CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206976Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz ,MD
NDA#	206976
Applicant Name	Institut Biochimique SA (IBSA)
Date of Submission	June 25, 2018
PDUFA Goal Date	December 25, 2018
Proprietary Name / Established (USAN) Name	Licart /diclofenac epolamine topical system, 1.3%
Dosage Forms / Strength	Topical System
Proposed Indication(s)	Topical treatment of acute pain due to minor strains, sprains, and contusions
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Christina Fang, MD, Joshua Lloyd, MD
Statistical Review	Katherine Meaker, MS; David Petullo, MS
Pharmacology Toxicology Review	Armaghan Emami, PhD, Jay Chang, PhD, R. Daniel Mellon, PhD.
CMC Review/OBP Review	Paresma Patel, PhD, James Norman, PhD, Cassandra Abellard, Caroline Strasinger, PhD
OPDP	L. Shenee Tombs, Sam Skariah
OSI	John Lee, MD; Janice Pohlman, MD, MPH; Kassa Ayalew, MD, MPH
OSE/DMEPA	Millie Shah, Pharm D; James Schlick, RPh, MBA; Vicky Borders-Hemphill, PharmD

OND=Office of New Drugs
OPDP: Office of Prescription Drug Promotion OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis OSI=Office of Scientific Investigations

1. Introduction

This is the second review cycle for NDA 206976, Licart (diclofenac epolamine) topical system, 1.3% from Institut Biochimique SA (IBSA) (the Applicant) submitted for the topical treatment of acute pain due to minor strains, sprains, and contusions. This is a 505(b)(2) application referencing literature and cross-referencing NDA 21234 for Flector Patch (diclofenac epolamine topical patch) 1.3%, owned by the Applicant and approved in 2007 for the same indication.

(b) (4) Licart topical system and the approved Flector Patch is the addition of (b) (4) heparin. The Applicant has provided data to demonstrate that the heparin (b) (4) is not itself released from the system. (b) (4) The other notable (b) (4) is that Licart is intended to be applied one topical system per 24 hours, and Flector is applied one topical system every 12 hours.

2. Background

Flector Patch was approved on January 31, 2007 for the treatment of acute pain due to minor strains, sprains and contusions. Flector is a 10 X 14 cm topical system, and contains 182 mg of diclofenac epolamine, a nonsteroidal anti-inflammatory drug, and a number of excipients. Licart, the subject of this NDA, is also a 10 X 14 cm topical system that contains 182 mg of diclofenac epolamine, as well as the addition of heparin sodium, (b) (4) (b) (4)

This NDA was originally submitted on March 4, 2015. A refuse-to-file letter was issued on April 29, 2015 because of multiple deficiencies that would not allow for a substantive review of the application. The application was resubmitted on May 27, 2016, and received a complete response action on March 24, 2017. The full list of deficiencies can be found in the appendix at the end of this review.

3. CMC/Device

The first cycle CMC review was conducted by Erika Englund (drug substance and product), James Norman (process), Paul Koushik, Erika Pfeiler (microbiology), Cassandra Abellard (facilities), Christina Cappacci-Daniel (facilities), Min Li (OBP), Sandra Suarez (OBP), Ciby Abraham (application technical lead). The CMC team recommended a complete response action.

The topical system is described below as stated in the original CMC review:

> The topical [redacted] consists of a [redacted] adhesive [redacted], containing the API which is [redacted] 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 [redacted] to the skin. The size of a single [redacted] The adhesive layer is applied to the non-woven polyester felt backing in the [redacted] The patches are contained in a re-sealable envelope [redacted] Each envelope can contain up to 5 topical [redacted]. The envelopes are packed into a carton box.

The review team identified a number of deficiencies that precluded approval from the CMC perspective at the end of the first cycle review. [redacted]

This second cycle CMC review focused on the responses to the 13 CMC deficiencies and the new batch information provided. Removal of the [redacted] addressed several of the previous deficiencies associated with the new manufacturing site and bridging of the two sites. The remaining deficiencies were addressed adequately in the resubmission and are briefly summarized below. The following has been excerpted verbatim from the CMC review.

[redacted]

The Applicant completed a clinical adhesion study of Licart topical system. The following is verbatim from the CMC review:

I concur with the CMC review team that the CMC deficiencies from the prior review cycle have been adequately addressed and that the data submitted support a 24-months expiry. There are no outstanding CMC issues that preclude approval at his time.

4. Nonclinical Pharmacology/Toxicology

The first and second cycle nonclinical reviews were conducted by Armaghan Emami, PhD, with secondary concurrence by Jay Chang, PhD, and R. Daniel Mellon, PhD. The deficiency noted during the first cycle review was an inadequate 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.

The following was excerpted verbatim from the second cycle pharmacology/toxicology review:

> 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.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology

The first cycle clinical pharmacology review was conducted by Srikanth C. Nallani, PhD, with secondary concurrence by Yun Xu, PhD. There were no outstanding clinical pharmacology issues from the first cycle. They did not identify any issues that would preclude approval from the clinical pharmacology perspective.

In the first cycle review, a comparison of multiple dose pharmacokinetic (PK) parameters demonstrated that very low levels of diclofenac from both Flector topical system and Licart topical system, consistent with the original Flector Patch application. The diclofenac is believed to act locally as an analgesic. An important (b) (4) between the two patches is that Flector is intended for every 12 hour application, and Licart for every 24 hours. This application is also supported by clinical studies to confirm that Licart is efficacious when applied every 24 hours.

Dr. Nallani made the following conclusions in his first cycle review:

> Study CRO-PK-12-272 showed that after a single cutaneous application of one Licart (b) (4) for a duration of 24 hours in 24 healthy volunteers, the residual content of heparin in the plaster was assessed to be no different from the content before application. With regard to diclofenac, about 3.6% of the initial content of DHEP, i.e. 6.5 mg, was released on average from the used medicated plasters. Heat, exercise and occlusion did not demonstrate a significant effect on absorption of diclofenac.
>
> Study CRO-PK-02-92 generally showed that systemic absorption of diclofenac is low, and that heparin, if absorbed, has very limited impact on coagulation. Note that heparin PK cannot be done due to lack of bioanalytical method for detecting heparin(s). However, aPTT , a measure of coagulation, is considered an acceptable PD measure to evaluate systemic effects.

I concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not applicable. This product is not an antimicrobial.

7. Clinical/Statistical-Efficacy

No new efficacy studies were provided in this submission. During the first review cycle, the clinical review was conducted by Christina Fang, MD, MPH, with secondary concurrence by Joshua Lloyd, MD. The statistical review was conducted by Kate Meaker, MS, with secondary concurrence by David Petullo, MS. The Applicant submitted four Phase 3 clinical studies in support of the efficacy of Licart topical system for the treatment of acute pain due to minor strains, sprains, and contusions. Dr. Fang concluded that two of the studies could not contribute to the efficacy evaluation due to limitations she identified during her review; refer to her review for more details. The remaining two Phase 3 studies that contributed to the efficacy review were studies FHp11 and FHp03.

Both studies were randomized, double-blind, placebo- and active-controlled, parallel-group, multiple-dose, clinical trials to evaluate the efficacy and safety of Licart topical system compared to placebo and to Flector topical system, one in in adults with a mild-to-moderate muscle contusion to the upper or lower limbs, the other in in adults with a grade I or II acute ankle sprain. The studies demonstrated efficacy of the Licart topical system compared to placebo, but the comparison to Flector topical system was invalid because it was dosed every 24 hours instead of every 12 as it is labeled. Neither study provided substantial data describing the time to onset of action.

Both of these studies provided adequate evidence of efficacy for the Licart topical system. There are no outstanding issues about efficacy that preclude approval.

8. Safety

During the first review cycle, Dr. Fang fully reviewed the safety database from the 11 clinical studies involving 874 subjects exposed to Licart, 657 of whom had from one to three weeks of exposure to a daily 24-hour patch application. There were no reports of deaths and one case of nonfatal serious adverse events (SAEs) presented as skin infection at injury site leading to hospitalization in a patient enrolled in the Flector group. The most common adverse events were application site reactions such as erythema, inflammation, irritation, pruritus, and rash. The results of dermal safety studies submitted by the Applicant had no signs of serious irritation or sensitization. A separate evaluation of phototoxicity and photoallergenicity was not conducted. While there were no signs of either from the clinical trial safety database, it does not appear that these studies included an adequate assessment for the potential for phototoxicity or photoallergenicity.

A safety update was submitted for review with the current resubmission. The following has been excerpted from Dr. Fang's review:

> Licart topical system was approved for marketing in Switzerland (trade name: Flectoparin® Tissugel) in July 2006 and introduced to the market there in November 2006. It was also approved for marketing in France (trade name: Flector Tissugel Héparine®) in August 2010 and had been marketed there since January 2011.
>
> There had been no significant safety actions related to the investigational uses of the product or safety signals from foreign marketing experience during the reporting interval that had a significant influence on the risk-benefit ratio, had an impact on the conduct of clinical trials or on the overall clinical development program, or suggest safety related changes to the proposed labeling based on the Applicant's report.
>
> The estimated exposure is approximately 5 million patients based on a sale volume of 38 million topical systems and an assumption of once a day use for seven days per patient and that all the topical systems sold were used. There was a total of 14 AEs reported by eight individuals. The AEs were mostly application site reactions such as erythema, exfoliation, pain, and swelling, skin reactions such as pruritus, generalized rash, contact eczema, exfoliative dermatitis, bullous dermatitis, and unspecified skin reaction.

There was one case of serious photosensitivity reaction in a patient with prior history of analogous skin reactions following application of other anti-inflammatory agents and subsequent sun exposure.

I agree with Dr. Fang that there are no safety concerns that preclude approval at this time.

9. Advisory Committee Meeting

This application was not brought to an advisory committee as there were no questions that required input from committee.

10. Pediatrics

This product triggers PREA for the proposed new dosing regimen of once a day application of a diclofenac topical system. The review division and Pediatric Research Committee (PeRC) have agreed with the Applicant's request for a partial waiver of pediatric studies in pediatric patients less than six years of age because this product would not be used in that age group, and a deferral of studies in pediatric patients 6-17 years of age.

Studies in this age group will include PK and safety, and efficacy can be extrapolated from findings in adults.

11. Other Relevant Regulatory Issues

Office of Scientific Investigations (OSI)
Inspections of two pivotal clinical sites were conducted during the first review cycle. Minor GCP regulatory deficiencies were noted but were not expected to impact data reliability and the data from both inspected CI sites appear reliable as reported in the NDA.

Office of Compliance, Center for Devices and Radiologic Health (CDRH)
The Office of Compliance at CDRH was consulted and concluded that NDA 206976 is approvable from the perspective of the applicable Quality System Requirements.

Financial Disclosure
No irregularities were noted upon review.

There are no other unresolved relevant regulatory issues

12. Labeling

The proprietary name, Licart, was reviewed by DMEPA and found acceptable. Suggested edits for labeling from DMEPA and OPDP were incorporated into the product labeling.

The Division of Pediatric and Maternal Health also provided input regarding pregnancy and lactation, and pediatric use in Section 8.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval
- Risk Benefit Assessment

The Applicant submitted this NDA for approval of Licart, a diclofenac topical system, for the topical treatment of acute pain due to minor strains, sprains, and contusions. This (b) (4) is (b) (4) to the Applicant's approved Flector Patch, differing in that Licart topical system includes a small amount of heparin intended to accelerate the release of diclofenac from the patch. Unfortunately, clinical trials were not designed appropriately to evaluate whether Licart topical system is superior to the Flector Patch, as Flector, labeled for dosing every 12 hours, was dosed only once daily in the comparative studies. The Applicant successfully demonstrated efficacy for the proposed indication in two adequate and well-controlled clinical studies, one in mild-to-moderate muscle contusion and one in patients with acute ankle spraint. The safety of the Licart topical system is supported by clinical study data and by the demonstration that the heparin does not leave the topical system, and does not have an effect on coagulation measures in study subjects. The most common

adverse events were local skin reactions. The overall benefit of Licart topical system outweighs its risks for the proposed indication.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

N/A

- Recommendation for other Postmarketing Requirements and Commitments

The following postmarketing requirement is intended to fulfill the requirements triggered by PREA:

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

Appendix

Deficiencies cited in the CR action letter dated March 24, 2017.

