

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-165

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 22-165
Submission Date(s): September 27, 2007
Brand Name: To Be Decided
Generic Name: Diclofenac Potassium Powder for Oral Solution
Dosage Form: Powder for Oral Solution
Dosage Strengths: 50 mg
Indication: Treatment of Acute Migraine Attacks in Adults with or without Aura
NDA type: 505B(2)
Sponsor: ProEthic Pharmaceuticals
IND: IND 73,073
Reviewer: Carol Noory
Team Leader: Veneeta Tandon, Ph.D.
OCP Division: DCP-1, HFD-860
OND Division: Neurology HFD-120

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I. EXECUTIVE SUMMARY

Diclofenac, a phenylacetic acid derivative, is a non steroidal anti-inflammatory drug (NSAID) that has been in clinical use for many years, particularly for the treatment of inflammatory and degenerative rheumatic diseases and soft-tissue rheumatisms. It is also effective in treating non-rheumatic painful and inflammatory conditions, such as dysmenorrhoea and post-operative pain. Diclofenac is available worldwide in a number of dosage forms for oral, rectal, intramuscular or topical administration. In the United States, diclofenac is available in two different salts, diclofenac sodium (Voltaren® 75mg delayed release tablet-NDA19-201 approved 7/28/88) and diclofenac potassium (Cataflam®-NDA 20-142 approved 11/24/1993), which are both marketed by Novartis Pharmaceuticals. Voltfast®/Catafast® (50 mg diclofenac potassium) sachet, a sugar-containing diclofenac potassium powder that is dissolved in water for oral administration, is marketed by Novartis in Italy (Voltfast®) since 2000 and in Egypt (Catafast®) since 2004. A sugar-free formulation of the sachet is marketed in Switzerland since 2006. (b) (4)

A list of the currently available products for diclofenac potassium and sodium, their route of administration and indication for use is summarized in the following table (Table 1):

Table 1: Summary of Approved Diclofenac-Salt Containing Formulations

Diclofenac Potassium

Route: Disease/Condition	Marketed Formulation(s)	Treatment Regimens
<i>Diclofenac Potassium</i>		
Oral:	Cataflam® (50 mg tablet) (Novartis)	50 mg PO BID/TID. Dosages > 150 mg/day PO are not recommended
Osteoarthritis	Cataflam® (50 mg tablet) (Novartis)	50 mg PO TID/QID. Dosages > 225 mg/day PO are not recommended
Rheumatoid arthritis	Cataflam® (50 mg tablet) (Novartis)	50 mg PO TID. For better relief, give 100 mg PO initially, and then follow with 50 mg doses. After the first day of therapy with a maximum dose of 200 mg PO, total doses should generally not exceed 150 mg/day.
Primary dysmenorrhea or for mild to moderate pain	Cataflam® (50 mg tablet) (Novartis)	

Diclofenac Sodium

Route: Disease/Condition	Marketed Formulation(s)	Treatment Regimens
<i>Diclofenac Sodium</i>		
Topical:	Solaraze® Gel, 3% (Doak Dermatologics)	Apply topically to lesions BID for 60–90 days
Ocular:	Voltaren® Ophthalmic Solution, 0.1% (Novartis Ophthalmics)	Instill one drop in the affected eye(s) four times daily, starting 24 hours after cataract surgery and continuing for two weeks.
Reduction of photophobia and ocular pain following corneal refractive surgery	Voltaren® Ophthalmic Solution, 0.1% (Novartis Ophthalmics)	Instill one to two drops in the affected eye(s) within one hour prior to surgery, then one to two drops 15 minutes after surgery and then QID beginning four to six hours after surgery and continuing for up to three days as needed
Oral:	Voltaren® (25, 50, and 75 mg tablets) or	VOLTAREN: 50 mg PO two BID/TID or 75 mg PO BID. Dosages > 150 mg/day are not recommended;
Osteoarthritis	Voltaren®-XR (100 mg tablet) (Novartis)	VOLTAREN-XR: 100 mg PO QD for chronic therapy. Dosages > 150 mg/day PO are not recommended.
Rheumatoid arthritis	Voltaren® (25, 50, and 75 mg tablets) or	VOLTAREN: 50 mg PO TID/QID or 75 mg PO QD. Dosages > 225 mg/day PO are not recommended;
	Voltaren®-XR (100 mg tablet) (Novartis)	VOLTAREN-XR: 100 mg PO QD for chronic therapy. In the rare cases where 100 mg/day is unsatisfactory, the dose may be increased to 100 mg PO BID if the benefits outweigh the risks. Dosages > 225 mg/day PO are not recommended.
Ankylosing spondylitis	Voltaren® (25, 50, and 75 mg tablets) (Novartis)	VOLTAREN: 100–125 mg/day PO in 4–5 divided doses. Usually 25 mg PO QID with an additional 25 mg dose at bedtime, if needed. When a satisfactory response is achieved, the dosage should be reduced to the minimum required to provide relief of symptoms. The safe and effective use of doses exceeding 125 mg/day PO has not been established for ankylosing spondylitis.

As shown in the table above, the maximum recommended dose of a diclofenac potassium product for the treatment of primary dysmenorrheal or mild to moderate pain is 150 mg/day.

ProEthic has developed a new, oral, water-soluble powder formulation (sachet) of diclofenac potassium, PRO-513. The sachet contents are mixed with water prior to dose administration. ProEthics is seeking approval for the 50 mg sachet for the indication of acute treatment of migraine attack with or without aura in adults and is not seeking approval for other indications previously approved for the Reference Listed Drug (Cataflam® NDA 20-142 approved 11/24/1993). The recommended dose for the treatment of migraine is 50 mg.

In support of the Clinical Pharmacology section of the application, the Sponsor has included two Phase I bioavailability and tolerability studies. One BA study was conducted by ProEthic using PRO-513, and one European study was conducted by Novartis using (b) (4) (a PRO-513 equivalent). The NDA also includes results from two Phase III efficacy and safety studies in migraine patients. An additional Phase III study conducted to evaluate the efficacy of the diclofenac sachet for an unrelated indication (treatment of moderate to severe post-surgical dental pain) is also included for safety evaluation.

The general pharmacokinetic characteristics of the diclofenac potassium sachet (powder for oral solution) were determined from the following studies:

- The ProEthics Study, PRO513-101, was a U.S. single-dose, 4-period crossover trial comparing the relative bioavailability of PRO-513 (diclofenac potassium powder for oral solution) to Cataflam® (diclofenac potassium) tablets under fed and fasting conditions.
- The Novartis study, CAT458C2101, was a European single dose, two-way, crossover study comparing the bioavailability of diclofenac-K sachets (powder for oral solution) to Cataflam® tablets in 24 healthy subjects.

The labeling of PRO513 is based on the Cataflam® tablet labeling. Several changes are recommended to clarify the sponsor's proposed label (See IV. DETAILED LABELING RECOMMENDATIONS pages 28-35). The sponsor's proposed labeling is attached (VI. Sponsor's Proposed Labeling) and can be found on pages 57 to 122. The Agency PLR labeling for a new NDA not yet approved has also been used for reference.

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 1 has reviewed NDA 22-165 and finds the Clinical Pharmacology section of the application acceptable. The labeling is acceptable provided that an agreement can be reached with the sponsor regarding the labeling recommendations proposed. The reviewer's labeling changes shown by track changes are given on pages 28 to 35 (See IV. DETAILED LABELING RECOMMENDATIONS).

1.2 Overall Summary of Clinical Pharmacology Findings

The sponsor originally submitted this NDA on 6/25/07. The submission was not filed due to non-clinical issues with the submission. The NDA was again submitted on 9/27/2007. PRO-513 contains diclofenac potassium, the same diclofenac salt used in Cataflam® tablets that are approved for use for different indications in the United States. PRO-513 sachet is a reformulation of a sachet originally marketed by Novartis in Italy in 2000 (Volfast®) and Egypt in 2004 (Catafast®). (b) (4)

In support of the clinical pharmacology section of the NDA, the sponsor submitted two pharmacokinetics studies comparing the sachet formulation to the Cataflam® tablet of the same strength. The pivotal study was conducted by ProEthics in the United States and a supportive study was conducted by Novartis in Europe.

