- Use of lithium, digoxin, anticoagulants, antidiabetic agents, cyclosporine, methotrexate, quinolone antimicrobials, other NSAIDs, steroids and diuretics
- Patients with allergic disorders, including asthma
- Patients with coagulation defects
- Patients with cardiac impairment
- Known hypersensitivity to aspirin
- Women who are breast-feeding

Amendment 2- December 12, 2001

- The description of the primary efficacy variable was modified:
  - The wording was changed from *Time to Pain Resolution* to *Time to Significant Pain Resolution*
- Changes to the statistical analysis plan:
  - Two efficacy analyses were planned – a primary (per-protocol) and an intent-to-treat
  - All patients who used the study patch on at least one occasion would be included in the intent-to-treat analysis. All patients who completed the study would be included in the primary analysis. All patients who received study patch would be included in the safety analysis
  - Time to Pain Resolution would be analyzed using Wilcoxon survival techniques
  - The Investigator's assessment of global response to therapy (5 point categorical scale) would be analyzed with a Cochran-Mantel-Haenszel test stratified by research center and gender
  - Analysis of the average pain scores by day would be performed using a repeated measures analysis of covariance with factors of treatment group, research study center and baseline VAS as covariate. For patients whose pain resolved prior to day 14, the last value of category pain recorded would be carried forward. For patients whose pain decreased to the level required to satisfy the study endpoint of patch discontinuation, a zero would be carried forward. For subjects withdrawing early due to treatment failure or treatment-related adverse events the last observation would be carried forward.
  - Patient and Investigator assessments of local tolerability to therapy would be analyzed by a Cochran-Mantel-Haenszel test stratified by research study center.
- The study procedures and assessments were modified:
  - At the exit visit patients would be instructed to complete an assessment of local tolerability but would no longer complete an evaluation of global response to treatment
- Protocol Changes
  - Exclusion criteria would include injury involving the digits or hands
  - Randomization would be implemented to provide balance in the number of males and females within each treatment group
  - For patients that do not achieve significant pain relief or discontinue wearing the patch the *Time to Significant Pain Resolution* will be set to 15 days
- Modification to definition of Per-protocol Evaluable Subject:
  - Inclusion /exclusion criteria met
  - Compliant with the study treatment (two patches per day; one application may be missed, but not during the final 48 hours prior to pain resolution)

- No noteworthy study protocol violations
- Completed daily diary evaluations and final examination or discontinued early due to treatment failure or adverse events and for whom evaluable data has been collected in the daily diary and an exit visit has been completed. For subjects withdrawing early the last observation will be carried forward.

- Modification of Analysis of Secondary Efficacy Variables
  - For patients who discontinue before the end of the 14-day treatment, the last value will be carried forward
  - For patients whose pain decreased to the level required to satisfy patch discontinuation, a zero will be carried forward
  - Patients will be instructed to discontinue wearing the patch and exit the study when they have satisfied the criteria for significant pain resolution and subsequently recorded a pain score of zero
- Study Discontinuation
  - Subjects must meet the criteria for significant pain resolution and, additionally, record a pain of zero on their last observation
- Modification to Sample Size
  - Recruitment of 350 evaluable per protocol (175 in each treatment arm)
  - Based on estimates taken from previous US and European clinical trials, a sample size of 175 patients per treatment group will have a power in excess of 80% to detect a difference in waiting-time distributions with a Type I error of 0.05. Estimates of the waiting-time curve distributions were derived from clinical data and a bootstrap simulation of these estimates was used to derive the power. It is anticipated that a minimum of 400 patients will be entered to achieve a minimum of 350 patients evaluable per protocol.
  - The implementation of the Time to Pain Resolution will use the time that has elapsed from the initial patch application to the time at which the patient records the fourth Spontaneous Pain of "2" or less. In the event that the patient never records four 12-hour intervals of pain levels of "2" or less, then the Time to Pain Resolution will be set to 15 days since the pain resolution did not occur within 14 days of treatment. Additionally, if a patient discontinues wearing the patch due to a lack of perceived efficacy, then the Time to Pain Resolution will be set to 15 days. In the event that a patient does not provide the time at which the end point is realized, then the time will be calculated as a difference between the date that the endpoint was realized and the date of the clinic-screening visit. If a patient does not provide either the date or the time at which the endpoint is realized, then the time at which the endpoint occurs will be estimated from the diary date sequence number.
  - The analysis of the average categorical pain would require estimation of missing date and time information. During the period when the patient is wearing the patch, missing date information would be estimated by linear interpolation using previous and subsequent non-missing date data. Subsequent to the patient discontinuing patch usage and termination of recording data, as required by the protocol, the dates would be linearly interpolated out to what would be the 14^{th} day of the study.

Amendment 3- June 25, 2002

- The inclusion criteria were modified:
  - Patients must have had an acute minor soft tissue injury within 7 days of study entry
- The exclusion criteria were modified:
  - Injury occurred more than 7 days prior to study entry
  - Use of OTC analgesic or short-acting NSAIDs within 6 hours of study entry (acetaminophen permitted up to the time of study entry)

The eligibility criteria were modified due to difficulties with participant enrollment. The third amendment was intended to accelerate recruitment by allowing patients to be enrolled within 7 days of injury instead of 36 hours and decreasing the exclusion time for over the counter analgesic products from 36 to 6 hours.

Modified Statistical Analysis Plan – November 22, 2004

A modified statistical analysis plan was developed by the applicant reportedly under blinded conditions. The original primary efficacy variable was time to pain resolution or discontinuation of treatment. A mean pain score would be calculated and used as a measure of pain reduction.

The applicant provided the following reasons for changing the statistical analysis plan:

- Patients may have a good response to treatment resulting in a pain score of "2" or less but discontinue the study prior to meeting the protocol definition of pain resolution, 4 assessments with a pain score of "2" or less. Under the original statistical analysis plan, these patients would technically be a failure even though they had a good response.
- The criteria for "time to pain resolution" and the requirement for four consecutive low scores were arbitrary. In this study, "2" was chosen but the applicant states "0" or "1" could easily have been selected. The initial rationale for requiring four consecutive low scores was to prevent sporadic pain-free periods from being counted as resolution. However, this method fails to capture patients who show a good response to treatment but drop out of the study as soon as they reach a low pain score.

The applicant maintains that the new statistical analysis was proposed under blinded conditions since the statistician did not have access to the randomization code but only had access to the clinical trial database.

Primary Efficacy Variable: Mean post-treatment pain score

The primary efficacy analysis would be based on the mean pain score over the 14 day treatment period. The mean post-treatment pain score was to be divided by the baseline score. The diclofenac and control groups would be compared using analysis of variance (ANOVA). The primary efficacy population would consist of patients treated with diclofenac or placebo patch and for whom post-treatment data was obtained (384 patients). The method of multiple imputation was used to impute missing data for the primary analysis of pain scores.

Study Results

The first patient was enrolled in the study on February 21, 2002, after two protocol amendments had been made. Following enrollment of 51 patients, on June 25, 2002 an additional third protocol amendment was added to improve participant enrollment.

Enrollment

Fourteen sites participated in the trial: 6 in the United Kingdom and 8 sites in Germany. Of the 418 patients randomized, all but one were treated. Enrollment at each site was as follows:

Table 10.1.1.a: Subject Enrollment-Study 00GB/Fp05

German Site No.	No. Patients Enrolled	No. Patients Completed	UK Site No.	No. Patients Enrolled	No. Patients Completed
11	44	38	21	20	16
12	20	18	22	2	1
13	52	35	23	18	11
14	84	57	24	60	40
15	60	41	25	5	4
16	6	4	26	3	3
17	30	30	-	-	-
18	14	9	-	-	-
Total	310	232	Total	108	75
Total UK/German Enrolled: 418			Total UK/German Completed: 307		

(Source: Applicant's Table Study Enrollment/Completion, Amendment 14 submitted 9/14/06)

Subject Disposition

A total of 418 subjects were enrolled (211 randomized to placebo, and 207 randomized to diclophenac). All but one patient in the placebo group received at least one patch. The outcome of patient disposition is dependent on the classification system employed. The applicant reclassified disposition status as based on the Exit Form of the CRF. The rationale provided by the applicant for this change was to correct potentially misleading categories and more accurately characterize the actual reason patients left the study. The applicant makes the following specific points:

1. The original discontinuation category "Study Admission Problems" is inappropriate because it is excessively broad and confusing since it includes issues with enrollment and post-admission problems such as non-compliance or need for prohibited medication. This category has been eliminated under the new classification system. Twenty eight patients were reclassified as "Completed 14 Days of Therapy" who were originally classified as "Study Admission Problems
2. The category "Discontinued in Favor of Another Therapy" not only fails to identify the other therapy but may have captured patients who required a concurrent medication prohibited by the protocol. As an example the applicant describes patients 21-015 and 18-338, both of whom took concurrent pain medications prohibited by the protocol at the time of patch discontinuation and exit from the study. They were originally classified as "Discontinued in Favor of Another Therapy" which was changed to "Withdrew Unresolved" (i.e. withdrew with a pain score of 3 or more).

3. Finally the applicant maintains that the new listing more accurately characterizes the actual reasons the patients discontinued the study. To illustrate this point the applicant describes 17 patients originally designated "Discontinued Due to Injury Resolution" but were reclassified as "Completed 14 Days of Therapy" since they had applied a patch for at least 14 days.

Nearly 50% of the patients under the new classification scheme had a pain score of 2 or less immediately prior to study exit and were classified as injury resolution. Patient disposition based on the applicant's reclassification is summarized in the table below.

Table 10.1.1.b: Patient Disposition-Study 00GB/Fp05

Reason	Diclofenac Epolamine Patch (DEP)	Placebo Patch (PP)	p Value♦
Completed - Injury Resolution*	112 (54.1%)	94 (44.5%)	0.063
Completed 14 Days of Therapy†	45 (21.7%)	56 (26.5%)	0.256
Withdrew Unresolved‡	37 (17.9%)	41 (19.4%)	0.708
Lost to Follow-up§	7 (3.4%)	8 (3.8%)	1.000
Adverse Event¶	4 (1.9%)	9 (4.3%)	0.260
Other•	2 (1.0%)	3 (1.4%)	1.000

* Defined as last pain score of 2 or less, with number of patients provided along with percentage of total in parenthesis. DEP = 11-238, 242, 244, 246, 247, 250, 251, 255, 256, 258, 260, 261, 262, 266, 381, 382, 386, 388; 12-495, 501, 504, 507, 508, 511; 13-517, 519, 521, 523, 526, 531, 535, 758, 761, 790, 792, 795; 14-539, 540, 541, 542, 549, 554, 559, 560, 561, 566, 571, 574, 575, 577, 579, 703, 708, 712, 718, 719, 730, 731; 15-628, 741, 743, 747, 750, 782, 785; 16-236; 17-273, 275, 278, 279, 281, 288, 289, 290, 293, 294, 297, 300, 301, 304, 307, 308; 18-310, 311, 313, 314, 344; 21-13, 17, 25, 26; 23-84, 85, 86, 116, 119, 120; 24-124, 129, 143, 146, 156, 157, 158, 421, 428, 430, 431, 437, 439; 25-163; 26-401. PP = 11-240, 241, 243, 245, 248, 249, 252, 253, 254, 257, 259, 263, 267, 383, 384, 385, 387; 12-494, 497, 502, 503, 505, 506; 13-513, 515, 518, 520, 525, 527, 530, 752, 753, 754, 757, 763, 788, 789; 14-537, 550, 570, 572, 580, 720, 728, 737; 15-602, 627, 742, 749, 774, 775; 16-235; 17-274, 276, 277, 280, 282, 283, 291, 292, 296, 298, 302, 303, 305, 306; 18-315, 316, 341, 342; 21-7, 12, 14, 19, 27, 29; 22-42; 23-87, 118; 24-121, 132, 140, 144, 147, 152, 155, 160, 424, 426, 427; 25-164, 165; 26-402, 403.

† DEP = 11-265, 272; 12-498, 509; 13-516, 532, 756, 764, 787, 798; 14-547, 556, 568, 709, 722, 725, 726, 738, 740; 15-601, 603, 608, 609, 615, 617, 619, 745, 767, 769, 771, 773, 777; 16-202; 21-11, 16, 18; 23-81, 90; 24-122, 128, 133, 135, 141, 150, 423. PP = 11-268; 12-493, 500, 510, 512; 13-524, 529, 536; 14-543, 546, 548, 562, 567, 573, 702, 704, 705, 710, 711, 714, 715, 717, 727, 733, 736, 739; 15-604, 605, 607, 613, 614, 618, 620, 744, 746, 748, 768, 779, 783, 784, 789; 16-201; 21-24, 28, 30; 23-92; 24-123, 131, 139, 149, 154, 159, 422, 434, 438; 25-161.

‡ DEP = 11-271; 13-514, 528, 751, 759, 766, 796, 797; 14-552, 569, 701, 707, 713, 716, 723, 734, 735; 15-606, 616, 621, 624, 626, 629, 776, 778; 16-203; 18-343; 21-023; 24-125, 130, 137, 138, 151, 153, 425, 446; 25-162. PP = 13-522, 534, 760, 762, 765, 791, 794; 14-538, 551, 552, 555, 558, 563, 565, 576, 578, 706, 721, 724, 729; 15-610, 611, 622, 623, 625, 630, 780; 18-312, 317, 338; 21-15, 21; 23-89, 107, 117; 24-126, 134, 136, 142, 432, 433.

§ DEP = 12-496, 499; 13-755; 14-564; 15-612, 781; 24-145. PP = 14-544; 15-770; 18-309; 23-82, 83; 24-127, 148, 429.

¶ DEP = 11-237 (leg cramps), 13-533 (itching), 23-91 (diarrhea, headache, nausea), 24-436 (blister/patch area). PP = 11-239 (burning), 11-264 (itching), 11-269 (skin sensitivity), 13-793 (irritation), 14-557 (vomiting, nausea, headache), 14-732 (burning), 15-772 (patch allergy), 21-20 (nausea), 23-88 (acute arthritis). The CRFs for these 13 patients can be found in Attachment 9.

• DEP = 14-545 (patient moved); 22-041 (fracture discovered). PP = 11-270 (hospitalized); 16-204 (patient not entered); 24-440 (hospitalized)

♦ P values were derived from Fisher's exact test.

(Source: Applicant's Table 3. Study Discontinuation, Final Study Report for 00GB/Fp05, pg. 31)

The breakdown of disposition determined by the FDA reviewer based on the data set as completed from the exit visit form of the CRF is summarized in the table below.

Table 10.1.1.c: 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

REVIEWER COMMENT:
Although the change in classification system may have added some clarity to patient disposition, it appears that the main outcome related to reclassification was an increase in the number of patients in categories "completed 14 days" and "injury resolution". The original classification system included information on protocol violations in the "Study Admission Problems"; this classification system does not contain that information. In the applicant's new classification system no distinction is made for patients who require additional therapy as long as they have completed 14 days of treatment. Clearly a patient at the end of 14 days still requiring therapy is worse off than a patient completing 14 days of therapy with the same pain score and not requiring therapy. The original classification system captured this difference. This reviewer finds that the changes in classification potentially limit the understanding of patient disposition results. The FDA has requested that the applicant reclassify patients based on the following criteria:

- Patients who "discontinued in favor of another therapy" or use of a prohibited analgesic medication should be classified as discontinuing due to lack of efficacy.
- Patients discontinuing due to *any* adverse event (including SAE or death) should be classified as discontinuing due an adverse event.
- Patients who "wished to withdraw for any other reason [than an AE, other therapy or injury resolution]" should be classified as discontinuing due to "other" reasons.
- Patients who were removed from the trial before completing 14 days of treatment because they were non-compliant with study procedures (e.g. diary entry) or did not meet eligibility criteria should be classified as discontinuing due to protocol violations.

- Patients who withdrew consent for *non treatment-related* reasons should be classified as discontinued due to withdrawal of consent. Patients who cite continued pain or adverse events as reasons for consent withdrawal should be reclassified appropriately.

Following the request the Applicant submitted the following revised disposition table (note that it closely mirrors the results found by the FDA by this reviewer):

Table 10.1.1.d: Applicant's Revised Disposition Table

	Diclofenac			Control		
	n	N	%	n	N	%
Based on Current Reclassification						
Completed 14 days of Therapy	37	207	17.9%	48	211	22.7%
Discontinued due to Injury Resolution	87	207	42.0%	67	211	31.8%
Discontinued due to Lack of Efficacy	21	207	10.1%	25	211	11.8%
Discontinued due to Adverse Event	4	207	1.9%	9	211	4.3%
Lost to Follow-up	4	207	1.9%	9	211	4.3%
Protocol Violation	48	207	23.2%	48	211	22.7%
Withdrew Consent	6	207	2.9%	5	211	2.4%

(Source: Amendment 16 received via e-mail)

Protocol Violations

Protocol violations included: failure to complete the daily diary, inadequate telephone follow-up, concomitant analgesic treatment, enrollment of ineligible patients, failure to apply two patches each day and randomization errors. The Table below summarizes the number of subjects with an important protocol deviation or violation.

Table 10.1.1.e: Protocol Deviations-Study 00GB/Fp05

Deviation*	Diclofenac Epolamine Patch (DEP)		Placebo Patch (PP)		p Value♦
Diary Completion†					
None	15 (7.2%)	n=207	18 (8.6%)	n=210	0.718
Partial	35 (16.9%)		38 (18.1%)		0.797
Telephone Follow-up‡					
None	7 (3.4%)	n=207	5 (2.4%)	n=210	0.573
Partial	64 (30.9%)		70 (33.3%)		0.602
Patch Compliance§					
No Information	12 (5.8%)	n=207	18 (8.6%)	n=210	0.344
Partial	41 (19.8%)		44 (21.0%)		0.809
Concomitant Analgesic Treatment¶	23 (11.3%)	n=203	34 (16.3%)	n=208	0.155
Ineligible Patient Enrollment#	23 (11.1%)	n=207	27 (12.8%)	n=211	0.652

* Number of patients provided, with the percentage of the total in parenthesis. For specific deviations, the site-patient number is provided for the patient with the deviation followed by information on the actual deviation in parenthesis. Parenthesis information is as follows: (1) Diary Completion - First number is number of days diary completed, the second is the total number of days it should have been completed. 0/0 and 1/1 correspond to None. (2) Telephone Follow-up - First number is number of times a patient was called, the second is the number of days on protocol. A 0 corresponds to None. (3) Patch Compliance - First number is number of patches missed, second number is number of patches that should have been applied. Includes patients with partial diary completion as well as those below. (4) Concomitant Analgesic Treatment - First number is the day treatment began, second is the number of days of treatment, with data being taken from patient diaries, telephone logs, and adverse event forms. (5) Ineligible Patient Enrollment - Eligibility criteria violated are in parentheses.

(Source: Applicant's Table 1 Protocol Deviations, Study Report for 00GB/ Fp05, pg 29.)

The diary contained no pain entries for 7.2% and 8.6% of patients in the diclofenac and placebo patch treatment groups, respectively. These patients were not included in the applicant's

efficacy evaluable population. An additional 16.9% and 18.1% of patients in the diclofenac and placebo groups, respectively, partially completed the diary. Compliance for the required telephone follow up was missing in over 40% of the patients in both groups. No patch compliance information was available on 12 and 18 patients in the diclofenac and placebo groups, respectively. These patients also had no pain entries. Another 20% of patients contained only partial patch compliance information. Concomitant analgesic treatment was 16.3% and 11.3% in the placebo and diclofenac groups respectively. There was no analysis of the number of pills utilized.

Ineligible patients fell into several categories with the most common reason being age outside 18-65 years (30%) followed by a history of cardiovascular disease or asthma (each 22%) and ongoing analgesic usage (14%).

Randomization errors included failure to assign males the lowest randomization number and females to the highest.

REVIEWER COMMENT:
The protocol violations impact on the ability to interpret the study results and further call into question the actual conduct of the study. The missing data from the pain diary directly impacts evaluation of pain, the primary endpoint. The concomitant use of prohibited medication although apparently used in both groups by approximately equal number of patients can have an effect on pain. The incomplete tally of patches applied and variation in phone contact could have an effect on the outcome of the study.

Demographics
The average age of patients was 38.9 years with diclofenac patch patients younger than the placebo, 37.7 vs 40.1 (statistically significant). Nearly all the patients (99.5%) were listed as Caucasian in the dataset except for two Asian patients and one "European". There were 206 males and 212 females enrolled in the study. Weight was similar in the two groups, 74.6 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 statistically significant lower baseline pain scores than placebo (7.3 vs 7.5). The demographic and medical characteristics are summarized in the table below.

Table 10.1.1.f: Patient Demographics and Medical Characteristics-Study 00GB/Fp05

Parameter*	Diclofenac Epolamine Patch (DEP)	Placebo Patch (PP)	p Value
Age (years)	37.7 ± 14.3 (18-82)	40.1 ± 14.8 (15-85)	0.094
Height (cm)	171.2 ± 9.5 (150-193)	171.3 ± 10.1 (146-197)	0.888
Weight (kg)	74.6 ± 14.1 (47-150)	76.0 ± 14.4 (46-125)	0.294
Body Mass Index (kg/m²)	25.5 ± 4.8 (16-48)	26.0 ± 4.9 (16-49)	0.331
Sex			
Male	100 (48.3%)	106 (50.2%)	0.697
Female	107 (51.7%)	105 (49.8%)	
Race			
Caucasian	207 (100%)	209 (99.1%)	0.499
Asian	0 (0.0%)	2 (0.9%)	
Medication/Concomitant Pathology	58 (28.0%)	68 (32.5%)	0.338
Drug Hypersensitivity	7 (3.4%)	13 (6.2%)	0.252
Injury Characteristics			
Time to Injury (days)	1.4 ± 1.6 (0-7)	1.4 ± 1.8 (0-8)	0.893
Injury Location			
Right	123 (59.4%)	114 (54.3%)	0.323
Left	84 (40.6%)	96 (45.7%)	
Ankle	43 (20.8%)	40 (19.0%)	
Shoulder	42 (20.3%)	39 (18.5%)	
Knee	32 (15.5%)	33 (15.6%)	
Foot	27 (13.0%)	25 (11.8%)	
Calf/Shin (lower leg)	19 (9.2%)	15 (7.1%)	
Wrist/Hand	11 (5.3%)	17 (8.1%)	0.663
Elbow	11 (5.3%)	14 (6.6%)	
Arm	9 (4.3%)	10 (4.7%)	
Thigh/Femur (upper leg)	7 (3.4%)	5 (2.4%)	
Hip	3 (1.4%)	7 (3.3%)	
Back	3 (1.4%)	2 (0.9%)	
Thorax	0 (0.0%)	4 (1.9%)	
Diagnosis			
Contusion	89 (43.0%)	89 (42.2%)	
Strain	69 (33.3%)	61 (28.9%)	0.601
Sprain	46 (22.2%)	56 (26.5%)	
Other	3 (1.4%)	5 (2.4%)	
Bruising	68 (32.9%)	67 (31.9%)	0.917
Swelling			
None	54 (26.1%)	45 (21.3%)	
Mild	86 (41.5%)	95 (45.0%)	0.416
Moderate	65 (31.4%)	68 (32.2%)	
Severe	2 (1.0%)	3 (1.4%)	
Active Range of Motion			
Full	25 (12.1%)	44 (20.9%)	
Restricted	170 (82.1%)	159 (75.4%)	0.013
Immobile	12 (5.8%)	8 (3.8%)	
Joint Stability	187 (94.9%)	190 (96.4%)	0.621
Skin Examination			
Normal	128 (61.8%)	139 (65.9%)	
Erythema	73 (35.3%)	67 (31.8%)	0.714
Abrasion/Laceration	6 (2.9%)	5 (2.4%)	
Mean Pain Score	7.3 ± 1.4 (5-10)	7.5 ± 1.3 (5-10)	0.115
Categorical Pain Score			
5	18 (8.7%)	14 (6.6%)	
6	46 (22.2%)	39 (18.5%)	
7	50 (24.2%)	44 (20.9%)	0.101
8	55 (26.6%)	71 (33.6%)	
9	24 (11.6%)	25 (11.8%)	
10	14 (6.8%)	18 (8.5%)	

* Mean ± standard deviation (plus range in parenthesis) provided for continuous variables, and number of patients with the percentage of total in parenthesis for categorical variables. P values derived from analysis of variance or Fisher's exact test.

