CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-234

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

1 Executive Summary

1.1 Recommendation

Information submitted in this complete response dated 7/27/2006 is acceptable provided that a mutually satisfactory agreement can be reached between the Agency and Sponsor regarding the labeling changes.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology Findings

Current submission is a complete response addressing deficiencies identified in the not approvable letter issued by the Agency on 10/18/2001. See Clinical Pharmacology review dated 10/04/2001 by Dr. Veneeta Tandon for further details on the submitted Clinical Pharmacology data and the Agency's assessment of it. From a Clinical Pharmacology perspective, the deficiencies relate mainly to the lack of validation reports for analytical methods used in the analysis of plasma samples from the submitted PK studies. Specifically, the following are the clinical pharmacology related issues (in italics) listed by the Agency and the responses to them by the sponsor (in bold);

• *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 report is of no regulatory significance in its current form and cannot be used for labeling purposes.*
IBSA Response: A validation report of the analytical methods employed in study #910195 (which is ~15 years old) is unavailable. Moreover, PK data derived from this study is notably different from three other studies summarized in the Table below which used validated analytical methods.

• *Study report PK-0033 lacks information on long term stability of plasma samples.*
IBSA Response: Information is presented in *Annex 21* that documents the stability of diclofenac in human plasma after storage for 4 hours at room temperature and after 48 hours in the autosampler. Stability information is presented after one, two, and three freeze/thaw cycles.

• *Study PK-9814 lacks an assay validation report. The methodology and lower limit of quantification differ from Study 910195 and PK-0033.*
IBSA Response: PK-9814 was performed with an *oral* dosage form of Diclofenac Epolamine ⟶ The methodology and lower limit of quantification differ from studies 910195 and PK-0033 because blood levels from the oral dosage form are much higher than with topical application of the drug. Furthermore, the study was examining only the levels of the counter-ion, Epolamine. It was provided in the NDA submission specifically

to provide additional safety information for the drug substance. Annex 22 contains the requested validation reports for study PK-9814.

• *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 acceptable.*

IBSA Response: One of the studies above (CRO-PK-00-33) includes an assay validation report, as do two additional PK studies (CRO-PK-98-13 and CRO-PK-02-76) which are provided in Annex 23 and Annex 24, respectively. Relevant plasma pharmacokinetic data from these three studies (plus 910915) is summarized below.

Diclofenac Epolamine Patch Pharmacokinetic Studies

Study (Year)	Study Design	Outcome			
910915* (1991)	DEP vs DEgel; 10 Subjects; Open label, randomized, two-way crossover; Dosing – bid days 1-7, am day 8; Application site – upper back; Primary PK parameters – C_{max}, T_{max}, AUC_{0-12}.		C_{max}	T_{max}	AUC_{0-12}
		DEP:	17.4 ng/mL	5.4 hr	119.3 ng•hr/mL
		DEgel:	28.1 ng/mL	3.1 hr	104.7 ng•hr/mL
CRO-PK-98-13 (1998)	DEP vs DEP+Heparin; 16 Subjects; Open label, randomized, two-way crossover; Dosing – bid days 1-7, am day 8; Application site – lumbar region of back, right side; Primary PK parameters – Css_{max}, Tss_{max}, AUCss.		C_{max}	T_{max}	AUC_{0-12}
		DEP:	3.6 ng/mL	2.2 hr	22.5 ng•hr/mL
		DEP+H:	3.5 ng/mL	3.7 hr	23.4 ng•hr/mL
CRO-PK-00-33 (2000)	DEP (Rest) vs DEP (Exercise); 6 Subjects; Open label, randomized, two-way crossover; Dosing – bid days 1-3, am day 4 (+rest or exercise for 12 hr); Application site – front thigh, right side; Primary PK parameters – Css_{max}, Tss_{max}, AUCss.		C_{max}	T_{max}	AUC_{0-12}
		DEP (R):	4.6 ng/mL	5.8 hr	36.0 ng•hr/mL
		DEP (E):	4.8 ng/mL	5.8 hr	43.8 ng•hr/mL
CRO-PK-02-76 (2002)	DEP; 10 Subjects; Open label; Dosing - am day 1, bid days 2-7 days, am day 8; Application site – upper inner arm; Primary PK parameters (single dose/SD, steady state/SS) – Css_{max}, Tss_{max}, AUCss.		C_{max}	T_{max}	AUC_{0-24}
		DEP (SD):	1.8 ng/mL	12.8 hr	20.0 ng•hr/mL
		DEP (SS):	3.5 ng/mL	3.6 hr	35.9 ng•hr/mL

* Three notable differences between study 910915 and the other three summarized in this table include: (a) the method of analysis was not validated; (b) the patch location was the upper back in contrast to the lumbar back, thigh, and upper arm, respectively; and (c) the patch was secured with an additional tape covering which may have affected the delivery of active through the skin due to increased application site occlusion. The mean DEPss AUC for all studies was 51.5 ng•hr/mL, and 34.6 ng•hr/mL excluding 910915.

• *In the NDA the applicant has not presented any information regarding dose ranging or dose selection. As part of their re-submission the applicant should provide a rationale as to their selection of the patch size and concentration and how these factors relate to clinical efficacy/safety.*

IBSA Response: Historically, the first product containing the Diclofenac Epolamine drug substance in Europe was a topical gel. The patch format was a follow-on product to the gel and was designed to display similar, overall drug-delivery characteristics as those of the existing product. The size of the patch along with its elastic properties have been the standard for such topical analgesic patches in Japan for many years. The size is incidentally identical to the vast majority of other analgesic patches produced by the manufacturer; the total reaching approximately ——— patches per year. The performance of this type of patch in terms of adherence to the skin and the capacity to accommodate movement of a limb joint is, to a large degree, dependent on size.

The drug concentration of 1.3% is the equivalent of 1% diclofenac sodium salt. This drug concentration, with its concomitant delivery profile, was accepted by the Sponsor as suitable for a product that will continuously deliver drug when 8applied to the skin, as opposed to the more sporadic drug delivery profile of intermittent gel application.