- Study PRO-513101** was conducted by ProEthics in the U.S. to compare the bioavailability of PRO-513 to that of 50 mg diclofenac potassium tablets (Cataflam®) under both fasting and fed conditions. This was an open-label, randomized, four-period, crossover study in which 36 healthy volunteers received one treatment of PRO-513 and one treatment of the Reference under fasting conditions, and then received one dose of each treatment under fed conditions; the treatment periods were separated by seven days washout. All subjects fasted for 10 hours at the start of each visit. Subjects who were randomized to the “fasting” group were given a single oral dose of the study medication; subjects who were randomized to the “fed” population were given a standardized, high-fat, high-calorie meal and then dosed with the study medication.

Relative Bioavailability:

The results of the U.S. study determined the following relative bioavailability under fed and fasting conditions. Results are shown in the following table:

Parameter	Test/Reference	Geometric LS Means		Geometric Mean ratio* (%)	90% Confidence Interval
		Test	Reference		
FASTED					
AUC0-inf (ng*hr/mL)	A vs B	1203.19	1060.40	113	107.10- 120.21
AUC0-t (ng*hr/mL)		1184.34	1043.87	113	106.86- 120.46
Cmax (ng/mL)		1502.19	1033.32	145	121.12-174.48
FED					
AUC0-inf (ng*hr/mL)	C vs D	1078.28	1035.70	104	98.05- 110.55
AUC0-t (ng*hr/mL)		1025.70	1032.38	99	93.75-105.29
Cmax (ng/mL)		433.22	714.33	61	50.83-72.36
A: PRO-513 (diclofenac potassium) sachet 50 mg fasting					
B: Cataflam® (diclofenac potassium) tablets 50 mg fasting					
C: PRO-513 (diclofenac potassium) sachet 50 mg fed					
D: Cataflam® (diclofenac potassium) tablets 50 mg fed					

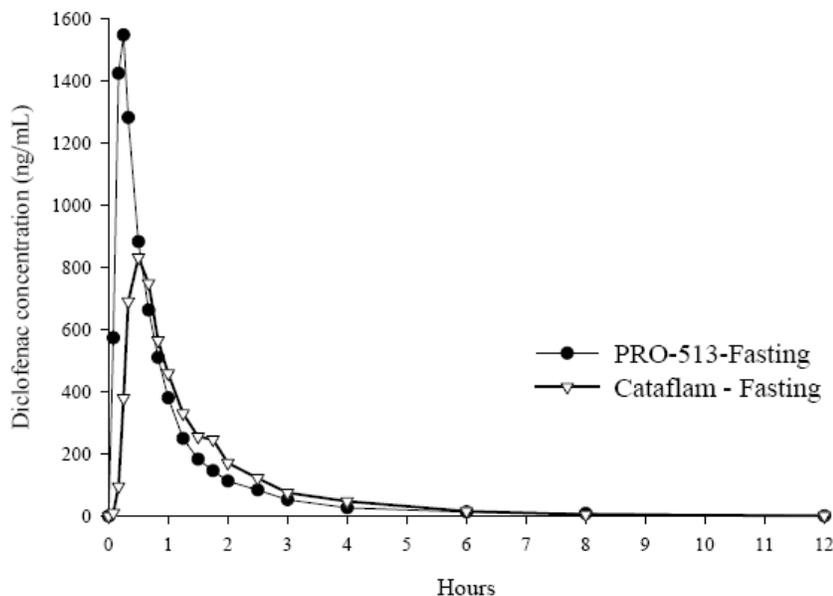
Fasted Conditions:

a. PRO-513 versus Cataflam® Tablets under Fasted Conditions:

- AUC:** Following single oral doses administered under fasting conditions, PRO-513 and Cataflam have similar AUC (total amount of diclofenac absorbed). The geometric mean ratio and 90% confidence intervals for PRO-513 versus Cataflam® tablets were 113% (107.10-120.21) for AUC(0-inf).
- Cmax:** Peak diclofenac concentrations following administration of PRO-513 were 45% higher than peak concentrations following administration of Cataflam®. The geometric mean ratio and 90% confidence intervals for PRO-513 versus Cataflam® tablets were 145% (121.12-174.48) for Cmax. The 90% CI for Cmax was outside the acceptable range of 80-125%.
- Tmax:** The median Tmax for PRO-513 was shorter than Cataflam® (0.25 hours versus 0.50 hours).

The plasma concentration-time profiles for the two treatments under fasted conditions are shown in the following figure.

Figure 11.4.1-1: Mean Plasma Diclofenac Concentrations by Treatment and Time Under Fasting Conditions



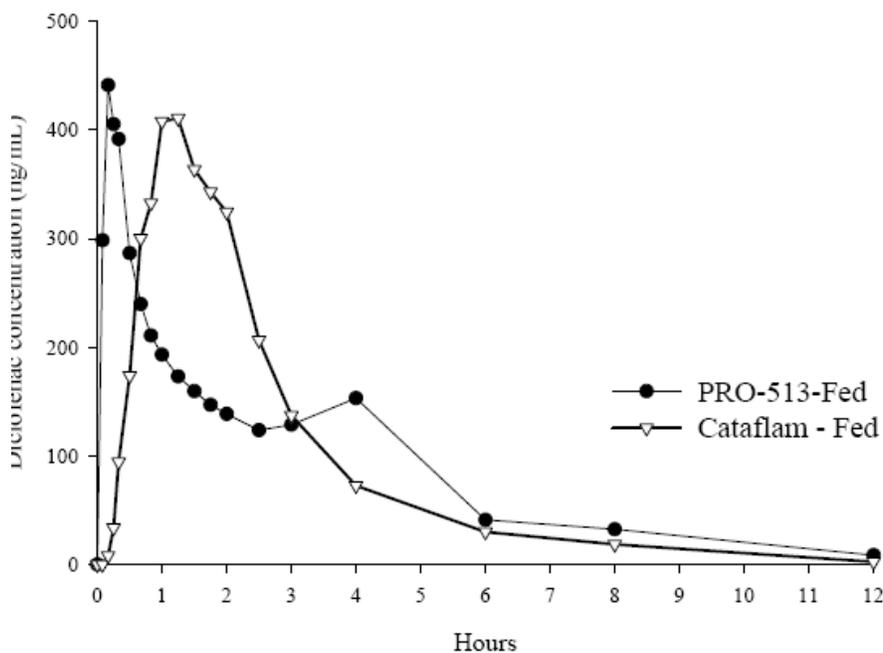
Fed Conditions:

b. PRO-513 versus Cataflam® Tablets under Fed Conditions:

1. **AUC:** Following single oral doses administered under fed conditions, PRO-513 and Cataflam® have similar AUCs (total amount of diclofenac absorbed). Geometric mean ratio and 90% confidence intervals for the differences between PRO-513 and Cataflam® tablets were 104% (98.05-110.55) for AUC_{0-∞}. The 90% confidence interval for the AUC_{0-∞} difference was within the 80%-125% interval.
2. **C_{max}:** Food decreased the mean diclofenac C_{max} for both PRO-513 and Cataflam® compared to the fasted state. Food had a more pronounced effect on peak diclofenac concentrations for PRO-513, producing a C_{max} that was 39% lower than for Cataflam®. Geometric mean ratio and 90% confidence intervals for the differences between PRO-513 and Cataflam® tablets were 61% (50.83-72.36) for C_{max}. The 90% confidence interval for the C_{max} difference fell completely below the lower equivalence limit of 80%.
3. **T_{max}:** Food increased the diclofenac T_{max} for Cataflam. The median T_{max} value for Cataflam® was significantly longer than for PRO-513 (1.25 hours versus 0.17 hours). Food did not significantly lengthen the diclofenac T_{max} for PRO513. Thus, PRO-513 was more rapidly absorbed than Cataflam® following a high-fat meal.

The plasma concentration-time profiles under fed conditions for the two treatments are shown in the following figure:

Figure 11.4.1-2: Mean Plasma Diclofenac Concentrations by Treatment and Time Under Fed Conditions



Food Effect

The study determined the effect of food on the bioavailability of PRO-513 and Cataflam® following a high-fat meal. The statistical results are shown in the following table.

