalmology: Not evaluated

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Hematology and Coagulation: Not evaluated

Urinalysis: Not evaluated

Clinical chemistry: Not evaluated

Gross Pathology: Not evaluated

Organ weight changes: Not evaluated

Histopathology findings: Not evaluated

Toxicokinetic data: Not evaluated

7 Genetic Toxicology

No new genotoxicity studies were submitted with this NDA. The Licart label will include genotoxicity information for diclofenac epolamine from the Flector patch label as the Applicant also owns this NDA 21234.

8 Carcinogenicity

No new carcinogenicity studies were submitted with this NDA. No studies are required for Licart (b) (4) since the indication is for acute use.

9 Reproductive and Developmental Toxicology

No new reproductive and developmental toxicology studies were submitted with the NDA. These studies are not needed since they have been included in previously approved drug product, the Applicant's own drug, Flector® Patch (NDA 21234).

As part of the requirement under the Pregnancy Lactation and Labeling Rule (PLLR), the Applicant conducted a review of the literature to determine if there were new reproductive and developmental toxicity data for diclofenac (SD 18, September 6, 2016). Nine studies were identified via an adequate search of relevant databases and the articles were submitted to the NDA. The Applicant stated that the primary criticism of these studies is that all were apparently conducted in the absence of blinding, a critical prerequisite for assuring that the results obtained were unaffected by reader bias, and possibly explaining the remarkably low error terms for some of the various assessments reported. Therefore, the Applicant did not believe it was appropriate to include them in the Licart (b) (4).

Out of the nine articles submitted, five reported potentially significant developmental findings and these were evaluated further by this reviewer (see below).

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Four out of the five preclinical studies were authored and conducted by the same investigative groups at one or more universities in Turkey. As such, the protocols used were very similar. After a closer examination of the study findings, none of the data were considered relevant by this reviewer (b) (4) to the Licart (b) (4).

1. Article title: Effects of prenatally exposed diclofenac sodium on rat heart tissue: a stereological and histological study (Gervrek et al., 2015)

   In this study pregnant rats were injected with diclofenac (1 mL, 1 mg/kg, IM) from the 5th to the 20th day of pregnancy. At the 20th postnatal week, all the offspring were euthanized and tissue samples were obtained by perfusion fixation. After routine histological procedures, the paraffin sections were stained with H&E and examined stereologically and histologically.

   Key findings: In this study the volume of the ventricle walls of the test group was found to be significantly less than that of the controls. However, no significant histological changes were found between control and test group.

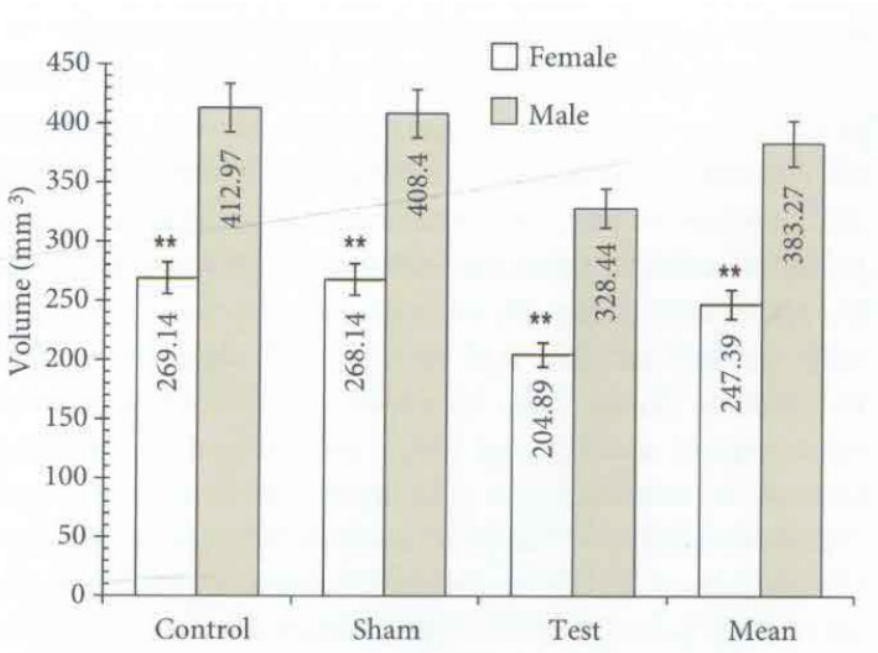

Figure 3. Average volume values for both sexes by group and total mean (**: P < 0.01).