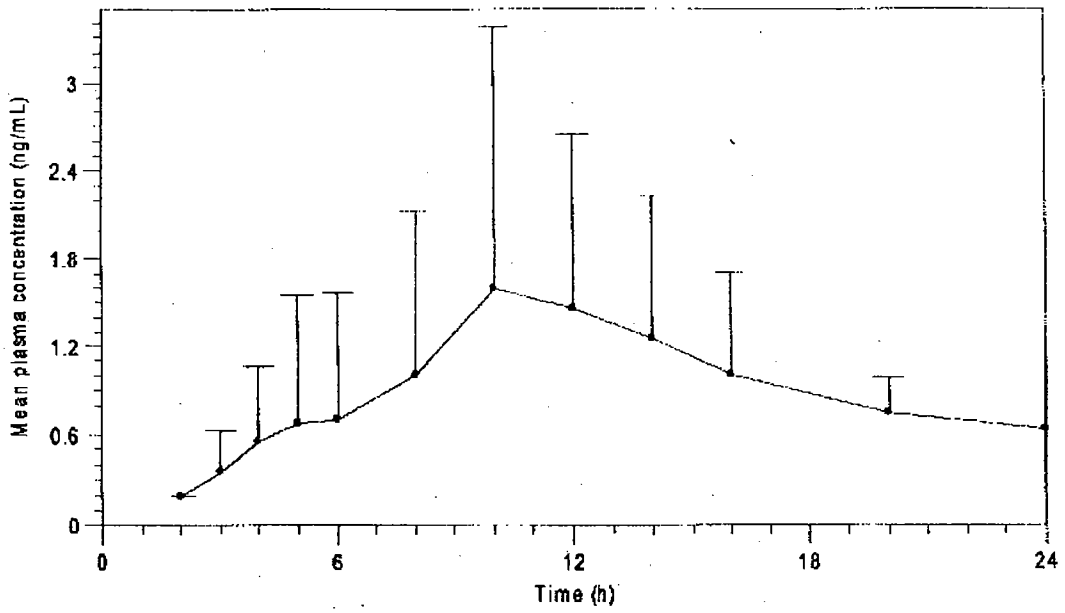
Findings from the new pharmacokinetic study (study # CRO-PK-02-76) :

In this study conducted in healthy male and female subjects, one Flector patch was applied on days 1 and 8 or twice on days 2 – 7 on the upper inner left arm. The plasma samples were analyzed employing a validated LC MS/MS method. First detectable plasma levels of diclofenamic acid were observed 2 – 8 hours following single patch application. Low peak plasma levels in the range of 0.68 – 6.1 ng/mL were observed between 10 – 20 hours post dose .

Main PK parameters of diclofenamic acid calculated in the 0-24h period (after single dose)

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-24} (ng×h/mL)	AUC_{0-12} (ng×h/mL)	AUC_{∞} (ng×h/mL)	$t_{½}$ (h)	MRT (h)
MEAN	1.77	12.8	19.99	8.67	30.21	12.39	26.07
SD	1.69	3.01	15.93	9.63	15.40	7.15	11.10
CV%	95.48	23.52	79.69	111.13	50.98	57.72	42.60
MIN	0.68	10	6.92	1.14	14.91	4.55	13.20
MAX	6.05	20	60.17	33.43	65.02	29.48	50.71
N	10	10	10	10	10	10	10

Plasma concentration vs time profile of diclofenac following single Flector Patch application:

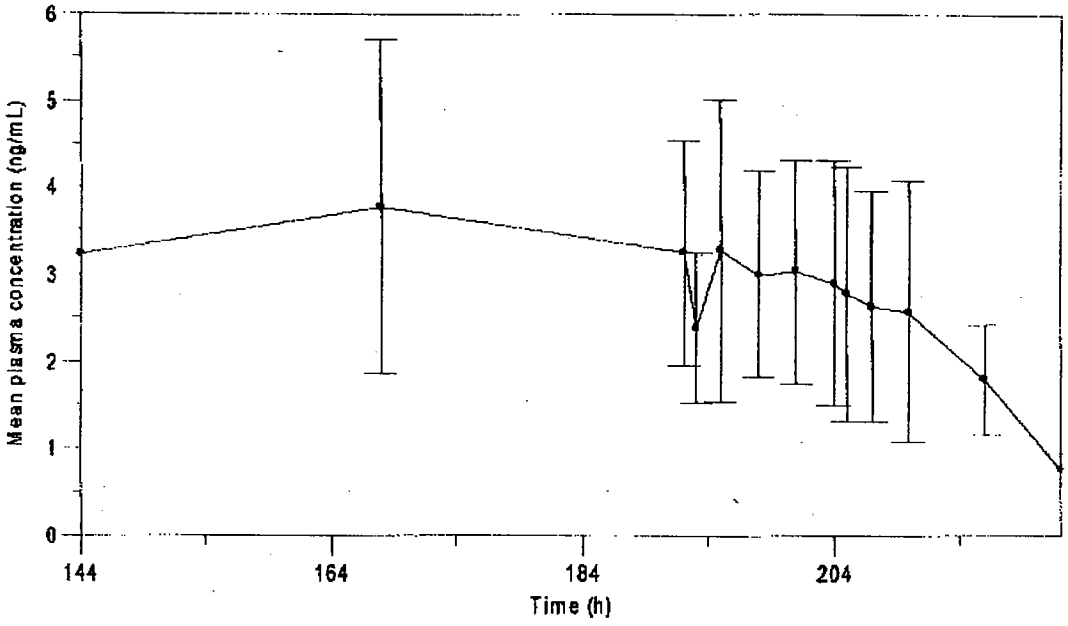


After multiple patch application, plasma levels of diclofenac were in the similar range at predose time points on days 6 & 7 (1.3 – 8.8 ng/mL) compared to Day 8 predose (1.8 -6.3 ng/mL) and at Cmax on Day 8 (2 -7.5 ng/mL). This indicates the achievement of steady state around Day 6 of Flector patch application with BID regimen. On an average, peak plasma levels (range 2.1 – 7.5 ng/mL) appear twice as much at steady-state compared to single dose. None the less, levels at steady state are also low **(see study synopsis in the appendix for additional study details)** .

Main PK parameters of diclofenamic acid calculated at steady state (after multiple doses) and at the elimination phase

	C_{max} (ng/mL)	C_{min} (ng/mL)	$C_{average}$ (ng/mL)	%PTF	AUC_{ss} (ng×h/mL)	t_{max} (h)	t½ (h)
MEAN	3.54	2.33	2.99	39.81	35.94	3.60	11.88
SD	1.57	0.90	1.29	15.48	15.43	3.95	4.03
CV%	44.35	38.63	43.14	38.88	42.93	109.72	33.92
MIN	2.12	1.20	1.75	23.96	21.06	0	7.43
MAX	7.49	4.35	5.94	70.92	71.24	12	21.56
N	10	10	10	10	10	10	10

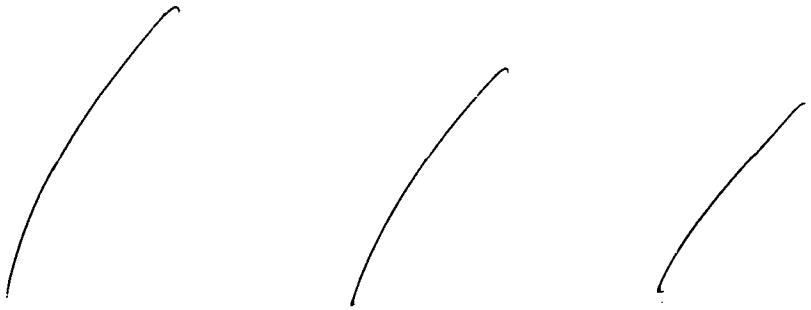
Plasma concentration vs time profile of diclofenac at steady state following application of multiple doses of Flector Patch:

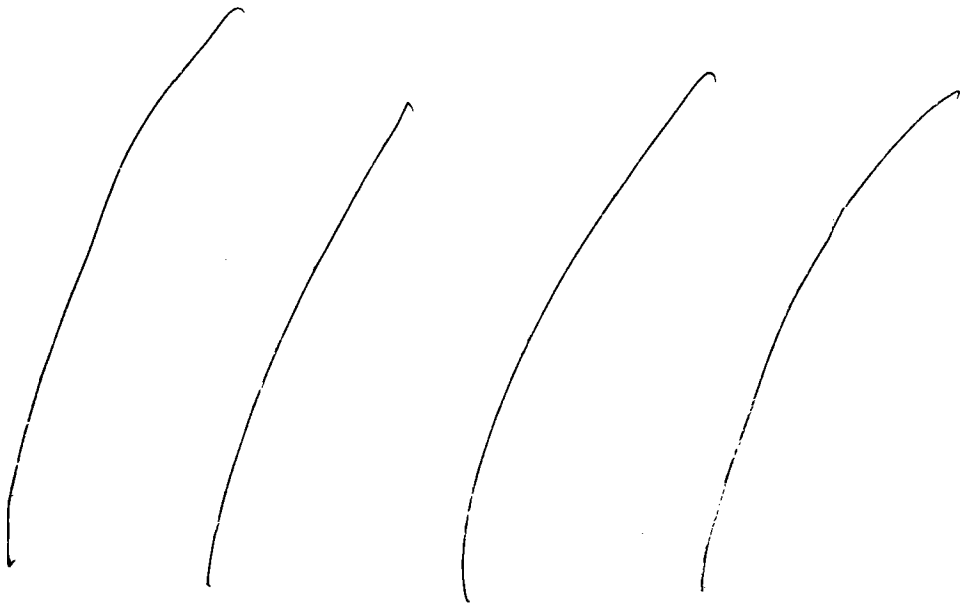


APPEARS THIS WAY
ON ORIGINAL

Overall, data submitted in this new study is reliable as the analytical assay was adequately validated and adequately describes the bioavailability of the product after single and multiple dose applications. Further, the analytical data provided for the previous studies and/or the explanations provided by the sponsor in response to the issues identified in the non approvable letter have been adequately addressed from a Clinical Pharmacology perspective.

2 Labeling





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✓ Draft Labeling

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3. Appendices

3.1 Study synopsis CRO-PK-02-76

Study report CRO-PK-02-76

Epicutaneous absorption of diclofenac epolamine after single dose and at steady state after administration of Flector EP Tissugel® to 10 male and female healthy volunteers

Single centre, open, multiple doses pharmacokinetic study

Test formulation(s):	Flector EP Tissugel®, epicutaneous plaster, containing 180 mg diclofenac epolamine
Reference formulation(s):	Not applicable
Sponsor:	IBSA – Institut Biochimique s.a. Via del Piano, PO Box 266 CH-6915 Pambio-Noranco, Switzerland Phone: +41.91.9857676
Investigator:	
Development phase:	Phase I
Version and date:	Final, 14NOV02

This study was conducted in accordance with Good Clinical Practice (GCP) and to ICH topic E6

2 SYNOPSIS

Name of Company: IBSA s.a., Switzerland **Name of Finished Product:** Flector EP Tissugel® **Name of active substance(s):** diclofenac epolamine	**TABULAR FORMAT** **REFERING TO PART IV OF THE DOSSIER** **Volume:** **Page:**	**(For National Authority Use only)**
Title of the study: Epicutaneous absorption of diclofenac epolamine after single dose and at steady state after administration of Flector EP Tissugel® to 10 male and female healthy volunteers		
Investigator(s): / / /		
Study center:		1
Publication (rererence):		
Studied period (years): 2002	**date of first enrolment:** JUN02 **date last vol. completed:** JUN02	**Phase of development:** I
Objectives: To revise the pharmacokinetic data obtained with Flector EP-Tissugel® in the last decade, while testing a recently manufactured batch		
Methodology: Single centre, open, multiple doses pharmacokinetic study		
Number of subjects (planned and analysed): 10 healthy male and female volunteers		
Diagnosis and criteria for inclusion: Males and females (not pregnant or lactating, using an appropriate method of contraception), 18-45 years old; 18-30 Kg/m^2; normal values of BP (100-139 mm Hg SBP and 50-89 mmHg DBP) and of HR (50-90 bpm), measured after 5 min of rest (sitting position); no clinically relevant abnormalities at ECG (12 leads); no clinically relevant abnormal physical findings, no abnormal laboratory values; no history of anaphylaxis to drugs or allergic reactions in general, which may affect the outcome of the study, in particular no history of hypersensitivity to NSAIDs; no relevant history of renal, hepatic, gastrointestinal, cardiovascular, respiratory, skin, haematological, endocrine or neurological diseases, that may interfere with the aim of the study, in particular no history of peptic ulcer, bronchial asthma and/or bronchospasm, urticaria; no skin abnormalities likely to be aggravated by the study medication, such as dermatological diseases or infections, rash, skin sensitive to topiçal preparations or adhesive dressings; no medication, including OTC products, during 2 weeks before the start of the study, in particular no use of NSAIDs; no participation in the evaluation of any drug, no blood donations for 3 months prior to this study; no history of drug, alcohol (>2 drinks/day, defined according to USDA Dietary Guidelines 2000) or tobacco abuse (>10 cigarettes/day); ability to comprehend the full nature and purpose of the study, including possible risks and side effects; ability to co-operate with the Investigator and to comply with the requirements of the entire study; written informed consent prior to inclusion in the study.		
Test product, dose, mode of administration, batch N°: Flector EP Tissugel®, epicutaneous plaster, containing 180 mg diclofenac epolamine (DHEP), corresponding to 150 mg diclofenamic acid. Plasters were applied once (days 1 and 8) or twice (days 2-7) a day to the upper inner part of the left arm. Batch 011002, expiry 10/2004		
Duration of treatment: 8 days		
Reference therapy, dose, mode of administration, batch N°: n.a.		
Criteria for evaluation: PK variables: After single dose: AUC_{0-12}, AUC_{0-24}, t_{max}, C_{max}, $t_{1/2}$, MRT; at the steady state: AUC_{ss}, $C_{average}$, C_{ssmax}, C_{ssmin}, t_{max}, %PTF; at the elimination phase: $t_{1/2}$. **Plaster adhesiveness:** adhesiveness score.		
Criteria for evaluation (safety): Local tolerability after plaster removal, AEs; Vital signs (BP, HR); ECGs; BW; Laboratory analysis		
Statistical methods: PK analysis was performed using Kinetica™ Version 4.0 InnaPhase Corporation, Philadelphia, USA. The data documented in this trial and the clinical parameters measured were described using classic descriptive statistics for quantitative variables and frequencies for qualitative variables		

Name of Company: IBSA s.a., Switzerland Name of Finished Product: Flector EP Tissugel® Name of active substance(s): diclofenac epolamine	TABULAR FORMAT REFERING TO PART IV OF THE DOSSIER Volume: Page:	(For National Authority Use only)

Results:

PK results

Following the single dose of Flector EP Tissugel, first detectable levels of diclofenamic acid were observed after a time ranging from 2 h (volunteer 10) to 8 h (volunteer 3) post-application. Levels of diclofenamic acid were still detectable in plasma 24 h after plaster application for all volunteers. Mean pharmacokinetic parameters for diclofenamic acid in 24 h, after single dose, are summarised below.

