CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206976Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA or BLA Number	206976
Link to EDR	\\cdsesub1\evsprod\NDA206976\0009
Submission Date	5/26/2016
Submission Type	*[Standard]*
Brand Name	Licart (b) (4)
Generic Name	Diclofenac (b) (4)
Dosage Form and Strength	Topical (b) (4)
Route of Administration	Topical application
Proposed Indication	Topical treatment of acute pain due to minor strains, sprains, and contusions.
Applicant	Institut Biochimique SA (IBSA)
Associated IND	*[111538]*
OCP Review Team	*[Srikanth C. Nallani, Ph.D.]*
OCP Final Signatory	*[Yun Xu, Ph.D.]*

Table of Contents

1. EXECUTIVE SUMMARY

1.1 Recommendations

The submitted PK studies are acceptable from a clinical pharmacology perspective. However, the clinical division has decided to issue a complete response action due to various CMC and clinical deficiencies.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Overview of the Product and Regulatory Background

In 2015, Institut Biochimique SA (IBSA) submitted a New Drug Application (NDA) for the Licart (b) (4), which the sponsor contends is (b) (4) to Flector® Patch (NDA 21234) except for the presence of a (b) (4) of heparin (b) (4) Licart (b) (4) is indicated for once daily use to treat pain due to minor strains, sprains and contusions. The original NDA 021234 for Flector Patch indicated that diclofenac plasma levels are very low compared to oral diclofenac (See Dr. Veneeta Tandon's original NDA21234 Page 5 review of dated 10/04/2001). The recommended dose of Flector Patch is one (1) patch to the most painful area twice a day. In this NDA, the company submitted a multiple dose PK study comparing plasma levels of diclofenac between Flector Patch and Licart (b) (4) formulations, and demonstrated that overall plasma levels of diclofenac are very low as noted with the Flector patch. There were deficiencies identified in the NDA submission from 2015 which were addressed in the current submission and hence the NDA was filed.

2.2 General Pharmacology and Pharmacokinetic Characteristics

The original NDA 021234 for Flector Patch indicated that diclofenac (diclofenamic acid) plasma levels are very low compared to oral diclofenac (See Dr. Veneeta Tandon's original NDA21234 Page 5 review of dated 10/04/2001). The recommended dose of Flector patch is one (1) patch to the most painful area twice a day. In this NDA, the company submitted a multiple dose PK study comparing plasma levels of diclofenac (diclofenamic acid) between Licart (b) (4) and Flector patch formulations, and demonstrated that overall plasma levels of diclofenac are very low as noted with the Flector patch.

2.3 Clinical Pharmacology Review Questions

2.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

Clinical pharmacology studies provide supportive evidence of safety and effectiveness for the NDA. The NDA is supported by clinical efficacy trials as indicated in the table below.

Clinical pharmacology submission consists of the following PK studies:

- CRO-PK-12-272: Multiple dose PK study. Part 1: single dose, non-randomized, open-label exploratory study. Part 2: multiple dose, randomized, open-label, cross-over bioavailability study.
- CRO-PK-98-13: Bioavailability study of a new topical formulation of Licart (DHEP) plaster containing heparin vs. the marketed formulation Flector patch (Flector EP Tissugel) in male and female healthy volunteers. This open, randomized, two-way crossover, multiple dose study was divided in two phases: 4 healthy volunteers were enrolled during the first, pilot phase, while 18 healthy volunteers participated in the subsequent main phase.
- CRO-PK-02-92: Multiple dose PK study evaluating heparin and diclofenac levels with patch application.

Blood samples in these studies were analyzed used validated LC/MS/MS method and detailed in Appendix 3.1.

CRO-PK-12-272 evaluated multiple dose PK of Licart (b) (4) The study had two parts: Part 1: single dose, non-randomized, open-label exploratory study. Part 2: multiple dose, randomized, open-label, cross-over bioavailability study. After single cutaneous application of one Licart (b) (4) for a duration of 24 hours in 24 healthy volunteers, (b) (4) See CMC review for final conclusions on the amount of diclofenac and heparin remaining in the patch.

During the second part of the study, One Licart (b) (4) was applied once a day (full 24 hours) for four consecutive days, during each of four study periods under four different treatment conditions. Plasma diclofenac levels at standard (rest) condition were compared with the following:

- Exercise: On each day of the moderate exercise period, subjects underwent three exercise sessions of 20 min each: the first session immediately after patch application, the second session 4 h post-application and the third session 8 h post-application.
- Occlusion: An occlusive bandage, beside the provided elastic net used in all four periods, was applied to each patch for the whole duration of the study period. The bandage was removed for 1 h twice daily at approximately 5 and 12 h post-application (during meals).
- Moderate heat exposure: At time zero, 4, 8 and 12 h after each application, the patch was warmed up with (20 min thermacare application).

Blood samples collected at 0, 1, 2, 4, 6, 8, 10, 12, 16, 20, and 24 hours after patch application. Heat, exercise and occlusion did not demonstrate a significant effect on absorption of diclofenac.

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

Study CRO-PK-98-13 was conducted in 1998 to bridge the Flector (diclofenac only) patch with the new Licart (b) (4) with heparin where both patches were manufactured in Switzerland. In this study both patches were applied as a twice a day (12 hour) application for seven days. At

steady-state plasma levels of diclofenac following application of Licart (b) (4) Maximum diclofenamic acid plasma concentration at steady state (Cssmax) averaged 3.5±2.04 ng/ml for test and 3.59±2.09 ng/ml for reference formulation. The two products showed comparable drug exposure at steady state.

Table: Day 8 Plasma diclofenac (diclofenamic acid) profile after 7 days b.i.d administration of Licart (b) (4) or Flector Patch.

Licart (b) (4)

Time (h)	Mean	SD	CV%	Max	Min	n*
0	2.74	3.07	112.23		(b) (4)	16
0.5	2.63	3.36	127.92			16
1	3.02	4.12	136.29			16
2	3.11	5.02	161.31			15
3	2.54	3.73	146.68			16
4	2.92	3.89	133.08			16
5	3.02	3.67	121.60			16
6	2.88	3.90	135.77			16
8	2.50	3.53	141.23			16
10	2.45	3.95	161.19			16
12	2.20	3.17	143.85			16
16	1.09	0.78	71.84			16
24	0.64	0.55	86.41			16

Subjects 7 and 14 were excluded

Flector Patch

Time (h)	Mean	SD	CV%	Max	Min	n*
0	2.14	1.51	70.82		(b) (4)	16
0.5	2.21	1.69	76.58			16
1	2.87	2.24	78.09			16
2	2.09	1.54	73.53			16
3	2.48	2.30	92.90			16
4	2.26	1.52	67.06			16
5	2.34	1.73	74.00			16
6	1.99	1.58	79.24			16
8	1.72	1.27	73.86			16
10	1.83	1.27	69.27			16
12	1.81	1.22	67.54			16
16	1.29	0.66	50.96			16
24	0.81	0.63	77.76			16

Subjects 7 and 14 were excluded

Table: Main PK parameters at steady state after 7-days b.i.d. administration, plus 1 administration in the morning of day 8, of formulation A (Licart (b) (4) from 1998) compared with Flector Patch (from 1998)

Licart (b) (4)					**Flector Patch (Reference)**			
	AUCss	Cssmin	CSSmax	TSSmax	AUCss	Cssmin	CSSmax	TSSmax
	(ng*h/mL)	(ng/mL)	(ng/mL)	(h)	(ng*h/mL)	(ng/mL)	(ng/mL)	(h)
MEAN	23.42	1.2	3.51	3.66	22.48	1.23	3.59	2.16
SD	11.93	0.57	2.04	3.88	10.44	0.56	2.09	1.85
CV%	50.95	47.25	58.24	106.25	46.45	45.93	58.28	85.82
MAX	58.32	2.33	9.02	12	46.27	2.61	9.89	5
MIN	9.45	0	1.12	0	8.02	0.5	1.28	0
N	16	16	16	16	16	16	16	16

Study CRO-PK-02-92 evaluated twice a day (12 hours) application of Licart (b) (4) for six days. Blood samples were collected pre-dose on Day 1, 2, 5 and 6, and 1 – 24 hours on Day 6. Peak plasma levels were 2.32 ng/mL.