Reviewer's note: The authors stated that it was not fully understood how the volume of the heart ventricular wall decreased with administration of diclofenac and suggested further investigation was warranted to determine possible diclofenac effects on reducing number of myocytes, decreasing of the size of the cells, or connective tissue between cells. No functional assessments were conducted to confirm if the changes reported were biologically or toxicologically relevant. In

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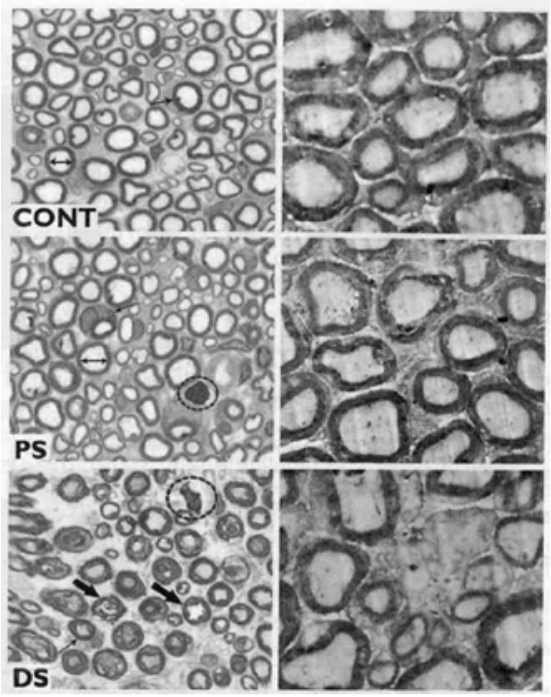
Reference ID: 4369106

addition, since this is the only nonclinical study that has shown effects of diclofenac on volume of the cardiac ventricle wall, it is not clear if this change is even adverse. Therefore, this reviewer does not consider it appropriate to describe these data in the Licart label at this time due to lack of adequate supporting data.
Of note, another NSAID, ibuprofen, has been shown to result in an increase in the incidence of membranous ventricular septal defects. This is described in the Caldolor label. However, it is unclear if this is a class effect and whether similar changes have been examined with treatment with diclofenac.

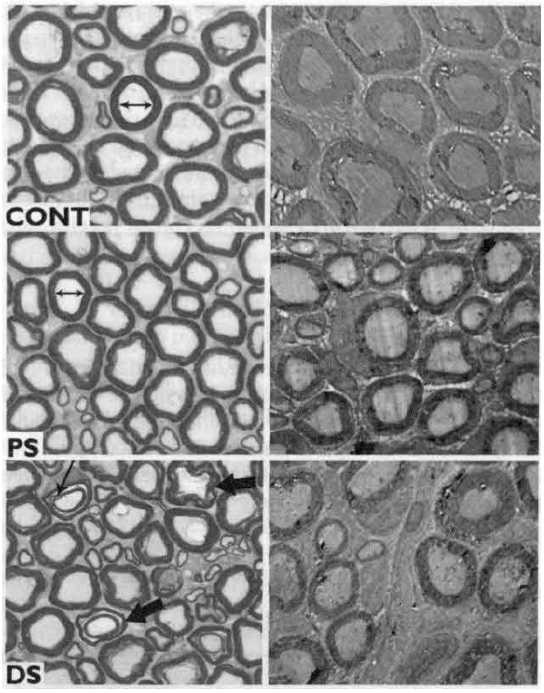
2. Article title: Evaluation of neuroprotection by melatonin against adverse effects of prenatal exposure to a nonsteroidal anti-inflammatory drug during peripheral nerve development (Keskin et al., 2015)

   In this study pregnant rats received diclofenac Na daily at 1 mg/kg (HED of 10 mg/60 kg person based on body surface area) intraperitoneally over 10 days of pregnancy (from the 10th to the 20th day of pregnancy). Male newborn rats were sacrificed at 4 and 20 weeks of age. Their right sciatic nerves were harvested, and nerve fibers were evaluated using stereological techniques.

   Key findings: In this study four week old male rats were reported to have significantly fewer sciatic nerve axons, a smaller myelinated axonal area, and a thinner myelin sheath in comparison to the saline controls. At 20 weeks of age, myelinated axon number in the test group was not only significantly lower but also the cross-sectional area of these axons was smaller than control groups.