CLINICAL

1. The product used in the clinical studies was manufactured at a different facility than the to-be-marketed product. You have not provided adequate information (refer to the Biopharmaceutics section below) to bridge these two products in order to establish the safety and effectiveness of the to-be-marketed product.

   Information needed to resolve the deficiency
   Conduct at least one adequate and well-controlled clinical efficacy trial to demonstrate the safety and effectiveness of the to-be-marketed product manufactured at the proposed commercial manufacturing site, (b) (4). We recommend that you discuss the design of this study with the Division in advance.

NONCLINICAL

2. Your application 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 were detected at levels exceeding the qualification threshold of 5 mcg/day.

   a. (b) (4)

   b. (b) (4)

   c. (b) (4)

   Information needed to resolve the deficiency
   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.

   - 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 evidence that none of the compounds can penetrate skin and, therefore, would not pose any risk to patients based on an accurate and reliable method to demonstrate compound size. Submit any literature articles that are intended to support this argument .

PRODUCT QUALITY

3. (b) (4)

(b) (4)

4. (b) (4)

(b) (4)

5. (b) (4)

(b) (4)

6. (b) (4)

(b) (4)

7. [redacted]

8. [redacted]

9. [redacted]

10. [redacted]

11. [redacted]

Process

12. [redacted]

13. [redacted]

(b) (4)

Biopharmaceutics

14. The weight-of-evidence approach (risk-based approach) to support the manufacturing site change from Teikoku (b) (4) is inadequate due to the following deficiencies:

a) (b) (4)

b)

Information needed to resolve the deficiencies

Given the inadequate data to support a risk-based approach, as a path forward for the evaluation of the proposed site change and as per SUPAC-MR guidance, in vivo data are needed for bridging the manufacturing site change. Because there is no unexpired drug product manufactured at Teikoku available to perform a head-to-head comparison of the two sites via a pharmacokinetic study, conduct one adequate and well-controlled clinical efficacy and safety study to bridge the products manufactured at different sites and to demonstrate the safety and effectiveness of the product manufactured at the proposed commercial manufacturing site, (b) (4). Also see Clinical comments.

15. (b) (4)

Information needed to resolve the deficiency

Provide additional data demonstrating the discriminating ability of the method towards meaningful changes of the critical material attributes or process parameters. These data are needed to support the adequacy of the method as a QC tool for drug product release and stability testing.

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

/s/

SHARON H HERTZ
12/19/2018

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Joshua Lloyd, MD and Ellen Fields, MD, MPH
Subject	Combined Division Director Summary Review and CDTL Memo
NDA#	206976
Applicant Name	Institut Biochimique SA (IBSA)
Date of Submission	May 27, 2016
PDUFA Goal Date	March 24, 2017
Proprietary Name / Established (USAN) Name	Licart (b) (4) /diclofenac epolamine (b) (4) 1.3%
Dosage Forms / Strength	Topical (b) (4)
Proposed Indication(s)	Topical treatment of acute pain due to minor strains, sprains, and contusions
Action/Recommended Action for NME:	Complete Response

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Christina Fang, MD
Statistical Review	Katherine Meaker, MS; David Petullo, MS
Pharmacology Toxicology Review	Armaghan Emami, PhD, Jay Chang, PhD, R. Daniel Mellon, PhD.
CMC Review/OBP Review	Erika Englund, PhD, James Norman, PhD, Paul Koushik, Erika Pfeiler, Cassandra Abellard, Christina Cappacci-Daniel, Min Li (OBP), Sandra Suarez (OBP), Ciby Abraham
Clinical Pharmacology Review	Srikanth C. Nallani, PhD; Yun Xu, PhD
OPDP	
OSI	John Lee, MD; Janice Pohlman, MD, MPH; Kassa Ayalew, MD, MPH
CDTL	Joshua Lloyd, MD
OSE/DMEPA	Millie Shah, Pharm D; James Schlick, RPh, MBA; Vicky Borders-Hemphill, PharmD,
DDDP	Hamid Tabatabai, MD; Snezana Trajkovic, MD; Kendall Marcus, MD

OND=Office of New Drugs
OPDP: Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
DDDP= Division of Dermatology and Dental Products

1. Introduction

Institut Biochimique SA (IBSA) (the Applicant) submitted NDA 206976 for Licart (b) (4) (diclofenac epolamine 1.3%) for the topical treatment of acute pain due to minor strains, sprains, and contusions. This is a 505(b)(2) application referencing literature and cross-referencing NDA 21234 for Flector Patch (diclofenac epolamine topical patch) 1.3%, approved in 2007 for the same indication, which the Applicant also owns. This NDA was originally submitted March 4, 2015, but was not filed due to numerous deficiencies.

(b) (4) Licart (b) (4) and the approved Flector patch is the addition of (b) (4) (b) (4) heparin to Licart. (b) (4) (b) (4) is not itself released from the patch. (b) (4) (b) (4). The other notable (b) (4) is that Licart is intended to be applied one patch per 24 hours, and Flector is applied one patch every 12 hours.

2. Background

Flector patch was approved on January 31, 2007 for the treatment of acute pain due to minor strains, sprains and contusions. Flector is a 10 X 14 cm topical patch, and contains 182 mg of diclofenac epolamine, a nonsteroidal anti-inflammatory drug, and a number of excipients. Licart, the subject of this NDA, is also a 10 X 14 cm topical patch that contains 182 mg of diclofenac epolamine, as well as the addition of heparin sodium, (b) (4) (b) (4)

This NDA was originally submitted on March 4, 2015. A refuse-to-file letter was issued on April 29, 2015 because of multiple deficiencies that would not allow for a substantive review of the application. Refer to the letter for additional details.