Diclofenamic acid plasma concentrations (ng/mL) on days 1, 2 and 5, mean±SD, n=12

Day 1	Day 2	Day 5
0 h	0 h	0 h
BQL	2.11±0.62	2.29±0.75

BQL= Below limit of quantification

Diclofenamic acid plasma concentrations (ng/mL) on day 6, mean±SD, n=12

Day 6											
0 h	1 h	2 h	3 h	4 h	5 h	6 h	8 h	10 h	12 h	16 h	24 h
1.93	1.44	1.62	1.93	2.04	2.12	2.09	1.57	1.50	1.62	2.26	2.36
±0.84	±0.72	±0.95	±0.92	±0.92	±0.88	±0.92	±0.65	±0.63	±0.69	±1.08	±1.03

Main PK parameters at steady state, mean±SD, n=12

τ (h)	AUCss (ng*h/mL)	Css_{min} (ng/mL)	Css_{max} (ng/mL)	Tss_{max} (h)	$Css_{average}$ (n /mL)
12	21.03±9.13	1.33±0.66	2.31±0.94	3.42±2.31	1.75±0.76
Range	41.94-11.37	2.82-0.70	4.39-1.27	6.00-0.00	3.49-0.95

This study also evaluated the potential of any absorbed heparin to cause changes in coagulation, since bioanalytical methods for detection of plasma heparin do not exist. The study population was exposed to a heparin daily dose ranging between 243.48 and 128.00 IU/kg BW, with a mean dose of 84.30±37.41 IU/kg BW. The mean total dose administered in 6 days (12 plasters) was 1105.62±224.32 IU/kg BW (range 1460.87-768.00 mg/kg BW).

Activated Partial Thromboplastin Time (aPTT), a measure of blood coagulation, was determined daily, from day 1 to day 5, 4 h after the morning application and on day 6 pre-dose and 1, 2, 3, 4, 5, 6, 8, 10, 12, 16 and 24 h after the morning application.

Table: The mean aPTT value obtained on days 1-5 are reported in the following table (n=12):

aPTT	Day 1 (Predose)	Day 1 (6h)	Day 2 (6 h)	Day 3 (6h)	Day 4 (6h)	Day 5 (6h)
Mean	33.58	31.75	32.17	32.17	31.92	33.08
SD	3.53	3.55	3.46	3.76	3.42	3.09

Table: aPTT values (sec) on day 6, mean±SD, n=12

Predose	1h	2h	3h	4h	5h	6h	8h	10	12h	16h	24h
31.42	31.92	32	32.42	31.75	31.5	32	30.83	30.83	31.17	31.58	31.67
2.71	3.75	3.57	3.29	2.99	3.21	4.02	3.81	3.66	3.86	4.66	3.7

Those randomly distributed observed changes are devoid of clinical significance.

2.3.2 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

IBSA is requesting a partial waiver for the requirement to perform (a) a study in children less than 6 years old, (b) a pediatric pharmacokinetic study, and (c) a clinical effectiveness study. IBSA considers a study of children < 6 years to be highly impractical given the paucity of children with minor sports injuries, and the reluctance of parents to allow children of any age with a self-limiting condition to be enrolled in a clinical study with a placebo arm. IBSA believes that a pediatric pharmacokinetic study of Licart pediatric is unnecessary considering the low systemic levels of diclofenac.

PeRC noted that it appears that sponsor intends to employ partial extrapolation with clinical studies in adults and one open-label study in the pediatric population for whom the product will be indicated. Therefore, this section should be revised to reflect the use of extrapolation of pediatric efficacy supported by the adult studies and the single planned pediatric study." While a dedicated pharmacokinetic study may not be needed, the inclusion of heparin in your formulation necessitates that you include pharmacokinetic assessments in your pediatric study.

2.4 Summary of Labeling Recommendations

No labeling recommendations are being made as the clinical division decided to give a complete response action to the NDA due to various issues.

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3. APPENDICES

3.1 Summary of Bioanalytical Method Validation and Performance

PK Study	CRO-PK-98-13	CRO-PK-02-92	CRO-PK-12-272	CRO-PK-12-272	Comments
Method Validation Report Number				(b) (4)	
Report date	March 23, 1999	September 11, 2003	October 1, 2013	June 2015	
Laboratory				(b) (4)	
Methodology	LC/MS/MS	LC/MS/MS	LC/MS/MS	LC/MS/MS	
Biological matrix	Human plasma	Human plasma	Human plasma	Human plasma	
Anticoagulant	Sodium Heparin	Sodium Heparin	Sodium Heparin	Sodium Heparin	
Calibration curve range	LLOQ: 0.500 (0.498) ng/mL ULOQ: 50.0 (50.4) ng/mL	LLOQ: 0.150 ng/mL ULOQ: 100.00 ng/mL	LLOQ: 0.100 ng/mL ULOQ: 50.00 ng/mL	LLOQ: 0.0500 ng/mL ULOQ: 5.00 ng/mL	
Analyte of interest	Diclofenac	Diclofenac	Diclofenac	Diclofenac	
Internal standard	(b) (4)	Diclofenac-D6	Diclofenac-$^{13}C_6$	Diclofenac-D4	
Inter-batch accuracy (% bias)	Low QC1 (1.25 ng/mL): -2.3% Medium QC2 (4.0 ng/mL): -0.2% Medium QC3 (12.0 ng/mL): 2.4% High QC4 (40.0 ng/mL): -0.1%	Low QC (0.20 ng/mL): 1.4% Medium QC (7.97 ng/mL): -3.5% High QC (79.71 ng/mL): 0.0%	Low QC (0.30 ng/mL): 5.0% Medium QC (3.00 ng/mL): -1.1% High QC (40.0 ng/mL): 0.0%	LLOQ (0.0500 ng/mL): 1.5% Low QC (0.150 ng/mL): -2.8% Medium QC (0.750 ng/mL): -4.7% High QC (4.00 ng/mL): -1.5%	
Inter-batch precision (CV)	Low QC1 (1.25 ng/mL): 7.8% Medium QC2 (4.0 ng/mL): 4.6% Medium QC3 (12.0 ng/mL): 3.8% High QC4 (40.0 ng/mL): 3.3%	Low QC (0.20 ng/mL): 3.7% Medium QC (7.97 ng/mL): 0.8% High QC (79.71 ng/mL): 0.4%	Low QC (0.30 ng/mL): 6.5% Medium QC (3.00 ng/mL): 6.0% High QC (40.0 ng/mL): 4.2%	LLOQ (0.0500 ng/mL): 10.2% Low QC (0.150 ng/mL): 3.7% Medium QC (0.750 ng/mL): 3.7% High QC (4.00 ng/mL): 2.1%	
Dilution integrity	Dilution was not applied because none of the samples tested during the clinical study were higher than ULOQ.	Dilution QC: 5.00 ng/mL (dilution factor: 2) % Bias: -0.86%	Dilution was not applied because none of the samples tested during the clinical study were higher than ULOQ.	Dilution QC: 40.0 ng/mL (dilution factor in plasma: 10) % Bias: 2.6% Precision: 2.7%	Dilution integrity was not assessed for the methods that did not apply any sample dilutions. None of the samples showed Diclofenac concentrations higher than ULOQ.
Selectivity	No interferences found using seven different batches of human plasma.	No interferences found using six different batches of human plasma.	Diclofenac: < 9.4% of the LLOQ. Diclofenac $^{13}C_6$: < 0.24% of the LLOQ.	Diclofenac: 0.0% of the LLOQ. Diclofenac-D4: 0.0% of the LLOQ.	
Short term or bench stability of samples before processing	4 hours at room temperature	Not performed. According to the precision and accuracy validation results, no deviations were observed, so the analytical method instructions were adequate.	12 hours at 20°C	17 hours at room temperature	