4-week male



20-week male

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A lower number of myelinated axons in the diclofenac group compared to controls were evident via quantitative light microscopy observation. Signs of morphological alteration and myelin deterioration were also detected. In 20 week-old rats, diclofenac administration caused axonal damage in most of the myelinated fibers with axonal shrinkage and swollen axons as common ultrastructural features. Vacuolization and lamellar separation of the myelin (myelin breakdown) were also commonly seen. These findings are consistent with this group's earlier reports on peripheral axon morphology changes in juvenile animals following administration of diclofenac during pregnancy (Canon et al. 2008; Ayranci et al. 2013). Interestingly, they also reported some changes following administration of saline. As the significance of these results is not clear, inclusion in labeling does not seem warranted at this time. Nonetheless, the Division will continue to monitor the literature for any additional data.

Reviewer's note: The same investigators published two additional articles with in vitro data suggesting that diclofenac may adversely impact neuronal development in vitro. In a study by Kudo et al. (2003), the authors showed that treatment with diclofenac (10 mcM) for 2 days induced the death of mouse neural stem cell (NSC) in a concentration dependent manner. They also showed that diclofenac inhibited the proliferation of NSCs and their differentiation into neurons. Treatment with diclofenac resulted in caspase-3 activation 6-hours post-treatment and nuclear condensation (a morphological change due to apoptosis of NSCs) 24-hours post-treatment, indicating that diclofenac may cause apoptosis of neuronal cells via activation of the caspase cascade. Similar studies with naproxen, indomethacin, aspirin, or ibuprofen did not result in cell death. These results suggest that COX-2 selective compounds like diclofenac play a more critical more in the development of the central nervous system compared to COX-1 selective compounds. Neural tube formation in rodents occurs approximately mid-gestation in rodents, on Gestational Day (GD) 10.5–11 with birth typically occurring on GD 20–21. In humans, this event occurs earlier during prenatal development, between GD 24 and 28 (3–4 weeks) (Bridgette et al, 2013). Note that NSAIDs, including diclofenac, are labeled with a warning that the drugs should not be used during the third trimester of pregnancy due to the potential impact on the ductus arteriosis. However, these data suggest that diclofenac may potentially affect neuronal development earlier during prenatal development (second trimester) and the results of these in vitro studies suggest the potential for adverse effects. However, it is not clear if the in vitro effects described above translate to functional neural deficits following in vivo use. There are no published studies and no Segment 3 pre- and post-natal development studies have been conducted with diclofenac to investigate behavioral or learning and memory changes on neonates. Further, the findings would be relevant to all diclofenac drug products, most of which result in significantly higher levels of diclofenac than this patch product. To date, we are not aware of any evidence of peripheral nerve damage with diclofenac products in humans. Without

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additional evidence of potential functional consequences, the data described above are not considered by this reviewer to be appropriate for the Licart label at this time.

3. Article title: Prenatal exposure to diclofenac sodium changes the morphology of the male rat cervical spinal cord: A stereological and histopathological study (Ozyurt et al., 2011).

   In this study pregnant rats received diclofenac Na daily at 1 mg/kg intraperitoneally over 15 days of pregnancy (from the 5th to the 20th day of pregnancy). Male newborn rats were sacrificed at 4 and 20 weeks of age.

   Key findings: Diclofenac-induced alterations in the rat cervical C1–C4 segments of the 4 week old offspring using unbiased stereological techniques included a significant decrease in the numbers of both motor and sensory neurons. Histopathological investigation showed chromatin condensation and cytoplasmic shrinkage, suggesting necrosis. Therefore, these data suggest that prenatal diclofenac exposure may lead to toxic changes in the neurons of the cervical spinal cord, as well as a reduction of the total volume and volume fraction of the grey/white matter of the cervical spinal cord segments. A severe decrease in the volume of white matter in both 4-week and 20-week old diclofenac group animals may be attributable to demyelization or possible glial cell loss in cervical spinal cord segments. This volumetric decrease was observed as fraction changes.

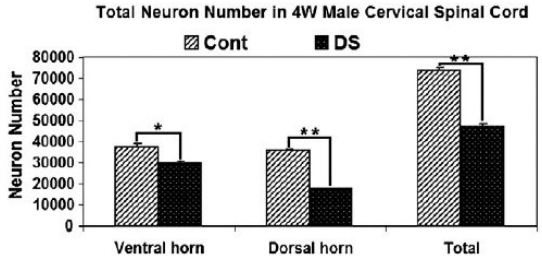

Fig. 3. Total neuron number in 4-week-old male rats' cervical spinal cord is seen.