The Applicant resubmitted the application on May 27, 2016, and it was deemed adequate for review.

3. CMC/Device

The CMC review was conducted by Erika Englund (drug substance and product), James Norman (process), Paul Koushik, Erika Pfeiler (microbiology), Cassandra Abellard (facilities), Christina Cappacci-Daniel (facilities), Min Li (OBP), Sandra Suarez (OBP), Ciby Abraham (application technical lead). The CMC team recommended a complete response action.

The patch is described below as stated in the CMC review:

> The topical (b) (4) consists of a (b) (4) adhesive (b) (4), containing the API which is (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. The size of a single (b) (4) is 10 ± 0.5 cm x 14 ± 0.7 cm, or approximately 140 cm2. The adhesive layer is applied to the

non-woven polyester felt backing in the amount of (b) (4). The total amount of (b) (4). The (b) (4) are contained in a re-sealable envelope made of (b) (4). Each envelope can contain up to 5 topical (b) (4) The envelopes are packed into a carton box. An expiry (b) (4)

The review team identified the following deficiencies (b) (4)

Drug Product

1. (b) (4)

(b) (4)

(b) (4)

2. (b) (4)

(b) (4)

(b) (4)

3. (b) (4)

(b) (4)

(b) (4)

4. (b) (4)

(b) (4)

(b) (4)

5. (b) (4)

(b) (4)

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6. (b) (4)

(b) (4)

(b) (4)

7. (b) (4)

(b) (4)

(b) (4)

8. (b) (4)

(b) (4)

(b) (4)

9. (b) (4)

(b) (4)

(b) (4)

Process

1. (b) (4)

(b) (4)

(b) (4)

2. (b) (4)

(b) (4)

(b) (4)

(b) (4)

Biopharmaceutics

1. The weight of evidence approach (risk based approach) originally proposed by the Agency to support the manufacturing site change (from Teikoku (b) (4) is insufficient due to the following deficiencies

   a. (b) (4)

   b.

Information needed to resolve the clinical hold deficiencies

Given the insufficient data to support a risk based approach as a path forward on the evaluation of the proposed site change and as per SUPAC-MR guidance, in vivo data are needed for bridging the manufacturing site change. Because there is no unexpired drug product manufactured at Teikoku available to perform a head to head comparison of the two sites via a clinical endpoint, a standalone clinical study is recommended to demonstrate the efficacy/safety of batches manufactured at the proposed commercial manufacturing site, (b) (4)

2. A discriminating dissolution method is needed for the drug product. Note that the demonstration of method discriminating ability should compare the in vitro release profiles (provide f2 values for each comparison between pre- and post-change) obtained from the meaningful variations (i.e., ± 10-20% change to the specification- ranges) of relevant critical manufacturing attributes (i.e., release controlling agents), while other unnecessarily large variations of critical attributes may not be considered appropriate without scientifically sound justification. Alternatively, modify or re- develop an in vitro release

method with full validation for quality control purpose. The in vitro release method development should include detailed description of the in vitro release test being proposed and the developmental parameters (i.e., selection of the equipment/apparatus, in vitro release media, agitation/rotation speed, pH, assay, sink conditions, etc.) investigated for the selection of the proposed method as the optimal.

Based on current practice, the acceptance criteria of the in vitro release test are set at multiple time points based on the mean value (i.e., mean value and ± 10% range and NLT 80% for the last specification time-point, unless there are in vivo BA/BE and/or IVIVC data supporting wider ranges) of n=12 units from batches tested in pivotal clinical studies (e.g., the in vivo BE study used for manufacturing site change). Additional in vitro release data from non-biobatches may be used as supportive documents on case-by-case basis. Note that the proposed in vitro release acceptance criteria with "no less than **% released" at all time points are not appropriate for MR products.

Information needed to resolve the clinical hold deficiencies

Provide additional data demonstrating the discriminating ability of the method towards meaningful changes of the critical material attributes or process parameters. These data are needed to support the adequacy of the method as a QC tool for drug product release and stability testing.

We concur with the CMC review team that these deficiencies preclude approval of Licart (b) (4).

4. Nonclinical Pharmacology/Toxicology

The nonclincal review was conducted by Armaghan Emami, PhD, with secondary concurrence by Jay Chang, PhD, and R. Daniel Mellon, PhD.

Dr. Emami stated in her review:

> 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

Neither the 4-week repeat-dose dermal rabbit toxicity study nor the dermal guinea pig hypersensitivity study showed toxic symptoms or local toxicity in the treated animals. In vitro data (Franz cell testing) showed that heparin is not released from the patch, presumably due to its high molecular weight. This data also showed that the release of diclofenac from

Licart (once daily patch) was approximately 2.4 fold greater than from Flector (twice daily patch).

According to Dr. Emami, the extractable and leachable evaluations were performed with appropriate study design methods and sample sets. All 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. She determined that the application did not include an adequate justification to support the safety of the eight leachable compounds whose structures were not fully elucidated in the leachables studies, but detected at levels exceeding the qualification threshold of 5 mcg/day, despite the use of several approaches by the Applicant.

The following deficiencies in the application that preclude approval of Licart were identified by the nonclinical review team:

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. We acknowledge that several approaches were employed to demonstrate that the compounds (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. 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.

- 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.

We concur with the conclusions reached by the pharmacology/toxicology reviewer that there are outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology

The clinical pharmacology review was conducted by Srikanth C. Nallani, PhD, with secondary concurrence by Yun Xu, PhD. They did not identify any issues that would preclude approval from the clinical pharmacology perspective.

In this application, the Applicant submitted a multiple dose pharmacokinetic (PK) study comparing plasma levels of diclofenac between Flector Patch and Licart (b) (4) formulations, and demonstrated that overall plasma levels of diclofenac are very low, as was consistent with the original Flector Patch application, and as would be expected. The diclofenac is believed to act locally as an analgesic. An importan (b) (4) between the two patches is that Flector is intended for every 12 hour application, and Licart for every 24 hours. This application is also supported by clinical studies to confirm that Licart is efficacious when applied every 24 hours.