(Source: Applicant's Table 4. Patient Demographics and other Baseline Characteristics, pg. 32)

REVIEWER COMMENT:
The difference in age is not great enough to have any effect on healing. The greater restriction in range of motion in the diclofenac group could represent more severe injury in this group but the pain scores are actually higher in the placebo group implying the exact opposite. The difference in baseline pain scores could have an effect on outcome if not taken into account in the analysis

Applicants Primary Efficacy Analysis-as based on the modified statistical analysis plan
As described in the new statistical plan, a multiple imputation method was used for the primary analysis of mean post-treatment pain scores. The applicant reports that in efficacy evaluable patients the diclofenac group had a 14.8% lower mean pain score using multiple imputation than the placebo group. When different methods were used to handle missing data, the diclofenac group continued to have lower overall mean pain scores of 18.2% and 9.8% with LOCF and GEE methods, respectively (see Table below). The efficacy population was defined as all patients who had at least one post-treatment pain assessment in the patient diary. This is different than the intention to treat (ITT) population routinely used and preferred by the FDA in efficacy analysis. The ITT population contains all randomized patients. The applicant maintains that pain score comparisons reached significance by the time the second patch was removed on day 1 (Figure 10.1.1.a).

Table 10.1.1.g: Primary Efficacy Outcome in EEP[1]- 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.

[1] Efficacy evaluable population

(Source: Applicant's Table 8. Efficacy Evaluable Population: Primary Outcome Variable, pg. 36)

Figure 10.1.1.a: Daily Mean Pain Scores for Diclofenac and Placebo Patients Over 14 Days- Study 00GB/Fp05

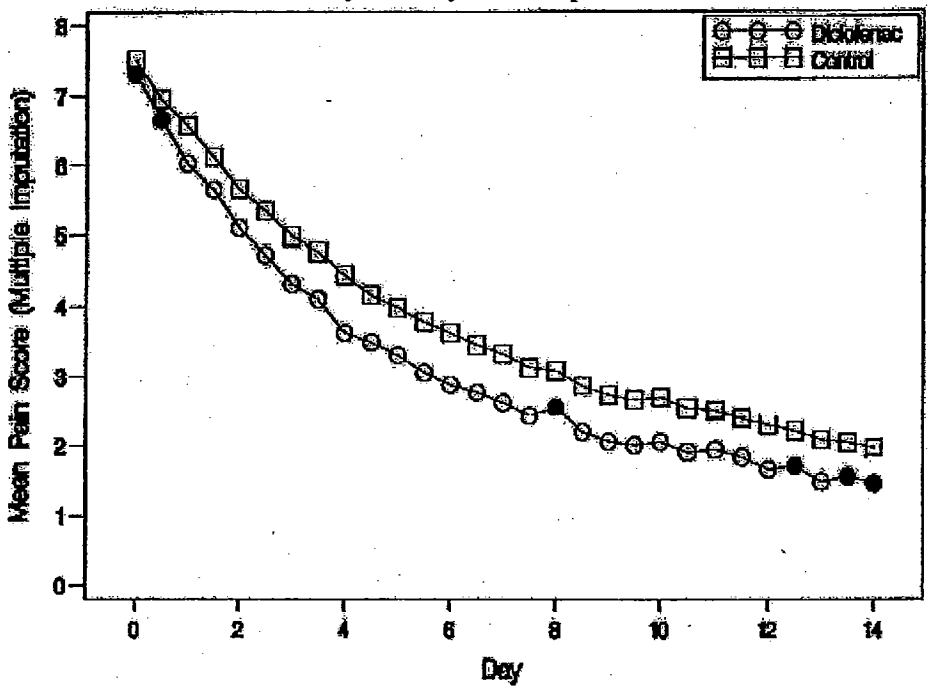

Figure 1. Daily mean pain scores for DEP and control (PP) patients over 14 days of treatment/follow-up using a multiple imputation method for missing data. P values are ≤0.045 for all data points except those in which the circle has been filled-in, the latter having p values <0.10 (except baseline or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

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

REVIEWER COMMENT:
The applicant states "interday pain score comparisons reached significance by the time the second patch was removed on day 1." This reviewer believes that any purported significance between the two groups in pain difference did not occur until at least the second day. According to the protocol, patch application occurs twice daily. Therefore the second patch is removed approximately 24 hours after application of the first patch which would be on the second day. The Applicant offers the following explanation in an e-mail dated December 7, 2005, "Day 1 was defined as a 24 hour period".

The FDAs 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."

For Study 00GB/Fp05 the use of a nominal day or 24 hour day is more than a difference in semantics but is relevant to the question of whether the patch has an onset of action suitable for acute pain. From a clinical perspective, the earliest evidence of any statistical difference in pain does not occur until the second day by the Applicant's own analysis. It is the contention of this reviewer that a one day delay for onset of analgesia is not acceptable for a product intended to treat acute pain. Furthermore the statistical difference observed on Day 2 (0.5 units on a VAS) does not appear to be clinically meaningful to this reviewer.

Secondary Outcome Variables
Investigator response to treatment was good to excellent in 58% of diclofenac treated patients compared to 48% of placebo. Range of motion differences for the two treatment groups approached statistical significance but no difference in effect was observed on swelling.

Time to pain resolution
Time to pain resolution, the primary outcome variable in the original protocol, varied according to the definition used for pain resolution, with the diclofenac group achieving pain resolution earlier than the placebo group (Table below).

Table 10.1.1.h: Time to Pain Resolution - Study 00GB/Fp05

Time to 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 to11.0)	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

(Source: Applicant's Table 13. Efficacy Evaluable Population: Secondary/Other Outcome Variables, pg. 41)

The estimate of the median time to pain relief 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 scores of ≤ 2. 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. Of note the Applicant in their analysis of time to pain resolution censored using 15.5 days as per their understanding of the protocol but in fact Protocol Amendment 2 changed the number of days from 15.5 to 15.

Time to pain resolution is not considered by the FDA to be a primary efficacy endpoint without supporting evidence of effectiveness from secondary endpoints. The clinical significance of a mean pain score of 10.0 days versus 13.5 is unclear

Additional analysis by the applicant revealed that patients treated with diclofenac had less pain than placebo, irrespective of the treatment center or the subgroup diagnosis.

REVIEWER'S SUMMARY OF EFFICACY – STUDY 00GB/Fp05
Although, the applicant reports efficacy based on their modified analysis plan, the FDA statistician concludes that the analyses are not meaningful due to the high rate of dropout. Setting aside the statistical issues, this study does not demonstrate that treatment with diclofenac compared to placebo patch results in clinically meaningful improvement in patients with sprains, strains and contusions. Furthermore there is no evidence of any analgesic effect for the first day of patch use.

Section 10.1.2 Protocol: 05-05-98

Title: A Clinical Study Comparing the Efficacy and Safety of Flector Tissugel (diclofenac epolamine patch) Versus Placebo in the Treatment of Minor Ankle Sprain

Primary Objective: To evaluate the analgesic and anti-inflammatory efficacy and safety of Flector Tissugel versus placebo applied once per day to patients with minor ankle sprain

Study Design: This was a double-blind, randomized, placebo-controlled, parallel group trial to be conducted at multiple sites in France.

Treatment Duration: 7 days

Study Population: The protocol specified enrollment of 120 subjects (60 subjects per group) at 10 centers

Key Inclusion Criteria:

Patients were to have met the following criteria:

1. Female or male subjects aged 18-65 years
2. Acute ankle pain within 48 hours of a traumatic ankle sprain
3. Pain score on visual analogue scale (VAS) of $\geq$ 50 mm
4. Requiring a 7-day treatment with topical NSAID

Exclusion Criteria:

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

1. Pregnant, breastfeeding or childbearing potential
2. Known allergy to aspirin, NSAIDs or the excipient
3. History of skin allergy
4. Open skin lesions within the injury area
5. Sprain occurred more than 48 hours prior to study entry

6. Recurring sprains
7. Sprains with pain less than 50 mm measured on VAS
8. Sprains treated by the application of a NSAID or any other topical agent within one week prior to study entry or treatment by local or oral enzyme therapy
9. Oral or parenteral treatment by corticosteroids, NSAIDs, or aspirin within seven days prior to study entry
10. Treatment with an analgesic 6 hours prior to study entry
11. Physiotherapy or alternative medicine (acupuncture, mesotherapy, homeopathy) treatment
12. Anticoagulation required during study
13. Participation in a clinical trial one month prior to study entry
14. Orthopedic or surgical treatment required (if severity of sprain in doubt, a radiograph will be performed and the severity will be graded by criteria of Ottawa)
15. Sprain treated prior to study entry

Study Medication:
The patch was to have been 10 cm x 14 cm and to have contained 182 mg of diclofenac epolamine. Patients were to have applied one patch of Tissugel or an identical appearing placebo patch containing no drug every morning for seven days. Each patch was to have been secured in place by means of a slightly elastic net compression bandage.

Permitted Concomitant Medications/Treatments:
The application of ice was to be allowed in both groups, but was to be reported on the CRF. The use of acetaminophen was to be allowed 3 hours after the first application of the patch. Acetaminophen use was to be recorded.

Prohibited Therapies
The subjects were not to be allowed to take any oral or topical NSAIDs, oral or topical enzyme therapy (enzyme therapy is a product that can be taken either by topical or oral route and induces fibrinolytic and anti-inflammatory activity) or any other local physiotherapy, physical therapy or alternative medicine. The use of acetaminophen was to be prohibited during the first three hours after application of the patch.

Study Procedures
Subjects were to have started the study after the screening visit (Day 0). Subjects were to have been evaluated at day 3 and day 7 at the same time of the day by the same person. Subjects were to have recorded their pain in a diary for the first three days.

Screening/Start of Treatment (Visit Day 0)
- History and general examination including height and weight
- A separate articular examination including:
  - status of skin
  - assessment of peri-articular edema by measuring the circumference of the injured and healthy ankle
  - functional disability measured on a verbal 4-point scale: absent, slight, moderate and severe
  - single foot leaning measured on a 3-point verbal scale: no pain, possible with pain,

impossible

- Assessment of pain
  - self assessment of pain on active mobilization using the VAS
    "pain on active mobilization" is defined by the applicant as "spontaneous pain" during normal daily activities
  - investigator assessment of pain at rest, pain on passive stretch and pain on pressure using a 4-point verbal score (no pain = 0, slight = 1, moderate = 2, severe = 3)
- Subjects were to have received a daily diary to record pain on a visual analog scale. Pain values were to have been recorded as follows:
  - D0: hourly for the first six hours and at 8 PM
  - D1 and D2: 8AM, 12 PM and 8PM
  - D3: 8AM

Treatment (Visit Day 3)
The following information and assessments were to be obtained:

- Concomitant treatments including use of acetaminophen and application of ice
- Measurement of ankle circumference
- Investigator assessment of pain at rest, pain on passive stretch and pain on pressure
- Single foot leaning
- Self-assessment of pain on active mobilization
- Global evaluation of both the investigator and the subject of the efficacy of treatment on a 4-point verbal scale: excellent, good, fair, nil
- Global evaluation of both the investigator and the subject of the safety of treatment on a 4-point verbal scale: excellent, good, fair, nil
- Adverse events
- Compliance

End of Treatment (Visit Day 7)
The same information and assessments were to be obtained as on Visit Day 3 with the following exceptions:

- Assessment of concomitant application of ice
- Record number of days until leaning was possible

Statistical Analysis
Primary Efficacy Outcome
The primary efficacy variable was to have been pain on active mobilization, self evaluated on a 100 mm visual analog scale (VAS). The definition of "pain on active mobilization" was spontaneous pain experienced by the patient during their normal daily activities and not pain experienced during a specific mobilization procedure. The primary analysis for the primary endpoint would be based on an intention to treat population. Subjects who had stopped treatment would be part of the efficacy analysis. The protocol defined primary endpoint was ambiguous due to the French to English translation. The FDA statistician interpreted the primary endpoint to be the VAS (assessed by the patient) at the physician's office on Day 7. This was supported by section 13.1 in the protocol that stated "Choice of primary criterion: VAS at D7".

Secondary Efficacy Outcomes

- Analgesic effect:
  - Pain at rest
  - Pain on passive stretch graded on a 4-point scale: 0 = no pain, 1= slight pain, 2 = medium pain, 3 = severe pain
  - Pain on pressure: external lateral ligament, front and medium fascicule graded according to the same 4-point scale as pain at rest
  - Single foot leaning: 0 = possible without any pain, 1 = possible but painful, 2 = impossible
- Assessment of the anti-inflammatory effect:
  - Difference in circumference between healthy and injured ankle
- Subject and investigator global assessment at the end of treatment graded on a 4-point scale: excellent, good, fair, bad (assessments "excellent" and "good" would be considered as positive)
- Tylenol consumption
- Withdrawal due to inefficacy
- Ice application from D0 to D3

Table 10.1.2.a: Efficacy and Safety Outcomes – Protocol 05-05-98

Treatment day	D0	D1	D2	D3	D4	D5	D6	D7
Visits to physician	1			2				3
Assessment:								
- Informed consent	X							
- Inclusion and exclusion criteria	X							
- Medical History – Physical examination	X							
- Articular examination:	X							
- Skin								
- Functional disability								
Concomitant therapy without concern with sprain	X			X				X
Primary efficacy variable								
Spontaneous pain on visual analog scale (VAS)	X			X				X
VAS on a daily diary by the patient	X	X	X	X				
Secondary efficacy variables								
Pain (at rest, on passive stretch, on palpation, single foot leaning)	X			X				X
Periarticular edema (mm)	X			X				X
Judgment of both patient and physician on therapy efficacy				X				X
Use of Paracetamol	-			X				X
Ice application	X			X				-
Compliance				X				X
Local and global Tolerability				X				X
Adverse Event				X				X
Improvement Lead-time				X				X

Patient: VAS recordings from D0 to D3 before the 2nd visit on a daily diary one application per day.

(Source: Applicant's Table Flow Chart: Efficacy and Safety Measurements, Final Study Report for Study 05-05-98 Section 9.5.1.)

Sample Size Calculation
Determination of sample size was based on previous study results employing VAS pain scoring and assumed a pretreatment value of 65 mm and a standard deviation of 10.9 mm. Assuming the placebo group improves 50%, a sample size of 60 subjects per group would allow demonstration of a superiority of 18% (with beta risk 10%) or 20% (with beta risk 20%).

Protocol Amendments
According to the sponsor there were no changes in the conduct of the study from that described in the protocol.

Study Results
The first patient was enrolled on June 30, 1998 and the last patient completed the study on May 14, 1999.

Enrollment
Nineteen sites in France participated in the study. The reason for the higher number of sites than planned was a lower enrollment rate than expected. A total of 134 patients were enrolled with 125 patients completing the protocol (Table 10.1.2.c). Sixty-six patients were randomized to placebo and 68 patients to Diclofenac patch. Enrollment at each site was a follows:

Table 10.1.2.b: Subject Enrollment-Study 05-05-98

Site No.	No. Patients Enrolled	No. Patients Completed	Site No.	No. Patients Enrolled	No. Patients Completed
1	1	1	11	1	0
2	3	3	12	24	24
3	3	3	13	3	3
4	8	8	14	2	2
5	1	1	15	4	4
6	15	13	16	1	1
7	3	3	17	24	22
8	12	12	18	13	13
9	3	8	19	5	3
10	8	1			
Total Enrolled: 134			Total Completed: 125		

(Source: Applicant's Table Study Enrollment/Completion, Amendment 14 submitted 9/14/06)

Subject disposition
Nine patients listed in Table 10.1.2.c terminated the study early.

Table 10.1.2.c: 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)	-

Table 10.1.2.d: Subject Drop Out - Study 05-05-98

Subject No.	Group	Reason for Early Termination
18	Placebo	Adverse Event: pruritus, stopped treatment at day 5
38	Placebo	Protocol violation: applied product every 6 hrs
42	Placebo	Lack of efficacy
157	Placebo	Lack of efficacy
181	Placebo	Lack of efficacy
45	Diclofenac	Uncertain[1]
54	Diclofenac	Lost to follow-up after enrollment
73	Diclofenac	Lost to follow-up[2]
173	Diclofenac	Lost to follow-up

[1] Comment in dataset indicates patient started competition
[2] Dataset indicates patient was lost to follow-up

Protocol Violations
One patient in the diclofenac group and one patient in the placebo group took an excluded analgesic drug, and 3 patients in the placebo group took excluded concomitant treatment. Table 10.1.2.e summarizes the patients with a protocol violation.

Table 10.1.2.e: Protocol Violations – Study 05-05-98

Subject No.	Group	Protocol Deviation	
8	Placebo	1 application of Ketum gel[1] on D1	
22	Placebo	1 tablet of Surgam[2]	
157	Placebo	Apranax[3]	
139	Diclofenac	1 sachet Migpriv antimigraine drug containing aspirin[4]	
129	Placebo	Efferalgan 500 analgesic reported at D3[5]	
37	Diclofenac	Missed 2 patches	
111	Placebo	Missed 3 patches	

[1] Ketoprofen (NSAID) [2] Tiaprofenic Acid (NSAID) [3] Naproxen (NSAID) [4] Oral lysine acetylsalicylate and metoclopramide [5] Tylenol #2

REVIEWER COMMENT:
It is not expected that the protocol violations significantly impacted the primary efficacy outcome because most of the violations (four out of five) occurred in the placebo group. Only one patient in the diclofenac group took an excluded analgesic drug. The prohibited medication, Migpriv, contains aspirin and metoclopramide and is indicated for the treatment of migraine headaches. There is no information in the dataset or final report as to why and when Patient 139 took the analgesic. The drug apparently was taken some time between day 3 and day 7 since the information is recorded on the D7 visit but not D3.

Demographics/Medical History:
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 and had lower body mass index than those treated with diclofenac patch (Table 10.1.2.f). 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. However, the difference in circumference in the injured versus healthy ankle was greater in the placebo than diclofenac group indicating possibly more severe injury in the placebo group.

Table 10.1.2.f: Patient Demographics – Study 05-05-98

	Flector Tissugel (n=68)	Placebo (n=66)	p-value*
Age: mean (S.D.)	33.3 (13.9)	29.7 (11.6)	0.1
Sex: M / F	33/35	39/27	0.2
Weight			
Males: mean (S.D.)	75.4 (11.0)	77.7 (19.2)	0.5
Females: mean (S.D.)	62.8 (12.6)	57.1 (9.2)	0.05
Height			
Males: mean (S.D.)	178 (11.0)	177 (19.2)	0.5
Females: mean (S.D.)	163 (7.1)	164 (7.9)	0.6
Body Mass Index			
Males: mean (S.D.)	23.9 (3.3)	24.8 (5.6)	0.5
Females: mean (S.D.)	23.6 (5.1)	21.1 (3.0)	0.05

* Fisher's exact test of heterogeneity for dichotomous variables, and Wilcoxon nonparametric test for quantitative variables.

(Source: Applicant's Table General Characteristics at Inclusion, Final Study Report for Study 05-05-98 Section 11.2)

The application of ice by the patient prior to study entry was similar for the two groups.

Table 10.1.2.g: Ice Application at Baseline – Study 05-05-98

Application of Ice	DEP	Placebo
Yes	25	27
No	43	39

Applicant's Efficacy Analysis

Overview

The Applicant found that VAS scoring for all patients was associated with a decrease in mean values over time for both treatment groups, but greater for the diclofenac treated patients than controls. Table 10.1.2.h displays the change in VAS spontaneous pain expressed as a percent of baseline over time. All subjects who used a patch were to be included in the intention to treat analysis. The average decrease in VAS measured 4 hours after the first application was two-fold greater for the diclofenac group than those given placebo. The diclofenac patch group showed significantly higher improvement than the placebo group at each time point except for day 1 at 8 am.

Table 10.1.2.h: Sponsor's Primary Analyses – Study 05-05-98

Decrease (%) in spontaneous pain measured by the patient: mean (s.d.) ; median (min-max).	Flector Tissugel ® (n=68)	Placebo (n=66)	P-value*
Last known value			
1 hour after 1st application	-7.7 (26.2), -2.0 (-100 to 67)	-5.9 (18.3), -2.7 (-60 to 37)	0.9
2 hours after 1st application	-11.6 (26.4), -7.9 (-100 to 67)	-7.8 (20.5), -4.9 (-60 to 45)	0.5
3 hours after 1st application	-18.3 (27.9), -14.5 (-100 to 67)	-11.3 (22.2), -6.8 (-66 to 55)	0.1
4 hours after 1st application	-23.9 (27.5), -16.9 (-100 to 42)	-11.1 (22.6), -11.2 (-67 to 62)	0.02
5 hours after 1st application	-26.6 (28.2), -23.3 (-100 to 42)	-13.0 (22.0), -11.6 (-66 to 62)	0.02
6 hours after 1st 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: Applicant's Table 10: VAS Spontaneous Pain, Final Study Report for Study 05-05-98 Section 11.4)

Secondary Variables

The secondary efficacy measures of pain at rest, pain on passive stretch, pain on pressure and the possibility of single foot leaning all showed a better response from treatment in the diclofenac group (Table 10.1.2.i).

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Table 10.1.2.i: Analgesic Efficacy on 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)

Ankle Swelling

The applicant noted no statistical difference in mean ankle swelling in the diclofenac and placebo groups on days 0, 3 and 7.

Subject and Investigator Global Assessment
Efficacy, as judged by both the patients and investigators, was superior for diclofenac patch treated patients on both days 3 and 7 (Table 10.1.2.j).

Table 10.1.2.j: 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)

Acetaminophen Use
There was no significant difference in acetaminophen use for the two treatment groups.

Table 10.1.2.k: Overall Acetaminophen Use (#500 mg Capsules)– Study 05-05-98

Overall consumption of paracetamol Mean (sd) and median (min-max)	Flector Tissugel® (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)

REVIEWER COMMENT:
The decreased pain in patients in the dicofenac group did not impact on their need for additional acetaminophen. The equivalent use of acetaminophen in both groups suggests that the patch at best has limited efficacy and casts doubt on the presumed benefit of diclofenac patch in reducing the need for additional analgesics and their associated side effects.

