

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-234

MEDICAL REVIEW



FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA AND RHEUMATOLOGY PRODUCTS

DIVISION DIRECTOR REVIEW AND BASIS FOR APPROVAL ACTION

DATE: January 31, 2007

DRUG: Flector® Patch, (diclofenac epolamine topical patch) 1.3%

NDA: 21-234

NDA Code: Type 3S NDA

SPONSOR: Institut Biochemique SA

INDICATION: For the topical treatment of acute pain due to minor strains, sprains and contusions

Institut Biochemique SA (IBSA) submitted their original application for the Flector® Patch on December 20, 2000. The Division of Analgesic, Anti-Inflammatory, and Ophthalmologic Drug Products took a Not-Approvable action on this application on October 18, 2001. The Not-Approvable letter cites the following deficiencies:

1. "The submitted studies fail to demonstrate efficacy of Diclofenac Epolamine Patch (DHEP) for _____ This determination was based on the following factors:

- Study 49459-01 failed to demonstrate efficacy based on the primary efficacy variables of pain intensity difference, sum of pain intensity difference, pain on pressure difference and sum of pain on pressure difference for Days 3, 7 and 14.
- Study 49459-02 failed to demonstrate efficacy, based on several deficiencies:

- When a significant imbalance in body weight between the treatment arms is incorporated into the analysis of the primary endpoint of time to pain resolution, no significant treatment difference was detected.
- The protocol specified endpoint analysis of daily pain score (a secondary endpoint) called for use of “nominal days on therapy,” while the submitted post hoc analysis employed a “24-hour” measure. The Division’s analysis employing nominal days demonstrated no statistically significant treatment effect. The Division noted that, “The nominal day is more relevant in view of the impact of activity and weight bearing on pain following injury. Time of measurement in relation to daily sleep/rest cycle is a critical issue that should be addressed in study design and analysis.”
- Each of the secondary efficacy variables failed to show a statistically significant treatment effect and a successful outcome on these variables would be necessary to fully interpret the clinical benefit proposed based on the derived endpoint of median time to pain resolution.

2. There were also 13 CMC deficiencies, and deficiencies in the Pharmacokinetic and Biopharmaceutics area that included:

- Absence of a complete assay validation report for Study 910195
- Absence of information on the long-term stability of the plasma samples for Study PK-0033; and
- Absence of an assay validation report for Study PK-9814.

An additional comment (not defined as a deficiency) was included in the letter that stated that, “...the applicant has not presented any information regarding dose ranging or dose selection. As part of their re-submission the applicant should provide a rationale as to their selection of the patch size and concentration and how these factors relate to clinical efficacy/safety.”

A Post-action Meeting was held on November 20, 2001, at which the applicant was informed that two additional efficacy studies would be required to support the indication. The sponsor submitted a response to the Not-Approvable letter in March of 2002. This response was considered incomplete as it contained no new clinical data and did not address the other deficiencies listed in the Not-Approvable letter. A letter to this effect was issued on April 16, 2003. The sponsor submitted this second response to the Not-Approvable letter on July 27, 2006 and it was considered a complete response by the current Division. This submission contains one new clinical pharmacology study and two clinical efficacy studies that had been initiated around the time of the Not-

Approvable action. The protocols for the two efficacy studies were not submitted to the Division for review or comment prior to the studies being performed.

Review of the CMC portion of this submission was completed by Sue-Ching Lin, Ph.D. Review of the pharmacology and toxicology data was completed by R. Daniel Mellon, Ph.D. Review of the clinical pharmacology and biopharmaceutics data was completed by Srikanth C. Nallani, Ph.D. A statistical review was completed by Barbara Elashoff, and Dionne L. Price, Ph.D provided a secondary statistical review. The clinical review was completed by Robert A. Levin, M.D. Mwangi A. Kashoki, M.D. provided a secondary clinical review. Consultations on this submission were obtained from the Division of Drug Marketing, Advertising and Communications (DDMAC) and the Office of Surveillance and Epidemiology (OSE).

Efficacy:

Two clinical trials were submitted in the original application in support of the efficacy of the Flector® Patch. Studies 49,459-01 (Study 01) and 49,459-02 (Study 02) both evaluated the efficacy of twice-daily application of the Flector® Patch for 14 days for the treatment of minor injuries, i.e., ankle and knee sprains, contusions. Study 1 did not have a clearly defined primary outcome measure while Study 2 employed “time to pain resolution” as the primary outcome variable. Neither study was able to demonstrate a statistically significant treatment effect. However, for this submission the sponsor reanalyzed the efficacy data for both trials employing “mean pain at study end divided by the baseline pain” as the efficacy variable. The clinical and statistical review teams reviewed this data and have determined that the results of these reanalyses, as well as a comparison of the mean pain scores over the study duration, suggest an analgesic effect for the Flector® Patch. As noted above, the Not-Approvable letter also noted concerns regarding treatment arm imbalances in body weight, the use of a 24-hour day measure rather than the protocol-specified “nominal days on therapy,” and the absence statistically significant results for the secondary outcome measures. While these concerns would, individually or as a group, raise questions about the efficacy results if those results were borderline, they are of questionable value considering the clear demonstration of efficacy provided by weight of evidence that includes the results of the studies described below.

Ms. Elashoff and Drs. Levin, Kashoki, and Price have provided thorough and complete reviews of the two new efficacy studies. As such, I will only briefly summarize the results.

Study 00GB/Fp05 (UK/German Study)

The Flector® Patch administered twice daily was compared to placebo for the treatment of minor soft tissue injuries (sprains, strains or contusions) over a two-week period in this randomized, parallel-group, double-blind, multicenter trial. The protocol-specified primary outcome measure was “time to pain resolution,” defined as the time from the

initial patch application to the fourth consecutive pain score of less than or equal to 2 on a 0 to 10 numerical rating scale of pain intensity. The sponsor modified the statistical analysis plan in a blinded fashion during the study after observing that there were numerous dropouts due to subjects having apparent efficacy (low pain scores) in spite of the fact that they had not met the specified four consecutive scores of less than or equal to 2. In the modified statistical analysis plan the sponsor employed the “mean pain score over the 14-day period divided by the baseline pain score” as the primary outcome variable. Dr. Price’s Table 3, page 7 of her review, (sponsor’s Table 8, Final Study Report) summarizes the results of the primary outcome analysis and is reproduced below:

Table 3: Efficacy Evaluable Population: Primary Outcome Variable
(Source: Applicant’s Table 8, Final Study Report)

Parameter*	Diclofenac Epolamine Patch	Placebo Patch	p-value†
Primary Outcome Variable			
Multiple Imputation Strategy	0.4 ± 0.2	0.5 ± 0.3	0.009
LOCF Analysis	0.4 ± 0.3	0.5 ± 0.3	<0.001
GEE Model Analysis	0.6	0.6	0.008

* Mean ± standard deviation provided where appropriate.

† P-values derived from multiple imputation ANOVA, repeated measures ANOVA, or GEE analysis, respectively. LOCF= last observation carried forward, GEE=general estimating equations.

The review team was concerned that the selected primary outcome variable would be difficult to interpret from a clinical perspective. As such, they also analyzed the data looking at two additional endpoints: the “mean change in pain from baseline to the end of the study” (the most common primary outcome variable employed for analgesic efficacy trials submitted in support of new drug applications); and by performing a responder analysis which permitted patients who discontinued from the study due to injury resolution to be considered responders. For the responder analysis, the team also assessed efficacy at Day 3, due to concerns that patients with minor injuries may have significant improvement in their symptoms by the third day leading to discontinuation of treatment, and thereby making it difficult to evaluate efficacy at Day 14. Dr. Price’s Table 4, page 7 of her review, summarizes the results of the first of these analyses and is reproduced below:

Table 4: Analysis of change from baseline to day 14

		Diclofenac Patch (n=207)	Placebo Patch (n=211)	
Baseline				
Change from Baseline to Day 14	Mean (Std deviation)	7.3 (1.3)	7.5 (1.3)	
<i>Imputation Strategy 1*</i>	LS Mean (SE)	-3.5 (0.2)	-2.8 (0.2)	
	LS Mean difference			-0.7 (-1.3,-0.07)
	p-value			0.029
<i>Imputation Strategy 2**</i>	LS Mean (SE)	-5.0 (.2)	-4.2 (.2)	
	LS Mean difference			-0.8 (-1.3,-0.2)
	p-value			0.007

p-values derived via an ANCOVA model with factors for treatment and center and baseline as a covariate.

*Imputation Strategy 1 = LOCF for all pts discontinuing due to injury resolution and BOCF for all other discontinuation reasons.

**Imputation Strategy 2 = LOCF for all pts discontinuing.

The responder analyses, both for Day 3 and Day 14, were strongly supportive of the above results.

Study 05-05-98 (French Study)

The Flector® Patch administered once-daily over 7 days as treatment for minor ankle sprain was compared to placebo in this double-blind, parallel-group, multicenter trial. The primary outcome measure was the “mean pain score at endpoint” on a 100-mm visual analogue scale of pain intensity. The results of that analysis are summarized in Dr. Price’s Table 7, page 11 of her review, (based on Ms. Elashoff’s review) and are reproduced below:

Table 7: Mean VAS as Day 3 and Day 7
(Source: Statistical Review of Ms. Elashoff’s)

		Diclofenac Patch (n=68)	Placebo Patch (n=66)	
VAS at Day 3	LS Mean (SE)	17.8 (3.2)	30.5 (3.5)	
	LS Mean difference			-12.7
	p-value			0.001
VAS at Day 7	LS Mean (SE)	12.1 (2.8)	21.4 (3.1)	
	LS Mean difference			-9.3
	p-value			0.004

p-values derived via an ANOVA model with terms for treatment and center.

As “mean pain score at endpoint” can be confounded by baseline differences, Dr. Price also analyzed the “mean change from baseline.” The results of that analysis, summarized in Dr. Price’s Table 10, page 13 of her review, are summarized below:

Table 9: Change from Baseline Analyses

	Diclofenac Patch (n=68)	Placebo Patch (n=66)	
Baseline			
Mean (Std deviation)	66.9 (10.6)	70.0 (11.8)	
Change from Baseline to Day 3			
Mean (Std deviation)	-49.9 (21.7)	-40.5 (22.0)	
LS Mean (SE)	-50.8 (2.5)	-39.6 (2.6)	
LS Mean difference			-11.2 (-18.4,-4.0)
p-value			0.003
Change from Baseline to Day 7			
Mean (Std deviation)	-56.0 (19.2)	-50.7 (20.1)	
LS Mean (SE)	-57.0 (2.2)	-49.8 (2.3)	
LS Mean difference			-7.2 (-13.6,-0.9)
p-value			0.027

Analysis conducted using ANCOVA with treatment as a factor and baseline pain as a covariate in the model.

Similar responder analyses at Days 3 and 7, as conducted for Study 00GB/Fp05, were again strongly supportive of the above outcomes.

Clinical Safety:

There were no serious adverse events in the clinical studies. The most common adverse event was “application site reaction” and this occurred with similar frequency in both the Flector® Patch and placebo patch groups. Dermatitis did occur with greater frequency (2% vs. 0.5%) in the Flector® Patch-treated subjects, but these events were generally mild and self-limited. GI events, most commonly nausea and dysgeusia, also occurred with increased frequency in the Flector® Patch-treated subjects (9% vs. 6%), but were also generally mild and resolved spontaneously. Discontinuations occurred infrequently and were due to “application site reactions,” again with the same frequency in both treatment arms.

CMC:

As per Dr. Kashoki's review, page 4:

Dr. Lin has concluded that the applicant has completely addressed all of the deficiencies identified in the Not Approvable letter. In particular, the applicant has addressed concerns regarding:

- Adequacy of the Drug Master File (DMF) for the diclofenac epolamine drug substance
- A letter of authorization (LOA) permitting the Agency to review the DMF of the Dalin PH fragrance
- The lack of information regarding the
 - composition of the felt backing material and release liner
 - analytical procedure and method validation for the drug substance
 - testing and reporting of stability of drug batches

Preclinical Safety:

While there were no preclinical approvability concerns noted in the Not-Approvable letter, on this review cycle Dr. Mellon noted the absence of appropriate exposure margins for the reproductive toxicology data in the original submission. From pages 8 and 9 of his review:

Inclusion of exposure margins in the product labeling provides useful information to the physician on the significance of the animal findings. Due to the absence of toxicokinetic data from the reproductive toxicology studies conducted with oral diclofenac epolamine, exposure margins based on toxicokinetic parameters can not be determined. Therefore, exposure margins must be made via a body surface area comparison. A worst case scenario of 100% absorption of the 180 mg per patch would be a gross overestimate of the total exposure clinically, since most of the drug remains in the patch. According to the sponsor's submission, based on analysis of residual diclofenac epolamine levels in patches following application, approximately 5% of the diclofenac epolamine is lost from the patch after topical application for a 24 hour application period. Since a patch contains 180 mg, and up to two patches could be applied per day for 12 hours, an individual could be exposed to a maximum of about 18 mg of diclofenac epolamine/day. Assuming 100% absorption of the 18 mg, this dose corresponds to 11.1 mg/m² based on body surface area for a 60 kg person. The oral doses used in the nonclinical reproductive toxicology studies can be compared to the clinical exposures based on body surface area comparisons. The rat oral dose of 6 mg/kg (36 mg/m²) results in approximately 3.2-times the maximum human exposure based on body surface area comparisons. The rabbit dose of 6 mg/kg (72 mg/m²) results in approximately 6.5-times the maximum human exposure based on body surface area comparisons. The table below summarizes the exposure margins obtained via the body surface area comparisons described above:

Species	Dose (mg/kg)	Dose (mg/m ²)	Exposure margin
Human ¹	18 mg/60 kg	11.1	--
Rat	3 mg/kg 6 mg/kg	18 36	1.6 3.2
Rabbit	3 mg/kg 6 mg/kg	36 72	3.2 6.5
¹ The maximum daily recommended dose in the human is based on predicted absorption of 5% of the diclofenac epolamine from a single patch application (9 mg) and a total of two patches applied per day (average 60 kg person).			

It is recognized that these exposure margins are likely smaller than what would be obtained if pharmacokinetic data were available to provide a more accurate exposure comparison. Since clinical pharmacokinetic data following topical application exists, the sponsor would only have to obtain comparable pharmacokinetic data (C_{max} and AUC_{0-t}) in rats and rabbits following oral administration of 3 and 6 mg/kg diclofenac epolamine. Such data would likely result in greater exposure margins. However, since the data would not result in a change in the pregnancy category and would not likely result in a reduction in the exposure margins, these studies should be recommended but not required.

Clinical Pharmacology and Biopharmaceutics:

As per Dr. Kashoki's review, page 5:

The applicant was unable to provide a validation report for one of the older pharmacokinetic studies (trial #910195), and noted that the data derived from this study were considerably different from the other studies that utilized validated analytical methods. Therefore the applicant conducted Study CRO-PK-02-76, a pharmacokinetic study evaluating the systemic levels of diclofenac epolamine following single- and multiple-dose administration of the patch. Dr. Nallani considered this study, its results, and the assay validation report to be acceptable. The assay validation reports submitted for the other previously conducted pharmacokinetic trials were also acceptable.

Discussion:

The sponsor has provided adequate evidence of the efficacy and safety of the Flector® Patch as delineated above. They have also resolved all of the CMC concerns, and they have addressed the Clinical Pharmacology and Biopharmaceutics deficiencies.

Action: Approval

Bob A. Rappaport, M.D.

Director

Division of Anesthesia, Analgesia and Rheumatology Products

Office of Drug Evaluation II, CDER, FDA

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/s/

Bob Rappaport
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MEDICAL OFFICER



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS
HFD-170, 10903 New Hampshire Ave., Silver Spring MD 20993**

MEDICAL TEAM LEADER MEMORANDUM - ADDENDUM

DATE: January 12, 2007

TO: File, NDA 21-234

FROM: Mwango A. Kashoki, M.D., M.P.H.
Medical Team Leader

RE: Supervisory Review of NDA 21-234
Diclofenac Epolamine Patch (Flector® Patch)
Institut Biochemique SA (IBSA)

Proposed Indication: _____ . due to strains, sprains and contusions

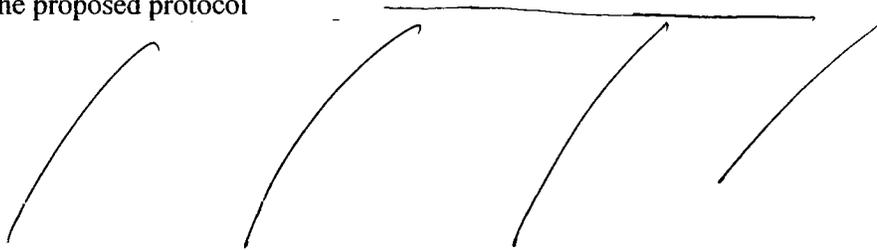
Pediatric Studies

In my initial memorandum, I incorrectly stated that the applicant had requested and had been granted a deferral of pediatric studies.

In fact, on February 21, 2001 the applicant requested a waiver of all pediatric studies. The Division of Analgesic, Anti-Inflammatory, and Ophthalmologic Drug Products (DAAODP) denied this waiver, stating that there was no justification a waiver and that pediatric patients could benefit from treatment with a topical non-steroidal anti-inflammatory product (denial letter issued November 26, 2001).

During the filing review of the current NDA submission, it was noted that the application did not contain any information relating to use of diclofenac patch in pediatric patients. In response to a request for this information, the applicant stated that they would either request a pediatric waiver, or submit a pediatric development plan within 3 months. The sponsor elected to do the latter, and submitted a synopsis of a pediatric protocol on December 14, 2006 (protocol submitted to the IND, I 49, 459).

In brief, the proposed protocol



It is my opinion that because the proposed indication and because any ambulatory child may experience sprains, strains, or contusions, studies in pediatric patients younger than should be performed. Studies in patients less than 2 yrs can be waived. Furthermore, a deferral of pediatric studies is acceptable until after approval of the product in adults. At that time, acceptable features of the study design can be considered.

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/s/

Mwango Kashoki
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MEDICAL OFFICER



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS
HFD-170, 10903 New Hampshire Ave., Silver Spring MD 20993**

MEDICAL TEAM LEADER MEMORANDUM

DATE: January 12, 2007

TO: File, NDA 21-234

FROM: Mwango A. Kashoki, M.D., M.P.H
Medical Team Leader

RE: Supervisory Review of NDA 21-234
Diclofenac Epolamine Patch (Flector® Patch)
Institut Biochemique SA (IBSA)

Proposed Indication: ' _____ ' due to strains, sprains and
contusions _____

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1. Action

Approval

2. Phase IV Requirements

Adequate collection of pharmacokinetic/toxicokinetic exposure data to further interpret the existing oral reproductive toxicology findings. In the absence of this bridging data, new Segment I, II, and III studies should be conducted.

3. Basis for recommendation

3.1. Background

Diclofenac epolamine is a salt of the non-steroidal anti-inflammatory drug (NSAID) diclofenac. There are no other approved products containing the epolamine salt of diclofenac. Diclofenac epolamine patch (to be referred to as "DEP" in this memorandum) is a topical delivery system that contains 1.3% diclofenac epolamine (180 mg) per patch. The applicant theorizes that epolamine - which is highly soluble and able to solubilize lecithin, a primary constituent of cell membranes - will facilitate skin absorption of diclofenac via increased cell permeability.