Parameter	Test/Reference	Geometric LS Means		Geometric Mean ratio* (%)	90% Confidence Interval
		Test	Reference		
PRO-513					
AUC0-inf (ng*hr/mL)	C vs A FED/FASTED	1076.34	1220.59	88	82.94-93.75
AUC0-t (ng*hr/mL)		1022.67	1200.63	85	80.29-90.37
Cmax (ng/mL)		432.76	1528.60	28	23.63-33.92
Cataflam®					
AUC0-inf (ng*hr/mL)	D vs B FED/FASTED	1029.55	1065.97	97	91.22-102.26
AUC0-t (ng*hr/mL)		1026.23	1049.33	98	92.22-103.72
Cmax (ng/mL)		701.52	1044.38	67	56.20-80.28

A: PRO-513 (diclofenac potassium) sachet 50 mg fasting
B: Cataflam® (diclofenac potassium) tablets 50 mg fasting
C: PRO-513 (diclofenac potassium) sachet 50 mg fed
D: Cataflam® (diclofenac potassium) tablets 50 mg fed

c. Pro-513 Fed vs. Fasted:

1. **AUC:** Following single oral doses of PRO-513 under fed and fasted conditions, there was a 12% reduction in AUC (0-inf) when PRO-513 was dosed with food. The geometric mean ratio and 90% confidence intervals for PRO-513 fed:fasted were 88% (82.94-93.75).
2. **Cmax:** Peak diclofenac concentration following administration of PRO-513 under fed condition was 72% less than when PRO-513 was dosed under fasting conditions. The geometric mean ratio and 90% confidence intervals for PRO-513 fed:fasted were 28% (23.63-33.92).
3. **Tmax:** The median Tmax for PRO-513 was shorter under fed condition compared to fasted conditions [0.17 hours (0.08, 4.0) versus 0.25 hours (0.17, 0.67)]

d. Cataflam® Tablets fed vs. fasted:

1. **AUC:** Following single oral doses Cataflam® under fed and fasted conditions, there was a 3% reduction in AUC (0-inf) when Cataflam® was dosed with food. The geometric mean ratio and 90% confidence intervals for Cataflam® fed:fasted were 97% (91.22-102.26).
2. **Cmax:** Peak diclofenac concentration following administration of Cataflam® under fed condition was 33% less than when Cataflam® was dosed under fasting conditions. The geometric mean ratio and 90% confidence intervals for Cataflam® fed:fasted were 67% (56.20-80.28).
3. **Tmax:** The median Tmax for Cataflam® was longer under fed condition compared to fasted conditions [1.25 hours (0.33, 8.0) versus 0.5 hours (0.25, 4.0)]

e. Safety:

According to the sponsor, of the 36 subjects treated, 12 (33.3%) experienced at least one treatment-emergent AE during the study. Across all treatments, the most commonly reported treatment-emergent AEs were I.V. catheter site pain (reported by 4 subjects, 11.1%), presence of red blood cells in urine (reported by 3 subjects, 8.3%), decrease in heart rate (reported by 2 subjects, 5.6%) and prolongation of bleeding time (reported by 2 subjects (5.6%)). All AEs were mild or moderate, and none was serious or resulted in study discontinuation. The following table summarizes the sponsor's overall summary of AEs.

Table 2: Overall Summary of Adverse Events

Subject Category	PRO-513 Fasting N=34	Cataflam® Fasting N=35	PRO-513 Fed N=35	Cataflam® Fed N=35	All Subjects N=36
	Number (%) of Subjects				
Number of Subjects with an AE	4 (11.8)	7 (20.0)	3 (8.6)	6 (17.1)	14 (38.9)
Treatment-emergent AE	4 (11.8)	7 (20.0)	3 (8.6)	6 (17.1)	12 (33.3)
Treatment-related AE	1 (2.9)	1 (2.9)	0 (0.0)	3 (8.6)	4 (11.1)
Discontinued due to AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious AE, including death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Severe AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source Data: [Appendix 15.3.1.1](#).

2. **Study CAT458C2101** was conducted by Novartis in Europe and compared (b) (4) (diclofenac potassium sachet) to 50 mg diclofenac potassium tablets (Cataflam®). This was an open-label, randomized, two-period, crossover study with a seven-day inter-period washout conducted in 24 healthy volunteers. The PK and statistical results are shown in the following table:

Parameter	Geometric LS Means		Geometric Mean ratio* (%)	90% Confidence Interval
	Sachet	Reference		
AUC _{0-inf} (ng*hr/mL)	933	874	107	96-119
C _{max} (ng/mL)	1380	660	209	162-271
T _{max} (hr)	0.25	0.50		
t _{lag} (hr)	NE	0.8		
t _{1/2} (hr)	2.0	2.1		
** Medians for t _{max} and t _{lag}				
NE not estimated				

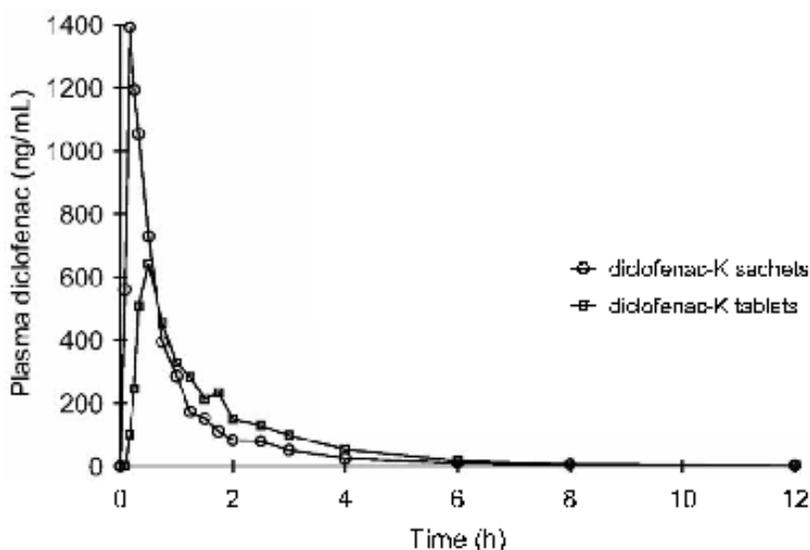
Relative Bioavailability (Novartis sachet vs. Tablets)

- AUC:** The extent of exposure (AUC 0-inf) was within the bioequivalence interval range of 80-125% for the two formulations following a single oral dose. The geometric mean ratio and 90% confidence intervals for the sachet vs the Cataflam® tablets were 107(95.9-119 %)for AUC(0-inf).
- C_{max}:** Mean peak plasma concentrations following administration of the sachet were (C_{max}) were 109% higher than peak concentrations following administration of Cataflam® tablets. The geometric mean ratio and 90% confidence intervals of the diclofenac-K sachet compared to Cataflam® tablet was 209% (162 to 271%), outside the acceptable range of 80-125%.
- T_{max}:** The mean time to peak plasma concentration (mean t_{max}) was significantly shorter with diclofenac-K sachets than with diclofenac-K tablets Peak plasma concentration was reached in 0.25 hours for the sachet versus 0.5 hours for the Cataflam® tablets.

The plasma concentration-time profile for the two treatments is shown in the following figure:

Figure 7-1 Average diclofenac plasma concentration versus time, by treatment

Values are arithmetic means. Top: linear coordinates. Bottom: semi-logarithmic coordinates



Reviewer comments to the Medical Officer:

Relative Bioavailability:

- **C_{max}:** It is noteworthy that the C_{max} for PRO-513 under fed and fasted conditions does not fall within the 90% confidence interval compared to Cataflam® Tablets under the same conditions. There is a 45% increase in the maximum concentration of the drug under fasted condition and a 39% reduction in maximum concentration when dosed with a high fat meal. In the Novartis study the sachet (same formulation as PRO-513) also showed an increase in the C_{max} (109%) under fasted conditions that did not fall within the 90% confidence intervals compared to the tablet. It is expected that a typical migraine patient would neither be completely fasted or fed with a high-fat meal at the onset of the migraine, but would be in a state between the two. Moreover, diclofenac potassium is approved for the treatment of dysmenorrheal and mild to moderate pain at doses up to 150 mg. Data at these doses of 100-150 mg could not be obtained. Although assuming linear PK, the exposure at 100 mg is likely to be doubled. Therefore a 45 - 109% increase in C_{max} may likely be within the range of C_{max} seen with a higher dose of 100 mg given the inter-subject variability of approximately 30-60% for C_{max} in the two studies. The clinical relevance of this is also being evaluated by the medical officer.