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-24} (ng×h/mL)	AUC_{∞} (ng×h/mL)	t½ (h)	MRT (h)
MEAN	1.77	12.8	19.99	30.21	12.39	26.07
SD	1.69	3.01	15.93	15.40	7.15	11.10
CV%	95.48	23.52	79.69	50.98	57.72	42.60
MIN	0.68	10	6.92	14.91	4.55	13.20
MAX	6.05	20	60.17	65.02	29.48	50.71
N	10	10	10	10	10	10

After day 1, multiple doses of Flector EP Tissugel were applied to the volunteers' left arm until study day 8 (2 plasters on days 2-7, 1 on day 8). Mean pharmacokinetic parameters for diclofenamic acid at the steady state and elimination phase are summarised below.

	C_{max} (ng/mL)	C_{min} (ng/mL)	$C_{average}$ (ng/mL)	%PTF	AUC_{ss} (ng×h/mL)	t_{max} (h)	t½ (h)
MEAN	3.54	2.33	2.99	39.81	35.94	3.60	11.88
SD	1.57	0.90	1.29	15.48	15.43	3.95	4.03
CV%	44.35	38.63	43.14	38.88	42.93	109.72	33.92
MIN	2.12	1.20	1.75	23.96	21.06	0	7.43
MAX	7.49	4.35	5.94	70.92	71.24	12	21.56
N	10	10	10	10	10	10	10

Statistical analysis by two-way ANOVA, with treatment and subjects as covariates, indicate that the differences in both C_{max} and AUC calculated after single dose and at steady state are statistically significant, with treatment having an effect ($p=0.0001$ for C_{max} and $p=0.026$ for AUC). The difference between T_{max} mean values was also significant (non-parametric Friedman test).

Adhesiveness

Adhesiveness of the first plaster (single dose, day 1) was quite low. With the use of an elastic net to keep plaster in place, plaster adhesiveness improved considerably and score 1 (i.e. 90% plaster adhered) was prevalent at most times.

Safety

No effect of treatment with Flector EP Tissugel on vital signs, ECGs and laboratory parameters was observed. Local tolerability of the plaster was very good, with absence of redness at the application site. Itching at the plaster application site and headaches were reported in 6 and 3 occasions respectively. All AEs were of mild intensity and did not require treatment.

Conclusions: After single dose of Flector EP Tissugel, diclofenamic acid C_{max} (1.77±1.69 ng/mL) was observed 12.8±3.01 h post-dose. Mean AUC_{0-24} and AUC_{∞} were 19.99±15.93 and 30.21±15.40 ng×h/mL respectively. At steady state, C_{ssmax} was 3.54±1.57 ng/mL and C_{ssmin} 2.33±0.90. The fluctuation (%PTF) between C_{ssmin} and C_{ssmax} was of 39.81±15.48%. AUCss was 35.94±15.43 ng×h/mL. Dose accumulation factor at steady state, calculated as AUC_{ss}/AUC_{∞} ratio, was 1.26 ± 0.34, thus negligible. Safety and local tolerability of Flector EP Tissugel were very good.

Date of the report: Final report 14NOV02

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/s/

Srikanth Nallani
1/19/2007 03:19:22 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
1/22/2007 06:37:05 AM
BIOPHARMACEUTICS

First Cycle 10/4/01

Clinical Pharmacology/Biopharmaceutics Review

NDA:	21-234
PRODUCT:	Diclofenac Epolamine Salt, 1.3% Adhesive Patch
SUBMISSION DATE:	12/18/00, 6/22/01
SUBMISSION TYPE:	3S
SPONSOR:	Institute Biochimique SA, Campbell, CA
REVIEWER:	Veneeta Tandon, Ph.D.
TEAM LEADER:	Dennis Bashaw, Pharm.D.

TABLE OF CONTENTS

RECOMMENDATIONS

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.

Comment:

- In the NDA the applicant has not presented any information regarding dose ranging or dose selection. As part of their re-submission the applicant provide a rationale as to their selection of the patch size and concentration and how these factors relate to clinical efficacy/safety.

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 report 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.

Veneeta Tandon, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation III

Team Leader: E. Dennis Bashaw, Pharm. D._____

LABELING COMMENTS

The labeling comments have been deferred at this time, until the sponsor provides complete assay validation for all the studies used for labeling. Until the assays are found acceptable, the study results do not carry any regulatory significance, as the validity of the data cannot be ascertained.

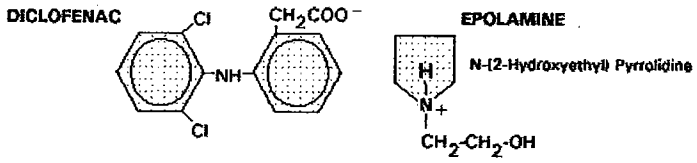
PRODUCT INFORMATION

Dosage Form: Adhesive Patch 1.3%

Indication: For the relief of pain due to strains, sprains

Pharmacologic Class: Nonsteroidal Anti-inflammatory Drug. A new salt of diclofenamic acid.

Chemical Name: (Hydroxy-2-ethyl)-1-Pyrrolidine Diclofenac Salt (DHEP),



Dosage and administration: It should be applied to the intact skin at the painful site. Apply one patch at a time within a 12-hour period,

Foreign marketing history: Diclofenac epolamine patch was first approved in Switzerland in 1993 and subsequently in many European, Latin American and Asian countries.

Formulation: The dimension of each patch is 14x10cm.

Ingredient	Purpose of Ingredient	Amount (mg/patch)
diclofenac salt (DHEP)	active ingredient	180
D-sorbitol solution (		
purified water		
1,3-butylene glycol		
sodium polyacrylate		
sodium carboxymethylcellulose		
kaolin		
propylene glycol		
gelatin		
polyvinylpyrrolidone (Povidone)		
titanium oxide		
tartaric acid		
dihydroxyaluminum aminoacetate		
polysorbate 80		
edetate disodium (EDTA)		
fragrance (Dalin PH)		
Totals		**14000.0**

OVERALL SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Diclofenac epolamine patch is intended for application to the intact skin at the painful site for the treatment of pain due to strains, sprains ——— The patch characteristics were determined from previous European experience with this dosage form.

The sponsor has conducted a total of 6 studies that describe the absorption, distribution, metabolism and excretion of diclofenac epolamine (DHEP) and the epolamine salt as such. The sponsor has conducted all the pharmacokinetic studies in healthy volunteers. The pharmacokinetics in patients ——— not been evaluated, although the absorption of diclofenac under exercise has been evaluated. The intended duration of treatment for the diclofenac epolamine patch is ——— . The sponsor has conducted the pharmacokinetic studies for a total duration of 7 days.

The sponsor has evaluated the plasma diclofenac levels after topical application of the patch. 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.