DEP is currently marketed in Asia, Europe, Latin America, and the Middle East.

Currently there is one other topical formulation of diclofenac that has been approved for marketing in the United States. Solaraze (diclofenac sodium 3% gel) is indicated for the treatment of actinic keratosis.

This is the third NDA cycle for DEP. The NDA was first submitted on December 20, 2000, for the indication of

The Division of Analgesic, Anti-Inflammatory, and Ophthalmologic Drug Products (DAAODP) reviewed the application and concluded that it was "not approvable" due to lack of demonstration of efficacy, numerous chemistry-related deficiencies, and the absence of validation of the assays used in clinical pharmacology studies (Action Letter dated October 18, 2001). During a post-action meeting (November 20, 2001), the company was advised that two additional clinical efficacy studies would be required to support the indication. The NDA was resubmitted in March 2002, but was considered incomplete because it did not contain any new clinical data nor did it address any of the other deficiencies identified in the initial Action Letter.

Notable aspects of the history of this application are the proposed treatment indication and the efficacy endpoints for the clinical trials. The applicant initially discussed both a indication. At the pre-NDA meeting in March 2000, the applicant clarified that approval of only the indication was sought. Following receipt of a summary report of the initial study in a sports injury population, DAAODP recommended that the applicant's second efficacy trial use a primary endpoint that evaluated average daily pain ((End-of-Phase 2 meeting, June 1998). However, the applicant opted for a "time to pain resolution" endpoint that DAAODP did not consider sufficient to characterize the analgesic effect of the drug product.

The current submission was received on July 27, 2006 and the NDA is considered a 505(b)(2) application because the applicant is referencing clinical pharmacology and non-clinical data that the applicant believes is in the public domain (i.e. is "common knowledge"). The submission contains one new clinical pharmacology study, as well as two new efficacy studies. The efficacy trials were conducted in Europe (i.e. not under

IND). Therefore the Agency did not provide any guidance regarding the studies' design and endpoints.

3.2. Chemistry, Manufacturing and Controls

The CMC review was performed by Sue Ching Lin, Ph.D.

The product is a non-sterile patch for topical application of diclofenac epolamine. The product is comprised of an adhesive material containing active drug which is applied to a non-woven polyester felt backing, and is covered with a polypropylene film release liner. The release liner is removed prior to application to the skin.

Each adhesive patch contains 180 mg of diclofenac epolamine (1.3%) in an aqueous base, and measures 10 cm x 14 cm. Five patches are packaged in a resealable pouch.

Dr. Lin has concluded that the applicant has completely addressed all of the deficiencies identified in the Not Approvable letter. In particular, the applicant has addressed concerns regarding:

- Adequacy of the Drug Master File (DMF) for the diclofenac epolamine drug substance
- A letter of authorization (LOA) permitting the Agency to review the DMF of the Dalin PH fragrance
- The lack of information regarding the
 - composition of the felt backing material and release liner
 - analytical procedure and method validation for the drug substance
 - testing and reporting of stability of drug batches

Sufficient data has been collected to support a 36- month expiration date. Stability data under conditions of use (i.e. stability after opening and then resealing the pouches) were required because diclofenac is not a volatile substance.

At the time of the writing of this memorandum, Dr. Lin considered the application acceptable for approval.

3.3. Pharmacology and toxicology

The 2001 Action Letter did not identify any non-clinical deficiencies, therefore the applicant did not submit any new non-clinical data in this submission. Drs. Daniel Mellon and Asoke Mukherjee reviewed the previous non-clinical information to verify that there were no outstanding issues.

Drs. Mellon and Mukherjee concluded that the applicant's segment I study (fertility and embryonic development) was conducted incorrectly, with dosing of Sprague Dawley rats out to postpartum day 21, and evaluation of treatment on growth, behavior, and reproductive performance of the F1 animals. Furthermore, while rat and rabbit

teratogenicity studies with oral diclofenac epolamine showed evidence of embryotoxicity (increased resorption of embryos), the absence of toxicokinetic data from these studies limited the potential clinical relevance of the findings (i.e. prevented calculation of exposure margins for the observed toxicities).

Dr. Mellon recommends that the applicant obtain adequate collection of pharmacokinetic/toxicokinetic exposure data to interpret the existing oral reproductive toxicology findings. In the absence of this bridging data, the applicant should appropriately conduct Segment I, II, and III studies.

3.4. Clinical Pharmacology

The clinical pharmacology data were reviewed by Srikanth Nallani, Ph.D. One new study was conducted to address the biopharmaceutical deficiency noted in the Not Approvable letter, namely that the NDA lacked complete assay validation reports for the analytical methods used in the analysis of plasma samples obtained in the pharmacokinetic studies.

The applicant was unable to provide a validation report for one of the older pharmacokinetic studies (trial #910195), and noted that the data derived from this study were considerably different from the other studies that utilized validated analytical methods. Therefore the applicant conducted Study CRO-PK-02-76, a pharmacokinetic study evaluating the systemic levels of diclofenac epolamine following single- and multiple-dose administration of the patch. Dr. Nallani considered this study, its results, and the assay validation report to be acceptable. The assay validation reports submitted for the other previously conducted pharmacokinetic trials were also acceptable.

Based on the data, Dr. Nallani found that peak plasma concentrations following DEP application range from 0.7-6 ng/mL, and occur between 10-20 hours following application. Steady state concentrations (1 -9 ng/mL) occur after five days of twice-daily dosing. These levels are at least one hundred-fold below those observed with a single oral dose of diclofenac 150 mg.

Dr. Nallani considered this NDA to be acceptable for approval.

Of note, as part of the initial NDA submission, the applicant provided data regarding the effects of exercise on the performance of the patch. The study showed that exercise increased the systemic absorption of diclofenac by approximately 35%. The increased plasma levels of diclofenac are still considerably below those observed following a single oral dose of 150 mg diclofenac.

The applicant did not evaluate the effects of the use of overlays on the performance of the DEP product. This reviewer does not consider such information to be necessary at this time because even if an overlay caused systemic absorption of the entire amount of diclofenac in the current patch (180 mg), the plasma levels would be in the range of those

observed following an oral dose of 150 mg diclofenac, and below those observed with the maximum recommended oral dose of diclofenac (200 mg).

3.5. Clinical Efficacy and Safety

Ms. Barbara Elashoff and Dr. Dionne Price conducted the primary and secondary statistical reviews, respectively. Dr. Robert A. Levin performed the efficacy and safety review.

3.5.1. Clinical efficacy

Two new randomized, double-blind, placebo-controlled studies were submitted in support of efficacy: Study 00GB/Fp05 (the UK/German study) and Study 05-05-98 (the French study). Neither of these protocols was reviewed by the Agency.

3.5.1.1. Study 00GB/Fp05 (UK/German study)

The UK/German study compared the effects of twice-daily dosing of DEP vs. placebo over two weeks in adult patients who had minor soft tissue injury (sprain, strain, or contusion). Of the 418 patients randomized to treatment, 417 (207 DEP and 210 placebo) used at least one patch. Patients' response to therapy was captured using a pain diary (pain intensity on 0-10 numerical rating scale (NRS)), and pain was recorded twice daily at the time the patch was removed. The use of other topical medications, ice, and analgesics was prohibited. The initial protocol-specified primary endpoint was the time to pain resolution, defined as the time from the initial patch application to the fourth consecutive pain score of ≤ 2 .

The review of the study was complicated by the fact that the applicant modified the statistical analysis plan following observation of a high number of premature dropouts by patients who had low pain scores, but who had not yet had 4 pain scores of 2 or less. Per the primary analysis, these patients would be considered treatment failures even though they had shown a good response to treatment. In the modified statistical analysis plan, the applicant used a different primary endpoint: the mean pain score over the 14-day period divided by the baseline score. The applicant claimed that the modified analysis was proposed by a statistician who was blinded to treatment assignment.

The selected primary endpoint is somewhat difficult to interpret clinically. Therefore the division evaluated efficacy using two additional endpoints: the mean change in pain from baseline to the end of the study (14 days), and the percentage of responders at study end. The former endpoint allows for evaluation of the average analgesic effect by the end of treatment. One drawback of this endpoint is that, because it is an average, it is difficult to use to predict the effect of treatment for an individual patient. The responder analysis, however, allows for prediction of how well a drug might work for an individual patient.

In addition to evaluating efficacy at the end of the 14-day trial, the division also calculated efficacy at an earlier time point (Day 3). This is because it is possible that the symptoms of minor soft tissue injury may naturally run a course of only a few days, with

patients in both groups gradually getting better over time, and thereby making it difficult to distinguish placebo from active treatment.

Review of the efficacy data for the study was further complicated by the large number of patient dropouts. For these patients, missing pain score data had to be imputed. In analgesic trials, the score used for imputation may be dependent on the reason for discontinuation; therefore proper classification of patients' disposition status is important. For the mean change in pain endpoint, the division used the last observation carried forward (LOCF) imputation for patients who discontinued due to injury resolution, and baseline observation carried forward (BOCF) imputation for all other premature discontinuations.

In analgesic trials, early discontinuations tend to be nonrandom. Often, more patients discontinue treatment due to adverse events in the active treatment arm, as compared to placebo where there are more patients who discontinue due to lack of efficacy. In this setting, the use of LOCF as the imputation method would result in imputing good scores for patients who dropout due to adverse events, a bad outcome. For a drug that is intended for only symptomatic treatment (pain) and confers no other significant benefit (such as reduced morbidity or mortality), demonstration of efficacy based on intolerable doses is not an acceptable outcome. However, in this study, the pattern of early discontinuations revealed that most patients had resolution of their pain and discontinued study medication for that reason. Therefore, use of the last observation would result in imputation of a good score for a good outcome.

In the UK/German study of DEP, the majority of participants who discontinued did so because their pain had improved, not because of an adverse reaction to treatment. Therefore it was appropriate to impute these patients' scores with the last observed score (i.e. to use LOCF imputation). A more conservative imputation method, BOCF, was used for patients who discontinued due to all other reasons, including adverse events.

Identification of the correct imputation score was difficult because the NDA had two datasets containing information on patient disposition status. Dataset *exit.xpt* reflected information as it appeared on the exit form of the Case Report Form (CRF). The *exit2.xpt* dataset contained disposition data based on the applicant's reclassification of patients' disposition status (refer to p.61-63 of Dr. Levin's review for details on the rationale and methods of reclassification). The applicant's changes resulted in considerably different information on patient disposition. For example, based on *exit.xpt*, 32% of placebo patients and 44% of DEP patients discontinued because of injury resolution. However, the data in *exit2.xpt* show that 45% of placebo patients and 54% of DEP withdrew due to injury resolution.

The division asked the applicant to reclassify patients based on criteria it has used in previous applications (p. 64 of Dr. Levin's review), and the resultant data were very similar to those obtained from *exit.xpt*. For this reason, and also because the *exit.xpt* data reflect the pre-specified disposition categories, disposition information in the *exit.xpt* dataset was used to determine which pain scores would be imputed.

Another challenge in the analysis of efficacy was the identification of the appropriate efficacy database. The applicant submitted two datasets for the patients' pain scores and patch use (i.e. number of patches). In the first dataset, *diary.xpt*, patch numbers were assigned based on the sequential order of application. Thus, for a patient who applied five patches but skipped the first of the twice daily doses on study day 2, the patches were numbered "1" through "5." To ensure an exact correlation with days from the start of treatment, the applicant created a modified dataset *adjdiary.xpt*¹. In this dataset, the same patient's patches would be numbered "1, 2, 4, 5, 6" and the corresponding pain scores listed accordingly. Whereas Ms. Elashoff utilized the *diary.xpt* dataset for her analyses, Dr. Price considered the *adjdiary.xpt* dataset to be the more appropriate one for calculation of effect of treatment by study day.

Based on Dr. Price's analyses, there was a small numerical difference (-0.7) in the change in mean pain scores between DEP and placebo, however this difference reached statistical significance (p = 0.03).

Dr. Price's Table 4: Analysis of change from baseline to day 14

		Diclofenac Patch (n=207)	Placebo Patch (n=211)	
Baseline	Mean (Std deviation)	7.3 (1.3)	7.5 (1.3)	
Change from Baseline to Day 14				
<i>Imputation Strategy 1*</i>	Mean (Std deviation)	-3.5 (3.4)	-2.8 (3.2)	
	LS Mean (SE)	-3.5 (0.2)	-2.8 (0.2)	
	LS Mean difference			-0.7 (-1.3,-0.07)
	p-value			0.029
<i>Imputation Strategy 2**</i>	Mean (Std deviation)	-5.0 (2.7)	-4.2 (3.0)	
	LS Mean (SE)	-5.0 (.2)	-4.2 (.2)	
	LS Mean difference			-0.8 (-1.3,-0.2)
	p-value			0.007

p-values derived via an ANCOVA model with factors for treatment and center and baseline as a covariate.

*Imputation Strategy 1 = LOCF for all pts discontinuing due to injury resolution and BOCF for all other discontinuation reasons.

**Imputation Strategy 2 = LOCF for all pts discontinuing.

Dr. Price's responder analyses, in which people who discontinued from the study due to injury resolution were considered responders, showed greater response rates in the DEP group compared to the placebo group, both early (day 3) and late (day 14) in the trial. The results were notable for quite high response rates in both groups, compared to what has been observed in previous trials of oral analgesics. For example, at a definition of 30% improvement in pain score on Day 14, 51% and 42% of DEP and placebo patients, respectively, were responders. The results were also notable for the fact that across all definitions of response, the DEP group showed a 10-20% greater response rate than the placebo group.

¹ UK/German study, Final Study Report, Statistical Analysis Plan, p. 5

To put the response rates into clinical context, this reviewer performed a number-needed-to-treat (NNT) analysis. To achieve a 50% response rate by day 3 in one patient, one would need to treat 6 persons with DEP. To achieve that same level of response by day 14, one would need to treat 9 patients with DEP.

3.5.1.2. Study 05-05-98 (French study)

The French study evaluated the efficacy of once-daily DEP dosing over 7 days in adults who had experienced minor ankle sprain. A total of 134 patients (68 DEP and 66 placebo) were randomized to treatment. Pain was assessed in the clinic on days 3 and 7 of the trial, using a 100 mm visual analog scale (VAS). Patients were allowed use of ice and acetaminophen (within 3 hours of patch application). Oral analgesics and other topical NSAIDs were not permitted.

Altogether, 94% of patients in each group completed the trial, with the most common reason for dropout being lack of efficacy (4% of placebo patients, 0% of DEP patients), and loss to follow-up (6% of DEP patients and 0% of placebo patients). Due to the high completion rate, handling of missing data was not a considerable problem.

The primary efficacy endpoint was not clearly stated, but appeared to be the mean pain score at endpoint. However, the applicant presented data showing the percent decrease in pain from baseline to multiple time points, including the end of the study. A consistent and statistically significant difference in the percent pain decrease was shown between DEP and placebo.

Dr. Price's comparison of the mean change from baseline between the treatment groups also showed greater efficacy of the DEP group than placebo, and the difference was statistically significant.

Dr. Price's Table 9: Change from Baseline Analyses

		Diclofenac Patch (n=68)	Placebo Patch (n=66)	
Baseline	Mean (Std deviation)	66.9 (10.6)	70.0 (11.8)	
Change from Baseline to Day 3	Mean (Std deviation)	-49.9 (21.7)	-40.5 (22.0)	
	LS Mean (SE)	-50.8 (2.5)	-39.6 (2.6)	
	LS Mean difference			-11.2 (-18.4,-4.0)
	p-value			0.003
Change from Baseline to Day 7	Mean (Std deviation)	-56.0 (19.2)	-50.7 (20.1)	
	LS Mean (SE)	-57.0 (2.2)	-49.8 (2.3)	
	LS Mean difference			-7.2 (-13.6,-0.9)
	p-value			0.027

Analysis conducted using ANCOVA with treatment as a factor and baseline pain as a covariate in the model.

Similar to the UK/German study, rates of response were very high in both the placebo and DEP groups, with greater percentage of responders in the DEP arm, at all definitions of response. These findings were observed at both Day 3 and Day 7 of the trial.

This reviewer repeated the NNT analysis. To have one patient achieve a 50% response rate by day 3, 4 patients would need to be treated with DEP. To have one patient achieve the same level of response by day 7, one would need to treat 12 patients with DEP.

3.5.1.3. Reanalysis of clinical efficacy of the initial NDA trials

Study 49, 459-01 (Study 01) and 49,459-02 (Study 02) were submitted in the initial NDA. Both trials evaluated the effects of twice-daily DEP on minor injuries (ankle and knee sprains; contusions), and treatment was for 14 days.

Study 01 did not clearly specify the primary endpoint. Endpoints included the summed pain intensity difference (SPID) and summed pain on pressure difference (SPOD). Per the data presented in the initial NDA, the applicant failed to show a difference of DEP from placebo, both at Day 3 and Day 14 of the trial. The primary endpoint for Study 02 was "time to pain resolution." Similarly for this trial, the initial NDA review found that the study failed on the primary endpoint, and the secondary endpoints were not supportive of efficacy.

For this NDA submission, the applicant reanalyzed the efficacy data for both trials using the "mean pain at study end divided by the baseline pain" as the efficacy variable. A variety of imputation strategies were employed in the reanalyses, including LOCF. The results of these analyses, as well as of a comparison of the mean pain score over the study duration, suggest an analgesic effect of DEP.

Efficacy conclusions

In this reviewer's opinion, the data show that treatment with DEP is more efficacious than treatment with placebo for the treatment of pain associated with minor strains, sprains, and contusions.

In this memorandum, the efficacy results and conclusions for the French and UK/German studies are based on data presented in Dr. Price's secondary statistical review. I elected to use Dr. Price's analyses because they were based on a more appropriate efficacy dataset (the UK/German study), and allowed for comparison of results between the French and UK/German studies.

For the UK/German study, although the primary and secondary statistical reviewers calculated the same efficacy endpoints (mean change in pain from baseline and percentage of responders), they found different results. This is because the reviewers used different efficacy datasets (Ms. Elashoff used the *diary.xpt* dataset; Dr. Price used the *adjdiary.xpt* dataset). Also, as Dr. Price stated in her review (p. 8), the two reviewers used different analysis methods for calculation of the "mean change in pain from

baseline" endpoint. Whereas Ms. Elashoff performed a test of the pain scores at the end of treatment and a test of the change in scores from baseline, Dr. Price performed an analysis of covariance (ANCOVA) of the change from baseline. Dr. Price explained that she prefers this method analysis because, by accounting for the baseline values, the precision of the analysis of covariance is increased. While each analysis is valid, Dr. Price's would have been the preferred, pre-specified analysis.

For the French study, Ms. Elashoff interpreted the protocol-defined primary endpoint to be the mean pain score on day 7 of the trial, and her primary analysis employed an ANOVA model with treatment and investigator as factors in the model. Dr. Price evaluated the change in pain from baseline, as well as the proportion of responders. Dr. Price's analysis of the former endpoint employed an ANCOVA model with factors for treatment and baseline pain as a covariate.

Of note, Dr. Levin based his review of efficacy on the applicant's analyses and on Ms. Elashoff's calculations. This is because Dr. Levin's review was completed at the time that Dr. Price's review had just been initiated. Thus, based on Ms. Elashoff's finding of a lack of efficacy for the UK/German study and on the initial NDA determination that the Studies 01 and 02 studies failed, Dr. Levin concluded that DEP was not efficacious.

