CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206976Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA (resubmission)
Submission Number	206-976
Priority or Standard	Standard
Submit Date(s)	June 23 (SD#46) and October 19, 2018 (SD#55)
Received Date(s)	June 25 (SD#46) and October 19, 2018 (SD#55)
PDUFA Goal Date	December 25, 2018
Division / Office	DAAAP/CDER/OND/ODE II
Reviewer Name	Christina Fang, M.D., M.P.H.
Established Name	Diclofenac epolamine topical system 1.3%
Trade Name	LICART
Therapeutic Class	External analgesic
Applicant	Institut Biochimique SA (IBSA)
Formulation	Topical system (with 182 mg diclofenac epolamine)
Dosing Regimen	One to the most painful area once daily (on intact skin)
Indication	Acute pain due to minor strains, sprains, and contusions
Intended Population	Patients in need of topical analgesics for acute pain

Background
NDA 206976 for Licart topical system containing diclofenac epolamine 1.3% as an active ingredient and heparin as an enhancer of transdermal penetration was originally submitted on March 4, 2015. The Applicant received a complete response letter from the Division (refer to the Letter to the Applicant dated March 24, 2017 for detail) with a list of deficiencies to be addressed for obtaining application approval. The efficacy results of the two pivotal phase 3 trials and safety findings from 11 clinical studies were reviewed and summarized in detail in the Clinical Review of the original NDA (refer to the Clinical Review filed to DARRTS on March 6, 2017 for detail) and provided evidence in support of a favorable benefit/risk ratio for recommendation of product approval.

The current NDA resubmission contains the Applicant's response to the Division's deficiency list and a safety update reported as post-marketing experiences on the use of product in Switzerland and France covering the reporting interval from July 2006 to December 2017.

Review of safety update
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: FlectorTissugelHéparine®) 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 (b) (4) patients based on a sale volume of (b) (4) 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, and one case of serious photosensitivity reaction.

The case of photosensitivity reaction was reported in a 61 years old male who had sun exposure the day following the first topical system application for epitrochleitis (medial epicondylitis) of the elbow and then had exfoliative skin reaction and bullous dermatitis consistent with a typical photosensitivity reaction. "No concomitant medications were reported to be in use by the patient at the time the topical system was used. Patient's medical history was positive for analogous skin reactions occurring after application of other anti-inflammatory agents following sun exposure. The treatment with the topical system was suspended. The case outcome is unknown".

The results of the study of phototoxicity potential by UVA irradiation in 20 human subjects and photoallergy maximization test in 25 human subjects were submitted with the original NDA and were reviewed by the consultant reviewer Dr. Hamid Tabatabai from the Division of Dermatology and Dental Products (refer to the consult review filed to DARRTS on January 11, 2017 for detail). The consult review concluded that Licart topical system is not irritating or sensitizing and the drug's potential for phototoxicity or photoallergenicity could not be determined because of the deviations in study design and conduct from typical studies of this kind. The recommendation was that "if the sponsor adequately assessed the local safety of the active diclofenac containing topical systems 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".

Review of labeling

Labeling review is summarized in Table 1 below in terms of the reviewer's recommended labeling revision corresponding to the labeling statements proposed by the Applicant and rationale for the changes.

Table 1 Review of labeling

Labeling Section	Applicant's proposal	Reviewer's recommendation	Rationale for change
6.1 Clinical Trials Experience	(b) (4)	A total of 874 subjects had exposure to one or more doses of Licart in eleven clinical studies conducted during the premarketing development of LICART. About 500 subjects were treated with LICART in six controlled multiple-dose trials. About 400 of them were exposed to 24-hour once a day application, for up to one week in 288 subjects and up to two weeks in 121 subjects.	Provide detailed exposure data in terms of total exposure, especially exposure in controlled multiple-dose studies and exposure to once a day application and the duration of such exposure
6.2 Postmarketing Experience	None	Case descriptions suggesting dermal allergic reactions and photoallergic reactions have been reported (b) (4) through foreign post marketing surveillance.	Based on review of safety update as above. (Flector labeling has the statements about foreign labeling for Flector topical system mentioned (b) (4) that dermal allergic reactions may occur with FLECTOR).
14.1 Clinical Studies	(b) (4)	Efficacy of LICART was demonstrated in two randomized, double-blind, parallel-arm, placebo- and active-controlled studies in patients with minor sprains, strains, and/or contusions. Patients were randomized equally to receive LICART topical system, a placebo topical system, or FLECTOR topical system and treatment was applied once daily (24 hours) for 7 or 14 days. One study enrolled adult patients aged 18-65 years with ankle sprain who had pain at a mean baseline pain intensity of at least 78 on 0-100 VAS scale. The second study enrolled adult patients aged 18-75 years with muscle contusion of the limb who had pain at a mean baseline pain intensity of at least 66 on 0-100 VAS scale. The primary efficacy endpoint was the mean change from baseline in pain on movement to Day 3 of treatment, where pain on movement was assessed twice daily (morning and evening) for 7 days in the study of ankle sprain and14 days in the study of muscle contusion. In both studies, LICART demonstrated a statistically significant difference versus placebo for the reduction in pain on movement at Day 3. (Remove the figures)	Refer to the Clinical Review Section 5.2 for major deficiencies identified in study design, conduct, and results for Study S-8 (the 2-arm study #18-12-98). The results described by the Applicant suggest comparative claim based on studies on half of the recommended Flector daily dosage for both Licart and Flector topical system s. Any comparative claim between the two active treatments needs to be supported by replicable data. The revised descriptions of clinical trials and result have a focus on baseline pain intensity, primary efficacy endpoints, frequency of pain measurements, and results in comparison to the placebo treatment.

Section 6.1 Clinical Trials Experience

As shown in the table below, 874 subjects were exposed to any dose of Licart in 11 clinical studies. Excluding about 300 subjects from the two dermatological safety studies 573 subjects in the other nine PK, PD, and efficacy studies were included in the common AE table in the labeling. A total of 496 subjects were treated with LICART in the six controlled multiple-dose trials, 409 of them had once a day application for 24 hours. Of the 409 subjects 288 were exposed for up to one week and 121 for up to two weeks. In comparison to the Applicant's descriptions of the number of patients exposed in the four efficacy trials the reviewer's proposed labeling revision has emphases on total exposure, multiple-dose exposure in controlled studies, experience to once a day 24-hour application, and duration of exposure to once a day application.

Table 2 Exposure per Study and Overall Exposure

Study	Protocol number	Licart	Flector	Heparin	Placebo	Total	Dosage
(S-1)	CRO-PK-98-13	22	22	-	-	22	Bid x 7.5 days
(S-2)	CRO-PK-02-92	12	-	-	-	12	Bid x 5.5 days
(S-3)	CRO-PK-12-272	38	-	-	-	38	Single dose in 14 subjects 24-hour qD x 4 doses in 24 subjects
(S-4)	EU01.2002	50	-	-	-	50	M/W/F dosing x3 weeks, then qD x 2 days
(S-5)	13FCDN-FHp03	248	-	-	-	248	24-hour qD x 21 days, then one 48-hour dosing
(S-6)	05I/FHp06	30	30	-	30	30	Single dose for one hour
(S-7)	07I/FHp04	26	26	26	26	104	24-hour qD x 7 days
(S-8)	18-12-98	120	-	-	119	239	24-hour qD x 7 days
(S-9)	99CH/FHp02	65	61	-	59	185	12-hour dosing daily x 10 days
(S-10)	05DCz/FHp11	121	115	-	119	355	24-hour qD x 14 days
(S-11)	06EUFHp03	142	145	-	142		24-hour qD x 7 days
Total		874	399	26	495	1712	

Source: Table 5.3.5.3.2 on page 25 of ISSE report.

Section 6.2 Postmarketing Experience

Skin reactions consistent with dermal allergic reactions were described in several cases and consistent with photoallergic reactions were reported in one case through foreign post marketing surveillance. The reporting rates of these skin reactions were extremely low, i.e., less than 10 cases per (b) (4) patient exposure (refer to safety review above).

Section 14.1 Clinical Studies

One of the three efficacy studies mentioned in the Applicant's description of clinical studies, protocol #18-12-98, had major deficiencies identified in study design (primary endpoint of not being a pain variable) and conduct (significant difference between the treatment groups in baseline pain intensity). The results showed similar proportions taking rescue in the two treatment groups, Licart versus placebo, at Day 1 and during the 7-day treatment period and 5-6% more patients in the Licart group used rescue than placebo at Day 2 and Day 3, suggesting a failed study.

Efficacy data from studies of Licart in NDA 206976 and studies of Flector in NDA 21234 are briefly summarized in the table below. Intra study comparison of Licart and Flector topical systems containing the same amount of diclofenac and applied once a day for about 24 hours showed that the effect size of Licart is about twice of that of Flector in the two studies under NDA 206976. Although the study of once daily application showed better effect sizes of treatment differences than the study of twice daily application in NDA 21234, the recommended dosage is twice daily application based on the approved labeling.

Any comparative claim between the two active treatments needs to be supported by replicable data.

The revised descriptions of clinical trials and their results try to emphasize on baseline pain intensity, primary efficacy endpoints, frequency of pain measurements, and results in terms of comparison to the placebo treatment.

Table 3 Summary of Efficacy Based on Data in the Original Submission of NDA 206976 and NDA 21234

	NDA 206976				NDA 21234	
Study	06EU/FHp03		05DCz/FHp11		05-05-98	00GB/Fp05
	One 24H application once daily for 7 days		One 24H application once daily for 14 days		One application/day for 7 days	One 12H application 2x/day for 14-days
Country	Italy, Ukraine, & Poland		Czech Republic & Germany		France	Germany & U.K.
Pain condition	Ankle sprain		Muscle contusion		Ankle sprain	Soft tissue injury (sprains, strains and contusions)
PI eligibility	≥50 mm VAS		≥50 mm VAS		≥50 mm VAS	≥5 on 0-10 scale
Primary endpoint	PID at Day 3		PID at Day 3		Time-specific PID	Time to pain resolution
Baseline PI	71-73 mm		67-68 mm		67-70 mm	7.3-7.5 (0-10 scale)
Treatment comparison to placebo						
PID by VAS	**Licart**	**Flector**	**Licart**	**Flector**	**Flector**	**Flector**
PID (POM) Patient diary	7-11mm over 3D 7-11mm over 7D	4.4-5.7 mm over 3D 4.4-5.8 mm over 7D	8-14 mm over 3D 8-16 mm over 14D	3-6 mm over 3D 3-8.5mm over 14D	<10 mm over 6H <12 mm over 3D (no time-specific scores after D3)	<0.7 (0-10 scale) over 14 days (i.e., <7 mm on 100 mm scale)
PID (POM) Clinic visit	10.7mm at Day 3 9.4 mm at Day 7	5.3 mm at Day 3 4.5 mm at Day 7	14 mm at Day 3 12 mm at Day 7 7 mm at Day 14	6.3 mm at Day 3 7.5 mm at Day 7 3.4 mm at Day 14	11 mm at Day 3 7 mm at Day 7	
Rescue allowed	Yes		Yes		Yes	No
% taking rescue	4% (73 vs 77% placebo)	0% (77 vs 77% placebo)	7% (10 vs 17% placebo)	2% (15 vs 17% placebo)	7% (19 vs 26% placebo)	5% (11 vs 16% placebo)

Conclusion

The updated safety data from foreign postmarketing experience did not change the benefit/risk ratio for recommendation of market approval of Licart topical system. Labeling Section 6 on Adverse Reactions and Section 14.1 on Clinical Studies need to be revised accordingly (refer to the recommended labeling statements summarized in Table 1 above).

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/

CHRISTINA L FANG
11/27/2018

JOSHUA M LLOYD
11/28/2018

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.

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

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 (b) (4) . The adhesive layer is applied to the

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

The review team identified the following deficiencies (as stated in the CMC review) in the application that preclude approval from the CMC perspective. (b) (4)

Drug Product

1. (b) (4)

(b) (4)

2. (b) (4)

(b) (4)

3. (b) (4)

(b) (4)

4. (b) (4)

(b) (4)

5. (b) (4)

(b) (4)

6. (b) (4)

(b) (4)

7. (b) (4)

(b) (4)

8. (b) (4)

9. (b) (4)

Process

1. (b) (4)

(b) (4)

2. (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 to (b) (4) is insufficient due to the following deficiencies

   a. (b) (4)

   b. (b) (4)

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)

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 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.

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) between 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 similar 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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOSHUA M LLOYD
03/23/2017

ELLEN W FIELDS
03/23/2017

CLINICAL REVIEW

Application Type	NDA
Submission Number	206-976
Priority or Standard	Standard
Submit Date(s)	March 4, 2015, May 26, and December 4, 2016
Received Date(s)	May 26, and December 5, 2016
PDUFA Goal Date	March 24, 2017
Division / Office	DAAAP/CDER/OND/ODE II
Reviewer Name	Christina Fang, M.D., M.P.H.
Established Name	Diclofenac Epolamine 1.3% (b) (4)
Trade Name	LICART (b) (4)
Therapeutic Class	External analgesic
Applicant	Institut Biochimique SA (IBSA)
Formulation	(b) (4) (182 mg diclofenac epolamine (b) (4))
Dosing Regimen	One (b) (4) to most painful area once a day (on intact skin)
Indication	Acute pain due to minor strains, sprains, and contusions
Intended Population	Patients in need of topical analgesics for acute pain

TABLE OF CONTENTS

TABLE OF TABLES

FIGURE

1. RECOMMENDATIONS/RISK BENEFIT ANALYSIS

1.1 Recommendation on Regulatory Action

Licart (b) (4) at the proposed use of once a day application has a favorable benefit/risk ratio as demonstrated by efficacy and safety findings in the current submission.

A complete response is recommended taking into consideration of uncertainty in drug's potential for phototoxicity and photoallergenicity and many other deficiencies identified by the CMC, non-clinical, and biopharmaceutical review teams.

1.2 Risk Benefit Analysis

The benefit of treatment with Licart (b) (4) (identified as Flector-H throughout the review) was shown as clinically meaningfully effect sizes of treatment differences in time-specific pain intensity difference (PID) and shorter time (one or a few days) to reach the same level of pain reduction in comparison to placebo patch and doubling of effect size of difference from placebo using the differences between Flector and placebo patch as a comparison, with effect sizes optimized from Day 3 to the end of study. It was shown also as less (6-8%) need for rescue in patients treated with Licart (b) (4) in comparison to placebo patch, especially during the first few days of treatment. These treatment effects were replicated in the second study of a similar design.

An acute analgesic onset has not been characterized because of lack of measurements of single-dose effects of the initial patch application. Data in the study that has hourly pain measurements during the first six hours were compromised due to treatment group imbalance in baseline pain intensity.

Licart (b) (4) was well tolerated as suggested by a very low total adverse event (AE) rate of 4% in close to 600 subjects exposed and very low rates of individual AEs of mostly <1% based on safety data pooled across nine of the 11 studies (the two dermatological safety studies were not included in the pooled data). The individual application site AEs were also mostly <1% based on safety data pooled across nine studies as well as pooled across four studies with exposure to daily application of 24-hour patch for 7-14 days in about 400 subjects.

The patch is not irritating or sensitizing based on the results of the two dermatological safety studies and its potentials for phototoxicity and photoallergenicity still need to be determined.

The benefit/risk ratio is favorable for short-term use of Licart (b) (4) once a day to relieve pain due to minor strains, sprains, and contusions.

1.3 Recommendations for Post marketing Risk Management Activities

None.

1.4 Recommendation for Other Post Marketing Study Commitments

Recommendations for post marketing study commitments will be provided at the next review cycle when all the deficiencies have been addressed by the Applicant at the NDA resubmission.

In terms of pediatric study requirements the product triggers PREA for the proposed new dosing regimen of once a day application. The Applicant has requested for a partial waiver of pediatric studies in patients less than six years of age and deferral in patients 6-17 years of age and their plans were accepted by the Review Division and PeRC. A revised iPSP incorporating the Division's comments and related pediatric protocol should be submitted through the IND for review.

2. INTRODUCTION AND REGULATORY BACKGROUND

2.1 Product Information

Licart (b) (4) containing diclofenac epolamine 1.3% and heparin is identical to Flector patch (refer to the NDA 21234 approved in 2007) except that heparin is added to the patch to enhance transdermal penetration of diclofenac to improve its bioavailability to local tissue (refer to the CMC review for detail). The proposed indication for Licart (b) (4) is the same as that for Flector patch, for the topical treatment of acute pain due to minor strains, sprains, and contusions. The proposed dosing regimen for Licart (b) (4) is once daily, which is different from twice a day dosing recommended for Flector patch.

2.2 Currently Available Treatment(s) for Proposed Indication(s)

Flector patch has the same indication as mentioned above. Other currently available treatments with similar indications include Salonpas patch (containing methyl salicylate 10% and menthol 3%) approved under NDA 22-029 and drug products containing active ingredients covered under External Analgesic Tentative Final Monograph such as methyl salicylate (10 to 60%), menthol (1.25 to 16%), camphor (exceeding 3 to 11%), and capsaicin (0.025 to 0.25%) in a variety of dosage forms.

2.3 Availability of Proposed Active Ingredient in the United States

The proposed active ingredient diclofenac is widely available in the United States in various dosage forms such as tablet, delayed-release tablet, extended-release tablet, capsule, solution, drops, gel, and patch as listed in the table below.

Table 1 Diclofenac Formulations

Active Ingredient	Proprietary Name	Appl No	Dosage Form
Diclofenac	Zorvolex	N204592	Capsule
Diclofenac Epolamine	Flector	N021234	Patch
Diclofenac Potassium	Zipsor	N022202	Capsule
Diclofenac Potassium	Cambia	N022165	For Solution
Diclofenac Potassium	Diclofenac Potassium	A075219	Tablet
Diclofenac Sodium	Solaraze	N021005	Gel
Diclofenac Sodium	Voltaren	N022122	Gel
Diclofenac Sodium	Dyloject	N022396	Solution
Diclofenac Sodium	Pennsaid	N020947	Solution
Diclofenac Sodium	Pennsaid	N204623	Solution
Diclofenac Sodium	Voltaren	N020037	Solution/Drops
Diclofenac Sodium	Diclofenac Sodium	A075185	Tablet, Delayed Release
Diclofenac Sodium	Diclofenac Sodium	A075492	Tablet, Extended Release

Source: Electronic Orange Book, 2017.

2.4 Important Issues with Consideration to Related Drugs

The main safety issues with related drugs are local irritation and hypersensitivity to the patch.

2.5 Summary of Presubmission Regulatory Activity Related to this Submission

The Sponsor had completed all the clinical studies in Europe before their initial contact with FDA in 2011. The Review Division advised the Sponsor at the pre-IND meeting, about the required information on single-dose

effects in terms of pain intensity reduction, pain relief, onset of action, and duration (proportion requesting rescue and time to rescue) of the initial patch application; submission of full protocols and synopsis of study results for preliminary comments at the pre-NDA meeting; conduct dermatological safety studies to determine drug's potential for cumulative irritation, contact sensitization, phototoxicity and photosensitization (refer to meeting minutes dated June 9, 2011 for detail). A follow-up request from the Review Division asked the Sponsor to conduct post-hoc analyses on time-specific PID based on pain data recorded in patients' daily diary, time to rescue after the initial patch and after each daily patch, and proportions of patients taking rescue, and provide pain graphs for efficacy studies (refer to the letter dated February 23, 2012). After receiving all the required information at the pre-NDA meeting the Review Division agreed that the proposed clinical data appeared sufficient to support filing of the NDA, taking into consideration of the frequent pain measurements available during the first six hours in Study 18-12-98 and similarities in study designs with efficacy studies of the NDA for Flector patch (refer to the meeting minutes dated December 13, 2012 for detail).

The original NDA was filed on March 4, 2015 and received refuse to file status with a long list of deficiencies related to inadequate Integrated Summary of Safety and inadequate safety dataset (refer to refuse to file letter dated April 29, 2015 for detail). The Sponsor was also requested to provide justifications as to how the results of the trials conducted entirely in Europe could apply to the US population. The Sponsor's justifications submitted on July 1, 2015 were considered acceptable to the Division (refer to the meeting minutes dated September 16, 2015).

2.6 Other Relevant Background Information

None.