- **Tmax:** The Tmax of PRO-513 is shortened compared to the Cataflam® Tablets under both fed and fasted conditions. PRO-513 is a solution and does not go through a period of dissolution after dosing. The sachet studied by Novartis (European study) also had a shorter Tmax compared to the tablet formulation. PRO-513 is labeled to be administered as a single dose for the acute treatment of migraine as opposed to the other indications approved for Cataflam® Tablets (rheumatoid and osteo arthritis and pain), which are administered chronically. Since the PRO-513 formulation is requesting marketing approval for the indication of treatment of acute migraine only and not for the treatment of rheumatoid or osteoarthritis, or primary dysmenorrheal, the impact of the shorter Tmax on acute adverse events will be evaluated by the medical officer.

Food Effect:

- **Cmax:** There is a 72% reduction in Cmax when PRO-513 is administered under fed conditions which may result in a reduction in effectiveness if the product is taken immediately after the intake of a high fat meal. Mild or moderate fat meal is likely to have a decrease in Cmax of a lesser magnitude, but could still impact effectiveness. The clinical effectiveness trials were conducted without regard to meals; hence the impact of concomitant meal intake could not be assessed. The Clinical Division could either recommend that the sponsor evaluate the effect of food on effectiveness or address this in labeling.

ClinPharmBriefing: September 19, 2008

Attendees: Eric Bastings, Ron Farkas, Mehul Mehta, Ramana Uppoor,
Veneeta Tandon, Ting Ong, Carol Noory

1.3. Signatures

Reviewer: Carol Noory Date: _____

Acting Team Leader: Veneeta Tandon Date: _____

cc list:

DFS: NDA 22-165

HFD-860: (NooryC, UppoorR, MehtaM, TandonV)

HFD-120: (ChenL, KatzR, LaughrenT, HeimannM, FreedL, BastingsE, FarkasR)

II. QUESTION BASED REVIEW

2.1 General Attributes of the Drug

2.1.1 What pertinent regulatory background or history contributes to the current assessment of this drug?

Diclofenac is a non steroidal anti-inflammatory drug (NSAID) that has been clinically used for many years for the treatment rheumatic diseases and non-rheumatic pain and inflammatory conditions. In the United States, diclofenac is available in two different salts, diclofenac sodium (Voltaren®) and diclofenac potassium (Cataflam®-NDA 20-142 approved 11/24/1993), which are both marketed by Novartis Pharmaceuticals. Voltfast®/Catafast® (50 mg diclofenac potassium) sachet, a sugar-containing diclofenac potassium powder that is dissolved in water for oral administration, is marketed by Novartis in Italy (Voltfast®) since 2000 and in Egypt (Catafast®) since 2004. A sugar-free formulation of the sachet is marketed in Switzerland since 2006. (b) (4)

2.1.2. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Diclofenac is a benzeneacetic acid derivative. The chemical name for diclofenac potassium is 2-[(2,6-dichlorophenyl)amino] benzeneacetic acid monopotassium salt.

Solubility: Under acidic pH diclofenac potassium is slightly soluble and increases as the pH increases to pH 7.5 and then plateaus. This relates directly to the solubility of the sachet in various liquids which may be used to dissolve the formulation prior to dosing.

Other name: PRO-513

Compendial Name: Diclofenac Potassium Eur. Ph.
(Diclofenac Potassium USP does not exist)

****Comment:** in the current USP 30 through the Second Supplement (Official December 1, 2007 to April 30, 2008) the diclofenac potassium monograph is available.

Chemical name(s): 2-(2,6-Dichlorophenyl)amino] benzene acetate, potassium salt)

Dosage Form and Strength: PRO-513 (50 mg diclofenac potassium powder for oral solution) is a buffered soluble powder, designed to be mixed with water prior to oral administration. PRO-513 is packaged in individual unit dose packets. Inactive ingredients include aspartame, flavoring agents (anise and mint), glycerol behenate, mannitol, potassium bicarbonate, and saccharin sodium.

Indication: PRO-513 is indicated for the treatment of acute migraine attacks with or without aura. This is a new indication for diclofenac potassium.

Manufacture and control : Mipharm is responsible for the manufacture, control, primary, secondary packaging and batch release of the drug product at the following facility:

MIPHARM S.p.A.
20141 Milan, Italy

Batch Size: The “to be marketed” batch size consists of approximately (b) (4) of powder formulation (corresponding to theoretical yield of (b) (4) sachets of 900 mg each).

2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

The proposed mechanism of action is the same as the RLD, Cataflam® tablets.

2.1.3. What are the proposed dosage(s) and route(s) of administration?

The proposed adult oral dose of PRO-513 is a single 50 mg packet to be used as treatment for a migraine attack. The sachet is supplied in single-dose packets containing 50 mg of buffered diclofenac potassium powder for oral solution. The sponsor has recommended that adult patients mix the contents of a single packet with 1 to 2 ounces (30 to 60 mL) of water immediately prior to oral administration. Although this does not reflect the amount of water (240 mL) used in the pivotal study, the chemist has indicated that the 30 to 60 mL volume recommended by the sponsor appears reasonable based on the solubility of the sachet above pH 7.

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the Clinical Pharmacology and Clinical Studies used to Support the Dosing or Claims?

This submission includes results from two Phase I bioavailability and tolerability studies as well as from two Phase III efficacy and safety studies; an additional Phase III study conducted to evaluate the efficacy of the diclofenac sachet for an unrelated indication also is included to support safety. In these studies, two were conducted by ProEthic using PRO-513, and three were conducted by Novartis using (b) (4) (a PRO-513 equivalent).

Clinical Pharmacology Claims: The sponsor conducted a single 4-period crossover study to compare the bioavailability of PRO-513 powder for oral solution mixed in 240 mL of water to the approved and marketed diclofenac-K tablets (Cataflam®) under fasting and fed conditions in 36 healthy volunteers. This study provided data on relative bioavailability of PRO-513 Sachet to the marketed Cataflam® tablet and the effect of food on both products. An additional study conducted by Novartis was submitted by the sponsor. The Novartis study compared (b) (4) (a PRO-513 equivalent) to 50 mg diclofenac potassium tablets (Cataflam®) with respect to bioavailability and tolerability under fasted conditions.

Clinical Claims: The two pivotal Phase III clinical studies included within this submission required subjects to receive a single dose of the test article (PRO-513 or (b) (4)) in order to treat one migraine attack. In the CAT458C2301 trial, 317 subjects were administered the study drug from as soon as they recognized the beginning symptoms of a migraine attack through to the peak of the attack; in PRO-513301, 690 subjects were administered treatment only after their symptoms reached a moderate to severe level. Thus, these studies confirmed the effectiveness of a dosing regimen in which one PRO-513 sachet is taken just before, during, or at the peak of a migraine attack. According to the sponsor, the two studies, independently and in combination, demonstrated that, with just one dose of PRO-513 subjects experienced a rapid onset of treatment effect (within 30 minutes); their average time to resolution of symptoms was 330 minutes; 19-22.3% of them had a sustained pain-free response; and, if their migraines recurred, they did so in not less than 24 hours.

Clinical Endpoints or Biomarkers: There were four co-primary endpoints: the percent of subjects who had no headache at two hours post-dosing; the percent of subjects who had no nausea at two hours post-dosing; the percent of subjects who had no photophobia at two hours post-dosing; and the percent of subjects who had no phonophobia at two hours post-dosing. In order for the study to demonstrate efficacy, PRO-513 had to be significantly ($p \leq 0.05$) superior to placebo with respect to the incidence of complete symptom control for all four primary endpoints.

2.2.2 Are the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters?

Yes, the parent compound was measured using a validated liquid chromatography method using tandem mass spectrometric detection (LC-MS/MS).

2.2.3. What are the characteristics of exposure/effectiveness relationships?

The exposure-response/effectiveness relationship was not evaluated.