3.5.2. Clinical Safety

Dermal safety studies (cumulative irritation, photoallergy, phototoxicity, and hypersensitivity) were reviewed during the first NDA cycle. The studies were not considered to show evidence of dermal toxicity.

In the clinical studies, there were no deaths or serious adverse systemic or dermal reactions. The most common adverse effect was "application site condition" and occurred in similar frequency in the two groups (~ 12% of patients). The most frequently reported dermal reactions that occurred in greater frequency in the active group was dermatitis (2% DEP vs. 0.5% placebo). Gastrointestinal disorders were the next most frequently occurring category of adverse reactions (9% DEP vs. 6% placebo), with nausea and dysgeusia being the most commonly described.

The incidence of discontinuation due to an adverse event was very low (3% of patients in each group), and "application site condition" was the most common reaction leading to discontinuation (2% of patients, each).

Thus, the safety profile of DEP appears to be quite favorable, and is consistent with the foreign experience described by the applicant.

4. Pediatric studies

The applicant requested a deferral of pediatric studies; this was granted.

5. *DMETS is concerned that some patients will use multiple Flector patches concurrently. From a medication safety perspective, DMETS is concerned with these practices since the safety and efficacy of the Flector Patch has not been studied under these conditions. Postmarketing experience with other transdermal delivery systems has shown that the use of multiple patches concurrently (intentional and unintentional) to be associated with adverse outcomes related to overdosage of the drug. Therefore, DMETS recommends that the sponsor update the insert labeling to include warnings on the effects of using multiple patches.*

As a topical delivery system, diclofenac epolamine patch, when used as directed, is associated with negligible systemic levels of diclofenac. The recommended dose of oral diclofenac for acute pain is 150 mg/day, and this has been associated with plasma levels of approximately 4500 ng.hr/mL. After a single application of diclofenac epolamine patch, diclofenac plasma level was approximately 40 ng.hr/mL. Thus, to reach or exceed this plasma exposure – an exposure that has been approved and considered safe by the Agency - patients would have to apply at least 100 diclofenac patches. This reviewer considers it unlikely that patients would demonstrate such an extent of misuse of the product.

Transdermal delivery systems that have been associated with adverse outcomes following multiple patch use contain active ingredients whose adverse effects are considerably more toxic effects than those associated with systemic diclofenac. For example, overdoses of lidocaine from transdermal products can have cardiotoxic effects, and transdermal fentanyl can lead to respiratory depression and death. Also, the active ingredients in these other transdermal delivery systems are much more systemically available than the diclofenac in DEP.

Therefore, because DEP is a topical product with minimal systemic exposure of an active ingredient that is not as toxic as some found in transdermal products, this reviewer does not agree with DMETS that the package insert for DEP should contain warnings on the effects of using multiple patches. However, it is appropriate to include language instructing patients to use the product only as directed.

5. *The dosage form "Patch" is not a recognized U.S. Pharmacopeia dosage form. DMETS recommends consulting the Office of New Drug Quality Assessment, specifically the CDER Labeling and Nomenclature Committee (LNC), on the proper designation of the dosage form. Once this has been resolved all labels and labeling should include the dosage form with the established name.*

The dosage form "patch" has been used in the labeling for other approved topical products (Lidoderm, NDA 20-612). Also, in the 12/14/06 CMC information request letter to the applicant, the Agency recommended "diclofenac epolamine topical patch" as the nonproprietary name. This name was accepted by the applicant and the labeling was revised accordingly.

6. *DMETS is concerned that the concomitant administration of other prescription and over-the-counter oral and/or topical analgesic products (e.g. NSAIDs, aspirin, acetaminophen, narcotics, Voltaren (oral diclofenac) and Solaraze (topical diclofenac)) with the Flector Patch could lead to medication errors and overdose. Additionally, in a hospital setting, research has shown that prescribing the same or similar medication to be given concurrently by two different routes of administration to be a common source of medication error. The same study indicated the prescribing of the same or similar medication to be given concurrently via the transdermal and oral route of administration as the second most common type of prescribing error. Although DMETS believes that this risk is decreased by the use of different proprietary names, we feel that there will be confusion by both patients and practitioners to more readily identify the commonality of the medications, even when given by different routes, thus, leading to a medication error. Therefore, DMETS recommends that the sponsor educate both healthcare providers and patients about the potential for harm associated with using the Flector Patch in conjunction with other analgesic agents.*

It is theoretically possible that harm could occur when using DEP concomitantly with oral NSAIDs. However, as stated above, DEP is not a transdermal delivery system and systemic absorption of diclofenac from this topical product is minimal. Therefore this reviewer is of the opinion that when DEP is used concomitantly with NSAIDs, it is more likely that any observed systemic effects would be due to the oral products than to DEP. Also, due to the low plasma of diclofenac levels, it is unlikely that systemic drug-drug interactions would be observed when DEP is used with other analgesic products.

Consequently, this reviewer does not consider it necessary to require the applicant to educate patients and healthcare providers on “the potential for harm” associated with using DEP with other analgesics.

7. *DMETS recommends that each patch be packaged individually in order to help prevent the application of all patches contained in the pouch at once and decrease the possibility that the effectiveness of the product may be affected if the pouches are accidentally left open once the patch is removed.*

As discussed under the response to DMETS’ comment #5, the risk of adverse effects (overdose/systemic toxicities) following simultaneous application of DEP is considerably low.

Also, as discussed in Section 3.2, data regarding stability of the product under conditions of use were not required because diclofenac is not a volatile substance. Additionally, the pouch contains instructions in red lettering specifying that the pouch must be resealed after opening.

Therefore, this reviewer does not consider it necessary to require individual packaging of patches. However, it is reasonable to request that the applicant to make the instructions about resealing much more prominent.

E. INSERT LABELING

1. DMETS was not provided evidence regarding exposure of the Flector Patch to heat or hot conditions. Post-marketing surveillance with other transdermal delivery systems has identified cases in which inadvertent exposure to heat sources (e.g. using heating pads with fentanyl transdermal systems; sun exposure with Ortho Evra) resulted in adverse events. DMETS recommends that the sponsor update the insert labeling to include warnings of exposure to heat or hot conditions if warranted.

2. DMETS was not provided evidence regarding the use of overlays with the Flector Patch. Post-marketing surveillance regarding the use of overlays with the fentanyl transdermal system was found to increase the rate and extent of absorption, which resulted in patient harm and death in some cases. The use of bandages, band aids and other overlays to secure the patch may unintentionally produce an increase in temperature at the site of absorption. DMETS is concerned that the use of such measures over part of or the entire system could likewise affect the absorption of diclofenac from the Flector Patch, thereby putting patients at risk if the drug is delivered too quickly or an excessive dose is delivered. Therefore, DMETS recommends that the sponsor update the insert labeling to include warnings on the use of overlays with the Flector Patch.

Because DEP is a *topical* product without significant systemic absorption, DMETS' concerns regarding the complications of transdermal products (as described in E1 and E2 above) are not applicable. Furthermore, in the event that heat or an overlay caused systemic absorption of the entire amount of diclofenac in the current patch (180 mg), the plasma levels would be in the range of those observed following an oral dose of 150 mg diclofenac, and below those observed with the maximum recommended oral dose of diclofenac (200 mg). Therefore the labeling need not include warnings about the effects of heat or overlays.

3. DMETS was not provided evidence regarding exposure of the Flector Patch to cold. Many healthcare practitioners recommend that patients apply cold compresses or ice to the strains, sprains and contusions associated with sports injury. DMETS is concerned that patients will apply cold compresses to the injured area in addition to the Flector Patch. In addition, DMETS questions how exposure cold conditions will affect the integrity of the transdermal system. Thus, DMETS recommends that the sponsor update the insert labeling to include warnings on the use of cold compresses or ice on the Flector Patch.

One of the four clinical protocols (the French study) allowed the concomitant use of ice with patch treatment. The data showed that by day 3 of the trial, approximately 25% of

this study's participants had used ice. These patients did not report decreased integrity of the patch system.

4. *DMETS was not provided evidence regarding the adhesion of the Flector Patch after exposure to sweat, bathing, swimming or showering. Based on post-marketing experience with other transdermal delivery systems, DMETS believes that exposing the patch to water or sweat may affect the adhesiveness of the patch thereby causing it to curl up on the edges, wrinkle or fall off. Hence, DMETS recommends that the sponsor update the insert labeling to include information and instructions on what to do in the event that a patch curls up on the edges, wrinkles or falls off.*

A study of the effect of exercise, skin hydration, and cutaneous blood flow was submitted in the initial NDA submission. The adhesiveness of the patch after 12 h of application was also evaluated in this study. The study found that the adhesiveness of the patch was not considerably affected.

In the event that the edges of the patch curl up or wrinkle, this reviewer considers it acceptable for patients to secure the edges with tape or band aids, and this information can be relayed in the labeling.

5. *DMETS was not provided evidence of the integrity of the Flector Patch in the event that the patch is cut. Based on post-marketing experience with other transdermal delivery systems (e.g. Daytrana), DMETS believes that cutting the patch could violate its integrity. Additionally, this transdermal system is very large and depending upon where the patient is applying the patch, they may cut the patch to fit at the application site. The release of the drug may be affected which could pose a health risk to the patients wearing the cut patches. Therefore, DMETS recommends that the sponsor update the insert labeling to include warnings on the effects of cutting the patch.*

The diclofenac epolamine patch is a drug-in-matrix system. Cutting of the patch will not release diclofenac.

6. *DMETS questions whether or not there will be irritation at the site of pain if a transdermal system is repeatedly placed in the same location on the skin for a period of two weeks. Can subsequent transdermal systems be located to a different area near the site of pain or should patients discontinue use? Therefore, DMETS recommends that the sponsor update the insert labeling to include instructions on whether or not that transdermal system can be rotated to different locations at the site of pain.*

Because the diclofenac epolamine patch is intended to exert its effects locally at the site of injury, repeated application at the same site is, by default, necessary. If the area of injury is sizeable, it may be possible to rotate the patch application sites. However, if the area of injury is relatively small and the patient develops irritation because of the patch, this reviewer recommends that the patient simply discontinue use.

7. Revise the insert labeling to include instructions on how to remove the patch and adhesive if they become difficult to remove from the patient's skin.

Data from adhesive strength testing that show that difficulties in removing the patch from the skin should not be a problem. Also, problems with patch removal were not reported in the safety data.

8 WARNINGS

In the section entitled 'Excessive Dosing', the package insert labeling states that "When combined with oral diclofenac and other NSAID therapy, the entire systemic burden should be taken into account". Due to DMETS concern that oral nonsteroidal anti-inflammatory agents (NSAIDS) will be used in combination with the Flector Patch, this section should include the type(s) of systemic burden the patient will experience if the product is taken with other NSAIDS.

Conformation of the proposed package insert of DEP to the NSAID template will allow for specification of all the serious and common adverse effects of any NSAID.

Because the systemic availability of diclofenac from this topical product is negligible, it is unlikely that there will be an additive systemic burden following concomitant use of other NSAIDs with the patch. Therefore the package insert need not contain language regarding the "systemic burden the patient will experience if the product is taken with other NSAIDS."

6. Data Quality and Integrity

At the time of this memorandum, the Division of Scientific Investigations (DSI) had not completed its inspections of the two selected clinical sites.

7. Summary and Conclusions

There were no CMC or clinical pharmacology deficiencies identified during this review.

With respect to the non-clinical portion of the application, there are no toxicokinetic data correlating plasma levels with observed adverse effects in the reproductive toxicology

Secondary Clinical Review and Evaluation

studies. Knowing at what systemic exposure the adverse animal findings were observed allows for determination of their potential clinical relevance at the expected human plasma levels. However, given that the systemic availability of diclofenac in humans after patch application is extremely low and that the _____, this reviewer does not consider it necessary for the applicant to provide the missing information prior to taking an action on the NDA. The data can be collected _____. Should the drug be approved on this cycle, language in the product label regarding pregnancy/teratogenic effects can describe the results of the reproductive toxicology studies and state that the clinical relevance of these findings is not yet clear.

Overall, the clinical data suggest an analgesic effect of DEP compared to placebo. The difference between groups in the average effect on pain is not substantial. However DEP does result in greater response rates among DEP-treated patients compared to placebo-treated patients. In light of the favorable safety profile of this product, and in the absence of any major irregularities observed upon clinical site inspection, I recommend that the drug be approved. Based on the nature of the conditions studied, I recommend that the approved indication be "treatment of pain associated with minor _____ sprains, strains and contusions." The product labeling should indicate that drug is approved for use in adults.

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Mwango Kashoki
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MEDICAL OFFICER

CLINICAL REVIEW

Application Type NDA 21-234
Submission Number 000
Submission Code 000AZ (Resubmission)

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Reviewer Name Robert A. Levin, MD
Team Leader Name Mwango A. Kashoki, MD, MPH
Review Completion Date December 29, 2006

Established Name Diclofenac Epolamine Patch
(Proposed) Trade Name Flector® Patch
Therapeutic Class NSAID
Applicant Institut Biochemique

Priority Designation Standard

Formulation Topical Patch
Dosing Regimen Twice daily
Indication Pain due to strain, sprains
And contusions
Intended Population Adults

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Clinical Review
Robert A. Levin, MD
N21-234, AZ
Diclofenac epolamine patch (Flector® Patch)

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer recommends that a not approvable action be taken on this NDA.

This application does not contain sufficient data to support a finding of efficacy for diclofenac epolamine patch (DEP) as treatment for sprains, strains and contusions

Although the overall risk associated with use of this product is small, approval of diclofenac patch in the absence of two adequate and well controlled studies is not warranted considering the widespread availability of other therapies for the proposed indication and the self-limited nature of the condition.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Not required.

1.2.2 Required Phase 4 Commitments

To comply with the Pediatric Research Equity Act (PREA), the applicant has proposed a pediatric protocol under the IND for diclofenac epolamine patch (IND 49,459). It is acceptable for the pediatric study to be conducted following approval of DEP in adults.

1.2.3 Other Phase 4 Requests

The Applicant should conduct Segment III reproductive toxicology studies for diclofenac epolamine.

1.3 Summary of Clinical Findings

One of the two efficacy trials included in the NDA resubmission failed to support the efficacy of diclofenac epolamine patch in the treatment of strains, sprains and contusions. The study design allowed for discontinuation of treatment upon injury resolution. This impacted the interpretation of efficacy as based on the applicant's modified primary endpoint. Setting aside the statistical limitations of the study, there was no clinically meaningful difference in pain between the diclofenac and placebo treated groups. Furthermore, the onset of any analgesic effect did not occur until repeated patch application in many patients. In general, products intended for treating acute pain should have a rapid enough onset of action to provide timely pain relief.

1.3.1 Brief Overview of Clinical Program

The applicant has proposed the trade name Flector® Patch. The Flector® Patch (to be referred to as diclofenac patch (DEP) for the remainder of this review) contains the NSAID diclofenac epolamine in a topical delivery system for the treatment of pain due to strains, sprains and contusions. The patch is intended for twice daily use in adults.

Biochemique Institut submitted four clinical trials: two trials previously submitted under the original NDA filing and two new studies. The two previous studies failed to demonstrate efficacy during the original FDA review and thus were evaluated only for safety in this review. The four clinical trials comprising the safety data base were conducted in a total of 1136 patients (572 treated with diclofenac patch and 564 treated with placebo patch).

The two new efficacy studies were conducted in 551 patients (275 treated with diclofenac patch and 276 treated with placebo patch). In the four studies, a total of 181 patients (87 DEP and 94 PBO) received patch twice daily for two weeks (at least 28 patches). 764 patients (380 DEP and 384 PBO) were treated once or twice daily for one week. Additional safety information included European experience with the patch.

1.3.2 Efficacy

The applicant submitted two studies (Protocol 05-05-98 and Protocol 00GB/Fp05) which were reviewed for efficacy.

Study 05-05-98 enrolled patients ages 18 to 65 years with an acute ankle sprain within 48 hours resulting in a pain score of ≥ 50 mm on the visual analogue scale. Use of NSAIDs within one week of study entry and during the study was prohibited, but use of acetaminophen was allowed. The study was one week in duration with a primary outcome measure of pain with activity measured on the visual analogue scale. Primary efficacy endpoint appeared to be the mean pain at the end of the study. Secondary outcome measures included subject and investigator global assessment at the end of treatment and acetaminophen consumption.

The study demonstrated a statistical treatment effect on the primary endpoint at the end of the study but the effect was larger at 3 days. The loss of efficacy in the diclofenac patch group compared to placebo group was probably related to spontaneous improvement in pain in the placebo group by the end of the study. Improvement in both placebo and treatment groups was over 90% at one week. Global patient satisfaction demonstrated improvement consistent with the changes noted in the primary endpoint. Improvement in pain was found to be statistically significant as early as four hours after patch application lending overall support to the finding of efficacy in this study. The number of patients using acetaminophen did not significantly differ between the two groups.

Protocol 00GB/Fp05 enrolled patients age 18 to 65 years with strains, sprains and contusions occurring within 72 hours of study entry and resulting in a pain score of at least 5 on a 0 to 10

numerical rating scale. Patients were not allowed to use acetaminophen or NSAIDs. Diclofenac epolamine patches were self-administered twice daily (every 12 hours) for two weeks or until the time of significant pain resolution (four consecutive pain scores of ≤ 2). Use of OTC analgesic or NSAIDs within 36 hours of study entry was initially prohibited. To improve patient recruitment the eligibility criteria were modified to allow for injury occurring up to 7 days prior to enrollment and NSAID or acetaminophen use up to 6 hours prior to enrollment.

The original primary efficacy endpoint was time to significant pain resolution or discontinuation of treatment. The Applicant found that many patients improved and discontinued treatment, however because they did not meet criteria for "pain resolution" were classified as prematurely dropping out. The Applicant proposed a modified statistical analysis plan, which was reportedly developed under blinded conditions where the statistician did not have access to the randomization code. The modified statistical plan used the available data for all patients. The primary efficacy endpoint was based on the mean post-treatment pain score divided by the baseline score.

The applicant found a statistical significance between treatment groups but the difference was numerically small. The clinical relevance of the difference is unclear. The analyses were potentially not meaningful due to the high rate of dropout prior to the end of the study. Statistical analysis by the FDA using pain intensity at the end of treatment (a preferred outcome measure in pain studies) demonstrated a nonstatistical and not clinically meaningful difference at the prespecified two-week endpoint.

In conclusion, Biochemie Institut failed to conclusively demonstrate in the UK/German Trial that the diclofenac patch is effective in providing clinically meaningful pain reduction. Therefore, in this reviewer's opinion, since only one trial demonstrated efficacy, the NDA submission failed to meet the regulatory requirement needed for approval.

1.3.3 Safety

No deaths or serious adverse events were identified in the safety data from the four studies submitted in this NDA. The most common adverse reaction was "application site condition" manifest most often as pruritus, dermatitis and burning. The placebo patch group also experienced application site reactions at a similar rate. Most of the skin reactions were mild and self limited. Other common adverse reactions included gastrointestinal events with nausea most common. Headache was also reported, again in similar frequency in diclofenac and placebo patch groups. Overall, the occurrence of adverse events was similar in the diclofenac and placebo patch groups. No apparent adverse drug interactions were identified. Patients on oral NSAIDs were excluded from studies.