PK Study	CRO-PK-98-13	CRO-PK-02-92	CRO-PK-12-272	CRO-PK-12-272	Comments
Stability of processed samples	24 hours at room temperature (autosampler) at -20°C for medium concentration Diclofenac (12.0 ng/mL).	3 days at 4°C (autosampler) and at -20°C for low, medium and high Diclofenac concentrations.	24 hours at 15°C for Diclofenac	66 hours at 2-8°C (autosampler temperature) for low, medium and high Diclofenac concentrations.	
Long-term stability of frozen samples	Not applicable. The samples were not retested after long-term storage.	50 days at -20°C for 5.00 and 100.00 ng/mL Diclofenac concentrations.	93 days at -20°C and -80°C for high Diclofenac concentration.	1990 days at ≤-18°C for 0.300 and 4.00 mg/mL Diclofenac concentration.	Long-term stability was not performed for the oldest study. The samples were analyzed in the same study and no re-analysis was made after long-term storage.
Freeze-thaw stability of samples	3 cycles for medium Diclofenac concentration (12.0 ng/mL).	3 cycles for 5.00 and 100.00 ng/mL Diclofenac concentrations.	3 cycles for high Diclofenac concentration. 2 cycles at low Diclofenac concentration.	3 cycles for low, medium and high Diclofenac concentrations.	
Stability of stock standard solution	Not performed. Stock standard solutions were stored at approx. -20°C. Calibration standard solutions and quality control standard solutions were freshly prepared every day.	Stability of stock standard solution was not performed, but the stability of calibration standards was demonstrated for 60 days at <-20°C for 10 ng/mL and 100 ng/mL Diclofenac concentrations.	16 days at -20°C. The stability of working standard solutions was also demonstrated for 16 days at -20°C for Diclofenac and 7 days at -20°C for Diclofenac $^{13}C_6$.	62 days at 2-8°C. The same solution was not allowed to be stored at ≤-18°C.	
Recovery	**Diclofenac** Recovery: Low SQC (1.25 ng/mL): 65.7% Medium SQC2 (4.00 ng/mL): 71.8% Medium SQC3 (12.0 ng/mL): 80.4% High SQC4 (40.0 ng/mL): 75.5% **Internal Standard** Recovery: Low SQC (1.25 ng/mL): 79.1% Medium SQC2 (4.00 ng/mL): 75.8% Medium SQC3 (12.0 ng/mL): 80.1% High SQC4 (40.0 ng/mL): 85.7%	**Diclofenac** Recovery: Low QC (0.15 ng/mL): 84.3% Medium QC (5.0 ng/mL): 81.5% High QC (100 ng/mL): 84.1% Precision: Low QC (0.15 ng/mL): 0.7% Medium QC (5.0 ng/mL): 0.6% High QC (100 ng/mL): 0.1% **Internal Standard** Internal std concentration 75.2 ng/50 µL Recovery: 85.3% Precision:0.7%	**Diclofenac** Recovery: Low QC (0.30 ng/mL): 109% Medium QC (3.00 ng/mL): 85% High QC (40.0 ng/mL): 74% Precision: Low QC (0.30 ng/mL): 6.0% Medium QC (3.00 ng/mL): 4.9% High QC (40.0 ng/mL): 4.4%	**Diclofenac** Recovery: Low QC (0.150 ng/mL): 66.1% Medium QC (0.750 ng/mL): 70.6% High QC (4.00 ng/mL): 67.8% Precision: Low QC (0.150 ng/mL): 4.4% Medium QC (0.750 ng/mL): 8.7% High QC (4.00 ng/mL): 10.2% **Internal Standard** Recovery: Low QC (0.150 ng/mL): 61.2% Medium QC (0.750 ng/mL): 68.0% High QC (4.00 ng/mL): 67.3% Precision: Low QC (0.150 ng/mL): 2.5% Medium QC (0.750 ng/mL): 7.9% High QC (4.00 ng/mL): 8.9%	

PK Study	CRO-PK-98-13	CRO-PK-02-92	CRO-PK-12-272	CRO-PK-12-272	Comments
Matrix effect (matrix factor)	Matrix effect was not assessed. Calibration was conducted from standard solutions diluted into the same matrix (human plasma) of the samples to be tested, so matrix affects, if present, affected both standards and samples. Moreover, no differences were observed in blank human plasma from different batches.	Matrix effect parameter was not assessed. Calibration was conducted from standard solutions diluted into the same matrix (human plasma) of the samples to be tested, so matrix affects, if present, affected both standards and samples. Moreover, no differences were observed in blank human plasma from different batches.	No significant matrix effect observed. Low QC (0.30 ng/mL): 1.6% Medium QC (3.00 ng/mL): 1.1% High QC (40.0 ng/mL): 1.1%	No significant matrix effect observed. Low QC (0.150 ng/mL): 0.999% High QC (4.00 ng/mL): 0.960%. This study assessed also: Hemolysed plasma effect: No effect up to 2% hemolysis. Low QC (0.150 ng/mL): CV = 2.9; Accuracy = 93.3% High QC (4.00 ng/mL): CV = 1.7; Accuracy = 101.0% Lipemic plasma effect: No effect observed. Low QC (0.150 ng/mL): CV = 11.7; Accuracy = 101.2% High QC (4.00 ng/mL): CV = 3.6; Accuracy = 95.7%	Matrix effects were not assessed for the methods that diluted calibration standard solutions with human plasma, since the matrix effect, if present, affected both standards and samples to be tested.
Carryover	Carryover parameter was not assessed. Blank plasma injected in the analytical sequence did not show significant carryover. Precision results at LLOQ were all acceptable in the validation study.	Carryover parameter was not assessed. Blank plasma injected in the analytical sequence did not show significant carryover. Precision results at LLOQ were all acceptable in the validation study.	No significant carryover observed. Diclofenac = 0.71% Diclofenac $^{13}C_6$ = 0.20%	No significant carryover observed. Diclofenac = 0.0% Internal Standard = 0.0%	Carryover was not assessed for the oldest method validations; regardless the verification of blanks and precision results of LLOQ did not show any carryover effect.
Incurred Sample Re-Analysis (ISR)	This parameter was not validated. None of the samples were re-analyzed.	Approx. 4% of the study samples were re-analyzed and the difference between the original and re-analysis results was <20% for all the samples.	This parameter was not validated. Nevertheless 100% of the study samples were re-analyzed by a second laboratory (ABL): the difference between the results obtained by the two laboratories was >20% for 2% of the samples. ABL results fully confirmed original data.	Approx. 10% of the study samples were re-analyzed and the difference between the original and re-analysis results was >20% only for the 1.5 % of the samples (1 out of 67).	ISR was demonstrated for all the studies except for the oldest for which this test was not required. For all the other studies, the test showed re-analysis was applicable. Because the analytical procedures and the test samples are highly comparable, the re-analysis results can also be extended to the oldest method.

3.2 Synopsis of Study CRO-PK-98-13.

Title of the study: Bioavailability study of a new topical formulation of Diclofenac epolamine plaster containing heparin vs the marketed formulation Flector EP Tissugel® in male and female healthy volunteers. Open, randomised, two-way crossover, multiple dose study.			
Investigator(s): Antonio Rusca, MD, FMH			
Study center: Cross Research s.a. – Phase I Unit, Via F.A. Giorgioli, CH-6864 - Arzo, Switzerland			
Publication (reference): N.A.			
Studied period (years): 1998	Date of first enrolment: 16NOV98 Date last vol. completed: 16DEC98		Phase of development: I
Objectives: Aim of the present study was to assess the bioavailability and to verify the bioequivalence of a new topical formulation of diclofenac epolamine plaster containing heparin vs the marketed formulation Flector EP Tissugel® after repeated epicutaneous administration (twice a day for 7 consecutive days plus 1 administration in the morning of day 8) in male and female healthy volunteers.			
Methodology: Open, randomised, two-way crossover, multiple dose study.			
Number of subjects (planned and analysed): 24 planned – 20 analysed.			
Diagnosis and criteria for inclusion: Inclusion criteria: Caucasian males and females, 18-45 years old, BW within ± 15% of ideal body weight, according to sex, age and build (Metropolitan Life Insurance Height and Weight Tables, *Appendix 6 of the Study protocol).* 100-140 mmHg SBP, 60-90 mmHg DBP, 60-80 bpm HR measured after 5 min of rest in the sitting position, no clinically relevant abnormalities at 12-leads ECG, no clinically relevant abnormal physical findings which could interfere with the objectives of the study, no clinically relevant abnormal laboratory values indicative of physical illness, no ascertained or presumptive hypersensitivity to the active principle and/or formulations' ingredients; history of anaphylaxis to drugs or allergic reactions in general, which the Investigator considers might affect the outcome of the study or allergic reactions to chemicals; no relevant history of renal, hepatic, gastrointestinal cardiovascular, haematological endocrine or CNS diseases, that might interfere with the aim of the study. No pregnant or lactating women, females with child-bearing potential could be admitted into the study but had to adopt one of the following contraceptive methods during the entire period of the study: systemic contraception (oral, implant), or diaphragm with intravaginal spermicide, or cervical cap, or intrauterine device, or condom with intravaginal spermicide; no medications during 2 weeks before the start of the study, which the Investigator considers might affect the validity of the study, no participation in the evaluation of any drug within 3 months prior to the start of the study, no blood donations during the 3 months prior to this study, no history of drugs or alcohol (60 g/day of alcohol) abuse; 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°: Formulation A: diclofenac epolamine plaster: 14x10 cm containing 180 mg of diclofenac epolamine and 5,600 I.U. of heparin. The plaster was applied on the right side of the back (lumbar region) twice a day for 7 consecutive days plus 1 administration in the morning of day 8 Batch n° 58/IB-43 (71T/IB-22). Expiry date: 01/2000.			

(b) (4)

DHEP/heparin | Page:

Reference therapy, dose, mode of administration, batch N°:
Formulation B: diclofenac epolamine plaster Flector Tissugel®: 14x10 cm containing 180 mg of diclofenac epolamine The plaster was applied on the right side of the back (lumbar region) twice a day for 7 consecutive days plus 1 administration in the morning of day 8.
Batch n° 58/IB-43 (980108). Expiry date: 01/2000.