2.2.4. Can the dose and dosing regimen be justified based on the studies conducted?

Yes, the dosing regimen is justified on the basis of the studies submitted. PRO-513 was designed to have an enhanced pharmacokinetic profile compared to 50 mg diclofenac potassium tablets (Cataflam®). The dose for PRO-513 was selected after an analysis of three well-controlled, randomized trials conducted with diclofenac potassium by Novartis in Western Europe and subsequently confirmed using data from a Phase I bioavailability trial that was conducted by ProEthic (Study PRO-513101).

The two pivotal Phase III studies submitted in this submission required subjects to take a single dose of the TEST drug (PRO-513 or (b) (4)) in order to treat one migraine attack. In the CAT458C2301 trial, subjects were administered the study drug as soon as they recognized the beginning symptoms of a migraine attack through to the peak of the attack; in PRO-513301,

subjects were administered treatment only after their symptoms reached a moderate to severe level. Thus, these studies confirmed the effectiveness of a dosing regimen in which one PRO-513 sachet is taken just before, during, or at the peak of a migraine attack.

2.3. Pharmacokinetic Characteristics

2.3.1. What are the single-dose pharmacokinetics of diclofenac sachets?

Study PRO-513101:

The US Study PRO-513101 was a single-dose, comparative bioavailability study of PRO-513 sachets and Cataflam® tablets under fasted and fed (high fat breakfast) conditions. A summary of the mean pharmacokinetic parameters of each treatment regimen is presented below in Table 3.

Table 3: Summary of Mean Pharmacokinetic Parameters by Treatment: (PRO-513101)

PK Parameters	PRO-513 Fasting	CATAFLAM Fasting	PRO-513 Fed	CATAFLAM Fed
	Mean ± SD (N)			
AUC _{0-inf} (ng*hr/mL)	1254.553 ± 305.8594 (33)	1097.941 ± 271.6524 (33)	1084.205 ± 244.9558 (28)	1071.353 ± 257.8039 (33)
AUC _{0-t} (ng*hr/mL)	1236.902 ± 298.0158 (34)	1078.546 ± 268.6459 (34)	1054.633 ± 249.6924 (35)	1062.189 ± 251.8584 (35)
C _{max} (ng/mL)	1618.323 ± 538.4472 (34)	1160.669 ± 451.5640 (34)	505.505 ± 305.3756 (35)	835.311 ± 448.8793 (35)
T _{max} (hr) Median (Min, Max)	0.25 (0.17, 0.67) (34)	0.50 (0.25, 4.00) (34)	0.17 (0.08, 4.00) (35)	1.25 (0.33, 8.00) (35)
K _{el} (1/hr)	0.56213 ± 0.170228 (33)	0.58675 ± 0.179386 (33)	0.38535 ± 0.162503 (28)	0.49030 ± 0.145831 (33)
t _{1/2} (hr)	1.346 ± 0.3990 (33)	1.286 ± 0.3736 (33)	2.148 ± 0.9390 (28)	1.561 ± 0.5505 (33)

Source Data: [Appendix 15.2.2 of CSR in Module 5.3](#)

Study CAT458C2101:

European pharmacokinetics, Study CAT458C2101, was a single-dose, two-treatment, two-period crossover study of the bioavailability of diclofenac potassium sachets powder for oral solution (b) (4) versus diclofenac potassium tablets (Cataflam®) in 24 healthy adult volunteers under fasting conditions. A summary of the mean pharmacokinetic parameters after a single dose of each treatment regimen is presented below in Table 4.

Table 4: Summary of Mean Pharmacokinetic Parameters by Treatment (Study CAT 458C2101)

Parameter	Unit	Arithmetic Mean \pm SD	
		Diclofenac-K sachets	Diclofenac-K tablets
C_{max}	ng/mL	1620 \pm 872	855 \pm 580
t_{max}	h (min)	0.233 \pm 0.0751 (14.0 \pm 4.51)	0.864 \pm 0.624 (51.8 \pm 37.4)
t_{lag}	h (min)	NE (NE)	0.0925 \pm 0.0473 (5.55 \pm 2.84)
AUC _{0-t}	ng•h/mL	1010 \pm 429	945 \pm 384
AUC _{0-∞}	ng•h/mL	1020 \pm 430	952 \pm 384
$t_{1/2}$	h	2.2 \pm 0.494	2.07 \pm 0.435

SD: standard deviation

NE: not estimable

2.3.2 General ADME Characteristics of the Drug

In the current application, reference is made to the basic pharmacokinetics and metabolism information for diclofenac potassium available in the labeling for Cataflam® tablets. According to the label, the diclofenac is 100% absorbed following oral administration based on urine recovery. However, due to first-pass metabolism, only about 50% of the absorbed dose is systemically available.

After diclofenac is absorbed from PRO-513 it is expected to have the same distribution, protein binding, metabolism, and elimination as the currently approved diclofenac formulations. The following comments can be made based on single-dose pharmacokinetics:

Absorption:

Study PRO-513101 shows that peak plasma levels are achieved in approximately 15 minutes in fasting volunteers, with a range of 0.17 to 0.67 hours. Food has no significant effect on the extent of diclofenac absorption. There is a decrease in the time to onset of absorption (10 minutes) with a range of 0.08-4.00 hours and a reduction in peak plasma levels of approximately 72% when administer following a high-fat meal.

Distribution, Metabolism and Elimination

The distribution and elimination characteristics are the same as that for the IR tablet formulation. The half-lives for the two dosage forms are similar. The mean half-life was about 1.4 hours in healthy subjects for the sachet formulation and 1.3 hours for the tablets formulation in healthy subjects. The metabolism section in the label is updated based on literature information to suggest that CYP 2C9, 2C8 and UGT 2B7 are involved in the metabolism of diclofenac, and CYP 3A9 in its formation of a minor metabolite.

2.3.3 What is the inter-subject variability in PK parameters?

PRO-513: Inter-subject variability for C_{max} and T_{max} tended to be smaller for diclofenac-K sachets than for diclofenac-K tablets. For C_{max} the inter-subject CV for the reference diclofenac-K tablet was 38.91 compared to 33.27 for the sachet. For T_{max} the inter-subject CV for the diclofenac-K tablet was 96.24 compared to 36.9 for the sachets. Residual (intra-) and inter-subject coefficients of variation (CV) for C_{max} and AUC for Study PRO-513101 are given in Table 5.

Table 5: Intra- and Inter-subject Variability of PK Parameters (PRO-513101)

i-2: Intra- and Inter-subject Variability of PK Parameters (PRO-153101)

Parameter	No. of Subjects	CV (%)	CV (%)	
		Intra-subject (Residual)	Sachet	Tablet
AUC _{0-t}	34	14.7	24.1	24.7
AUC _{0-∞}	33	13.9	24.4	24.9
C _{max}	34	46.9	33.3	38.9
t _{max}	34	—	36.9	96.2

CV: coefficient of variation

Inter-subject variability for C_{max} and T_{max} tended to be smaller for diclofenac-K sachets than for diclofenac-K tablets. For C_{max} the inter-subject CV for diclofenac-K tablet was 67.8 compared to 53.8 for the sachet. For T_{max} the inter-subject CV for the diclofenac-K tablet was 72.3 compared to 32.2 for the sachets. An analysis of the within and between subject variation of C_{max}, T_{max}, and AUC from Study CAT458C2101 is presented below in Table 6.

Table 6: Intra-and Inter-subject Variability (Study CAT 458C2101)

(Study CAT458C2101)

Parameter	No. of Subjects	CV (%)	CV (%)	
		Intra-subject (Residual)*	Sachet	Tablet
AUC _{0-t}	24	22	42.4	40.6
AUC _{0-∞}	24	21.7	42.2	40.3
C _{max}	24	55.7	53.8	67.8
t _{max}	24	—	32.2	72.3

CV: coefficient of variation

* Residual error from ANOVA

2.4. Intrinsic Factors

2.4.1 What intrinsic factors influence exposure and/or response and what is the impact of any difference in exposure on the pharmacodynamics? Based on what is known about exposure response relationships and their variability, is dose adjustment needed for any of the subgroups?

The general intrinsic factors that affect the pharmacokinetics of diclofenac were evaluated using the diclofenac potassium IR tablet and were provided in the initial NDA (NDA 20-142). The language in the labeling should be the same as that approved for the Cataflam® labeling.