Diclofenac epolamine patch has been marketed in Europe and the adverse reaction profile overseas is similar to the findings in the four studies reviewed.

Altogether, the safety profile of the product appears adequately elucidated from the four studies submitted and the overseas experience. Use of the product as indicated is associated with minimal risk.

1.3.4 Dosing Regimen and Administration

The applicant proposed twice daily dosing of the patch. This dosing regimen is based on the approved European dosing. In this resubmission, Study 05-05-98 evaluated once a day patch application for one week, whereas Study 00GB/Fp05 compared twice daily dosing for two weeks. The trials in the original NDA also studied twice daily dosing for two weeks. Based on the results of the latest trials, twice daily application of DEP is inefficacious, while once daily DEP decreases pain more than placebo. The recommended dosing regimen supported by the clinical trials submitted in the NDA is — patch application.

1.3.5 Drug-Drug Interactions

DEP is a topical product with minimal systemic absorption. Therefore the risk of drug-drug interaction is low. Oral NSAIDs were prohibited during the studies, therefore the potential for any additive effect from the combination of oral NSAIDs and DEP on adverse events is not known.

1.3.6 Special Populations

The diclofenac patch has not been studied specifically in a geriatric population. Therefore systemic exposure in the elderly after patch application is unknown. The elderly may be less likely to tolerate adverse reaction as well as younger patients.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

The Flector® Patch (diclofenac epolamine patch) contains the NSAID diclofenac epolamine in a topical delivery system. The proposed indication is the treatment of pain due to strains, sprains and contusions. Each adhesive patch measures 10 cm x 14 cm and contains 1.3 % diclofenac (180 mg). The patch is approved in Europe, where it is indicated for twice daily usage for up to 14 days for the treatment of pain due to sprains, contusions and periarthropathies. It should be applied only to intact skin at the painful site. The patch is intended for use in adults as a stand-alone analgesic and not for use with oral NSAIDs.

2.2 Currently Available Treatment for Indications

Pain due to strains, sprains and contusions is often treated with non-pharmacologic therapy. The treatment paradigm for minor sprains, strains and contusions is R.I.C.E. (rest, ice, compression, and elevation). In the acute phase, the use of ice is recommended to reduce pain and inflammation. For injuries involving weight bearing joints, crutches to limit weight bearing may be beneficial. For ankle sprains, a brace to provide immobilization may facilitate recovery, especially for more severe injuries.

It is common in clinical practice to combine pharmacologic and non-pharmacologic therapies in the treatment of minor — injuries. Acetaminophen or oral NSAIDs are first line therapy for pain control. Products and methods available for the treatment of strains, sprains and contusions include:

Non-pharmacologic

- Ice (for the first 48 hours)
- Rest: Braces, splints and slings to help immobilize the injured joint/limb
- Ambulatory assistive devices (crutches, canes) to reduce weight bearing on the injured limb
- Elastic compression bandages to reduce swelling
- Elevation of the injured limb to reduce swelling

Pharmacologic

- Oral NSAIDs, aspirin and acetaminophen
- Narcotics for more severe pain
- Topical over the counter products:
 - Anesthetic/counterirritants (often produce a burning or cooling sensation)
Menthol: Bengay, Flexall Gel
Trolamine salicylate: Aspercreme, Myoflex, Mobisyl and Sportscreme
 - Capsaicin (topical agent works by depleting substance P): Nuprin Patch, Zostirx

There are over-the-counter (OTC) topical agents available for the treatment of pain from strains, sprains and contusions, but no prescription topical agent has been approved by the FDA for these indications. Some of the OTC products specifically mention sports related injuries in their label. The evidence supporting the effectiveness of these OTC products is not robust. At this time there is no FDA approved topical formulation of diclofenac for the relief of pain.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient in the diclofenac patch, diclofenac epolamine, is not a new molecular entity but does contain a new salt, epolamine. Diclofenac is approved as a tablet for oral administration in the United States. It is marketed under the name Voltaren, Cataflam, Arthrotec and Diclofenac Sodium in 25, 50 and 75 mg doses. There is also a 100 mg Voltaren-XR Extended Release Tablet. The maximum daily dose ranges from 100 to 200 mg/day depending on the indication. Diclofenac is also approved as a topical gel (Solaraze) for the treatment of actinic keratosis and as an ophthalmic solution (Voltaren Ophthalmic). Solaraze (diclofenac sodium) gel 3% is indicated for twice daily application for up to 90 days.

Diclofenac, as with all oral non-steroidal anti-inflammatory drugs (NSAIDS), poses serious cardiovascular and gastrointestinal risks (see section 7.1.5.4).

2.4 Important Issues With Pharmacologically Related Products

See Section 2.3

2.5 Presubmission Regulatory Activity

Key milestones in the clinical development program of the diclofenac patch are summarized below.

<p>December 1995 IND 49,459 opened</p>	<p>Original indication: Pain associated with _____</p> <ul style="list-style-type: none"> The applicant discussed the concept of a _____ indication with the FDA in May 1995 during an NDA meeting for another product. From this discussion the applicant concluded that the FDA would accept an indication for a topical medication which would limit systemic use of NSAIDS. _____ was the specifically suggested indication.
<p>06/16/1998 End of Phase 2 meeting</p>	<p>The Division made several comments to the Applicant:</p> <ul style="list-style-type: none"> Additional Pharmacology and Toxicology information required: <ul style="list-style-type: none"> - Segment 2 reproductive toxicity in rabbit - Segment 3 reproductive toxicity in rat - Dermal 28 day study will support up to 2 weeks use for an NDA - More information is needed to assess the potential for phototoxicity

	<ul style="list-style-type: none"> - More information is needed on epolamine • Additional pharmacokinetic information needed: <ul style="list-style-type: none"> - Assessment of release -Residual patch contents - Accounting of the epolamine (PK) - Exercise induced changes in absorption in a standard US population • Should use pain alone as the endpoint • “Plan another pivotal study for _____”
<p>03/28/2000 Pre NDA meeting</p>	<p>The Division provided the following comments to the Applicant:</p> <ul style="list-style-type: none"> • The pre-specified analysis for Study 49459 did not show a positive result • At least one more efficacy study should be conducted. If the results of the second study 49459-2 are very strong, it is possible that the first study 49459 could be supportive. However, the FDA has significant reservations about the ability of the first study to be supportive, given that it failed on both primary endpoints at all three time-points • Determine diclofenac levels after dosing • Pediatric rule needs to be addressed • Studies to assess irritation, phototoxicity, photoallergy and contact sensitization are needed.
<p>12/20/2000 NDA submission</p>	<p>Initial NDA submission</p> <ul style="list-style-type: none"> • Contained two efficacy studies and the following clinical photosafety studies: <ul style="list-style-type: none"> - Human Repeat Insult Patch Test - Photoallergy Maximization Test - Evaluation of Phototoxicity Potential by UV-A Irradiation - 21 Day Relative Cumulative Irritancy Study
<p>10/18/2001 Non-Approval Letter</p>	<ul style="list-style-type: none"> • Study 49459-01 failed to demonstrate efficacy based on the efficacy variables of pain intensity difference, sum of pain intensity difference, pain on pressure difference and sum of pain on pressure difference • Study 49459-02 failed to demonstrated efficacy and several deficiencies were noted: <ul style="list-style-type: none"> - The primary endpoint, days to pain resolution, was based on a post hoc decision to use 24-hour days rather than nominal days on therapy. When the nominal day was used there was no statistically significant difference on any study day. • All secondary efficacy variables failed to show any significant difference between treatment groups in study 49459-02. • No information regarding dose ranging or dose selection was provided. At NDA resubmission, the applicant should provide a rationale for patch size and concentration

<p>11/20/2001 Meeting to discuss clinical issues in Non-Approval Letter</p>	<p>The Division made the following comments:</p> <ul style="list-style-type: none"> • Pain as a primary measure is critical to any understanding of an analgesic • Demonstration of efficacy based on a time to resolution would need to be interpreted in the context of the results of secondary endpoints. • The Applicant did amend the protocol to include average daily pain and thus had demonstrated an understanding of the Division's advice. • Two pivotal trials would be needed in any future NDA given that both submitted trials failed.
<p>11/26/2001 Pediatric waiver</p>	<p>Pediatric waiver request denied</p>
<p>03/28/2002 Sponsor's response to Non-Approval Letter</p>	<p>The applicant refuted the FDA's finding of lack of efficacy in Study 49459-02: The applicant concurred that Study 49459-01 failed to demonstrate efficacy based on the primary variables</p>
<p>04/16/2003 Second FDA Non-Approval Letter</p>	<p>The following comments by the Agency were made in response to the Applicant's March 28, 2002 response to the non-approval letter:</p> <ul style="list-style-type: none"> • Study 49459-01 (US-01) failed to demonstrate efficacy on all primary efficacy endpoints and cannot be used as supportive evidence for efficacy in any future submissions • For Study 49459-02 (US-02): <ul style="list-style-type: none"> ▪ When the significant imbalance in body weight is incorporated in the analysis of the primary endpoint of time to pain resolution, no significant treatment difference was detected (p=0.072) ▪ The primary endpoint, days to pain resolution is a derivative of a secondary endpoint, i.e. the daily pain score ▪ The decision to use 24-hour rather than nominal days on therapy was a post-hoc decision. When the nominal day is used there is no statistically significant difference on any study day ▪ All the secondary efficacy variables failed to show any significant difference between treatment groups ▪ Consistency of results for secondary endpoints of average daily pain, as well as patient and investigator reported global response to therapy, are necessary to fully interpret the clinical benefit based on the derived endpoint of median time to pain resolution • As part of the re-submission, the applicant should provide a rationale as to their selection of the patch size and concentration, and how these factors relate to clinical efficacy/safety

2.6 Other Relevant Background Information

None.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

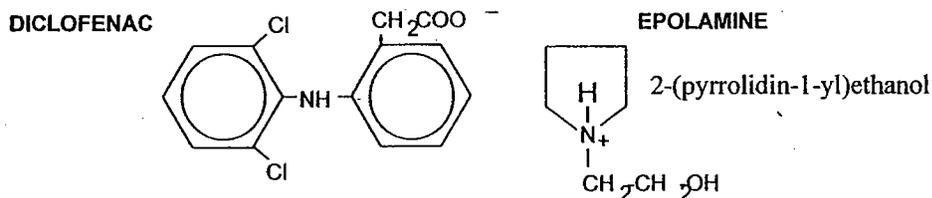
Much of the information below is based on the Applicant's proposed product label and discussions with the respective reviewers.

3.1 CMC (and Product Microbiology, if Applicable)

Please see the Chemistry review (pending at the time of this review) for a detailed discussion of the CMC data.

The Flector® Patch (10 cm x 14 cm) is comprised of an adhesive material containing 1.3% diclofenac epolamine which is applied to a non-woven polyester felt backing and covered with a polypropylene film release liner. The release liner is removed prior to application to the skin.

Diclofenac epolamine is chemically designated as (2-(pyrrolidin-1-yl) ethanol diclofenac salt, has an n-octanol/water partition coefficient of 8 at pH 8.5, and the following structure:



Each adhesive patch contains 182 mg of diclofenac epolamine (13 mg per gram adhesive) in an aqueous base. It also contains the following inactive ingredients: 1,3-butylene glycol, dihydroxyaluminum aminoacetate, disodium edetate, D-sorbitol, fragrance (Dalín PH), gelatin, kaolin, propylene glycol, sodium carboxymethylcellulose, sodium polyacrylate, tartaric acid, titanium dioxide, and purified water.

3.2 Animal Pharmacology/Toxicology

See the Pharmacology/Toxicology reviews (pending at the time of this review) for a detailed discussion of the non-clinical issues related to this product.

In the review of the original NDA submission, no non-clinical deficiencies were communicated to the Applicant.

During this review cycle the pharmacology team noted that the Applicant has not completed basic pharmacology studies for diclofenac. They are relying upon the existing knowledge that this is a cyclooxygenase inhibitor.

The Applicant has not completed safety pharmacology studies. Previous experience with diclofenac, as well as other NSAIDs, provides reasonable assurance that we understand the effects of diclofenac/NSAIDs. Therefore safety pharmacology studies were not specifically requested and were not considered necessary for the NDA application.

The Applicant did not complete a full nonclinical ADME profile for diclofenac epolamine. They did absorption studies, PK evaluations (distribution metabolism) for the new salt epolamine alone. They did not conduct metabolism studies nor elimination studies nor distribution studies with diclofenac epolamine, since once in the body the drug would behave like diclofenac.

For this NDA, the Applicant does not appear to have Segment III reproductive toxicology data for diclofenac. The NDA is a 505(b)(1) application, so the Agency can not rely upon previous Segment III findings for any other approved product.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

This review was based on clinical study reports and datasets for four efficacy trials and foreign postmarketing safety data. The datasets were utilized for confirmatory data analysis as well as for additional exploratory analyses.

4.2 Tables of Clinical Studies

The phase 3 trials submitted in support of safety and efficacy of the diclofenac patch are summarized in Table 4.2.a. The two US studies previously reviewed by the FDA and found not to demonstrate efficacy were evaluated only for safety.

Table 4.2.a: Phase 3 Safety and Efficacy Studies

Study Number Country Length of Study	Design	Primary Efficacy Variables	Secondary Efficacy Variables
05-05-98 France 1 Week	R,DB,PC 2-arm, PG*	Mean pain (VAS) with activity at end of study	Global response to therapy Pain at rest, pain on passive stretch
00GB/Fp05 UK/Ger 2 Weeks	R,DB,PC 2-arm, PG	Post-treatment pain (11-point NRS) with activity Initial endpoint time to pain resolution	Global response to therapy
49,459-01** US 2 Weeks	R,DB,PC 2-arm, PG	PID, SPID, POPD, SPOPD***	Global response to therapy
49,459-02** US 2 Weeks	R,DB,PC 2-arm, PG	Time to Pain Resolution	Average daily pain score Global response to therapy

*PG = parallel group

** Evaluated for safety only

***PID = Pain intensity difference

SPID = Summed pain intensity difference

POPD = Pain on pressure difference

SPOPD = Summed pain on pressure difference

4.3 Review Strategy

For this application, two studies, Protocol 00GB/Fp05 and 05-05-98 were reviewed for efficacy. The efficacy review was conducted together with Dr. Barbara Elashoff and Dr. Dionne Price, Division of Biometrics. Key findings from their analyses are included in this review. A detailed description of all analyses and findings can be found in Dr. Elashoff's and Dr. Price's reviews. Studies 49,459-01 (US-01) and 49,459-02 (US-02) submitted in the original NDA were not reviewed for efficacy since the initial review by the FDA concluded that both studies failed to demonstrate efficacy.

Data from all four studies were included in the safety analysis.

4.4 Data Quality and Integrity

The Division of Scientific Investigation (DSI) inspected two sites, one site for each study. The Division selected for Protocol 00GBFp05 site 11 due to the finding of a treatment-by-center interaction for this site, for Protocol 05-05-98 site 12 due to the high enrollment.

The DSI investigation was not completed at the time of this review.

4.5 Compliance with Good Clinical Practices

Each of the clinical trials appeared to be conducted under acceptable ethical standards in accordance with the Declaration of Helsinki and with approval of the appropriate Ethics Committee. Patients were appropriately informed and written consent was obtained prior to study enrollment. There were minor protocol violations in Study 05-05-98 which were not considered to have an influence on the study results. Study 00GB/Fp05 had a significant number of protocol violations that impacted on the interpretation of the efficacy findings and are described in detail under Section 6, Integrated Review of Efficacy.

4.6 Financial Disclosures

Biochemique Institut submitted Form FDA 3454 Financial Interests for both Trial 00GB/Fp05 and Trial 05-05-98. Review of this form revealed no financial conflict for the clinical investigators.

5 CLINICAL PHARMACOLOGY

Please see the Pharmacology review (pending at the time of this review) for a detailed discussion of the Clinical Pharmacology section.

5.1 Pharmacokinetics

Absorption of Diclofenac

Following single diclofenac patch application on the upper part of the inner arm, peak plasma concentrations of diclofenac (range 0.7 – 6 ng/mL) were noted between 10 – 20 hours after application. Steady plasma levels in the range of 1.3 – 8.8 ng/mL were noted after five days with twice a day Flector Patch application.

Distribution of Diclofenac

Clearance and volume of distribution of oral diclofenac are about 350 mL/min and 550 mL/kg respectively. More than 99% of diclofenac is reversibly bound to human plasma albumin.

Metabolism and Excretion of Diclofenac

Diclofenac is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites. Approximately 65% of the dose is excreted in urine, and approximately 35% in bile.

5.2 Pharmacodynamics

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic, and antipyretic activity. As with other NSAIDs, its mode of action is not known; its ability to inhibit prostaglandin synthesis, however, may be involved in its anti-inflammatory activity, as well as contribute to its efficacy in relieving pain associated with inflammation.

Applicant's endpoints

The primary efficacy variable for Study 05-05-98 was spontaneous pain experienced with normal activity, assessed on a 100 mm visual analog scale. The primary endpoint was pain at the end of the study.

For Study 00GB/Fp05, the primary efficacy variable was spontaneous pain on a 0 to 10 numerical pain rating scale. The primary endpoint was the time to significant pain resolution (defined as 4 scores of ≤ 2).

Acceptability of Applicant's Endpoints

The endpoint chosen for Study 05-05-98 is adequate and consistent with current recommendations by the Division. For Study 00GB/Fp05 the initial efficacy end point was time to significant pain resolution. This same endpoint was used in Study 49459-02 submitted in the original NDA and was determined to be unacceptable as a stand alone primary endpoint. The FDA's thinking about appropriate primary endpoints was communicated to the Applicant several times in meetings and letters. In the FDA Non-Approval letter dated 4/16/03 it was again reiterated, "Consistency of results for secondary endpoints of average daily pain... are necessary to fully interpret the clinical benefit proposed based on the derived endpoint of median time to pain resolution."

Change in Primary Endpoint - Study 00GB/Fp05

Without input from the Division regarding Study 00GB/Fp05, the Applicant modified the statistical analysis plan and changed the primary endpoint from "time to significant pain resolution" to a measure of average daily pain. The following rationale for the change was provided by the applicant:

- Patients may have a good response to treatment but discontinue the study prior to meeting the protocol definition of pain resolution. Under the original statistical analysis plan, these patients would technically be a failure even though they had a good response.
- The definition of pain resolution was arbitrarily made. The initial rationale for requiring four consecutive low scores was to prevent sporadic pain-free periods from being counted as resolution. However, this method failed to capture patients who had a good response to treatment but dropped out of the study as soon as they reach a low pain score.

The Applicant maintains that the modified statistical analysis plan was proposed under blinded conditions since the statistician did not have access to the randomization code. Under the modified plan, the mean post-treatment score was divided by the baseline score to determine the primary endpoint. The primary endpoint would be fraction of pain reduction over the 14-day treatment period.

While, the Applicant's choice of the primary endpoint is an evaluation of pain after treatment, the expression of post-treatment pain as a proportion of baseline pain complicates the ability to understand what constitutes clinically meaningful change from baseline or between treatment groups

6.1.3 Study Design

The Applicant submitted two protocols (05-05-98 and 00GB/Fp05) in support of efficacy of diclofenac patch in the treatment of pain due to strains, sprains and contusions. Each trial was a Phase 3 randomized, double-blind, placebo-controlled, parallel group study in patients 18 to 65 years old.