Criteria for evaluation (pharmacokinetics):
plasma diclofenamic acid concentratons, Css_{max}, Css_{min}, AUCss, tss_{max} AUMCss $Css_{average}$, CLss %PTF, %swing after multiple dose administration of both test and reference formulation in two subsequent periods.

Criteria for evaluation (safety):
AEs, BP, HR, BW, ECGs, laboratory analysis

Statistical methods:
For Css_{max} and AUCss, analysis of variance (ANOVA) was performed on log-transformed data, T_{max} was analysed by non-parametric Friedman test, Css_{max} and AUCss were compared based on Latin square ANOVA for a cross-over design: the 90% CI for the ratio of the averages (population geometric means) of the values for the test and reference and the two one-sided t-tests of Schuirmann at the level of significance of 5%, acceptance criterion for BE was the 90% confidence interval of the ratio of the mean test to the mean referencevalues be included within the range 0.80-1.25 for AUCss and 0.70-1.43 for C_{max}.
Vital signs were compared within treatments vs. pre-dose values and between treatments using t test

Results:
During the preliminary phase (n=4), the subjects received a mean DHEP daily dose of 5.76±0.76 mg/kg BW and 179.24±23.71 IU of heparin, for a total dose of 43.21±5.71 mg/kg BW of DHEP and 1344.27±177.80 IU/kg BW of heparin.
Mean diclofenamic acid plasma levels after administration of test (formulation A, DHEP/heparin plaster) and reference (formulation B, Flector EP Tissugel®) products measured during the preliminary phase are reported in the following table:

Preliminary phase: mean diclofenac plasma concentrations (ng/mL) after 7-days b.i.d. administration, plus 1 administration in the morning of day 8, of formulation A (test)

Time (h)	0	0.5	1	2	3	4	5	6	8	10	12	16	24
Mean	4.07	3.71	3.58	3.71	3.27	3.53	3.86	4.52	5.06	6.53	7.68	2.09	0.4
SD	2.36	1.81	1.67	1.67	0.77	1.23	1.91	1.91	3.59	4.75	6.31	0.86	0.81

Preliminary phase: mean diclofenac plasma concentrations (ng/mL) after 7-days b.i.d. administration, plus 1 administration in the morning of day 8, of formulation B (reference)

Time (h)	0	0.5	1	2	3	4	5	6	8	10	12	16	24
Mean	3.86	3.09	3.45	3.46	2.83	3.03	3.77	3.49	3.45	3.71	4.95	2.94	1.04
SD	2.03	1.88	1.98	1.57	1.36	1.42	1.42	1.31	1.93	1.69	2.55	2.01	0.72

As expected, every subject showed detectable diclofenamic acid plasma concentration at the first sampling time (predose). Maximum diclofenamic acid plasma concentration at steady state (Css_{max}) averaged 8.98±5.05 ng/mL for test and 5.53±2.35 ng/mL for reference formulation; minimum plasma concentration at steady-state (Css_{min}) was in average 2.52±1.09 ng/mL for test formulation and 2.44±1.41 for reference formulation. Maximum plasma concentration value was reached in 6.13±6.79 h (Tss_{max}, test formulation) and in 9.00±6.00 h (Tss_{max}, reference formulation). Average concentrations ($Css_{average}$) resulted in 4.79±2.55 ng/mL for test and 3.55±1.50 for reference formulation.
The area under the concentration/time curve at steady-state (AUCss) was calculated as 57.47±30.59 ng/mL*h and 42.61±17.98 ng/mL*h.

The following tables show mean obtained steady-state PK parameters:

Preliminary phase: main PK parameters at steady state after 7-days b.i.d. administration, plus 1 administration in the morning of day 8, of formulation A (test)

	AUCss (ng/mL*h)	AUMCss (ng/mL*h)	Css_{min} (ng/mL)	Css_{max} (ng/mL)	Tss_{max} (h)	$Css_{average}$ (ng/mL)	%Ptf	%AUCdf	%Swing	CLss (mL/h)
MEAN	57.47	398.90	2.52	8.98	6.13	4.79	124.40	23.33	258.61	3.45
SD	30.59	257.96	1.09	5.05	6.79	2.55	41.92	16.51	183.28	2.28
CV%	53.23	64.67	43.35	56.19	110.81	53.23	33.70	70.74	70.87	66.19
MAX	[redacted] (b) (4)									
MIN										
N	4	4	4	4	4	4	4	4	4	4

Preliminary phase: main PK parameters at steady state after 7-days b.i.d. administration, plus 1 administration in the morning of day 8, of formulation B (reference)

	AUCss (ng/mL*h)	AUMCss (ng/mL*h)	Css_{min} (ng/mL)	Css_{max} (ng/mL)	Tss_{max} (h)	$Css_{average}$ (ng/mL)	%Ptf	%AUCdf	%Swing	CLss (mL/h)
MEAN	42.61	270.10	2.44	5.53	9.00	3.55	87.04	17.40	148.10	4.18
SD	17.98	120.63	1.41	2.35	6.00	1.50	32.95	7.59	107.19	2.21
CV%	42.19	44.66	57.88	42.43	66.67	42.19	37.85	43.63	72.38	52.80
MAX	[redacted] (b) (4)									
MIN										
N	4	4	4	4	4	4	4	4	4	4

The subjects included in the final phase received a mean daily dose of 5.48±0.97 mg/kg BW of DHEP and 170.52±30.21 IU/kg BW of heparin, for a total dose of 41.11±7.28 mg/kg BW of DHEP and 1278.93±226.59 IU/kg BW of heparin.

Mean diclofenamic acid plasma levels after administration of test (formulation A, DHEP/heparin plaster) and reference (formulation B, Flector EP Tissugel®) products measured during the final phase are reported in the following tables:

Final phase: mean diclofenac plasma concentrations (ng/mL) after 7-days b.i.d. administration, plus 1 administration in the morning of day 8, of formulation A (test)

Time (h)	0	0.5	1	2	3	4	5	6	8	10	12	16	24
Mean	2.74	2.63	3.02	3.11	2.54	2.92	3.02	2.88	2.5	2.45	2.2	1.09	0.64
SD	3.07	3.36	4.12	5.02	3.73	3.89	3.67	3.9	3.53	3.95	3.17	0.78	0.55

Subjects 7 and 14 were excluded

Final phase: mean diclofenac plasma concentrations (ng/mL) after 7-days b.i.d. administration, plus 1 administration in the morning of day 8, of formulation B (reference)

Time (h)	0	0.5	1	2	3	4	5	6	8	10	12	16	24
Mean	2.14	2.21	2.87	2.09	2.48	2.26	2.34	1.99	1.72	1.83	1.81	1.29	0.81
SD	1.51	1.69	2.24	1.54	2.3	1.52	1.73	1.58	1.27	1.27	1.22	0.66	0.63

Subjects 7 and 14 were excluded

As expected, every subject showed detectable diclofenamic acid plasma concentration at the first sampling time (predose). Achievement of steady-state condition was indicated by the similar diclofenac plasma concentration values observed at predose (2.74±3.07 ng/mL for test formulation and 2.14±1.51 ng/mL for reference) and at 12 h post-dose (2.20±3.17 ng/mL for test formulation and 1.81±1.22 ng/mL for reference).

Mean diclofenamic acid levels showed a tendency to increase during the observation period up to the 5 h sampling time (test formulation) and up to the 3 h (reference formulation), scoring 3.02±3.67 ng/mL and 2.48±2.30, respectively.