3. ETHICS AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Integrity

Efficacy and safety data serving as bases for the review were available with acceptable quality.

3.2 Compliance with Good Clinical Practices

The plans to ensure compliance with Good Clinical Practices (GCP) included a long list of steps for study site monitoring and list of responsibilities of the Investigators and the Sponsor. All study documentation and results might be reviewed by the Quality Assurance Units of the Sponsor and/or Regulatory Authorities for quality assurance.

The findings from study site inspections by FDA are still pending.

3.3 Financial Disclosures

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).

4. SIGNIFICANT EFFICACY/SAFETY FINDINGS RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry Manufacturing and Controls

Refer to the CMC Review.

4.2 Clinical Microbiology (if applicable)

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

Refer to the Pharmacology/Toxicology Review by Dr. Armaghan Emami dated February 22, 2017.

4.4 Clinical Pharmacology

Refer to the Clinical Pharmacology Review by Dr. Srikanth Nallani dated February 17, 2017.

4.4.1 Mechanism of Action

4.4.2 Pharmacodynamics

4.4.3 Pharmacokinetics

5. SOURCES OF CLINICAL DATA AND REVIEW STRATEGY

5.1 Tables of Clinical Studies

Table 2 Overview of Clinical Studies

Type	Study#, site, date	Section	Design	Treatment	N	Population
PK Relative bioavailability	CRO-PK- 98-13 Arzo, Switzerland 11/16-20/1998	5.3.3.1.2 (S-1)	Single-center randomized Open-label 2-way crossover multiple-dose	Flector-H Flector *bid* x7d & one on day 8 (15 patches in 8 days)	20	Healthy Volunteers
PK Absorption of diclofenac & heparin	CRO-PK- 02-92 Arzo, Switzerland 2/2003 – 3/2003	5.3.3.1.1 (S-2)	Single-center Open-label multiple-dose	Flector-H 12-hour application *bid* x5d & one patch on day 6 (11 patches in 6 days)	12	Healthy Volunteers
PK Absorption under various conditions	CRO-PK- 12-272 Arzo, Switzerland 6/2013 – 9/2013	5.3.3.1.3 (S-3)	Part 1 Single-dose Open-label Part 2 randomized Open-label 4-way crossover multiple-dose	1. Flector-H one to R & one to L arm x24 hours (one for diclofenac & one for heparin level) 2. Flector-H once/day x4d under a. normal behavior b. moderate exercise c. under occlusion d. moderate heat exposure	24 14	Healthy Volunteers
Derm safety Tolerability repeat insult patch test	EU01.2002 L'Aquila, Italy 2/2003 – 4/2003	5.3.3.1.4 (S-4)	Randomized double-blind placebo-controlled	Flector-H and placebo applied simultaneously Once per day on M/W/F x3 weeks during induction;	50	Healthy Volunteers

irritation & sensitization				Once per day x2 days as challenge.		
Derm safety Tolerability irritation and sensitization	13FCDN/ FHp03 Montreal Canada 10/13 – 1/2014	5.3.3.1.5 (S-5)	Single-center Randomized single-blind vehicle- & active-controlled within-subjects comparison	Flector-H and controls applied simultaneously Once per day x21 days 14-day rest, one 48-hour application	248	Healthy Volunteers
PD	05I/FHp06 Chieti, Italy 11/2005 – 12/2005	5.3.4.1.1 (S-6)	Randomized double-blind vehicle- and active-controlled crossover	Flector-H Flector placebo	30 30 30	
PD	07I/FHp04 Chieti, Italy 1/2008 – 5/2009	5.3.4.1.2 (S-7)	Single-center Randomized double-blind Full factorial 4-arm parallel	Flector-H Flector Heparin plaster Placebo plaster Once daily x 7 days	26 26 26 26	Otherwise healthy subjects with a latent algogenic condition (subcutaneous and/or muscle hyperalgesia).
Efficacy	18-12-98 18 sites France 11/1999 – 6/2001	5.3.5.1.3 (S-8)	Multiple-center Randomized double-blind vehicle-controlled 2-arm parallel	Flector-H Placebo One plaster daily x 7 days	120 119	acute ankle sprain
Efficacy	99CH/FHp02 16 sites Switzerland, Italy, Hungary 12/1999 – 2/2002	5.3.5.4.1 (S-9)	Multiple-center Randomized double-blind vehicle- and active-controlled 3-arm parallel	Flector-H Flector Placebo One 12-hour plaster daily x 10 days	65 61 59	Acute soft tissue injury
Efficacy	05DCZ/ FHp11 20 sites Czech Republic, Germany 6/2006 – 5/2007	5.3.5.1.2 (S-10)	Multiple-center Randomized double-blind vehicle- and active-controlled 3-arm parallel	Flector-H Flector Placebo One plaster daily x 14 days	121 115 119	muscle contusion
Efficacy	06EU/FHp03 13 sites Italy, Ukraine, Poland 1/2007 – 6/2007	5.3.5.1.1 (S-11)	Multiple-center Randomized, double-blind, vehicle- and active-controlled 3-arm parallel	Flector-H Flector Placebo One plaster daily x 7 days	142 145 142	acute ankle sprain

Source: Table 5.3.5.3.2 on page 25 of ISSE.

5.2 Review Strategy

The two pharmacodynamics trials, Studies S-6 and S-7 were phase 1-2 studies of exploratory in nature and the findings could not be used to support efficacy, and thus, will not be reviewed here. There were four controlled efficacy studies under the proposed indication, Study S-8 (protocol # 18-12-98), Study S-9 (protocol # 99CH/FHp02), Study S-10 (protocol #05DCz/FHp11) and Study S-11 (protocol #06EU/FHp03). The proposed once-a-day application of 24-hour patch was studied in three studies S-8, S-10, and S-11.

Study S-9 will not be reviewed for efficacy because of 12-hour patch application per day and lack of pain parameter as a primary efficacy endpoint (complete disappearance of bruise was the only primary efficacy endpoint).

Study S-8 had primary endpoint as decrease in edema of injured ankle not an endpoint related to pain evaluation. It was briefly reviewed originally because it was the only study that had some more frequent pain measurements during the first six hours after the start of the initial patch application. A key deficiency was identified during the review that baseline pain intensity was significantly different between the treatment groups making the rest of analyses of pain data invalid. Plus, the results showed that proportions taking rescue were the same between the two treatment groups at Day 1 and during the 7-day treatment period and 5-6% more patients in the Flector-H groups used rescue than placebo at Day 2 and Day 3, suggesting a failed study. Therefore, Study S-8 will not be included in the detailed review of individual studies.

Study S-10 and Study S-11 had a number of design issues since the studies were completed in Europe before the Sponsor's initial contact with the FDA Review Division. There were no plans for characterization of the single-dose effects of the initial patch for determination of acute onset and dosing interval. Nevertheless, the data from these two studies will provide information on multiple-dose effects and will be reviewed in detail.

5.3 Discussion of Individual Studies

5.3.1 Study of Muscle Contusion (S-10, Protocol 05DCz/FHp11)

5.3.1.1 Protocol

Study S-10 (protocol 05DCz/FHp11) was planned as a multiple-center, randomized, double-blind, reference- and placebo-controlled, parallel, multiple-dose study of efficacy and tolerance of Flector-Heparin (Flector-H) patch in treating mild-to-moderate contusions to be conducted in Czech Republic and Germany. Flector patch at half of the recommended dosage (proposed daily 24-hour application versus approved 12-hour twice a day application) was to have been included as a reference control.

Eligible patients were to have been adults aged 18-65 years of Caucasian race having a unilateral mild-to-moderate muscle contusion of upper or lower limbs that happened within 72 hours before the study entry accompanied with a superficial hematoma of a maximal size of 10 x 14 cm localized at the affected site, with pain on standardized movement (most painful movement identified at inclusion) $\geq$ 50 mm on a 100-mm visual analogue scale (VAS), and without previous treatments. The muscle injury was to have been not requiring orthopedic, surgical, or physiotherapeutic treatments other than three times a day ice applications for not more than 20 minutes in duration over the first two days of treatment.

Eligible patients were to have been randomly assigned to one of the three treatments: Flector-H patch, Flector patch, and matching placebo patch of 10 x 14 cm in size to be applied directly to the injured site (secured in place by small adhesive tapes at the corners or along the margins of the patch or loose fitting elastic net) and receive the first application by the Investigator at the study site followed by home application of 24-hour patch (at least 20 consecutive hours) every morning (about the same time of the day) for 14 consecutive days. Ice applications on the affected area was to have been allowed with restricted use of not more than 20 minutes each time of up to three times a day during the first two days of treatment.

Efficacy data to be collected were to have included patients' recording in their daily diary pain intensity (PI) on the 100 mm VAS scale for pain on movement (the most painful movement identified at the inclusion visit) twice a day: in the morning before patch application and at about 12 hours later, presence and severity of hematoma using a 4-point categorical scale every morning before patch application, and amount (number of tablets) of rescue; Investigator's assessment of superficial hematoma extension by use of image tracing software; patient's and Investigator's global evaluation using a 5-point categorical scale (4 = excellent, 3 = good, 2 = fair, 1 = poor, and 0 = none).

Two planned primary efficacy endpoints involved comparisons of Flector-H to Flector in terms of reduction of pain on movement and in terms of time to reach a complete hematoma disappearance. The planned secondary efficacy endpoints included PID for pain on movement and time to reach a complete resolution of hematoma by comparing Flector-H to placebo and Flector to placebo, respectively; amount of rescue (mean daily dose and total dose); superficial hematoma extension recorded by the Investigator; global evaluation by patient and by the Investigator.

Safety monitoring was planned to include reports of local and systemic adverse events (AEs) with regard to frequency, nature, and severity, and patient's and Investigator's global evaluation of degree of tolerance using a 5-point categorical scale (4 = excellent, 3 = good, 2 = fair, 1 = poor, and 0 = none).

Protocol amendments

There were two protocol amendments. Amendment 1 involved change of one efficacy parameter, time to superficial hematoma disappearance from a primary endpoint to a secondary endpoint and addition of PID at Day 3 as part of primary analysis. Amendment 2 involved replacement of the study sites unable to recruit any patients.

The reviewer's brief summary of the major components of the final version of the protocol is presented in the table below.

Table 3 Reviewer's Summary of the Final Version of the Protocol

Study #	S-10, Protocol 05DCz/FHp11
Objectives	To study efficacy and tolerance of Flector-H patch in treating mild-to-moderate muscle contusions
Design	Multiple-center, randomized, double-blind, reference- (Flector patch) and placebo-controlled, parallel, multiple-dose
Sample population	• Adults aged 18-65 years of Caucasian race • Having unilateral mild-to-moderate muscle contusion of limbs within 72 hours before inclusion • With pain on most painful movement ≥ 50 mm on 100-mm VAS scale • With superficial hematoma of a maximal size of 10 x 14 cm at affected site • Muscle injury not requiring orthopedic, surgical, or physiotherapeutic treatments other than the use of ice (≤20 minutes for up to 3x/day during the first two days of treatment)
Treatment	One of the three: Flector-H, Flector, or placebo patch (10 x 14 cm) One patch every morning attached to the skin for ≥20 consecutive hours x14 days, with patch secured by small adhesive tapes or loose elastic net if needed
Rescue	Paracetamol 500 mg up to 4 gm per day
Efficacy data	Patient daily diary • PI (100 mm VAS) 2x a day for pain on movement (most painful movement identified at inclusion) • Presence and severity of hematoma using a 4-point categorical scale every morning • Amount of rescue to be recorded as number of tablets Clinic visits • Superficial hematoma extension by use of image tracing software • Global evaluation (5-point scale) by patients and Investigator
Efficacy parameter	Primary efficacy endpoint • PID for pain on movement at Day 3, Flector-H compared to Flector Secondary efficacy endpoints • PID for pain on movement at Day 3, Flector-H vs placebo and Flector vs placebo • Time to reach complete disappearance of hematoma based on patient diary • Changes from baseline in superficial hematoma extension by Investigator • Amount of rescue (mean daily dose and total dose) • Patient and Investigator's Global Evaluation
Safety monitoring	• Local and systemic AEs (frequency, nature, and severity) during study • Patient and Investigator's Global Evaluation of degree of tolerance at Day3 and Day 7

Reviewer's comments about the study design

- PID at Day 3 has not been commonly recognized as a primary efficacy endpoint for evaluation of acute analgesic effects.
- Important efficacy data to support for an acute analgesic indication such as frequent pain measurements during the first 24-hours and single-dose onset and duration were missing from the study.
- The reference control Flector patch planned to be dosed once a day is not considered an active control because it was used at half of the recommended dosage.
- Comparison of Flector-H to placebo should probably be the focus of primary analysis.
- Time should be recorded in the patient diary for taking all the rescue doses to get the data for time to rescue.
- Patients should have been allowed to stop patch application if they are no longer in need of pain medication.
- Local skin reactions to the patch should be measured by standardized scales to have a systematic assessment of symptom severity.

5.3.1.2 Results

Demographic and other baseline characteristics

The study sample population for efficacy analyses (ITT) consisted of 354 patients basically of nonelderly adult Caucasian patients (mean age of 39 years, age range of 18-75 years, and 100% Caucasian), about 36% of which were females.

The three treatment groups were approximately balanced with regard to demographic and baseline characteristics such as age, sex, race, weight, height, BMI, and pain intensity (PI) for pain on movement. Mean baseline PI was around high 60s for pain on movement on the 100-point scale.

Table 4 Demographics and Baseline Characteristics, ITT Population

Study S-10 (05DCz/FHp11) Demographics & Baseline Characteristics	Flector-H (N=121)	Flector (N=115)	Placebo (N=118)	Total (N=354)	p-value
Age (years)					>0.1
Mean (SD)	38.6 (15.3)	40.4 (13.6)	37.6 (13.8)	38.8	
Median	37.0	41.0	36.5		
Min-Max	18 - 75	18 - 66	18 - 65		
Sex, N (%)					>0.5
Male	75 (62.0%)	76 (66.1%)	77 (65.3%)	228 (64.4%)	
Female	46 (38.0%)	39 (33.9%)	41 (34.7%)	126 (35.6%)	
Race, N (%)					
Caucasian	121 (100%)	115 (100%)	118 (100%)	354 (100%)	
Weight (kg)					>0.5
Mean (SD)	76.6 (15.1)	77.0 (14.0)	78.3 (16.6)		
Median	75.0	78.0	78.0		
Min-Max	47.0 - 140.0	40.0 - 110.0	49.0 - 140.0		
Height (cm)					>0.5
Mean (SD)	174.3 (8.69)	174.4 (8.29)	174.5 (9.17)		
Median	175.0	175.0	175.0		
Min-Max	156.0 - 194.0	150.0 - 195.0	150.0 - 196.0		
BMI (kg/m^2)					>0.5
Mean (SD)	25.1 (4.01)	25.2 (3.43)	25.6 (4.48)		
Median	24.6	24.9	25.1		
Min-Max	15.9 - 38.8	16.9 - 38.6	18.8 - 41.8		
Baseline pain on movement by VAS					>0.1

Mean (SD)	67.7 (11.3)	66.8 (10.8)	68.4 (11.8)		
Median	65.0	66.0	65.0		
Min-Max	34.0 - 99.0	35.0 - 95.0	47.0 - 100.0		

Source: Table T5 on page 65 and Table T7 on p69 of the study report and clarification Table 1a on page 22 of the response to information request in the submission dated December 5, 2016.

Study sites

The study was conducted at 20 European sites, 10 sites in Germany (132 patients, 37% of study sample) and 10 sites in Czech Republic sites (223 patients, 63% of study sample). The distribution of patients per site per country is listed in the table below.

Table 5 Distribution of Patients by Study Sites

Number of patients per site	65	43	36	30	27	26	23	19	16	15	10	5	2
Number of sites													
Germany		1			1		1		1		1	1	4
Czech Republic	1		1	1		1		1		2	1	1	1

Source: Table 5.3.5.3.1.1 on pages 21-22 of the ISSE report.

Patient disposition

Most patients (93%) completed the study. Of the 24 dropouts 10 were due to symptom improvement (four patients in the Flector-H group, three in the Flector group, and three placebo patients), five due to adverse events (three in the Flector group and two in the placebo group), four due to withdrawn consent, one due to lack of efficacy, one due to lost medication, one due to incorrect dose, and two with reasons unspecified.

Table 6 Patient Disposition, Safety Population

Study S-10 (05DCz/FHp11) Patient Disposition, N (%)	**Flector-H (N=121)**	**Flector (N=115)**	**Placebo (N=119)**	**Total (N=355)**
Completed study per protocol	116 (95.9%)	107 (93.0%)	108 (90.8%)	331 (93.2%)
Prematurely discontinued	5 (4.1%)	8 (7.0%)	11 (9.6%)	24 (6.8%)
Reasons for withdrawal from study				
Symptom improvement	4	3	3	10
Adverse events	0	3	2	5
Withdrawn consent	-	1	3	4
Lack of efficacy	-	1	-	1
Lost medication	-	-	1	1
Incorrect dose	-	-	1	1
Unspecified	1	-	1	2

Source: Table T2 on page 58 of the study report and clarification Table 2 on pages 23-24 of the response to information request in the submission dated December 5, 2016.

Protocol deviations

About 40% of the study population had protocol deviations. The proportions were similar between the Flector and placebo group, 42% and 43%, respectively, and lower in the Flector-H group, 35%. The most frequently reported protocol deviation was missing dose shown as 50 counts of missing one patch application and 19 counts of missing two or more patch applications with counts not very different between the treatment groups. The other more frequently reported protocol deviations included deviations from minor eligibility criteria (59 counts), missing scheduled pain measurement in daily diary (45 counts), dosing time error in patch application (35 counts), and clinic visit outside time window (11 counts). These deviations are not expected to have a major or differential impact on study outcomes because of relatively small numbers of protocol deviation in specific categories and lack of dramatic differences between the treatment groups.

Table 7 Summary of Protocol Deviations/Violations, Safety Population

Study S-10 (05DCz/FHp11) Protocol deviations/violations	Flector-H (N=121)	Flector (N=115)	Placebo (N=119)	Total (N=355)
#Patients with ≥ 1 Deviation/Violation, N (%)	42 (34.7%)	48 (41.7%)	51 (42.9%)	141 (39.7%)
Counts of Specific Deviation/Violation				
Major eligibility criteria	3	2	0	5
Minor eligibility criteria	26	18	15	59
Missing one patch application	13	19	18	50
Missing two or more patch applications	3	9	7	19
Dosing time error in patch application[2]	9	13	13	35
Missing scheduled pain measurement in daily diary	11	14	20	45
Taking excluded medication	0	0	1	1
Other – clinic visit outside time window	3	5	3	11
Total Counts	68	80	77	225

Source: Table T3.1 on page 59 and Table T3.2 on page 60 of the study report and clarification Table 3 on pages 24-25 of the response to information request in the submission dated December 5, 2016.

Exposure

The exposure information is summarized in the table below in terms of exact number of doses exposed and cumulative exposure. At least three quarters of patients had exactly 15 doses and more than 90% had at least 14 doses. The distribution in terms of the number of doses exposed was similar between the treatment groups.

Table 8 Number of Doses Exposed

Study S-10 (05DCz/FHp11) Exposure	Flector-H (N=121)	Flector (N=115)	Placebo (N=119)
#Doses, n (%)			
1 Dose	0	0	4 (3%)
2 Doses	0	1 (1%)	0
5 Doses	0	1 (1%)	0
6 Doses	2 (2%)	0	1 (1%)
7 Doses	0	2 (2%)	0
9 Doses	0	1 (1%)	1 (1%)
10 Doses	0	2 (2%)	1 (1%)
11 Dose	1 (1%)	1 (1%)	1 (1%)
12 Doses	0	1 (1%)	0
13 Doses	1 (1%)	1 (1%)	3 (3%)
14 Doses	14 (12%)	19 (17%)	18 (15%)
15 Doses	103 (85%)	86 (75%)	90 (76%)
Cumulative			
≥ 2 Doses	121 (100%)	115 (100%)	115 (97%)
≥ 3 Doses	121 (100%)	114 (99%)	115 (97%)
≥ 6 Doses	121 (100%)	113 (98%)	115 (97%)
≥ 7 Doses	119 (98%)	113 (98%)	114 (96%)
≥ 8 Doses	119 (98%)	111 (97%)	114 (96%)
≥ 10 Doses	119 (98%)	110 (96%)	113 (95%)
≥ 11 Dose	119 (98%)	108 (94%)	112 (94%)
≥ 12 Doses	118 (98%)	107 (93%)	111 (93%)
≥ 13 Doses	118 (98%)	106 (92%)	111 (93%)
≥ 14 Doses	117 (97%)	105 (91%)	108 (91%)
≥ 15 Doses	103 (85%)	86 (75%)	90 (76%)

Source: Table 4 on pages 25-26 of the response to information request in the submission dated December 5, 2016.