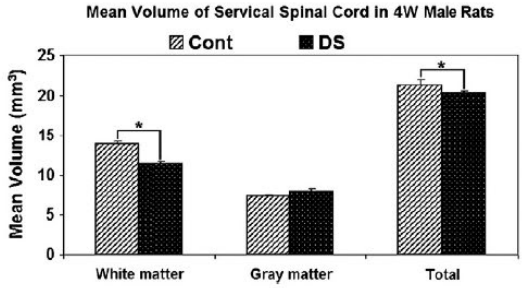

Fig. 5. Mean volume of cervical spinal cord in 4-week-old male rats is seen.

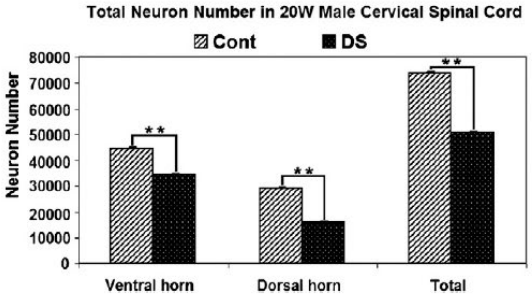

Fig. 4. Total neuron number in 20-week-old male rats' cervical spinal cord is seen.

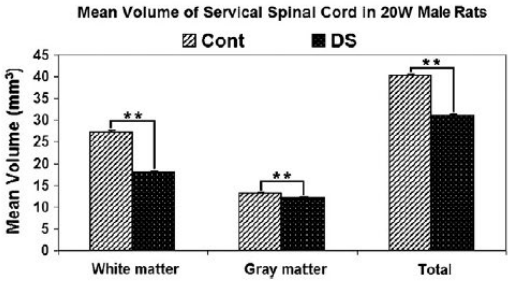

Fig. 6. Mean volume of cervical spinal cord in 20-week-old male rats is seen.

Reviewer's note: As noted above, the morphological changes reported by these authors suggest differences following diclofenac treatment; however, there were no

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functional assessments made and diclofenac has been approved for many years without any evidence of neurotoxicity in humans. These findings will continue to be monitored, but at this time, they need not be included in product labeling as the clinical signifciance is not clear.

4. Article title: Effects of melatonin on diclofenac sodium treated rat kidney: a stereological and histopathological study (Khoshvaghti et al., 2015)

   In this study pregnant rats received diclofenac daily at 3.6 mg/kg intraperitoneally over 10 days of pregnancy (from the 5th to the 15th day of pregnancy). In this article it is not clear at what ages the newborns were sacrificed.

Table 1. Morphometrical evaluations in the control and experimental groups with their ±SEM.

Estimation	Cont	PS	DS	DS + MEL
Total volume of proximal tubules (mm^3)	1203 ± 217*	909 ± 139	1539 ± 528	2158 ± 241¥
Total volume of distal tubules (mm^3)	1792 ± 235*	1543 ± 281	1915 ± 586	2830 ± 577¥
Mean volume of glomerulus (μm^3)	162 ± 14*	158 ± 23	117 ± 19	156 ± 16¥
Mean numerical density of glomeruli (gL/mm^3)	178 ± 30*	169 ± 18	156 ± 37	161 ± 22
Total number of the glomeruli (mm^3)	416,229 ± 1200*	381,992 ± 5400	279,268 ± 900	398,098 ± 1300¥

Note: *, ¥ show significant differences between the CONT/PS and DS, also between the DS and DS + MEL groups at $p < 0.05$ level.

Key findings: The results indicated that diclofenac application during pregnancy resulted in decreases in mean volume, numerical density, and total number of the glomeruli. Light microscopic investigation showed congestion in blood vessels and shrinkage of the Bowman's space in the diclofenac group. Moreover, there was degeneration in nephrons including glomerulosclerosis and tubular defects, and an increase in the connective tissue in the kidneys of the diclofenac-treated group.

Reviewer's note: Although the results of the study demonstrate renal adverse effects, they are limited in terms of design to fully characterize the finding. The study only tested one dose and it is not clear if the dose of 3.6 mg/kg caused any maternal toxicity. Moreover, the number of animals and the age of neonate that were sacrificed are not reported. The kidney effects are not inconsistent with kidney effects with NSAIDs label. The effects of NSAIDs on the kidney of animals have been studied extensively. However, there is a little knowledge about the effects of the NSAIDs including diclofenac on renal tissue of the developing kidney. Komhoff et al. showed similar results in the rat, changes on kidney by COX-2 inhibitors. In this study, administration of a COX-2–selective inhibitor (SC58236), started during pregnancy until weaning, significantly impaired development of the renal cortex and reduced glomerular diameter in both mice and rats (Komhoff et al., 2000). Gan et al., showed that diclofenac exerts its action via inhibition of prostaglandin synthesis by inhibiting cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) with relative equipotency (Gan TJ, 2010). Therefore, diclofenac as a COX-2 inhibitor may cause impaired renal development.