Study 05-05-98 was a one-week study of once daily patch application in patients with ankle sprain. The study was conducted in a total of 134 patients (68 diclofenac and 66 placebo) at 19 sites in France. Patients at baseline had pain scores on activity of ≥ 50 mm on the visual analog scale. Pain intensity scores were recorded in a pain diary hourly for the first six hours and at 8 PM on the first day (D0), then three times a day for the next two days (D1, D2), and on the morning of the third day (D3). Clinic visits occurred at the start of the study (D0), Day 3 and Day 7 at which time VAS pain scores were obtained. The protocol did not specify whether ambulatory assistive devices or braces would be allowed, nor was there a provision to capture this information. The use of the previously mentioned devices could effect outcome and in clinical practice are often prescribed in the management of ankle sprains.

Study 00GB/Fp05 was a two-week study that evaluated twice daily diclofenac patch versus placebo in the treatment of minor strains, sprains or contusions. A total of 417 patients (207 diclofenac and 210 placebo) participated at fourteen sites: 6 in the United Kingdom and 8 in Germany. Patients at baseline had pain scores with activity of ≥ 5 on a numerical rating scale. Concomitant analgesics were disallowed. Pain intensity scores were recorded in a pain diary twice daily at the time that each patch was removed. Patients were assessed in the clinic on the first and last day of the study.

6.1.4 Efficacy Findings

Protocol 05-05-98

(Refer to the Appendix for a detailed description of the study design, protocol amendments, statistical analyses, and study results.)

Title: Multicenter, randomized study in parallel groups comparing efficacy and safety of Diclofenac Patch vs. placebo in the treatment of minor ankle sprains.

Subject disposition:

All of the 134 patients randomized (68 diclofenac and 66 placebo) took at least one patch. A total of 125 patients (64 diclofenac and 61 placebo) completed treatment. Table 6.1.4.a shows the patient disposition, and the reasons for early study termination. The most common reason for trial discontinuation in the diclofenac group was loss to follow up for 4 patients. In the placebo group the most common reasons for study discontinuation were lack of efficacy for three patients followed by adverse event and non-compliance, each for one patient.

Table 6.1.4.a: Subject Disposition – Study 05-05-98

Group	Placebo, N (%)	DEP, N (%)
Enrolled	66 (100)	68 (100)
Completed	61 (92)	64 (94)
Reasons		
Lack of Efficacy	3 (4.5)	-
Adverse Event	1 (1.5)	-
Lost to Follow-up	-	4(6)
Injury Resolved	-	-
Non-compliance	1 (1.5)	-

Extent of exposure:

Of the 134 patients treated with patch, 122 patients (63 diclofenac and 59 placebo) were administered all seven doses.

Demographics:

There were 62 women (35 in the diclofenac group and 27 in the placebo group) and 72 men (33 in the diclofenac group and 39 in the placebo group) enrolled in the study. The patient's ages ranged from 18 to 65 with a mean of 33.3 for diclofenac group and 29.7 for placebo group. Women treated with placebo weighed less (placebo 57.1 kg vs. DEP 62.8 kg) and had lower body mass index than those treated with diclofenac patch. The mean pain at baseline on a 100 mm VAS was 66.9 for the DEP group and 70.0 for the placebo group. There was no significant difference in time to study enrollment after ankle injury or severity of injury as measured by the initial ankle sprain disability.

Applicant's Efficacy Analysis:

Primary Endpoint: There was a statistically greater decrease in mean pain scores in the diclofenac group at each time point from hour 4 to the end of the study, with the exception of Day 1 at 8 am (Table 6.1.4.b).

Table 6.1.4.b: Applicant's Primary Analyses – Study 05-05-98

Decrease (%) in spontaneous pain measured by the patient: mean (s.d.); median (min-max).	Flector Tlesugel® (n=68)	Placebo (n=66)	P-value*
Last known value			
1 hour after 1 st application	-7.7 (26.2), -2.0 (-100 to 67)	-5.9 (18.3), -2.7 (-60 to 37)	0.9
2 hours after 1 st application	-11.6 (26.4), -7.9 (-100 to 67)	-7.8 (20.5), -4.9 (-60 to 45)	0.5
3 hours after 1 st application	-18.3 (27.9), -14.5 (-100 to 67)	-11.3 (22.2), -6.8 (-66 to 55)	0.1
4 hours after 1 st application	-23.9 (27.5), -16.9 (-100 to 42)	-11.1 (22.6), -11.2 (-67 to 62)	0.02
5 hours after 1 st application	-26.6 (28.2), -23.3 (-100 to 42)	-13.0 (22.0), -11.6 (-66 to 62)	0.02
6 hours after 1 st application	-27.5 (30.9), -23.7 (-100 to 63)	-14.8 (23.7), -12.9 (-66 to 64)	0.02
Day 0, 8 pm	-26.4 (31.4), -21.3 (-100 to 67)	-13.6 (24.7), -12.7 (-79 to 55)	0.02
Day 1, 8 am	-38.3 (30.8), -38.5 (-100 to 23)	-28.3 (28.1), -28.7 (-94 to 43)	0.08
Day 1, noon	-47.5 (29.1), -48.9 (-100 to 10)	-33.5 (25.5), -35.8 (-97 to 23)	0.005
Day 1, 8 pm	-55.8 (27.0), -59.1 (-100 to 5)	-35.3 (30.9), -41.1 (-100 to 37)	0.0001
Day 2, 8 am	-59.4 (29.0), -64.6 (-100 to 17)	-44.5 (27.8), -46.3 (-100 to 41)	0.002
Day 2, noon	-64.7 (27.0), -70.5 (-100 to 0)	-49.4 (27.1), -51.0 (-100 to 17)	0.0006
Day 2, 8 pm	-68.6 (26.3), -75.5 (-100 to 0)	-50.0 (32.0), -57.4 (-100 to 43)	0.0002
Day 3, 8 am	-71.8 (25.5), -75.8 (-100 to 0)	-56.8 (28.3), -65.7 (-100 to 8)	0.001
Day 3 Consultation	-74.7 (29.3), -84.2 (-100 to 40)	-59.4 (30.7), -69.1 (-100 to 19)	0.0006
Day 7 Consultation	-84.3 (24.8), -93.2 (-100 to 0)	-74.0 (25.8), -79.9 (-100 to 27)	0.002

* Wilcoxon nonparametric test on the rank of the value.

(Source: Applicants Table 10: Analgesic Effect Results, Final Study Report for Protocol 05-05-98 Section 11.4)

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Secondary Endpoints: Evaluations of pain upon manipulation of the injured ankle (rest, passive stretch, pressure and single foot leaning) showed a better response to treatment for the diclofenac compared to the placebo group (Table 6.1.4.c).

Table 6.1.4.c: Applicant's Analgesic Efficacy of Secondary Variables – Study 05-05-98

	Flector Tissugel ® (n=68)	Placebo (n=66)	p-value*
Pain at rest			
Day 0			
None / Low / moderate / high	10 / 32 / 24 / 2	11 / 28 / 23 / 4	0.8
Day 3 or last known value			
None / Low / moderate / high	49 / 18 / 1 / 0	33 / 25 / 8 / 0	0.002
Day 7 or last known value			
None / Low / moderate / high	60 / 8 / 0 / 0	41 / 19 / 6 / 0	0.001
Pain on passive stretch			
Day 0			
None / Low / moderate / high	0 / 4 / 36 / 28	0 / 4 / 29 / 33	0.4
Day 3 or last known value			
None / Low / moderate / high	12 / 34 / 20 / 2	4 / 26 / 30 / 6	0.003
Day 7 or last known value			
None / Low / moderate / high	30 / 29 / 7 / 2	17 / 22 / 23 / 4	0.001
Pain on palpation			
Day 0			
None / Low / moderate / high	0 / 0 / 23 / 45	0 / 2 / 21 / 43	0.7
Day 3 or last known value			
None / Low / moderate / high	7 / 28 / 25 / 8	2 / 19 / 29 / 16	0.007
Day 7 or last known value			
None / Low / moderate / high	20 / 33 / 12 / 3	8 / 25 / 20 / 13	0.001
Possibility of single foot leaning			
Day 0			
Ok without pain / ok with pain / impossible	4 / 52 / 12	6 / 44 / 16	0.7
Day 3 or last known value			
Ok without pain / ok with pain / impossible	36 / 31 / 1	23 / 37 / 6	0.002
Day 7 or last known value			
Ok without pain / ok with pain / impossible	56 / 11 / 1	37 / 28 / 1	0.001

* Chi square Mantel Haenszel test for trend.

(Source: Applicants Table 11: Analgesic Effect Results, Final Study Report for Protocol 05-05-98 Section 11.4)

With respect to both the patients' and investigators' overall judgment of efficacy diclofenac patch treated patients had a superior effect on both days three and seven compared to placebo. (Table 6.1.4.d).

Table 6.1.4.d: Applicant's Table of Investigator and Patient Global Assessment Study 05-05-98

Global judgment		Flector Tissugel® (n=68)	Placebo (n=66)	p-value*
Day 3	Efficacy as judged by the patient None / fair / good / excellent	3 / 3 / 28 / 34	3 / 8 / 38 / 17	0.001
	Efficacy as judged by the physician None / fair / good / excellent	3 / 7 / 27 / 31	5 / 10 / 39 / 12	0.001
Day 7	Efficacy as judged by the patient None / fair / good / excellent	5 / 1 / 24 / 38	6 / 12 / 24 / 24	0.001
	Efficacy as judged by the physician none / fair / good / excellent	4 / 7 / 23 / 34	5 / 13 / 29 / 19	0.001

* Chi square Mantel Haenszel test for trend.

On day 3 "bad" was assigned to 4 patients with missing values (3 active, 1 placebo)

On day 7 "bad" was assigned to 5 patients with missing values (4 active, 1 placebo)

(Source: Applicant's Table 13: Global Judgment-Efficacy, Final Study Report for Protocol 05-05-98 Section 11.4)

There was no statistical difference in mean ankle swelling in the diclofenac and placebo groups on days 0, 3 and 7 (Table 6.1.4.e). Similar ankle edema in both groups suggests that there was no significant difference in the severity of injury or the degree of recovery during the study. There was no statistical difference in acetaminophen use between the two treatment groups (Table 6.1.4.f). Similar acetaminophen use in the diclofenac and placebo groups implies that there was no significant difference in the need for supplemental analgesics.

Table 6.1.4.e: Applicant's Assessment of Perimalleolar Edema - Study 05-05-98

Perimalleolar edema in mm : Mean (sd) and median (min-max)	Flector Tissugel® (n=67)	Placebo (n=66)	p-value*
Day 0			
Healthy ankle	241 (27.1), 240 (140-285)	237 (27.3), 240 (126-290)	0.4
Injured ankle	254 (27.2), 256 (150-300)	253 (29.1), 260 (127-302)	0.9
Diff. Between injured and healthy ankle	13.3 (10.7), 10.0 (-10-40)	16.2 (13.4), 13.5 (0-60)	0.3
Day 3 or last known value			
Healthy ankle	241 (26.9), 240 (140-285)	238 (27.2), 240 (126-290)	0.5
Injured ankle	247 (27.7), 245 (140-295)	247 (29.9), 251 (127-304)	0.8
Diff. Between injured and healthy ankle	5.9 (7.8), 5.0 (-10-25)	8.9 (11.1), 5.0 (-5-50)	0.2
Day 7 or last known value			
Healthy ankle	241 (26.7), 240 (140-284)	239 (27.2), 240 (126-290)	0.5
Injured ankle	244 (26.8), 245 (140-300)	245 (29.3), 250 (126-296)	0.8
Diff. Between injured and healthy ankle	3.3 (5.7), 0.0 (-10-20)	6.7 (9.9), 2.0 (-10-40)	0.2
Change between Day 0 and Day 3			
Injured ankle	-7.1 (9.8), -5.0 (-40-15)	-6.0 (12.1), -5.0 (-40-60)	0.8
Diff. Between injured and healthy ankle	-7.3 (10.0), -5.0 (-40-15)	-7.3 (8.4), -5.0 (-40-15)	0.6
Change between Day 0 and Day 7			
Injured ankle	-9.8 (10.0), -10.0 (-40-8)	-8.1 (12.5), -8.5 (-40-40)	0.7
Diff. Between injured and healthy ankle	-9.9 (10.2), -10.0 (-40-5)	-8.6 (10.6), -8.5 (-40-15)	0.9

* Wilcoxon non parametric test on the rank of the value.

(Source: Applicant's Table 12: Perimalleolar Edema, Final Study Report for Protocol 05-05-98 Section 11.4)

**Table 6.1.4.f: Applicant's Table of Overall Acetaminophen Use (#500 mg Capsules)
 Study 05-05-98**

Overall consumption of paracetamol Mean (sd) and median (min-max)	Flector Tiasogel® (n=68)	Placebo (n=66)	p-value*
Between Day 0 and Day 3	1.5 (3.9), 0 (0 - 16)	1.8 (4.0), 0 (0 - 16)	0.6
Between Day 0 and Day 7	1.9 (5.7), 0 (0 - 30)	2.4 (6.3), 0 (0 - 36)	0.5

* Wilcoxon non parametric test on the rank of the value.

(Source: Applicant's Table 14: Overall Paracetamol Consumption, Final Study Report for Protocol 05-05-98 Section 11.4)

Reviewers Efficacy Analysis

Primary Endpoint:

Mean pain score (VAS) on Day 7

Analysis of VAS on Day 7 for the intention-to-treat population shows that the diclofenac group was statistically significantly superior to the placebo group on the 100 mm Visual Analog Scale for pain, with a mean score 9.3 mm less than placebo (Table 6.1.4.g).

The statistician identified two treatment centers (Bichon and De Lustrac) that had a large treatment effect. The statistically significant treatment-by-investigator interaction makes it difficult to accurately estimate the overall magnitude of the treatment effect.

**Table 6.1.4.g: Primary Efficacy Endpoint: Mean Pain Score at Day 7
 (Least Squares Means ± SE) - Study 05-05-98**

Day 7

N=134*	Flector	Placebo	Difference / p-value
VAS at Day 7	12.076±2.816	21.384±3.089	9.308/ 0.0041

* Intent-to-treat population

Secondary Endpoints:

1. Mean pain score (VAS) on Day 3

The analysis of the mean pain score on Day 3 also demonstrated a statistically significant difference, with the diclofenac group superior to placebo (Table 6.1.4.h).

**Table 6.1.4.h: Secondary Efficacy Endpoint: Mean Pain Score at Day 3
 (Least Squares Means ± SE) -Study 05-05-98**

N= 134	Flector	Placebo	Difference / p-value
VAS at Day 3	17.760±3.158	30.471±3.47	12.711/ 0.0005

2. Percent Patients Improved

In the protocol (Section 8.1), it was stated that, "At the end of treatment, the subjects will be considered improved and therapy efficient, if the relative evolution shows a diminution of the

VAS value of at least 20 mm minimum between study entry and end of the study.” One of the secondary endpoints analyzed by the statistician was percent of patients improved, as based on a 20 mm difference in pain score (VAS) between baseline and end of study. The analysis found that the difference between the two treatment groups at Day 7 was negligible (2%) but the difference between the two groups at Day 3 was 11% (Table 6.1.4.i)

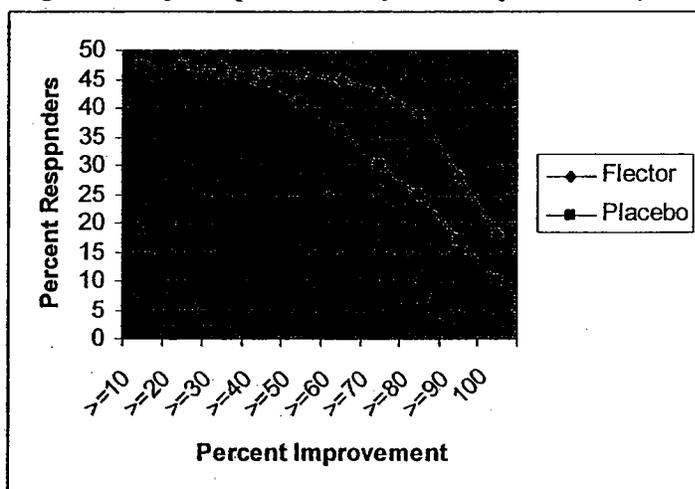
Table 6.1.4.i: Percent of Patients Improved by ≥ 20 mm from baseline to endpoint – Study 05-05-98

	Day 3	Day 7
Flector	62/68 = 91%	63/68 = 93%
Placebo	53/66 = 80%	61/66 = 92%

3. Responder Analysis

A responder analysis was performed to compare the number of responders in each group, as based on the percent improvement in pain from baseline to the end of the study (Day 7). The percent of responders as shown in Figure 6.1.4.j was greater in the diclofenac group for all definitions of improvement.

Figure 6.1.4.j: Responder Analysis – Response at Day 7 – Study 05-05-98



4. Reviewers' analysis secondary

There was no statistically significant difference in the number of patients using ice (25 diclofenac and 27 placebo) or the number of occurrences of ice being applied. Pain at rest, pain on passive stretch and pain on pressure were all graded on a 4 point scale (0: absent, 1: slight, 2: moderate, 3: severe). At Day 3 and Day 7 the diclofenac group demonstrated statistically significant lower mean pain scores over the placebo group for all three measures.

Conclusions for Study 05-05-98:

Based on the Division's analysis, there is a statistically significant difference in the mean pain score at Day 7 (9.3 mm on 100 mm VAS) between the diclofenac group and the placebo group. Although the numerical magnitude of the improvement was small, the clinical relevance of the change was supported by secondary outcomes. The diclofenac group was superior to the placebo group with respect to mean pain score on Day 3, responder analysis, and onset of analgesia. As based on table 6.1.4.i, the apparent decline in some efficacy at the end of the study is likely related to spontaneous improvement in pain in the placebo group.

Protocol 00GB/Fp05

Title: A randomized, double-blind, placebo controlled study of the analgesic efficacy and safety of diclofenac epolamine patch in minor soft tissue injury.

Subject disposition:

Of the 418 patients randomized, 417 (207 diclofenac and 210 placebo) took at least one dose of patch. One patient randomized to the placebo group did not use drug. Table 6.1.4.k shows the patient disposition, and the reasons for early study termination. The most common reason for trial discontinuation was injury resolution (44% diclofenac and 32% placebo), followed by inappropriate enrollment or non-compliance with the protocol (22% diclofenac and 24% placebo) and another therapy (10% diclofenac and 10% placebo).

Table 6.1.4.k: Patient Disposition-Study 00GB/Fp05

Reason For Study Discontinuation	Diclofenac Patch	Placebo Patch	Combined
Used at least one patch	207 (%)	210 (%)	417 (%)
Completed 14 Days of Therapy	21 (10)	35 (17)	56 (13)
Injury Resolution	92 (44)	68 (32)	160 (38)
Another Therapy	20 (10)	22 (10)	44 (11)
Adverse Event*	4 (2)	8 (4)	12 (3)
Study Admission Problems**	46 (22)	51 (24)	97 (23)
Withdraw for Another Reason***	22 (11)	23 (11)	45 (11)

* No SAE or deaths occurred

** Includes inappropriate enrollment, non-compliance with the protocol, or need for a prohibited medication

*** Defined on the CRF as patient wishes to withdraw from the study for another reason

Extent of exposure:

Of the 417 patients treated with at least one patch, 181 patients (87 diclofenac and 94 placebo) received at least 28 patches (14 days). The exposure calculated is only an estimate of true exposure since it was obtained from diary.xpt dataset in which patch use was recorded for only 387 patients.