The following studies were submitted by the Applicant (as noted in Dr. Nallani's review):

- CRO-PK-12-272: Multiple dose PK study. Part 1: single dose, non-randomized, open- label exploratory study. Part 2: multiple dose, randomized, open-label, cross-over bioavailability study. [This study included assessments of PK at rest, with exercise, occlusion, and heat, and Licart was applied for 24 hours].
- CRO-PK-98-13: Bioavailability study of a new topical formulation of Licart (DHEP) plaster containing heparin vs. the marketed formulation Flector patch (Flector EP Tissugel) in male and female healthy volunteers. This open, randomized, two-way crossover, multiple dose study was divided in two phases: 4 healthy volunteers were enrolled during the first, pilot phase, while 18 healthy volunteers participated in the subsequent main phase. [Licart and Flector were both applied every 12 hours].
- CRO-PK-02-92: Multiple dose PK study evaluating heparin and diclofenac levels with patch application. [This study evaluated every 12 hour application of Licart for 6 days, and also assessed the potential of any absorbed heparin to cause changes in coagulation, because the Applicant did not have a bioanalytical assay for heparin].

Dr. Nallani made the following conclusions in his review:

Study CRO-PK-12-272 showed that after a single cutaneous application of one Licart (b) (4) for a duration of 24 hours in 24 healthy volunteers, the residual content of heparin in the plaster was assessed to be no different from the content before application. With regard to diclofenac, about 3.6% of the initial content of DHEP, i.e. 6.5 mg, was released on average from the used medicated plasters. Heat, exercise and occlusion did not demonstrate a significant effect on absorption of diclofenac.

The plasma PK parameters are shown below under all conditions:

PK parameter	Patch application condition			
	Standard (rest)	Exercise	Occlusion	Moderate heat
C_{max} (ng/mL)	1.01 ± 0.64	1.22 ± 0.76	1.14 ± 0.74	1.23 ± 0.73
T_{max} (h)	6.0 (4.0-20.0)	12.0 (0.0-24.0)	6.0 (0.0-24.0)	6.0 (0.0-20.0)
AUC_T (ng/mL×h)	18.58 ± 11.63	22.77 ± 14.39	21.94 ± 14.25	23.07 ± 14.29
C_{min} (ng/mL)	0.49 ± 0.31	0.62 ± 0.42	0.63 ± 0.47	0.69 ± 0.46
PTF (%)	68.18 ± 18.43	66.04 ± 15.84	58.22 ± 14.14	58.63 ± 9.45

Source: Dr. Nallani's review, p. 5

Study CRO-PK-98-13 demonstrated that the systemic levels of diclofenac are of every 12 hours for Licart, which is different than the intended dosing regimen of every 24 hours.

Study CRO-PK-02-92 generally showed that systemic absorption of diclofenac is low, and that heparin, if absorbed, has very limited impact on coagulation. Note that heparin PK cannot be done due to lack of bioanalytical method for detecting heparin(s). However, aPTT , a measure of coagulation, is considered an acceptable PD measure to evaluate systemic effects.

We concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not applicable. This product is not an antimicrobial.

7. Clinical/Statistical-Efficacy

The clinical review was conducted by Christina Fang, MD, MPH, with secondary concurrence by Joshua Lloyd, MD. The statistical review was conducted by Kate Meaker, MS, with secondary concurrence by David Petullo, MS.

The Applicant submitted four Phase 3 clinical studies in support of the efficacy of Licart (b) (4) (also referred to as Flector-H) in the topical treatment of acute pain due to minor strains, sprains, and contusions. Dr. Fang concluded that two of the studies could not contribute to the efficacy evaluation due to limitations she identified during her review; refer to her review for more details. The remaining two Phase 3 studies that contributed to the efficacy review were studies FHp11 and FHp03.

Study FHp11

Study FHp11 was a Phase 3, randomized, double-blind, placebo- and active-controlled, parallel-group, multiple-dose, multicenter clinical trial to evaluate the efficacy and safety of Licart (b) (4) compared to placebo patch and to Flector patch. The study was conducted from June 2006 through May 2007 in Germany and the Czech Republic. Eligible patients were 18 to 65 years of age with a mild-to-moderate muscle contusion to the upper or lower limbs within 72 hours prior to enrollment and a minimum pain score with standardized movement of 50 mm on the 100 mm visual analog scale (VAS). Patients were randomized to treatment with Licart (b) (4), Flector patch, or placebo patch, which was applied directly to the injured site and was secured in place with either tape or netting. Treatment was applied every 24 hours in the morning with a 14-day treatment duration, and the patch was worn for at least 20 consecutive hours. Although Flector patch was administered according to this schedule, this is half the approved every 12-hour dosing regimen. Acetaminophen rescue was available. Pain intensity assessments on movement were collected in a daily diary in the morning prior to patch application and approximately 12 hours later. The primary efficacy variable was change from baseline to Day 3 for pain on movement using the 100 mm VAS in all randomized patients who received at least one dose of study medication and for whom there was at least one post-baseline efficacy assessment. The Applicant referred to this population as the intent-to-treat (ITT) population. The primary comparison was intended to demonstrate superiority of Licart (b) (4) to Flector patch.

A total of 355 patients were randomized and received treatment. However, one placebo subject did not have on-treatment pain scores due to withdrawing consent after randomization. Ms. Meaker noted that the ITT definition used in this study was not standard. However, only this one subject was excluded from what would otherwise be a standard ITT population, and Ms. Meaker determined use of this definition did not impact the results or conclusions of the study. The majority of subjects were male (64%), Caucasian (100%), and from the Czech Republic (63%) with a mean age of 39 years. Baseline pain intensity on movement was approximately 65 mm on the 100 mm VAS. Demographic characteristics were relatively balanced across treatment groups.