The following tables show mean obtained steady-state PK parameters:

Name of Company: IBSA, Switzerland Name of Finished Product: DHEP/Heparin plaster Name of active substance(s): DHEP/heparin	TABULAR FORMAT REFERRING TO PART 5.3 OF THE DOSSIER Volume: Page:	(For National Authority Use only)

Final phase: main PK parameters at steady state after 7-days b.i.d. administration, plus 1 administration in the morning of day 8, of formulation A (test)

Subject	AUCss (ng/mL*h)	AUMCss (ng/mL*h)	Css_{min} (ng/mL)	Css_{max} (ng/mL)	Tss_{max} (h)	$Css_{average}$ (ng/mL)	%Ptf	%AUCdf	%Swing	CLss
MEAN	23.42	132.33	1.20	3.51	3.66	1.95	118.36	18.67	203.70	7.75
SD	11.93	69.91	0.57	2.04	3.88	0.99	67.28	10.74	155.36	3.37
CV%	50.95	52.83	47.25	58.24	106.25	50.95	56.84	57.52	76.27	43.46
MAX	[redacted] (b) (4)									
MIN										
N	16	16	16	16	16	16	16	16	15	16

Final phase: main PK parameters at steady state after 7-days b.i.d. administration, plus 1 administration in the morning of day 8, of formulation B (reference)

	AUCss (ng/mL*h)	AUMCss (ng/mL*h)	Css_{min} (ng/mL)	Css_{max} (ng/mL)	Tss_{max} (h)	$Css_{average}$ (ng/mL)	%Ptf	%AUCdf	%Swing	CLss
MEAN	22.48	126.49	1.23	3.59	2.16	1.87	129.77	15.99	213.59	7.97
SD	10.44	60.76	0.56	2.09	1.85	0.87	81.21	7.92	158.93	3.61
CV%	46.45	48.03	45.93	58.28	85.82	46.45	62.58	49.50	74.41	45.34
MAX	[redacted] (b) (4)									
MIN										
N	16	16	16	16	16	16	16	16	16	16

Maximum diclofenamic acid plasma concentration at steady state (Css_{max}) averaged 3.51±2.04 ng/mL for test and 3.59±2.09 ng/mL for reference formulation; minimum plasma concentration at steady-state (Css_{min}) was 1.20±0.57 ng/mL (test formulation) and 1.23±0.56 (reference formulation). Maximum plasma concentration value was reached in 3.66 ± 3.88 h (Tss_{max}, test formulation) and in 2.16 ± 1.85 h (Tss_{max}, reference formulation). Average concentrations ($Css_{average}$) resulted in 1.95 ± 0.99 ng/mL for test and 1.87 ± 0.87 for reference formulation. The area under the concentration/time curve at steady-state (AUCss) was calculated as 23.42±11.93 mg/mL*h for test and 22.48±10.44 mg/mL*h for reference formulation.

Conclusions: While the sponsor wanted to conclude that at steady-state the two products are bioequivalent, Agency does not recognize BE at steady-state. However, it is generally clear that the systemic levels of diclofenac are comparable (and low as noted in the original Flector patch NDA 21234. It should be noted that the study employed a dosing regimen (twice a day 12 hr application) different from the product dosage and administration for the Licart [redacted] (b) (4) (Once a day).

3.3 Synopsis of Study CRO-PK-02-92

Name of Company: IBSA **Name of Finished Product:** na **Name of active substance(s):** diclofenac epolamine/ heparin sodium	**TABULAR FORMAT** **REFERRING TO PART IV OF THE DOSSIER** **Volume:** **Page:**	**(For National Authority Use only)**

Title of the study: safety evaluation of a new transdermal plaster containing diclofenac epolamine (DHEP) and heparin sodium

Investigator(s): Antonio Rusca, MD, FMH

Study centre: Cross Research s.a. – Phase I Unit, Via F.A. Giorgioli, CH-6864 - Arzo, Switzerland

Publication (reference): na

Studied period (years):	**Date of first enrolment:** 27FEB03	**Phase of development:**
2003	**Date last vol. completed:** 15MAR03	I

Objectives: to evaluate the risk of epicutaneous absorption of heparin sodium after repeated application of the new plaster

Methodology: phase I, single centre, open, multiple dose safety study.

Number of subjects (planned and analysed): 6 healthy male and 6 healthy female volunteers planned and analysed

Diagnosis and criteria for inclusion: sex: males and females (in menopause or using reliable contraceptive methods and not lactating), aged 18-64 years, 18 kg/m^2 < BMI < 30 kg/m^2, normal values of BP: systolic (100-139 mm Hg), diastolic (50-89 mm Hg) and HR (50-90 bpm), measured after 5 min of rest in the sitting position. No clinically relevant abnormalities in 12-leads ECG, no clinically relevant abnormal findings that could interfere with the objectives of the study. Laboratory analysis: no clinically relevant abnormal values (haematology, blood chemistry, urinalysis, virology, drug screening), in particular no aPTT or PT tests out of normality range. Allergies: no history of anaphylaxis to any drugs or allergic reactions in general which the Investigator considered might affect the outcome of the study, in particular no hypersensitivity to NSAIDs and heparin and no history of atopy or skin allergic reaction. Organ function: no clinically significant dysfunction. Diseases: no relevant history of diseases, that might interfere with the aim of the study, of renal, hepatic, gastrointestinal, cardiovascular, haematological, respiratory, endocrine, neurologic or skin diseases. In particular no history of peptic ulcer, bronchial asthma and/or bronchospasm, diabetes, urticaria and no history of bleeding disorder. Skin condition: no abrasion, excoriation or incised wound on the back (application site). Medications: no medications including OTC products during 2 weeks prior to the start of the study, that could influence the results of the study, especially no use of NSAIDs and other drugs interfering with blood coagulation. Investigative drug trials: no participation in the evaluation of any drug during 3 months before the start of the study. Blood donation: no blood donation during the 3 months before the start of the study. Life style: no history of alcohol (>2 drinks/day, defined according to USDA Dietary Guidelines 2000), caffeine (>5 cups/day of coffee or tea) or tobacco (>10 cigarettes/day) abuse and drug use. Full comprehension: ability to comprehend the full nature and purposes 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. Informed consent: signed informed consent prior to the inclusion in the study

Test product, dose, mode of administration, batch N°: flector Heparin Tissugel (each plaster containing 180 mg DHEP and 5,600 IU heparin sodium) for epicutaneous administration, batch n° 0210122

Duration of treatment: b.i.d. application for 6 consecutive days

Reference therapy, dose, mode of administration, batch N°: n.a.

Criteria for evaluation (PK and PD): PK: diclofenamic acid plasma concentration, AUCss (τ=12 h), Css_{max}, Css_{min}, $Css_{average}$ and Tss_{max}, PD: aPTT values; adhesiveness

Criteria for evaluation (safety): AEs, vital signs, ECGs, laboratory analysis, local tolerability

9.4.2 Identity of investigational product(s)

Study medication	Flector / Heparin Tissugel containing 180 mg DHEP (equivalent to 150 mg diclofenac) and 5,600 IU heparin sodium
Chemical name	diclofenac epolamine / heparin sodium
Manufacturer	Teikoku Seyaku Co. Ltd/IBSA Institut Biochimique sa
Pharmaceutical form:	plaster

Statistical methods: PD parameters (aPTT), local tolerability and adhesiveness data score were described using classic statistics (mean, SD, CV%, minimum and maximum values) for quantitative variables and frequencies for qualitative variables. PK analysis was performed by means of the validated software Kinetica™ 4.2, Innaphase. The statistical analysis was performed using either SAS version 8.2 for Windows or Kinetica™ 4.2, Innaphase.

Results: study formulation was applied b.i.d. to 12 healthy volunteers of both genders on the back, one application in the morning and one in the evening, for 6 consecutive days for a total of 12 applications. DHEP was administered at the mean daily dose of 5.92±1.20 mg/Kg BW (range 7.83-4.11 mg/Kg BW), while heparin at the mean daily dose of 184.30±37.41 IU/Kg BW (range 243.48-128.00 IU/Kg BW). The mean age of the population was 21.75±2.90 y, and BMI was 21.34±1.97 kg/m^2.

aPTT was determined daily, from day 1 to day 5, 6 h after the morning application and on day 6 pre-dose and 1, 2, 3, 4, 5, 6, 8, 10, 12, 16 and 24 h after the morning application. The mean aPTT value obtained on days 1-5 are reported in the following table (n=12):

aPTT values (sec) over time, days 1-5, mean±SD, n=12

Subject	Day 1 (pre dose)	Day 1 6h	Day 2 6h	Day 3 6h	Day 4 6h	Day 5 6h
aPTT	33.58 ±3.53	31.75 ±3.55	32.17 ±3.46	32.17 ±3.76	31.92 ±3.42	33.08 ±3.09

Statistically significant changes vs. baseline were found comparing day 1 (pre-dose) with day 1 (6h), comparing day 2 (6h) with day 1 (pre-dose), comparing day 3 (6h) with day 1 (pre-dose) and comparing day 4 (6 h) with day 1 (pre-dose) values. These randomly distributed changes are casual and devoid of scientific and clinical significance. It's a fact that significance was found for the lowering of the aPTT mean value while the marker of a systemic absorption of heparin would have been an increase. The mean aPTT values obtained on day 6 are reported in the following table (n=12):

aPTT values (sec) on day 6, mean±SD, n=12

Predose	1 h	2 h	3 h	4 h	5 h	6 h	8 h	10 h	12 h	16 h	24 h
31.42 ±2.71	31.92 ±3.75	32.00 ±3.57	32.42 ±3.29	31.75 ±2.99	31.50 ±3.21	32.00 ±4.02	30.83 ±3.81	30.83 ±3.66	31.17 ±4.86	31.58 ±4.66	31.67 ±3.70

Statistical analysis (t test for paired sample data) performed on the obtained values did not show significant difference between the pre-dose values when compared to those obtained at the different time-points on day 6.