Sabry et al. examined histological and ultrastructural studies on the effect of diclofenac on the renal cortex of fetuses of albino mice. Twenty pregnant female mice were allocated into 2 groups. The first group served as control and each

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animal was injected intraperitoneally (IP) with the solvent of the drug, daily for 8 days during pregnancy from Day 7 till Day 14 of gestation. The second group is the treated group; each animal was injected (IP) daily with 1.5 mg/kg body weight of diclofenac for 8 days. The light microscopic investigation and morphometric data showed that diclofenac has negative effects on the kidney and could disrupt the normal renal morphology and structure (Sabry et al., 2014).

Siu et al. (2000) reported that diclofenac crosses the human placenta easily (probably due to low molecular weight of 318.15 Dalton) during the first trimester. Thirty patients undergoing surgical termination of pregnancy between 8 and 12 weeks gestation were given two doses of diclofenac (50 mg) before the procedure. Corresponding samples of maternal serum, amniotic fluid, coelomic fluid and fetal tissue were analyzed. Diclofenac was detectable in all fetal tissue samples, with a concentration similar to that found in maternal venous samples. Maternal serum diclofenac concentrations ranged from 24.6-842.4 ng/mL and the fetal tissue drug concentration ranged from 17.4-665.7 ng/g. It was observed in present study that toxic effect was in the kidney because of diffusion and excretion of diclofenac through the renal tissue (Siu et al., 2000).

Note that diclofenac concentration after applying a topical Licart patch for 24 hours in human samples is about 1 ng/mL which is significantly lower than when diclofenac is used orally or intravenously.

Following review of the literature, this reviewer believes that diclofenac may cause adverse effects on renal tissue of the kidney in early prenatal development. However, the publication provided by the Applicant (Khoshvaghti et al., 2015) describes a study that was not designed to fully characterize the effects of diclofenac on kidney development and the kidney is a known target organ of toxicity for NSAIDs. In addition, very low diclofenac exposure (approximately 1 ng/mL) after Licart use reduces this concern. No additional labeling recommendations appear necessary at this time.

5. Article title: Role of apoptosis in mediating diclofenac-induced teratogenesis: An in vitro approach (Singh et al., 2015)

Singh et al. examined the effect of diclofenac on the developing rat embryo using a whole rat embryo culture model. Embryos were exposed to diclofenac concentrations of 0, 3.75, 7.5, and 15 mcg/mL during the critical period of organogenesis.

Key findings: Growth and developmental parameters such as weight of embryos, crown-rump length, and number of somites were found to be lower in the embryos exposed to high concentrations of diclofenac (7.5 and 15 mcg/mL), which is about 7,500 to 15,000-times the peak plasma concentration of diclofenac following 24 hour dermal application of Licart patches in human subjects (C_{max} 1.01 ± 0.64 ng/mL; data from Study CRO-PK-12-272). Concentrations of 3.75 mcg/mL did not produce evidence of teratogenicity. Also, flow cytometric analysis and DNA

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quantitation of cultured rat embryos were performed to verify the involvement of apoptosis in mediating diclofenac-induced teratogenic effects.

Reviewer's note: Although the teratogenic effects in the in vitro study can be a surrogate to flag a hazard identification, the exposure of diclofenac after 24 hours dermal patch of Licart is very low with a safety margin of 7500-fold based on the in vitro study. Therefore, the risk to humans based on this study is minimal and not considered appropriate by this reviewer for the Licart label.

10 Special Toxicology Studies

10.1 (b) (4) dermal hypersensitivity study in guinea pig

Study title: DHEP/HEPARIN TISSUGEL: Contact Hypersensitivity in Albino Guinea Pigs, Maximization-test	
Study no.:	850887
Conducting laboratory and location:	(b) (4)
Date of study initiation:	September 29, 2003
GLP compliance:	Yes
QA statement:	Yes
Drug (test article), lot #:	DHEP/HEPARIN TISSUGEL *Diclofenac epolamine and heparin containing medicated plaster (180 mg DHEP + 5600 I.U. Sodium Heparin/plaster)* Batch Number 0210122

Method

The study was performed in 25 Albino male guinea pigs (4-6 week old and 371-439 g body weight). Ten males were injected intradermally with a physiological saline (PS) extract of the (b) (4), another ten males with a PSS extract of a (b) (4) placebo patch (without diclofenac but otherwise identical to (b) (4), and another five with PS.