The absorption, distribution, metabolism and excretion of the epolamine cation have been evaluated after oral administration of either ^{14}C-epolamine or Flector-EP ——— Epolamine N-oxide was the major metabolite of eoplamine. The sponsor does not specify the mechanism of formation of this metabolite.

The results of three studies (#910195, PK 0033 and PK 9814) cannot be used for labeling, as they lack an assay validation report that is complete and as such is not acceptable. Without a validated assay, the studies carry no regulatory significance, as the validity of the results cannot be ascertained. These studies although technically not acceptable, have been reviewed because the poor organization of the material required that a full review be done to ascertain the missing data. None of the results from these studies can be used in regulatory decisions until the assay validation is found acceptable. The assay validation information was not requested from the sponsor during the review because at the time such a request was to be made, multiple other deficiencies in other review disciplines had also been identified. The overall extent and nature of these deficiencies were such that ——— Thus, request for submission of the analytical deficiencies was deferred to the expected NA letter to the sponsor.

The clinical endpoints are not discussed in this review, as the application is not found acceptable from the clinical perspective due to numerous reasons.

INDIVIDUAL STUDY REVIEW

Absorption and excretion of diclofenac-EP after cutaneous repeated application of two different dosage forms in healthy volunteers: plaster vs gel (Study 910195):

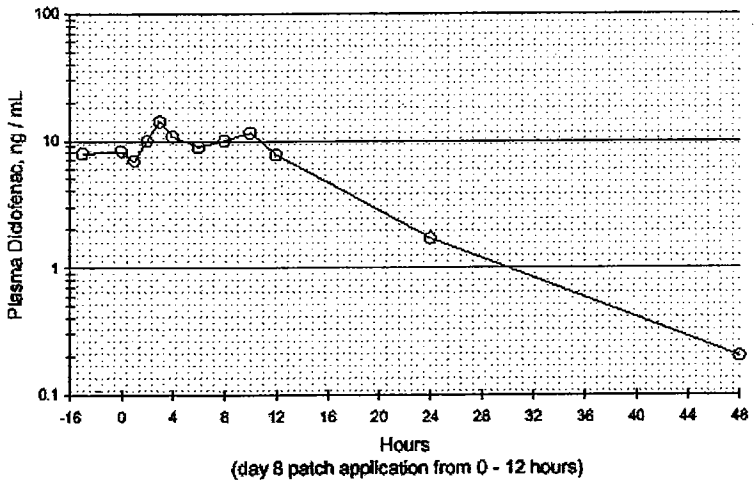
Absorption only through the plaster will be reviewed here because the gel dosage form is not the to-be-marketed formulation and has no relevance to this application. The sponsor has used the results of this study for labeling.

Study Design: Single-center, open, randomized, two way cross-over study.
Study Population: 10 healthy male volunteers, ages 22-28 yrs.
Test Product: Flector EP-Plaster, batch 62/IB-22, containing 188.5 mg DHEP, corresponding to 146.1 mg of diclofenac Na
Drug Administration: Topical epicutaneous administration of 12 hours application period, twice a day for 7 days and one application on 8th Day on upper part of the back of volunteers on an area of 15x10 cm (dimensions of the plaster). The subjects fasted overnight on the day of the blood sampling before study drug administration
Plasma Samples: At pre-dose, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24 and 48 h post-administration of the last dose for the determination of diclofenic acid.
Urine Samples: At 0-4, 4-8, 8-12, 12-24 and 24-48 hours after the last dose
Assay: Diclofenac plasma levels
Methodology: GC-MS
LLOQ 0.5 ng/mL in plasma, 1 ng/mL in urine
Validation Inter, Intra and stability not reported
Observations: The plasma pharmacokinetic parameters of diclofenac calculated after the 15th dose is shown in the following Table:

Pharmacokinetic parameter**	Mean	S.D.	CV%	Range Min.	Max
Cmax (ng/ml)	17.4	13.5	77.7	7.6	40.0
tmax (hours)	5.4	3.7	69.4	2.0	12.0
Cn (ng/ml)	3.8	2.4	86.8	1.0	7.4
tn (hours)	26.4	12.4	46.9	12.0	48.0
AUCn (h·ng/ml)	176.1	107.5	61.1	69.2	394.6
AUC(0-12)(h·ng/ml)	119.3	75.7	63.5	47.0	269.8
MRTn (hours)	9.1	3.1	33.4	5.9	16.9
AUC(0-12)(h·ng/ml)	119.3	75.7	63.5	47.0	269.8
Fa/B(0-12)	0.29	0.18	36.0	0.14	0.43
Fa/B(n)	0.33	0.14	41.2	0.13	0.51

** = calculated after the last (15th) dose.

The mean plasma diclofenac blood concentrations after application of 15 patches is shown in the following figure:



The amount excreted in the urine after topical application of the plaster is shown in the following Table:

Collection interval (h)*		Excretion (ml)	Concentration (ng/ml)	Amount excreted (ng)	% of last dose partial	% of last dose cumul.
0-4	Mean	279	22.8	4681.3	0.003	0.003
	S.D.	141	22.2	4656.9	0.003	0.003
4-8	Mean	202	19.8	3531.8	0.003	0.006
	S.D.	94	16.4	2619.1	0.002	0.005
8-12	Mean	198	15.6	3094.2	0.002	0.008
	S.D.	62	12.4	2616.4	0.002	0.007
12-24	Mean	610	5.7	3379.1	0.003	0.011
	S.D.	291	4.9	2594.7	0.002	0.009
24-48	Mean	1439	0.1	118.3	<0.001**	0.013
	S.D.	555	0.4	374.1	<0.001**	0.008
0-48	Mean			17742.0		0.013
	S.D.			10588.2		0.008

* = after the last (15th) dose.
** = 0 for mean and S.D. calculation.

- The mean plasma concentration was 7.9, 8.2, and 7.7 ng/ml, 12 hours after the 8th, 14th, and 15th applications, respectively, suggesting that steady state levels of drug had been reached. The mean and range of concentrations at each sampling time point are attached in the Appendix I on page 18.
- Eight of the ten subjects had detectable levels of plasma diclofenac (range — ng/ml) 24 hours after final patch application, but by 48 hours drug could only be found in two of the subjects (— ng/ml).
- The Cmax ranged from 7.6-40 ng/mL and the Tmax also varied from 2-12 hours.
- The inter-individual variability was very high.
- The plasma level of diclofenac appeared to be sustained over the 12 hour period.

- Urinary excretion of diclofenac over 48 hours following the last treatment was negligible, ranging from 0.004 to 0.026% of the administered dose.