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 can effect outcome and in clinical practice are often prescribed in the management of ankle sprains.

Ice
There was similar use of ice for the two groups during the study (10 in the placebo group and 13 in the diclofenac group).

REVIEWER'S SUMMARY OF EFFICACY – PROTOCOL 05-05-95
This study suggests that treatment with diclofenac patch compared to placebo patch is associated with statistically significant and clinically meaningful improvement in pain in patients with ankle sprain. Treatment effect is sustained and occurs as early as four hours after patch application. The apparent decline in some efficacy at the end of the study is likely from spontaneous improvement in patients on placebo due the self-limited nature of ankle sprain. Secondary pain outcome measures and investigator and subject assessments also demonstrate superiority over placebo.

10.3 LINE-BY-LINE LABELING REVIEW

See Section 9.4

REFERENCES

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Robert A. Levin
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Mwango Kashoki
1/10/2007 10:44:18 AM
MEDICAL OFFICER

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

MEDICAL OFFICER REVIEW

DIVISION OF ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMIC DRUG PRODUCTS HFD-550

NDA# 21-234

DICLOFENAC EPOLAMINE PATCH (DHEP)

Submission Date:	December 20, 2000
Reviewer Received Date:	January 18, 2001
Review Completed:	September 29, 2001
Drug Name:	Diclofenac Epolamine Patch
Applicant:	Institut Biochimique SA
Pharmacologic Category:	Topical non-steroidal Analgesic
Proposed Indication:	Pain
Dosage Form and Route:	Diclofenac Patch 1.3%, for local application BID
Project Manager:	Barbara Gould
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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on Approvability

Diclofenac Epolamine Patch 1.3% (DHEP) should not be approved for the indication of pain associated with ——— The overall risk associated with this product is small if used as directed but the sponsor has failed to demonstrate the efficacy of this product for the proposed indication of ———. DHEP appears to have little clinical utility in this setting.

The sponsor identified two pivotal Phase III trials in support of their claim:

Study 01 (49,459-01): Patients with pain secondary to a minor sports related injury (strain, sprain, contusion) applied a diclofenac patch or placebo patch to the affected area twice a day, for two weeks. **Primary efficacy** analyses showed that DHEP did not separate from placebo patch for any of the 4 subgroups (of the pre-specified primary endpoint) at any of the three pre-specified time points (days 3, 7, and 14) for either the per-protocol (PP) or Intent-to-treat (ITT) grouping. The four subgroups are as follows:

Pain intensity difference (PID) : lowest p≥ 0.104 at day 14 in PP group

Summed Pain intensity difference (SPID) : lowest p≥0.099 at day 14 in PP group

Pain on Pressure difference (POPD) : lowest p≥0.369 at day 3 in PP group

Summed Pain on Pressure difference (SPOPD) : lowest p> 0.357 at day 3 in PP group

Secondary efficacy variables of *Patient Global Response to Therapy* and *Investigator Global Response to Therapy* did not show separation from placebo. Except for minor skin irritation at the application site, there were no serious adverse events.

Study 02 (49,459-02): Patients with pain secondary to a minor sports related injury as above, applied DHEP or placebo patch to the affected area twice a day, for up to two weeks. The **Primary efficacy variable**, *Time to Pain Resolution,* determined by the sponsor, was measured as the amount of time, measured in days, that patients wore the patch during the two week period. No pre-specified clinically relevant treatment difference was described in the protocol. According to the sponsor, *" a shorter time to pain resolution is a favorable outcome, while a longer time to pain resolution is a less favorable outcome. Patients curtail use of the product when their pain is gone or nearly gone"*. The separation from placebo patch claimed by the sponsor (9 days for diclofenac patch vs. 12.3 days for placebo patch, (p=.016) has unclear clinical relevance given the self-limiting nature of the pain model. This study had a failed randomization such that patients in the placebo arm were on average 10 pounds heavier than patients in the DHEP arm. This is a key factor in injuries to weight bearing joints such as ankles and knees.

When this difference was accounted for in an FDA statistical re-analysis of the data the statistical significance of the data was lost (p=0.072).

The sponsor has not provided any evidence from the literature to support "*days to pain resolution*" as a validated metric for assessing acute analgesia.

The primary endpoint described above was a non-validated metric derived from a Secondary efficacy endpoint: *Average Daily Pain Score.* These patient pain scores were reported as statistically significant ($p \leq 0.042$), favoring the active patch, beginning on day 6 and continuing through day 13. The sponsor used a non-pre-specified post-hoc statistical analysis after their review of the data to derive this positive effect. Upon FDA request, the sponsor re-analyzed the data for average daily pain scores using the pre-specified protocol. This time DHEP did not separate from placebo (lowest p=0.075, day 10, ITT population) at any day during the 2 week trial period. Two other Secondary efficacy endpoints of *Patient Global Response to Therapy* and *Investigator Global Response to Therapy* were not statistically significant. Except for minor skin irritation at the application site, there were few serious adverse events.

In conclusion, the pivotal studies do not support the use of DHEP in the treatment of — pain.

The safety of this product can be divided into two categories: *US* and *Oversees*

Data derived from US product clinical trials: Diclofenac Epolamine Patch 1.3%

In general, the data derived from the US trials shows that Diclofenac Epolamine Patch is well tolerated, with minor skin irritation as the most common side effect. This irritation is manifest as rash or pruritis at the application site and resolves upon discontinuation of the patch. The occurrence of pruritis was $\leq 7\%$ in the DHEP treated group and this was less than the occurrence of pruritis in the placebo patch group, $< 14\%$.

Data derived from Europe, Asia, and Latin America: where the product has been marketed since 1993 as either Flector Tissugel 1% or Flector EP tissugel 1%.

Diclofenac Epolamine Patch was first approved in Switzerland in 1993 and since then has been approved in 21 other countries. As of 11/16/2000 the drug has not been withdrawn in any country. Approximately — patches have been distributed. The safety profile oversees appears to be similar to that seen in the US trials.

II. Summary of Clinical Findings

A. Overview of DHEP Clinical Program

Product Name:	Diclofenac Epolamine Patch (DHEP) 1.3%
Class:	Topical NSAID
Proposed Mechanism of action:	Unknown, but may act at the site of application
Route of Administration:	Transdermal, at the site of injury
Indication:	— pain (sprain, strain, contusion)
Dose:	One patch Q12 hours prn, maximum 14 days

The clinical program for DHEP included four phase I dermatologic studies (safety) and two phase III pivotal trials. One pharmacokinetic study was done with the to-be-marketed product. No pharmacodynamic studies with DHEP have been done. Over 550 patients were exposed to DHEP in the clinical trials

B. Efficacy

Phase III Pivotal Trials: Two Studies submitted as pivotal: Study 01 and Study 02

Study 01 (49,459-01) – Randomized, double-blind, placebo controlled, 2-center study. 222 patients were randomized, 206 in the per-protocol analysis, 213 in the ITT analysis. Patients with minor sports injury wore the patch at the affected site for 2 weeks with Q12 hour dosing. The most frequent injury was ankle sprain (27%) followed by knee sprains or contusions (12.5%).

Primary efficacy analyses showed that the DHEP did not separate from placebo patch for any of the 4 subgroups (italics below) in the primary endpoint at any of the three time-points (days 3, 7, 14) for either PP or ITT grouping.

Pain intensity difference (PID) : lowest p≥ 0.104 at day 14 in PP group

Summed Pain intensity difference (SPID) : lowest p≥0.099 at day 14 in PP group

Pain on Pressure difference (POPD) : lowest p≥0.369 at day 3 in PP group

Summed Pain on Pressure difference (SPOPD) : lowest p> 0.357 at day 3 in PP group

Secondary efficacy variables of *patient global response to therapy* and *investigator global response to therapy* were not statistically significant vs. placebo patch.

Study 02 (49,459-02) - Randomized, double-blind, placebo-controlled, 4-center study. 411 patients were randomized, 365 in the PP population and 372 in the ITT population. Patients with minor sports injuries wore the patch for two weeks with $Q12^0$ dosing. On average, patients in the placebo group weighed 10 lbs more than those in the active patch group (p=0.010). This difference was not seen in the first pivotal trial. The most frequent injury was ankle sprain (23%) followed by knee sprains or contusions (17%).

Primary efficacy variable was *Time to Pain Resolution,* measured in days. The assessment tool for this metric was a 0-10 *category* pain scale:

no pain										severe pain
0	1	2	3	4	5	6	7	8	9	10

Pain was considered "resolved" if the pain level fell to "2 or less" on the scale for two consecutive days (4 consecutive measures at 12-hour intervals). The sponsor proposed efficacy based on separation from placebo patch because patients on DHEP withdrew at 9 days vs. 12.3 days for placebo patch. (p=0.016). According to the sponsor, *"a shorter time to pain resolution is a favorable outcome, while a longer time to pain resolution is a less favorable outcome. This pattern of treatment is closer to the actual usage in those European countries where the product is now marketed. Patients curtail use of the product when their pain is gone or nearly gone".*

Secondary endpoints of *patient* and *investigator global response to therapy (5-point verbal scale)* were not statistically significant. The third and last secondary endpoint of *Average Daily Pain Score (from scale above)* was claimed by the sponsor to be statistically significant for days 6-13 (PP population) ($p \leq 0.042$). In the ITT population this is only true at days 7-13 ($p \leq 0.037$). Three of the four investigator sites showed no significant differences at <u>ANY</u> *Average Daily Pain Score.* No positive or negative trends for efficacy were observed. The only investigator with significant results for this secondary endpoint was Dr. Rowbotham (highest enroller).

REVIEWER'S COMMENT: Adults with minor sprains, strains and contusions [redacted] *are the targeted population for this topical NSAID product. Because* [redacted] *would represent a totally new indication it is impossible to relate the lack of efficacy of this product with other treatments such as oral NSAIDs and narcotics. Current guidance for assessing efficacy of* ***acute pain*** *drugs (oral, IV, IM) requires that the test product be compared to placebo in terms of:*

1.) Pain Relief (PR) ----------measured by a categorical or VAS
2.) Pain Intensity (PI)----------measured by a categorical or VAS
3.) Pain Intensity Difference (PID)----------difference between baseline PI and treatment PI
4.) Onset of Action----------must show effect within the first hour
5.) Duration of Effect----------must be established for dosing interval

***Patient global responses** to treatment and **total pain relief scores (TOTPAR)** are only considered as secondary supportive metrics for acute pain efficacy.*

***Study 01** tested some of these Pain metrics but was unable to demonstrate significance versus placebo. Because no studies to determine site of action were done with DHEP one can only speculate as to where the bulk of active ingredient might actually produce any proposed effect. Thus, two general issues remain outstanding:*

1.) the small amount of drug that does enter systemic circulation is not adequate enough to produce a clinically meaningful anti-inflammatory/analgesic response in an acute or sub-chronic pain model.

2.) little evidence exists to support the claim that the drug actually works at the site of application; i.e. in the joint space or at the myofacial/muscle layers.

***Study 02** tested the pain response as a function of "time to pain resolution" without comparing the daily pain response on DHEP versus placebo as a primary endpoint. The clinical utility of assessing pain by this metric is unclear. While 50% of the patients on DHEP were considered treatment "successes" at day 9, the study also showed that 40% of patients on placebo patch were also treatment "successes" at day 9. This treatment difference of 10% is not clinically robust, especially for a minor disease process that spontaneously resolves. Furthermore, failure to separate from placebo based on average daily pain scores or patient global responses further casts doubt on the relevance of a mathematically derived primary endpoint. Based on these findings, this drug has not demonstrated superiority versus placebo. This pain model may serve as a proof of concept metric but fails to demonstrate any significant clinical benefit, especially in a pain model with such a wide range of pain responses (mild to severe).*

There are no US controlled studies comparing DHEP with other treatments. If in fact a topical NSAID product can be developed that provides adequate acute pain relief with very little systemic side-effect (GI, liver or renal toxicity) then a significant contribution can be made to the existing oral NSAID armamentarium. Unfortunately DHEP failed to demonstrate such efficacy. By design, a topical NSAID product that claims to have little plasma uptake will typically fail when tested as an "Acute Analgesic".

C. Safety

Phase I dermatology studies:

Study # C11080 : Flector EP Tissugel was considered non-irritating in a 21-day cumulative irritancy study in 20 volunteers.

Study # C1108: Flector EP Tissugel was considered to be non-phototoxic in 20 human volunteers.

Study # B9356: Flector EP Tissugel was found to be non-photo allergenic in 27 human volunteers.

Study # 006-91: DHEP plaster did not elicit any skin reactions indicative of a delayed contact or immediate hypersensitivity in 25 healthy volunteers.

Over 550 patients were exposed to DHEP at or above the proposed dose during the US clinical trials. Only 2 "severe" events were documented, both were related to skin irritation (rash/pruritis) and spontaneously resolved within 24-48 hours of patch removal. Most of the complaints about skin irritation were listed as "mild" and were seen more often in the placebo group. The dermatologic side-effect profile in humans is similar to that observed in animals. From the European safety database presented in the NDA there appears to be a wide margin of safety in terms of skin reactions. In France, two cases of contact eczema were reported from 1998-99, both resolved. No cases were reported in Italy during a 5 month period in 1999 while Switzerland had one reported case of axillary lymph node enlargement reported in 1999. However, four cases of GI hemorrhage were reported in Israel in 1995; these patients were wearing some form of diclofenac patch and were also on concomitant aspirin or other NSAID therapy at the time of event.

The potential for drug-drug interaction exists given the target population and unanticipated use of this product with oral NSAIDS. Review of various European labels for Flector EP 1% reveals very little with regard to clinically tested methods for ascertaining safety when DHEP is used with oral NSAIDS. Case reports from Israel may suggest an increased GI toxicity potential. Patients in the US trials were not tested while on concomitant oral NSAID therapy, therefore the safety of DHEP when used in combination with oral NSAIDS remains an unresolved safety issue. The language used in the European labeling regarding drug interactions reads as follows:

"due to poor systemic absorption during the use of DHEP, the interactions occurring with oral administration of diclofenac are not very likely" (from Swiss label)

Evidence to support this claim was not presented in the US clinical trial data. Therefore, if DHEP were to be approved,

A potential risk with this product is that of masking a more serious injury. For example, a patient with a suspected rectus abdominus contusion might in reality have a partial tear of the spleen. A patient with a suspected contused rib may in reality have a small pneumothorax. One of the patients in study 02 actually had a fractured toe instead of a contusion. This patient sought definitive care from a physician but remained on therapy for 14 days. Although these risks exist for any analgesic, the psychological disconnect of a topical NSAID being used as monotherapy (local therapy) increases concern over potential masking

D. Dosing

The sponsor provided no specific pharmacodynamic studies with DHEP in support of their NDA. Instead, the foreign experience was relied upon for choice of dose. Because no treatment effect was established it is difficult to assess whether this was due to a simple lack of efficacy or the fact that the concentration of active drug is not high enough in the patch. It is worth mentioning here that only 5% of the active drug is actually released from the patch in any 12 hour period; and this translates to approximately 9 mg (18 mg/day if using proposed BID dosing). Effective oral analgesic doses of diclofenac range from 50-200 mg/day. Typically these dose range issues are addressed in phase II studies where dose-toxicity and dose-response are determined. Specific comment on dose modification and relationship to known pharmacology cannot be made, quite simply, because data has not been presented for analysis.

E. Special Populations

The targeted population for this product is adults No gender, ethnic or racial differences regarding safety were discovered in the US trials. The trials did not attempt to specifically determine if any differences actually existed, but based on the demographic data and safety outcome of the trials no signal was seen. Since efficacy was not demonstrated, no comment is possible regarding special populations.

Patients with hepatic or renal disease were not studied in the trials. Given the potential for concomitant use of oral NSAIDS in this population, drug interaction studies with DHEP and oral NSAIDS should be addressed.

Pediatric and pregnant patients were not studied as part of the US clinical trials. In the sponsor's proposed package labeling it states that DHEP

he label also states that DHEP should be avoided in late pregnancy This language

This is not the case with DHEP and the label should simply state that th

Topical NSAIDS for the pediatric population seem like a natural extension for this product. In Italy DHEP is indicated for children. If the product can at some point demonstrate efficacy in the adult population then pediatric studies should be conducted to address the pediatric rule. The sponsor has not addressed the pediatric rule with the current NDA.

Based on the clinical review this drug appears safe if used as directed but has not demonstrated superiority versus placebo in the treatment of strains, sprains, and contusions. Multiple deficiencies are detailed in the Chemistry, Pharm/tox, PK and Statistical reviews. From a chemical standpoint very little of the active substance is actually released from the patch and what is released has only nanogram quantities of penetration through the skin to potential sites of action.

The first pivotal trial (Study 01) submitted for efficacy failed on all primary efficacy endpoints. The second pivotal trial (Study 02) employed a study design that has not been validated and was only able to demonstrate statistical differences by using a post-hoc statistical analysis that was not included with the original protocol.

The sponsor's failure to account for excess body weight in the placebo arm of study 02 was problematic; and as described above, this excess weight issue eliminated any separation from placebo despite the post-hoc statistical analysis provided by the sponsor. The clinical relevance of the study design is not supported by the data. From a clinical perspective DHEP should not be approved.

CLINICAL REVIEW

I. Introduction and Background

A. Purpose Statement

Diclofenac Epolamine Patch (Trade name: *PATCH*) is an NSAID class topical patch containing 1.3% Diclofenac epolamine. Each patch contains 180 mg of diclofenac as the active ingredient and is indicated for twice daily usage for up to 14 days in the treatment of pain associated with [redacted] sprain, strain, contusion). The product is applied at the site of injury to intact skin in adults. The product has been studied as a stand-alone analgesic and not in use with other oral NSAIDS.

B. State of Armamentarium for Indication(s)

The indication for [redacted] Patients will often take OTC pain relievers such as aspirin, ibuprofen, or acetaminophen to treat the pain associated with a strained muscle or sprained ankle. If a patient feels the need for stronger analgesia then narcotic based prescription analgesics are available. Because these injuries, [redacted] are usually self-limiting, the patient will typically self-medicate for a few days and reduce the use of oral medication as a titration.

Topical products such as *BenGay*, *Flexall 454*, and *Icy Hot* are available OTC in the US market. These pain salves rely on counter-irritation to "fool the hurt" by creating a superficial feeling of cold or heat over a sore muscle (Consumer Reports, 1998). Methyl nicotinate and methyl salicylate cause the skin to feel hot while menthol and camphor make the skin feel cold. Other topical OTC creams like *Aspercreme*, *Myoflex*, and *Sportscreme* feature trolamine salicylate (a cousin of aspirin) as the active ingredient. Robust clinical evidence to support the claim that trolamine actually penetrates skin to provide a truly local effect is lacking. It is highly questionable how much of the product actually reaches the muscle or joint underneath the application site.

OTC Capsaicin based products like *Zostrix, Capsagel*, and *Capzasin-P* rely on the counter irritant effect of heat to "fool the hurt". Decreasing transmission of afferent pain signals to the brain is thought to be the primary mechanism of action of these creams. These products are used most often in neuropathic pain states such as shingles and *diabetic* neuropathy although "simple backache" and "sprains and strains" language appear in some labels.

Many of the OTC products [redacted] mention sprains, strains or arthritis specifically in their label. The general language used in these labels or the PDR suggests that the products are safe and

provide "temporary relief" of these minor injuries or arthritic related conditions. The 1999 PDR language for Doublecap™ states that *"Capsaician is so effective it is the #1 doctor recommended topical analgesic"*. According to a company spokesman, this product is no longer marketed by Breckenridge Pharmaceutical Inc.

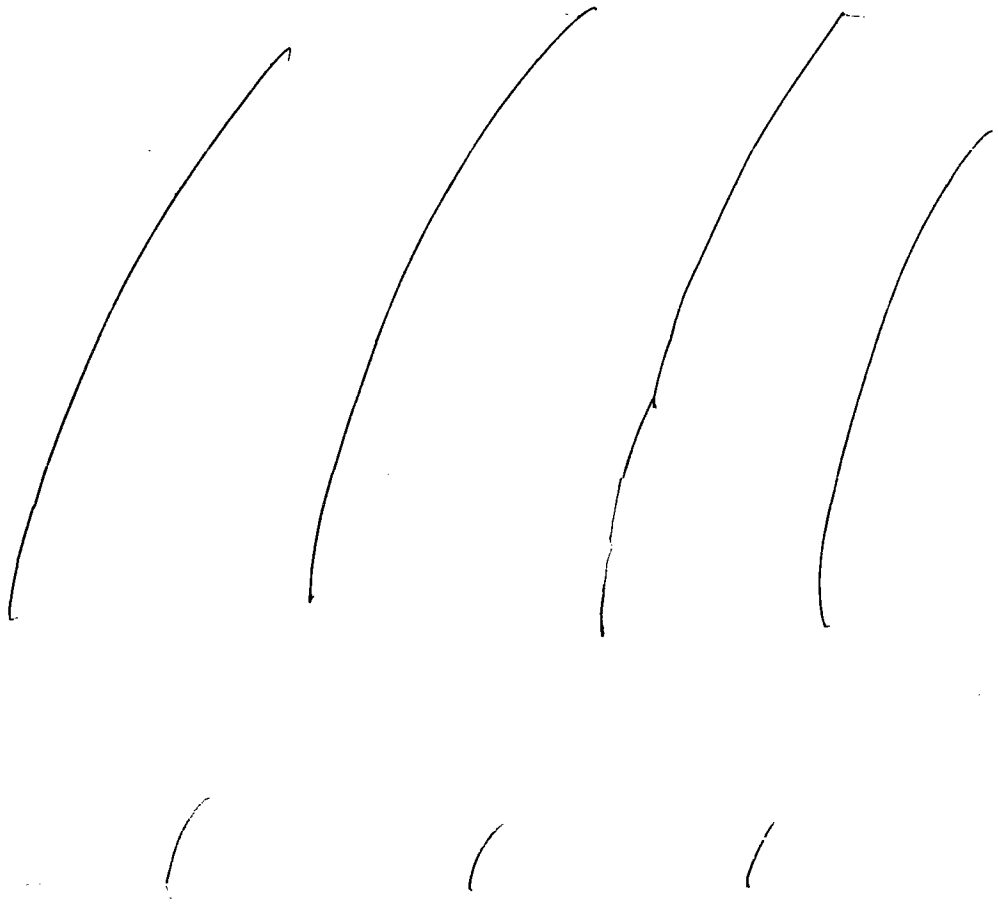
The aforementioned listing of topical analgesic products is not meant to be all inclusive but does show that topical NSAIDS have been approved in OTC creams despite their unproven clinical utility. Topical NSAID *patches* have thus far been limited to oversees marketing in both OTC and prescription formulations.