Determination of plasma diclofenamic acid was performed on day 1 (pre-dose), on day 2 (before morning application), on day 5 (before morning application) and on day 6 at pre-dose and 1, 2, 3, 4, 5, 6, 8, 10, 12, 16 and 24 h after the morning application. Mean results are reported in the following tables:

Diclofenamic acid plasma concentrations (ng/mL) on days 1, 2 and 5, mean±SD, n=12

Day 1	Day 2	Day 5
0 h	0 h	0 h
BQL	2.11±0.62	2.29±0.75

BQL= Below limit of quantification

Diclofenamic acid plasma concentrations (ng/mL) on day 6, mean±SD, n=12

Day 6											
0 h	1 h	2 h	3 h	4 h	5 h	6 h	8 h	10 h	12 h	16 h	24 h
1.93 ±0.84	1.44 ±0.72	1.62 ±0.95	1.93 ±0.92	2.04 ±0.92	2.12 ±0.88	2.09 ±0.92	1.57 ±0.65	1.50 ±0.63	1.62 ±0.69	2.26 ±1.08	2.36 ±1.03

Main diclofenamic acid PK parameters determined at steady state (τ=12 h) were the following (±SD):

Main PK parameters at steady state, mean±SD, n=12

τ (h)	AUCss (ng*h/mL)	Css_{min} (ng/mL)	Css_{max} (ng/mL)	Tss_{max} (h)	$Css_{average}$ (n /mL)
12	21.03±9.13	1.33±0.66	2.31±0.94	3.42±2.31	1.75±0.76
Range	41.94-11.37	2.82-0.70	4.39-1.27	6.00-0.00	3.49-0.95

During an observation period of 12 h, AUC_{ss} was 21.03±9.13 ng*h/mL (range 41.94-11.37 ng*h/mL), mean Css_{min} scored 1.33±0.66 (range 2.82-0.70 ng/mL) while mean Css_{max} was 2.31±0.94 ng/mL (range 4.39-1.27 ng/mL), achieved in 3.42±2.31 h. Average diclofenamic acid plasma concentration was 1.75±0.76 ng/mL (range 3.49-0.95 ng/mL).

The Css_{min} of diclofenac, as calculated in the report, is obtained from the mean values of Cmin for each subject (= 1.33 ± 0.66 ng/ml). The concentration at steady state before application of the last plaster is $Css_{12hours}$ (= 1.62 ± 0.69 ng/ml), a value close to the concentration at T0 (1.93 ± 0.84 ng/ml), which consequently confirms the steady state-condition.

Adhesiveness was evaluated each time a plaster was detached. Differences in adhesiveness were found between males and females: mean summed score was of 31.67±4.76 for males while females showed a mean adhesiveness summed score of 21.33±5.20. This difference is probably due to the denser presence of hairs on the skin of male subjects.

Conclusions: The release of diclofenac epolamine and the subsequent absorption through the skin into the systemic circulation was low, continuous and constant and allowed the achievement of steady-state condition. Heparin was not absorbed at systemically effective concentrations.

On the basis of the absence of AEs and aPTT clinically relevant changes or statistically significant increase, it can be concluded that the DHEP/heparin combination at the studied dose levels is safe and the potential risk of transdermal absorption of heparin at systemically effective concentrations is excluded, while an excellent local and systemic tolerability is shown.

Date of the report: Final version, 28OCT03

Reviewer conclusions: The study generally shows that systemic absorption of diclofenac is low, and that heparin, if absorbed, has very limited impact on coagulation. Note that heparin PK cannot be done due to lack of bioanalytical method for detecting heparin(s). However, aPTT , a measure of coagulation, is considered an acceptable PD measure to evaluate systemic effects.

3.4 Synopis of Study CRO-PK-12-272

Name of Company: IBSA Institut Biochimique S.A., Switzerland	**TABULAR FORMAT**		**(For National Authority Use only)**
Name of Finished Product: Flectoparin® Tissugel	**REFERRING TO PART OF THE DOSSIER**	5.3	
Name of active substance(s): Diclofenac and heparin	**Volume:**		
	Page:		

Title of the study:
Two parts study aimed at evaluating the diclofenac epolamine (DHEP) and heparin residual content in [redacted] (b) (4) after 24 h application and the effects of exercise, occlusion and heat on diclofenac absorption in healthy volunteers after once-per-day applications of [redacted] (b) (4) for 4 consecutive days

Investigators: *Principal investigator*: Milko Radicioni, MD; *Co-Investigator*: Antonio Rusca, MD, FMH

Study centre: CROSS Research Phase I Unit, Via F. A. Giorgioli 14, CH-6864 Arzo, Switzerland

Publication (reference):

Studied period (years):	**Date of first enrolment:**	**17JUN13**	**Phase of development:**
2013	**Date last vol. completed:**	**22SEP13**	**I**

Objectives:
Part 1: to evaluate DHEP and heparin residual content in [redacted] (b) (4) after 24 h application to the inner upper part of the arms of healthy subjects.
Part 2: to evaluate the effects of various treatment conditions (standard rest, moderate exercise, under occlusion and moderate heat exposure) on the diclofenac plasma absorption profile after [redacted] (b) (4) administration to healthy subjects.
Part 1:
Primary end-point: to measure DHEP and heparin residual content in [redacted] (b) (4) after 24 h application
Secondary end-point: to assess the patch safety and local tolerability profile after 24 h application
Part 2:
Primary end-point: to compare the diclofenac pharmacokinetic (PK) profile after four days of once-per-day patch exposure under three non-standard conditions (moderate exercise, under occlusion and moderate heat exposure) vs. reference condition (standard rest)
Secondary end-point: to compare the patch safety and local tolerability profiles under the four treatment conditions investigated (standard rest, moderate exercise, under occlusion and moderate heat exposure)

Methodology:
Part 1: single dose, non-randomised, open-label, exploratory study
Part 2: multiple dose, randomised, open-label, cross-over bioavailability study

Number of subjects (planned and analysed):
Part 1: Twenty-four (24) healthy male and female subjects were planned and analysed.
Part 2: Fourteen (14) healthy male and female subjects were planned and randomised. All 14 subjects received at least one application of the investigational product and were included in the safety analysis. Thirteen (13) of the 14 randomised subjects completed the study per protocol and were included in the PK analysis.

Diagnosis and criteria for inclusion:

Inclusion criteria (Part 1 and Part 2):

1. *Sex and age*: male and female healthy subjects, 18-45 years old inclusive;
2. *Body Mass Index:* 18.5-30 kg/m^2 inclusive;
3. *Vital signs*: systolic blood pressure 100-139 mmHg, diastolic blood pressure 50-89 mmHg, heart rate 50-90 bpm, measured after 5 min at rest in the sitting position;
4. *Full comprehension*: 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;
5. *Informed consent*: signed written informed consent before inclusion in the study;
6. *Drug abuse*: negative drug test at screening;

Diagnosis and criteria for inclusion, continued:

Inclusion criteria (Part 1 and Part 2), continued:

7. *Contraception and fertility (females only)*: females of child-bearing potential had to use at least one of the following reliable methods of contraception:
    a. Hormonal oral, implantable, transdermal or injectable contraceptives for at least 2 months before the screening visit
    b. A non-hormonal intrauterine device [IUD] or female condom with spermicide or contraceptive sponge with spermicide or diaphragm with spermicide or cervical cap with spermicide for at least 2 months before the screening visit
    c. A male sexual partner who agreed to use a male condom with spermicide
    d. A sterile sexual partner

    Female participants of non-child-bearing potential or in post-menopausal status for at least 1 year were admitted. For all female subjects, pregnancy test result had to be negative at screening.

Exclusion criteria (Part 1 and Part 2):

1. *Physical findings*: clinically significant abnormal physical findings which could interfere with the objectives of the study;
2. *Laboratory analyses*: clinically significant abnormal laboratory values indicative of physical illness;
3. *Allergy*: ascertained or presumptive hypersensitivity (including allergies) to the active principle and/or formulations' ingredients or related drugs, namely non-steroidal anti-inflammatory agents (NSAIDs) and/or opioid derivatives; history of anaphylaxis to drugs or allergic reactions in general, which the investigator considered could affect the outcome of the study;
4. *Diseases:* significant history of renal, hepatic, gastrointestinal, genitourinary, cardiovascular, respiratory (including allergic asthma, allergic or chronic bronchitis or other pulmonary diseases), skin, haematological, endocrine or neurological diseases that could interfere with the aim of the study;
5. *Medications*: medications, including over the counter and herbal medications, for 2 weeks before the start of the study, in particular NSAIDs and medications containing diclofenac. Hormonal contraceptives for females were allowed;
6. *Investigative drug studies*: participation in the evaluation of any investigational product for 3 months before this study, calculated from the first day of the month following the last visit of the previous study;
7. *Blood donation*: blood donations for 3 months before this study;
8. *Drug, alcohol, caffeine, tobacco*: history of drug, alcohol (>1 drink/day for females and >2 drinks/day for males, defined according to USDA Dietary Guidelines 2010), caffeine (>5 cups coffee/tea/day) or tobacco abuse (≥10 cigarettes/day);
9. *Diet*: Abnormal diets (<1600 or >3500 kcal/day) or substantial changes in eating habits in the 4 weeks before this study;
10. *Pregnancy*: pregnant or lactating women

Exclusion criteria (Part 2 only):

11. *Electrocardiogram (ECG) 12-leads (supine position)*: clinically significant abnormalities;
12. *Perceived exertion test:* very strong or extremely strong exertion (scores from 7 to 10 according to Borg's Category Ratio (CR)-10 scale) perceived during the moderate exercise session (20 min) performed at screening.