2.5. Extrinsic Factors

2.5.1. What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

The influence of extrinsic factors on the pharmacokinetics of diclofenac has been described in the Cataflam® (NDA 20-142) label. No new drug interaction studies have been conducted with diclofenac potassium sachet.

2.6. General Biopharmaceutics

2.6.1. What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?

The to-be-marketed sachet formulation is used in the pivotal clinical trial and the pivotal bioavailability study. (b) (4)

2.6.2 What is the composition of the sachet product that was studied in the bioequivalence studies in this submission?

PRO-513 is formulated as a stable granulate suitable for oral administration. Each packet of granulate (900 mg per packet) is designed to deliver a 50 mg dose of diclofenac potassium when mixed in water. The excipients are compendial ingredients commonly used in various foods and pharmaceutical products. This (b) (4). The composition is given in Table 7.

Table 7: Composition of the Sachet Dosage Form

Table 1.1.1-1: Composition of the Dosage Form

Ingredient	Weight	Function	Reference Standard	
Diclofenac Potassium	50.0* mg	Active	DMF (b) (4)	
Glyceryl Behenate	(b) (4)		NF	
Saccharin Sodium		USP		
Anise Flavor		In-house		
Potassium Bicarbonate		USP		
Mint Flavor		In-house		
Aspartame		NF		
(b) (4) Mannitol		USP**		
(b) (4) Mannitol		USP**		
Total		900.0 mg		

*May include (b) (4) (b) (4) Mannitol in addition to the USP compendial testing, have an additional (b) (4) specification.

Patients will be instructed to reconstitute the powder for oral solution tap water.

2.6.3 Were other liquids tested as possible diluents for the diclofenac powder?

Yes, since it is possible that patients may choose to use various other beverages to dissolve the sachet powder instead of tap water, the sponsor studied the dissolution of diclofenac potassium in eight beverages (Coca Cola™, Ginger Ale, Diet Coca Cola™, White Wine, Orange Juice, Beer, Coffee and Milk).

At pH less than 4 which includes the following beverages Coca Cola™, Ginger Ale, Diet Coca Cola™, White Wine, Orange Juice, diclofenac potassium does not dissolve. A patient attempting to dissolve the contents of their sachet in these liquids would take no measurable dose (provided the patient only swallows the solution).

At pH over 4.5, diclofenac potassium has some solubility. Beer at pH 4.6 provided 6% dissolved diclofenac potassium. Higher pH beverages, like coffee and milk provided more diclofenac solubility; however, the diclofenac assays did show considerable variation. The conclusion of this study strongly supports only the use of tap water to constitute the powder into an oral solution and this should be indicated in the package insert.

2.6.4. What is the relative bioavailability of the diclofenac sachet compared to the marketed IR tablets of diclofenac potassium?

Under Fasted Conditions:

The relative bioavailability of diclofenac potassium 50 mg sachets versus the marketed diclofenac potassium 50 mg tablet (Cataflam®) was investigated under fasted conditions by both Novartis and ProEthics. Both formulations were similar in terms of extent of absorption, as the 90% confidence intervals for AUC_{0-∞} were contained within the 80–125% limits of bioequivalence. The absorption rate for the diclofenac potassium sachets was significantly faster than Cataflam® tablets, as indicated by shorter T_{max} (0.25 compared to 0.5 h for both studies), and increased C_{max} (45% increase for the ProEthics study and 109% increase for the Novartis study). The mean plasma half-life of diclofenac potassium was approximately 2 hours (1.4 in the ProEthics study) after oral administration of 50 mg diclofenac potassium sachet and did not differ significantly from the reference tablet.

The mean pharmacokinetic parameters of PRO-513 and the Novartis Sachet compared to Cataflam® tablets in healthy subjects in the fasted state are given in the following table.

Table 8: Analysis of Relative Bioavailability (Fasted)

		FASTED			
PRO-513101		Geometric LS Means			
Parameter	Test/Reference	Test	Reference	Geometric Mean ratio* (%)	90% Confidence Interval
AUC _{0-inf} (ng*hr/mL)	PRO-513 Sachet/Tablet	1203.19	1060.40	113	107- 120
AUC _{0-t} (ng*hr/mL)		1184.34	1043.87	113	107- 120
C _{max} (ng/mL)		1502.19	1033.32	145	121-174
T _{max}		0.25 (0.17-0.67)	0.50 (0.25-4)		
T _{1/2}		1.4	1.3		
CAT458C2101		Geometric LS Means			
Parameter	Test/Reference	Test	Reference	Geometric Mean ratio* (%)	90% Confidence Interval
AUC _{0-inf} (ng*hr/mL)	Novartis Sachet/Tablet	933	874	107	95.9-119
AUC _{0-t} (ng*hr/mL)		926	865	107	96.1-119
C _{max} (ng/mL)		1380	660	209	162-271
T _{max}		0.25 (0.18-0.32)	0.5 (0.24-1.5)		
T _{1/2} (h)		2.0	2.1		

Under Fed Conditions:

The relative bioavailability of diclofenac potassium 50 mg sachets (PRO-513) versus the marketed diclofenac potassium 50 mg tablet (Cataflam®) was investigated under fed conditions. Both formulations were similar in terms of extent of absorption, as the 90% confidence interval

for AUC_{0-∞} was contained within the 80–125%. The T_{max} for the PRO-513 sachets was faster than Cataflam® tablets (0.17 vs. 1.25 h) and the C_{max} was decreased by 39%. The mean plasma half-life of diclofenac potassium was approximately 2 hours (2.15) after oral administration of 50 mg diclofenac potassium sachet and did not differ from the reference tablet under fed conditions. The mean pharmacokinetic parameters of PRO-513 under fed conditions are given in the following table (Table 9).

Parameter	Test/Reference	Geometric LS Means		Geometric Mean ratio* (%)	90% Confidence Interval
		Test	Reference		
AUC _{0-inf} (ng*hr/mL)	C vs D	1078.28	1035.70	104	98.05- 110.55
AUC _{0-t} (ng*hr/mL)		1025.70	1032.38	99	93.75-105.29
C _{max} (ng/mL)		433.22	714.33	61	50.83-72.36
T _{max} (h)		0.017 (0.08-4)	1.25 (0.33-8)		
t _{1/2}		2.15	1.56		
C: PRO-513 (diclofenac potassium) sachet 50 mg fed					
D: Cataflam® (diclofenac potassium) tablets 50 mg fed					

2.6.5 What is the effect of food on the bioavailability of PRO-513 and how does it differ from the food effect on Cataflam® tablets?

The presence of food does not alter the extent of absorption of diclofenac potassium for either the Cataflam® tablets or the sachet. For the PRO-513 sachet, the T_{max} is shorter under fed conditions (0.17 vs. 0.25 h), but there was a prolonged T_{max} for Cataflam with food (1.25 vs. 0.50). The reduction of C_{max} with a high fat meal was greater with the diclofenac sachet compared with to Cataflam® tablets. The mean fed-to-fasted ratio (90% confidence interval) from diclofenac for the sachet (PRO513) C_{max} was 28% (23.63-33.92) indicating a 72% reduction in peak diclofenac concentrations when PRO-513 is administered with food which may result in a reduction of efficacy. A secondary diclofenac peak appeared approximately 4 hours after drug administration and was temporally related to a meal served 4 hours following drug administration. The mean fed-to-fasted ratio (90% confidence interval) for diclofenac from the tablets (Cataflam®) for C_{max} was 67% (56.20 – 80.28) indicating a 33% reduction in peak diclofenac concentrations when Cataflam® is administered with food. The time to maximum concentration (T_{max}) was increased when the tablet was administered with food (1.25 vs. 0.5 h). The effect of food on the bioavailability of PRO-513 and Cataflam® tablets is shown in the following table (Table 10).