Overall, very few patients discontinued from the study; however, all discontinuations came from the German sites. The patient disposition is detailed below:

	Flector-H	Flector	Placebo
Randomized (All received treatment)	121 (100%)	115 (100%)	119 (100%)
Withdrew Consent (Day 1) No On-treatment Pain Scores Recorded	0	0	1 (1%)
Protocol Defined Intent-to-Treat	121 (100%)	115 (100%)	118 (99%)
Discontinued During Treatment			
Adverse Event	0	2 (2%)	2 (2%)
Lack of Efficacy	0	1 (1%)	0
Patient reported "Recovered/No pain"	4 (3%)	4 (3%)	2 (2%)
Other	1 (1%)	1 (1%)	6 (5%)
Total Discontinued	5 (4%)	8 (7%)	10 (8%)

Source: Ms. Meaker's statistical review
All percentages are calculated based on Randomized N per group as denominator.

Ms. Meaker confirmed the primary analysis using the ANCOVA model specified in the protocol. The protocol included a last observation carried forward (LOCF) imputation method for missing pain scores during the treatment period. Although this is not the currently preferred approach, Ms. Meaker determined that use of this imputation method did not impact the results or conclusions from the study. Ms. Meaker noted "[t]he single primary comparison was a superiority test of [Licart] to Flector. Comparisons of each of the active treatment groups to placebo on the primary endpoint were planned as secondary analyses. The same ANCOVA model was used. There was no adjustment for multiplicity." Ms. Meaker further noted that "[o]n the primary efficacy endpoint, at Day 3 on treatment, the [Licart] treatment group was statistically significantly better than the Flector treatment group ($p<0.001$) and both active treatment groups were superior to placebo." The results of the primary analysis are described below:

ITT Subjects		Flector-H N=121	Flector N=115	Placebo N=118
Pain on Movement Unadjusted Mean (SD)	Baseline	68 (11)	67 (11)	69 (12)
	Day 3	49 (21)	56 (17)	64 (16)
	Day 8	25 (17)	32 (20)	40 (20)
	Day 15	9 (13)	13 (15)	17 (17)
	Baseline to Day 3:	-18 (18)	-10 (13)	-4 (15)
	Baseline to Day 8:	-42 (17)	-35 (21)	-28 (22)
	Baseline to Day 15:	-59 (16)	-54 (19)	-51 (20)
Primary Efficacy: [a] Change from Baseline to Day 3 for Pain on Movement (Planned ANCOVA model: Trmt + Baseline Pain)	Adjusted Mean	-18	-10	-4
	Diff.: Flector-H. vs. Flector	-8		
	(p-value)	<0.001		
	Diff. vs. placebo	-14	-6	
	(p-value)	<0.001	0.007	
Secondary: Proportion Who Took Rescue (paracetamol)	Baseline to Day 15: Yes (%)	12 (10%)	17 (15%)	20 (17%)

Source: Ms. Meaker's statistical review
a The adjusted means and p-values were obtained from ANCOVA model including effects for treatment and baseline pain.

As noted above, there was a substantial reduction in pain intensity after Week 1 and Week 2, and these reductions are similar between treatment groups at the Day 15 time point, which likely reflects the natural history of the condition. Proportion of patients taking rescue was overall low with a lower proportion of patients taking rescue in the Licart group.

Ms. Meaker noted "no significant difference in the treatment effect between countries, i.e. the direction and magnitude of the treatment effect was not different."

Study FHp03

Study FHp03 was a Phase 3, randomized, double-blind, placebo- and active-controlled, parallel-group, multiple-dose, multicenter clinical trial to evaluate the efficacy and safety of Licart (b) (4) compared to placebo patch and to Flector patch. The study was conducted in 2007 in Italy, Poland, and the Ukraine. Eligible patients were 18 to 65 years of age with a grade I or II acute ankle sprain within 48 hours prior to enrollment and a minimum pain score with movement of 50 mm on the 100 mm VAS. Patients were randomized to treatment with Licart (b) (4), Flector patch, or placebo patch, which was applied directly to the injured site and was secured in place with netting. Treatment was applied every 24 hours in the morning with a 7-day treatment duration, and the patch was worn for 23.5 hours. Although Flector patch was administered according to this schedule, this is half the approved every 12-hour dosing regimen. Acetaminophen rescue was available. Pain intensity assessments on movement, at rest, and while leaning on the injured limb were collected in the morning prior to patch application and approximately 12 hours later. The primary efficacy variable was change from

baseline to Day 3 for pain on movement using the 100 mm VAS in all randomized subjects who received at least one dose of treatment and had at least one on-treatment pain assessment. The primary comparison was intended to demonstrate superiority of Licart (b) (4) to Flector patch.

A total of 430 patients were randomized and received treatment. Similar to the previous study, a non-standard definition was used for the ITT population. However, Ms. Meaker determined that the use of this definition did not impact the results or conclusions of the study. The majority of subjects were male (59%), Caucasian (99%), and from Poland (60%) with a mean age of 35 years. Baseline pain on movement was 72 mm on the 100 mm VAS. Demographic characteristics were relatively balanced across treatment groups.

Very few patients discontinued from the study. Three patients discontinued from the study prior to the Day 3 visit, two in the placebo group and one in the Flector group, due to lost to follow-up. Two additional patients discontinued between days 3 and 7, but no reasons were provided. Disposition is summarized below:

	Flector-H	Flector	Placebo
Randomized	142 (100%)	146 (100%)	142 (100%)
Received Study Treatment	142 (100%)	145 (99%)	142 (100%)
Discontinued Prior to Day 3 No Pain Scores Recorded	0	1 (1%) 1 (1%)	2 (1%)
Protocol Defined Intent-to-Treat	142 (100%)	143 (98%)	140 (99%)
Discontinued between Day 3 and Day 7 LOCF imputation applied from Day 3 or later logbook pain scores if available.	1 (1%)	0	1 (1%)

Source: Ms. Meaker's statistical review
All percentages are calculated based on Randomized N per group as denominator.