Reviewer's comment:

- *The sponsor has used the results of this study for labeling purposes. Upon request the sponsor reconfirmed that the formulation of the patch used is this study is the same as to be marketed formulation. However, the study report states that the Flector EP Plaster, contained 188.5 mg of DHEP and the dimensions of the plaster was 15x10 cm. The to-be-marketed formulation has a dimension of 14x10 cm with 180 mg of DHEP. The product used in this study is Flector EP plaster as opposed to Flector EP Tissugel used in study PK0033 (Influence of exercise study), which has 180 mg of DHEP. The results of this study are also published in "Drugs Exptl. Clin. Res. XIX(3);89-95(1993), which also state the drug content as 188.5 mg and the dimension of the plaster as 15x10 cm. The sponsor's response to the higher amount of DHEP in this formulation was that 188.5 mg is still within the approved specifications for this product in stability studies (specifications on content: —) and the product has been manufactured using the same formulation. The review chemist agrees with the sponsor's response. The increase of 8.8 mg in DHEP content will not make a significant difference in systemic absorption of the drug, as the amount absorbed is less than 5% of the total available drug product in the patch (see following Study#003, which is a follow up of this current study.*
- *Most importantly, the sponsor has not submitted the complete assay validation report, An assay report is submitted, but it does not have any details of the validation components, like inter-, intra-day accuracy and precision of the assay, long term stability, freeze-thaw stability of samples, recovery etc. Due to lack of complete validation report for the study, the results from this study cannot be used for labeling purposes and as such this study is non reviewable. Any conclusions from this study should be held in suspension until the sponsor provides complete assay validation. This was not requested from the sponsor, as all the review disciplines have numerous review deficiencies and it was decided by the review team to list them in the action letter.*
- *The sponsor has named the evaluable drug in plasma as "diclofenamic acid", which may not be the chemically correct term. The correct term is "diclofenic acid" and is usually referred to as diclofenac. In this review the terms diclofenic acid and diclofenac have been used interchangeably.*

Residual diclofenac after 12-hours topical application in human with flector-EP plaster (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-hout topical application was 176.73 (3.46%), suggesting that 95.1% of DHEP remains in the plaster.

Influence of exercise on the absorption of diclofenac epolamine (DHEP) in healthy male volunteers administered epicutaneously Flector EP-Tissugel® (Study PK-0033)

The transdermal absorption can be influenced by skin temperature, hydration state of the skin, cutaneous blood flow and these parameters can be modified by physical activity. The objective of this study was the evaluation of the absorption profile of diclofenic acid from diclofenac epolamine plaster in subjects at rest and after induced physical exercise.

Study Design:	Single-center, open, randomized, two way cross-over study.
Study Population:	6 healthy male volunteers, ages 18-35 yrs.
Test Product:	Flector EP-Tissugel®, batch 000315, containing 180 mg DHEP
Drug Administration:	Topical administration of 12 hours application period, twice a day for 7 days on front thigh of volunteers. The subjects fasted overnight on the day of the blood sampling before study drug administration
Plasma Samples:	At pre-dose, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16 and 24 h post-administration of the last dose for the determination of diclofenic acid.

Subjects judged the intensity of exercise as the rating of perceived exertion by means of the 20-point Borg rating scale:

< 10	very light
10-11	light
12-13	moderate
14-16	hard
17-19	very hard
20	maximal

All subjects perceiving lower than "hard" exertion were included in the study. Subjects underwent standardized physical exercise (20 minutes of cycling with a bicycle ergometer every hour for 12 hours) or were in the resting condition (light routine ambulant daily activity) according to the randomization schedule after a three days washout period.

Analytical Validation: <u>Diclofenic acid in human plasma</u>:

Methodology:	LC/MS/MS
LLOQ:	0.5 ng/mL
Intra assay Accuracy and precision:	% CV between 1.5-5.1
Inter assay Accuracy and precision:	% CV between 0.5-6.0

Stability:	4 hrs at room temperature before extraction 48 hrs autosampler stability 3 freeze/thaw cycles
Recovery:	Extraction recovery at 1.5, 12 and 40 ng/mL ranged from 18.8% to 20.8 %.

Reviewer's Comment:

- *The sponsor has used the drug name as 'diclofenamic acid' throughout this report.*
- *Long term stability has not been provided.*

Observations:

The mean (SD) diclofenic acid pharmacokinetic parameters for resting and exercising volunteers are reported in following Table. Diclofenic acid absorption occurred both in resting and exercising volunteers, but at a 35% higher extent in the exercising volunteers as would be expected. The individual subject data is given in the Appendix on page 19.

	Resting volunteers	Exercising volunteers
$C_{pre\text{-}dose}$ (ng/mL)	2.358 ± 0.913	3.542 ± 0.884
C_{min} (ng/mL)	1.884 ± 0.959	2.760 ± 1.098
C_{max} (ng/mL)	4.607 ± 2.522	4.807 ± 1.710
$C_{average}$ (ng/mL)	2.996 ± 1.763	3.650 ± 1.415
t_{max} (h)	5.8 ± 4.8	5.8 ± 4.4
$AUC_{0\text{-}12}$ (ng×h/mL)	35.950 ± 21.160	43.801 ± 16.981
$AUC_{0\text{-}24}$ (ng×h/mL)	55.134 ± 25.256	64.887 ± 26.435
AUC_{∞} (ng×h/mL)	65.245 ± 30.524	74.478 ± 30.272
$t_{1/2}$ (h)	8.87 ± 4.38	7.21 ± 2.59
K_e (h^{-1})	0.093 ± 0.042	0.106 ± 0.034

The mean ratios and 90% confidence intervals of exercise vs. rest main parameters is shown in the following Table:

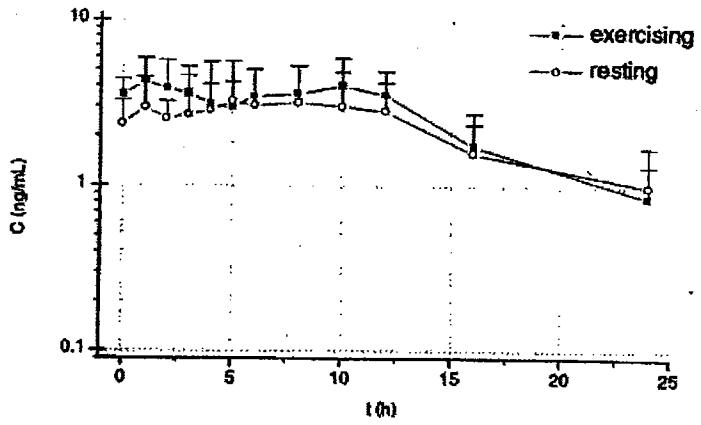
	Mean ratio	90 % C.I.
$AUC_{0\text{-}12}$ (ng×h/mL)	1.35 ± 0.31	1.0775 – 1.6204
C_{max} (ng/mL)	1.19 ± 0.52	0.8162 - 1.5343
$C_{average}$ (ng/mL)	1.35 ± 0.31	1.0775 – 1.6204
$AUC_{0\text{-}24}$ (ng×h/mL)	1.21 ± 0.10	1.118 – 1.3016

- This shows that there was a 35% increase in exposure and $C_{average}$ in the exercising subjects. This increase was also statistically significant (p=0.0436). The 19% increase in Cmax was not statistically significant (p=0.489), though the 90% confidence interval was not within the bioequivalence acceptable limits of 80-125%.
- The investigator also evaluated the adhesiveness of each patch immediately before removal after 12 h of application by selecting a score (1=closely

adhered to skin and 6=completely peeled of from the skin). Mean±SD adhesiveness assessed on patches 1 to 7 by the investigator was 1.57±0.41 in the resting group and 1.30±0.36 in the exercising group. The patch corners were slightly peeled in the resting group.