C. Important Milestones in Product Development

1) Submitted to the division electronically on Dec 20, 2000

2) Assigned to Dr. Stauffer on Jan 18, 2001

3) Originally submitted to the division in December 1995 as IND # 49,459. The original indication sought by the sponsor was



4) An EOP2 meeting was held with the sponsor on June 16, 1998. As per the FDA meeting minutes, the sponsor was informed that the results for Study 01 did not show a positive result based on preliminary review of data provided in the

background packet. It was also clarified by the division that: *"The success of the study is based on the strength of the analysis. For a clear primary analysis the sponsor should use pain alone as the endpoint."*

5) A pre-NDA meeting was held with the sponsor on Feb 1, 2000. This meeting addressed issues regarding formatting of the electronic NDA submission and did not contain any discussions regarding clinical content of the NDA

6) A second pre-NDA meeting was held with the sponsor on March 28, 2000. It was at this meeting that the division expressed significant reservations regarding the two pivotal trials (49,459-01 and 49,459-02) identified by the sponsor. Basically, the first pivotal trial failed on its primary endpoints. Results from the second pivotal trial were not presented to the division at that time. The sponsor was told at the meeting that post-hoc analysis of the data from the first study was problematic. From Larry Caldwell's April 10, 2000 meeting minutes it is clear that the sponsor needed to resolve this issue as reflected in this quote from those minutes: *"during the discussion between the Agency statistical team leader, Stan Lin, and the statistician for the sponsor, John Quiring, the mechanism for positioning the first study (No. 49459) as supportive was not resolved. The sponsor requests that this issue be discussed more in depth than time allowed during the meeting. We would like to hold such a discussion, either in person or by phone conference, after the results of the second study (No. 49459-2) are known but before the filing of the NDA".* According to Dr. Lin's recollection, no subsequent phone conversations or meetings ever took place between himself or Larry Caldwell or John Quiring prior to the NDA filing. There is no record of any subsequent communication, either formal or informal, of the proposed discussions. The NDA was submitted nine months later

7) The sponsor was advised to submit their dermal safety information to the division prior to the NDA so that the Dermatology division could consult on the data. This was not done.

8) Post NDA submission: Dr. Rowbotham's site was chosen as the field investigation site as a routine exercise in the auditing of investigators during the review process. This study site had the highest enrollment and the only statistically significant data for average daily pain score in study 02

9) A tele-con with the sponsor was held on June 29, 2001 to discuss problems with the statistical analysis which became evident after the field investigation. Briefly, the raw data from study 02, at all four study sites, did not translate in any meaningful way to the tabulated data presented in the NDA.

10) A second and third tele-con was held with the sponsor on July 16, 2001 and July 24, 2001 to once again fully understand how exactly the sponsor analyzed the data

from study 02. The statistician for the sponsor acknowledged that the pre-specified statistical analysis was not followed. A programming error was also identified. These issues were not resolved in any acceptable way thus raising concerns over the quality of the data analysis.

D. Other Relevant Information

This drug is approved in at least 9 European countries, 8 Latin American countries, Singapore, Hong Kong, Israel, and Lebanon. No data from the NDA suggests that the product was ever rejected for registration for safety or efficacy reasons. The indications vary somewhat between countries but all focus on musculoskeletal derangements. For example, the Italian label is quite specific:

INDICATIONS
FLECTOR TISSUGEL can be used for the topical treatment of:
- Isolated rheumatological inflammatory peri-articular/tendinous disorders (tendinitis, bursitis, epicondylitis, peri-arthritis)
- extra-articular rheumatological inflammatory disorders (fibrositis, myositis, torticollis)
- rheumatic-degenerative painful diseases in arthritis area (gonarthrosis, coxarthrosis)
- inflammatory pathologies originating from traumas (contusions, sprains, strains, dislocations)

The French label is more general:

INDICATIONS
FLECTOR TISSUGEL is indicated for symptomatic short-term treatment of painful events of gonarthrosis and the treatment of tendinitis of upper and lower limbs

A large portion of the current sales come from Italy and Switzerland, which account for about —— patches per year.

E. Important Issues with Pharmacologically Related Agents

Topical NSAIDs have been available in Europe, South America, and Asia since the 1970's. Various creams, gels, and plasters have been prescribed to treat dysmenorrhea, OA, RA, nonspecific musculoskeletal pain, and ankylosing spondylitis. Many of these products are available as OTC patches. It is estimated that nearly 20% of people taking oral NSAIDs will develop side-effects. Approximately 75,000 people per year with OA or RA are hospitalized in the US due to GI bleeding caused by oral NSAIDs. The FDA suggests 10,000-20,000 deaths annually can be explained by NSAID use (Paulus,1985).

Much of the human experience with 1% dermal diclofenac comes from a European gel formulation, Voltaren Emulgel®. This product is approved for inflammation of tendons,

ligaments, muscle and joints, and localized forms of degenerative and soft-tissue rheumatism. In published literature a few cases of contact dermatitis have been reported with topical diclofenac. Photo-allergic contact dermatitis and maculopapular eruptions caused by delayed hypersensitivity to diclofenac have been observed. These cases may have involved allergy to the active drug or to the vehicle of the gel. Four cases of GI hemorrhage have been reported by Zimmerman et al in 1995. Two of these patients required blood transfusions prompting the authors to recommend caution when prescribing topical NSAIDs to patients with a history of peptic ulcer. In severe renal impairment, 50 mg/day PO of diclofenac for two days can show a 4-fold increase in the total conjugated metabolites versus individuals with normal renal function. In addition, because diclofenac undergoes significant hepatic metabolism, there may be important PK variations in patients with hepatic disorders (hepatitis, cholestasis, cirrhosis, and ascites). The mechanism for diclofenac-induced hepatotoxicity is still unclear although an allergic mechanism has been proposed because of the associated eosinophilia and skin rash seen in some patients (Ramakrishna et al. 1994). Diclofenac has a low volume of distribution (Vd), therefore much of the intact drug distribution beyond the peripheral circulation or central compartment is very small. The concentrations of diclofenac in cerebrospinal fluid are 8.22% of those in plasma, showing it does not easily cross the blood-brain-barrier.

REVIEWER'S COMMENT: The vast majority of the existing toxicity data is from oral diclofenac. With oral diclofenac (usual dose 50-200 mg/day), the overall incidence of side-effects has been reported to be about 30% (Biscarini, 1996). Up to 20% of regular NSAID users can be expected to develop an ulcer. If in fact the transdermal delivery of NSAIDs can be just as effective as oral or intravenous/intramuscular injection, and carry a better safety profile, then a significant addition can be made to the analgesic options for OA patients with localized symptoms at a single joint. Likewise, if DHEP were able to demonstrate a clinically meaningful effect for an acutely inflammed joint or soft tissue injury then the analgesic options for patients who can't tolerate oral NSAIDS would be expanded. The topical delivery route would be especially helpful in children with these sorts of injuries.

II. Clinically Relevant Findings from Chemistry, Animal Pharmacology and Toxicology, and Biopharmaceutics

There appear to be no Chemistry, Manufacturing, and Control issues that specifically impact the safety of this product. The impact on efficacy however is another issue; and for a background on the chemical-clinical reason for selecting DHEP as the lead agent I have included a quote from the sponsor's Efficacy Summary (vol 9, p5-6) in the NDA:

"The rationale for using a topical formulation of diclofenac epolamine for treating the [redacted] any other localized inflammatory condition for that matter) is two-fold. First, the amount of drug substance that will be absorbed and systematically distributed following application of a pharmaceutical product to the skin is substantially less than for orally or parenterally administered therapeutic agents, an important consideration given the inherent toxicity of the NSAIDs, particularly when they are taken over a protracted period of time. Secondly, it has been recently shown [redacted]

s. The high water solubility of this particular diclofenac salt form assures that it would be completely dissolved in any gel-like topical preparation and, therefore, available for rapid absorption, while its surfactant properties should further facilitate transdermal penetration through enhancement of membrane permeability".

REVIEWER'S COMMENT: The theory described above is not supported by the PK evidence given that only 5% of the active drug is actually released from the patch.

For a detailed review please see Sue-Ching Lin's Chemistry review.

The Animal toxicology was reviewed by Dr. Amouzadeh. For a complete detailed analysis please see his review. The italics below are taken directly from his summary:

In a rat model, DHEP patch and gel applied topically were effective in inhibiting carrageenan-induced paw edema.

Both acute and chronic oral toxicity studies were performed in rats and dogs. DHEP displayed toxicity attributable to the diclofenac moiety, while EP alone displayed toxicity only at doses higher than those encountered from conventional oral dosage.

ADME studies in the rat suggest a saturable metabolic pathway for the EP moiety, but steady state blood levels are still achieved with chronic dosing.

Topically, DHEP gel is slightly irritating to rabbit eyes. Neither the DHEP patch nor the gel is irritating to rabbit skin.

Several in vitro genotoxicity studies elicited no evidence of genotoxicity when the test articles were present at reasonable concentrations.

Reproductive toxicity studies in rats and rabbits produced no remarkable observations with F0, F1, and F2 generations.

MEDICAL REVIEWER'S COMMENT: From a clinical perspective these findings do not have any negative impact for human exposure. Mild skin irritation seen in some of the animal models is consistent with the side-effect profile seen in the marketed products oversees.

The Biopharmaceutics review was done by Dr. Tandon and her analysis and recommendations are summarized (italics, directly quoted) below:

The NDA is unacceptable from the Office of Clinical Pharmacology and Biopharmaceutics perspective. The labeling recommendations have been deferred until the application is found acceptable by the review team.

Deficiencies:

- *The pivotal biostudy (#910195) that measures exposure from the diclofenac epolamine patch does not have a complete assay validation report associated with it. It lacks information on inter- and intraday precision/accuracy, stability and recovery. This study is of no regulatory significance in it's current form and cannot be used for labeling purposes.*
- *Study report PK-0033 lacks information on long term stability of plasma samples.*
- *Study PK-9814 lacks an assay validation report. The methodology and lower limit of quantification differ from Study 910195 and PK-0033.*

The results from all these studies are unevaluable until the sponsor provides a complete acceptable assay validation. The results can be accepted for labeling only after the assay validation has been found acceptable

MEDICAL REVIEWER'S COMMENT: From a clinical standpoint these deficiencies do not impact the overall decision regarding approvability. However, a brief clinical discussion of the PK/PD will follow in the next section

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

The bioavailability and PK of several 1% diclofenac gels, creams, patches and solutions have been reported in the literature. Davies and Anderson, 1997 describe a study where healthy volunteers received 1% diclofenac cream on the back. The drug was detectable in plasma(1.3 µg/L) 2 hours after application, remained steady at 6-10 µg/L, and decreased to 0.4 µg/L 98 hours after the last application (probable BID dosing). Another study described by the same investigators showed diclofenac gel applied to 1 knee of patients with bilateral knee effusions had uptake (about 85% of the peak concentration) in the contralateral(non-treated) knee. Locally enhanced topical delivery (LETD) may allow drug penetration directly to the site of action while minimizing systemic toxicity (McNeill et al 1992). LETD does occur in humans in the skin, subcutaneous fatty tissues, and muscle. The evidence is inconclusive whether LETD occurs in deeper tissues such as the synovial joint (Grahame, 1995). Synovial membrane is the proposed primary site of action for NSAIDs in RA and OA. Phospholipid systems for topical diclofenac products may act as penetration enhancers, thereby augmenting the uptake of drug through the stratum corneum and into other epidermal components/local blood supply. Stratum corneum partitioning is the rate limiting step in percutaneous penetration (Martin M. Okun, MD. Ph.D., Former Clinical Team Leader, Division of Dermatologic Drug Products, FDA, internal communication).

The basic PK properties for DHEP were explored in **Study # 910195**. It should be noted that this study was conducted with Flector-EP plaster *(a product similar to DHEP patch*

but not the to-be-marketed product. Flector-EP plaster contains 188.5 mg of active product versus 180 mg of active product in DHEP):

Study # 910195 : DHEP was applied to the upper backs of 10 healthy volunteers Q12 for 7 consecutive days and for 12 hours on the eighth day. Mean plasma concentration was 7.9 and 8.2 ng/ml 12 hours after the eighth application (day 4) and fourteenth application (day7), respectively, suggesting that trough levels of drug had reached steady state. Eight of the 10 subjects had detectable plasma levels 24 hours after final patch application, but by 48 hours only two subjects had detectable levels.

Mean Diclofenac blood levels after twice daily application for 7 days, with a final 12-hour application on day 8 of DHEP Patch to healthy volunteers (n=10). Blood samples were taken: a single sample on day 5 (data point at t = minus 12 hours), and from the time of dosing on day 8 at t = 0, 1, 2, 3, 4, 6, 8, 10, 12, 24, and 48 hours.

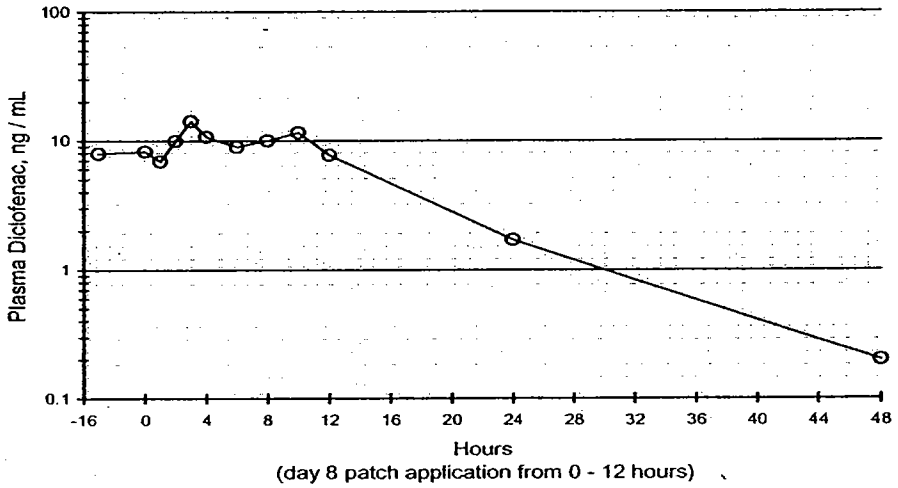


Figure 1. Mean Diclofenac Blood Levels after BID dosing for 7 days

Residual diclofenac in the patch after a 12 hour application was explored in **Study #003**:

This trial was conducted in 20 healthy volunteers (10M & 10F, ages 20-62) to evaluate the drug-release of diclofenac after a 12-hour topical application period of a plaster containing diclofenac hydroxyethylpyrrolidine (DHEP) in humans. The flector-EP plaster was applied topically for a total duration of 12 hours on the forearm of each subject. The mean (%CV) DHEP content (mg/plaster) before topical treatment was 185.78 mg (2.6%). The mean (%CV) residual DHEP content after 12-hour topical application was 176.73 (3.46%), suggesting that 95.1% of DHEP remains in the plaster.

The diclofenac plasma concentration from the patch is about 500 times lower than that after a 50 mg oral dose of diclofenac sodium. About 95% of the DHEP remains in the patch, suggesting less than 5% of the total drug in the patch is available for absorption.

In an effort to substantiate the claim that DHEP works locally the sponsor referenced a 1993 article entitled:

Pharmacokinetics of Diclofenac Hdroxyethyl-pyrrolidine (DHEP) Plasters in Patients with Monolateral Knee Joint Effusion (Publ: Gallachi, Drugs Exptl. Clin. Res. XIX(3) 97-100, (1993)

This study on the pharmacokinetics of diclofenac hydroxyethyl-pyrrolidine (DHEP) plasters in patients with monolateral knee joint effusion showed that DHEP was well tolerated during the 5-day treatment period. Drug concentrations in synovial fluid were detectable (1.02 ng/ml) although lower than those found in plasma (3.74 ng/ml). The absorption of diclofenac after the last dose on the 5th day of treatment varied among the 8 patients. Differences in individual skin conditions should be considered to account for the lateral variability. Four hours after the application of DHEP plaster, a statistical difference between plasma and synovial fluid diclofenac concentrations was observed ($p<0.05$), the average concentration of drug in the synovial fluid being 35.9% of that found in plasma. By comparison, the AUC and C_{max} following a 50 mg single oral dose of Voltaren® is 1429ng-hr/ml and 1417ng/ml, respectively.

In the above study patients were dosed every 12 hours for five days but were not assessed for pain relief.

REVIEWER'S COMMENT: The aforementioned PK studies reveal significant problems with DHEP. The graph demonstrates that only nanogram/ml levels of active drug are present in the plasma after a 12 hour period. From a safety standpoint this is desirable, but from an efficacy standpoint it demonstrates a possible explanation for the lack of clinical analgesic effect. If so little drug is available in the plasma then one might expect a large concentration in the synovial fluid or membranes based on proximity to the topical application. This was not the case in the above study because even ***less*** *diclofenac is found in the synovium. Recall that synovial fluid diclofenac concentration is only 35.9% of the plasma concentration. One must believe that only nanogram levels of active drug at the site of injury can account for a clinically meaningful benefit. The knee joint effusion study did not attempt to correlate any analgesic effect with synovial fluid concentration of DHEP. The fact that only 5% of active drug (approximately 9mg at steady state) can be released from one DHEP patch may account for such low synovial fluid levels. Recall that the approved oral dose of diclofenac is 50 –200 mg per day.*

Basic PK properties of DHEP are as follows:

Diclofenac (anion)
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 the urine, and approximately 35% in the bile.

Epolamine (cation)
Single and multiple doses of DHEP granules (50 mg), corresponding to 18 mg of epolamine, were orally administered to human volunteers (Study # PK9814). Epolamine

was rapidly absorbed after each dose with C_{max} – 11.7 ±3.7 ng / ml, and t_{max} = 0.34±0.12 hours. Epolamine was nearly completely eliminated in urine, relative to the dose administered, within 24 hours of dosing: 1.5% as unchanged epolamine, and 93.5% as epolamine N-oxide, the principal metabolite.

The potential for transdermal diclofenac to interact with other NSAIDS exists, as evidenced from oversees safety reports. This is also true with regard to how this drug may act if used in patients with impaired hepatic and/or renal function. The pivotal US trials with DHEP did not include patients with abnormal LFTs or reduced kidney function therefore its safety in this patient population is unknown. Effects of body weight/fat, gender, race were not explored specifically in the clinical trials although no significant differences or trends were detected upon review of the data.

B. Pharmacodynamics

The sponsor did not include any pharmacodynamic studies with DHEP as part of the NDA. Therefore no comment can be made regarding dose-response, mechanism of action, or dosing interval. Because no treatment effect was established one can only speculate on the explanations for failure in the pivotal trials. Clearly, if efficacy were to be demonstrated, then further studies would be needed to elucidate the PK/PD relationship.

IV. Description of Clinical Data and Sources

A. Overall Data

The NDA was submitted electronically and in hard copy format. Included were two pivotal phase III trials, four phase I skin sensitivity/safety studies and six PK studies. Also included were 20 studies or study reports from various efficacy trials done in Europe. Not all the studies were properly controlled or randomized, and some were open label. Some of the reports were in German or French and therefore not evaluated. The tabulation and organization of these supporting documents was poor and it is unclear if any of these supporting studies were actually done with the to-be-marketed product, DHEP. This data was treated as background information.

B. Clinical Trials

The table below summarize the clinical trials (non-PK) presented in the application:

Table 1. Clinical Trials

Phase III Pivotal Trials	Sponsor's Results (ITT analysis)		
Study (49459-01) – randomized, double-blind, placebo controlled 2-center study. 222 patients randomized, 213 in ITT analysis. Patients wore DHEP for 14 days with BID dosing. Most common injury was ankle sprain (27%). Measurements were taken at days 3, 7, and 14	Primary endpoints (4)	lowest p-value	(day)
	Pain intensity difference	0.108	3
	Summed pain intensity diff.	0.109	14
	Pain on pressure difference	0.463	3
	Summed pain on pressure diff.	0.451	3
Study (49459-02) – randomized, double blind, placebo controlled 4-center study. 411 patients randomized, 372 in ITT analysis. Patients wore DHEP for up to 14 days with BID dosing. Most common injury was ankle sprain (23%).	Primary endpoint (1)	DHEP	Placebo
	Days to pain "resolution" Measured at 4 consecutive 12 hour time points. Rating ≤ 2 on a 0 thru 10-point pain scale is considered a "success" p-value =0.016	day 9	day 12.3
Phase I Dermal Safety Studies	**Sponsor's Results**		
Study C11080 - 21 day cumulative irritancy study in 20 volunteers using Flector EP Tissugel (European product)	Relative irritation scores out of a possible 1200 Was 0.0 and therefore deemed non-irritating		
Study C1108 - Phototoxicity study in 20 volunteers using Flector EP Tissugel (European product)	Subjects wearing the patch were exposed to UV light for 24°, 48°, and 7days. Skin irritation scores considered non-phototoxic by sponsor		
Study B9356 – Photo-allergenicity study in 27 volunteers using Flector EP Tisssugel (European product)	Subjects wearing the patch were challenged 6 times (twice weekly) with UV light. Skin reaction scores were taken at 24° and 72° and deemed non-photo-allergenic		
Study 006-91 – Hypersensitivity study in 25 volunteers using DHEP (similar to US to-be-marketed product). Study done in 1991 and used a placebo control patch	Subjects exposed to patch for 3 weeks, changing the patch every 48 hours. No descriptive statistics reported but sponsor claims no immediate/delayed reactions seen		

C. Postmarketing Experience

Postmarketing data from Oversees was included in the NDA: (see italics below and table next page, NDA vol. 1, *Labeling* tab)

Foreign Marketing/Label History

Diclofenac Epolamine Patch was first approved in Switzerland in 1993, and has subsequently been approved for marketing in a number of European, Latin American, and Asian countries. A large portion of current sales come from Switzerland and Italy, which together account for about — envelopes, o — patches per year. The total distribution in all territories to date has been approximately — envelopes, or — patches. The table below lists approved marketing registrations at the time of this writing.

Table 2. Foreign Marketing

COUNTRY	REGISTRATION DATE	REGESTRATION NO.
Europe		
SWITZERLAND	6/25/1993	52'022
SLOVAK REPUBLIC	7/25/1994	29/0472/94-S
FRANCE	8/22/1994	AMM 337 830
HUNGARY	5/7/1996	OGYI-T.: 5032
ITALY (2 REGISTRATIONS)	9/5/1996	AIC 027757032 (5) AIC 027757044 (10)
CZECH REPUBLIC	9/25/1996	29/361/96-C
GREECE	6/11/1997	35545/96
AUSTRIA	10/7/1999	1-23243
BELGIUM	1/17/2000	152 IS 217 F 16
Latin America		
ARGENTINA	7/10/1995	36'917
COSTA RICA	4/1999	3301-VH-7990
GUATEMALA	3/1999	PF-21159
PANAMA	4/1999	49872
COLOMBIA	3/1999	M012530
MEXICO	11/1998	530M98
PARAGUAY		02950/119701
ECUADOR	4/1998	22.035-04-98
Asia		
SINGAPORE	1/28/2000	SIN11270P
HONG KONG	1/3/1996	HK-39900
ISRAEL	2/1998	1089328525
MYANMAR	9/4/2000	050817192
Middle East		
LEBANON	11/16/2000	236711/99

D. Literature Review

The sponsor provided 20 additional studies in their literature review. This section of the NDA was not tabulated and not all reports were in English. All of these studies were from Europe and only 13 were placebo controlled. Only one study tested DHEP specifically in children (mostly adolescents) and this was open label, retrospective, and primarily an anecdotal experience report by the author. Many of the controlled studies were poorly controlled and did not account for concomitant medication, crutch use, ice, immobilization, ace wraps, or casts. These studies were regarded as background information, and in general, did not lend positive support to DHEP as an effective analgesic. This reviewer conducted a PUBMED and MEDLINE search using the key words: diclofenac, pain, sports, sports injury, pediatric, topical, and local. The original article published in the April 2000 issue of the *Journal of Pain and Symptom Management*, which describes the results of Study-01, was not included in the sponsor's literature review.