Efficacy results

Primary efficacy endpoint: reduction of pain on movement from baseline at Day 3

As shown in the table below pairwise treatment comparison revealed statistically significant treatment difference between Flector-H and Flector. Treatment differences were also statistically significant between Flector-H and placebo and between Flector and placebo (Note: these were secondary endpoints based on the protocol). Effect sizes of treatment differences were 7.6 for Flector-H versus Flector, 13.9 for Flector-H versus placebo, and 6.3 for Flector versus placebo. Effect size of treatment difference for Flector-H versus placebo doubled in comparison with Flector (once daily application) versus placebo.

Table 9 PID Reduction of Pain on Movement, Day 3 Compared to Baseline

Study S-10 (05DCz/FHp11) Primary efficacy endpoint	**Flector-H (N=121)**	**Flector (N=115)**	**Placebo (N=118)**
N	119	115	116
Adjusted Mean reduction in PI for pain on movement	-19.1	-11.4	-5.2
Difference from **Placebo**	-13.9	-6.25	
95% CI	(-17.6, -10.1)	(-10.1, -2.44)	
P-value	<0.001	0.001	
Difference between Flector-H and Flector treatments	-7.62		
95% CI	(-11.4, -3.84)		
P-value	<0.001		

Source: Table 12.1.1 on page 101 of the study report.

Secondary and other efficacy endpoints

Time-specific PI for pain on movement

Mean time-specific PI scores are summarized in the table below. Baseline PI was balanced between the treatment groups. PI reduction of >50% started to show around Day 6 in the Flector-H group, Day 8 in the Flector group, and Day 10 in the placebo group, about two days earlier comparing Flector-H to Flector and then Flector to placebo as shown in the table below.

Table 10 Summary of Time-Specific PI for Pain on Movement

Study S-10 (05DCz/FHp11)		Predose	Day 2		Day 3		Day 4		Day 5		Day 6		Day 7		Day 8	
			H0	H12	H0	H12	H0	H12	H0	H12	H0	H12	H0	H12	H0	H12
Flector-H (N=142)	**N**	121	119	119	118	117	118	119	118	119	119	119	118	119	119	119
	Mean	**67.7**	61.7	56.4	50.8	47.8	44.3	41.7	38.9	36.0	33.0	32.2	29.5	28.0	26.3	24.1
	SD	11.3	19.5	21.2	23.0	21.1	21.6	20.9	20.5	19.5	19.5	18.9	18.6	18.1	18.0	17.1
Flector (N=142)	**N**	115	114	113	114	114	114	114	114	114	114	114	112	112	112	113
	Mean	**66.8**	65.1	62.1	58.4	55.0	51.6	49.7	46.2	44.5	41.1	39.8	37.1	36.2	32.1	31.5
	SD	10.9	16.3	17.5	17.5	17.6	19.3	19.2	19.8	19.9	19.7	19.7	19.4	20.0	20.0	20.6
Placebo (n=140)	**N**	119	116	114	114	115	115	115	113	115	115	115	114	114	113	112
	Mean	**68.5**	69.8	66.1	65.6	61.6	58.0	54.8	51.3	49.5	48.1	46.4	44.7	44.0	41.8	39.5
	SD	11.8	13.6	16.0	16.7	16.4	18.7	17.7	20.1	19.6	20.1	19.4	20.8	20.5	20.5	21.0

Table 10 Summary of Time-Specific PI for Pain on Movement (cont.)

Study S-10 (05DCz/FHp11)		Day 9		Day 10		Day 11		Day 12		Day 13		Day 14		Day 15	
		H0	**H12**	**H0**	**H12**	**H0**	**H12**	**H0**	**H12**	**H0**	**H12**	**H0**	**H12**	**H0**	**H12**
Flector-H (N=142)	**N**	118	119	119	118	119	119	115	118	117	116	117	117	109	85
	Mean	21.5	21.1	18.3	17.5	15.5	15.6	14.1	13.7	12.1	12.0	10.4	10.6	9.1	7.1
	SD	16.1	17.1	15.9	16.3	15.0	15.4	14.4	15.0	14.4	14.6	13.4	14.5	12.7	11.9
Flector (N=142)	**N**	113	112	113	112	112	110	109	110	109	108	106	109	105	84
	Mean	28.7	27.8	24.9	24.6	22.1	21.3	19.2	18.3	16.2	17.1	14.1	14.3	12.7	10.3
	SD	20.0	20.5	20.0	19.3	19.2	19.1	17.7	18.2	16.6	18.2	15.7	16.3	15.1	13.8
Placebo (n=140)	**N**	114	112	113	114	113	114	112	114	114	114	111	112	106	81
	Mean	36.9	35.3	32.0	31.9	29.2	28.3	26.0	25.1	23.3	22.1	19.9	18.5	17.0	13.7
	SD	20.8	19.7	20.5	21.2	21.7	21.9	21.5	20.8	21.1	19.0	18.5	17.9	17.2	16.4

Source: Table 5.1 on pages 26-27 of the response to information request in the submission dated December 5, 2016.

Time-specific PID for pain on movement

Mean time-specific PID data are summarized in the table below. The effect size of treatment difference between Flector-H and placebo reached 7.8-9.4 (on 100 mm scale) on Day2 and 14.4 on Day 3. During the time interval of Days 3-13 the effect sizes of treatment differences were mostly in the range of 11-15 for Flector-H versus placebo, mostly in the range of 4-7 for Flector versus placebo, and mostly in the range of 6-9 for Flector-H versus Flector.

Table 11 Summary of Time-Specific PID for Pain on Movement

Study S-10 (05DCz/FHp11)		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7		Day 8	
		H0	H12	H0	H12	H0	H12	H0	H12	H0	H12	H0	H12	H0	H12
Flector-H (N=142)	N	119	119	118	117	118	119	118	119	119	119	118	119	119	119
	Mean	6.0	11.3	16.8	19.9	23.3	26.0	28.8	31.7	34.7	35.5	38.1	39.7	41.4	43.6
	SD	14.5	17.4	19.5	17.2	18.6	18.1	18.6	17.5	17.9	17.0	17.9	17.6	18.3	17.5
Flector (N=142)	N	114	113	114	114	114	114	114	114	114	114	112	112	112	113
	Mean	1.7	4.8	8.5	11.9	15.3	17.3	20.8	22.4	25.8	27.1	29.9	30.7	34.7	35.4
	SD	11.5	12.9	13.9	14.6	16.9	16.6	18.0	18.3	19.1	18.7	19.7	20.3	20.7	21.6
Placebo (n=140)	N	116	114	114	115	115	115	113	115	115	115	114	114	113	112
	Mean	-1.8	1.8	2.4	6.5	10.0	13.3	16.7	18.6	19.9	21.7	23.2	23.9	26.2	28.4
	SD	13.4	15.0	16.6	16.2	19.4	18.7	21.2	20.7	22.0	20.6	22.3	22.3	22.2	22.5
Comparison															
Flector-H vs Placebo	Diff in mean	7.8	***9.4***	***14.4***	***13.4***	***13.3***	***12.7***	***12.2***	***13.1***	***14.8***	***13.8***	***14.9***	***15.8***	***15.2***	***15.2***
Flector vs Placebo	Diff in mean	3.5	3.0	6.1	5.4	5.3	4.0	4.1	3.8	5.9	5.4	6.7	6.9	8.5	7.0
Flector-H vs Flector	Diff in mean	4.3	6.4	8.3	8.1	8.0	8.7	8.1	9.3	8.9	8.5	8.2	9.0	6.7	8.2

Table 11 Summary of Time-Specific PID for Pain on Movement (cont.)

Study S-10 (05DCz/FHp11)		Day 9		Day 10		Day 11		Day 12		Day 13		Day 14		Day 15	
		H0	H12	H0	H12	H0	H12	H0	H12	H0	H12	H0	H12	H0	H12
Flector-H (N=142)	N	118	119	119	118	119	119	115	118	117	116	117	117	109	85
	Mean	46.1	46.5	49.4	50.3	52.2	52.1	53.7	53.9	55.6	55.8	57.4	57.2	58.7	61.1
	SD	17.0	17.7	17.1	18.0	17.7	17.9	16.9	17.8	18.0	17.9	17.2	18.1	16.2	17.3
Flector (N=142)	N	113	112	113	112	112	110	109	110	109	108	106	109	105	84
	Mean	38.2	39.0	42.0	42.2	44.7	45.3	47.6	48.4	50.5	49.7	52.6	52.4	54.2	58.2
	SD	21.2	22.2	22.0	21.4	21.6	21.9	20.9	21.8	20.1	21.9	19.9	20.5	19.6	18.5
Placebo (n=140)	N	114	112	113	114	113	114	112	114	114	114	111	112	106	81
	Mean	31.0	32.8	35.9	36.0	38.8	39.6	42.0	42.8	44.7	45.8	48.3	49.4	50.8	54.6
	SD	22.2	21.5	22.5	22.7	23.4	23.6	23.9	22.9	23.0	21.4	21.6	21.1	20.5	21.0
Flector-H vs Placebo	Diff in mean	***15.1***	***13.8***	***13.5***	***14.3***	***13.3***	***12.5***	***11.7***	***11.1***	***10.9***	***10.0***	***9.1***	7.8	7.9	6.4
Flector vs Placebo	Diff in mean	7.2	6.2	6.1	6.2	5.9	5.7	5.6	5.6	5.9	4.0	4.3	3.0	3.4	3.5
Flector-H vs Flector	Diff in mean	7.9	7.6	7.4	8.0	7.5	6.8	6.1	5.5	5.0	6.0	4.8	4.8	4.5	2.9

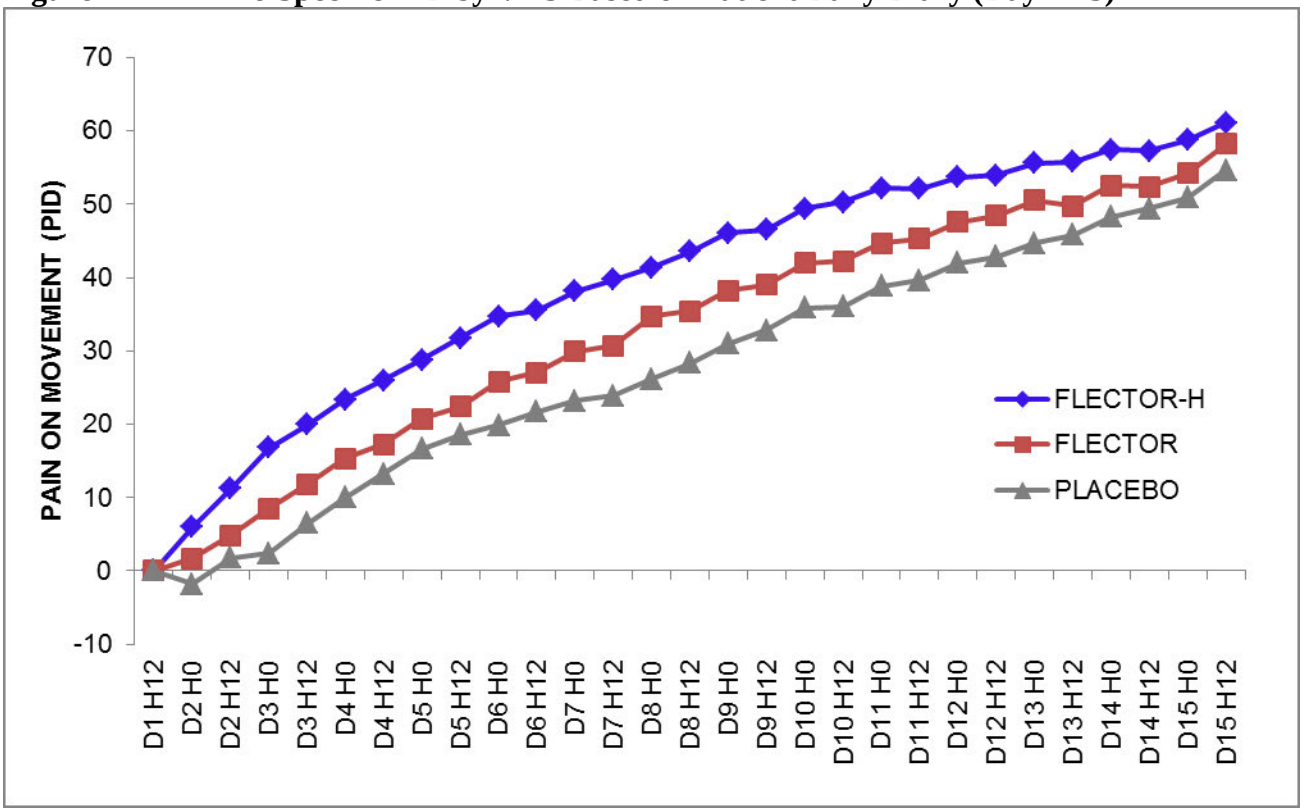
Source: Table 5.2 on pages 28-29 of the response to information request in the submission dated December 5, 2016.

As shown in the figure below, PID curves representing three treatments started to separate before Day 3 and reached the level of close to the maximum separation on Day 3 and continue to rise in a parallel fashion from Day 3 to Day 13. Effect sizes of treatment differences between Flector-H and placebo in comparison to Flector versus placebo, appeared more than doubled during Days 3-7 and approximately doubled during Days 8-13. There were no obvious curve fluctuations within each dosing interval.

Reviewer's comments

- Based on time-specific PID curves, treatment effect of Flector-H could be interpreted as shortened time interval of about four days to reach the same level of pain reduction in comparison to placebo and about two days to reach the same level of pain reduction in comparison to Flector from Days 3 to 13 (estimated by looking at intersections between a horizontal line and pain curves). Treatment effect of Flector-H could also be interpreted as approximate doubling of effect size of treatment difference from placebo in comparison to Flector versus placebo at a given time point during Days 3 and 13 (estimated by looking at intersections between a vertical line and pain curves).
- The lack of distinct peaks and troughs in each dosing interval where pain was measured at mid dosing interval and end of dosing interval could probably be explained by almost continuous attachment of patch to the skin and anticipated constant release of drug to local tissue. Therefore, the use of peak-trough as part of traditional way to measure durability of multiple-dose effects of orally administered analgesics would not apply in this case.
- The continuous rise in placebo response curve is probably due to high placebo response from the patch itself combined with spontaneous resolution of pain with time as part of natural recovery after acute injury.
- It would be very helpful if the onset and duration of single-patch could be characterized before the start of multiple-dose study to provide support for an acute onset and proposed dosing interval.

Figure 1 Time-Specific PID by VAS Based on Patient Daily Diary (Day 1-15)



Source: Figure 5.2 on page 30 of the response to information request in the submission dated December 5, 2016.

Rescue data

Rescue data are summarized in the table below, in terms of the number of rescue dose and proportion rescued on specific days and during the treatment period. Proportions of patients taking rescue were 8% in the Flector-H group, 11% in the Flector group, and 16% in the placebo group at Day 1. Treatment differences comparing Flector-H to placebo were small and mainly noticeable in terms of 0.8 less mean rescue doses during the 14-day period and 6-8% less patients taking rescue on Day 1, Day 2, and during the 14-day period, in the Flector-H group.

Reviewer's comments

- The proportions taking rescue are consistent with those reported from other studies of external analgesics.
- Time to rescue was not recorded in the study. Median time to rescue could not have been used to measure single-dose duration in this case anyway because of less than 50% of all the treatment groups taking rescue.

Table 12 Rescue Data and Other Secondary Endpoints

Study S-10 (05DCz/FHp11) Rescue data	Flector-H (N=121)	Flector (N=115)	Placebo (N=118)	Difference from placebo for	
				Flector-H	Flector-H
# of rescue doses on Day 1, mean	0.12	0.20	0.27	-0.08	-0.07
# of rescue doses on Day 2	0.10	0.15	0.24	-0.05	-0.10
# of rescue doses on Day 3	0.08	0.15	0.08	-0.07	0.06
# of rescue doses for Days 1-15	0.40	1.23	1.21	0.81	-0.02
Proportion rescued on Day 1, %	8%	11%	16%	-8%	-5%
Proportion rescued on Day 2	7%	9%	13%	-6%	-4%
Proportion rescued on Day 3	4%	8%	7%	-3%	1%
Proportion rescued for Days 1-15	10%	15%	17%	-7%	-2%

Source: Table 6 on pages 30-31 of the response to information request in the submission dated December 5, 2016.

5.3.1.3 Summary of Findings and Discussion

Study design

The study was designed with a primary focus on the comparison between Flector-H and Flector using the average pain reduction at Day 3 as the primary endpoint. The important components required for evaluation of analgesic effects for an acute indication such as frequent pain measurements during the initial 24 hours and single-dose onset and duration, were missing from the study.

Study conduct

The study was conducted in two European countries, Germany (37% patients) and Czech Republic (63% patients). The treatment groups were approximately balanced with regard to demographic characteristics such as age, sex, race, weight, height, BMI, and pain intensity (PI) at baseline. Mean baseline PI was 60+ for pain on movement. There was a low rate of dropouts of 7% mostly due to symptom improvement, adverse events, and withdrawal of consents. The reported protocol deviations involved 35% of Flector-H patients, 42% of Flector patients, and 43% of placebo patients, with the most frequently reported being missing one or more patch application, minor eligibility criteria deviation, missing scheduled pain measurements, and dosing time error. The deviations are not considered as having a major or differential impact on study outcomes.

Efficacy

Treatment difference between Flector-H and Flector in primary endpoint, PID at Day 3, was statistically significant. Effect size of treatment difference between Flector-H and placebo doubled in comparison to the difference between Flector and placebo. The maximum PID curve separation was maintained from Day 3 to Day 13. Time to >50% reduction in time-specific PI occurred around Day 6 for Flector-H, Day 8 for Flector, and Day 10 for placebo. Time to reach the same level of pain reduction was four days earlier for Flector-H and two days earlier for Flector when each was compared to placebo. There were no distinct peaks and troughs of pain curves in each dosing interval due to nearly continuous contact with the patch and anticipated steady release of diclofenac from the patch. Rescue data revealed small treatment differences between Flector-H and placebo mainly as 6-8% less patients using rescue on Day 1 and 2, and during the entire study.

5.3.1.4 Conclusion

Flector-H patch is effective in treating pain after several doses of patch applied once a day as shown in sizable treatment differences from placebo, doubling treatment effects in comparison to one half of the daily dose of Flector patch, and shorter time interval to achieve same level of pain reduction than the controls.

An acute onset has not been characterized in the study.