Table 10: Food Effect					
		Geometric LS Means			
Parameter	Test/Reference	Test	Reference	Geometric Mean ratio* (%)	90% Confidence Intervals
	PRO-513	FED	FASTED		
AUC _{0-inf} (ng*hr/mL)	C vs A	1076.34	1220.59	88	82.94-93.75
AUC _{0-t} (ng*hr/mL)		1022.67	1200.63	85	80.29-90.37
C _{max} (ng/mL)		432.76	1528.60	28	23.63-33.92
T _{max}		0.17	0.25		
Parameter	Cataflam®	FED	FASTED	Geometric Mean ratio* (%)	90% Confidence Intervals
AUC _{0-inf} (ng*hr/mL)	D vs B	1029.55	1065.97		
AUC _{0-t} (ng*hr/mL)		1026.23	1049.33	98	92.22-103.72
C _{max} (ng/mL)		701.52	1044.38	67	56.20-80.28
T _{max} (h)		1.25	0.5		
A: PRO-513 (diclofenac potassium) sachet 50 mg fasted					
B: Cataflam® (diclofenac potassium) tablets 50 mg fasted					
C: PRO-513 (diclofenac potassium) sachet 50 mg fed					
D: Cataflam® (diclofenac potassium) tablets 50 mg fed					

The following statement regarding the absorption of diclofenac when administered with food appears in the Cataflam® labeling: “Food has no significant effect on the extent of diclofenac absorption. However, there is usually a delay in the onset of absorption and a reduction in the peak plasma levels of approximately 30%.” The ProEthics Sachet should have the following statement regarding the absorption when administered with food: “Food has no significant effect on the extent of diclofenac absorption. The time to onset of absorption is more rapid (0.17 hours with a range of 0.08 to 4.0 hours) and there is a reduction in peak plasma levels of approximately 70%. In addition, in the DOSE and ADMINISTRATION section, the following statement regarding the reduction in peak plasma levels and a possible reduction in efficacy should be added: “Taking TRADENAME with food may cause a delay and a reduction in efficacy compared to taking TRADENAME on an empty stomach.”

2.7. Analytical

2.7.1. Were the correct moieties identified and properly measured?

The parent compound was identified and properly measured in both the ProEthic’s study and the Novartis study.

2.7.2. What bioanalytical methods are used to assess concentrations?

In Study CAT458C2101 and PRO-513101, diclofenac concentrations were determined using validated liquid chromatography methods using tandem mass spectrometric detection (LC/MS/MS).

In PRO-513101, human EDTA plasma samples were assayed using a method with an LOQ of 5.09 ng/mL and a linear range of 5.09-2546.40 ng/mL. Stability data available at the time of the assay indicated that diclofenac was stable in human plasma samples stored at -20°C for 486 days. No significant degradation of diclofenac was observed in plasma samples stored at room temperature for 24 hours or after four consecutive freeze/thaw cycles. In-process samples were stable for 75 hours at room temperature.

For Study CAT458C2101, heparinized plasma samples were assayed using a method with an LOQ of 0.5 ng/mL, linear range of 0.5–200 ng/mL, a mean recovery within 80 and 120%, and a coefficient of variation ≤ 20%. Samples with concentrations beyond the upper limit of the calibration range were reassayed after dilution with blank matrix. At the time the analysis was conducted, stability data demonstrated that diclofenac was stable in human plasma samples stored at -20°C for at least 3 months. No significant degradation of diclofenac was observed in plasma samples stored at room temperature during 4 hours or after three consecutive freeze/thaw cycles. In-process samples were stable for at least 18 hours at room temperature or two days at -20°C.

A summary of the ProEthics method are shown in Table 11. The summary of the Novartis analytical method are shown in Table 12.

Table 11: ProEthics Bioanalytical Method Validation Parameters	
Analyte	Diclofenac
Matrix	Human EDTA Plasma
Internal Standard	diclofenac-d4
Method Peak Area	HPLC-MS/MS
Limit of Quantitation (LOQ)	5.09 ng/mL
Upper Limit of Quantitation (ULOQ)	2546.40ng/mL
Calibration curve range	5.09 to 2546.40 ng/mL
Linearity (Peak Area)	weighted (1/C2) least squares linear regression
Correlation Coefficient n=7	0.9989
Slope (n=7)	0.89
Intercept (n=7)	0.1823
Inter-day precision (%CV)	1.61 to 3.98
Inter-day accuracy (% bias)	-2.05 to 1.69
Quality Control Samples n=28	
Between-run Precision % CV	4.22 to 6.20%
Between-run Accuracy	97.87 to 100.17%
Within run Accuracy	100.06% to 107.50%
Within run Precision	0.96 to 3.865
Recovery-Analyte	82.57, 83.86 and 86.59%
Recovery-Internal Standard n=18	Mean 83.85%

Stability		
Analyte in matrix % change in 24 hrs	Low	-3.51
Analyte in matrix % change in 24 hrs	High	-1.46
Room Temperature	40 hours	99.68-103.94%
-20 °C	486 days	Mean change 2.23%
Thaw/Freeze cycles - 4cycles		
% CV	Low	2.76
% CV	High	1.37
% Nominal	Low	98.27
% Nominal	High	98.19%

Table 12: Summary of Bioanalytical Method Used in the Novartis Study		
Analyte	Diclofenac	
Matrix	Plasma	
Internal Standard	(b) (4)	
Method Peak Area	HPLC-MS/MS	
Analysis Dates	May 14, 2003 and June 13, 2003.	
Limit of Quantitation (LOQ)	0.5 ng/mL	
Calibration curve range	0.5 - 2 - 10 - 20 - 50 - 100 - 150 - 200 ng/mL	
Linearity	least-squares regression weighting factor of 1/C ²	
Correlation Coefficient	0.99800	
Slope	0.00123	
Recovery	80.7 (SD=4.99)	
Intercept	0.0000162	
Inter-day precision	1.79 to 7.02	
Inter-day accuracy	-1.09 to 2.03	
Quality Control Samples n=28		
Precision % CV	1 ng/mL	13.6 %
	40 ng/mL	7.70 %
	160 ng/mL	8.70 %
Accuracy % Rel. error	1 ng/mL	-7.08 %
	40 ng/mL	-8.22 %
	160 ng/mL	-7.79 %
Stability		
Room Temperature	24 hours	No significant degradation
-20 °C	3 months	No significant degradation
Thaw/Freeze cycles	3 cycles	No significant degradation

III. LITERATURE

The sponsor conducted a literature search as requested by FDA to

- a. Identify CYP enzymes involved in the metabolism of diclofenac for labeling purposes (FDA letter of 29 November 2005)
- b. Determine the inhibition and induction potential of diclofenac
- c. Evaluate possible drug-drug interactions with diclofenac (FDA response from letter of 29 November 2005).
- d. Determine if adequate information on use of diclofenac in patients with hepatic impairment.

In addition, the reviewer also conducted a literature search to determine current information which may need to be included in the label.

Metabolism:

- Tang W. **The metabolism of diclofenac-enzymology and toxicology perspectives.** *Curr Drug Metab.* 2003 Aug; 4(4): 319-29. Review.

Tang (2003) found diclofenac is a nonsteroidal anti-inflammatory drug bearing a carboxylic acid functional group. As a result, the metabolism of diclofenac in humans partitions between acyl glucuronidation and phenyl hydroxylation, with the former reaction catalyzed primarily by uridine 5'-diphosphoglucuronosyl transferase 2B7 while the latter is catalyzed by cytochrome P450 (CYP)2C9 and 3A4. Further hydroxylation of diclofenac glucuronide was shown to occur in vitro with recombinant CYP2C8, which may be of clinical significance in terms of defining major metabolic routes involved in the elimination of diclofenac in humans. The 4'-hydroxylation of the drug appears to represent a feature reaction for CYP2C9 catalysis, and this regio selective oxidation is presumably dictated by interactions of the carboxylate moiety of the substrate with a putative cationic residue of the enzyme. Several other residues of CYP2C9 were identified in studies with site-directed mutants that influence substrate binding affinity and specificity, including Arg97, Phe114, Asn289 and Ser286. The 5-hydroxylation of diclofenac is subject to CYP3A4 cooperativity elicited by quinidine. In this case, enhancement by quinidine of diclofenac metabolism in vitro was attributed to increases in the V(max) with little contribution from changes in the K(m) value. These cooperative interactions in recombinant systems, however, appeared to be influenced by enzyme host membranes of various cDNA-directed expressing CYP3A4. Nevertheless, the in vivo significance of CYP3A cooperativity was demonstrated in a pharmacokinetic study in monkeys, wherein the hepatic clearance of diclofenac increased 2-fold when quinidine was co-administered.