Demographics

The average age of patients was 38.9 years with diclofenac patch patients younger than the placebo, 37.7 vs 40.1 years. Nearly all the patients (99.5%) were Caucasian. There were 206 males and 212 females enrolled in the study. Weight was similar in the two groups, 74.6 kg and 76.0 kg in the diclofenac and placebo groups, respectively. The frequency of diagnoses was contusion (43% in diclofenac group and 42% in placebo group), strain (33% in diclofenac group and 29% in placebo group), and sprain (22% in diclofenac group and 27% in placebo group). The ankle and shoulder joints were most frequently involved. Almost 50% of the injuries involved the ankle, foot or knee. The diclofenac group experienced restricted range of motion statistically more frequently than placebo (87.9 vs. 78.2%). The diclofenac group had a statistically significant lower average pain score than placebo (7.3 vs. 7.5). The demographic and medical characteristics are summarized in the Appendix Table 10.1.1.f.

Applicant’s Efficacy Analysis:

Primary Efficacy Analysis-as based on the modified statistical analysis plan

The new primary endpoint was the mean post-treatment pain score expressed as a proportion of the baseline pain score. The efficacy population was defined as all treated patients who had at least one post-treatment pain assessment (the “efficacy evaluable population”. The Division prefers using the intention-to-treat (ITT) population for statistical analysis (i.e. all randomized and treated patients).

Applicant’s Efficacy Findings

Primary Endpoint: As described in the modified statistical plan, a multiple imputation method was used for the primary analysis of mean post-treatment pain scores to handle missing data. In the efficacy evaluable patients, the difference in the calculated outcome (the mean pain score at study end as a fraction of the baseline score) for the diclofenac group was 14.8% lower than that of the placebo group, using multiple imputation. Different analyses were performed with last observation carried forward (LOCF) and generalized estimating equations (GEE) imputation to determine if outcome was dependent on the method used to handle missing data. The diclofenac group continued to have lower values than placebo group of 18.2% and 9.8% with LOCF and GEE methods, respectively (Table 6.1.4.1).

Table 6.1.4.1: Applicant’s Primary Efficacy Outcome in Efficacy Evaluable Population Study 00GB/Fp05

Parameter*	Diclofenac Epolamine Patch	Placebo Patch	p Value†
Primary Outcome Variable			
Multiple Imputation Analysis	0.404 ± 0.242	0.474 ± 0.255	0.009
LOCF Analysis	0.435 ± 0.268	0.532 ± 0.293	<0.001
GEE Model Analysis	0.568	0.630	0.008

* Mean ± standard deviation provided where appropriate.

† P values derived from multiple imputation ANOV, repeated measures ANOV, or GEE analysis, respectively. LOCF = last observation carried forward, GEE = general estimating equations.

(Source: Applicant’s Table 8. Efficacy Evaluable Population: Primary Outcome Variable, Final Report for Protocol 00GB/Fp05, pg. 36)

The applicant also reported that interday pain score comparisons reached significance by the time the second patch was removed on day 1 (Figure 6.1.4.m). This reviewer believes that statement is misleading since any statistically significant difference between the two groups did not occur until at least the second day (discussed under Reviewers' Analysis)

Figure 6.1.4.m: Daily Mean Pain Scores for Diclofenac and Placebo Patients Over 14 Days- Study 00GB/Fp05

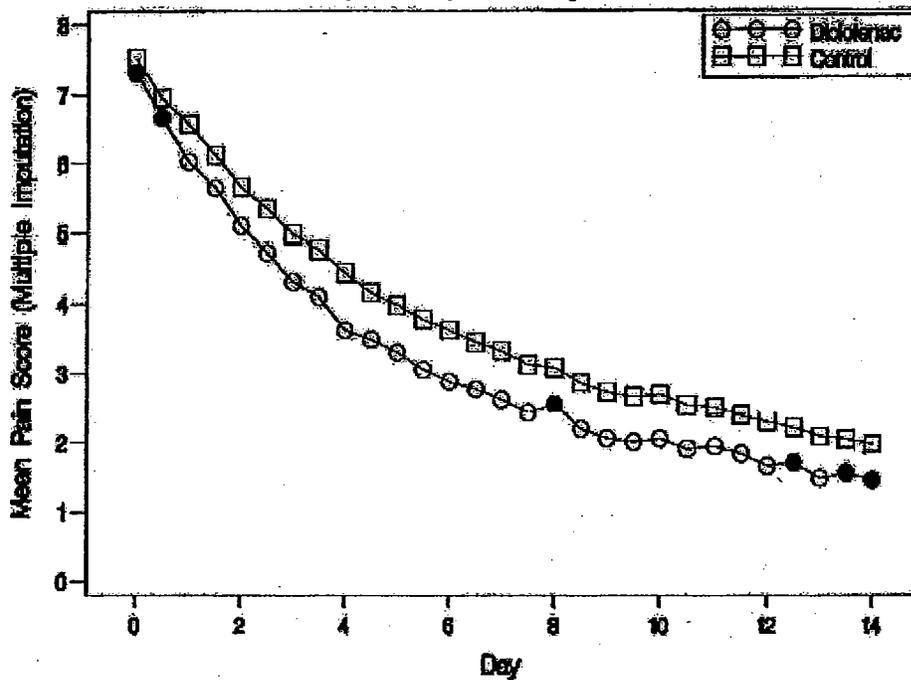


Figure 1. Daily mean pain scores for DEP and control (PP) patients over 14 days of treatment/follow-up using a multiple imputation method for missing data. P values are ≤ 0.045 for all data points except those in which the circle has been filled-in, the latter having p values < 0.10 (except baseline or day 0 in which it is 0.127 for the DEP/PP mean pain scores of 7.31 and 7.52, respectively).

(Source: Applicant's Figure 1, Final Report for Protocol 00GB/Fp05, pg. 47)

Secondary Outcome Variables

Investigator assessment of global response to treatment was "good" to "excellent" for 58% of diclofenac treated patients compared to 48% of placebo. There was no statistical difference in range of motion and swelling for the two treatment groups but range of motion differences approached statistical significance, due primarily to a higher percentage of DEP patients with restricted mobility at baseline able to move freely at the end of treatment (70.3% vs 59.9%, $p = 0.058$). Time to pain resolution, the primary outcome variable in the original protocol, varied according to the definition used for pain resolution but resulted in less time for pain resolution in patients on diclofenac therapy (Table 6.1.4.n). The estimate of the median time to significant

pain resolution of diclofenac was 10 days and for placebo 13.5 days, when patients were censored at 15 days and injury resolution was defined as 4 consecutive pain scores of ≤ 2 (on an 11-point NRS).

Table 6.1.4.n: Time to Pain Resolution - Study 00GB/Fp05

Definition of "pain" resolution	Diclofenac Patch No. Days (Range)	Placebo Patch No. Days (Range)	p Value
Score 0	12.0 (9.0 to 13.0)	14.0 (11.0 to NC)	0.060
Score ≤ 1	9.0 (6.5 to 11.0)	10.5 (9 to 13)	0.020
Score ≤ 2	5.5 (4.5) to 6.5)	7.5 (6.5 to 8.5)	0.007
4 Score ≤ 2	10.0 (8.0 to 12.0)	13.5 (10.0 to NC)	0.010

(Adapted from: Applicant's Table 13. Efficacy Evaluable Population: Secondary/Other Outcome Variables, Final Report for Protocol 00GB/Fp05, pg. 41)

Reviewers' Analysis of Efficacy

The primary statistical reviewer at the FDA rejected the results of the applicant's primary analysis and most of the secondary analyses as not meaningful due to the high rate of dropout (> 80%) by the end of the study.

The Division performed the following preferred analyses:

Mean pain scores at end of the study

Analysis comparing the mean pain scores of patients at the end of the study was performed with imputed data for dropouts. Patients who discontinued due to injury resolution received a score equal to their last score. Patients who discontinued for any reason other than injury resolution, received a score equal to their baseline score. Patients who completed the study received their last score. The results of the analysis are shown in Table 6.1.4.o below.

Table 6.1.4.o: Reviewer's Analysis: Mean Pain Score at Endpoint and Change in Mean Pain Score from Endpoint – Study 00GB/Fp05

N=418	Diclofenac n=	Placebo n=	Difference / p-value
Endpoint (imputed)	2.90±0.23	3.60±0.25	-0.699 / 0.03663
Change from Baseline (imputed)	-4.40±0.22	-3.91±0.23	-0.486 / 0.1222

The difference in mean pain scores at study end (day 14) was approximately half a point (which is similar to that found by looking at the raw means with no imputation), and was statistically significant. This analysis does not take into account that the pain scores were lower for the diclofenac group at baseline.

The difference in the mean change from baseline value to study end was a little less than half a point (which is also similar to that found by looking at the raw means with no imputation) but not statistically significant tested at an alpha-level of 0.05. This analysis includes the baseline pain scores.

Responder analysis

The percentages of patients who “responded” at the end of the study are presented in Table 6.1.4.p below. Patients who discontinued due to injury resolution were counted as “responders”, patients who discontinued for other reasons were counted as “non-responders”, and patients who completed the study without injury resolution were counted if they met a percent improvement criteria.

Table 6.1.4.p: Responder Analysis Day 14 – Study 00GB/Fp05

Improved by:	Diclofenac n-195 n (%)	Placebo n=192 n (%)
10%	150 (76.9)	141 (73.4)
20%	149 (76.4)	138 (71.9)
30%	145 (74.4)	129 (67.2)
40%	144 (73.8)	125 (65.1)
50%	142 (72.8)	123 (64.1)
60%	137 (70.3)	114 (59.4)
70%	130 (66.7)	106 (55.2)
80%	124 (63.6)	101 (52.6)
90%	114 (58.5)	99 (51.6)

The percentages of patients that improved by 10% were high in both the treatment and placebo groups (77% and 73%, respectively). The percent responders in the placebo group drops off gradually, as the definition of response increases from 10% improvement to 90% improvement. The percent responders in the treatment group, however does not drop off as quickly. It remains as high as 70% in all Diclofenac patients until the definition of response is greater than 60% improvement. At no point is the difference between diclofenac and placebo responders greater than 12%. Responder analysis at Day 3 was also done (see Dr. Dionne Price’s Statistical Review) and showed similar results. Although the diclofenac response is numerically better than placebo at both 3 and 7 days, the difference is of unclear clinical significance.

Other Analyses:

Time to onset of analgesia

The applicant states that interday pain score comparisons reached significance by the time the second patch was removed on day 1. This reviewer believes that statement is misleading since any statistically significant difference between the two groups did not occur until at least the second day. The Applicant provides the following explanation, “Day 1 was defined as a 24 hour period”.

The FDA's preference to use the nominal day rather than 24 hour day was previously discussed with the Applicant in regards to Study 49459-02 submitted in the original NDA. In the Non-approval letter dated 10/18/01 the FDA stated, "The nominal day is more relevant in view of the impact of activity and weight bearing on pain following injury."

In Study 00GB/Fp05 the interpretation of how long it takes for pain relief to occur is influenced by the definition of "day" used. From a clinical perspective, statistical difference in pain does not occur until the second nominal day by the Applicant's own analysis. It is the contention of this reviewer that a one day delay in onset of analgesia is not acceptable for a product intended to treat acute pain. Furthermore the absolute difference in mean pain score observed on Day 2 (approximately 0.5 units on a NRS) does not appear to be clinically meaningful to this reviewer.

Effect of number of patches used on mean pain

The statistician also did a descriptive analysis of the effect of the number of patches used on mean pain score. The patients who dropped out the earliest (i.e. used fewer patches) had the quickest decline in mean pain scores and those who used more patches appeared to have a slower decline in mean pain scores (i.e. longer time for onset of action). For patients who used at least 24 patches there does not appear to be any effect on pain for approximately 3 days. These results add support to the assertion that patients do not obtain pain relief until one or more days after using the patch.

Time to pain resolution

The estimate of the median time to significant pain resolution of diclofenac was 10 days and for placebo 13.5 days, when patients were censored at 15 days and injury resolution was defined as 4 consecutive pain scores of ≤ 2 (on an 11-point NRS). However, the clinical significance of this difference is uncertain and the statistician notes that the statistical significance is less than definitive due to the high rate of missing data and dropouts. Time to pain resolution is not considered by the Division to be a primary efficacy endpoint without supporting evidence of effectiveness from secondary endpoints.

Limitations of Applicant's Analysis

There were a large number of patient dropouts and missing diary entries. Of the 417 patients initially treated only 384 were included in the Applicant's efficacy evaluable study population (i.e. randomized and treated patients who had ≥ 1 post-baseline pain score). The exact number of dropouts is unclear because the Applicant submitted two different datasets with discontinuation information. One of the datasets closely followed the Exit Case Report Form and the other data set was revised by the Applicant based on re-interpretation of the data in the CRF. Nevertheless, many patients did not complete 14 days of treatment.

The decision of the applicant to modify the statistical analysis plan following completion of the study is not consistent with usual statistical practices. In general if the original endpoint does not demonstrate efficacy, a new statistical analysis plan is not permitted by the FDA. However, Study 00GB/Fp05 poses a unique situation since failure to demonstrate efficacy appeared to be related to patients dropping out of the study due to improvement, yet not meeting the protocol

definition for pain resolution. For this reason, modification of the statistical analysis plan appears reasonable. However, if the Division accepts this new plan, the efficacy should be convincing and not marginal.

Conclusions -Study 00GB/Fp05

Although, the applicant reports efficacy based on their modified analysis plan, the FDA statistician concludes that their analyses are not meaningful due to the high rate of dropout. This reviewer does not find the difference in mean pain (about 0.5 units) at study end to be clinically meaningful. The applicant's own analysis shows no statistically significant difference in pain between the diclofenac and placebo groups until the second day.

6.1.5 Clinical Microbiology

Not applicable

6.1.6 Efficacy Conclusions

The applicant submitted two studies in support of the efficacy of diclofenac patch for the treatment of pain due to strains, sprains and contusions. The findings of the French study demonstrated a statistically significant difference in effect on the visual analog pain scale score when assessed at one week. This effect was supported by secondary outcome measures. Furthermore an analgesic effect was noticed as early as four hours after patch application.

For Study 00GB/Fp05, the primary statistical reviewer at the FDA rejected the applicant's primary endpoint and most of the secondary analyses as not meaningful due to the high rate of dropout (> 80%). By the end of Day 1, 20% and by Day 7, 50% of patients had dropped out and by the end of the study only 13% in the diclofenac and 18% of patients in the placebo group remained in the study. In general, the dropouts were not due to random events but were related to improvement in pain, the intended primary endpoint of the study. This high dropout rate related to improvement in primary endpoint in both placebo and diclofenac groups makes statistical analysis difficult.

The difference in change between pain scores at baseline and end of study in placebo and diclofenac patch treated groups imputed by the FDA statistician was 0.486 with a p value of 0.12. This reviewer does not believe this represents a clinically meaningful change. Furthermore, there was no analgesic effect noted on the first day of patch use. It is the opinion of this reviewer that Study 00GB/Fp05 fails to demonstrate efficacy of diclofenac patch in the treatment of strains, sprain and contusions.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

In support of this New Drug Application, Institut Biochimique is relying on safety information from four clinical trials: US Study 49,459-01, US Study 49,459-02, French Study 05-05-98 and UK/German Study 00GB/Fp05. Additional safety information on diclofenac patch is based on post-marketing experience overseas.

The primary electronic datasets employed in the safety analysis for exposure, disposition and adverse events are listed in Table 7.1.a.

Table 7.1.a: Datasets Used for Safety Analysis

Study Database	Variable	Type
ISS Dataset	safety.xpt	Integrated safety dataset
Study 05-05-98	db050598.xpt	Combined safety and efficacy dataset
Study 00GB/Fp05	exit.xpt	Exit form dataset to determine disposition
	diary.xpt	Patient diary
	advent.xpt	Adverse event dataset
US-01 and US-02	efficacy.xpt	Efficacy dataset to determine drug exposure
	exit.xpt	Exit dataset to determine disposition

Several issues were noted related to safety information in the NDA. First, there were differences in the coding used in the study datasets and lack of straightforward documentation of patch use. For Study 00GB/Fp05, there were two data sets for disposition status due to reclassification by the Applicant. The FDA requested that the Applicant perform a reclassification of patient disposition based on specific categories (details in Section 7.1.3.1). Because there was no straight forward documentation of patch use the Division relied on derived variables to indicate patch use, or used time-related variables (time of patch application) to determine the number of patches used during the trials.

For Study 05-05-98, there were discrepancies in coding for disposition. The dataset for this study, dataset db050598, listed patients 41, 43, and 158 as having dropped out of the study (variable DROP_J7), yet data regarding patch use (variables QUOT_J3 and MAN_A_J7) suggested that these patients used a patch over the entire duration of the trial. Also, these patients were not included in the Applicant's list "Subjects Dropped out from the Study" (Final Study Report for Protocol 05-05-98, Section 10.1)

Because the ISS dataset did not capture information on discontinuation due to adverse events, individual study reports and their respective datasets were used for determination of disposition status. In response to questions about inconsistencies in the disposition data, the Applicant submitted a revised listing of disposition and of patients who had protocol deviations (E-mail dated December 7, 2006).

7.1.1 Deaths

No deaths were reported during the four clinical trials of diclofenac patch.

7.1.2 Other Serious Adverse Events

There were no serious adverse events (SAEs). However, the Applicant coded in the ISS safety.xpt dataset three patients as having SAEs. Two of these patients in the diclofenac group (patients 10536 and 20122 from U.S. studies 49,459-01 and 49,459-02, respectively), each experienced an adverse event that was graded as “severe” in the original combined US ISS ae.xpt dataset (variable SESEV). Neither of these patients met the definition of having a serious adverse event. Patient 10536 presented with fever and skin breakdown after using wet diclofenac patches for five days. The patch was discontinued and the patient was evaluated at an outpatient urgent care facility where he was started on tetracycline. On follow-up the area was noted to be healing without any evidence of infection. Patient 20122 reported at their final visit severe nausea and emesis of 24 hours duration. The patient felt that the nausea/emesis was due to something he ate. There was no mention of hospitalization in the case report form.

The third patient, patient 40-440 (Study 00GB/Fp05), was also coded in the ISS dataset as having experienced a serious adverse event (hospitalization). The patient was in the placebo group and her narrative is below:

This was a 24 year old woman enrolled in the study on 6/04/03 with a contusion of the left wrist. On examination, there was no bruising and range of motion was full but swelling was present from the mid-phalanges to the mid-forearm. The patient started patch application on the day of inclusion and continued treatment up to 6/07/03. During her last phone contact on 6/10/03 she communicated that she had been examined by her GP who sent her to the hospital due to worsening of her pain. There was no further contact with the patient and her personal diary was not retrieved. Although she was coded as experiencing an SAE (hospitalization), the interpretation of the personnel involved in the study was that she only consulted the emergency room for radiographic examination of the wrist.