The primary analysis was conducted using an ANCOVA model. Ms. Meaker noted that "[t]he protocol also specified that Last Observation Carried Forward (LOCF) imputation would be applied to all missing values during the treatment period." However, she determined that use of this imputation method did not impact the results or conclusions from the study. Ms. Meaker noted that "the single primary comparison was a superiority test of [Licart] to Flector. Comparisons of each of the active treatment groups to placebo on the primary endpoint were planned as secondary analyses. The same ANCOVA model was used. There was no adjustment for multiplicity." Ms. Meaker further noted that "[o]n the primary efficacy endpoint, at Day 3 on treatment, the [Licart] treatment group was statistically significantly better than the Flector treatment group (p=0.002) and both active treatment groups were superior to placebo. The magnitudes of the treatment differences were also consistent at Day 7." The results of the primary analysis are described below:

ITT Subjects		Flector-H N=142	Flector N=142	Placebo N=140
Pain on Movement Unadjusted Mean (SD)	Baseline	72 (12)	73 (12)	71 (12)
	Day 3	48 (18)	54 (18)	58 (17)
	Day 7	18 (14)	24 (18)	27 (21)
	Baseline to Day 3:	-24 (16)	-19 (17)	-14 (13)
	Baseline to Day 7:	-54 (16)	-49 (19)	-44 (20)
Primary Efficacy: [a] Change from Baseline to Day 3 for Pain on Movement (ANCOVA model)	Adjusted Mean	-24	-19	-14
	Diff.: Flector-H. vs. Flector	-5		
	(p-value)	0.002		
	Diff. vs. placebo	-11	-5	
	(p-value)	<0.001	0.005	
Secondary Efficacy: [a] Change from Baseline to Day 7 for Pain on Movement (ANCOVA model)	Adjusted Mean	-54	-49	-45
	Diff.: Flector-H. vs. Flector	-5		
	Diff. vs. placebo	-9	-4	
Secondary: Proportion Who Took Rescue (paracetamol)	Baseline to Day 3: Yes (%)	98 (69%)	103 (73%)	104 (74%)
	Baseline to Day 7: Yes (%)	104 (73%)	109 (77%)	107 (76%)

Source: Ms. Meaker's statistical review
a The adjusted means and p-values were obtained from ANCOVA model including effects for treatment and baseline pain.

Similar to the previous study, a substantial reduction in pain intensity was observed at Day 7 for all treatment groups, although the finding was more pronounced in the Licart group. The overall finding likely reflects the natural history of the condition. A substantially higher proportion of patients took rescue in this study compared to the other study. However, rescue medication use was comparable between treatment groups.

Conclusions

Both Dr. Fang and Ms. Meaker concluded that studies FHp11 and FHp03 demonstrated the effectiveness of Licart (b) (4) in the proposed indication. Dr. Fang noted that both studies contained limited data to evaluate the onset of action in this acute pain indication. I concur with both Dr. Fang's and Ms. Meaker's overall conclusions. However these studies were conducted using a product that was manufactured at a different site than the to-be-marketed product, and the Applicant did not provide adequate information to bridge the two products. Therefore, the data submitted are alone inadequate for demonstrating the effectiveness of the to-be-marketed product. Furthermore, the studies are inadequate for supporting a comparative claim against Flector patch because Flector patch was not administered according the approved dosing regimen in the clinical studies.

8. Safety

The following is a summary of the safety results from Dr. Fang's review:

> The safety database contains safety data from 11 clinical studies involving a total of 1712 subjects. Exposure to Flector-H was reported in 874 subjects, 657 of whom had 1-3 weeks of exposure to 24-hour patch applied daily.
>
> There were no reports of deaths and one case of nonfatal serious adverse events (SAEs) presented as skin infection at injury site leading to hospitalization in a patient enrolled in the Flector group. Of the eight cases of AE-related dropouts two were in the Flector group and none in the Flector-H group.
>
> AEs were reported in 4-5% subjects with individual AEs being mostly <1% and mainly noticeable as application site reactions such as erythema, inflammation, irritation, pruritus, and rash…
>
> ...Flector-H is well tolerated based on safety findings.

Dr. Fang noted that the case of nonfatal SAE involved a 55 year-old male with a history of diabetes who experienced severe pain, intermittent claudication, and skin infection of the injured foot while on Flector patch. The patient was hospitalized, study drug was terminated, and the infection resolved on antibiotic therapy. Dr. Fang concluded that this event was unlikely to be associated with treatment with Flector, and I concur with her assessment.

Hamid Tabatabai, MD from the Division of Dermatology and Dental Products (DDDP) evaluated the dermal safety studies, with secondary concurrence from Snezana Trajkovic, MD (Clinical Team Leader, DDDP) and Kendall Marcus, MD (Division Director, DDDP). The following is a summary of the dermal safety results from Dr. Tabatabai's review:

> Based on results of dermal safety studies submitted by the applicant, it is reasonable to conclude that diclofenac/heparin patch is not irritating or sensitizing.
>
> Because the design and conduct of phototoxicity and photoallergenicity studies differs from typical studies used in evaluation of phototoxicity and photoallergenicity, the conclusion whether diclofenac/heparin patch has the potential for phototoxicity or photoallergenicity, could not be made. However, if the sponsor adequately assessed the local safety of the active diclofenac containing patches in actual use conditions during the phase 3 trials, then the primary review division may reasonably conclude that they have an adequate safety database for product labeling.

Although the Phase 3 studies captured adverse events (AEs) related to local safety, it is unclear if these studies included an adequate assessment for the potential for phototoxicity or photoallergenicity. According to the medical review for the original submission for Flector patch (refer to clinical review dated 10/9/2001 by Joseph Stauffer, DO), the dermal safety studies for that product, which included phototoxicity and photoallergenicity studies, did not provide adequate evidence of safety due to a variety of limitations even though, according to the Applicant, these studies did not demonstrate evidence of dermatologic toxicity. A Not Approvable action was taken on the original submission. However, the issues with the dermal safety studies were not considered approvability issues (refer to review conducted by Robert Levin, MD, dated 1/8/2007); the application was subsequently approved on January 31, 2007. (b) (4) the Licart (b) (4) and the Flector patch is the addition of heparin as a (b) (4) excipient.