- The residual content in diclofenac epolamine patches at Day 7 and 14 suggested a higher release during exercise (3.5%) as compared to that during rest (2.8%).
- The levels of diclofenic acid at baseline were 50% higher in the group of subjects who afterwards underwent exercise in comparison to the group who remained resting. This difference was statistically significant (p=0.0103), suggesting that the absorption differences in the exercised and resting individual may be partly due to different basal condition attributable to normal variability. The 35% increase in exposure in subjects who underwent exercise could therefore be an artifact of the baseline levels and the relatively small number of subjects studied.

The Mean (SD) plasma concentration of diclofenic acid from the plaster in the resting and exercising individual is shown in the following figure.



Comparison to oral diclofenac:

The plasma levels reached after oral administration is 1.5 µg/mL after a single 50 mg diclofenac dose. These levels are 500 times higher than that reached after the topical application of diclofenac plaster (from Physicians Desk Reference).

Single and multiple dose pharmacokinetics in males and female healthy volunteers administered Flector-EP — according to three daily dose regimen (Study PK9814):

The sponsor has used the results of this study to describe the metabolism and excretion of the epolamine cation.

The aim of the present study was to investigate the plasma and urinary pharmacokinetics of epolamine and its main metabolite, epolamine N-oxide at steady state, in healthy volunteers receiving the highest allowed treatment regimen of Flector-EP® (diclofenac-epolamine).

Study Population:	Eight healthy volunteers (4M & 4F)
Dosage Administration:	Treated orally with diclofenac-EP for 8 consecutive days at the dose (as diclofenac) of 50 mg t.i.d. A 50 mg dose corresponds to 18.25 mg of epolamine. The 3 daily doses were administered at 8:00 am, 12:00 pm, and 8:00 pm with meals on Days 2-7 and once daily on Days 1 and 8.
Samples:	Plasma and urine were collected on day 1 (single dose) and 8 (multiple doses) before drug intake and up to 24 h after treatment. In addition a plasma sample was collected at day 5 and 7 before drug intake.
Analysis:	Epolamine and epolamine N-oxide were determined in plasma and urine by validated HPLC methods with MS spectrometry detection. LLOQ 10 ng/mL. Assay validation has not been provided.

Observations:

Epolamine in Plasma

Epolamine plasma concentrations after single and multiple doses

	Single Dose	Multiple Dose
Cmax (ng/mL)	11.77± 3.66	19.07±9.22
Tmax (h)	0.34 ± 0.12	0.37 ± 0.13
AUC (ng.h/mL)	53.16 + 14.47	109.88 ±30.88
T1/2 (h)	NA	NA
Accumulation ratio (Css,max/Cmax)		1.62

NA= not available Note: The sponsor has not mentioned whether the AUC is 0-t or 0-inf etc.

- After a single 50 mg dose of Flector EP — ®, corresponding to 18.25 mg of epolamine, the plasma pharmacokinetics of epolamine were characterised by rapid absorption.
- After repeated doses of Flector EP — (50 mg t.i.d.) for 8 consecutive days, steady-state conditions were reached at day 5.
- The sponsor was not able to calculate the terminal half-life of epolamine as the plasma concentrations in the terminal phase were few and very close to the limit of quantification. However, based on least square fitting of the data, the sponsor has reported the t1/2 to be 6 hours after a single dose and the t1/2 at Day 8 was estimated to be 8.7 hours. The value obtained by subtracting the Css min value from the Css, max value (13.85 ± 8.24 ng/mL) did not differ significantly from the mean Cmax value obtained after the single dose (11.77 ± 3.66 ng/mL). Thus indicating that the

alteration of the epolamine pharmacokinetics after repeated administrations of Flector EP — may not due to alteration in the epolamine absorption rate.

Epolamine in urine

- The amount of eloplamine excreted in the urine on Day 1 was 266.340 µg and that at Day 8 was 609.230 µg. The total amount excreted on Day 1 corresponded to 1.46% of the dose. This was based on an unvalidated assay procedure. Since the amount of unchanged epolamine excreted in the urine was very low, the sponsor did not pursue the validation of the assay and also did not measure unchanged epolamine concentrations in any other study.

Epolamine N-oxide (major metabolite) in plasma

Epolamine N-oxide plasma concentrations after single and multiple doses

	Single Dose	Multiple Dose
Cmax (ng/mL)	637.6 ± 199.58	753.67 ± 333.85
Tmax (h)	0.56 ± 0.17	0.68 ± 0.26
AUC (ng.h/mL)	2055.4 ± 661.06	3442.0 ± 1210.4
T1/2 (h)	5.61 ± 2.06	8.22 ± 1.40
Accumulation ratio (Css,max/Cmax)		1.18

- An increase in t1/2 of both epolamine and epolamine N-oxide was observed after multiple doses. This increase may be due to the saturation of the main biotransformation pathway for epolamine as hypothesized by the sponsor.

Epolamine N-oxide in urine

Epolamine N-oxide urine concentrations after single and multiple doses

	Single Dose	Multiple Dose
Total Amount Excreted in Urine (µg)	19492.58± 2205.48	33048.36 ± 5948.70
% of Dose Excreted in Urine	93.58	-
CL_R (mL/h)	11.35 ± 4.07	9.81± 3.66

The results of this study are in agreement with the result of the mass balance study, in which it was demonstrated that after the administration of 300 mg of radiolabeled, epolamine to three healthy volunteers, approximately 98% of the urinary radioactivity was due to the major epolamine metabolite epolamine N-oxide.

Reviewer's Comment:

- *The sponsor has not provided an assay validation for this study. This request was also not made during the review cycle for reasons stated earlier. The results of this study should be held in suspension, until a complete assay validation has been provided and is found acceptable.*

- *The sponsor has also not provided individual subject data for this study, which was provided by the sponsor upon request.*

In vitro binding to plasma proteins and to human serum albumin (Study 9703335):

Binding of ^{14}C-ethylpyrrolidine (^{14}C -EP) to plasma proteins was evaluated using equilibrium dialysis in a multi-dialysis system. The minimum dialysis time required to obtain equilibrium was 2 hours.

Dialysis of different concentrations of ^{14}C -EP against human serum albumin (2 g/l), human serum albumin at physiologic concentration (40 g/l) and human plasma proteins revealed that a negligible protein binding occurred. The percent bound to these were less than 6% in most cases, with the exception of 7% being bound with a ^{14}C -EP concentration of 16 μM and 12% being bound with a drug concentrations of 2 μM.

Metabolism study in man after single oral administration of the drug (Study 930499):

Study population: 3 healthy male
Test formulation: 300 mg of ^{14}C-EP taken orally (radioactive dose 48.9 μCi)
Urine sampling time: 0-4, 4-8, 8-12, 12-24, 24-48 and 48-72 hrs.