I concur with the opinion of the applicant that it is likely that she was not hospitalized but only consulted the emergency room for worsening wrist pain. In my review, I considered this patient to have discontinued therapy due to lack of efficacy.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Disposition for Studies 05-05-98, 00GB/Fp05, 49,459-01, 49,459-02 is summarized in Table 7.1.3.1.a. In the four studies, a total of 1185 patients were randomized (590 diclofenac and 595 placebo). For Study 49,459-01, disposition status was not systematically collected since there

was no exit form. Disposition status was estimated based solely on information in study reports in section 10.1 in the original NDA.

The percent patients completing the study was 25 and 32 percent in the diclofenac and placebo groups, respectively. The most common reason for study discontinuation was injury resolution: 47% in the diclofenac group and 37% in the placebo group. Adverse events accounted for 3% of the drop-outs in both treatment groups.

In comparing the studies, Study 00GB/Fp05 was notable for more drop-outs mainly because of injury resolution and protocol violations. Assignment of disposition status was complicated by several issues. The Applicant reclassified the disposition status from what was coded on the exit form of the CRF. The reclassification resulted in several patients being coded as having completed the study rather than not (as initially coded on the CRF).

In response to the Division's questions about inconsistencies in the number of dropouts in Study 05-05-98, the applicant revised the number of patients who dropped out from seven to nine. The applicant states that the most likely explanation for patients 41, 43, and 158 being listed as dropouts (variable DROP_J7) was data entry error. The explanation for not listing these patients in the table of dropouts was that probably a different source was used to generate the list. Patients 181 and 42 were initially not included by the Applicant as having dropped out. Patient 181 was a dropout not listed under the variable dropout (variable DROP_J7) but listed for date of dropout (DROPD_J7) and reason (DROPM_J7). There is no explanation as to why patient 42 who was appropriately listed as a dropout in the dataset was not included in the original Applicant's table of dropouts.

Three additional patients (37, 111, 184) were added by the Applicant to the listing of protocol deviations and one patient (129) was removed since it was patient 184 that received an unauthorized medication (Efferalgan) and not patient 129. Patient 37 and patient 111 did not complete the required number of patch applications.

Table 7.1.3.1.a: Reviewer's Analysis: Patient Disposition: Studies 49,459-01, 49,459-02, 05-05-98, 00GB/Fp05

Status	Diclofenac					Placebo				
	49,459-01	49,459-02	05-05-98	00GB/Fp05	Total	49,459-01	49,459-02	05-05-98**	00GB/Fp05	Total
Randomized	110	205	68	207	590	112	206	66	211	595
Intention-to-treat	106	191	68	207	572	107	181	66	210	564
Completed 7/14 days**	100 (94)	37 (18)	64 (94)	21 (10)	222 (39)	102 (95)	55 (27)	61 (92)	35 (17)	(253) (45)
Injury resolution	0 (0)	133 (65)	0 (0)	92 (44)	225 (47)	0 (0)	111 (54)	0 (0)	68 (32)	179 (37)
Lack of efficacy	0 (0)	7 (3)	0 (0)	20 (10)	27 (6)	0 (0)	6 (3)	3 (5)	22 (10)	30 (6)
Adverse Event	3 (3)	12 (6)	0 (0)	4 (2)	19 (3)	1 (1)	4 (2)	1 (2)	8 (4)	14 (3)
Withdrew	1 (1)	16 (8)	0 (0)	22 (11)	39 (7)	0 (0)	30 (15)	0 (0)	23 (11)	53 (11)
Lost to follow-up	5 (5)	0 (0)	4 (6)	0 (0)	9 (2)	5 (5)	0 (0)	0 (0)	0 (0)	5 (1)
Admission/Violation***	1 (1)	0 (0)	0 (0)	46 (22)	47 (8)	4 (4)	0 (0)	1 (2)	51 (24)	56 (10)
No Reason	0 (0)	0 (0)	0 (0)	2 (1)	2 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

**Study 05-05-98, 7 days duration, once-daily patch application

***Inappropriate enrollment, non-compliance with protocol

7.1.3.2 Adverse events associated with dropouts

Thirty-two patients dropped out for 50 adverse events that did not meet the definition of serious. Adverse events leading to withdrawal are listed in Table 7.1.3.2.a.

Table 7.1.3.2.a: Discontinuations Due to Adverse Events All Studies

Adverse Event Body System/Preferred Term	Number of patients	
	Placebo* 564 (%)	Diclofenac* 572 (%)
<i>Application Site Condition (Total)</i>	9 (1.60)	14 (2.45)
BURNING	2 (0.35)	1 (0.17)
PRURITUS	4 (0.71)	4 (0.70)
DERMATITIS	0	4 (0.70)
APPLICATION SITE IRRITATION	1 (0.18)	2 ¹ (0.35)
APPLICATION SITE REACTION	2 (0.35)	1 (0.17)
ATROPHY	0	1 ² (0.17)
VESICLES	0	1 (0.17)
<i>Musculoskeletal and Connective Tissue Disorders (Total)</i>	2 (0.35)	2 (0.35)
PAIN	2 ³ (0.35)	1 ³ (0.17)
MUSCLE CRAMP	0	1 (0.17)
<i>Psychiatric Disorders (Total)</i>	0	2 (0.35)
ANXIETY	0	1 (0.17)
CONFUSION	0	1 (0.17)
<i>Nervous System Disorders (Total)</i>	2 (0.35)	5 (0.87)
HYPOAESTHESIA	0	1 (0.17)
PARESTHESIA	1 (0.18)	2 (0.35)
HEADACHE	1 (0.18)	1 (0.17)
SOMNOLENCE	0	1 (0.17)
<i>General Disorders (Total)</i>	2 (0.35)	2 (0.35)
SWEATING	0	1 (0.17)
RIGORS	0	1 (0.17)
<i>Eye Disorders (Total)</i>	1 (0.18)	1 (0.17)
CONJUNCTIVITIS	1 (0.18)	1 (0.17)
<i>Gastrointestinal Disorders (Total)</i>	3 (0.53)	6 (1.05)
DYSPEPSIA	1 (0.18)	2 (0.35)
NAUSEA	2 (0.35)	3 (0.52)
DIARRHEA	0	1 (0.17)
<i>Respiratory, Thoracic and Mediastinal Disorders (Total)</i>	0	1 (0.17)
RESPIRATORY DISTRESS	0	1 (0.17)
Total	17 (3.01)	33 (5.77)

* Number of patients who received at least one patch

¹ Infection (Patient 10536) cleared with tetracycline

² Skin came off with patch (Patient 20782). In CRF resolution reported in 24 hours.

³ Patient 20326 in the placebo group believes that she had a re-injury

The most frequently occurring adverse event leading to study discontinuation was “application site condition” (2.4% of diclofenac patients vs. 1.6% of placebo patients). The type of application site conditions occurring more frequently on the diclofenac patch group than the placebo group was dermatitis (0.7% vs 0%, respectively).

7.1.3.3 Other significant adverse events

None

7.1.4 Other Search Strategies

None

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Adverse events were elicited from the patient by a questionnaire. For Study 05-05-98 the translation provided by the applicant asked, “Has any inconvenience occurred when applying a Tissugel (patch)?” This wording may have been interpreted by patients to not include adverse reactions they felt were unrelated to the patch. This may partly explain the lower incidence of adverse events in Study 05-05-98.

The potential missing safety data in the French Study due to vague wording in the questionnaire on adverse events does not limit understanding the overall safety profile of the drug. There is adequate safety information from the three other studies in addition to the overseas experience. There is no unanticipated safety signal noted in any of the studies. Skin irritation related to application of patch would be expected. The skin symptoms appeared to be mild and in general resolved with discontinuation of the patch

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were coded using COSTART for Study 49,459-01 (US-01) and Study 49,459-02 (US-02) and a modified MedDRA system for Study 00GB/Fp05. In Study 05-05-98 adverse events were not coded according to the applicant due to the relatively small number of events. In order to compare adverse events in all four studies, the Applicant recoded the data from the two US studies and Study 05-05-98 using a modified MedDRA system.

The appropriateness of the Applicant’s coding was assessed by comparing the preferred to the verbatim terms recorded by investigator within the ISS safety data set, focusing on the events that led to discontinuation of study participation. The Applicant’s coding was found to be reasonably accurate except for the following exceptions: coding an infection as “Application site irritation” in Patient 10536 and coding the verbatim term “layer of skin came off” as the

preferred term "Application site atrophy" in Patient 20782. The CRF for Patient 20782 did not further describe the application site condition but indicated resolution occurred in 24 hours implying that the initial skin reaction was superficial.

7.1.5.3 Incidence of common adverse events

There were a total number of 337 adverse events in 1136 patients. Overall, the frequency of adverse events was similar between the groups (29% of DEP and 30% of PBO patients). The most frequently occurring adverse events were application site conditions (11% of DEP and 12% of PBO) followed by gastrointestinal disorders (9% of DEP and 6% of PBO) and nervous system disorders (2% of DEP and 3% of PBO). Pruritus was the most common application site disorder occurring in 5.4% of DEP and 7.8% of PBO patients followed by dermatitis occurring in 1.6% of DEP and 0.5% of PBO patients. Application of both the diclofenac and placebo patch appear to be associated with skin reactions. The application site reactions appear to be self limited and resolve with patch removal. There does not appear to be an association between diclofenac patch application and incidence of generalized adverse reactions. However, patients receiving oral NSAIDs were not eligible for study participation making it impossible to assess any additive effect the combination of oral NSAIDs and topical diclofenac patch would have on adverse events.

Study 05-05-98 was remarkable for a significantly lower rate of adverse events 3.7% compared to 30% in the other studies. Out of a population of 134 patients in Study 05-05-98, there were only 5 adverse events (2 in DEP and 3 in PBO). The low incidence of adverse events in Study 05-05-98 may have been due to the question patients were asked in attempting to elicit adverse events or to the shorter duration of study 05-05-98 (1 week).

The potential missing safety data in the French Study due to vague wording in the questionnaire on adverse events does not limit understanding the overall safety profile of the drug. There is adequate safety information from the three other studies in addition to the overseas experience. There is no unanticipated safety signal noted in any of the studies. Skin irritation related to application of patch would be expected. The skin symptoms appeared to be mild and in general resolved with discontinuation of the patch.

7.1.5.4 Common adverse event tables

Table 7.1.5.4.a Most Common Adverse Events ($\geq 1\%$ of patients) – All Studies*

	Diclofenac N=572		Placebo N=564	
	N	Percent	N	Percent
Total Number of all AEs	165	28.85	172	30.50
<i>Application Site Conditions</i>				
<i>Total</i>	64	11.19	70	12.41
Pruritus	31	5.42	44	7.80
Dermatitis	9	1.57	3	0.53
Burning	2	0.35	8	1.42
Other	22	3.83	15	2.84
<i>Gastrointestinal Disorders</i>				
<i>Total</i>	49	8.57	33	5.85
Nausea	17	2.97	11	1.95
Dysgeusia	10	1.75	3	0.53
Dyspepsia	7	1.22	8	1.42
Other	15	2.58	11	1.95
<i>Nervous System Disorders</i>				
<i>Total</i>	13	2.27	18	3.19
Headache	7	1.22	10	1.77
Paresthesia	6	1.05	8	1.42
Somnolence	4	0.70	6	1.06
Other	4	0.69	3	0.54

* Studies 49,459-01, 49,459-02, 05-05-98, 00GB/Fp05
 116 patients in the diclofenac group and 134 patients in the placebo group had AEs (Patients may have had more than one AE)

7.1.5.5 Identifying common and drug-related adverse events

See Section 7.1.5.4

7.1.5.6 Additional analyses and explorations

None

7.1.6 Less Common Adverse Events

Diclofenac patch as with all *oral* non-steroidal anti-inflammatory drugs (NSAIDS) poses serious cardiovascular and gastrointestinal risks. These risks are described in a boxed warning of the product label for diclofenac.

Cardiovascular Risk

NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction and stroke which can be fatal. This risk may increase with duration of use. Use is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft surgery.

Gastrointestinal Risk

NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.

Other known effects of NSAIDS include fluid retention, edema , renal toxicity, hepatic enzyme elevation and bronchospasm in patients with aspirin-sensitive asthma.

The systemic risks associated with oral diclofenac are not likely to occur in patients using diclofenac patch since plasma concentrations are negligible (0.6%) compared to oral administration.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

There were no laboratory tests done to assess effect of treatment on laboratory values.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Not applicable

7.1.7.3 Standard analyses and explorations of laboratory data

Not applicable

7.1.7.4 Additional analyses and explorations

None

7.1.7.5 Special assessments

None

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs were done for screening purposes only and not to assess effect of treatment.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Not applicable

7.1.8.3 Standard analyses and explorations of vital signs data

None

7.1.8.4 Additional analyses and explorations

None

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

ECG testing was not performed to assess the effect of treatment on cardiac parameters

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Not applicable

7.1.9.3 Standard analyses and explorations of ECG data

Not applicable

7.1.9.4 Additional analyses and explorations

None

7.1.10 Immunogenicity

See Section 3.2

7.1.11 Human Carcinogenicity

Not applicable

7.1.12 Special Safety Studies

Dermatologic safety studies were performed and submitted in the first NDA submission (see the primary medical review from the first NDA review cycle). The medical officer noted that the studies were conducted with a smaller patch and unclear drug concentration for Study C11080. However, these items were not considered an approvability issue. The studies did not demonstrate evidence of dermatologic toxicity and the Applicant's conclusions are summarized below.

Study 006-91 "Human Repeat Insult Patch Test with DHEP Plasters"

Diclofenac patch and placebo patch did not elicit any skin reactions indicative of a delayed contact or immediate hypersensitivity.

Study B9356 "Photoallergy Maximization Test on 25 Human Volunteers"

Diclofenac patch was found to be non-photo allergenic

Study C1108 "Evaluation of Phototoxicity Potential by UV-A Irradiation on 20 Human Volunteers"

Diclofenac patch was considered to be non-phototoxic in this study.

Study C11080 "21-Day Relative Cumulative Irritancy Study (20 Human Volunteers)"

Diclofenac patch was considered to be non-irritating in this study.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Diclofenac is an NSAID that is not associated with any known abuse or withdrawal phenomena when administered orally. Topical patch application with diclofenac results in lower exposure than oral administration and can be expected to have no withdrawal phenomena or abuse potential.

7.1.14 Human Reproduction and Pregnancy Data

Effects of diclofenac patch on human reproduction and pregnancy were not studied in clinical trials. There were no reported pregnancies in any of the trials.

Per the product label for oral diclofenac "language from pregnancy section":

The effects of diclofenac on labor and delivery in pregnant women are unknown. Because of the known effects of prostaglandin-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus), use of diclofenac during late pregnancy should be avoided and, as with other nonsteroidal anti-inflammatory drugs, it is possible that diclofenac may inhibit uterine contractions and delay parturition.

7.1.15 Assessment of Effect on Growth

Not applicable

7.1.16 Overdose Experience

The maximum dose of the patch used in clinical trials was one patch twice daily for two weeks. No cases of systemic overdose were reported.

7.1.17 Postmarketing Experience

From June 1993 to February 2006, a total of 133 adverse events in 81 patients were reported to the IBSA Pharmacovigilance Unit, with 34 events in 16 subjects classified as serious. The applicant states that during this time approximately ~~100,000~~ diclofenac patches were sold. Assuming that each subject was treated with 2 patches per day for 14 days, that would correspond to ~~100,000~~ patients or an incidence of 2.1 adverse events per 100,000 treated patients. Skin disorders comprised the largest category of adverse reactions. There were nine gastrointestinal disorders of which five involved ulcers or bleeding. There were no details provided except for two cases of duodenal ulcer: one patient took oral NSAIDs and aspirin on a daily basis and the other case concerned an elderly patient with a history of previous bleeding duodenal ulcers.

The foreign postmarketing experience is consistent with the safety profile of the submitted studies. There are no unexpected safety issues identified.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

See Section 7.1

7.2.1.1 Study type and design/patient enumeration

7.2.1.2 Demographics

The patient characteristics in the four studies are summarized in the Applicant's table below. See the Appendix for complete details.

Table 7.2.1.2a: Demographic Characteristics for all 4 Studies

Parameter*	Diclofenac Epolamine Patch Studies			
	US-1	US-2	French	UK/German
Age (years)	30.5 ± 10.8	32.8 ± 10.1	31.5 ± 12.9	38.9 ± 13.6
Weight (lbs)	167.4 ± 33.4	171.9 ± 38.4	152.3 ± 35.7†	166.0 ± 31.3
Sex				
Male	153 (68.9%)	270 (69.1%)	72 (53.7%)	206 (49.3%)
Female	69 (31.1%)	121 (30.9%)	62 (46.3%)	212 (50.7%)
Injury Characteristics				
Time to Injury (d)	1.9 ± 0.8 (0-3)	2.0 ± 0.9 (0-10)	0.8 ± 0.6 (0.02-2)	1.4 ± 1.7 (0-8)
Mean Pain Score	6.2 ± 1.1	6.4 ± 1.2	6.8 ± 1.1	7.4 ± 1.3
Location				
Right	117 (52.7%)	217 (52.8%)	72 (53.7%)	237 (56.7%)
Left	104 (46.8%)	185 (45.0%)	61 (45.5%)	180 (43.1%)
Unknown	1 (0.5%)	9 (2.2%)	1 (0.7%)	1 (0.2%)
Ankle	58 (26.1%)	93 (22.6%)	134 (100%)	83 (19.9%)
Shoulder	19 (8.6%)	45 (10.9%)	-	81 (19.4%)
Knee	28 (12.6%)	76 (18.5%)	-	65 (15.6%)
Foot	17 (7.7%)	19 (4.6%)	-	52 (12.4%)
Calf/Shin (lower leg)	17 (7.7%)	25 (6.1%)	-	34 (8.1%)
Wrist/Hand	23 (10.4%)	29 (7.1%)	-	28 (6.7%)
Elbow	10 (4.5%)	24 (5.8%)	-	25 (6.0%)
Arm	5 (2.3%)	11 (2.7%)	-	19 (4.5%)
Thigh/Femur (upper leg)	22 (9.9%)	25 (6.1%)	-	12 (2.9%)
Hip	7 (3.2%)	16 (3.9%)	-	10 (2.4%)
Back	10 (4.5%)	27 (6.6%)	-	5 (1.2%)
Thorax	2 (0.9%)	14 (3.4%)	-	4 (1.0%)
Other	4 (1.8%)	7 (1.7%)	-	-
Diagnosis				
Contusion	47 (21.2%)	91 (22.1%)	-	178 (42.6%)
Strain	76 (34.2%)	168 (40.9%)	-	130 (31.1%)
Sprain	85 (38.3%)	132 (32.1%)	134 (100%)	102 (24.4%)
Other	14 (6.3%)	20 (4.9%)	-	8 (1.9%)
Swelling				
None	72 (32.6%)	198 (48.2%)	-	99 (23.7%)
Mild	81 (36.7%)	161 (39.2%)	253.5 ± 28.0 mm	181 (43.3%)
Moderate	57 (25.8%)	49 (11.9%)	-	133 (31.8%)
Severe	11 (5.0%)	3 (0.7%)	-	5 (1.2%)

* Data for French and UK/German studies taken from individual reports provided in Amendment 13, while US-1 and US-2 data was extracted from the data bases for those studies and are provided in Attachment 6. Means ± SD (and ranges given, along with numbers of patients and proportions express as percent. Swelling in the French study was expressed as ankle circumference (in mm), and was a mean 14.7 mm larger than the uninjured contralateral ankle.