I concur with Dr. Fang's and Dr. Tabatabai's conclusions. However the studies were conducted using a product that was manufactured at a different site than the to-be-marketed product, and the Applicant did not provide adequate information to bridge the two products. Therefore, the data submitted are alone inadequate for demonstrating the safety of the to-be-marketed product.

9. Advisory Committee Meeting

This application was not brought to an advisory committee as there were no questions that required input from committee.

10. Pediatrics

There were no pediatric data in the NDA submission. The product triggers PREA for the proposed new dosing regimen of once a day application. The review division and Pediatric Research Committee (PeRC) have agreed with the Applicant's request for a partial waiver of pediatric studies in pediatric patients less than six years of age because this product would not be used in that age group, and a deferral of studies in pediatric patients 6-17 years of age. Studies in this age group will include PK and safety, and efficacy can be extrapolated from findings in adults.

11. Other Relevant Regulatory Issues

- Office of Scientific Investigations (OSI)
  As stated in the report from OSI dated March 9, 2017:
  Two (pivotal) studies for this NDA were audited on-site at good clinical practice (**GCP**) inspections of two foreign clinical investigator (**CI**) study sites: (1) Site 19 in Study 05DCz/FHp11, Jirí Neumann, M.D. (Dritec, Czech Republic); and (2) Site 01 in Study 06EU/FHp03, Jacek Kwarecki, M.D., Ph.D. (Warsaw, Poland).

  At both CI sites, a Form FDA 483 was issued for minor GCP regulatory deficiencies unlikely to be significant to impact data reliability or the rights, safety, or welfare of

subjects. The data from both inspected CI sites appear reliable as reported in the NDA.

- Office of Compliance, Center for Devices and Radiologic Health (CDRH)
  The Office of Compliance at CDRH was consulted to evaluate the Applicant's compliance with the relevant Quality System Requirements for approvability of the NDA. They determined an inspection was not required for the manufacture site of the drug product (b) (4) for another product was deemed acceptable. They concluded that NDA 206976 is approvable from the perspective of the applicable Quality System Requirements.

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

There are no other unresolved relevant regulatory issues

12. Labeling

- The proprietary name, Licart, was reviewed by the Division of Medication Prevention and Analysis (DMEPA) and found acceptable. Refer to review dated August 26, 2016.
- DMEPA reviewed the labeling and provided input to identify deficiencies that may lead to medication errors. This will be revisited upon resubmission of the NDA.
- The Division of Pediatric and Maternal Health also provided input regarding pregnancy and lactation, and pediatric use in Section 8. This will be revised upon resubmission of the NDA.
- Labeling for this application was not completed because of the Complete Response (CR) action.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action
  Complete Response

- Risk Benefit Assessment
  The Applicant submitted this NDA for approval of a diclofenac (b) (4), Licart, for the topical treatment of acute pain due to minor strains, sprains, and contusions. This (b) (4) is (b) (4) to the Applicant's approved Flector Patch, differing in that Licart (b) (4)

includes a (b) (4) of heparin (b) (4) (b) (4) The Applicant demonstrated that the heparin does not leave the patch, and does not have an effect on coagulation measures in study subjects. Both Flector and Licart result in very low plasma levels of diclofenac, as would be expected, and the patches act locally to decrease pain. The Applicant submitted X Phase 3 studies to demonstrate the efficacy and safety of Licart, and it's superiority in terms of efficacy comparted to Flector.

The Applicant conducted two adequate and well-controlled clinical studies, one in patients with mild-to-moderate muscle contusion and one in patients with acute ankle sprain, to evaluate the efficacy of Licart (b) (4) in the topical treatment of acute pain due to minor strains, sprains, and contusions. Both demonstrated a statistically significant treatment effect on the primary endpoint, change from baseline to Day 3 for pain on movement as measured on a 100 mm VAS, as compared to Flector patch administered at half the approved dosing regimen. The clinical safety review demonstrated that Licart (b) (4) was well tolerated. However these studies were conducted using a product that was manufactured at a different site than the to-be-marketed product, and the Applicant did not provide adequate information to bridge the two products. Therefore, the data submitted are alone inadequate for demonstrating the safety and effectiveness of the to-be-marketed product. These studies would also not support a comparative efficacy claim versus Flector, because Flector was not administered in these studies according to the labeled instructions. In order to demonstrate efficacy and safety for the to-be-marketed formulation, at least one positive adequate and well-controlled study conducted with this formulation is needed.

A large number of deficiencies were identified by the CMC and biopharmaceutics review team. These are detailed earlier in this review, and include lack of adequate data for the drug product, lack of a robust analytical method which is fully validated for the measurement of heparin in the drug product including lack of an adequate assay method, and lack of an in vivo adhesion study. The biopharmaceutics team determined that the weight of evidence approach (risk based approach) originally proposed by the Agency to support the manufacturing site change (from Teikoku (b) (4)) is insufficient.

Given the insufficient data to support a risk based approach as a path forward on the evaluation of the proposed site change and as per SUPAC-MR guidance, in vivo data are needed for bridging the manufacturing site change. Because there is no unexpired drug product manufactured at Teikoku available to perform a head to head comparison of the two sites via a clinical endpoint, a standalone clinical study is recommended to demonstrate the efficacy/safety of batches manufactured at the proposed commercial manufacturing site, (b) (4)

There are also nonclinical deficiencies identified that preclude approval. 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.

Therefore, I recommend a CR action for this NDA. Once the Applicant has resolved the identified deficiencies, they may resubmit this NDA for review.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  N/A

- Recommendation for other Postmarketing Requirements and Commitments
  N/A

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/s/

JOSHUA M LLOYD
03/23/2017

ELLEN W FIELDS
03/23/2017