5.3.1.5 Appendix

Eligibility criteria (copied from the protocol)

Inclusion criteria

Patients must satisfy the following criteria in order to participate in the study:

1. Outpatients of both gender
2. Aged at least 18 and at most 65 years
3. Of Caucasian race
4. Having a unilateral mild-to-moderate muscle contusion of upper or lower limbs that happened within 72 hours before the study entry
5. Having a superficial hematoma of a maximal size of 10 x 14 cm, localized at the affected site
6. With pain on standardized movement of at least 50 mm on a 100-mm visual analogue scale (VAS)
7. Whose injury does not need an orthopedic or surgical treatment
8. Whose injury does not need physiotherapy other than 3 daily ice applications of not more than 20 minutes duration for the first two days of treatment, if applicable
9. Female subjects of childbearing potential (i.e., not status post hysterectomy or tubal ligation) must be using an appropriate method of contraception according to the definition of Note 3 of ICH M3 Guideline (implants, injectable, combined oral contraceptives, some IUDs, sexual abstinence or vasectomized partner) and must be willing to continue using it throughout the whole study period,
10. Female subjects of childbearing potential must have a negative urine pregnancy test at screening/inclusion visit
11. Subjects must be able to comprehend the full nature and purpose of the study, including possible risks and side effects, to co-operate with the Investigator, to comply with the requirements of the entire study and to return for the required examinations,
12. Subjects must sign a written informed consent to the participation prior to inclusion in the study

Exclusion criteria

Patients with the following characteristics will have to be excluded from study participation:

1. A major injury (fracture, tear of ligament/muscle/cartilage, nerve injury)
2. Open skin lesion within the injured area
3. History of three or more prior injuries (minor or major) to the actually injured region in the past
4. Injury occurred more than 72 hours prior to study entry
5. Injury is midline or involves the spine
6. Hematoma is bigger than the size of one Tissugel plaster (10 x 14 cm)
7. Hematoma has a maximum diameter smaller than 4 cm
8. Pain on movement <50 mm on a 100-mm Huskisson-type VAS
9. Prior use of topical medication to involved area within 24 hours of study entry
10. Prior use of OTC analgesic or NSAIDs (ibuprofen, ketoprofen) within 36 hours of study entry (acetaminophen permitted)
11. Prior use of narcotic analgesics within 7 days of study entry
12. Prior use of systemic anti-inflammatory steroidal drugs, by any route of administration, within 60 days of study entry
13. Prior use of long-acting NSAIDs such as piroxicam or naproxin since injury
14. Concomitant use of drugs which may be susceptible to interactions with diclofenac or which may affect safety if used concomitantly (lithium, digoxin, anticoagulants, antidiabetic agents, cyclosporine, methotrexate, quinolone antimicrobials, other NSAIDs, steroids and diuretics)
15. Known hypersensitivity to diclofenac or other NSAID drugs (including aspirin)
16. Prior history of GI bleeds/ulcers, liver/kidney disease
17. Patients with coagulation defects, • Patients with cardiac impairment
18. Pregnant women and women who are breast-feeding
19. Patients participating or having been involved in other clinical investigations during the three months preceding the entry of this study
20. Patients suffering from psychiatric diseases, not allowing the observance of the protocol, alcohol or drug abuse < 1 year
21. Patients not able to understand the purposes of the study
22. Patients refusing to give a written informed consent
23. Patients not reliable, according to the investigator's opinion

5.3.2 Study of Ankle Sprain (S-11, Protocol 06EU/FHp03)

5.3.2.1 Protocol

Study S-11 (protocol 06EU/FHp03) was planned as a multiple-center, randomized, double-blind, reference- and placebo-controlled, parallel, multiple-dose study of efficacy and tolerance of Flector-Heparin (Flector-H) patch in treating acute ankle sprains to be conducted in Poland, Ukraine, and Italy. Flector patch at half of the recommended dosage (proposed daily 24-hour application versus approved 12-hour twice a day application) was to have been included as a reference control.

Eligible patients were to have been adults aged 18-65 years having an acute ankle sprain involving lateral ligaments occurring within 48 hours before inclusion, accompanied with peri-malleolar edema and pain on movement (during daily activities) ≥ 50 mm on a 100-mm visual analogue scale (VAS), and with no previous treatments. Sprain was to have been grade I or II not requiring orthopedic, surgical, or physiotherapeutic treatments other than standardized ice/cold packs application.

Eligible patients were to have been randomly assigned to one of the three treatments: Flector-H patch, Flector patch, and matching placebo patch 10x14 cm in size to be applied directly to the injured site (secured in place by loose fitting elastic net) and receive the first application by the Investigator at the study site followed by home application of 24-hour patch (30-minute allowed for changing of patch) every morning for seven consecutive days.

Other than planned rescue medication, paracetamol 500 mg tablets up to 3 gm per day for insufficient pain relief, no other topical or systemic analgesic/anti-inflammatory treatments or alternative medicine (e.g., ultrasound, electrotherapy, ionization, acupuncture, homeopathy, mesotherapy, ice, and cold packs) were to have been allowed.

Efficacy data to be collected were to have included patients' recording in their daily diary pain intensity (PI) on the 100 mm VAS scale for pain on movement (normal daily activities), pain at rest, and pain while leaning on the injured lower limb twice a day: at about 8 am before patch application and 12 hours later and amount (number of tablets) of rescue; Investigator's assessment of edema extension by measuring submalleolar perimeter in comparison to the contralateral joint at three clinic visits (Days 1, 3, and 7); patient's and Investigator's global evaluation using a 5-point categorical scale (4 = excellent, 3 = good, 2 = fair, 1 = poor, and 0 = none) at visits 2 and 3.

The planned primary efficacy endpoint was change of pain intensity (PID) for pain on movement (normal daily activities) from baseline at Day 3 (using the average of two daily PI scores from Day 3) in comparison of Flector-H and Flector. The planned secondary efficacy endpoints included PID for pain on movement at Day 3 comparing Flector-H to placebo and Flector to placebo, respectively; daily average PI for pain on movement, pain at rest, and pain while leaning on the injured lower limb during the study; changes from baseline in edema extension at Day 3 and Day 7; amount of rescue (mean daily dose and total dose) at Day3 and Day 7; and global evaluation by patient and by the Investigator at Days 3 and 7.

Safety monitoring was planned to include reports of local and systemic adverse events (AEs) with regard to frequency, nature, and severity, and patient's and Investigator's global evaluation of degree of tolerance using a 5-point categorical scale (4 = excellent, 3 = good, 2 = fair, 1 = poor, and 0 = none).

Protocol amendments

There was one protocol amendment involving changing of one monitor for monitoring clinical site activities in Poland.

The reviewer's brief summary of the major components of the protocol is presented in the table below.

Table 13 Reviewer's Summary of the Protocol

Study #	S-11, Protocol 06EU/FHp03
Objectives	To study efficacy and safety of Flector-H patch in treating acute ankle sprains
Design	Multiple-center, randomized, double-blind, reference- (Flector patch) and placebo-controlled, parallel, multiple-dose
Sample population	• Adults aged 18-65 years • Having an acute ankle sprain involving lateral ligaments within 48 hours before inclusion, • With pain on movement (during daily activities) ≥ 50 mm on 100-mm VAS • With presence of peri-malleolar edema and without previous treatment • Sprain of grade I or II not requiring orthopedic, surgical, or physiotherapeutic treatments other than standardized ice/cold packs application.
Treatment	One of the three: Flector-H, Flector, or placebo patch (10 x 14 cm) One patch every morning x7 days with patch secured by loose fitting elastic net for 23.5 hours
Rescue	Paracetamol 500 mg up to 3 gm per day
Efficacy data	Patient daily diary • PI (100 mm VAS) 2x a day for pain on movement, at rest, and on leaning on injured limb • Amount of rescue to be recorded as number of tablets Clinic visits • Edema extension - submalleolar perimeter versus contralateral joint at Days 1, 3, and 7 • Global evaluation (5-point scale) by patients and Investigator at Days 3 and 7
Efficacy parameter	Primary efficacy endpoint • PID for pain on movement at Day 3 (average of 2 PI scores), Flector-H compared to Flector Secondary efficacy endpoints • PID for pain on movement at Day 3, Flector-H vs placebo and Flector vs placebo • Time-specific PI for pain on movement, pain at rest, and pain on leaning during study • Changes from baseline in edema extension at Day 3 and Day 7 • Amount of rescue (mean daily dose and total dose) at Day3 and Day 7 • Patient and Investigator's Global Evaluation at Day3 and Day 7
Safety monitoring	• Local and systemic AEs (frequency, nature, and severity) during study • Patient and Investigator's Global Evaluation of degree of tolerance at Day3 and Day 7

Reviewer's comments about the study design

- The study design and protocol detail in Study S-11 were very similar to those of Study S-10 (refer to the reviewer's comments about study design in the review of Study S-10). Evaluation of single-dose effects of the initial patch, especially the onset of pain relief was still not included.

5.3.2.2 Results

Demographic and other baseline characteristics

The study sample population for efficacy analyses (ITT) consisted of 424 patients basically of nonelderly adult Caucasian patients (mean age of 35 years, age range of 18-65 years, and 98.6% Caucasian), about 40% of which were females.

The three treatment groups were approximately balanced with regard to demographic and baseline characteristics such as age, sex, race, weight, height, BMI, and pain intensity (PI) for pain on movement, pain at rest, and pain while leaning on injured limb. Mean baseline PI by 100-point scale was around low 70s for pain on movement, mid 40s for pain at rest, and around high 70s for pain while leaning on injured limb.

Table 14 Demographics and Baseline Characteristics, ITT Population

Study S-11 (06EU/FHp03) Demographics & Baseline Characteristics	Flector-H (N=142)	Flector (N=142)	Placebo (N=140)	Total (N=424)	p-value
Age (years)					>0.5
Mean (SD)	35.2 (12.5)	35.2 (13.2)	34.8 (12.9)	35.1 (12.9)	
Median	33	32	32	32.5	
Min-Max	18 - 65	18 - 64	18 - 63	18-65	
Sex, N (%)					>0.5
Male	81 (57.0%)	85 (59.9%)	83 (59.3%)	249 (58.7%)	
Female	61 (43.0%)	57 (40.1%)	57 (40.7%)	175 (41.3%)	
Race, N (%)					>0.1
Caucasian	141 (99.3%)	139 (97.9%)	138 (98.6%)	418 (98.6%)	
African American	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (0.2%)	
Asian	1 (0.7%)	1 (0.7%)	0 (0.0%)	2 (0.5%)	
Other (specify)	0 (0.0%)	1 (0.7%)	2 (1.4%)	3 (0.7%)	
Weight (kg)					>0.1
Mean (SD)	74.8 (13.6)	76.4 (14.3)	75.6 (15.5)	75.6 (14.5)	
Median	73.5	75	75	74.5	
Min-Max	48.0-110.0	45.0-118.0	42.0-119.0	42.0-119.0	
Height (cm)					>0.1
Mean (SD)	172.2 (9.55)	173.3 (8.27)	173.1 (9.16)	172.9 (9.00)	
Median	173	174	173	173	
Min-Max	154.0-198.0	146.0-193.0	152.0-195.0	146.0-198.0	
BMI (kg/m^2)					>0.5
Mean (SD)	25.2 (3.81)	25.4 (4.16)	25.2 (4.79)	25.3 (4.26)	
Median	24.6	24.8	24.2	24.7	
Min-Max	17.6- 33.8	16.7- 39.3	16.6- 40.4	16.6-40.4	
Baseline pain on movement by VAS					>0.1
Mean (SD)	72.2 (12.0)	72.7 (12.4)	71.4 (11.9)	72.1 (12.1)	
Median	73	72	72	72	
Min-Max	46.0- 96.0	46.0- 99.0	45.0-100.0	45.0-100.0	
Baseline pain at rest by VAS					>0.1
Mean (SD)	48.1 (20.0)	44.8 (20.7)	46.0 (21.9)	46.3 (20.9)	
Median	51	46.5	51	50	
Min-Max	1.0- 80.0	0.0- 80.0	0.0- 87.0	0.0-87.0	
Baseline pain while leaning on injured limb					>0.5
Mean (SD)	79.5 (19.4)	79.1 (18.3)	78.0 (19.1)	78.9 (18.9)	
Median	84	84	81.5	83	
Min-Max	13.0-100.0	21.0-100.0	14.0-100.0	13.0-100.0	

Source: Table T7 on pages 67-68 and Table T15 on pages 83 of the study report and clarification Table 1a on pages 6-7 of the response to information request in the submission dated December 5, 2016.

Study sites

The study was conducted at 13 sites in three European countries. The distribution of patients per site per country is listed in the table below. Most patients were recruited in the two East European countries (92%), Poland and Ukraine (46% from each country).

Table 15 Distribution of Patients by Study Sites

Number of patients per site	90	60	57	42	36	32	22	18	13	10	1
Number of sites											
Poland	1		1			1		1			
Ukraine		1		1	2		1				1

Italy									2	1	

Source: Table 5.3.5.3.1.1 on pages 23-24 of the ISSE report.

Patient disposition

Almost all, except three patients, completed the study. Three dropouts, one on Flector and two on placebo, were all due to lost to follow-up.

Table 16 Patient Disposition, Safety Population

Study S-11 (06EU/FHp03) Patient Disposition, N (%)	**Flector-H (N=142)**	**Flector (N=145)**	**Placebo (N=142)**	**Total (N=429)**
Completed study per protocol	142	144	140	426
Prematurely discontinued	0	1 (0.7%)	2 (1.4%)	3 (0.7%)
Reasons for withdrawal from study				
Lost to follow-up	-	1	2	3

Source: Table T2 on page 60 of the study report and clarification Table 2 on page 8 of the response to information request in the submission dated December 5, 2016.

Protocol deviations

About 34% of the study population had protocol deviations. The proportions were similar between the Flector-H and placebo group, 39% and 37%, respectively, and lower in the Flector group, 27%. The most frequently reported protocol deviation was missing dose shown as 58 counts of missing one patch application and 8 counts of missing two or more patch applications with counts not very different between the treatment groups. The other more frequently reported protocol deviations included incorrect assignment of treatment number (33 counts), dosing time missing (25 counts), dosing time error in patch application (22 counts), and missing or miss-timed scheduled pain measurement in daily diary (18 counts each). These deviations are not expected to have a major or differential impact on study outcomes because of relatively small numbers of protocol deviation in specific categories and lack of dramatic differences between the treatment groups.

Table 17 Summary of Protocol Deviations/Violations, Safety Population

Study S-11 (06EU/FHp03) Protocol deviations/violations	**Flector-H (N=142)**	**Flector (N=145)**	**Placebo (N=142)**	**Total (N=429)**
No. of Patients with ≥ 1 Deviation/Violation, N (%)	55 (38.7%)	39 (26.9%)	52 (36.6%)	146 (34.0%)
Counts of Specific Deviation/Violation				
Eligibility criteria	1	2	4	7
Daily diary missing	0	2	2	4
Missing one patch application	22	16	20	58
Missing two or more patch applications	2	3	3	8
Dosing time missing in patch application	13	6	6	25
Dosing time error in patch application	10	4	8	22
Missing scheduled pain measurement in daily diary	9	4	5	18
Miss-timed pain measurement based on daily diary	11	4	3	18
Dosing error in taking rescue	0	1	0	1
Missing rescue data (rescue taken but not recorded)	0	1	0	1
Taking excluded medication	0	0	0	0
Using excluded treatment device	0	0	0	0
Other – incorrect assignment of treatment number	12	7	14	33
Total Counts	80	50	65	195

Source: Table T3 on page 61 and Table T4 on page 62 of the study report and clarification Table 3 on pages 8-9 of the response to information request in the submission dated December 5, 2016.

Exposure

The exposure information is summarized in the table below in terms of number of doses exposed. About two thirds of patients had exactly eight doses and about 80% had at least eight doses. The distribution in terms of the number of doses exposed was similar between the treatment groups.

Table 18 Number of Doses Exposed

Study S-11 (06EU/FHp03) Exposure	**Flector-H (N=142)**	**Flector (N=145)**	**Placebo (N=142)**
#Doses, n (%)			
3 Doses	1 (1%)	0	1 (1%)
4 Doses	0	2 (1%)	1 (1%)
5 Doses	0	0	1 (1%)
6 Doses	3 (2%)	5 (3%)	6 (4%)
7 Doses	28 (20%)	22 (15%)	19 (13%)
8 Doses	91 (64%)	100 (69%)	95 (67%)
9 Doses	14 (10%)	9 (6%)	13 (9%)
10 Doses	5 (4%)	7 (5%)	6 (4%)
Cumulative			
≥ 3 Doses	142 (100%)	145 (100%)	142 (100%)
≥ 4 Doses	141 (99%)	145 (100%)	141 (99%)
≥ 5 Doses	141 (99%)	143 (99%)	140 (99%)
≥ 6 Doses	141 (99%)	143 (99%)	139 (98%)
≥ 7 Doses	138 (97%)	138 (95%)	133 (94%)
≥ 8 Doses	110 (77%0	116 (80%)	114 (80%)
≥ 9 Doses	19 (13%)	16 (11%)	19 (13%)
≥ 10 Doses	5 (4%)	7 (5%)	6 (4%)

Source: Table 27 on page 115 of the study report and clarification Table 4 on page 11 of the response to information request in the submission dated December 5, 2016.

Efficacy results

Primary efficacy endpoint: pain on movement reduction from baseline at Day 3

As shown in the table below pairwise treatment comparison revealed statistically significant treatment difference between Flector-H and Flector. Treatment differences were also statistically significant between Flector-H and placebo and between Flector and placebo (Note: these were secondary endpoints based on the protocol). Effect sizes of treatment differences were 5.4 for Flector-H versus Flector, 10.5 for Flector-H versus placebo, and 5.1 for Flector versus placebo. Effect size of treatment difference between Flector-H and placebo doubled relative to the difference between Flector and placebo.

Table 19 Reduction of Pain on Movement, Day 3 Compared to Baseline

Study S-11 (06EU/FHp03) Primary efficacy endpoint	**Flector-H (N=142)**	**Flector (N=142)**	**Placebo (N=140)**
Adjusted mean reduction in PI for pain on movement	-24.2	-18.8	-13.7
Difference from **Placebo**	-10.5	-5.06	
95% CI	(-14.0, -6.98)	(-8.57, -1.55)	
P-value	<0.001	0.005	
Difference between Flector-H and Flector treatments	-5.43		
95% CI	(-8.93, -1.94)		
P-value	0.002		

Source: Table 18.1 on page 86 of the study report.

Secondary and other efficacy endpoints

Time specific pain measurements

Time-specific PI for pain on movement

Mean time-specific PI scores are summarized in the table below. Baseline PI was balanced between the treatment groups. PI reduction of >50% started to show around the morning evaluation of Day 5 in the Flector-H group, the evening evaluation of Day 5 in the Flector group, and the morning evaluation of Day 6 in the placebo group, about one-half day earlier comparing Flector-H to Flector and then Flector to placebo as shown in the table below.

Table 20 Summary of Time-Specific PI for Pain on Movement

Study S-11		Predose	Day 2		Day 3		Day 4		Day 5		Day 6		Day 7		Day 8	
			H0	**H12**	**H0**	**H12**	**H0**	**H12**	**H0**	**H12**	**H0**	**H12**	**H0**	**H12**	**H0**	**H12**
Flector-H (N=142)	**N**	142	141	141	142	141	141	140	141	140	137	140	137	126	117	51
	Mean	**72.2**	64.4	58.2	50.2	45.7	40.5	37.4	32.0	29.7	23.4	24.4	19.4	17.6	14.6	14.5
	SD	12.0	14.9	16.9	18.7	18.9	19.1	19.4	18.4	17.6	16.2	16.0	14.9	14.6	13.9	13.7
Flector (N=142)	**N**	142	142	142	142	142	142	141	142	142	139	142	137	125	121	57
	Mean	**72.7**	66.7	61.2	55.6	51.9	44.9	42.5	37.5	35.1	28.5	29.5	24.1	22.8	17.3	14.2
	SD	12.4	14.4	16.8	18.1	18.8	19.8	19.3	19.0	19.2	19.2	18.3	18.4	18.0	16.0	14.5
Placebo (n=140)	**N**	140	140	139	140	140	140	139	139	139	138	139	136	126	117	56
	Mean	**71.4**	67.0	64.2	59.7	56.0	49.0	46.8	41.6	39.0	31.7	34.0	27.7	26.0	22.2	20.6
	SD	11.9	15.4	15.8	16.8	18.6	18.7	20.1	20.1	20.3	21.2	20.3	21.1	20.7	21.1	21.3

Source: Table 5.1a on pages 12-13 of the response to information request in the submission dated December 5, 2016.

Time-specific PID for pain on movement, pain at rest, and pain on leaning

Treatment comparisons of mean time-specific PID are summarized for each of the three endpoints: PID for pain on movement, pain at rest, and pain on leaning in the table below. Effect sizes of treatment differences between each pair of the three treatment groups were largest for pain on movement and smallest for pain at rest. The patterns of relative effect sizes of differences between the treatment groups were similar for all three endpoints. In terms of PID for pain on movement during the time interval of Days 3-7 the effect sizes of treatment differences were in the range of 9.4-11.2 for Flector-H versus placebo, the range of 4-5.8 for Flector versus placebo, and in a similar range of 4.1-5.8 for Flector-H versus Flector. Effect sizes of treatment differences between Flector-H and placebo doubled in comparison to the differences between Flector and placebo at various time points.