Observations:

- The metabolite present in urine was identified to be pyrrolidine N-oxide.
- Urinary route was not the preferred route of excretion.
- The radioactivity accumulated at the end of the collection time (72 h) accounted, on average, for 30.41±6.72 % of the administered dose. A noticeable amount of radioactivity was quickly excreted in the first 8 hour period (22.12 ± 5.87 %), followed by minor quantities in the subsequent intervals. The individual subject data is provided in Appendix I on page 20.
- The fact that only a small part of the administered dose was recovered in urine gives rise to a number of possible hypotheses. (i) most of the remaining radioactivity could be eliminated with feces without being absorbed or (ii) fecal elimination may result from biliary excretion of the chemical, having undergone G.I. absorption and entero-hepatic recycle with or without metabolism (free or conjugated derivatives).

Reviewer's Comment:

- *The sponsor has not proposed a mechanism of formation of the metabolite of epolamine.*

Literature Review:

The sponsor has submitted two literature articles as well, the summary of which has been given below.

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))

In a study on the pharmacokinetics of diclofenac hydroxyethyl-pyrrolidine (DHEP) plasters in patients with monolateral knee joint effusion showed that the patch 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.

Local Tolerability and Pharmacokinetics Profile of a New Transdermal Delivery System, Diclofenac Hydroxyethyl-pyrrolidine Plaster (Publ: Assandri, Drugs Exptl. Clin. Res. XIX(3) 89-95, (1993))

A study of the local tolerability and pharmacokinetic profile of the diclofenac epolamine patch concluded that the plasma concentration vs. time curve measured at the steady-state showed a sustained kinetic profile in all volunteers, very likely attributable to a constant release of the active principle from the plaster through the skin to the general circulation. Plasma levels of the drug were however about 100 times lower (Cmax = 17.4 ± 13.5, range 7.6 to 40 ng/ml) compared to those achievable following systemic dosing (about 1500 ng/ml, after 50 mg enteric coated Voltaren®), while AUC values, which more correctly define bioavailability, were still 10 (AUCn) to 20 (AUC0-12) times lower than after oral Voltaren®. Consistent with other studies, approximately 95% of the diclofenac salt was retained on the plaster matrix after 15 hours of application, while the dose released as diclofenac should be in the range of 5-10 mg. This figure, even though low, seems high enough to suggest a good anti-inflammatory and analgesic effect when dealing with local administration at the painful site. Additionally, the safety data obtained in the present studies indicated that DHEP plaster has a very good local tolerability in both animals and man, with no evidence of untoward skin reactions or sensitization phenomena.

APPENDIX I
(STUDY DATA)

STUDY 910195

Table 1

DIEP. Absorption and excretion of Diclofenac-EP after cutaneous repeated application of two different dosage forms in healthy volunteers: plaster vs gel.

Route of administration : epicutaneous.

Administered dose : 188.5 mg of DIEP/subject/application, corresponding to 148.1 mg of Diclofenac sodium salt.

Dose regimen : repeated (twice a day for 7 consecutive days plus 1 application on day 8).

Treatment A : plaster.

Mean, S.D., CV% and range values (n=10).

Plasma concentrations of Diclofenac as ng/ml.

Sampling time (hours)	Mean	S.D.	CV%	Range min.	Range max.
Day 5	7.9	5.6	70.5		
day 8 (basal)	8.2	3.4	41.4		
1.00*	6.9	3.5	51.4		
2.00*	9.9	7.3	73.8		
3.00*	14.1	14.0	99.1		
4.00*	10.7	7.7	72.4		
6.00*	8.9	5.0	56.3		
8.00*	10.0	8.5	85.3		
10.00*	11.5	8.5	73.7		
12.00*	7.7	3.8	49.9		
24.00*	1.7	1.2	72.6		
48.00*	0.2	0.5	211.9		

* = after the last (15th) dose.

TABLE 15 **Individual diclofenamic acid plasma pharmacokinetic parameters after DHEP plaster in resting and exercising subjects**

	Subject	C_{max} (ng/mL)	C_{min} (ng/mL)	$C_{minimum}$ (ng/mL)	T_{max} (h)	$T_{1/2}$ (h)	AUC_{0-12} (ng×h/mL)	AUC_{0-24} (ng×h/mL)	AUC_{∞} (ng×h/mL)	Ke (h^{-1})
RESTING	1			3.089	12	15.78	37.065	63.349	100.545	0.044
	2			4.916	3	4.64	58.988	72.348	75.142	0.149
	3			1.292	2	9.95	15.505	24.196	30.628	0.070
	4			5.330	4	5.81	63.966	91.148	98.670	0.119
	5			1.623	12	8.19	19.478	32.596	39.315	0.085
	6			1.725	2	N.A.	20.702	47.170	47.170	N.A.
EXERCISING	1			4.043	8	10.79	48.510	75.364	99.048	0.064
	2			4.793	6	6.14	57.517	80.223	88.043	0.113
	3			1.768	0	10.13	21.221	33.065	42.063	0.068
	4			5.579	10	5.74	66.946	103.868	114.692	0.121
	5			2.720	10	5.97	32.643	42.347	45.535	0.116
	6			2.997	1	4.50	35.970	54.456	57.486	0.154

1 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

APPENDIX II

SPONSOR'S LABEL

11 Page(s) Withheld

_____ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

APPENDIX III

FILING- REVIEW FORM

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-234	Brand Name	Diclofenac Epolamine Patch, 1.3%w/w
OCPB Division (I, II, III)	III	Generic Name	Diclofenac Epolamine salt
Medical Division	550	Drug Class	NSAID
OCPB Reviewer	Veneeta Tandon	Indication(s)	Treatment of pain
OCPB Team Leader	Dennis Bashaw	Dosage Form	Adhesive patch
		Dosing Regimen	BID for
Date of Submission	12/19/00	Route of Administration	Topical, dermal
Estimated Due Date of OCPB Review		Sponsor	Institut Biochimique SA
PDUFA Due Date	10/19/01	Priority Classification	3S
I. Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	X	1		
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	X	1		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:	X	4		
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				

Data sparse:				
II. Biopharmaceutics	[redacted]	[redacted]	[redacted]	[redacted]
Absolute bioavailability:				
Relative bioavailability -	[redacted]	[redacted]	[redacted]	[redacted]
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -	[redacted]	[redacted]	[redacted]	[redacted]
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies	[redacted]	[redacted]	[redacted]	[redacted]
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	**X**	**2**		
Total Number of Studies	[redacted]	**5 in vivo+1 in vitro**		

Filability and QBR comments

II.	**"X" if yes**	**Comments**
III. Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
IV. Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	**Are diclofenac and epolamine systemically absorbed after topical application of the patch and how does the systemic absorption from topical diclofenac patch preparation compare to systemic absorption from oral diclofenac? Does in the absorption of diclofenac change under conditions of exercise?**	
Other comments or information not included above		
Primary reviewer Signature and Date	**Veneeta Tandon**	
Secondary reviewer Signature and Date	**Dennis Bashaw**	

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

/s/

Veneta Tandon
10/4/01 10:29:08 AM
BIOPHARMACEUTICS

Dennis Bashaw
10/4/01 10:38:22 AM
BIOPHARMACEUTICS