The intradermal test item extract applied at a 50% (w/w) formulation of the test item extract in a 1:1 (v/v) mixture of Freund's Complete Adjuvant and PS and diluted in an emulsion with Freund's Complete Adjuvant (FCA)/physiological saline. The epidermal induction of sensitization was conducted under occlusion with the undiluted test item extract one week after the intradermal induction and following pretreatment of the test areas with 10% sodium lauryl sulfate (SLS) approximately 27 hours prior to extract application. The placebo animals were treated in the same conditions but with the placebo extract. The animals of the control group were intradermally induced with

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the blank (PS) and FCA/physiological saline, and epidermally induced with the blank (PS) under occlusion following pretreatment with 10 % SLS.

Two weeks after epidermal induction the control, test, and placebo animals were challenged by epidermal application with the test item extract at 100% and 75% in PS, the placebo extract at 75% in physiological saline and the blank (PS) under occlusive dressing.

Cutaneous reactions were evaluated at 24 and 48 hours after removal of the dressing.

Results

Skin Reactions after the Challenge Procedure

	after 24 hours	after 48 hours
	positive / total % positive of total	positive / total % positive of total
CONTROL GROUP		
Test item extract at 100 % (left cranial flank)	0 / 5 0	0 / 5 0
Test item extract at 75 % in physiological saline (left caudal flank)	0 / 5 0	0 / 5 0
Placebo extract at 75 % in physiological saline (right cranial flank)	0 / 5 0	0 / 5 0
Blank (physiological saline) (right caudal flank)	0 / 5 0	0 / 5 0
TEST GROUP		
Test item extract at 100 % (left cranial flank)	0 / 10 0	0 / 10 0
Test item extract at 75 % in physiological saline (left caudal flank)	0 / 10 0	0 / 10 0
Placebo extract at 75 % in physiological saline (right cranial flank)	0 / 10 0	0 / 10 0
Blank (physiological saline) (right caudal flank)	0 / 10 0	0 / 10 0
PLACEBO GROUP		
Test item extract at 100 % (left cranial flank)	0 / 10 0	0 / 10 0
Test item extract at 75 % in physiological saline (left caudal flank)	0 / 10 0	0 / 10 0
Placebo extract at 75 % in physiological saline (right cranial flank)	0 / 10 0	0 / 10 0
Blank (physiological saline) (right caudal flank)	0 / 10 0	0 / 10 0

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No toxic symptoms were noted in the guinea pigs of the control or test group.

None of the control-, test- and placebo animals showed skin reactions after the challenge with either the test item extract at 100 % or 75 % in PS, the placebo extract at 75% in PS or the blank (PS) only.

10.2 UV-Visible absorption spectrum of heparin sodium salt

Study 00WS17 (Module 4.2.3.7.7 RAS-18.125.168b), has shown that the heparin component of the (b) (4) is not absorbed in the UV/visible spectrum (range of 290 to 600 nm) confirming that this compound is not expected to cause photosensitivity.

10.3 Extractable study (RAS-19.001020d)

On 11/21/2016, the Applicant submitted a response to the nonclinical Information Request (IR) dated 07/29/2016 that included an extractable/leachable evaluation and a revised toxicological risk assessment.

Extraction studies were conducted by an (b) (4) and tested the following three (b) (4) packaging components (b) (4) (b) (4) that could potentially come into contact with the product:

- Embossed polyester felt backing non-woven material (b) (4)
- Polypropylene release liner (b) (4)
- Envelope (b) (4)

Two different extraction techniques were used during the study, (b) (4) in three different screening solvents, (b) (4)

Table 3.2.P.2.6.1: Extraction Parameters

Drug Product Packaging Part	Amount of Tested Part	Extraction Method	Extraction Solvent	Extraction Duration	Extraction Temperature
Release Liner	(b) (4)				
Felt Backing					
Envelope					

(b) (4)

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/s/

ARMAGHAN EMAMI
02/22/2017

JAY H CHANG
02/22/2017

RICHARD D MELLON
02/22/2017
I concur.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS

PHARMACOLOGY/TOXICOLOGY MEMO TO FILE

NDA Number:	206976
Supporting Document Number:	9
Submit Date / Received Date:	10-7-15 / 10-7-15
Type of Submission:	Investigator IND
Sponsor:	IBSA Institut Biochimique SA
Reviewer:	Newton H. Woo, PhD
Supervisor:	R. Daniel Mellon, PhD
Division:	Division of Anesthesia, Analgesia, and Addiction Products
HFD #:	170
Date of Memo:	November 9, 2015
Drug:	(b) (4)
Indication:	Topical treatment of acute pain due to minor strains, sprains, and contusions.
RE:	**Review request of a leachable study protocol**

Recommendation: The Applicant's proposed leachables assessment appears adequately designed with the exception of their strategy for selecting potential leachables to be monitored over stability. External comments to the Applicant can be found at the conclusion of this review.