V. Clinical Review Methods

A. Focus of Medical Review

Both pivotal Phase III trials were thoroughly reviewed. The primary emphasis for this review was ascertaining efficacy from these two trials. The four dermatologic phase I studies were reviewed collectively and are summarized in the integrated safety analysis. Other materials reviewed included papers from various literature sources (see references) and the 20 supporting studies included with the NDA as described previously.

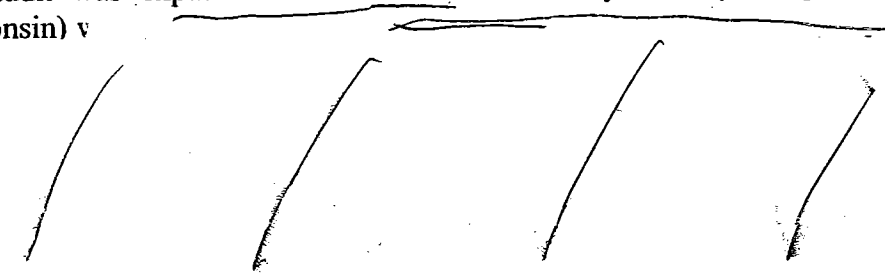
B. Documents Consulted During Review

All administrative correspondence between the sponsor and the division dating back to 1995 was reviewed for this NDA. This correspondence related to the current submission as well as IND# 49,459 which was the original submission by the sponsor for DHEP. The Clinical review for NDA# 20-612 was also consulted as this was the first product (Lidocaine patch, Hind Healthcare,Inc.) that the sponsor had successfully negotiated through the division. Dr. Rowbotham and Dr. Galer were primary investigators for some of the pivotal efficacy trials during the development of Lidoderm® patch and were both principal investigators for pivotal trials relating to DHEP. Dr. Larry Caldwell served as the representative for Hind Healthcare. From an historical perspective this data was important because topical analgesic development is still an evolving process, particularly in terms of validated efficacy parameters for pain.

C. Data Quality and Integrity

A routine DSI audit was requested because this product is considered a new chemical entity. Because the first pivotal trial (49,459-01) failed to demonstrate efficacy, audit selection was based on the clinical site (Dr. Rowbotham, UCSF) that enrolled the largest amount of patients for study 49,459-02. This was the only site that had what appeared to be a positive trend favoring DHEP in terms of *average daily pain scores*. These *average daily pain scores* represent the data used to derive the primary efficacy endpoint.

The audit was expanded to the other three study sites (Chicago, New York, and Wisconsin) v



2 Page(s) Withheld

_____ Trade Secret / Confidential

_____ Draft Labeling

✓ Deliberative Process

D. Ethical Standards During Conduct of Clinical Trials

It appears from the data in the NDA that no patients were harmed in any way during the trials and that appropriate informed consent was obtained at the study sites. Clearly there had been a change from protocol during the statistical analysis that the sponsor has acknowledged, thus prompting the heightened importance of late review cycle exchanges between the sponsor and the FDA. This admission by the sponsor of not following the pre-specified statistical protocol came only after the first DSI field investigator (San Francisco) called me to clarify the raw data she had reviewed did not "match up" with the tabulated data presented in the NDA. No protocol amendments or clarifications were submitted. When the investigators at the individual clinical sites (Rowbotham and —, were asked about the data discrepancies they stated that they stood by their data and that any questions should be directed to the sponsor, Larry Caldwell.

The data integrity from the Chicago site is under DSI review at this stage because of the field investigator's findings and the inability to corroborate whether or not patient diaries were actually completed by patients actually enrolled in the trial. After speaking with Dr. Carreras (Rockville, FDA, DSI) today, August, 20 2001, he stated he will —

— It should be stated here that Dr. — was cited by DSI in 1998 where during an unrelated clinical trial he enrolled two patients that did not meet inclusion criteria; and for not performing an investigative analysis/cultures in two patients. This unresolved issue stands as one of many clinical deficiencies with this product.

One final observation regarding regulatory deficiencies is reflected (in this case not included) in the NDA submission. The results from study 01 failed on all primary endpoints as noted by the sponsor. The results of that study appeared to be published in a refereed journal, *Journal of Pain and Symptom Management*; vol 19(4) in April of 2000. The abstract from that article is presented below:

> *Sports-related soft tissue injuries, such as sprains, strains, and contusions, are a common painful condition. Current treatment includes oral nonsteroidal anti-inflammatory drugs (NSAIDs), which have a high incidence of intolerable gastrointestinal side effects. Topically applied drugs have the potential to act locally in the soft tissues without systemic effects. This study assessed the efficacy and safety of topical diclofenac (NSAID) patch applied directly to the painful injury site for the treatment of acute minor sports injury pain. Adult subjects (N = 222) were recruited from two communities for a multicenter, randomized, placebo-controlled, parallel design study. All subjects had suffered a painful minor sports injury within the prior 72 hours of study entry. Either a diclofenac epolamine or placebo topical patch was applied directly to the skin overlying the painful injured site twice daily for 2 weeks. Measures of pain intensity were performed in a daily diary and at clinic visits on days 3, 7, and 14.* ***Diclofenac patch was superior to placebo patch in relieving pain.*** *Statistical significance was seen on clinic days 3 (P = 0.036) and 14 (P = 0. 048), as well as the daily diary pain ratings at days 3, 7, and 14 (P < or =0.044) .No statistically significant differences were seen in any safety or side-effect measures with the diclofenac patch as compared to the placebo patch.*

Diclofenac epolamine patch is an effective and safe pain reliever for treatment of minor sports injury pain. *The advantages of this novel therapy include its ease of use and lack of systemic side effects.*

This abstract presents the data in a very positive light with statistically significant results and yet none of the p-values cited in the abstract appear in the NDA data set. Was ***all*** the data presented to the journal reviewers? This question will be further explored in the efficacy review section of this NDA. In addition, there is no mention of this article in Dr. Rowbotham's CV; and in Dr. Galer's CV it only states that this article was submitted for review to JAMA. This article appeared in the April 2000 issue of *Journal of Pain and Symptom Management* and the NDA was filed in December of 2000. Whether this is a simple oversight in updating the CV's of primary investigators or omitted by design remains unclear. Over eight months had passed between the publication of that article and the NDA submission date.

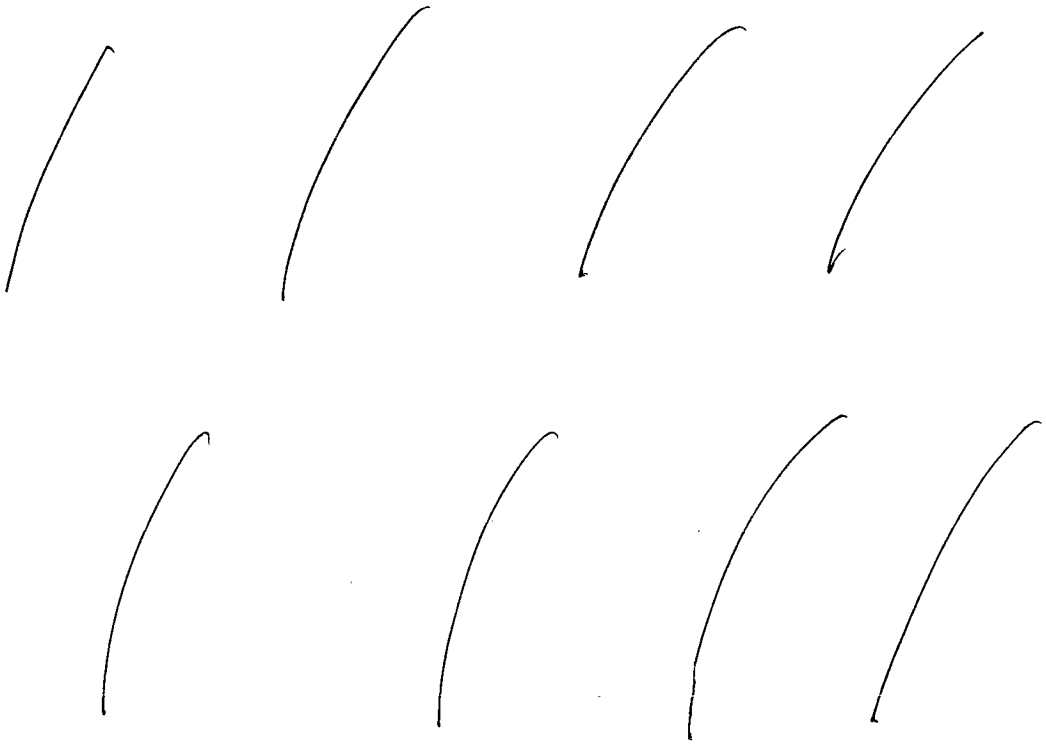
E. Financial Disclosure

There were no financial disclosures that cast doubt on any of the findings.

VI. Integrated Review of Efficacy

A. Medical Officer Conclusions and Critical Differences from Sponsor's Proposed Label Claims

The Sponsor's efficacy labeling language is taken from the proposed package insert and presented below (italics):



The data from the pre-specified primary intent-to treat analysis clearly demonstrates that DHEP did not separate from placebo as evidenced from the table below which was presented in the NDA (Vol 9, page 88):

Table 3. Primary Efficacy Data Study 01

Primary Efficacy Variable Analysis
Clinical Visit With Investigator
Intent-to-Treat Patients

	ACTIVE			PLACEBO			
	LSMEAN	STDERR	N	LSMEAN	STDERR	N	P-VALUE[a]
Pain Intensity Difference (PID)							
Day 3	2.69	0.18	106	2.27	0.18	106	0.108
Day 7	4.00	0.20	106	3.66	0.20	106	0.228
Day 14	5.25	0.18	106	4.87	0.18	106	0.132
Summed Pain Intensity Difference (SPID)							
Day 3	8.40	0.53	106	7.26	0.53	106	0.132
Day 7	24.58	1.23	106	22.13	1.23	106	0.161
Day 14	61.30	2.27	106	56.15	2.27	106	0.109
Pain on Pressure Difference (POPD)							
Day 3	1.22	0.36	105	1.59	0.36	105	0.463
Day 7	2.44	0.36	105	2.61	0.36	105	0.747
Day 14	3.89	0.38	105	3.87	0.38	104	0.970
Summed Pain on Pressure Difference (SPOPD)							
Day 3	4.13	1.03	105	5.24	1.03	105	0.451
Day 7	14.04	2.26	105	15.91	2.27	104	0.560
Day 14	41.26	4.60	105	42.79	4.62	104	0.814

[a] P-values from a two-way analysis of variance with factors of treatment and site.

The efficacy labeling language [redacted] iled randomization with [redacted]. At the request of HFD-550, the official explanation from the sponsor's statistician regarding the protocol deviation can be found in his own words communicated via fax to the division on July 16, 2001. See shaded paragraph below:

The second question relates to the analysis of category pain scores by day. The protocol states " An analysis of the category pain scores by day will be performed. The last value of category pain will be carried forward for those patients who discontinue before the end of the 14-day treatment". Procedural aspects of the clinical trial complicated this analysis, which relate to the manner in which the patients enter the trail (sic). Some entered the trail (sic) in the morning while others entered in the afternoon. The case report form asked the patient to record patch 1 and 2 for a nominal day (1, 2, 3, etc). The difficulty in the deceptively simple statement in the protocol describing the analysis is the definition of "day". Two interpretations of "day" are possible. Day could refer to the nominal day that is found on the case report form or "day" could refer to 24-hour periods since the application of the first patch by the investigator at baseline exam. The "day" of the observation will differ for some patients depending on which definition of "day" is used. The difference is usually no more than a half of a day due to the am/pm enrollment time.

In a second fax to the division on July 23, 2001 the sponsor's statistician once again attempted to explain how he derived the final data for the average daily pain scores in **Study 02**. See shaded paragraph below in his own words:

An explanation of the method used to calculate the average daily pain for each subject can be found in 02 report.pdf in the last two paragraphs on page 32, continuing on the top of page 33. However, during review of the analysis, it was discovered that the implementation of these methods was not followed exactly and there was also a programming error. The following presents an expanded description of how the average daily pain scores were computed. First, the elapsed times between the baseline observation and subsequent diary observations were computed and organized into 24-hour periods. The observations that fell within the first 24-hour period were associated with Treatment Day 1. Those that fell within the second 24-hour period were associated with Treatment Day 2 and so on. Second, when subjects stopped treatment and hence stopped recording data, the subsequent data through the 14-day study period was set equal to zero. This method was used to extrapolate all of the patients' data to the end of the study, rather than carrying the last observation forward. Third, due to a programming error, the last observation was also replaced with a zero. This was applied to both treatment groups. The net effect of this replacement was to bias the average daily pain curves downward. The other choice was to carry the last observation forward which would bias the curves upward.

The statistical re-analysis (500 pages) requested by the division arrived on August 21, 2001. The sponsors' own re-analyzed data clearly demonstrate that separation from placebo was **not** achieved when the pre-specified statistical plan was followed (Last Observation Carried Forward, LOCF). See accompanying graph and table:

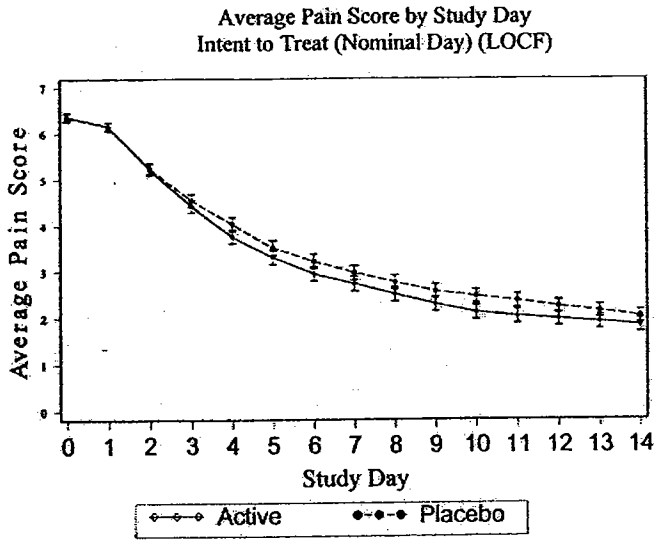


Figure 3. Average Daily Pain Score, From Pre-Specified Data Analysis

Table 4. Average Pain Score by Study Day, Intent to Treat, (Nominal Day) (LOCF)

	DHEP Plaster Active			DHEP Plaster Placebo			
Study Day	N	LSMean	StdErr	N	LS Mean	StdErr	P-Value
Day 0	191	6.34	0.09	181	6.32	0.09	0.920
Day 1	191	6.13	0.04	181	6.13	0.04	0.993
Day 2	191	5.13	0.10	181	5.17	0.11	0.775
Day 3	191	4.31	0.12	181	4.43	0.12	0.427
Day 4	191	3.57	0.13	181	3.85	0.14	0.128
Day 5	191	3.13	0.14	181	3.33	0.15	0.296
Day 6	191	2.77	0.14	181	3.04	0.15	0.164
Day 7	191	2.54	0.14	181	2.78	0.15	0.218
Day 8	191	2.30	0.14	181	2.56	0.15	0.185
Day 9	191	2.12	0.14	181	2.39	0.15	0.159
Day 10	191	1.96	0.14	181	2.30	0.15	0.075
Day 11	191	1.87	0.14	181	2.20	0.15	0.081
Day 12	191	1.82	0.14	181	2.09	0.14	0.159
Day 13	191	1.78	0.14	181	2.01	0.15	0.222
Day 14	191	1.72	0.14	181	1.92	0.15	0.306
Overall Treatment Effect							0.153
Treatment-by- Time Interaction Effect							0.389

B. General Approach to Efficacy Review

As stated previously only two trials were considered pivotal by the sponsor. Each of these trials involved minor sports injuries. Study 01 **(Sports 01)** tested DHEP on an around the clock basis with BID dosing for 14 days. Various metrics to assess pain were used. Primary and secondary efficacy endpoints were established by the sponsor:

Primary Efficacy vs. Placebo

- *Spontaneous Pain VAS (10 cm, from "no pain" to "severe pain")*
- *Pain on Pressure (algometer reading compared to contralateral side)*

These variables were recorded during all clinical sessions for: baseline, third day visit, seventh day visit and fourteenth day visit.

Secondary Efficacy vs. Placebo

- *Eight secondary variables were identified by the sponsor and will be described in detail in section C (next section) of this review*

The statistical evidence of the failure of this trial to establish efficacy can be found in the body of Table 3, shown previously. Note also the sponsor's conclusion (italics) regarding this trial (also taken from the NDA, Volume 9, pages 60 and 77).

Sponsor's Efficacy Conclusions (NDA, vol. 9, page 60)

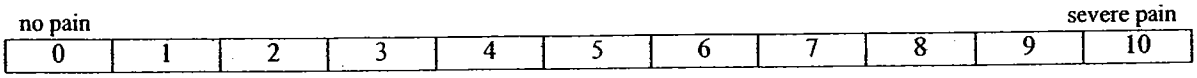
The efficacy data were analyzed according to the methods specified in the protocol. The results for the primary efficacy analyses showed no statistically significant differences between treatments for pain intensity difference (PID), summed pain intensity difference (SPID), pain on pressure difference (POPD), or summed pain on pressure difference (SPOPD)($p \geq 0.099$).

Sponsor's Efficacy Conclusions (NDA, vol. 9, page 77)

The so-called "objective" measure of pain on pressure using the algometer, although seemingly consistent within a given patient, is apparently unaffected by the active drug article. Likewise, the global preference measures, whether recorded by the patient or the investigator, do not reflect any statistical difference between treatment groups.

The second pivotal trial **(Sports 02)** tested DHEP versus placebo in sports injuries for up to two weeks. Patients applied the patch to the painful area on a BID schedule and entered pain scores on a modified numerical/categorical VAS (see below):

Primary Efficacy variable was *Time to Pain Resolution,* measured in days. The assessment tool for this metric was a 0-10 *category* pain scale:



Pain was considered "resolved" if the pain level fell to "2 or less" on the scale for two consecutive days (4 consecutive measures at 12-hour intervals). The sponsor claims they had a separation from placebo patch because patients on active patch withdrew at 9 days vs. 12.3 days for placebo patch. (p=0.016). According to the sponsor, "a shorter time to pain resolution is a favorable outcome, while a longer time to pain resolution is a less favorable outcome. This pattern of treatment is closer to the actual usage in those European countries where the product is now marketed. Patients curtail use of the product when their pain is gone or nearly gone".

Secondary Efficacy endpoints of *patient* and *investigator global response to therapy (5-point verbal scale)* were not statistically significant. The third and last secondary endpoint of *Average Daily Pain Score (from scale above)* was claimed by the sponsor to be statistically significant for days 6-13 (PP population) ($p \leq 0.042$). In the ITT population this is only true at days 7-13 ($p \leq 0.037$). Three of the four investigator sites showed no significant differences at **ANY** *Average Daily Pain Score.* The only investigator with significant results was Dr. Rowbotham at UCSF.

The statistical significance of the primary endpoint does not exist in the ITT group when the excess body weight (10 pounds on average) of the placebo group is included as a co-variable in the statistical re-analysis. The tables below from Dr. Choi's review reflect this point:

Table 5. Sponsor's Efficacy analysis results of primary endpoints

Population	Treatment group	Median time (days)	95% CI. For median time	P-value
ITT	Active	9.0	(7.8, 10.5)	0.016
	Placebo	12.3	(10.3, >15)	
PP	Active	8.8	(7.5, 10.3)	0.009
	Placebo	12.4	(10.3, >15)	

Table 6. FDA Re-analysis adding body weight as a factor, using Cox's Model

Population	Independent factors	P-value for Treatment comparison
ITT	Treatment group, Investigator, Body Weight	0.072
	Treatment group, Investigator	0.019
PP	Treatment group, Investigator, Body Weight	0.045
	Treatment group, Investigator	0.011

C. Detailed Review of Trials by Indication

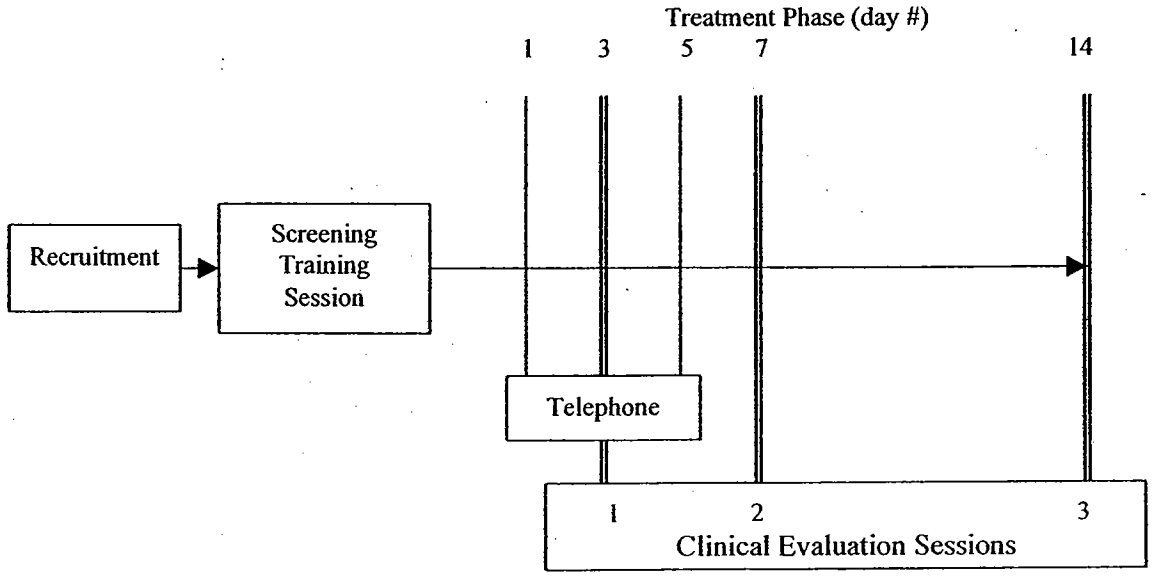
"Treatment of pain _____ was the indication chosen by the sponsor. Each clinical trial was done in support of this one claim. Throughout this section of the Medical Review tables from Dr. Choi's Statistical review will be integrated.

Study 01 (49,459-01) – Randomized, double-blind, placebo controlled, 2-Center study. 222 patients were randomized, 206 in the per-protocol analysis, 213 in the ITT analysis. Patients with minor sports injury wore the patch at the affected site for 2 weeks with $Q12^0$ dosing. The most frequent injury was ankle sprain (27%) followed by knee sprains or contusions (12.5%).

Half of the patients were randomized to receive the active agent and half received placebo (vehicle). Placebo patches were identical in appearance and utilized the same formula as the active patches, without the active principal, diclofenac epolamine.