Test product, dose, mode of administration, batch N°:

Diclofenac N-(2-hydroxyethyl)-pyrrolidine (DHEP) medicated plaster formulated with heparin (Flectoparin® Tissugel®, IBSA, Switzerland). Each medicated plaster (or patch) contains 181 mg DHEP and 5600 I.U. sodium heparin. Clinical batch N. 002D13-043; expiry date: MAR16.

Test product, dose, mode of administration, batch N°, continued:

Part 1: Two DHEP-Heparin medicated plasters were applied to the inner upper part of the arms (one patch to the right arm and one patch to the left arm) using a loose fitting elastic net sleeve (supplied in the commercial package of the product and approved for usage with the Flector® Patch both in Europe and in USA) in order to avoid inadvertent detachment. Patches were applied in the morning (8:00 a.m.±1 h) and kept in place for 24 h. Before the application, the application site was shaved, if necessary, and cleaned.

Part 2: One DHEP-Heparin patch was applied once a day for four consecutive days, during each of four study periods under four different treatment conditions (one condition per study period; see below) according to the randomisation list. Each patch was kept in place for 24 h, using the loose fitting elastic net sleeve supplied in the commercial package of the product, in order to avoid inadvertent detachment. During the study, subjects were exposed to a total of 16 plasters (4 patches/period, 4 periods). Patches were applied in the morning (8:00 a.m.±1 h) to the front thigh, specifically on the right and left thighs, alternatively, in the four study periods, so that any potential local adverse reaction would have been resolved before the subsequent applications in the subsequent period. Before the first application of each study period, the application site was shaved, if necessary, and cleaned. Wash-out interval after the last application of each study period was of at least 5 days. The following exposure conditions were investigated:

Condition A (standard rest - reference condition): no special conditions.

Condition B (moderate exercise): on each day of the moderate exercise period, subjects underwent three exercise sessions of 20 min each: the first session immediately after patch application, the second session 4 h post-application and the third session 8 h post-application. Subjects were asked to ride a stationary bicycle at 50% of their Heart Rate Reserve (HRR) above their heart rate at rest (HR_{rest}), i.e. ($HR_{max} - HR_{rest}$) x 50% plus HR_{rest}. HRR and HR_{rest} were calculated for each subject at screening.

Condition C (under occlusion): an occlusive bandage, beside the provided elastic net used in all four periods, was applied to each patch for the whole duration of the study period. The bandage was removed for 1 h twice daily at approximately 5 and 12 h post-application (during meals).

Condition D (moderate heat exposure): immediately after, as well as 4, 8 and 12 h after each application, the patch was warmed up with a heat wrap for 20 min, for a total heat exposure for the period of 5 h and 20 min, with patch in place.

Criteria for evaluation (pharmacokinetics):

Part 1: Primary variables: residual amount of DHEP measured in milligrams (mg) and residual amount of heparin measured in International Units (I.U.) present in used plasters.

Secondary variables: treatment emergent-adverse events (TEAEs), vital signs (blood pressure [BP], heart rate [HR]), body weight (BW), local tolerability, adhesiveness scores.

Part 2: Primary variables: diclofenac plasma C_{max} and AUC_{τ} for each treatment period

Secondary variables: diclofenac plasma T_{max}, C_{min}, PTF% and F_{rel} for each treatment period; TEAEs, vital signs (BP, HR), BW, laboratory parameters, ECG, local tolerability, adhesiveness scores.

Criteria for evaluation (safety):

Part 1: TEAEs; vital signs (BP, HR); physical examinations performed at screening and final visit/early termination visit (ETV); laboratory tests performed at screening. Local tolerability evaluated in all subjects before patch application and immediately after patch removal. Skin reactions were graded according to a 4-grade score scale.

Part 2: TEAEs; vital signs (BP, HR); physical examinations; laboratory tests performed at screening and final visit/ETV; ECG performed at screening and final visit/ETV. Local tolerability evaluated in all subjects before the first patch application and every day immediately after patch removal (before subsequent patch applications). Skin reactions were graded according to a 4-grade score scale.

Statistical methods:

Part 1: DHEP and heparin patch residual content data were listed and summarised by descriptive statistics.

Part 2: Steady state PK parameters C_{max}, T_{max}, AUC_{τ}, C_{min}, PTF%, F_{rel} (relative bioavailability; calculated as ratio AUC_{τ} [test B, C and D condition]/AUC_{τ} [reference condition A]) were calculated for every treatment period. The statistical and pharmacokinetic analyses were performed using SAS® version 9.1.3 service pack 4 for Windows and Phoenix WinNonlin version 6.3, Pharsight Corporation. C_{max} and AUC_{τ} of the three treatment conditions under investigation (moderate exercise, under occlusion, moderate heat exposure) were compared to the reference condition (standard rest) using analysis of variance (ANOVA) for a cross-over design. Period, group, sequence and subject within sequence were taken into consideration as sources of variation. ANOVA was performed on log-transformed data. T_{max} were compared using Friedman test. The pharmacokinetic data and clinical parameters were described using classic descriptive statistics for quantitative variables and frequencies for qualitative variables.

Results:

Pharmacokinetics (Part 2 only)

Main PK parameters of diclofenac after four 24-h applications of the DHEP-Heparin patch under four treatment conditions are summarised in the following table:

Table 1 Diclofenac main plasma PK parameters (mean ± SD) after 4-day o.d. applications of DHEP-heparin patch under the 4 treatment conditions. N=13

PK parameter	A Standard rest	B Moderate exercise	C Under occlusion	D Moderate heat exp.
C_{max} (ng/mL)	1.01±0.64	1.22±0.76	1.14±0.74	1.23±0.73
T_{max} (h)	6 (4–20)	12 (0-24)	6 (0-24)	6 (0-20)
AUCτ (ng/mL×h)	18.58±11.63	22.77±14.39	21.94±14.25	23.07±14.29
C_{min} (ng/mL)	0.49±0.31	0.62±0.42	0.63±0.47	0.69±0.46
PTF (%)	68.18±18.43	66.04±15.84	58.22±14.14	58.63±9.45

Values are arithmetic means ± SD, except for T_{max}: median (min - max)

Results of PK parameter comparisons between treatment conditions are presented in the following table:

Table 2 Statistical analysis results. N=13

Treatment comparison	PK parameter	Geometric mean ratio	
		PE%	90% CI
B vs. A	C_{max}	111.20%	89.57 – 138.07%
	AUC_{τ}	112.11%	93.41 – 134.55%
C vs. A	C_{max}	112.69%	94.90 – 133.82%
	AUC_{τ}	117.62%	100.38 – 137.83%
D vs. A	C_{max}	112.90%	89.22 – 142.86
	AUC_{τ}	114.20%	91.76 – 142.12

PE%: point estimate, ratio of geometric means; Condition A: Standard rest-reference condition; Condition B: Moderate exercise; Condition C: Under occlusion; Condition D: Moderate heat exposure

Diclofenac C_{max} and AUCτ values for test treatment conditions B (moderate exercise), C (under occlusion) and D (moderate heat exposure) were, on average, higher than for the reference treatment A (standard rest), as confirmed by PE% values of approximately 111 – 113% for C_{max} and of 112 – 118% for AUCτ. As a consequence, the corresponding 90% CIs overlapped the upper limit of the 80.00 – 125.00% range and the three test conditions could not be claimed bioequivalent to the reference conditions in terms of rate and extent of diclofenac absorption. Differences in T_{max} values between test treatments B, C and D and reference treatment A, however, were not statistically significant ($p \geq 0.2568$).

Results, continued:

DHEP and heparin residual patch content (Part 1 only)

A lower (mean ± SD) amount of DHEP was present in used (168.66±2.62 mg) as compared to reference (175.15±5.35 mg) patches. No relevant changes in heparin content were measurable after a 24-application.