Table 21 Treatment Comparison of Mean PID Based on Time-Specific Measurements

Study S-11	Day 2		Day 3		Day 4		Day 5		Day 6		Day 7		Day 8	
	H0	**H12**	**H0**	**H12**	**H0**	**H12**	**H0**	**H12**	**H0**	**H12**	**H0**	**H12**	**H0**	**H12**
Pain on movement														
Flector-H vs Placebo	3.4	6.9	***10.3***	***11.2***	***9.4***	***10.3***	***10.6***	***10.3***	***9.4***	***10.5***	***9.5***	***9.7***	***8.9***	***6.7***
Flector vs Placebo	1.6	4.4	5.3	5.3	5.4	5.7	5.5	5.2	4.0	5.8	4.3	4.6	6.2	7.7
Flector-H vs Flector	1.8	2.6	4.9	5.8	4.1	4.7	5.2	5.1	5.4	4.8	5.2	5.1	2.7	-1.0
Pain at rest														
Flector-H vs Placebo	2.8	5.9	6.1	7.2	8.1	7.4	7.6	7.9	6.9	7.6	7.0	7.4	7.2	6.8
Flector vs Placebo	1.4	2.5	2.4	3.5	3.7	3.1	3.6	3.6	3.4	3.2	3.0	2.9	3.6	4.9
Flector-H vs Flector	1.4	3.5	3.7	3.8	4.4	4.2	4.0	4.3	3.5	4.4	4.0	4.5	3.6	1.9
Pain on leaning														
Flector-H vs Placebo	1.6	5.4	8.1	8.1	7.0	9.4	9.5	8.8	8.7	10.4	9.0	8.6	8.8	6.8
Flector vs Placebo	2.1	3.4	4.4	4.0	3.8	5.0	4.3	3.6	4.0	4.6	3.9	3.6	4.9	8.8
Flector-H vs Flector	-0.5	2.0	3.7	4.1	3.2	4.4	5.2	5.2	4.7	5.8	5.1	5.0	4.0	-2.1

Source: Three tables below.

Time-specific PID curves are presented in the figures below following each summary table of mean time-specific PID scores for pain on movement, pain at rest, and pain on leaning, respectively. The PID curves in all the figures had a similar pattern that they started to separate before Day 3 and reached the level of close to

the maximum separation on Day 3 and continue to rise in a parallel fashion from Day 3 to Day 7. There were no curve fluctuations within each dosing interval, where pain was measured at mid and end of dosing interval.

Reviewer's comments

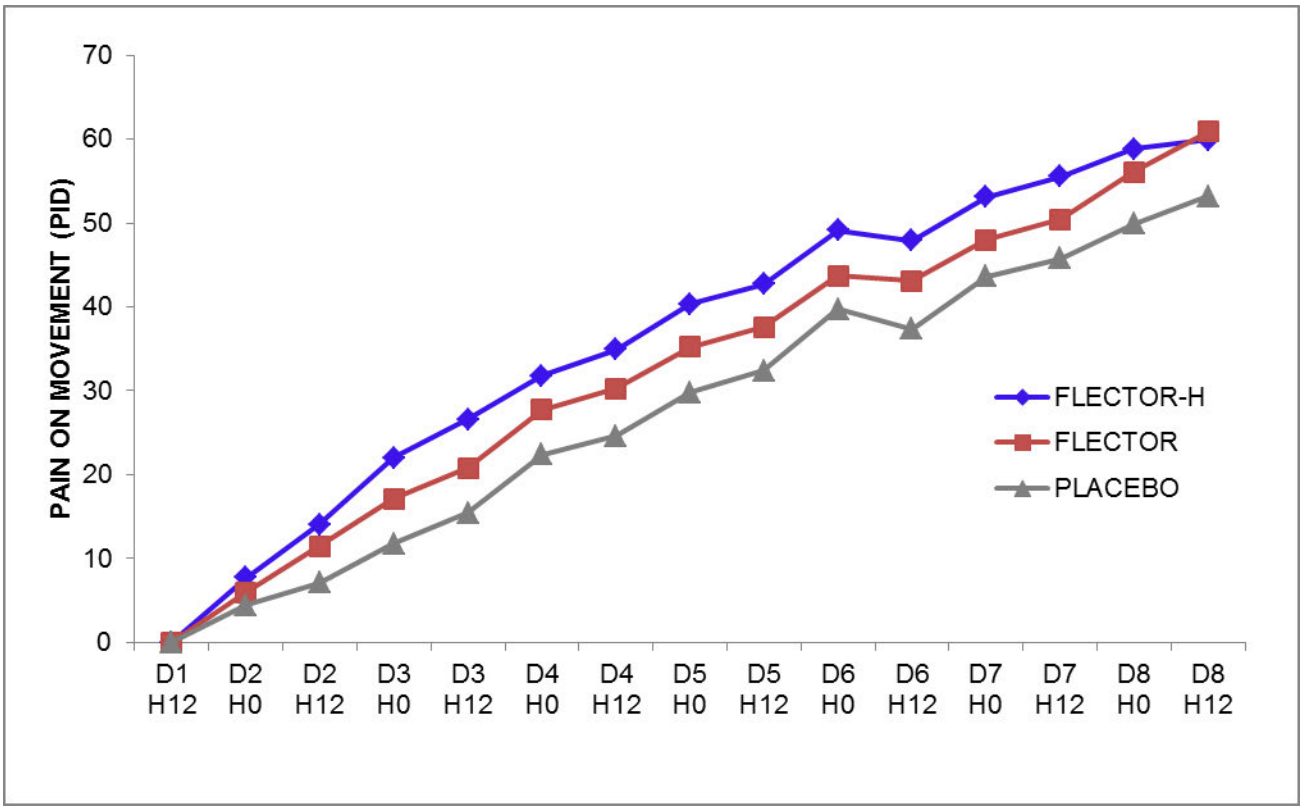
- Similar to the interpretations of the findings of Study S-10, treatment effect of Flector-H in Study S-11for pain on movement could be interpreted as shortened time interval of about one day to reach the same level of pain reduction in comparison to placebo and about one half-day to reach the same level of pain reduction in comparison to Flector from Day 3 to 7 (estimated by looking at intersections between a horizontal line and pain curves). Treatment effect of Flector-H could also be interpreted as approximate doubling of effect size of treatment difference from placebo in comparison to Flector versus placebo at a given time point during Days 3 and 7 (estimated by looking at intersections between a vertical line and pain curves).
- Comparing PID data in terms of pain on movement, pain at rest, and pain on leaning, the most sensitive endpoint for detecting treatment differences would be pain on movement.

Table 22 Summary of Time-Specific PID for Pain on Movement

Study S-11		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7		Day 8	
		H0	**H12**	**H0**	**H12**	**H0**	**H12**	**H0**	**H12**	**H0**	**H12**	**H0**	**H12**	**H0**	**H12**
Flector-H (N=142)	**N**	141	141	142	141	141	140	141	140	137	140	137	126	117	51
	Mean	7.8	14.1	22.0	26.6	31.8	34.9	40.4	42.7	49.1	47.9	53.2	55.5	58.8	59.9
	SD	10.7	12.9	16.0	16.8	17.8	18.1	17.9	17.5	17.3	16.7	16.4	16.4	15.9	15.4
Flector (N=142)	**N**	142	142	142	142	142	141	142	142	139	142	137	125	121	57
	Mean	6.0	11.5	17.1	20.8	27.8	30.3	35.2	37.6	43.8	43.1	48.0	50.4	56.1	60.9
	SD	11.7	15.0	16.9	18.2	18.7	18.5	19.3	19.4	20.3	19.7	19.6	18.5	17.3	16.5
Placebo (n=140)	**N**	140	139	140	140	140	139	139	139	138	139	136	126	117	56
	Mean	4.4	7.1	11.8	15.4	22.4	24.6	29.8	32.4	39.7	37.4	43.7	45.8	49.9	53.2
	SD	10.9	10.9	12.0	15.0	15.2	17.1	18.2	18.5	20.6	19.7	20.2	19.8	19.6	19.0
Flector-H vs Placebo	**Diff in Mean**	3.4	6.9	**10.3**	**11.2**	**9.4**	**10.3**	**10.6**	**10.3**	**9.4**	**10.5**	**9.5**	**9.7**	8.9	6.7
Flector vs Placebo	**Diff in Mean**	1.6	4.4	5.3	5.3	5.4	5.7	5.5	5.2	4.0	5.8	4.3	4.6	6.2	7.7
Flector-H vs Flector	**Diff in mean**	1.8	2.6	4.9	5.8	4.1	4.7	5.2	5.1	5.4	4.8	5.2	5.1	2.7	-1.0

Source: Table 5.2a on page 17 of the response to information request in the submission dated December 5, 2016.

Figure 2 Time-Specific PID by VAS Based on Patient Daily Diary – Pain on Movement



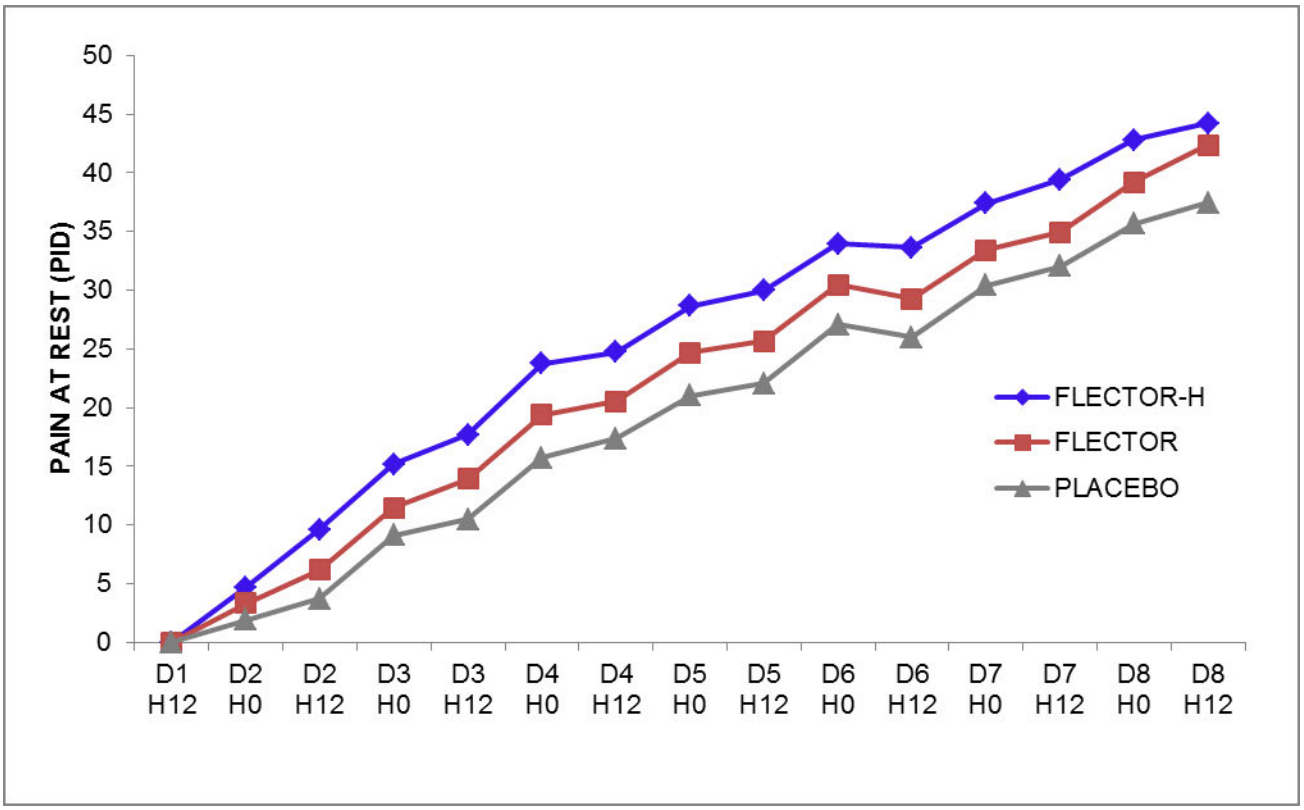
Source: Figure 5.2a on page 18 of the response to information request in the submission dated December 5, 2016.

Table 23 Summary of Time-Specific PID for Pain at Rest

Study S-11		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7		Day 8	
		H0	**H12**	**H0**	**H12**	**H0**	**H12**	**H0**	**H12**	**H0**	**H12**	**H0**	**H12**	**H0**	**H12**
Flector-H (N=142)	**N**	141	141	141	140	140	139	140	139	137	139	136	125	117	51
	Mean	4.7	9.6	15.2	17.7	23.8	24.7	28.7	30.0	34.0	33.6	37.4	39.4	42.8	44.2
	SD	10.2	13.1	15.2	16.2	16.8	17.7	17.3	17.9	18.7	17.9	18.8	18.8	17.9	17.4
Flector (N=142)	**N**	142	142	141	142	142	141	142	142	139	142	137	125	121	57
	Mean	3.3	6.2	11.5	13.9	19.4	20.5	24.7	25.7	30.5	29.2	33.4	35.0	39.2	42.4
	SD	12.9	14.5	14.7	18.1	16.7	17.9	18.9	18.9	23.0	20.3	23.2	23.7	22.2	20.7
Placebo (n=140)	**N**	140	139	140	140	140	139	139	139	138	139	136	126	117	56
	Mean	1.9	3.7	9.1	10.5	15.7	17.4	21.0	22.0	27.1	26.0	30.4	32.0	35.6	37.5
	SD	11.8	14.0	14.4	16.0	16.2	17.5	17.1	17.7	20.2	18.7	20.1	20.5	19.6	20.6
Flector-H vs Placebo	**Diff in mean**	2.8	5.9	6.1	7.2	8.1	7.4	7.6	7.9	6.9	7.6	7.0	7.4	7.2	6.8
Flector vs Placebo	**Diff in mean**	1.4	2.5	2.4	3.5	3.7	3.1	3.6	3.6	3.4	3.2	3.0	2.9	3.6	4.9
Flector-H vs Flector	**Diff in mean**	1.4	3.5	3.7	3.8	4.4	4.2	4.0	4.3	3.5	4.4	4.0	4.5	3.6	1.9

Source: Table 5.2b on pages 18-19 of the response to information request in the submission dated December 5, 2016.

Figure 3 Time-Specific PID by VAS Based on Patient Daily Diary – Pain at Rest



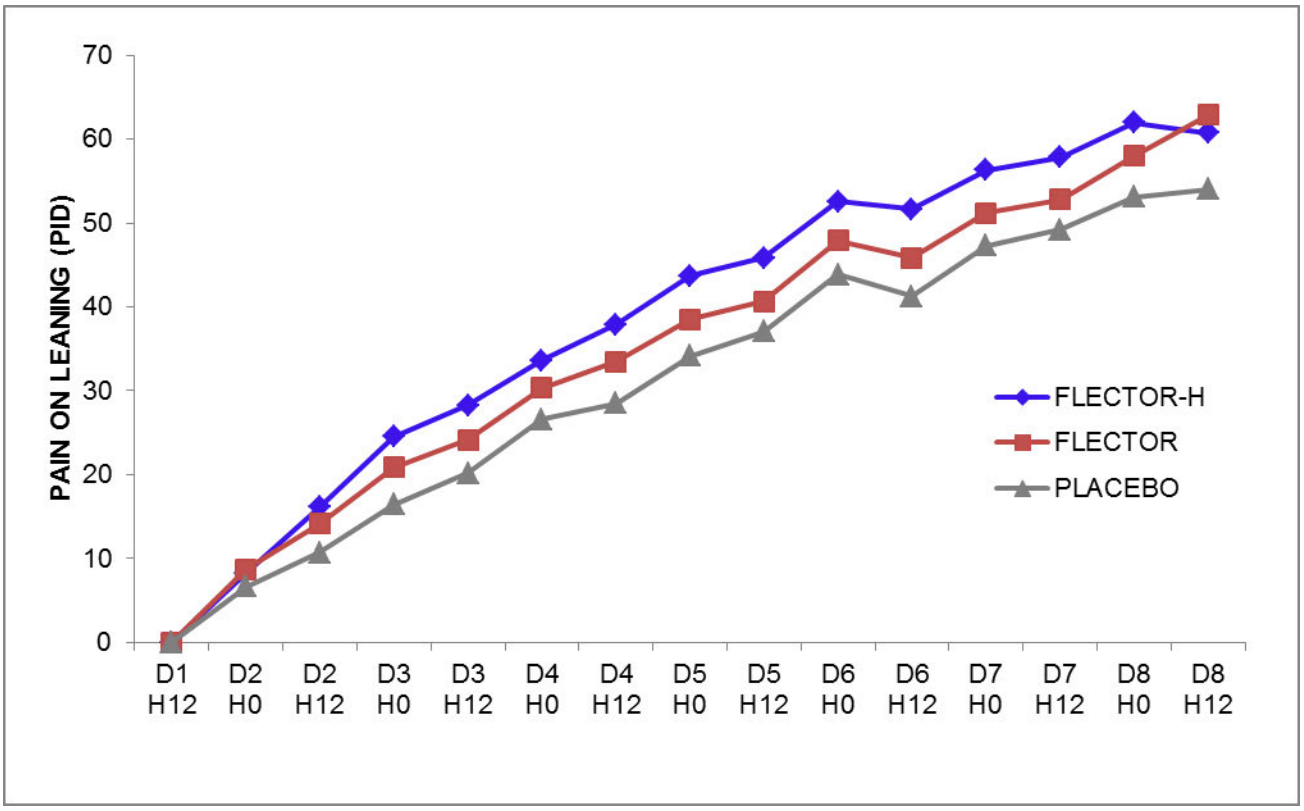
Source: Figure 5.2b on page 19 of the response to information request in the submission dated December 5, 2016.

Table 24 Summary of Time-Specific PID for Pain on Leaning

Study S-11		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7		Day 8	
		H0	**H12**	**H0**	**H12**	**H0**	**H12**	**H0**	**H12**	**H0**	**H12**	**H0**	**H12**	**H0**	**H12**
Flector-H (N=142)	**N**	141	141	142	141	141	140	141	140	138	140	136	125	117	51
	Mean	8.3	16.1	24.5	28.3	33.6	37.9	43.7	45.8	52.6	51.7	56.3	57.8	62.0	60.8
	SD	11.6	15.3	19.4	20.3	20.6	22.0	21.7	22.7	22.4	21.7	22.3	23.3	21.0	21.2
Flector (N=142)	**N**	142	142	142	142	142	141	142	142	139	142	137	125	121	57
	Mean	8.7	14.2	20.9	24.2	30.4	33.5	38.5	40.7	47.9	45.9	51.2	52.8	58.0	62.9
	SD	13.1	13.8	16.9	19.1	20.4	20.3	20.6	20.6	22.6	21.7	22.6	23.5	22.6	22.0
Placebo (n=140)	**N**	140	139	140	140	140	139	139	139	138	139	136	126	117	56
	Mean	6.7	10.7	16.5	20.2	26.6	28.5	34.2	37.1	43.9	41.3	47.3	49.2	53.2	54.0
	SD	11.6	14.3	14.9	16.6	18.0	19.2	20.2	20.0	22.4	22.1	22.1	22.7	23.2	22.1
Flector-H vs Placebo	**Diff in mean**	1.6	5.4	8.1	8.1	7.0	9.4	9.5	8.8	8.7	10.4	9.0	8.6	8.8	6.8
Flector vs Placebo	**Diff in mean**	2.1	3.4	4.4	4.0	3.8	5.0	4.3	3.6	4.0	4.6	3.9	3.6	4.9	8.8
Flector-H vs Flector	**Diff in mean**	-0.5	2.0	3.7	4.1	3.2	4.4	5.2	5.2	4.7	5.8	5.1	5.0	4.0	-2.1

Source: Table 5.2c on page 20 of the response to information request in the submission dated December 5, 2016.

Figure 4 Time-Specific PID by VAS Based On Patient Daily Diary – Pain on Leaning



Source: Figure 5.2c on page 21 of the response to information request in the submission dated December 5, 2016.