During the Training Session, the baseline Measures of Spontaneous Pain VAS and Pain on Pressure were recorded using an algometer (Day 1). Subjects were asked to complete the measures of pain relief, and functionality, twice daily (at patch application) on Treatment Days 1-14. Dosage in this study was standard for all patients. The research Coordinator telephoned the subjects on treatment days 1 and 5 to confirm that there were no problems with compliance and completion of the daily diary. During the three Clinical Evaluation Sessions on treatment days 3, 7, and 14, the subject returned to the clinic for measures of Spontaneous Pain VAS and Pain on Pressure using the algometer.

The following diagram presents an overview of the study design, including: recruitment, screening evaluation/training, two-week treatment phase, telephone follow-up calls and the three clinical evaluation sessions.



Objectives
The purpose of this placebo-controlled clinical study was to test the analgesic efficacy and safety of a two-week treatment with Diclofenac Epolamine Patch in minor sports injury (sprain, strain, contusion)

Primary Efficacy Variables

- Spontaneous Pain VAS (10 cm, from "no pain" to "severe pain")
- Pain on Pressure (algometer reading compared to contralateral side)
  These variables were recorded during all clinical sessions for baseline, Day 3, 7, and 14 clinic visit.

Secondary Efficacy Variables

- Spontaneous Pain, Visual Analog Scale (baseline and diary)
- Relief from Spontaneous Pain, 5-Point Verbal Scale (diary)
- Relief from Pain on Pressure/Movement, 5-Point Verbal Scale (diary)
- Functional Improvement, 5-Point Verbal Scale (diary)
- Patient assessment of local tolerability, 5-point verbal scale (day 3,7,14 clinic visit)
- Investigator assessment of local tolerability, 5-point verbal scale (day 3,7,14 clinic visit)
- Patient Assessment of the Global Response to Therapy, 5-point verbal scale (day 3,7,14 clinic visit)
- Investigator's Assessment of the Global Response to Therapy, 5-point verbal scale (day 3, 7, and 14 clinic visit)

Disposition of subjects
At the time of study closure 222 patients had been randomized. Of these, 202 patients completed the protocol as planned, while 20 patients were dropped from the study before completion of the protocol. Nine of these drop-outs have been excluded from the intent-to-treat analysis, because no data exist for these patients beyond the clinic visit at study enrollment. Table A of appendix summarizes the enrollment.

Demographics and Baseline Characteristics
Table C of appendix summarizes the characteristics of the patient demographics at baseline for the ITT patients. A summary of patient's race was not submitted. Table B summarizes the baseline values of the primary efficacy variables. Aside from the lack of race information, the treatment groups were well balanced.

Sponsor's Statistical Analysis and Results of Efficacy
The primary efficacy variables were designated in the protocol as: the investigator recorded pain experienced in the course of normal activities (VAS), and pain on pressure (algometer reading of the injured site minus the contralateral site). Each of

these was collected at days 1, 3, 7, and 14. The value at the post-baseline day was to be subtracted from that of baseline (initial value in clinic or at home) for each measure creating a pain intensity difference (PID) for each post-baseline day and patient. PIDs were to be analyzed by a two-way analysis of variance with factors of treatment group and research study center at days 3, 7, and 14. The PID and Pain on Pressure Difference (POPD) scores were calculated and analyzed in a similar manner. A summed pain intensity difference (SPID) was to be computed for each day and treatment group for the PIDs and SPIDs as a weighted (by previous time interval) sum of the PID scores. The SPIDs were also to be analyzed by the two-way ANOVA at days 3, 7, and 14. The SPID and Summed Pain on Pressure Difference (SPOPD) scores were calculated and analyzed in a similar manner. For the secondary efficacy variables, two-way ANOVA and Cochran-Mantel-Haenszel test stratified by center were used.

Table 7. Sponsor's Analysis of the Primary Efficacy Variables for ITT Patients.

Variable	Day	Active			Placebo			P-Value
		N	Lsmean	Stderr	N	Lsmean	Stderr	
PID	Day 3	106	2.69	0.18	106	2.27	0.18	0.108
	Day 7	106	4.00	0.20	106	3.66	0.20	0.228
	Day 14	106	5.25	0.18	106	4.87	0.18	0.132
SPID	Day 3	106	8.40	0.53	106	7.26	0.53	0.132
	Day 7	106	24.58	1.23	106	22.13	1.23	0.161
	Day 14	106	61.30	2.27	106	56.15	2.27	0.109
POPD	Day 3	105	1.22	0.36	105	1.59	0.36	0.463
	Day 7	105	2.44	0.36	105	2.61	0.36	0.747
	Day 14	105	3.89	0.38	104	3.87	0.38	0.970
SPOPD	Day 3	105	4.13	1.03	105	5.24	1.03	0.451
	Day 7	105	14.04	2.26	104	15.91	2.27	0.560
	Day 14	105	41.26	4.60	104	42.79	4.62	0.814

STATISTICAL REVIEWER'S COMMENT: As shown in the table, none of the primary analysis results show statistical significance. Moreover, for the analyses of POPD and SPOPD, each active treated group is worse than each placebo treated group. Therefore, this study does not support the efficacy of the drug.

MEDICAL REVIEWER'S COMMENT: The primary endpoints chosen by the sponsor failed to produce a positive treatment effect and represent only a partial listing of acute pain primary endpoints typically recommended by this division. Pain Intensity (PI), Pain Relief (PR), Combined PR and PID (PRID), Onset, and Duration are typically required for demonstration of efficacy and a clinically meaningful benefit. Use of the algometer was described by the sponsor (after the data was analyzed) as a poor tool to assess pain. Would the sponsor have had the same conclusion if the POPD and SPOPD shown a positive result?

Secondary efficacy variables of *patient global response to therapy* and *investigator global response to therapy* were not statistically significant vs. placebo patch. See Table F in appendix for detailed result.

Four other secondary efficacy variables *derived from patient daily diary entries* (2 entries/day) showed statistical significance at all three (days 3, 7, 14) evaluation points in the ITT population.

Summed pain intensity difference (SPID) : *highest $p \leq 0.033$ at day 14*

Total Spontaneous Pain Relief (TOTPAR) : *highest $p \leq 0.023$ at day 14*

Total Pressure and Movement Pain Relief (TOTPMR) : *highest $p \leq 0.046$ at day 3*

Summed Functional Improvement Score (SFIS) : *highest $p \leq 0.035$ at day 14*

Table 8. Secondary Efficacy Variable Analysis, Study 01

Variable	Day	Active			Placebo			P-Value[a]
		N	Lsmean	Stderr	N	Lsmean	Stderr	
ITT								
SPID	Day 3	105	10.08	0.63	106	7.93	0.63	0.017
	Day 7	105	26.40	1.29	106	21.83	1.29	0.013
	Day 14	105	56.07	2.23	106	49.30	2.22	0.033
TOTPAR	Day 3	104	8.47	0.38	105	6.87	0.38	0.003
	Day 7	104	19.27	0.75	105	16.36	0.75	0.007
	Day 14	104	37.78	1.34	105	33.45	1.33	0.023
TOTPMR	Day 3	105	7.87	0.37	105	6.82	0.37	0.046
	Day 7	105	18.34	0.72	105	16.05	0.72	0.027
	Day 14	105	36.55	1.29	105	32.66	1.29	0.034
SFIS	Day 3	105	8.15	0.37	105	7.01	0.37	0.029
	Day 7	105	18.87	0.73	105	16.39	0.73	0.017
	Day 14	105	37.06	1.33	105	33.07	1.33	0.035
Per-Protocol								
SPID	Day 3	102	9.81	0.64	103	8.07	0.63	0.053
	Day 7	102	25.99	1.30	103	22.21	1.29	0.041
	Day 14	102	55.59	2.23	103	50.22	2.22	0.090
TOTPAR	Day 3	101	8.42	0.38	102	6.99	0.38	0.009
	Day 7	101	19.24	0.76	102	16.61	0.76	0.015
	Day 14	101	37.85	1.34	102	33.99	1.34	0.043
TOTPMR	Day 3	102	7.87	0.37	102	6.96	0.37	0.086
	Day 7	102	18.41	0.73	102	16.34	0.73	0.046
	Day 14	102	36.77	1.29	102	33.27	1.29	0.056
SFIS	Day 3	102	8.13	0.38	102	7.08	0.38	0.051
	Day 7	102	18.91	0.74	102	16.59	0.74	0.027
	Day 14	102	37.25	1.34	102	33.54	1.34	0.052

a. P-values for treatment comparisons from a 2-way ANOVA with factors of site and treatment

MEDICAL REVIEWER'S COMMENT: The positive results for secondary endpoints must be interpreted in light of failed randomizations for baseline swelling and baseline active- range-of-motion at one of two clinical study sites. Significantly more patients in the placebo arm had ***moderate baseline swelling*** *and significantly more patients in the placebo arm had* ***moderate baseline active-range-of-motion affected*** *than patients in the active treatment arm. These unbalanced baselines were not addressed by the sponsor and may explain the statistically significant results. Even though baseline pain VAS was balanced, patients in the placebo arm may have had a "higher hurdle" to overcome when asked to rate their pain upon movement or when asked about functional improvement or total pain relief. See Table G in appendix for detail*

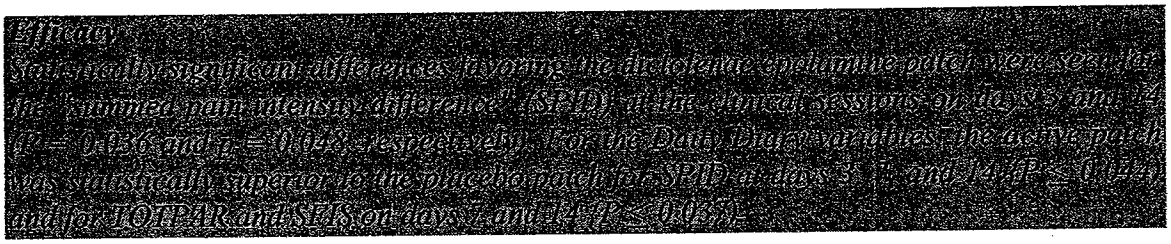
One final secondary endpoint of *patient assessment of local tolerability* of the active vs. placebo patch had varying results, with no clear pattern of greater tolerability. See Table H in appendix for detail.

Concomitant medication use during **Sports-01** was not appreciable and did not appear to affect the negative outcome of the trial. See Table 9 below:

Table 9. Concomitant Medication Use During Study-01

RELATIONSHIP	ACTIVE	PLACEBO
Related to sports injury	25 (0.87%)	57 (1.96%)
Not related to sports injury	41 (1.42%)	55 (1.89%)
Reason not recorded	119 (4.13%)	180 (6.20%)
No medication taken	2693 (93.57%)	2612 (89.94%)
Total	2878	2904

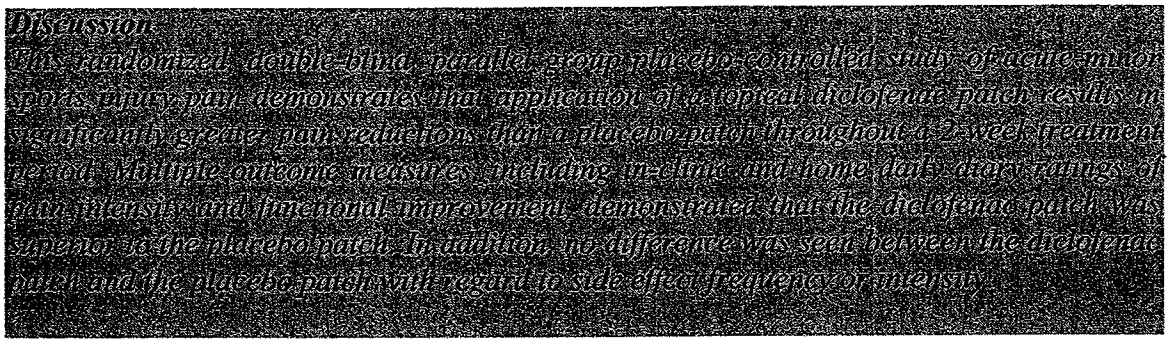
The results of this trial were also published in the *Journal of Pain and Symptom Management*, (Vol 19, No. 4 April 2000, p. 287-294). The title of the article is ***Topical Diclofenac Patch Relieves Minor Sports Injury Pain: Results of a Multicenter Controlled Clinical Trial.*** This is disturbing, given the results of the trial by the sponsor's own admission failed to demonstrate a clinically/statistically significant benefit for the data presented in the NDA. Furthermore, the article does not state that the trial had pre-specified *primary* and *secondary* efficacy variables. An example to illustrate this point can be seen in the following text (shaded italics below and next page) taken directly from the journal article:



Efficacy

Statistically significant differences in favor of the diclofenac epolamine patch were seen for the summed pain intensity difference (SPID) at the clinical sessions on days 3 and 14 ($p = 0.036$ and $p = 0.042$, respectively) for the Data Base variables. The active patch was statistically superior to the placebo patch for SPID at days 3 and 14 ($p < 0.04$) and for TOTPAR and SPID on days 7 and 14 ($p < 0.05$).

REVIEWER'S COMMENT: None of the p-values cited in the journal article can be found in the NDA. The p-values for SPID (ITT) cited in the NDA for days 3 and 14 are p=0.132 and p=0.109, respectively. The p-values for SPID (PP) cited in the NDA for days 3 and 14 are p=0.151 and p=0.099, respectively.



REVIEWER'S COMMENT: The ***Discussion*** *language in the journal article completely contradicts the sponsor's own NDA conclusions regarding DHEP superiority for in-clinic (primary) efficacy measurements. See below:*

Sponsor's Efficacy Conclusions, Sports 01, (NDA, vol. 9, page 60)
The efficacy data were analyzed according to the methods specified in the protocol. The results for the primary efficacy analyses showed no statistically significant differences between treatments for pain intensity difference (PID), summed pain intensity difference (SPID), pain on pressure difference (POPD), or summed pain on pressure difference (SPOPD)($p \geq 0.099$).

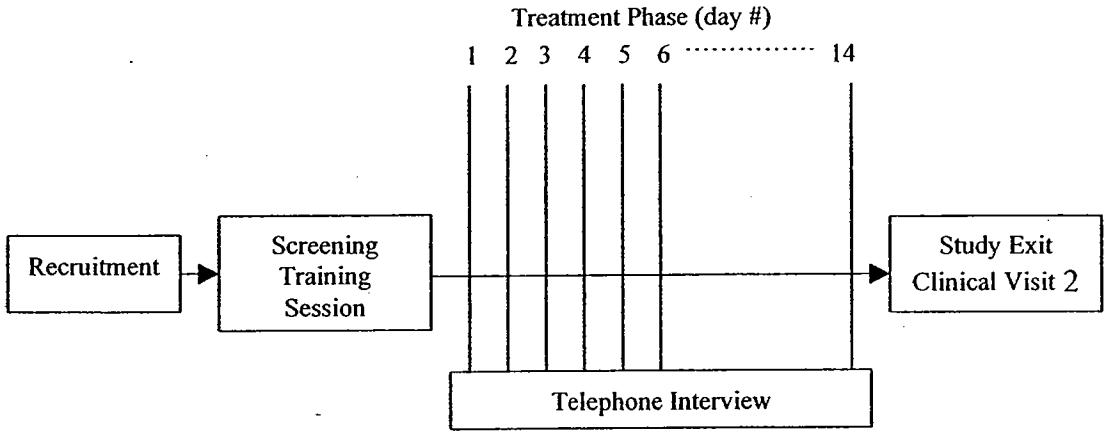
Sponsor's Efficacy Conclusions, Sports 01, (NDA, vol. 9, page 77)
The so-called "objective" measure of pain on pressure using the algometer, although seemingly consistent within a given patient, is apparently unaffected by the active drug article. Likewise, the global preference measures, whether recorded by the patient or the investigator, do not reflect any statistical difference between treatment groups.

REVIEWER'S CONCLUSION: The primary endpoints chosen by the sponsor were appropriate but incomplete as described previously. This trial failed to demonstrate efficacy based on the failure of DHEP to separate from placebo in all primary efficacy endpoints. Statistical significance claimed by the sponsor for Secondary endpoints may have been confounded by failed baseline swelling and range-of-motion randomizations. DHEP does appear to be safe on skin if used for a short period of time, but chronic episodic or prn usage is a more likely scenario given the off-label use potential for mild aches and pains, arthritis and muscle spasm.

Study 02 (49,459-02) - Randomized, double-blind, placebo-controlled, 4-center study. 411 patients were randomized, 365 in the PP population and 372 in the ITT population. Patients with minor sports injuries wore the patch for two weeks with $Q12^0$ dosing. On average, patients in the placebo group weighed 10 lbs more than those in the active patch group (p=0.010). This difference was not seen in the first pivotal trial. Most injuries were ankle sprains (23%) followed by knee sprains or contusions (17%).

Approximately half of the patients were randomized to receive the active agent and half received placebo (vehicle). The following diagram presents an overview of the study

design, including: recruitment, screening evaluation/training, two-week treatment phase, telephone follow-up calls and the three clinical evaluation sessions.



During the Training Session, the baseline Measures of the 0-10 Category pain scale was recorded. Patients were asked to complete the measures of pain and adverse events twice daily (at patch application on Treatment Days 1-14. Additionally, patients were instructed to complete their evaluation of global response to treatment and assessment of local tolerability at the exit visit. The research coordinator telephoned each patient on a daily basis during the treatment phase (at least 6 days per week). These daily contacts are to confirm that there no problems with compliance and completion of the daily diary.

Objectives

The purpose of this placebo-controlled clinical study was to test the analgesic efficacy and safety of a two-week treatment with Diclofenac Epolamine Patch in minor sports injury (sprain, strain, and contusion).

Primary Efficacy Variable

- **Time to Pain Resolution**

Secondary Efficacy Variables

- **Investigator's Assessment of the Global Response to Therapy 5-point verbal scale**
- **Patient's Assessment of the Global Response to Therapy, 5-point verbal scale**

The **primary efficacy** variable described in the protocol was **Time to Pain Resolution** based on daily pain assessments using the 0 – 10 category pain scale (10 cm, from "no pain" to severe pain). Daily measure of pain was recorded at the clinic office at baseline and daily at the time of each patch removal. The pain was considered to be resolved if the pain level fell to "2" or less on the 0-10 category pain scale for two consecutive days (4 consecutive measures at 12-hour intervals).

The assessment tool for this metric was a 0-10 *category* pain scale:

no pain										severe pain
0	1	2	3	4	5	6	7	8	9	10

This variable was based on the study day at which either pain resolution occurred and the study patch was no longer needed or the patient discontinued wearing the patch and pursued an alternative treatment. Additionally, the patient was required to discontinue wearing the study patch if pain resolution had not occurred at the end of the 14th study day.

The Time to Pain Resolution was **defined in the protocol** as the study **day** corresponding to the second of two consecutive days that a patient recorded a category pain of "2" or less. In the event that the patient never recorded two consecutive days of pain levels of "2" or less, then the Time to Pain Resolution was set to 15 days since pain resolution did not occur within 14 days of treatment. Additionally, if a patient discontinued wearing the patch due to a lack of perceived efficacy, then the Time to Pain Resolution was set to 15 days. The **day** defined by the protocol is the **Nominal Day**.

The **actual implementation** of the Time to Pain Resolution used the **time** that had elapsed from the initial patch application to the time at which the patient recorded the fourth Spontaneous Pain of "2" or less. In the event that the patient never recorded four 12-hour intervals of pain levels of "2" or less, then the Time to Pain Resolution was set to 15 days since the pain resolution did not occur within 14 days of treatment. Additionally, if a patient discontinued wearing the patch due to a lack of perceived efficacy, then the Time to Pain Resolution was set to 15 days. Some patients did not provide either the date or the time at which the end point was realized. In that event the time was estimated from the diary date sequence number. The **day** actually implemented was the **24-hour day**.

REVIEWERS COMMENT: The use of the 24-hour day (not pre-specified) versus the nominal day (pre-specified) was discovered after discussions with the field investigator who noticed that tabulated average daily pain scores did not correspond with the tabulated data in the NDA. The average daily pain scores (a secondary efficacy variable) were the base from which the "time to pain resolution" was derived. The sponsor also carried forward a zero instead of the last observation in tabulating the average daily pain scores. This was a deviation from statistical protocol and a major confounder in the mathematical derivation of the primary outcome variable.

Disposition of subjects

At the time of study closure, 411 patients had been randomized. Of these, 365 patients completed the protocol as planned, while 46 patients were dropped from the study before completion of the protocol. Thirty-nine of these dropouts were excluded from the intent-to-treat analysis because no data exist for these patients beyond the clinic visit at study enrollment. Although data from the remaining 7 dropouts are incomplete, those patients are included in the intent-to-treat analyses, but excluded from the per-protocol analyses. Therefore, 372 patients are included in the intent-to-treat analyses and 365 patients are included in the per-protocol analysis. See Table A in Appendix.

Patient Demographics and Baseline

The two treatment groups were not fairly randomized because body weight of the patients was significantly different between treatment groups with mean difference of 10 lbs and p-value of 0.01 for both ITT and Per-Protocol patients. See Table D in Appendix.

STATISTICTAL REVIEWER'S COMMENT: The primary efficacy variable was reanalyzed with a body weight adjustment and reported in Reviewer's Comments. For the races, 336(93%) patients were unknown and only 24 (7%) patients were observed. For other variables, about 5% of the data are missing for each variable. In conclusion, the summary of the demographics disproves a fair and balanced randomization.

Sponsor's statistical analyses and results for efficacy

The primary efficacy variable, Time to Pain Resolution, was analyzed using a Wilcoxon survival test as specified in the protocol, stratified by research study center. Significance was declared at the p=0.05 level. The analysis results showed the p-values to be less than 0.05 for both ITT and PP patients. The following table (*seen previously as Table 5*) summarizes the analysis results of the primary efficacy endpoints. Note that these sponsor's analyses were not adjusted for body weight.

Sponsor's Efficacy analysis of primary endpoints

Population	Treatment group	Median time (days)	95% CI. for median time	P-value
ITT	Active	9.0	(7.8, 10.5)	0.016
	Placebo	12.3	(10.3, >15)	
PP	Active	8.8	(7.5, 10.3)	0.009
	Placebo	12.4	(10.3, >15)	

Secondary analysis results are summarized in Table K of the appendix. None of them show a significant difference between treatment groups.

STATISTICAL REVIEWER'S COMMENT: As stated above, a significant difference of body weight was detected between the two treatment groups. So, the sponsor's efficacy analyses including previous table may not be valid because of the randomization issue. This reviewer reanalyzed the primary endpoint adding body weight as a covariate to check the sensitivity of the analysis results to the unbalanced body weight. Since body weight is a continuous variable, a Cox's proportional hazard model with maximum likelihood estimates was used as follow. The analysis results are summarized in the following table (seen previously as Table 6).