Background/Prior Regulatory History

IBSA Institut has developed (b) (4) that contains diclofenac epolamine and heparin for the treatment of pain (b) (4). The sole difference between (b) (4) compared to the original Flector Patch (originally approved in 2007) is the addition of the (b) (4) heparin, which is believed to enhance movement of the active ingredient of diclofenac from the poultice to the intended skin.

At the preIND and preNDA meeting, the Division communicated to the Applicant that the safety of the patch must be adequately justified and recommended that the Application submit leachables data for the patch over stability along with a toxicological risk assessment for any compounds that exceeded 5 mcg/day.

However when the original NDA was submitted, the Applicant did not provide any leachables data but instead submitted an extraction data along with an argument that attempted to justify the safety of the patch. The submitted justification was not deemed adequate and a refuse-to-file letter was issued with the clinical and nonclinical deficiencies outlined. An excerpt of the letter stating the nonclinical deficiency is shown below:

> 5. You have not submitted leachable data for your final drug product. We communicated to you at the pre-IND and at the pre-NDA meetings that the NDA submission must include a full leachable profile for your product, including identification of and justification for the safety of those compounds that may transfer from the patch to the skin. We acknowledge that you are intending to use the extraction study to justify the lack of leachables assessment, however, you have not provided adequate support for your assertion that a safety evaluation based exclusively on results from an extraction study can adequately predict what any leachables that could be released from the product under conditions of use. Therefore, we cannot conduct an adequate toxicological risk assessment to support your drug product formulation.
>
> Conduct a leachable study for your product that evaluates leachable levels at appropriate timepoints within the shelf-life of your product to allow for trend analysis and quantitate all leachables at the end of shelf-life. The analysis for potential leachables should be guided by the results of your extraction studies. Provide justification for your testing conditions. Provide a safety assessment for all leachables that exceeds a total daily intake threshold of 5 mcg/day.

The Applicant subsequently requested a follow-up Type A meeting and the following nonclinical information was conveyed to the Applicant.

> **FDA Response**
>
> **Your justification for not performing a leachable study on the basis of results from an extractables study is not adequate. During initial review of your NDA submission, we identified several significant issues with the extractables data and associated toxicological risk assessment.** [redacted] (b) (4)
>
> [redacted] (b) (4)
>
> **Second, as stated in your initial extraction report of the backing layer, release liner, and external container closure, there were a** [redacted] (b) (4) **of extractables detected, many of which were not able to be identified. We cannot conduct a risk assessment of an unknown compound. Third, a Cramer Classification approach was utilized to classify the leachables and justify the lack of risk assessment. As stated in the preNDA meeting minutes dated December 13, 2012, a toxicological risk assessment should be provided for any extractable/leachable that results in a daily exposure level that exceeds 5 mcg/day. Therefore, to provide a biologically relevant hazard assessment of your patch and container closure system, you must conduct a leachables assessment that will evaluate at least three batches of your drug product over the course of stability.**
>
> **Your proposed leachable protocol appears to evaluate acceptable time-points. However, your leachables assessment must be conducted employing appropriate testing conditions that are adequately justified (temperature, agitation, solvent solutions, duration) to provide a worst-case scenario for clinical conditions of use. Provide a safety assessment for all leachables that exceeds a total daily intake threshold of 5 mcg/day. Clearly identify any compounds that contain structural alerts for genotoxicity. From a genetic toxicology perspective, we will allow up to 120 mcg/day for an acute indication for most potentially genotoxic impurities.**

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Proposed Leachables assessment (PRS-18.125.002a)

Analytical Methods: **ADEQUATE**

Briefly, [redacted] A limit test method will be developed and validated in order to verify if substances are present in quantities exceed the qualification threshold (5 mcg/day), corresponding to an estimated AET of [redacted] (1 patch/day).

Experimental Methods: **ADEQUATE**

[redacted]

Monitoring of Potential Leachables: **INADEQUATE**

For each sample of [redacted], the following will be analyzed for leachables: solvent (blank) and solvent collected in 24 h after patch incubation. The Applicant has proposed the following:

> After Hazard and Risk assessment as per the Extractable study performed on packaging for the FlectorPlus patch, and considering the route of administration of the drug product (topical), which allows in general limited absorption of xenobiotics, the following comments pertain:
>
> 1. [redacted]
> 2.
> 3.
> 4.