Rescue data

Rescue data are summarized in the table below, in terms of the number of rescue dose and proportion rescued on specific days and during the treatment period. Proportions of patients taking rescue were 65% in the Flector-H group, 70% in the Flector group and 71% in the placebo group, in the first two days. Rescue data were very similar between Flector and placebo. Treatment differences comparing Flector-H to placebo were small and

mainly noticeable in terms of 1.6 less mean rescue doses during the 7-day period and 6-7% less patients using rescue during the first three days of treatment period, in the Flector-H group.

Reviewer's comments

- Proportions taking rescue in the first two days were relatively high, very rarely seen in the studies of external analgesics. Data on median time to rescue would have been assessable when there we more than 50% of the sample population taking rescue.
- Relatively heavy use of orally administered rescue (>70% patients taking rescue and average use of 4.3 to 5.9 doses among treatment groups, counting those not taking rescue) raise the suspicion on treatment effects attributable to diclofenac patch since topically applied analgesics usually have much smaller effects than orally administered analgesic

Table 25 Rescue Data and Other Secondary Endpoints

Study S-11 (06EU/FHp03) Rescue data	Flector-H (N=142)	Flector (N=142)	Placebo (N=140)	Difference from placebo for	
				Flector-H	Flector-H
# of rescue doses on Days 1-2, mean	1.8	2.3	2.3	-0.5	0.0
# of rescue doses on Day 3	1.1	1.3	1.4	-0.3	-0.1
# of rescue doses for Days 1-8	4.3	5.7	5.9	-1.6	-0.2
Proportion rescued on Days 1-2, %	***65%***	***70%***	***71%***	-6%	-1%
Proportion rescued on Day 3	44%	51%	52%	-7%	-1%
Proportion rescued for Days 1-8	73%	77%	77%	-4%	0%

Source: Table 6 on page 21 of the response to information request in the submission dated December 5, 2016.

5.3.2.3 Summary of Findings and Discussion

Study design

The study was designed with a primary focus on the comparison between Flector-H and Flector using the average pain reduction at Day 3 as the primary endpoint. The important components required for evaluation of analgesic effects for an acute indication such as frequent pain measurements during the initial 24 hours and single-dose onset and duration, were missing from the study.

Study conduct

The study was conducted in three European countries, two of which Poland (46% patients) and Ukraine (46% patients) had most patients. The treatment groups were approximately balanced with regard to demographic characteristics such as age, sex, race, weight, height, BMI, and pain intensity (PI) at baseline. Mean baseline PI was 70+ for pain on movement and pain on leaning and 40+ for pain at rest. There were only three cases of dropouts, all due to lost to follow-up. The reported protocol deviations involved 39% Flector-H patients, 27% Flector patients, and 37% placebo patients with the most frequently reported being missing one patch application (58 counts), and were approximately balanced between the treatment groups. They are not considered as having a major or differential impact on study outcomes.

Efficacy

Treatment difference between Flector-H and Flector in primary endpoint, PID at Day 3 was statistically significant. Effect size of treatment difference between Flector-H and placebo doubled in comparison to the difference between Flector and placebo. The maximum PID curve separation was maintained from Day 3 to Day 7. Time to >50% reduction in time-specific PI occurred around Day 5 and Day 6. Time to reach the same level of pain reduction was one day earlier for Flector-H and one half-day earlier for Flector using placebo as a

comparison. Pain on movement was shown to be a more sensitive measure than pain at rest and pain on leaning.

In terms of rescue data there were small treatment differences between Flector-H and placebo (1.6 less rescue doses during study and 6-7% less patients using rescue in first three days) and no difference between Flector and placebo. Relatively heavy use of orally administered rescue in >70% patients during the study (rarely seen in studies of external analgesics) might have a major confounding effect on study results.

5.3.2.4 Conclusion

Flector-H patch is effective in treating pain after several doses of patch applied once a day as shown in sizable treatment differences from placebo, doubling treatment effects in comparison to one half of the daily dose of Flector patch, and shorter time interval to achieve same level of pain reduction than controls.

An acute onset has not been characterized in the study.

5.3.2.5 Appendix

Eligibility criteria copied from the protocol

General inclusion criteria
Patients must satisfy the following criteria in order to participate in the study:

1. Outpatients of both genders.
2. Aged between 18 and 65 years.
3. Subjects must sign a written informed consent to the participation prior to inclusion in the study.
4. Female subjects of childbearing potential must have a negative urine pregnancy test at screening/inclusion visit.
5. Female subjects of childbearing potential (i.e. not status post hysterectomy or tubal ligation) must be using an appropriate method of contraception according to the definition of Note 3 of ICH M3 Guideline (implants, injectable, combined oral contraceptives, some IUDs, sexual abstinence or vasectomized partner) and must be willing to continue using it throughout the whole study period..
6. Subjects must be able to comprehend the full nature and purpose of the study, including possible risks and side effects, to co-operate with the Investigator, to comply with the requirements of the entire study and to return for the required examinations.

Study specific inclusion criteria:
1. Patients having an acute ankle sprain, involving the external lateral ligaments (i.e. with inversion mechanism), occurred within 48 hours before inclusion
2. With presence of peri-malleolar edema (difference between the sub-malleolar perimeter of injured and healthy ankle of at least 20 mm).
3. With pain on movement ≥ 50 mm on a 100-mm visual analogue scale (VAS).
4. Ankle sprain severity: grade I or II.
5. Sprain must not require an orthopedic or surgical treatment, nor a physiotherapeutic treatment (in case of doubt, a radiographic evaluation will be done).
6. Sprain must not have been previously treated (ice/cold packs applications and paracetamol *per os* are permitted).
7. Absence of any open skin lesion or any dermatological condition (e.g. skin infection, eczema) affecting the injured area.

Exclusion Criteria
Patients with the following characteristics will have to be excluded from study participation:

<u>Ankle sprain with the subsequent features will have to be excluded:</u>
1. Injury occurred more than 48 hours prior to study entry.
2. Pain on movement <50 mm on a 100-mm Huskisson-type VAS.
3. Severe ankle sprain (grade III) or sprain suggesting associated lesions, i.e., sprains requiring an orthopedic or surgical treatment, or physiotherapeutic treatment.
4. Absence of peri-malleolar edema (difference between the sub-malleolar perimeter of injured and healthy ankle < 20 mm).
5. Open lesion or any dermatological condition affecting the injury skin area.
6. Patients with acquired or congenital hyperlaxity, with history of dislocation or fracture or other diseases (such as rheumatic degenerative or chronic inflammatory pathologies) affecting the injured joint.
7. Surgery to the affected joint dated less than one year.
8. Three or more prior injuries to the actually injured ankle in the past.
9. Relapsing sprains already treated during the 6 months preceding the study.

<u>Forbidden treatments:</u>
1. Prior use of topical medication to involved area since injury
2. Prior use of OTC analgesic or NSAIDs (ibuprofen, ketoprofen) within 48 hours of inclusion in the study (paracetamol permitted).
3. Prior use of narcotic analgesics within 7 days of study entry.
4. Prior use of systemic anti-inflammatory steroidal drugs, by any route of administration, within 60 days of study entry.

5. Prior use of long-acting NSAIDs such as piroxicam or naproxen since injury.
6. Concomitant use of drugs which may be susceptible to interactions with diclofenac or which may affect safety if used concomitantly (lithium, digoxin, anticoagulants, antidiabetic agents, cyclosporin, methotrexate, quinolone antimicrobials, other NSAIDs and diuretics).

Forbidden medical conditions:

1. Known hypersensitivity to diclofenac or other NSAID drugs (including aspirin or paracetamol).
2. Prior history of GI bleeds/ulcers, liver/kidney disease.
3. Patients with coagulation defects.
4. Patients with cardiac impairment.
5. Pregnant women and women who are breast-feeding.
6. Patients participating or having been involved in other clinical investigations during the three months preceding the entry of this study.
7. Patients suffering from psychiatric diseases, not allowing the observance of the protocol, alcohol or drug abuse during the 1-year period preceding the inclusion.
8. Patients not able to understand the purposes of the study.
9. Patients refusing to give a written informed consent.
10. Patients not reliable, according to the investigator's opinion.

6. INTEGRATED REVIEW OF EFFICACY

Efficacy summary

The two pivotal studies, S-10 and S-11, were designed similarly and conducted in Europe in mostly nonelderly adult Caucasian patients. In both studies, demographics and baseline pain intensity were balance between the treatment groups; dropout rates were low; proportion of total protocol deviation and deviations in the major categories were not dramatically different between the treatment groups and not expected to have a major or differential impact on study outcomes.

Primary comparison between Flector-H and Flector resulted in statistically significant difference in PID at Day 3. Effect sizes of treatment differences in time-specific PID between Flector-H and placebo were sizable and were approximately doubled in magnitude in comparison to the difference between Flector and placebo from Day 3 to almost the end of the evaluation period in both studies. In the same evaluation period of Day 3 to the end of study it took a shorter time interval to reach the same level of PID for Flector-H in comparison to placebo (a difference of four days in Study S-10 and one day in Study S-11) and in comparison to Flector (a difference of two days in Study S-10 and one half-day in Study S-11). The time to reach at least 50% pain reduction was Day 6 for Flector-H, Day 8 for Flector, and Day 10 for placebo treatment in Study S-10 and early Day 5 for Flector-H, late Day 5 for Flector, and early Day 6 for placebo (12 hours apart) in Study S-11.

Treatment effects of Flector-H were also shown as less patients taking rescue than placebo during the initial days of treatment (6-8% less in the first two days in Study S-10 and 6-7% less in the first three days in Study S-11) and less use of rescue (0.8 less total rescue doses in Study S-10 and 1.6 less total rescue doses in Study S-11).

Flector-H patch was shown to be effective in treating pain after several doses of patch applied once a day as demonstrated by sizable treatment differences from placebo, doubling treatment effects in comparison to one half of the daily dose of Flector patch, and shorter time interval to achieve same level of pain reduction than controls, starting on treatment Day 3, as well as less need for rescue, especially during the first few days of treatment.

An acute onset had not been characterized in the study.

6.1 Proposed Indication

The proposed indication of Flector-H patch is for the topical treatment of acute pain due to minor strains, sprains, and contusions.

6.2 Methods/Study Design

Study S-10 and S-11 had similar designs of having both Flector patch and placebo patch as controls, having all European study sites, having the same prima efficacy endpoint comparing Flector-H to Flector in terms of reduction of pain on movement at Day 3, and having similar data collection using patient's daily diary to record pain scores measured twice a day and amount of rescue. The major differences between the two studies included pain condition and treatment duration that patients with muscle contusion were treated for 14 days in Study S-10 and patients with acute ankle sprain were treated for 7 days in Study S-11. In addition to assessment of pain on movement, pain at rest and pain on leaning (on injured limb) were evaluated in Study S-11.

Key parameters required for evaluation of single-dose effects of the initial patch were missing in both studies. The missing information included frequent pain measurements during the first dosing interval, time to onset of pain relief, and time to taking rescue as a measure of duration. The Sponsor of the studies never requested input from FDA. The studies had been completed years before their initial contact with the Review Division.

6.3 Demographics

In both studies sample population consisted of mainly nonelderly adult Caucasian patients and about 40% females. The three treatment groups were approximately balanced with regard to demographic and baseline characteristics such as age, sex, race, weight, height, and BMI. Mean baseline pain intensity was slightly below 70 mm (on 100 mm scale) in Study S-10 and slightly above 70 mm in Study S-11 and was balanced amount treatment groups.

6.4 Patient Disposition and Protocol Deviations

Dropout rates were low 7% (24 of 355 patients) in Study S-10 and 0.7% (3 of 429 patients) in Study S-11. Reasons for dropouts consisted of mainly symptom improvement (10 cases), AEs (5 cases), and withdrawn consent (4 cases) in Study S-10 and lost to follow-up (all 3 cases) in Study S-11.

Among the treatment groups, protocol deviations were reported in 35-43% in Study S-10 and 27-39% in Study S-11. The most frequently reported was missing one patch application, 50 counts in Study S-10 and 58 counts in Study S-11. The major categories of other more frequently reported protocol deviations were missing or miss-timed scheduled pain measurements and dosing time missing or dosing time error in patch application. The proportion of total protocol deviation and deviations in the major categories were not dramatically different between the treatment groups and are not expected to have a major or differential impact on study outcomes.

6.5 Analysis of the Primary Endpoint(s)

Primary efficacy endpoint was pain reduction for pain on movement at Day 3 in comparison of Flector-H and Flector. Treatment difference was statistically significant between Flector-H and Flector. Pairwise comparisons between Flector-H and placebo and between Flector and placebo showed also statistically significant treatment differences. Effect sizes of treatment differences between Flector-H and placebo were sizable, about 14 mm in Study S-10 and about 11 mm in Study S-11. Effect sizes of treatment differences for Flector-H versus placebo were approximately doubled in comparison of Flector versus placebo in both studies.

Table 26 PID Reduction of Pain on Movement, Day 3 Compared to Baseline

	Study S-10 (05DCz/FHp11)			**Study S-11 (06EU/FHp03)**		
Primary efficacy endpoint	**Flector-H (N=121)**	**Flector (N=115)**	**Placebo (N=118)**	**Flector-H (N=142)**	**Flector (N=142)**	**Placebo (N=140)**
N	119	115	116			
Adjusted Mean PID movement, D3	-19.1	-11.4	-5.2	-24.2	-18.8	-13.7
Difference from **Placebo**	-13.9	-6.25		-10.5	-5.06	
95% CI	(-17.6, -10.1)	(-10.1, -2.44)		(-14.0, -6.98)	(-8.57, -1.55)	
P-value	<0.001	0.001		<0.001	0.005	
Difference Flector-H vs Flector	-7.62			-5.43		
95% CI	(-11.4, -3.84)			(-8.93, -1.94)		
P-value	<0.001			0.002		

6.6 Secondary and Other Endpoint(s)

Secondary and other pain-related efficacy endpoints consisted of mainly parameters derived from time-specific pain measurements and rescue data.

In terms of time-specific PID for pain on movement effect sizes of treatment differences between Flector-H and placebo were consistent with findings from Day 3, mostly in a range of 11-15 mm during Days 3-13 in Study S-10 and mostly in a range of 9-11 mm during Days 3-7 in Study S-11. Doubling of effect sizes in comparison of Flector-H versus placebo and Flector versus placebo and maximum pain curve separation were maintained from Day 3 to about the end of the scheduled evaluation period in both studies. Among the three endpoints studied in S-11: pain on movement, pain at rest, and pain on leaning, pain on movement appeared to be the most sensitive measure of treatment differences.

To reach the same level of PID (from Day 3 to the end of evaluation period), treatment duration for Flector-H was shortened by four days comparing to placebo and by two days comparing to Flector in Study S-10 and by one day comparing to placebo and by one half-day comparing to Flector in Study S-11. The time to reach at least 50% pain reduction was around Day 6 for Flector-H, Day 8 for Flector, and Day 10 for placebo treatment in Study S-10 and early Day 5 for Flector-H, late Day 5 for Flector, and early Day 6 for placebo (12 hours apart) in Study S-11.

Table 27 Treatment Comparison of Pain Data for Pain on Movement

	Study S-10 (05DCz/FHp11)	**Study S-11 (06EU/FHp03)**
Time interval	**Days 3-13**	**Days 3-7**
PID scores	Fluctuation	Fluctuation
Flector-H vs Placebo	14.4-15.8-10.0, mostly between 11-15	10.3-11.2-9.4, mostly between 9.4-11.2
Flector vs Placebo	6.1-8.5-4.0, mostly between 4-7	5.3-5.8-4.0, mostly between 4-5.8
Flector-H vs Flector	8.3-9.3-6.0, mostly between 6-9	4.9-5.8-4.1, mostly between 4.1-5.8
Time to similar PID		
Flector-H vs Placebo	4 days earlier	1 days earlier
Flector vs Placebo	2 days earlier	0.5 days earlier
Flector-H vs Flector	2 days earlier	0.5 days earlier

Treatment differences between Flector-H and placebo in the use of rescue were noticeable mainly as 0.8 less total rescue doses and 6-8% less patients taking rescue on Day 1, Day 2, and during evaluation period in Study S-10 and 1.6 less total rescue doses and 6-7% less patients taking rescue during the first three days of the 7-day evaluation period in Study S-11.

Proportions of patients taking rescue were in a range expected for external analgesics in Study S-10 and much larger than expected in Study S-11. Relatively heavy use of orally administered rescue might confound the study results since oral formulations are much stronger than topically applied analgesics.

Table 28 Summary of Rescue Data

	Study S-10 (05DCz/FHp11					**Study S-11 (06EU/FHp03)**				
	Flector-H (N=142)	**Flector (N=142)**	**Placebo (N=140)**	**Difference from placebo for**		**Flector-H (N=142)**	**Flector (N=142)**	**Placebo (N=140)**	**Difference from placebo for**	
				Flector-H	**Flector**				**Flector-H**	**Flector**
Total #rescue doses during study	0.40	1.23	1.21	0.81	-0.02	4.3	5.7	5.9	-1.6	-0.2
Proportion rescued on Day 1	8%	11%	16%	-8%	-5%	***65%***	***70%***	***71%***	-6%	-1%
Proportion rescued on Day 2	7%	9%	13%	-6%	-4%					
Proportion rescued on Day 3	4%	8%	7%	-3%	1%	44%	51%	52%	-7%	-1%
Proportion rescued during study	10%	15%	17%	-7%	-2%	73%	77%	77%	-4%	0%

6.7 Subpopulations

Subgroup analyses of primary efficacy endpoint with respect to sex and country revealed similar trends (refer to the statistical review by Dr. Katherine Meaker dated February 10, 2017 for detail). Subgroup analyses based on age and race could not be adequately performed because patients were mostly nonelderly Caucasians.

6.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Single-dose duration has not been studied. It is a challenge to study multiple-dose duration while the patch is in continuous contact with skin leading to no peaks or troughs of pain response within each dosing interval. A dose-ranging study of different dosing intervals would have been required. The proposed once-a-day dosing was based on experience with twice-a-day dosage recommended for Flector patch and anticipated more diclofenac available locally with help from heparin.

6.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The persistence of efficacy and/or tolerance effects could not be evaluated because of the termination of pain data collection after the use of the last patch and natural pain resolution soon after an acute injury.

6.10 Additional Efficacy Issues/Analyses

None.

7. INTEGRATED REVIEW OF SAFETY

Safety summary

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 patch is not irritating or sensitizing based on results of dermatological safety studies. Its potential for phototoxicity or photoallergenicity could not be determined due to variations in study design and conduct.

Flector-H is well tolerated based on safety findings.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety database consisted of a total of 11 clinical studies of Flector-H patch including three bioavailability (S-1, S-2, S-3), two skin irritation/sensitization (S-4, S-5), two pharmacodynamic (S6, S7), and four controlled clinical trials (S-8, S-9, S-10, S-11) as listed in the study inventory table in the review section 5.2.

7.1.2 Categorization of Adverse Events

AEs were categorized by body systems and grouped under three treatments: Flector-H, Flector, and placebo for comparison. Information on AEs per study and AEs divided by categories of application site AEs and non-application site AEs were also available.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

Safety data were pooled from nine of the 11 clinical studies (except the two dermatological safety studies) to estimate and compare incidence.

7.2 Adequacy of Safety Assessments

The major safety concern for the topically applied patch is local tolerance. Safety assessments with AE monitoring and periodic measurements of degree of tolerance are considered adequate.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 874 subjects were exposed to Flector-H in 11 studies. Five of the 11 studies had safety data related to 24-hour patch application once a day for a week or longer, Studies S-5, S-7, S-8, S-10, and S-11. The maximum exposure included exposure of 248 subjects in the 21-day study (Study S-5), 121 subjects in the 14-day study (Study S-10), and 288 subjects in three 7-day studies (Studies S-7, S-8, and S-11). The study populations consisted of mainly nonelderly adult Caucasian.