Re-analysis results adding body weight as a factor, using Cox's Model

Population	Independent factors	P-value for treatment comparison
ITT	Treatment group, Investigator, Body Weight	0.072
	Treatment group, Investigator	0.019
PP	Treatment group, Investigator, Body Weight	0.045
	Treatment group, Investigator	0.011

As shown in the table, p-values from Cox's model without body weight are similar to the ones from sponsor's Wilcoxon test. But when the analysis is adjusted to body weight by adding as an independent factor, we can find a big inflation of the p-values for both ITT and PP population. Especially for ITT population, no significant difference between the treatment groups was detected. This result tells us that the sponsor's conclusion of significant efficacy was effected by the difference of body weight between treatment groups. Moreover, all the analysis results of secondary efficacy variables failed to show the significant separation of the test drug treated patients from placebo treated patients as shown in the appendix. Therefore, this study does not show a sufficient evidence of the drug

CLINICAL REVIEWER'S COMMENT: Even if the sponsor's ***original post-hoc data analysis*** *was accepted as significant statistical evidence for superiority, a close examination of the following figures (NDA, vol 9, study 02, pages 80 and 75) will show the* ***failure of DHEP to demonstrate a clinically meaningful treatment effect*** *(see next page).*

Figures 4 and 5 depict the ***same data set derived from the same daily diaries*** *but expressed two different ways. In Figure 4,* ***Average Pain Score by Study Day****, the active and placebo arms virtually overlap. Data from the four study sites is incorporated here but it is the contribution from the highest enroller that creates what little separation does exist. There was no separation from placebo in the data from the other three investigators. Compare this graph with Figure 3, which depicts the correct pre-specified data analysis.*

Figure 5, ***Time to Pain Resolution****, is derived from the average daily pain scores recorded in patient diaries. The y-axis, "Patients with success", describes patients who rated their pain as $\leq$ 2 on the 10-point numerical scale for four consecutive diary entries. This "success" does not represent "pain* ***resolution****" but rather a $\leq$ 60%* ***reduction*** *in pain from a baseline of 5 out of 10 required to enter the study.*

A 10% treatment difference between DHEP and placebo exists at day 9. This difference does not suggest a clinically relevant difference and does not account for the failed randomization with respect to body weight. When body weight is accounted for the p-value changes from 0.016 (statistically significant) to 0.072 (not statistically significant). Average daily pain scores are a more clinically meaningful primary endpoint.

Average Pain Score by Study Day
Intent-to-Treat Patients

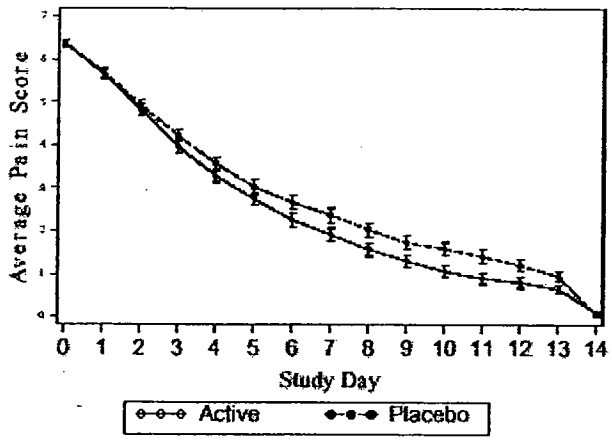
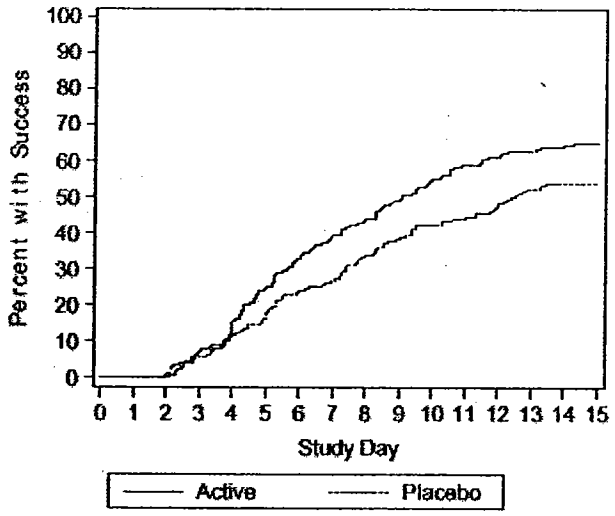


Figure 4. Average Daily Pain Score, From Original NDA

Time to Pain Resolution
Intent-to-Treat Patients



Comparison of time to pain resolution between treatments, p-value+ 0.016

	Median Time (days)	**95% C.I. for Median Time**
Active	9.0	(7.8, 10.5)
Placebo	12.3	(10.3, >15)

Figure 5. Time to Pain Resolution, From Original NDA

Concomitant medication use during **Sports-02** was not appreciable and did not appear to affect the negative outcome of the trial. See table below:

Table 10. Concomitant Medication Use During Study- 02

MEDICATION	ACTIVE	PLACEBO
Acetaminophen	4 (0.2%)	0 (0.0%)
Advil	0 (0.0%)	3 (0.2%)
Alka seltzer	0 (0.0%)	1 (0.1%)
Allergy-anti-histamine	0 (0.0%)	1 (0.1%)
Antibiotic crème	0 (0.0%)	2 (0.1%)
Antibiotic creme on abrasions on other side of leg	0 (0.0%)	1 (0.1%)
Aspirine (aspirin%)	0 (0.0%)	2 (0.1%)
Celebrex	0 (0.0%)	2 (0.1%)
Codein	0 (0.0%)	3 (0.2%)
Hyfrattreat'l-mineral ice	1 (0.1%)	0 (0.0%)
Ibuprofen	3 (0.2%)	0 (0.0%)
Motrin	1 (0.1%)	0 (0.0%)
Sinutab	0 (0.0%)	1 (0.1%)
Tylenol	0 (0.0%)	3 (0.2%)
No medication taken	1549 (95.9%)	1634 (96.6%)
Medication information not recorded	58 (3.6%)	37 (2.2%)
Total	1617	1690

D. Efficacy Conclusions

The data presented in the NDA failed to demonstrate statistically significant relief of daily pain for the use of DHEP in the treatment ——— . When controlled for statistically significant differences in weight between groups the sponsor's primary endpoint failed to demonstrate a statistically significant change. DHEP also failed to suggest a *clinically meaningful benefit* in the *acute* treatment of these types of injuries. Even if statistical superiority had been shown, the fact that so few patients get any early pain relief reflects the natural course of the disease process rather than some effect from DHEP. This raises the question of validity of the primary endpoint. The secondary endpoint, *Average Daily Pain*, seems a more appropriate choice as a clinically relevant outcome measure but DHEP failed to demonstrate a significant treatment effect or even a positive trend in the relief of pain.

From the outset the proposed indication of " [redacted] is

[redacted] This *indication* should be abandoned [redacted] As a proof-of-concept however, these minor injuries [redacted] may provide a unique patient population for testing the efficacy of topical products in an ***acute or sub-chronic setting***. Clearly the dental pain models used historically for oral analgesics would not be appropriate for studying transdermal/topical analgesic drug delivery platforms which claim to have *site-of-application* effects. The heterogeneity of injuries seen in this NDA raises questions about how a study population and indication may be defined in the future.

One must consider the nature of the injury, *i.e.* an acute eversion ankle sprain (grade I-III), versus the sub-chronic nature of wrist flexor tendonitis, versus lateral blunt trauma to the knee causing hematoma/effusion. It is **pain** and **not necessarily inflammation**, that unite these uniquely different injuries. No doubt, the subjective pain experience is difficult to objectify and yet ***that is the hurdle*** that must be cleared by any analgesic. While the historic pain measurements of onset, magnitude, duration and multi-dose effect were born of the dental pain model they still hold as unique and critical parameters for analgesics when studied in an acute (post–surgical or not) setting.

Study-01 failed to show that DHEP could produce analgesic effects using endpoints previously used in acute pain models. Perhaps that is why the sponsor attempted to study DHEP in another way.....using *"time to pain resolution"* as a *derived* outcome from daily pain measurements in Study 02. Obviously, if daily pain measurements fail to produce any statistically significant or clinically meaningful benefit then surely a derived measure should fail as well. **Study-02**, despite numerous post-hoc statistical manipulations, was unable to produce a significant p-value much less a clinically meaningful benefit. There were multiple problems with this trial, including:

- A failed randomization with respect to body weight, which when accounted for as a covariate, produced a statistically insignificant result in the primary efficacy measure

- Only one study site (highest enroller) had trends favoring DHEP in average daily pain scores. This raises concern over how credible even the sponsor's submitted (post-hoc) statistical analysis may be in calculating *average daily pain scores*. Recall that

average daily pain scores were the basis of *time to pain resolution.* Favorable trends at the high enroller site are lost when body weight is added as a covariate.

- Defining *time to pain resolution* as ≤ 2 on a 0-10 category pain scale. Pain resolution should be *zero* on the scale and not ≤ 2, which reflects pain *reduction* **not** *resolution*

- Creating baseline pain score bias in the language of the informed consent where patients were told "how high" their pain had to be (at least 5 on the 0-10 category pain scale) before entering the trial. Patients were paid for trial participation.

- Creating leading bias in the *average daily pain score*, patient daily diary, by having the format of the diary such that patients could see their previous pain score from the prior patch application. Ideally these Q12° pain ratings by the patients should be a static measurement without any influence of the previous measurement.

- Using post-hoc statistical manipulations rather than the pre-specified protocol analysis to derive average daily pain scores and time to pain resolution. The statistical plan originally specified the *Nominal Day* as a way to capture data for the *Day of Pain Resolution.* It also specified that the last observation be carried forward (LOCF) if patients did not complete the 14 day course of BID dosing. Instead, the sponsor used the *24-hour day* to capture data for *Day of Pain Resolution.* This is a crucial point because in using the *24-hour day* to derive daily pain scores some patients had two values averaged together on some days and on other days three pain scores were averaged together thus giving very inconsistent results. Instead of LOCF, a *zero* was carried forward for people who didn't complete the 14 day dosing regimen. The results of these post-hoc changes gave statistically significant results. These results do not represent the true outcome of Study 02. No statistical significance or clinically robust outcome was produced when the pre-specified statistical plan was followed. See Tables I and J in the appendix.

- Ongoing DSI field investigations into the behavior of a study nurse at the Chicago site during Study 02. Handwriting on some of the patient daily diaries appeared to resemble the handwriting of the study nurse.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The safety of this product can be divided into two categories: *US* and *Oversees*

Data derived from US product clinical trials: Diclofenac Epolamine Patch 1.3%

In general, the data derived from the US trials shows that DHEP is well tolerated in healthy adults. Minor skin irritation was the most common side effect. This irritation is manifest as rash or pruritis at the application site and resolves upon discontinuation of patch. The occurrence of pruritis was $\leq 7\%$ in the DHEP treated group and this was less

than the occurrence of pruritis in the placebo patch group, < 14%. The sponsor did not provide an explanation for this fact.

Data derived from Europe, Asia, and Latin America: where the product has been marketed since 1993 as either Flector Tissugel 1% or Flector EP tissugel 1%.

Diclofenac Epolamine Patch was first approved in Switzerland in 1993 and since then has been approved in 21 other countries. As of 11/16/2000 the drug has not been withdrawn in any country. Approximately —— patches have been distributed. The safety profile oversees is similar to that seen in the US trials.

B. Patient Exposure

Over 550 patients were exposed to DHEP at or above the proposed dose during the US clinical trials. Only 2 "severe" events were documented, both were related to skin irritation (rash/pruritis) and spontaneously resolved within 24-48 hours of patch removal. Most of the complaints about skin irritation were listed as "mild" and were seen more often in the placebo group. The dermatologic side-effect profile in humans is similar to that observed in animals. From the European safety database there appears to be a wide margin of safety in terms of skin reactions. In France, two cases of contact eczema were reported from 1998-99, both resolved. No cases were reported in Italy during a 5 month period in 1999 while Switzerland had one reported case of axillary lymph node enlargement reported in 1999. However, four cases of GI hemorrhage were reported in Israel in 1995; these patients were wearing some form of diclofenac patch and were also on concomitant aspirin or other NSAID therapy at the time of event.

C. Specific Findings of Safety Review

From an acute skin safety perspective DHEP was studied in 92 volunteers during European Safety Studies.

Phase I Dermal Safety Studies	Results
Study C11080 - 21 day cumulative irritancy study in 20 volunteers using Flector EP Tissugel (European product)	Relative irritation scores out of a possible 1200 Was 0.0 and therefore deemed non-irritating
Study C1108 - Phototoxicity study in 20 volunteers using Flector EP Tissugel (European product)	Subjects wearing the patch were exposed to UV light for 24°, 48°, and 7days. Skin irritation scores considered non-phototoxic by sponsor
Study B9356 – Photo-allergenicity study in 27 volunteers using Flector EP Tisssugel (European product)	Subjects wearing the patch were challenged 6 times (twice weekly) with UV light. Skin reaction scores were taken at 24° and 72° and deemed non-photo-allergenic
Study 006-91 – Hypersensitivity study in 25 volunteers using DHEP (similar to US to-be-marketed product). Study done in 1991 and used a placebo control patch	Subjects exposed to patch for 3 weeks, changing the patch every 48 hours. No descriptive statistics reported but sponsor claims no immediate/delayed reactions seen

Study # C11080 : Flector EP Tissugel was considered by the sponsor to be non-irritating in a 21-day cumulative irritancy study in 20 volunteers. Problems with the study include:

- The size of the "Tissugel" patch was 2.5cm x 2.5 cm, not the to-be-marketed size of 10cm x 14cm. The concentration of drug or actual mg strength of drug per dose is unclear from the study report. It appears that a much smaller dose was tested

- Demographic breakdown according to gender was highly unbalanced:
  18 Females 2 Males

- Poor demographic representation according to race:
  16 Caucasian 4 Hispanic 0 Black 0Asian

- Demographic breakdown according to age not described

Study # C1108: Flector EP Tissugel was considered by the sponsor to be non-phototoxic in 20 human volunteers. Problems with the study include:

- Use of smaller patch, described in first bullet of Study # C11080

- Demographic breakdown according to gender was highly unbalanced: 18 F to 2 M

- Poor demographic representation according to race:
  16 Caucasian 3 Hispanic 0 Black 1 Asian

- Demographic breakdown according to age not described

- Eleven subjects in this study were also enrolled in study C#11080

Study # B9356: Flector EP Tissugel was found to be non-photo allergenic in 27 human volunteers. Problems with this study include:

- Use of smaller patch, described previously

- Demographic breakdown according to gender was highly unbalanced
  23 Female 4 Male

- Poor demographic representation according to race:
  26 Caucasian 1 Hispanic 0 Black 1 Asian

- Demographic according to age not described

Study # 006-91: DHEP plaster did not elicit any skin reactions indicative of a delayed contact or immediate hypersensitivity in 25 healthy volunteers. Problems with this study include:

- No demographic breakdown according to race was included
- Demographic according to age not described

REVIEWER'S COMMENT: From a regulatory perspective these Dermatologic studies do not provide adequate evidence of safety due to the bulleted problems listed above. The sponsor was asked to provide the results of these studies well in advance of filing the NDA. This was not done, despite the fact that three of the four safety studies were done with a European approved product. Study # 006-91 was done in Italy over 10 years ago. Study # B9356 was completed in July 1999. Data provided from these four studies may not represent the final US to-be-marketed product either in appearance or dose and thus cannot stand alone as a sufficient Dermatologic safety data base.

D. Adequacy of Safety Testing

In the US DHEP was studied in healthy adults with minor acute orthopedic injuries. The drug appears safe in this population, despite its lack of demonstrated efficacy. See Table 11 below:

Table 11. Adverse Events During Pivotal US Clinical Trials

Treatment Effect P-Values for Adverse Events
Occurring at a Frequency of >=5% (of Patients) Overall, by Body System
(Sports 01 and Sports 02 Pooled)
(Intent-to-Treat Patients)

	Active	Placebo	p-value+
Number of Patients	297	288	
Patients Reporting Events	84 (28%)	96(33%)	0.210
Body as a Whole	16 (5%)	18 (6%)	0.725
Digestive System	21 (7%)	19 (7%)	0.871
Nervous System	18 (6%)	16 (6%)	0.861
Skin	45 (15%)	56 (19%)	0.190
Pruritus	22 (7%)	39 (14%)	0.021

+ Fisher's Exact test was used to compare the proportion of patients in each treatment group by body system and for those adverse events that were reported by at least five percent of the patients in either group. Counts reflect numbers of patients in each treatment group reporting one or more adverse events that map to the COSTART body system. At each level of summarization (body system or event) patients are only counted once. Percentages of patients in each treatment group are also given.

The more important issue with DHEP is its safety profile in the elderly and patients on chronic NSAID therapy for arthritic conditions. This population is the primary target for off-label use and as such a safety profile needs to be established if DHEP were to ever be approved for ***any*** indication. The sponsor indicated that drug interactions were not studied during the US clinical trials. See italic comment below taken from the NDA, Volume 9, page 68 of safety summary:

Drug interactions were not examined during the course of this study. However, the common interactions, based on previous research, related to diclofenac include aspirin, digoxin, methotrexate, cyclosporine, lithium, oral hypoglycemics, and diuretics.

REVIEWER'S COMMENT: Long term daily or chronic-episodic use is the most probable usage pattern to evolve with DHEP, and for that matter, any topical NSAID. Pre-marketing controlled clinical and actual use studies lasting 6 months or more are the best way to assess long term safety data in patients on chronic concomitant medication or patients with major organ insufficiencies such as diabetes, hepatic/renal insufficiency, or hypertension. In their absence, [redacted] *rom sponsors should be the standard for this evolving drug delivery system.*

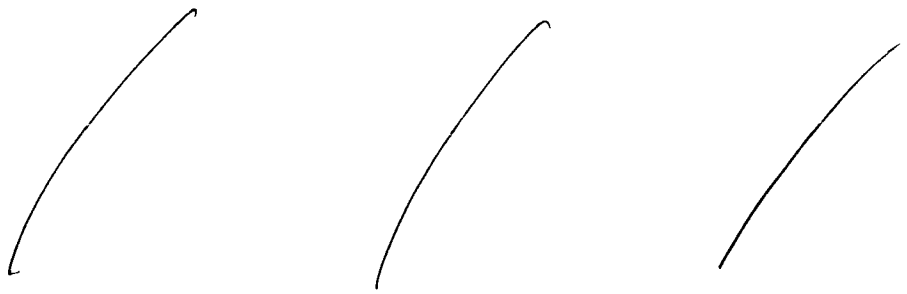
E. Summary of Critical Safety Findings and Limitations of Data

Given the large European exposure and data from the US trials, DHEP appears safe if used as directed in healthy adults. Chronic episodic off-label use has not been specifically addressed in this NDA although it appears that DHEP would probably be safe in this context in healthy adults.

From the European safety database there appears to be a wide margin of safety in terms of skin reactions. In France, two cases of contact eczema were reported from 1998-99, both resolved. No cases were reported in Italy during a 5 month period in 1999 while Switzerland had one reported case of axillary lymph node enlargement reported in 1999.

The safety of DHEP in the pregnant, elderly and pediatric populations has not been adequately assessed in a controlled or semi-controlled fashion. The use of post-marketing data from foreign marketing of related products, while helpful, is incomplete and inadequate as a robust safety database in these populations. The pregnant patient is more likely to consider a topical product, for safety reasons, over an oral product for the treatment of an acute ankle injury or the sub-chronic "aches and pains" that often occur during the weight gain in late pregnancy.

In the sponsor's proposed package labeling it states that [redacted]



The geriatric population adds the additional issues of end-organ insufficiencies and concomitant drug use with DHEP. Oversees Case reports provide a limited but realistic potential problem with topical NSAIDS.

Four cases of GI hemorrhage were reported in Israel in 1995; these patients were wearing some form of diclofenac patch and were also on concomitant aspirin or other NSAID therapy at the time of event.

The potential for drug-drug interaction exists given the target population and unanticipated use of this product with oral NSAIDS. Review of various European labels for Flector EP 1% reveals very little with regard to clinically tested methods for ascertaining safety when DHEP is used with oral NSAIDS. Patients in the US trials were not tested while on concomitant oral NSAID therapy, therefore the safety of DHEP when used in combination with oral NSAIDS remains an unresolved safety issue. The language used in the European labeling regarding drug interactions reads as follows:

"due to poor systemic absorption during the use of DHEP, the interactions occurring with oral administration of diclofenac are not very likely" (from Swiss label)

Evidence to support this claim was not presented in the US clinical trial data. Therefore, if DHEP were to be approved,

Children are an excellent target for a product like DHEP but there is very little data in this population with regard to acute/sub-chronic skin sensitivity or acute efficacy. The US trials with DHEP did not include a pediatric or adolescent sub-population.

VIII. Dosing Regimen and Administration Issues

DHEP failed to demonstrate a clinically meaningful or statistically significant treatment effect. By design, the sponsor chose not to study the dose response effect of their product. Therefore, little if anything can be concluded in terms of dose or frequency of administration. These issues are typically addressed in multiple Phase II studies where the sponsor pushes the dose response curve of the test product.

The chemistry and PK deficiencies summarized earlier in this review may shed some light on the real problem with this product. It is a major technical problem if the active ingredient can barely separate from the adhesive patch. It is conceptual problem if the sponsor cannot describe or scientifically prove the actual mechanism of action of DHEP. The stratum corneum has evolved as a protective barrier to environmental insults of the skin. This skin layer becomes the rate limiting step for diclofenac after drug separation from adhesive . The bloodstream is another rate limiting step because clearly there is systemic uptake, albeit very small, of diclofenac. Until the sponsor can modify their product and demonstrate, even in animal models, the true site of action of DHEP, one can only speculate on proper dose, optimal dose frequency, or

IX. Use in Special Populations

From a statistical standpoint there did not appear to be any gender effects with regard to efficacy (lack of efficacy). Body weight however was a significant variable for the second pivotal trial and proved to be the statistical undoing for Study 02. Obviously more body weight applied to a weight-bearing joint during an acute injury will produce a greater degree of pain experience.

The sponsor did not stratify patients by age but review of the CRFs reveals that the majority of patients were healthy and under the age of 30. If DHEP had shown some clinical benefit or significant safety signal then further critical analysis would have demanded a closer look at patients 65 or over.

No racial differences were detected in Study 01 but the sponsor did not provide a racial breakdown for Study 02. If DHEP had shown some clinical benefit or significant safety signal then further critical analysis would have demanded a closer look at patients by race.

The Pediatric program was not properly addressed by the sponsor as discussed in section VI. No justification for excluding pediatric patients from the trials was provided by the sponsor. To state simply that DHEP is not indicated for pediatric use is not adequate. Pediatric patients are an important target population for topical NSAID products and as such should be studied in a controlled clinical trial.

Clinical data is also needed from patients on chronic concomitant analgesic medication and patients with hepatic or renal insufficiency. These patients will provide the most important safety database for this and other topical NSAIDS. These patients will most likely be the most frequent users of topical analgesics.

X. Conclusions and Recommendations

A. Conclusions

Based on the evidence presented in two pivotal clinical trials DHEP failed to demonstrate significant differences compared to placebo. When the original pre-specified protocol was followed in Study 02 no meaningful clinical trends were seen. Based on the safety data derived from these clinical trials as well as skin safety data derived from 4 clinical trials done in Europe, the product appears safe if used as directed in healthy adults for up to two weeks. This product has very little risk in this population but does not have any clinical benefit.

Post-marketing data from Europe does produce a safety signal that is concerning with regard to DHEP use in patients on concomitant NSAID therapy. This issue needs further exploration in a controlled clinical fashion, particularly in the elderly population.