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(b) (4)

It appears the Applicant will only analyze those extractables that were classified with a (b) (4) applied principles of the Cramer Classification approach, which is not currently adopted by the Agency to qualify safety of chemicals in drug products.

The Applicant states if potential leachables do not exceed the qualification threshold, the limit test will be used. In this case, some leachables will be chosen as representative of the leachable profile for routine testing and both release and during shelf-life. Further investigation of unknown leachables will be conducted. An attempt will be made to perform an extractable versus leachable correlation for the unknown leachable.

Reviewer's Comment: The Applicant will be required to submit an adequate scientific justification for the selection of potential leachables that will be monitored over stability. This justification should be based on extraction results and on good scientific principles taking into consideration the whole patch. As previously communicated in a Type A meeting preliminary comments, the Applicant will be reminded that extractables data from the drug adhesive matrix has not been collected.

Timepoints: **ADEQUATE**
Leachable concentrations will be evaluated at several time-points within the shelf-life of the product up to the end of shelf-life (see Applicant's table below).

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Batch	Manuf. Date	Storage condition
1509141 [redacted] / envelope and 5 [redacted] / envelope	09/2015	Room Temperature
1509161 [redacted] / envelope and 5 [redacted] / envelope	09/2015	Room Temperature
1503211 [redacted] / envelope and 5 [redacted] / envelope	03/2015	Room Temperature
1411211 [redacted] / envelope and 5 [redacted] / envelope	11/2014	25°C/ 60% R.H.
		40°C/ 75% R.H.
1411261 [redacted] / envelope and 5 [redacted] / envelope	11/2014	25°C/ 60% R.H
		40°C/ 75% R.H.
1411271 5 [redacted] / envelope	11/2014	25°C/ 60% R.H
		40°C/ 75% R.H.
1411281 [redacted] / envelope and 5 [redacted] envelope	11/2014	25°C/ 60% R.H
		40°C/ 75% R.H.
1211141 5 [redacted] / envelope	11/2012	25°C/ 60% R.H.
1211161 [redacted] / envelope	11/2012	25°C/ 60% R.H
12071212 5 [redacted] envelope	07/2012	25°C/ 60% R.H

Container: **ADEQUATE**

[redacted]

Solvent: **ADEQUATE**

[redacted]

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Duration: **ADEQUATE**
The duration of incubation is 24 h, which is the recommended application duration for [redacted].

Temperature: **ADEQUATE**
The temperature will be set at 43°C Celcius, which is the temperature the Applicant found in the literature that human skin can tolerate and to simulate overlay and human activity temperatures.

Agitation: **ADEQUATE**
[redacted]

Brief Discussion
In the Applicant's proposed leachables assessment, the strategy for selecting leachables compounds to be monitored over stability is not adequate. In our Type A meeting minutes, we noted that the Cramer Classification approach was being utilized but clarified that any extractable/ leachable resulting in a daily exposure level that exceeds 5 mcg/day must be further evaluated. Therefore the Applicant's rationale for [redacted] based on the Cramer Classification for the leachables assessment is not acceptable. As per our boilerplate, the results of the extraction studies should be used to assure that the Applicant is adequately monitoring the drug product stability samples for potential leachables. With regards to all other design elements of the leachables assessment the Applicant has taken into consideration all of the Division's previous recommendations and therefore appears adequate.

EXTERNAL COMMENT (TO APPLICANT):
Your proposed protocol for the leachable assessment appears to be adequately designed with acceptable study conditions and time-points. However, your justification to only evaluate those extractables that were associated with [redacted] is unacceptable. As part of your safety assessment of the patch, you must provide adequate justification for the selection of the potential leachables that you will be monitoring over stability. This justification should be based on results of the extraction studies and good scientific principles that take into account the whole patch. As communicated to your earlier, you have not conducted an extractables assessment of the drug adhesive matrix and you must conduct this extraction study to ensure your leachable assessment will evaluate all relevant potential leachables.

For your overall risk assessment, submit a toxicological risk assessment for any leachable that exceeds 5 mcg/day. From a genetic toxicology perspective, any leachable that contains a structural alert for mutagenicity must not exceed 120 mcg/day for an acute indication or be adequately qualified for safety. The risk assessment should be based on the maximum level of each leachable detected in long-term stability samples.

Reference ID: 3847067
Reference ID: 4369106

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/s/

NEWTON H WOO
11/13/2015

RICHARD D MELLON
11/13/2015
I concur.