Table 29 Table Exposure per Study and Overall Exposure

Study	Protocol number	Flector-H	Flector	Heparin	Placebo	Total	Dosage
(S-1)	CRO-PK-98-13	22	22	-	-	22	Bid x 7.5 days
(S-2)	CRO-PK-02-92	12	-	-	-	12	Bid x 5.5 days
(S-3)	CRO-PK-12-272	38	-	-	-	38	Single dose in 14 subjects 24-hour qD x 4 doses in 24 subjects
(S-4)	EU01.2002	50	-	-	-	50	M/W/F dosing x3 weeks, then qD x 2 days
(S-5)	13FCDN-FHp03	248	-	-	-	248	24-hour qD x 21 days, then one 48-hour dosing
(S-6)	05I/FHp06	30	30	-	30	30	Single dose for one hour
(S-7)	07I/FHp04	26	26	26	26	104	24-hour qD x 7 days
(S-8)	18-12-98	120	-	-	119	239	24-hour qD x 7 days
(S-9)	99CH/FHp02	65	61	-	59	185	12-hour dosing daily x 10 days
(S-10)	05DCz/FHp11	121	115	-	119	355	24-hour qD x 14 days
(S-11)	06EUFHp03	142	145	-	142		24-hour qD x 7 days
Total		874	399	26	495	1712	

Source: Table 5.3.5.3.2 on page 25 of ISSE report.

7.2.2 Explorations for Dose Response

Daily patch application of 12 hours was studied in one phase 3 efficacy study and 24-hour daily application was studied in the other three phase 3 efficacy studies.

7.2.3 Special Animal and/or in Vitro Testing

Refer to the Pharmacology/Toxicology Review.

7.2.4 Routine Clinical Testing

Routine clinical testing with vital signs, physical exams, and laboratory tests had not been included in the placebo-controlled phase 3 studies.

7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to the Clinical Pharmacology review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Local skin tolerance to the patch was rated and monitored throughout the study.

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred during any of the clinical studies.

7.3.2 Nonfatal Serious Adverse Events

There was only one case of serious adverse events (SAEs) in the entire NDA safety database. Three SAEs, severe pain, intermittent claudication (Charcot's foot), and diabetes were reported in Study S-10 in a 55 years old Caucasian male assigned to the Flector group who was hospitalized for skin infection of the injured foot

while on treatment with Flector patch. The study drug was terminated and infection resolved with antibiotic treatment. These events were unlikely to be associated with Flector treatment.

7.3.3 Dropouts and/or Discontinuations

There were eight cases of early dropouts due to AE, three in the Flector group, three in the placebo group, and two in the heparin group, all reported from two studies S-7 and S-10. None of the subjects treated with Flector-H dropped out due to AEs.

7.3.4 Significant Adverse Events

No significant AEs were expected because of low systemic availability of the study drug.

7.3.5 Submission Specific Primary Safety Concerns

None.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Treatment emergent adverse events (AEs) pooled across clinical studies except the two dermatological safety studies are listed in the table below. The percentages of subjects with at least one AE were very low, only 4-5% among treatment groups and were similar between the treatment groups (4% for Flector-H, 4.3% for Flector, and 5.1% for placebo). The most commonly reported AE was application site pruritus with six AEs reported in five subjects in each of the Flector-H and Flector groups and 14 AEs reported in 11 subjects on placebo. The next more common AEs reported in either Flector-H or Flector group were headache in three (0.5%) subjects on Flector-H and three (0.8%) subjects on Flector and application site irritation in three (0.5%) subjects on Flector-H, one (0.3%) subject on Flector, and three (0.6%) subjects on placebo.

Table 30 Treatment Emergent AEs Pooled from Nine Studies

	Flector-H (N = 573)		Flector (N = 399)		Placebo (N = 492)	
	#AEs	#Subjects	#AEs	#Subjects	#AEs	#Subjects
Total AEs / subjects with AEs from All Studies	33	23 (4.0%)	30	17 (4.3%)	37	25 (5.1%)
Cardiac disorders	1	1 (0.2%)	0	0	0	0
Dizziness	1	1 (0.2%)	0	0	0	0
Endocrine disorders	0	0	1	1 (0.3%)	0	0
Diabetes mellitus	0	0	1	1 (0.3%)	0	0
Eye disorders	1	1 (0.2%)	0	0	0	0
Blepharospasm	1	1 (0.2%)	0	0	0	0
Gastrointestinal disorders	3	3 (0.5%)	0	0	0	0
Abdominal pain	2	2 (0.3%)	0	0	0	0
Abdominal pain upper	1	1 (0.2%)	0	0	0	0
General disorders and administration site conditions	12	9 (1.6%)	13	8 (2.0%)	27	20 (4.1%)
Application site erythema	0	0	1	1 (0.3%)	4	3 (0.6%)
Application site inflammation	0	0	0	0	1	1 (0.2%)
Application site irritation	3	3 (0.5%)	2	1 (0.3%)	3	3 (0.6%)
Application site pruritus	6	5 (0.9%)	6	5 (1.3%)	14	11 (2.2%)
Application site rash	1	1 (0.2%)	1	1 (0.3%)	0	0
Application site reaction	1	1 (0.2%)	0	0	3	3 (0.6%)
Edema peripheral	1	1 (0.2%)	0	0	0	0
Pain	0	0	1	1 (0.3%)	1	1 (0.2%)
Product adhesion issue	0	0	2	2 (0.5%)	0	0

Pyrexia	0	0	0	0	1	1 (0.2%)
Immune system disorders	0	0	1	1 (0.3%)	1	1 (0.2%)
Dermatitis atopic	0	0	0	0	1	1 (0.2%)
Urticaria	0	0	1	1 (0.3%)	0	0
Infections and infestations	0	0	3	3 (0.8%)	0	0
Localized infection	0	0	2	2 (0.5%)	0	0
Smallpox	0	0	1	1 (0.3%)	0	0
Injury, poisoning and procedural complications	1	1 (0.2%)	1	1 (0.3%)	0	0
Ligament sprain	0	0	1	1 (0.3%)	0	0
Traumatic hematoma	1	1 (0.2%)	0	0	0	0
Musculoskeletal and connective tissue disorders	3	3 (0.5%)	1	1 (0.3%)	5	3 (0.6%)
Arthralgia	1	1 (0.2%)	0	0	2	1 (0.2%)
Bone pain	0	0	0	0	1	1 (0.2%)
Musculoskeletal stiffness	1	1 (0.2%)	1	1 (0.3%)	1	1 (0.2%)
Neck pain	1	1 (0.2%)	0	0	0	0
Pain in extremity	0	0	0	0	1	1 (0.2%)
Nervous system disorders	7	5 (0.9%)	3	3 (0.5%)	0	0
Dizziness	1	1 (0.2%)	0	0	0	0
Headache	5	3 (0.5%)	3	3 (0.8%)	0	0
Paresthesia	1	1 (0.2%)	0	0	0	0
Psychiatric disorders	1	1 (0.2%)	0	0	1	1 (0.2%)
Sleep disorder	1	1 (0.2%)	0	0	1	1 (0.2%)
Reproductive system and breast disorders	2	2 (0.3%)	1	1 (0.3%)	0	0
Dysmenorrhea	2	2 (0.3%)	0	0	0	0
Menopausal symptoms	0	0	1	1 (0.3%)	0	0
Respiratory, thoracic & mediastinal disorders	1	1 (0.2%)	0	0	0	0
Cough	1	1 (0.2%)	0	0	0	0
Skin and subcutaneous tissue disorders	1	1 (0.2%)	5	2 (0.5%)	2	2 (0.4%)
Blister	0	0	0	0	1	1 (0.2%)
Skin burning sensation	0	0	4	1 (0.3%)	0	0
Skin irritation	0	0	1	1 (0.3%)	0	0
Skin lesion	1	1 (0.2%)	0	0	1	1 (0.2%)
Vascular disorders	0	0	1	1 (0.3%)	1	1 (0.2%)
Hematoma	0	0	0	0	1	1 (0.2%)
Intermittent claudication	0	0	1	1 (0.3%)	0	0

Source: Table 5.3.5.3.16b on pages 44-45 of the ISSE report.

Safety data from individual studies suggested that application site AEs were mostly reported in four studies (S-7, S-8, S-10, and S-11) of double-blind and placebo-controlled design with 24-hour daily application of at least seven days. Therefore, these AEs are pooled from the four studies as summarized in the table below. Other than pruritus (1.2% for Flector-H, 1.4 % for Flector, and 2.7% for placebo) most individual application site AEs were still <1%. The lower total proportions of application site AEs in the Flector-H and Flector groups than placebo group suggested that the application site AEs were caused mainly by prolonged skin contact with the patch with or without the active ingredients.

Table 31 Application Site AEs from Four 7- to 14-Day Studies of 24-Hour Daily Application

	Flector-H (N = 406)		**Flector (N = 286)**		**Placebo (N = 403)**	
	#AEs	#Subjects	#AEs	#Subjects	#AEs	#Subjects
Total AEs / subjects with AEs from four studies	11	8 (2.0%)	14	8 (2.8%)	25	18 (4.5%)
General disorders and administration site conditions						
Application site erythema	0	0	1	1 (0.3%)	4	3 (0.7%)
Application site inflammation	0	0	0	0	1	1 (0.2%)
Application site irritation	3	3 (0.7%)	2	1 (0.3%)	3	3 (0.7%)
Application site pruritus	6	5 (1.2%)	4	4 (1.4%)	14	11 (2.7%)
Application site rash	1	1 (0.2%)	1	1 (0.3%)	0	0
Application site reaction	1	1 (0.2%)	0	0	2	2 (0.5%)
Pain	0	0	1	1 (0.3%)	1	1 (0.2%)
Infections and infestations						

Localized infection	0	0	1	1 (0.3%)	0	0
Skin and subcutaneous tissue disorders						
Blister	0	0	0	0	1	1 (0.2%)
Skin burning sensation	0	0	4	1 (0.3%)	0	0

Source: Table 5.3.5.3.19 on pages 53-54 of the ISSE report.

7.4.2 Laboratory Findings

Routine chemistry and hematology laboratory tests were obtained pre and post treatment in healthy volunteers in the three PK studies. There were very few cases of shifts from normal baseline to abnormal post treatment value in a limited number of lab parameters. It is difficult to interpret the findings without comparison due to lack of a control group in these studies.

7.4.3 Vital Signs

Vital signs were not obtained in the clinical studies.

7.4.4 Electrocardiograms (ECGs)

There was no plan for ECG testing.

7.4.5 Special Safety Studies/Clinical Trials

According to Dr. Hamid Tabatabai's conclusion in the consult review from the Division of Dermatology and Dental Products dated January 11, 2017, Flector-H patch is not irritating or sensitizing and the drug's potential for phototoxicity or photoallergenicity could not be determined because of deviations in study design and conduct from typical studies of this kind.

7.4.6 Immunogenicity

Refer to the conclusion about dermatological safety study results above.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Dose dependency of AEs could not be adequately assessed because only 65 subjects were exposed to 10-day treatment with 12-hour daily application of Flector-H (Study S-9), not comparable to 409 exposed to 7- to 14-day treatment with 24-hour daily application of Flector-H (Studies S-7, S-8, S-10, and S-11).

7.5.2 Time Dependency for Adverse Events

Time dependency for adverse findings could not be adequately assessed due to very low rates of AEs.

7.5.3 Drug-Demographic Interactions

It is a challenge to try to analyze drug-demographic interactions when the AE reporting rates are very low. Analyses of drug-demographic interactions based on age and race are not applicable because of very limited subpopulation sample sizes of elderly and non-Caucasian. Analysis based on sex conducted by the Applicant did not suggest differential AE rates. Differential AE reporting rates based on study sites were noticed that nearly all AEs were reported from German sites in Study S-10 and from sites in Poland in Study S-11.

7.5.4 Drug-Disease Interactions

Drug-disease interactions could not be evaluated based on limited data in the NDA submission.

7.5.5 Drug-Drug Interactions

There was no plan to study drug-drug interactions in the NDA.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Refer to the professional drug labeling for Flector.

7.6.2 Human Reproduction and Pregnancy Data

Refer to the consult review for pregnancy and lactation labeling for the NDA by Dr. Christos Mastroyannis from the Maternal Health Review team dated January 31, 2017.

7.6.3 Pediatrics and Assessment of Effects on Growth

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 PeRC have agreed with the Sponsor's plans for partial waiver of pediatric studies in pediatric patients less than six years of age and deferral in pediatric patients 6-17 years of age. A revised iPSP incorporating the Division's comments and related pediatric protocol should be submitted through the IND for review.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Topical patch containing diclofenac is not anticipated to have potentials for drug overdose, drug abuse, or problems with withdrawal and rebound.

7.7 Additional Submissions / Safety Issues

There were no additional submissions of human safety data.

8. POSTMARKETING EXPERIENCE

According to the Applicant the drug product was commercialized in Switzerland since November 2006 and in France since January 2011. Based on global sale volume of about (b) (4) patches an estimate of (b) (4) patients might have potentially used the product. No serious adverse drug reactions had been reported and no safety signals from any sources (spontaneous reports, published literature, clinical trials, and epidemiological studies) have been detected based on post-marketing surveillance.

9. APPENDICES

9.1 Literature Review and other Important Relevant Materials/References

Literature review was not provided in this submission.

9.2 Labeling Recommendations

Labeling recommendations will not be provided in this review cycle because the deficiencies listed in the Agency's complete response letter need to be addressed by the Applicant before finalization of labeling.

9.3 Advisory Committee Meeting

There is no Advisory Committee Meeting planned for this product.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTINA L FANG
03/06/2017

JOSHUA M LLOYD
03/06/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring MD 20993

Tel 301-769-2110
FAX 301-796-9895

M E M O R A N D U M

Date: 12/13/2016

From: Hamid Tabatabai, MD, Medical Officer, DDDP

Through: Kendall Marcus, MD, Division Director, DDDP
Snezana Trajkovic, MD, Clinical Team Leader, DDDP

To: Sharon Hertz, MD, Acting Division Director, DAAAP

CC: Joshua Lloyd, MD, Clinical Team Leader, DAAAP
Christina Fang, MD, Medical Officer, DAAAP
Barbara Gould, CPMS, DDDP
J. Paul Phillips, RPM Team Leader, DDDP
Tisha Washington, RPM Staff, DDDP

Re: DDDP Consult #1783: Please review dermal safety studies from dermatology perspective.

Materials Reviewed:

- Study EU01.2002: Human Repeated Insult Patch Test" of DHEP/Heparin Tissugel (diclofenac epolamine /sodium heparin)

- Study 13FCDN-FHp03:Skin irritation and sensitization evaluation of (b) (4) : a Phase 1, 'Repeated Insult Patch Test' (RIPT) investigation to support the safety and tolerability of the medicated plaster (patch) formulation, in human healthy volunteers

- Evaluation of phototoxicity potential by UV-A irradiation on 20 human subjects

- Photoallergy Maximization test on 25 human subjects

Conclusion:
Based on results of dermal safety studies submitted by the applicant, it is reasonable to conclude that diclofenac (b) (4) 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 (b) (4) 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.

Background:
Diclofenac epolamine (DHEP) is a salt of diclofenac, a non-steroidal anti-inflammatory drug (NSAID) marketed in many countries since 1990. Flector patch is a topical formulation of DHEP that was approved in 2007 under NDA 21234. The applicant developed a new patch product containing DHEP and heparin indicated for the topical treatment of acute pain due to minor strains, sprains, and contusions. The applicant submitted results of 4 dermal safety studies in support of their application. The review of these studies is presented below.

Review

Evaluation of Irritation and Sensitization Potential

Study EU01.2002

Principal investigator: Prof. Ketty Peris
Clinica Dermatologica Di L'Aquila, 20 May 2003

Study Title: DHEP / Heparin Tissugel (diclofenac epolamine – sodium heparin): study on the skin irritation and sensitization potential ("human repeated insult patch test"-RIPT).

Study population: 50 healthy male and female subjects 18-55 years of age

Study design: This was Phase 1, randomized, single center, double-blind, placebo-controlled study.

Study procedures: This study consisted of three phases: Induction Phase, Rest Phase, and Challenge Phase.

Test products:

- Diclofenac/heparin patch [DHEP/Heparin Tissugel (adhesive plaster 10 x 7 cm)]
- Placebo patch [(Placebo Tissugel) (adhesive plaster 10 x 7 cm)]

a) Induction phase: On the day of study start, two areas on the contralateral sides of subjects' backs were selected and layers of the skin epithelium were removed with hypoallergenic strip. Diclofenac/heparin or Placebo patches were applied to the skin on subjects' backs on Mondays, Wednesdays, and Fridays, for three consecutive weeks, for a total of 9 applications. Patches remained in place for 48 hours during weekdays and, for 72 hours during the weekends.

Rest phase: This phase lasted 10 days (Day 20 to Day 30) during which, patches were not applied.

Challenge phase: On Day 31, layers of the skin epithelium were removed with a hypoallergenic strip and new patches were applied to naïve skin sites according to the same procedures used during the induction phase. One hour after application, the plaster was partially removed to verify the onset of skin reactions (immediate hypersensitivity); the plasters were re-applied and left in place for an additional 23 hours. On Day 32, patches from the previous day were removed and new patches were applied. Again, one hour after application, the plaster was partially removed to verify the onset of skin reactions (immediate hypersensitivity); the plasters were re-applied and left in place for an additional 23 hours. On Day 33, test patches were removed and an examination of the skin areas was performed. The areas were re-examined after 48 hours (Day 34) and 72 hours (Day 35), without any further application of test patches.
The following 7-point scale was used for evaluation of skin reactions during induction and challenge phases:

0 = Normal skin
1 = light erythema
2 = moderate erythema
3 = intense erythema
4 = erythema with edema or papules
5 = erythema with exudative vesicles or blisters
6 = erythema spread beyond margin of application site

Safety monitoring
Safety monitoring included physical examination and laboratory testing (hematology; chemistry; urinalysis, pregnancy test) at Baseline and at the end of study. In addition, evaluation for adverse events was conducted.

Study results:
During the indication phase, mean skin reaction scores in diclofenac/heparin and placebo treated sites were low. Similar irritation scores were reported for both patch sites. The results are presented in Table 1 below.

Table 1: Mean irritation score during induction phase (mean +/- SD)

Day	Number of subjects	Placebo	diclofenac / heparin

3	**50**	**0.02 +/- 0.14**	**0.06 +/- 0.31**
5	**50**	**0.04 +/- 0.28**	**0.04 +/- 0.19**
7	**50**	**0.00 +/- 0.00**	**0.04 +/- 0.19**
9	**50**	**0.02 +/- 0.14**	**0.08 +/- 0.34**
11	**50**	**0.00 +/- 0.00**	**0.06 +/- 0.24**
13	**50**	**0.00 +/- 0.00**	**0.02 +/- 0.14**
15	**50**	**0.00 +/- 0.00**	**0.02 +/- 0.14**
17	**50**	**0.08 +/- 0.57**	**0.04 +/- 0.19**
19	**49**	**0.02 +/- 0.14**	**0.06 +/- 0.32**

Source: Sponsor's submission

During the challenge phase, similar skin reaction scores were reported for both treatment sites. The results are presented in Table 2 below.

Table 2: Mean sensitization score during challenge phase (mean +/- SD)

Day	Number of subjects	placebo	diclofenac / heparin
31	**49**	**0.02+/-0.14**	**0.02+/-0.14**
32A	**49**	**0.02+/-0.14**	**0.02+/-0.14**
32B	**49**	**0.02+/-0.14**	**0.02+/-0.14**
33	**49**	**0.02+/-0.14**	**0.02+/-0.14**
34	**49**	**0.00+/-0.00**	**0.00+/-0.00**
35	**49**	**0.00+/-0.00**	**0.00+/-0.00**

Source: Sponsor's submission

Safety: No adverse events or laboratory abnormalities were reported during the conduct of this trial.

Reviewer's comments: The applicant combined the evaluation of irritation and sensitization of their product in a single study. For combined irritation/sensitization studies, it is recommended that the study include at least 200 evaluable subjects and that during the induction phase, patches be applied for 21 days over period of 3 weeks. The applicant's study included only 50 subjects who received nine patch applications over 3-week period. In addition, the sponsor did not include positive and negative controls needed to facilitate interpretation of study results. The study design of this study differs from design of studies typically used for evaluation of irritation/sensitization potential of topical drug products. Due to these differences, meaningful interpretation of study results could not be made. Therefore, based on the results of this study, the conclusion whether the diclofenac (b) (4) has the potential for irritation/sensitization cannot be made.