The safety and efficacy of DHEP in children has not been addressed in accord with the pediatric rule and therefore must be addressed in any further studies of DHEP

The safety and efficacy of DHEP has not been studied in a rigorous fashion in pregnant patients. It is understandable from an ethical standpoint that this drug may never be evaluated in a prospective, randomized, placebo controlled clinical trial of pregnant patients. Until such data can be evaluated we can only rely on labeling to give patients and physicians accurate information, that is,

Conceptually, the use of is better suited as a proof-of-concept model rather than a pain model attempting to demonstrate a robust clinical effect. This statement is based on the failure of DHEP to separate from placebo in an acute setting using VAS scores for the sponsor's chosen primary efficacy endpoints in Study 01. This statement is also based on the failure of DHEP to produce a clinically meaningful effect, "*shorter time (days) to pain resolution*" in Study 02. This effect was even further reduced, and statistical significance not reached, when body weight was accounted for in a statistical re-analysis of the data from Study 02.

Topical NSAIDs may be better suited for the treatment of chronic conditions such as Osteoarthritis and Rheumatoid arthritis. In these disease states the efficacy focus is on Pain, Function, and Patient Global responses to the study drug.

B. Recommendations

The following list of deficiencies and recommendations will be organized into three general categories: **CONCEPTUAL, CLINICAL AND STATISTICAL, REGULATORY**

1.) CONCEPTUAL

- The chosen indication ' should be abandoned

- The use of *"time to pain resolution"* should be validated. Specific evidence from the literature can be sent to the division for review. This metric may be of interest in the

acute or sub-chronic setting; however, the anecdotal evidence from European usage of DHEP does not provide sufficient robust validation of this pain metric. If a clinically meaningful benefit can be demonstrated as proof-of-concept then the division is open to further discussion on this subject. The use of a combined numerical and classic VAS is a good idea in terms of limiting patient confusion. But these should be static measurements without any bias from previous scores, *i.e. the previous VAS score from 12 hours ago should not be seen by the subject while they are completing their current VAS entry.* When patients complete daily diaries in this fashion, they have biased their current entry as they may think back to 12 hours ago. Ideally, they should focus on what their pain level is *at the present moment.*

- The 10% treatment difference seen in Study 02, which by itself was too small to be clinically relevant, was based on weight biased data and post-hoc statistical analyses. More discussion of this subject will be in the clinical and statistical section to follow.

- Concurrence with the sponsor on abandoning the algometer used in Study 01 as a tool to assess pressure pain cannot be given at this time. The counter-argument can be made that it is possible that the algometer is in fact a very good tool but that DHEP simply doesn't work.

- It seems that more drug should actually separate from the patch than just 5%. It is difficult to believe that only nanogram levels of diclofenac, either in plasma or joint spaces or fascia, can produce a clinically meaningful benefit, as claimed by the all the oversees clinical data. More Phase II work is needed.

2.) CLINICAL AND STATISTICAL

- By the sponsor's own admission, Study 01 failed on all primary efficacy endpoints. This trial cannot be used as even supportive evidence for the efficacy of DHEP. The results of this trial were published in a refereed journal eight months prior to the submission of the NDA. This paper was not referenced, acknowledged, or included in the NDA. This is a clinical and regulatory deficiency. The sponsor's statistician, John Quiring, Ph.D., was acknowledged in that paper as well as Institut Biochimique SA (Switzerland). Larry Caldwell, Ph.D. was not mentioned in the paper. The conclusion presented in the journal article painted DHEP in a very positive light, with no mention of the failed primary efficacy endpoints. In addition, no statistical values cited in the paper can be found in the NDA. This may represent a breach of professional integrity.

- Data from the second study cannot be used as evidence of effectiveness because independent validity of the primary endpoint is uncertain. The results from both *time to pain resolution* and the more clinically relevant *average daily pain score did not* reach statistical significance. Furthermore, the sponsor's method of calculating their primary endpoint used a post-hoc statistical analysis that deviated from the pre-specified method in the NDA.

- Secondary efficacy endpoints in Study 02 derived from patient daily diaries were originally shown by the sponsor to be clinically meaningful and statistically significant. Only 1 of 3 study sites demonstrated efficacy in terms of average daily pain scores. This site was the highest enroller, thus producing a statistically significant number representing a very small treatment effect. Once again the sponsor used a post-hoc method, and upon their own re-analysis, reported data that was not statistically significant. In the future it is highly recommended that all sponsors follow the protocol and notify the FDA of any planned deviations prior to submitting data.

- Dermatologic safety data from Europe does not reflect the US population nor the primary target population for this drug. The sponsor should consult the 2001 Code of Federal Regulations vol.21, section 312.120 for further guidance regarding clinical studies not conducted under an IND. Specifically, these dermatologic safety studies should have a fair balance of subjects according to the most recent US census in terms of gender, race and ethnicity.

3.) REGULATORY

- As discussed earlier, it is a regulatory requirement that the sponsor conduct an adequate and representative literature search. In this case the one paper that should have been included in the NDA, because it represented pivotal clinical trial data from Study 01, was not even mentioned. This was a serious deficiency.

- Deficiencies from the Chemistry, Pharm/tox and PK disciplines can be found in their individual reviews.

- [redacted]

- This drug should not be approved.

APPENDIX

Table A: Summary of Patient Enrollment and Validity

		ACTIVE	PLACEBO	TOTAL
Study 01	Patients Enrolled	110	112	222
	Patients Excluded from Safety/Intent-to-Treat	4	5	9
	Patients Included In Safety/Intent-to-Treat	106	107	213
	Patients Excluded from Per-Protocol	4	3	7
	Patients Included In Per-Protocol	102	104	206
Study 02	Patients Enrolled	205	206	411
	Patients Excluded from Safety/Intent-to-Treat	14	25	39
	Patients Included In Safety/Intent-to-Treat	191	181	372
	Patients Excluded from Per-Protocol	3	4	7
	Patients Included In Per-Protocol	188	177	365

Table B: Baseline measurements of the primary efficacy variables, ITT

	VARIABLE	ACTIVE	PLACEBO	P-VALUES
Study 01	Baseline VAS			
	Mean	6.20	6.29	0.578 [a]
	SD	1.02	1.10	
	Range	3.8 – 8.8	3.6 – 9.5	
	Baseline POP			
	Mean	5.62	5.81	0.688 [a]
	SD	3.72	3.32	
	Range	-14.0 – 12.2	-2.0 – 14.0	
Study 02	Categorical Pain on day			
	0	1 (1%)	0 (0%)	0.986 [b]
	4	51 27(%)	56 (31%)	
	5	60 (31%)	45 (25%)	
	6	46 (24%)	42 (23%)	
	7	22 (12%)	31 (17%)	
	8	9 (5%)	2 (1%)	
	9	2 (1%)	3 (2%)	
	10	0	2	
	Unknown			

a. P-values for treatment comparisons from a 2-way ANOVA with factors of site and treatment
b. P-values from Cochran-Mantel-Haenszel test for row mean scores, adjusted for site

Table D: Patient Demographics; Study 02, ITT

Variable	Descriptive Statistics	ACTIVE	PLACEBO	TOTAL	P-Values
Number of Patients		191	181	372	
Age (yrs)	N	181	172	353	0.611 [a]
	Mean	32.65	33.06	32.85	
	SD	9.49	10.70	10.08	
	Range	18.3-56.5	18.1-70.8	18.1-70.8	
Sex	Male	117 (64%)	124 (72%)	241 (68%)	0.093 [b]
	Female	65 (36%)	48 (28%)	113 (32%)	
	Unknown	9	9	18	
Race	White	14 (70%)	10 (63%)	24 (67%)	0.640 [b]
	Black	5 (25%)	5 (31%)	10 (28%)	
	Hispanic	1 (5%)	0 (0%)	1 (3%)	
	Asian	0 (0%)	0 (0%)	0 (0%)	
	Other	0 (0%)	1 (6%)	1 (3%)	
	Unknown	171	165	336	
Weight (lbs)	N	178	170	348	0.010 [a]
	Mean	165.76	175.69	170.61	
	SD	36.37	39.14	38.02	
	Range	95.0-297.0	103.0-302.0	95.0-302.0	
Heart Rate	N	188	175	363	0.551 [a]
	Mean	71.73	71.03	71.39	
	SD	10.52	10.56	10.53	
	Range	44.0-108.0	46.0-105.0	44.0-108.0	
Systolic Blood Pressure	N	187	176	363	0.138 [a]
	Mean	117.66	119.95	118.77	
	SD	13.85	14.80	14.34	
	Range	88.0-175.0	86.0-186.0	86.0-186.0	
Diastolic Blood Pressure	N	187	176	363	0.318 [a]
	Mean	74.43	75.38	74.89	
	SD	9.46	10.66	10.06	
	Range	51.0-101.0	50.0-120.0	50.0-120.0	
Temperature	N	178	170	348	0.472 [a]
	Mean	97.96	97.88	97.92	
	SD	0.85	0.86	0.85	
	Range	95.1-99.7	94.4-99.9	94.4-99.9	

a. P-values for treatment comparisons from a 2-way ANOVA with factors of site and treatment
b. P-values from Cochran-Mantel-Haenszel test for row mean scores, adjusted for site

Table E: Primary efficacy Variable analysis: Study 01

Variable	Day	Active			Placebo			P-Value [a]
		N	Lsmean	Stderr	N	LSmean	Stderr	
ITT								
PID	Day 3	106	2.69	0.18	106	2.27	0.18	0.108
	Day 7	106	4.00	0.20	106	3.66	0.20	0.228
	Day 14	106	5.25	0.18	106	4.87	0.18	0.132
SPID	Day 3	106	8.40	0.53	106	7.26	0.53	0.132
	Day 7	106	24.58	1.23	106	22.13	1.23	0.161
	Day 14	106	61.30	2.27	106	56.15	2.27	0.109
POPD	Day 3	105	1.22	0.36	105	1.59	0.36	0.463
	Day 7	105	2.44	0.36	105	2.61	0.36	0.747
	Day 14	105	3.89	0.38	104	3.87	0.38	0.970
SPOPD	Day 3	105	4.13	1.03	105	5.24	1.03	0.451
	Day 7	105	14.04	2.26	104	15.91	2.27	0.560
	Day 14	105	41.26	4.60	104	42.79	4.62	0.814
Per-Protocol								
PID	Day 3	102	2.68	0.19	104	2.28	0.18	0.126
	Day 7	102	4.03	0.20	104	3.69	0.20	0.237
	Day 14	102	5.33	0.17	104	4.93	0.17	0.104
SPID	Day 3	102	8.40	0.54	104	7.30	0.54	0.151
	Day 7	102	24.72	1.25	104	22.30	1.24	0.172
	Day 14	102	62.00	2.26	104	56.73	2.23	0.099
POPD	Day 3	102	1.14	0.36	104	1.60	0.36	0.369
	Day 7	102	2.40	0.36	104	2.62	0.36	0.660
	Day 14	102	3.89	0.38	104	3.87	0.38	0.971
SPOPD	Day 3	102	3.91	1.04	104	5.26	1.03	0.357
	Day 7	102	13.65	2.27	104	15.91	2.25	0.481
	Day 14	102	40.86	4.63	104	42.79	4.58	0.768

a. P-values for treatment comparisons from a 2-way ANOVA with factors of site and treatment

Table F: Secondary Efficacy Variable analysis: Global Response to Treatment, Intent–to-Treat Patients, Study 01

	ACTIVE	PLACEBO	P-VALUE[a]
Number of Patients	106	107	
Investigator's Global Response to Treatment			
Day 3			
No Improvement	12 (11%)	17 (16%)	0.386
Mild Improvement	33 (31%)	32 (30%)	
Moderate Improvement	37 (35%)	35 (33%)	
A Lot of Improvement	21 (20%)	22 (21%)	
Complete Resolution	2 (2%)	0 (0%)	
Not Reported	1	1	
Day 7			
No Improvement	1 (1%)	10 (10%)	0.287
Mild Improvement	24 (24%)	15 (15%)	
Moderate Improvement	28 (27%)	35 (34%)	
A Lot of Improvement	43 (42%)	37 (36%)	
Complete Resolution	6 (6%)	6 (6%)	
Not Reported	4	4	
Day 14			
No Improvement	6 (6%)	9 (9%)	0.345
Mild Improvement	6 (6%)	5 (5%)	
Moderate Improvement	12 (12%)	15 (15%)	
A Lot of Improvement	40 (40%)	40 (39%)	
Complete Resolution	37 (37%)	33 (32%)	
Not Reported	5	5	
Patient Assessment of the Global Response to Therapy			
Day 14			
None	8 (8%)	9 (9%)	0.887
Poor	5 (5%)	5 (5%)	
Fair	19 (19%)	19 (19%)	
Good	35 (35%)	34 (33%)	
Excellent	34 (34%)	35 (34%)	
Not Reported	5	5	

[a] P-values obtained from the Cochran-Mantel-Haenszel test for row mean scores, adjusted for site

Table G: Baseline Variable Demographics, ITT, Investigator Rowbotham, Study 01

VARIABLE	ACTIVE	PLACEBO	TOTAL	P-VALUES
Baseline VAS	5.90	6.18	6.04	0.219[a]
Mean	1.02	1.28	1.16	
SD	3.9-8.8	3.6-9.5	3.6-9.5	
Range				
Baseline Pain on Pressure (POP)				
Mean	5.48	6.19	5.84	0.328[a]
SD	4.08	3.37	3.74	
Range	-14.0-12.0	0.0-14.0	-14.0-14.0	
Baseline Skin Irritation				
None	46 (82%)	42 (78%)	88 (80%)	0.812[b]
Mild	4 (7%)	7 (13%)	11 (10%)	
Moderate	6 (11%)	5 (9%)	11 (10%)	
Severe	0 (0%)	0 (0%)	0 (0%)	
Baseline Swelling				0.040[b]
None	24 (43%)	19 (35%)	43 (39%)	
Mild	28 (50%)	20 (37%)	48 (44%)	
Moderate	4 (7%)	15 (28%)	19 (17%)	
Severe	0 (0%)	0 (0%)	0 (0%)	
Baseline Active Range-of-Motion Affected				0.011[b]
None	38 (68%)	23 (43%)	61 (55%)	
Mild	11 (20%)	18 (33%)	29 (26%)	
Moderate	7 (13%)	12 (22%)	19 (17%)	
Severe	0 (0%)	1 (2%)	1 (1%)	
Not Reported	0	0	0	
Baseline Severity of Injury				0.158[b]
Mild	33 (59%)	26 (48%)	59 (54%)	
Moderate	23 (41%)	26 (48%)	49 (45%)	
Severe	0 (0%)	2 (4%)	2 (2%)	

[a] P-values for treatment comparisons from a one-way analysis of variance with factor of treatment. [b] P-values from Cochran-Mantel-Haenszel test for row mean scores.

Table H: Patient Assessment of Patch Local Tolerability, Study 01

	ACTIVE	PLACEBO	P-VALUE[a]
Patient Assessment			
Day 3			0.021
None	0(0%)	0(0%)	
Poor	1(1%)	2(2%)	
Fair	6(6%)	13(12%)	
Good	34(32%)	41(39%)	
Excellent	65(61%)	50(47%)	
Not Reported	0	1	
Day 7			
None	0(0%)	1(1%)	0.173
Poor	0(0%)	0(0%)	
Fair	4(4%)	7(7%)	
Good	34(33%)	37(36%)	
Excellent	64(63%)	58(56%)	
Not Reported	4	4	
Day14			
None	0(0%)	0(0%)	0.093
Poor	1(1%)	0(0%)	
Fair	5(5%)	10(10%)	
Good	27(27%)	36(35%)	
Excellent	68(67%)	56(55%)	
Not Reported	5	5	

[a]P-values obtained from the Cochran-Mantel-Haenszel test for row mean scores, adjusted for site.

Table I: Average pain score, 24-hour day with Zero Carried Forward, Study 02

	Day	Active			Placebo			P-Value
		N	Lsmean	Stderr	N	LSmean	Stderr	
ITT	Day 0	191	6.34	0.09	181	6.32	0.09	0.920[a]
	Day 1	191	5.93	0.05	181	5.92	0.06	0.981[b]
	Day 2	191	4.77	0.11	181	4.88	0.11	0.445[b]
	Day 3	191	3.89	0.13	181	4.16	0.13	0.116[b]
	Day 4	191	3.18	0.15	181	3.50	0.15	0.116[b]
	Day 5	191	2.63	0.15	181	2.94	0.16	0.137[b]
	Day 6	191	2.14	0.15	181	2.59	0.16	0.030[b]
	Day 7	191	1.76	0.15	181	2.24	0.16	0.023[b]
	Day 8	191	1.43	0.15	181	1.96	0.15	0.009[b]
	Day 9	191	1.19	0.15	181	1.66	0.15	0.018[b]
	Day 10	191	0.98	0.14	181	1.52	0.15	0.005[b]
	Day 11	191	0.77	0.14	181	1.34	0.14	0.002[b]
	Day 12	191	0.71	0.13	181	1.16	0.13	0.011[b]
	Day 13	191	0.62	0.12	181	0.99	0.13	0.025[b]
	Day 14	191	0.54	0.12	181	0.85	0.12	0.057[b]
Per-Protocol	Day 0	188	6.33	0.09	177	6.34	0.09	0.936[a]
	Day 1	188	5.92	0.05	177	5.92	0.06	0.990[b]
	Day 2	188	4.76	0.11	177	4.89	0.11	0.369[b]
	Day 3	188	3.86	0.13	177	4.15	0.13	0.091[b]
	Day 4	188	3.15	0.15	177	3.48	0.15	0.094[b]
	Day 5	188	2.57	0.16	177	2.92	0.16	0.095[b]
	Day 6	188	2.09	0.15	177	2.57	0.16	0.020[b]
	Day 7	188	1.71	0.15	177	2.21	0.16	0.015[b]
	Day 8	188	1.37	0.15	177	1.94	0.16	0.005[b]
	Day 9	188	1.13	0.15	177	1.63	0.15	0.011[b]
	Day 10	188	0.92	0.14	177	1.50	0.15	0.003[b]
	Day 11	188	0.72	0.14	177	1.32	0.14	0.001[b]
	Day 12	188	0.64	0.13	177	1.14	0.13	0.004[b]
	Day 13	188	0.55	0.12	177	0.98	0.13	0.009[b]
	Day 14	188	0.47	0.12	177	0.83	0.12	0.021[b]

a. P-values for treatment comparisons from a 2-way ANOVA with factors of site and treatment
b. P-values from a 2-way ANCOVA with factors of treatment and investigator as factors and baseline severity as the covariate

Table J: Average pain score, Nominal Study Day, Last Observation Carried Forward (LOCF), Study 02

	Day	Active			Placebo			P-Value
		N	Lsmean	Stderr	N	LSmean	Stderr	
ITT	Day 0	191	6.34	0.09	181	6.32	0.09	0.920[a]
	Day 1	191	6.13	0.04	181	3.13	0.04	0.993[b]
	Day 2	191	5.13	0.10	181	5.17	0.11	0.775[b]
	Day 3	191	4.31	0.12	181	4.43	0.12	0.427[b]
	Day 4	191	3.57	0.13	181	3.85	0.14	0.128[b]
	Day 5	191	1.13	0.14	181	3.33	0.15	0.296[b]
	Day 6	191	2.77	0.14	181	3.04	0.15	0.164[b]
	Day 7	191	2.54	0.14	181	2.78	0.15	0.218[b]
	Day 8	191	2.30	0.14	181	2.56	0.15	0.185[b]
	Day 9	191	2.12	0.14	181	2.39	0.15	0.159[b]
	Day 10	191	1.96	0.14	181	2.30	0.15	0.075[b]
	Day 11	191	1.87	0.14	181	2.20	0.15	0.081[b]
	Day 12	191	1.82	0.14	181	2.09	0.14	0.159[b]
	Day 13	191	1.78	0.14	181	2.01	0.15	0.222[b]
	Day 14	191	1.72	0.14	181	1.92	0.15	0.306[b]
Per-Protocol	Day 0	188	6.33	0.09	177	6.34	0.09	0.936[a]
	Day 1	188	6.13	0.04	177	6.12	0.04	0.856[b]
	Day 2	188	5.12	0.10	177	5.17	0.11	0.680[b]
	Day 3	188	4.28	0.12	177	4.43	0.13	0.367[b]
	Day 4	188	3.54	0.13	177	3.84	0.14	0.103[b]
	Day 5	188	3.09	0.14	177	3.32	0.15	0.250[b]
	Day 6	188	2.72	0.14	177	3.03	0.15	0.115[b]
	Day 7	188	2.50	0.15	177	2.77	0.15	0.161[b]
	Day 8	188	2.26	0.14	177	2.55	0.15	0.137[b]
	Day 9	188	2.08	0.14	177	2.38	0.15	0.116[b]
	Day 10	188	1.91	0.15	177	2.29	0.15	0.049[b]
	Day 11	188	1.83	0.14	177	2.20	0.15	0.054[b]
	Day 12	188	1.78	0.14	177	2.08	0.15	0.111[b]
	Day 13	188	1.73	0.14	177	2.00	0.15	0.156[b]
	Day 14	188	1.67	0.14	177	1.91	0.15	0.214[b]

a. P-values for treatment comparisons from a 2-way ANOVA with factors of site and treatment

b. P-values from a 2-way ANCOVA with factors of treatment and investigator as factors and baseline severity as the covariate

Table K: Secondary efficacy Variable analysis, Study 02

Population	Variable	Category	ACTIVE	PLACEBO	TOTAL	P-values[a]
	Number of patients		191	181	372	
	Patients' Global Assessment	None	16 (8%)	15 (8%)	31 (8%)	0.118
		Poor	14 (7%)	11 (6%)	25 (7%)	
		Fair	32 (17%)	55 (30%)	87 (23%)	
		Good	67 (35%)	57 (31%)	124 (33%)	
		Excellent	62 (32%)	43 (24%)	105 (28%)	
	Investigators' Global Assessment	None	13 (7%)	15 (8%)	28 (8%)	0.158
		Poor	16 (8%)	13 (7%)	29 (8%)	
		Fair	39 (21%)	51 (29%)	90 (24%)	
		Good	63 (33%)	56 (31%)	119 (32%)	
		Excellent	59 (31%)	43 (24%)	102 (28%)	
Per-Protocol	Number of patients		188	177	365	
	Patients' Global Assessment	None	16 (9%)	14 (8%)	30 (8%)	0.143
		Poor	14 (7%)	11 (6%)	25 (7%)	
		Fair	31 (16%)	54 (31%)	85 (23%)	
		Good	65 (35%)	55 (31%)	120 (33%)	
		Excellent	62 (33%)	43 (24%)	105 (29%)	
	Investigators' Global Assessment	None	13 (7%)	15 (9%)	28 (8%)	0.174
		Poor	16 (9%)	12 (7%)	28 (8%)	
		Fair	38 (20%)	50 (29%)	88 (24%)	
		Good	62 (33%)	55 (32%)	117 (32%)	
		Excellent	58 (31%)	42 (24%)	100 (28%)	

a. P-values from Cochran-Mantel-Haenszel test stratified by research study center

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