† Please note that the differences in weight between the US and French studies cannot be explained by the higher proportion of females in the latter study (least square means adjusted for sex were 161.1, 165.0, 150.9, and 166.2 for the US-1, US-2, French and UK/German Studies, respectively).

(Source: Applicant's Table 4: Diclofenac Epolamine Patch Studies: Patient Baseline Characteristics, ISS report)

7.2.1.3 Extent of exposure (dose/duration)

Table 7.2.1.3.a provided by the Applicant summarizes the dose and duration experience, by clinical trial with diclofenac and placebo patch. A total of 1185 patients enrolled in the four studies (49,459-01, 49,459-02, 05-05-98 and 00GB/Fp05) were randomly assigned to treatment with the diclofenac epolamine patch (590 patients), or placebo patch (595 patients). There were 18,904 diclofenac and placebo patch applications or 244,537 hours of exposure. Patients were treated once daily for a week in the French study or twice daily for up to two weeks in all other studies.

Table 7.2.1.3.a: Applicant's Table of Diclofenac Patch Exposure

Study	Number of Patients*	Number of Patches†	Number of Hours Exposed‡	Adverse Events§	Incidence of Adverse Events¶	
US-1	DEP = 106	2762 (26.3)	34,020 (324)	22	20.8	
	PP = 107	2735 (25.8)	33,708 (318)	28	26.2	
US-2	DEP = 191	2961 (15.5)	35,755 (187)	34	17.8	
	PP = 181	3095 (17.1)	38,010 (210)	39	21.5	
French	DEP = 68	453 (7.0)	10,872 (167)	1	1.5	
	PP = 65	436 (6.7)	10,452 (161)	1	1.5	
UK-German	DEP = 203	3198 (16.4)	40,248 (206)	17	8.4	
	PP = 208	3245 (16.9)	41,472 (216)	20	9.6	
Total	DEP =	568	9374 (16.5)	120,896 (213)	74	13.0
	PP =	562	9530 (17.0)	123,642 (227)	88	15.7

* Number of patients for whom data on AEs was available. Please note that the number of patients with patch application information was somewhat lower for three of the studies (US-1, 105 & 106; French, 65 & 65; and UK/German, 195 & 192 for DEP and PP, respectively), resulting in an underestimate of the number of patches applied and hours of exposure.

† Total number of patches that were applied is provided, with mean number of patches per patient given in parenthesis.

‡ Total number of hours that patches were applied is provided, with mean number of hours of exposure per patient given in parenthesis.

§ The total number of patients with adverse events possibly/probably related to treatment was taken from Table 11.

¶ Incidence estimates derived by dividing the number of patients with adverse events possibly/probably related to treatment by the total number of patients and multiplying by 100.

(Source: Applicant's Table 12. Diclofenac Epolamine Patch Studies: Adverse Events vs Product Exposure, ISS Study Report)

APPEARS THIS WAY
 ON ORIGINAL

This reviewer calculated exposure based on number of patients exposed for specific days and cumulative number patches (Table 7.2.1.3.b). The table shows that a total of 181 patients (87 treated with diclofenac patch and 94 treated with placebo patch) received patch twice daily for two weeks (at least 28 patches). 764 patients (380 DEP and 384 PBO) were treated once or twice daily for one week.

Table 7.2.1.3.b: Exposure all 4 studies: US 01, US 02, 00GB/Fp05, 05-05-98

Exposure No. patches	French ¹ n = 134				US ³ /UK/German ^{2,4} n = 1029				Total All 4 Studies n=1163	
	DEP		PBO		DEP		PBO		DEP	PBO
	n=68	%	n=66	%	n=504	%	n=498	%	580	583
At least 1	68	100	66	100	490	97	478	96	558	544
At least 3	65	96	66	100						
At least 6					464	92	451	91	464 ⁵	451 ⁵
At least 7	63	93	59	89						
At least 14 (7 days)	-		-		317	62	325	65	317	325
7 Days (1 or 2 Patches/day)									380	384
At least 27	-		-		135	26	150	29	135	150
At least 28 (14 days)	-		-		87	17	94	18	87	94

¹ French Study = QD dosing

² US and UK/German Study = BID dosing

³ Exposure based on use of surrogate variables (TIMEE & TIMEM)

⁴ Exposure based on XPT data set; exposure calculated is only an estimate of true exposure

⁵ Number of patches used based only on UK/German study since patch use not available on day 6 in French Study

There were limitations in determining the patch exposure for the following studies:

Study US-01:

Based on the efficacy data set using the variable "SAFETY" [Intent-to-Treat Valid] we obtained information about patients who were randomized and took at least one dose (106 diclofenac and 107 placebo). However, based on variable TIMEM 1 [a measure of first patch use] the same data set indicates the following 98 diclofenac, 97 placebo took the first patch. Twenty-five patients have no data recorded regarding first patch use (8 diclofenac, 10 placebo, 7 treatment unknown) Because the TIMEM and TIMEE variables were used as surrogates for actual patch use and may not have been accurately or consistently recorded, exact information about product exposure can only be estimated.

UK/German:

Exposure data were obtained from diary.xpt data set in which PATCH was the variable representing patch number (#patches). Under this variable the first patch was coded as "0" and the patch at 28 days as "27". In this data set patch use was recorded for only 387 patients (195 diclofenac, 192 placebo). Therefore the exposure calculated is only an estimate of true exposure. Patient 204 (placebo) was randomized but not treated

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

Not reviewed

7.2.2.2 Postmarketing experience

See Section 7.1.1.7

7.2.2.3 Literature

Label for approved diclofenac products reviewed

7.2.3 Adequacy of Overall Clinical Experience

See Section 7.2.1 for a discussion of the adequacy of the extent and duration of exposure to treatment with diclofenac patch.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

See Section 3.2

7.2.5 Adequacy of Routine Clinical Testing

Safety testing in the clinical studies included examination of the skin application site and questioning about adverse events. Safety was assessed at the follow-up visits as well as during telephone contacts. The safety testing was adequate given the unlikely occurrence of systemic adverse events from the low concentration of drug with topical application. Local application site reactions would likely be identified by the patient.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

See Section (Clinical Pharmacology)

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

NSAIDs are associated with gastrointestinal, cardiovascular and renal adverse events. However, topical administration of diclofenac patch is less likely to cause such events. The evaluation for treatment-emergent adverse events was adequate.

7.2.8 Assessment of Quality and Completeness of Data

The information supplied in the NDA submission contained errors with patient disposition in both Study 05-05-98 and Study 00GB/Fp05. Not every patient treated in Study 00GB/Fp05 had safety data.

7.2.9 Additional Submissions, Including Safety Update

Safety update was not submitted

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

From the four clinical trials the most common adverse effect of diclofenac patch is "application site conditions". Dermatitis and pruritus were the predominant adverse events involving skin. The skin reactions were self limited and resolved with discontinuing the patch. No serious adverse events occurred. The incidence of "application site conditions" was 11% in DEP and 12 % in placebo patients.

The post-marketing safety profile is similar to that observed in the four efficacy trials. The data submitted in this NDA have not addressed chronic episodic use although it appears that diclofenac patch would probably be safe in this context in healthy adults.

The safety of diclofenac patch in the pregnant, elderly and pediatric populations has not been adequately assessed in this NDA.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Not applicable

7.4.1.2 Combining data

See Section 7.4.1.1

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

The data from the French (once daily dosing) study showed fewer overall adverse events than the other trial (twice daily dosing). This however, could have been due to the methods used to elicit adverse events, rather than differences in dosing (see section 7.1.5)

7.4.2.2 Explorations for time dependency for adverse findings

See Section 7.1.5.6

7.4.2.3 Explorations for drug-demographic interactions

There were no drug-demographic interactions with regards to safety

7.4.2.4 Explorations for drug-disease interactions

Not applicable

7.4.2.5 Explorations for drug-drug interactions

Not applicable

7.4.3 Causality Determination

See Section 7.1

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The applicant proposes a dosing regimen of one patch (10 x14) cm bid
The clinical trial population did not include geriatric patients older than 65 years.

In the non-approval letter dated 4/16/2003, the FDA told the applicant that as part of their re-submission they should provide a rationale as to their selection of the patch size and concentration and how these factors relate to clinical efficacy/safety. The applicant's response relies on the historical use of this size patch for many years. Regarding the determination of

concentration the applicant states, "This drug concentration, with its concomitant delivery profile, was accepted by the Sponsor as suitable for a product that will continuously deliver drug when applied to the skin, as opposed to the more sporadic drug delivery provided from intermittent gel application."

The applicant has not provided any studies to justify their selected patch size or concentration. It appears that their selection rests on prior experience. There is no indication as to how the frequency of dosing was determined. Study 05-05-98 was dosed once daily and appeared to demonstrate efficacy while Study 00GB/Fp05 with the same size and concentration patch was dosed twice daily and failed to demonstrate efficacy.

The clinical trial data do not support the proposed dosing of one patch twice daily.

8.2 Drug-Drug Interactions

DEP is a topical product with minimal systemic absorption. Therefore the risk of drug-drug interaction is low. Oral NSAIDs were prohibited during the studies, therefore the potential for additive adverse events is not known.

8.3 Special Populations

The diclofenac patch has not been studied specifically in a geriatric population. As with any NSAID, the elderly are unlikely to tolerate adverse reaction as well as younger patients.

8.4 Pediatrics

To comply with the Pediatric Research Equity Act (PREA), the applicant has proposed a pediatric protocol under the IND for diclofenac epolamine patch (IND 49,459). It is acceptable for the pediatric study to be conducted following approval of DEP in adults.

8.5 Advisory Committee Meeting

Not applicable

8.6 Literature Review

Not applicable

8.7 Postmarketing Risk Management Plan

Not applicable

8.8 Other Relevant Materials

None

9 OVERALL ASSESSMENT

9.1 Conclusions

One of the two efficacy trials included in the NDA resubmission failed to support the efficacy of diclofenac epolamine patch in the treatment of strains, sprains and contusions. With regard to the failed study, the study design allowed for discontinuation of treatment upon injury resolution. This resulted in substantial patient dropout which impacted the interpretation of efficacy, as based on the applicant's modified primary endpoint. Setting aside the statistical limitations of the study, there was no clinically meaningful difference in pain between the diclofenac and placebo treated groups. Furthermore, the onset of any analgesic effect did not occur until repeated patch application in many patients.

Although the overall risk associated with use of this product is small, approval of diclofenac patch in the absence of two adequate and well controlled studies is not warranted considering the widespread availability of other therapies for the proposed indication due to the self-limited nature of the condition.

9.2 Recommendation on Regulatory Action

This reviewer recommends that a not approvable action be taken on this NDA.

Diclofenac Epolamine Patch should not be approved for the indication of pain due to strains, sprains and contusions since the applicant has not demonstrated efficacy in two trials. Study 00GB/Fp05 failed to demonstrate clinically meaningful improvement and statistical significance of diclofenac patch compared to placebo patch in the primary endpoint. Although, the overall risk associated with this product is small if used as directed, a variety of other analgesic products and non-pharmacologic therapies are available. Approval of the Diclofenac Patch in the absence of two convincing studies of efficacy is not warranted considering the availability of other therapies for the proposed indication.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Not applicable

9.3.2 Required Phase 4 Commitments

See section 8.4

9.3.3 Other Phase 4 Requests

The Applicant should conduct Segment III reproductive toxicology studies for diclofenac epolamine.

9.4 Labeling Review

A detailed review of the product label was not performed given the lack of demonstration of efficacy and recommendation against approval of the product.

9.5 Comments to Applicant

The following will be required should the Applicant resubmit the NDA:



The following are recommendations:

1. The applicant's proposed indication of _____ is not supported by the data contained in the NDA.



10 APPENDICES

10.1 Review of Individual Study Reports

The applicant submitted two new trials in support of NDA 21-234, protocol 00GB/Fp05 and protocol 05-05-98 and two previously submitted studies, protocol 49,459-1 and protocol 49,459-2.

10.1.1: Protocol: 00GB/Fp05

Title: A Randomized, Double-Blind, Placebo Controlled Study of the Analgesic Efficacy and Safety of Diclofenac Epolamine Patch in Minor Soft Tissue Injury

Primary Objective: To evaluate the analgesic efficacy and safety of diclofenac epolamine patch in minor soft tissue injury (sprain, strain, or contusion)

Study Design:

This was a Phase 3, randomized, double-blind, placebo-controlled, parallel group clinical trial conducted at 14 sites in the United Kingdom and Germany.

Treatment Duration: 14 days

Sample Size: The protocol specified recruitment of 350 patients (175 patients in each treatment arm).

Key Inclusion Criteria:

Patients were to have met the following criteria:

1. Aged 18 to 85 years
2. Minor soft tissue injury (sprain, strain or contusion) within 72 hours of study entry
3. Spontaneous pain of at least 5 on the 0-10 category pain scale
4. The injury was to be considered by the investigator to be clinically significant
5. Female patients of childbearing potential were to practice an acceptable method of contraception with a documented negative urine pregnancy test

Exclusion Criteria:

Patients were to be excluded if any of the following applied:

1. A major soft tissue injury (fracture, severe second degree or greater tear of ligament/muscle/tendon, or common nerve injury)
2. An open skin lesion within the injured area

3. Prior injury to the same site within the past 3 months
4. Three or more other prior injuries (minor or major) to the region in the past.
5. The injury occurred more than 72 hours prior to study entry
6. Prior use of topical medication to involved area within 48 hours of study entry
7. Injury was midline or involved the spine
8. Prior use of OTC analgesic or NSAIDs within 36 hours of study entry (acetaminophen permitted)
9. Prior use of narcotic analgesics within 7 days of study entry
10. Prior use of systemic anti-inflammatory steroidal drugs, by any route of administration within 60 days of study entry
11. Prior use of long-acting NSAIDs since injury
12. Prior history of any chronic pain disorder
13. Prior history of GI bleeds/ulcers, liver/kidney disease
14. Known hypersensitivity to diclofenac or other NSAID drugs

Study Medication:

Diclofenac epolamine patches consist of 1.3% diclofenac epolamine in a _____ adhesive applied to a non-woven polyester felt backing. Each patch is 10 X 14 cm in size. The _____ is composed of gelatine, _____, disodium edetate, tartaric acid, d-sorbitol, kaolin, sodium polyacrylate, sodium carboxymethylcellulose, purified water, dihydroxyaluminum aminoacetate, propylene glycol, methyl paraben, propyl paraben, polysorbate 80, titanium dioxide, 1,3-butylene glycol and diclofenac epolamine 180 mg (1.3% by weight).

Placebo patches were to be identical in appearance and contain the same formula as the active patches except for the principal ingredient, diclofenac epolamine.

Prohibited Therapies:

No other topical applied medications, salves, ice bandage or other wrapping were to have been used. Analgesics of any other kind, including NSAIDs and anti-inflammatory steroids were not to have been taken.

Study Procedures:

Screening/Inclusion (Visit 1 and Treatment day 1)

Subjects were to have signed an informed consent form. The patient's demographic characteristics and medical history including injury type and location, date of injury, examination of the skin at the injured site, active range of motion, presence of swelling and/or bruising, level of pain and vital signs were to have been recorded in the Case Report Form (CRF). Patients were to have been included in the study protocol if inclusion criteria were met and written informed consent was obtained.

Patients would be assigned a patient number and the first patch of the corresponding blinded study medication applied. The patient was to have received a Daily Diary with forms to be

completed each time the patch was removed. The Daily Diary was to include the following information:

- Time of patch removal (twice per day, morning and evening)
- 0-10 numerical pain rating
- Use of any “rescue” or alternative pain-killing medication (time, dose and reason for taking)- this would be the time at which the patient discontinues study patch application and leaves the study
- Reporting of any other symptoms (adverse events)

Treatment Phase

Diclofenac epolamine or placebo patches were to have been self-administered twice daily (every 12 hours) for two weeks or until the time of pain resolution. The patch was to have been secured in place with a loose fitting net sleeve. Patients were to be instructed that bathing should take place between scheduled patch removal and application of the next patch.

Patients were to complete measures of pain (caused by normal activity and movement) and report their symptoms twice daily on each day of treatment. At the exit visit, patients were to complete their evaluation of global response to treatment and assessment of local tolerability.

Telephone Follow-up

Telephone contact was to have occurred with each patient on a daily basis during the treatment phase (at least 5 days per week). The telephone contact was to have confirmed that there were no problems with compliance and completion of the daily diary. The patients’ pain scores were to have been reviewed and patients were to have been informed about their eligibility to discontinue wearing the study patch and scheduling of a study exit clinical visit.

Study Exit (Visit 2)

During the exit session patients were to have returned their completed daily diary, Patient Assessment of the Global Response to Therapy, and Local Tolerability as well as used and unused test patches. The investigator was to have completed an Investigator’s Assessment of the Global Response to Therapy and the Investigator Assessment of Local Tolerability. All of these questions were to have been based on a 5-point scale (none, poor, fair, good and excellent).

Study Termination:

Subjects could discontinue study participation for the following reasons:

- Pain resolved prior to 14 days (pain was considered resolved if the score fell to “2” or less for four consecutive 12-hour periods)
- Injury was unresponsive to treatment and the patient elected to discontinue treatment
- An adverse event occurred which was possibly/probably treatment related
- Study admission problems such as inappropriate enrolment, non-compliance with the protocol schedule, or a need for a concurrent medication prohibited by the protocol
- Serious Adverse Event or Death
- Patient wishes to withdraw from the study for another reason

Statistical Analysis:

Efficacy Measures

Time to Pain Resolution

0-10 Pain Scale

Investigator's Assessment of the Global Response to Therapy

Primary Efficacy Outcome: Time to Pain Resolution

The primary endpoint was to have been based on the study day at which either pain resolution occurred or the patient discontinued wearing the patch and pursued alternative treatment. If pain resolution did not occur at the end of the 14th study day, the patient would have been required to discontinue wearing the study patch. The Time to Pain Resolution was to have been the time that elapsed from the initial patch application to the time at which the patient recorded the fourth spontaneous pain of "2" or less. If a patient discontinued wearing the patch or never recorded a score of 2 or less for four consecutive periods, then the Time to Pain Resolution was to have been set to 15 and a half days.

Secondary Efficacy Outcomes:

- Investigator's Assessment of the Global Response to Therapy, 5-point verbal scale
- 0-10 categorical rating of pain, daily (last value carried forward)

Safety Measures:

Safety was to have been assessed by:

- Patient assessment of local tolerability to therapy (5-point verbal scale)
- Investigator assessment of local tolerability (5-point verbal scale)
- Reporting of adverse events

Sample Size Calculation

A sample size of 200 patients per treatment group was calculated to have a power in excess of 85 percent to detect a difference in waiting-time distributions with a Type I error of 0.05. The sponsor concluded that a sample size of 175 patients per treatment group would be justified.

The statistical analysis for efficacy was to have been carried out in the Intention-to-Treat Population (ITTP), intended as the population actually exposed to investigational drug. An additional statistical analysis for efficacy was to have been carried out in the Per Protocol Population (PPP), intended as all the patients who actually completed the treatment cycle, according to the procedures described in the protocol.

Key Protocol Amendments:

Amendment 1-April 3, 2001

- One inclusion criteria was modified
 - The upper age for participation in the study was reduced from 85 to 65 years
- Six exclusion criteria were added/modified