Adhesiveness (Part 1 and Part 2)

Number of subjects for each adhesiveness score, representing the percentage of patch adhering area (i.e. "0%-detached", "< 50%", "≥ 50 - < 75%", "≥ 75 - < 90" and ">90%") was assessed just before each plaster removal. In study Part 1, patches adhered for most subjects and both arms between 75 and 90% of the area. Adhesion between 50 and 75% was reported for only 1 subject (4.2%) for the left arm and 4 subjects (16.7%) for the right arm. In study Part 2, all plasters under all four treatment conditions adhered for at least 75% of the adhesion area. Notably, all patches adhered for ≥ 90% of the adhesion area for most subjects during moderate exercise and under occlusion conditions.

Safety (Part 1 and Part 2)

Local tolerability of the investigational patch was excellent: no erythema, dryness, swelling or exfoliation at the application site was detected throughout the 2 study parts.

In study Part 1, only one TEAE, i.e. headache, was reported. The TEAE was deemed as treatment-related.

In study Part 2, 8 TEAEs were reported by 5 of the 14 randomised subjects (35.7%). The most common TEAE was dysmenorrhoea (2 [14.3%] subjects), followed by abdominal pain, neck pain, dizziness and headache (1 [7.1-7.7%] subject each).The abdominal pain event was judged as treatment-related. All the reported AEs were of mild or moderate intensity and resolved by study end. No serious or significant adverse events were reported throughout the study.

Conclusions:

Twenty-four (24)-h patch applications for 4 days under the test treatment conditions (i.e. moderate exercise, under occlusion and moderate heat exposure) resulted in a slightly higher diclofenac systemic bioavailability than applications under the reference rest condition, as indicated by test/reference point estimate values of approximately 111 – 113% for C_{max} and 112 – 118% for AUC_{τ}. As a consequence, the 90% CIs overlapped the upper limit of the 80.00 to 125.00% range specified by the current guidelines and the three test treatment conditions could not be claimed bioequivalent to the rest condition in terms of rate or extent of diclofenac absorption. Differences in T_{max}, however, were not statistically significant.

Test treatment conditions did not appear to modify the adhesiveness of the patch, as demonstrated by adhesion areas of at least 75% at patch removal for all subjects (Part 2).

Local tolerability of the DHEP-Heparin patch was excellent under all study conditions and at both application sites (upper arm and thigh).

After 24-h application to the skin (upper arm), about 6.5 mg of the DHEP appears to have been released from the patch, an amount which is certainly consistent with the limited systemic exposure observed in the PK part (Part 2) of the study. Of note, no changes in heparin content were measurable pre-/post-application.

Date of the report: Final version 1.0, 07APR14

3.5 Clinical Pharmacology Filing Form

CLINICAL PHARMACOLOGY FILING FORM

Application Information			
NDA/BLA Number	206976	**SDN**	000
Applicant	Institute Biochimique	**Submission Date**	5/26/2016
Generic Name	Diclofenac (b) (4)	**Brand Name**	(b) (4)
Drug Class	NSAID		
Indication	For treating minor pains, strains and contusions		
Dosage Regimen	Once every twelve hours		
Dosage Form	Topical (b) (4)	**Route of Administration**	Topical
OCP Division	DCP2	**OND Division**	DAAAP
OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**	
Division	Srikanth C. Nallani, Ph.D.	Yun, Xu, Ph.D.	
Pharmacometrics			
Genomics			
Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	5/26/2016	**74-Day Letter Date**	8/8/2016
Review Due Date	2/10/2017	**PDUFA Goal Date**	3/24/2017

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☑ Yes

☐ No

If yes list comment(s)

We have noticed that the patch product used in the clinical trial was manufactured at a different site compared to the product used in the PK studies (CRO-PK-98-13, CRO-PK-02-92 and CRO-PK-12-272) and planned to-be-marketed. We have not seen any data submitted to support the manufacture of the to-be-marketed formulation at the new manufacturing site to be of similar performance characteristics as the patch manufactured at a site for use in the pivotal clinical trials.

Hence, we require you to clarify if there is difference, such as formulation, manufacturing sites, from the products used in the clinical trial and the PK studies to the final to-be-marketed product. Provide justification with data to support that the results from these studies can be used to support your final to-be-marketed product.

Is there a need for clinical trial(s) inspection?

☐ Yes
☑ No
If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☐ Yes ☑ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type		Count	Comment(s)
In Vitro Studies			
☐ Metabolism Characterization			
☐ Transporter Characterization			
☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☐ Bioequivalence			
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☐ Single Dose		
	☑ Multiple Dose	1	• CRO-PK-98-13: Bioavailability study of a new topical formulation of DHEP plaster containing heparin vs. the marketed formulation Flector EP Tissugel in male and female healthy volunteers. This open, randomized, two-way crossover, multiple dose study was divided in two phases: 4 healthy volunteers were enrolled during the first, pilot phase, while 18 healthy volunteers participated in the subsequent main phase. • CRO-PK-02-92: Multiple dose PK study comparing diclofenac levels between the new patch with heparin and old patch without heparin. • CRO-PK-12-272: Another multiple dose PK study. Part 1: single dose, non-randomized, open-label exploratory study. Part 2: multiple dose, randomized, open-label, cross-over bioavailability study.
Patients	☐ Single Dose		

	☐ Multiple Dose		
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☐ Pediatrics			
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
☑ Effects on Primary Drug		Effect of heat, exercise and occlusive bandage were also determined in study CRO-PK-12-272.	
☐ Effects of Primary Drug			
Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
Pharmacokinetics/Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
☐ QT			
Pharmacometrics			
☐ Population Pharmacokinetics			
☐ Exposure-Efficacy			
☐ Exposure-Safety			

Total Number of Studies	**In Vitro**		**In Vivo**	3
Total Number of Studies to be Reviewed				3

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	The sponsor submitted two new studies and past studies with old patch to document very low plasma levels of diclofenac following topical application.
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐Yes ☐No ☑N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☑Yes ☐No ☐N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☐Yes ☐No ☑N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	Biopharmaceutics and clinical pharmacology summaries were not submitted originally. Resubmission has the information.
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting	☑Yes ☐No ☐N/A	Electronic dataset were not submitted in the original submission. See comments below.

studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?		
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☐Yes ☐No ☑N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☐No ☑N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☐Yes ☐No ☑N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

Filing Memo

In 2015, Institut Biochimique SA (IBSA) submitted a New Drug Application (NDA) for the [redacted] (b) (4) which the sponsor contends is [redacted] (b) (4) l to Flector® Patch (NDA 21234) except for the presence of a [redacted] (b) (4) of heparin [redacted] (b) (4) The original NDA 021234 indicated that diclofenac plasma levels are very low compared to oral diclofenac. In this NDA, the company submitted a multiple dose PK study comparing plasma levels of diclofenac between old and new patch formulations, and demonstrated that overall plasma levels of diclofenac are very low as with the original patch.

There were deficiencies identified in the NDA submission from 2015. Previous comments included a request to submit the following to resolve the deficiencies:

a) Summary of biopharmaceutics and clinical pharmacology supporting the new formulation.
b) On 7/1/2016 electronic dataset of the PK data from studies CRO-PK-02-92, and CRO-PK-98-13.

With the new NDA the sponsor also submitted data for CRO-PK-12-272.

Since the original NDA deficiencies are addressed, the NDA is fileable.

Note: The formulations used in the different PK studies are listed below for record.

Test product, dose, mode of administration, batch No: Study # Study CRO-PK-12-272.

Diclofenac N-(2-hydroxyethyl)-pyrrolidine (DHEP) medicated plaster formulated with heparin (Flectoparin®

Tissugel*, IBSA, Switzerland). Each medicated plaster (or patch) contains 181 mg DHEP and 5600 I.U.

sodium heparin. Clinical batch N. 002D13-043; expiry date: MAR16.

Study CRO-PK-98-13:

Test product, dose, mode of administration, batch N°:

Formulation A: diclofenac epolamine plaster: 14x10 cm containing 180 mg of diclofenac epolamin and 5,600 I.U. of heparin. The plaster was applied on the right side of the back (lumbar region) twic a day for 7 consecutive days plus 1 administration in the morning of day 8

Batch n° 58/IB-43 (71T/IB-22). Expiry date: 01/2000.

Study CRO-PK-02-92

9.4.2 Identity of investigational product(s)

Study medication	Flector / Heparin Tissugel containing 180 mg DHEP (equivalent to 150 mg diclofenac) and 5,600 IU heparin sodium
Chemical name	diclofenac epolamine / heparin sodium
Manufacturer	Teikoku Seyaku Co. Ltd/IBSA Institut Biochimique sa
Pharmaceutical form:	plaster

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

/s/

SRIKANTH C NALLANI
02/09/2017

YUN XU
02/10/2017