<u>Study 13FCDN-FHp03:</u>

Principal investigator: Dr. Robert Bissonnette

Study title: Skin Irritation and Sensitization Evaluation of (b) (4) a Phase 1, 'Repeated Insult Patch Test' (RIPT) Investigation to Support the Safety and Tolerability of the Medicated Plaster (patch) Formulation, in Human Healthy Volunteers

Study population: 248 male and female healthy volunteers between 18-65 years of age.

Study design: This was a Phase 1, single center, investigator-blinded, randomized, vehicle and reference controlled, within subject comparison. Study completed in Montreal, Quebec between 10/8/2013 to 1/21/2014.

Test patches:

- Diclofenac/heparin patch (b) (4)
- Diclofenac patch (Flector patch)
- Vehicle patch (includes heparin and all excipients)
- Positive control (0.1% sodium lauryl sulfate) patch
- Negative control (0.9% saline) patch

Study procedures: This study consisted of 3 phases: Induction phase, Rest phase and Challenge phase.

Induction phase: During this phase, test patches (diclofenac/heparin patch; diclofenac patch; vehicle patch; positive and negative control patches) were applied every 24 hours to the subjects' backs for 21 consecutive days.

Rest phase On Day 22, patches were removed and the subjects entered into a 14-day rest period during which no patch application was performed.

Challenge phase: After the rest period, the challenge phase consisted of a single 48-hour patch application on the naïve skin area. After 48 hours, patches were removed and evaluated at 30minutes, 24, hours, 48 hours and 72 hours.

Evaluation Criteria: "Dermal Response" and "Other Effects" were evaluated using the following scales:

Dermal response:
0 = no evidence of irritation
1 = minimal erythema, barely perceptible
2 = definitive erythema, readily visible, edema or minimal – papular response
3 = erythema and papules
4 = definite edema
5 = erythema, edema and papules
6 = vesicular eruption
7 = strong reaction spreading beyond test site

Other effects:

A = slight glazed appearance
B = marked glazing
C = glazing with peeling and cracking
F = glazing with fissures
G = film of dried serous exudate covering all of part of the patch site
H = small petechial erosions and/or scabs
The mean cumulative irritation score (calculated as the sum of all combined "Dermal Response" and "Other Effects" scores observed at each observation divided by the total number of observations) and the total cumulative irritation score for all the study subjects was calculated for each test product, and a statistical analysis of the comparative results was performed.

For each study product, each subject with a combined score of 2 or greater at 48 or 72 hours after patch removal during the Challenge Phase was individually evaluated for potential sensitization.

A subject was considered to be potentially sensitized if all of the following criteria were met:
a. The subject had at least one evaluation occurring at more than 24 hours (e.g., at 48 or 72 hours) after the removal of the Challenge Phase patch.
b. The subject had a combined "Dermal Response" and "Other Effects" numeric score of at least 2 at their last evaluation during the Challenge Phase.
c. In general, the combined "Dermal Response" and "Other Effects" numeric scores obtained during the Challenge Phase evaluations were higher than the combined "Dermal Response" and "Other Effects" numeric scores obtained during the Induction Phase.

If the subject completed a Re-Challenge Phase (the above 3 criteria were met during both the Challenge Phase and the Re-challenge Phase), those subjects were to be considered as sensitized.

Safety monitoring
Safety evaluation included through assessment of adverse events, vital signs and clinical laboratory (ALT/AST) values.

Study results
Irritation:
For the diclofenac/heparin patch, diclofenac patch and Vehicle patch, the daily dermal response scores varied from 0 to 3 with a mean of 0 to 0.1, and it was constant over time. For the Positive control, the daily dermal response scores varied from 0 to 6 with a mean of 0.4 to 1.8 and, it was constant over time. For the Negative control, the daily dermal response scores varied from 0 to 5 with a mean of 0.2 to 1.5, and it was constant over time. Dermal response scores for the induction phase of this study are presented in Appendix 1.

Sensitization:

No subjects presented with sensitization at the Flector (diclofenac) patch and Vehicle patch sites.

One subject each presented with a questionable sensitization at the (b) (4) (diclofenac/(b) (4) site and positive control patch site. Five subjects presented with a questionable sensitization at the Negative control patch sites. All subjects with questionable sensitization reactions re-challenged and were all considered non-sensitized upon re-challenge.

Safety:
No serious adverse events were reported during the conduct of this study.
Of 219 subjects (88.3%), 111 (50.7%) subjects experienced 180 adverse reactions during the Induction phase. Of 206 subjects (83.0%), 24 (11.7%) subjects experienced a total of 29 adverse reactions during the Challenge phase.

In the Induction phase, the proportions of subjects who experienced adverse reactions were 33.5% with the Positive control, 28.0% with the Negative control, 1.0% with the Vehicle and 0.5 % each, for (b) (4) and Flector patch. Most commonly reported adverse reactions were application site discomfort, 34% and 27.6% for the Positive and Negative controls, respectively.

Contact dermatitis was reported in 40.9% and 53.7% for the Positive and Negative controls respectively. The contact dermatitis was reported by investigators as being related to the adhesive tape used to maintain the control patches in place.

Reviewer's comments:
This study was adequate in design and conduct for evaluation of irritation and contact sensitization potential of the test product. The study results indicate that a significant irritation or contact sensitization did not occur during this study.

3) Evaluation of phototoxicity potential by UV-A irradiation on 20 human subjects:
Conducted 7/24/2000 to 7/31/2000

Study Director: Shyla Cantor, Ph.D./AMA laboratories

Study title: Evaluation of phototoxicity potential by UV-A irradiation on 20 human subjects

Study population: 20 male and female subjects 18-62 years old with Fitzpatrick skin type I - III

Study design: This was a randomized, single center, double blind, placebo-controlled study.

Study procedures:

Test patches:

- Diclofenac/heparin [(Flector EP Tissugel)-pre-cut patches 2.5 x 2.5 cm]
- Pre-cut patch - Hydrophilic ointment (Negative control)

For all subjects, the inner left arm was designated as a control site (non-irradiated) while the inner right arm was designated as a test site (irradiated). On the first day of the study, skin test sites were stripped with hypo-allergenic tapes 3 times to remove layers of cornified epithelium. Test patches were applied to both left and right arms, but only the right arm was irradiated with UV-A light dosage of greater than 4.4 mW/cm^2. The test sites were then covered by Readi-Bandages and remained in place for 24 hours. The next day, patches were removed and skin reactions were recorded immediately post patch removal and, after 24 hours, 48 hours, and 7 days after removal. The following scoring scale was used for grading of skin reactions:

Scoring Scales
0 = no effect
1+ = minimal, faint, uniform or spotty erythema
1 = pink, uniform erythema covering most or all of the contact sites
2 =pink-red erythema visibly uniform in entire contact site
3 =bright red erythema with or without petechiae or papules
4 = deep red erythema with or without vesiculation or weeping

Safety monitoring: The applicant did not provide information regarding safety monitoring during the conduct of this study.

Study results: No skin reactions were noted at any of test sites.

Safety: No adverse events were reported during the conduct of this study.

Reviewer's comments:
For the phototoxicity studies, it is recommended that the study includes at least 30 evaluable subjects. The irradiation dose and light recommended for phototoxicity evaluation are $16J/cm^2$ of ultraviolet A light (UVA) and 0.75 MED of UVA/ultraviolet B (UVB). The irradiation light and dose used by the sponsor was 4.4 mW/cm^2 of UVA light that equates to 4.23 J/cm^2 when using the following conversion factor (1 mW/ Second= 0.001 Joules). The irradiation of patches should have been performed after patches were in place for 24 hours and not immediately after the patch placement as done by the applicant.

The study design of this study differs from design of studies typically used for evaluation of phototoxicity potential of topical drug products. Due to these differences, meaningful interpretation of study results could not be made. Therefore, based on the results of this study, the conclusion whether the diclofenac/heparin patch has the potential for phototoxicity cannot be made.

4) Photoallergy Maximization test on 25 human subjects
Conducted 6/7/1999-7/16/1999

Study Director: Shyla Cantor, Ph.D./AMA Laboratories
Study title: Photoallergy maximization test on 25 human subjects
Study population: 27 male and female healthy volunteers 18-59 years of age with Fitzpatrick skin type I - III.

Study design: This was a randomized, single center, double-blind, placebo controlled study.

Test patches included:
- Diclofenac / heparin patch (Flector EP Tissugel) 2.5 x 2.5 cm
- Patch Materials only (Vehicle control)
- Hydrophilic ointment (Blank control)

Study procedures:
Minimal Erythema Dose (MED) was determined (in seconds of exposure time) for each subject prior to initiation of study.

This study consisted of three phases:

a) Induction phase: On Day 1, duplicate skin test sites (2.5 x 2.5 cm), to which 62.5µl of the test substance was evenly applied, were designated on subjects' backs. Skin test sites were then covered with Readi-Bandage occlusive patches. Skin test sites were wiped clean after 24 hours and only one of the two sites was irradiated with 3 MEDs of simulating solar irradiation. The other patch site remained non-irradiated. This sequence was repeated twice weekly for 3 weeks, for a total of 6 exposure cycles. Five skin sites were selected as controls :
    - Normal intact skin, untreated (Control)
    - Patch materials only, no product, no exposure (Vehicle Patch)
    - Patch materials with 4 J/cm^2 UV-A exposure (Vehicle Patch)
    - Hydrophilic ointment USP- patched, non-irradiated(Blank patch)
    - Hydrophilic ointment USP – patched and irradiated(Blank Patch)

b) Rest phase: This phase lasted 10-14 days during which there was no patch application or irradiation.

c) Challenge phase: During this phase, patches were applied to naive skin sites and left in place for 24 hours. After 24 hours, patches were removed and test products were wiped off followed by irradiation with 10 J/cm^2 of UV-A light. Skin reactions were scored 48 hours and 72 hours after irradiation.

Scoring Scale: The same scale was use as the one used for phototoxicity evaluation (see above).

Safety monitoring:
The applicant did not provide information regarding safety monitoring during the conduct of this study.

Study results: No skin reactions were noted at any of test sites.

Safety: No adverse effects were reported during the conduct of this study.

Reviewer's comments:
For the photoallergenicity study, it is recommended that the study includes at least 45 evaluable subjects. The sponsor's study included 27 subjects. In the challenge phase of photoallergenicity study, it is recommended that skin reactions be evaluated at 30 minutes, 24, 48, and 72 hours after patch removal and irradiation. The sponsor's study only evaluated skin reactions at 48 and 72 hours post irradiation. The radiation intensity in this study was at 10 J/cm^2 of UV-A, not the recommended 16 J/cm ^{2} of UV-A and 0.75 MED of UV-A / UV-B.

The study design of this study differs from design of studies typically used for evaluation of photoallergenicity potential of topical drug products. Due to these differences, meaningful interpretation of study results could not be made. Therefore, the conclusion whether the diclofenac (b) (4) has the potential for photoallergenicity, cannot be made.

Reviewer's conclusion regarding four dermal safety studies submitted by the applicant:
Based on results of dermal safety studies submitted by the applicant, it is reasonable to conclude that diclofenac (b) (4) is not irritating or sensitizing.

Due to differences in study designs and conduct typically used to evaluate the phototoxicity and photoallergenicity, the conclusion whether diclofenac/heparin patch has the potential for phototoxicity or photoallergenicity, could not be made.

Hamid Tabatabai, MD
Medical Officer
Department of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Appendix

Dermal Response Scores, Induction Phase Study 13FCDN-FHp03

Characteristic	Statistic	(b) (4)	Flector	Vehicle	Positive Control	Negative Control
Number of subjects	Number	208	208	210	215	214
Day 2	Mean (S.D.)	0.1 (0.22)	0.0 (0.18)	0.1 (0.26)	0.4 (0.55)	0.2 (0.45)
	Median	0	0	0	0	0
	IQ Range	0 - 0	0 - 0	0 - 0	0 - 1	0 - 0
	Min-Max	0 - 1	0 - 1	0 - 2	0 - 2	0 - 2
	N	208	208	210	215	214
Day 3	Mean (S.D.)	0.0 (0.23)	0.0 (0.21)	0.1 (0.28)	0.9 (0.81)	0.4 (0.61)
	Median	0	0	0	1	0
	IQ Range	0 - 0	0 - 0	0 - 0	0 - 2	0 - 1
	Min-Max	0 - 2	0 - 1	0 - 2	0 - 3	0 - 2
	N	208	208	210	215	214
Day 4	Mean (S.D.)	0.1 (0.25)	0.0 (0.25)	0.0 (0.18)	1.5 (0.90)	0.9 (0.82)
	Median	0	0	0	2	1
	IQ Range	0 - 0	0 - 0	0 - 0	1 - 2	0 - 2
	Min-Max	0 - 2	0 - 2	0 - 1	0 - 6	0 - 3
	N	208	208	210	215	214
Day 5	Mean (S.D.)	0.0 (0.21)	0.0 (0.25)	0.0 (0.20)	1.6 (0.94)	1.2 (0.89)
	Median	0	0	0	2	1
	IQ Range	0 - 0	0 - 0	0 - 0	1 - 2	0 - 2
	Min-Max	0 - 2	0 - 2	0 - 2	0 - 6	0 - 3
	N	208	208	210	212	213
Day 6	Mean (S.D.)	0.0 (0.17)	0.1 (0.29)	0.0 (0.17)	1.8 (0.82)	1.5 (0.87)
	Median	0	0	0	2	2
	IQ Range	0 - 0	0 - 0	0 - 0	1 - 2	1 - 2
	Min-Max	0 - 1	0 - 2	0 - 1	0 - 3	0 - 3
	N	208	208	210	208	213
Day 7	Mean (S.D.)	0.1 (0.38)	0.1 (0.40)	0.1 (0.30)	1.7 (0.89)	1.5 (0.90)
	Median	0	0	0	2	2
	IQ Range	0 - 0	0 - 0	0 - 0	1 - 2	1 - 2
	Min-Max	0 - 3	0 - 3	0 - 2	0 - 3	0 - 3
	N	208	208	210	205	210

NOTE : N=number of subjects S.D.=standard deviation IQ=Interquartile. PPI=Per-Protocol Population for evaluation of skin irritation. Program: tl4_02_01_01.sas, Generated on: 10JUN2014 17:53, Source: Listing 16.2.6.1.

Day 8	Mean (S.D.)	0.1 (0.27)	0.1 (0.36)	0.1 (0.27)	1.6 (0.94)	1.5 (0.96)
	Median	0	0	0	2	2
	IQ Range	0 - 0	0 - 0	0 - 0	1 - 2	1 - 2
	Min-Max	0 - 2	0 - 2	0 - 2	0 - 6	0 - 3
	N	191	191	192	190	194
Day 9	Mean (S.D.)	0.1 (0.31)	0.1 (0.36)	0.1 (0.26)	1.6 (0.95)	1.5 (0.91)
	Median	0	0	0	2	2
	IQ Range	0 - 0	0 - 0	0 - 0	1 - 2	1 - 2
	Min-Max	0 - 2	0 - 2	0 - 2	0 - 6	0 - 3
	N	191	191	192	190	193
Day 10	Mean (S.D.)	0.0 (0.24)	0.1 (0.31)	0.0 (0.24)	1.5 (0.95)	1.4 (1.00)
	Median	0	0	0	2	2
	IQ Range	0 - 0	0 - 0	0 - 0	1 - 2	0 - 2
	Min-Max	0 - 2	0 - 2	0 - 2	0 - 4	0 - 3
	N	191	191	192	184	191
Day 11	Mean (S.D.)	0.1 (0.27)	0.1 (0.31)	0.0 (0.19)	1.5 (0.90)	1.5 (0.96)
	Median	0	0	0	2	2
	IQ Range	0 - 0	0 - 0	0 - 0	1 - 2	1 - 2
	Min-Max	0 - 2	0 - 2	0 - 1	0 - 3	0 - 3
	N	191	191	192	182	190
Day 12	Mean (S.D.)	0.1 (0.35)	0.1 (0.31)	0.0 (0.24)	1.6 (0.86)	1.5 (0.98)
	Median	0	0	0	2	2
	IQ Range	0 - 0	0 - 0	0 - 0	1 - 2	0 - 2
	Min-Max	0 - 2	0 - 2	0 - 2	0 - 3	0 - 3
	N	191	191	192	176	184
Day 13	Mean (S.D.)	0.1 (0.31)	0.1 (0.32)	0.0 (0.19)	1.7 (0.86)	1.5 (0.92)
	Median	0	0	0	2	2
	IQ Range	0 - 0	0 - 0	0 - 0	1 - 2	1 - 2
	Min-Max	0 - 2	0 - 2	0 - 2	0 - 3	0 - 3
	N	191	191	192	171	178

Day 14	Mean (S.D.)	0.1 (0.42)	0.1 (0.35)	0.0 (0.20)	1.7 (0.80)	1.5 (0.90)
	Median	0	0	0	2	2
	IQ Range	0 - 0	0 - 0	0 - 0	1 - 2	1 - 2
	Min-Max	0 - 2	0 - 2	0 - 2	0 - 3	0 - 3
	N	191	191	192	164	171
Day 15	Mean (S.D.)	0.1 (0.32)	0.1 (0.44)	0.0 (0.10)	1.5 (0.87)	1.2 (0.97)
	Median	0	0	0	2	1
	IQ Range	0 - 0	0 - 0	0 - 0	1 - 2	0 - 2
	Min-Max	0 - 2	0 - 2	0 - 1	0 - 5	0 - 5
	N	191	191	192	162	168
Day 16	Mean (S.D.)	0.1 (0.35)	0.1 (0.33)	0.0 (0.20)	1.5 (0.90)	1.2 (1.03)
	Median	0	0	0	2	1
	IQ Range	0 - 0	0 - 0	0 - 0	1 - 2	0 - 2
	Min-Max	0 - 2	0 - 2	0 - 2	0 - 5	0 - 4
	N	191	191	192	160	166
Day 17	Mean (S.D.)	0.1 (0.30)	0.1 (0.35)	0.0 (0.16)	1.5 (0.95)	1.3 (0.99)
	Median	0	0	0	2	1
	IQ Range	0 - 0	0 - 0	0 - 0	1 - 2	0 - 2
	Min-Max	0 - 2	0 - 2	0 - 2	0 - 5	0 - 3
	N	191	191	192	156	163
Day 18	Mean (S.D.)	0.1 (0.26)	0.1 (0.35)	0.0 (0.16)	1.5 (0.88)	1.2 (0.95)
	Median	0	0	0	2	1
	IQ Range	0 - 0	0 - 0	0 - 0	1 - 2	0 - 2
	Min-Max	0 - 2	0 - 2	0 - 1	0 - 3	0 - 3
	N	191	191	192	154	159
Day 19	Mean (S.D.)	0.1 (0.26)	0.1 (0.41)	0.0 (0.25)	1.6 (0.86)	1.3 (0.96)
	Median	0	0	0	2	1
	IQ Range	0 - 0	0 - 0	0 - 0	1 - 2	0 - 2
	Min-Max	0 - 2	0 - 2	0 - 2	0 - 3	0 - 3
	N	191	191	192	152	157
Day 20	Mean (S.D.)	0.1 (0.32)	0.1 (0.35)	0.0 (0.12)	1.6 (0.85)	1.4 (0.96)
	Median	0	0	0	2	2
	IQ Range	0 - 0	0 - 0	0 - 0	1 - 2	1 - 2
	Min-Max	0 - 2	0 - 2	0 - 1	0 - 3	0 - 3
	N	191	191	192	145	154
Day 21	Mean (S.D.)	0.1 (0.27)	0.1 (0.33)	0.0 (0.21)	1.6 (0.87)	1.3 (1.04)
	Median	0	0	0	2	2
	IQ Range	0 - 0	0 - 0	0 - 0	1 - 2	0 - 2
	Min-Max	0 - 2	0 - 2	0 - 2	0 - 3	0 - 3
	N	191	191	192	141	151
Day 22	Mean (S.D.)	0.1 (0.31)	0.1 (0.28)	0.0 (0.26)	1.4 (0.89)	1.3 (1.07)
	Median	0	0	0	1	1
	IQ Range	0 - 0	0 - 0	0 - 0	1 - 2	0 - 2
	Min-Max	0 - 2	0 - 2	0 - 2	0 - 3	0 - 5
	N	191	191	192	139	151

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HAMID N TABATABAI
01/11/2017

SNEZANA TRAJKOVIC
01/11/2017

KENDALL A MARCUS
01/11/2017