- Prueksaritanont, T. Li, C. Tang C, Kuo Y, Strong-Basalgya, K and Carr, B. **Rifampin induces the in vitro oxidative metabolism but not the in vivo clearance of diclofenac in rhesus monkeys.** *Drug Metab Disp.* 2006 Nov; 34(11): 1806-10. Epub 2006 Aug 23.

Prueksaritanont et al (2006) examined the effects of rifampin on in vitro oxidative metabolism and in vivo pharmacokinetics of diclofenac, a prototypic CYP2C9 marker substrate. In monkey hepatocytes, rifampin markedly induced diclofenac 4'-hydroxylase activity. However, pretreatment with rifampin did not alter the pharmacokinetics of diclofenac obtained after IV or intrahepatic portal vein administration of diclofenac to monkeys. In monkey liver microsomes, diclofenac underwent, predominantly, glucuronidation, and, modestly, oxidation; the intrinsic clearance value for the glucuronidation pathway accounted for > 95% (versus about 75% in human liver microsomes) of the total (glucuronidation + hydroxylation) intrinsic clearance value. In monkey hepatocytes, the hydroxylation was also a minor component (< 10%) relative to the glucuronidation, supporting the liver microsomal finding. Collectively these data suggested that the oxidative metabolism is not the major in vivo clearance mechanism in diclofenac in either untreated or rifampin-treated monkeys and, conceivably, also in humans, raising a question about the utility of diclofenac as an in vivo CYP2C9 probe.

- Tang W, Stearns RA, Wang RW, Chiu SH, Baillie TA. **Roles of human hepatic cytochrome P450s 2C9 and 3A4 in the metabolic activation of diclofenac.** *Chem Res Toxicol.* 1999 Feb;12(2):192-9.

Recently, it was shown that diclofenac was metabolized in rats to reactive benzoquinone imines via cytochrome P450-catalyzed oxidation. These metabolites also were detected in human hepatocyte cultures in the form of glutathione (GSH) adducts. This report describes the results of further studies aimed at characterizing the human hepatic P450-mediated bioactivation of diclofenac. The reactive metabolites formed in vitro were trapped by GSH and analyzed by LC/MS/MS. Thus, three GSH adducts, namely, 5-hydroxy-4-(glutathion-S-yl)diclofenac (M1), 4'-hydroxy-3'-(glutathion-S-yl)diclofenac (M2), and 5-hydroxy-6-(glutathion-S-yl)diclofenac (M3), were identified in incubations of diclofenac with human liver microsomes in the presence of NADPH and GSH. The formation of the adducts was taken to reflect the intermediacy of the corresponding putative benzoquinone imines. While M2 was the dominant metabolite over a substrate concentration range of 10-50 microM, M1 and M3 became equally important products at ≥ 100 microM diclofenac. The formation of M2 was inhibited by sulfaphenazole or an anti-P450 2C9 antibody (5-10% of control values). The formation of M1 and M3 was inhibited by troleandomycin, ketoconazole, or an anti-P450 3A4 antibody (30-50% of control values). In studies in which recombinant P450 isoforms were used, M2 was generated only by P450 2C9-catalyzed reaction, while M1 and M3 were produced by P450 3A4-catalyzed reaction. Good correlations were established between the extent of formation of M2 and P450 2C9 activities ($r = 0.93$, $n = 10$) and between the extent of formation of M1 and M3 and P450 3A4 activities ($r = 0.98$, $n = 10$) in human liver microsomal incubations. Taken together, the data suggest that the biotransformation of diclofenac to M2 is P450 2C9-dependent, whereas metabolism of the drug to M1 and M3 involves mainly P450 3A4. Although P450s 2C9 and 3A4 both catalyze the bioactivation of diclofenac, P450 2C9 is capable of producing the benzoquinone imine intermediate at lower drug concentrations which may be more clinically relevant.

- Ngui JS, Tang W, Stearns RA, Shou M, Miller RR, Zhang Y, Lin JH, Baillie TA. **Cytochrome P450 3A4-mediated interaction of diclofenac and quinidine.** *Drug Metab Dispos.* 2000 Sep; 28(9):1043-50

The metabolism of diclofenac to its 5-hydroxylated derivative in humans is catalyzed by cytochrome P450 (CYP)3A4. This reports that the in vitro this biotransformation pathway is stimulated by quinidine. When diclofenac was incubated with human liver microsomes in the presence of quinidine, the formation of 5-hydroxydiclofenac increased approximately 6-fold relative to controls. Similar phenomena were observed with diastereoisomers of quinidine, including quinine and the threo epimers, which produced an enhancement in the formation of 5-hydroxydiclofenac in the order of 6- to 9-fold. This stimulation of diclofenac metabolism was diminished when human liver microsomes were pretreated with a monoclonal inhibitory antibody against CYP3A4. In contrast, neither cytochrome b(5) nor CYP oxidoreductase appeared to mediate the stimulation of diclofenac metabolism by quinidine, suggesting that the effect of quinidine is mediated through CYP3A4 protein. Further kinetic analyses indicated that $V(\max)$ values for the conversion of diclofenac to its 5-hydroxy derivative increased 4.5-fold from 13.2 to 57.6 nmol/min/nmol of CYP with little change in $K(m)$ (71-56 microM) over a quinidine concentration range of 0 to 30 microM. Conversely, the metabolism of quinidine was not affected by the presence of diclofenac; the $K(m)$ value estimated for the formation of 3-hydroxyquinidine was approximately 1.5 microM, similar to the quinidine concentration required to produce 50% of the maximum stimulatory effect on diclofenac metabolism. It appears that the enhancement of diclofenac metabolism does not interfere with quinidine's access to the ferriheme-oxygen complex, implicating the presence of both compounds in the active site of CYP3A4 at the same time. Finally, a approximately 4-fold increase in 5-hydroxydiclofenac formation was observed in human hepatocyte suspensions containing diclofenac and quinidine, demonstrating that this type of drug-drug interaction occurs in intact cells.

- Bort R, Macé K, Boobis A, Gómez-Lechón MJ, Pfeifer A, Castell J. **Hepatic metabolism of diclofenac: role of human CYP in the minor oxidative pathways.** *Biochem Pharmacol.* 1999 Sep 1;58(5):787-96.

The aim of this study was to re-examine the human hepatic metabolism of diclofenac, with special focus on the generation of minor hydroxylated metabolites implicated in the idiosyncratic hepatotoxicity of the drug. Different experimental approaches were used: human hepatocytes, human microsomes, and engineered cells expressing single human CYP (cytochromes P450). Human hepatocytes formed 3'-hydroxy-, 4'-hydroxy-, 5-hydroxy-, 4',5-dihydroxy-, and N,5-dihydroxydiclofenac, as well as several lactams. Formation of 4'- and 5-hydroxydiclofenac by human liver microsomes followed a Michaelis-Menten kinetics (K_m 9 +/- 1 microM; V_{max} 432 +/- 15 pmol/min/mg and K_m 43 +/- 5 microM; and V_{max} 15.4 +/- 0.6 pmol/min/mg, respectively). Secondary metabolites were detected after incubation of 5-hydroxydiclofenac with human liver microsomes, yielding 4',5-dihydroxydiclofenac (K_m 15 +/- 1 microM; V_{max} 96 +/- 3 pmol/min/mg) and small amounts of N,5-dihydroxydiclofenac (non-Michaelis-Menten kinetics). Based on microsome studies and the incubations with human hepatocytes and engineered cells, we estimated that in vivo CYP2C9 would be exclusively responsible for the 4' hydroxylation of diclofenac (>99.5%) as well as 5-hydroxydiclofenac (>97%). CYP2C9 was exclusively responsible for the formation of 3'-hydroxydiclofenac. Multiple regression analysis evidenced that the rate of production of 5-hydroxydiclofenac in human microsomes followed the algorithm: $0.040 \times S\text{-mephenytoin } 4'\text{-hydroxylation} + 0.083 \times \text{tolbutamide methylhydroxylation}$, (multiple correlation coefficient = 0.969). However, the incubation of diclofenac with cell lines expressing different human CYP suggested that 7 isoforms could be involved. Comparison of data obtained with CYP-expressing cells and human hepatocytes suggests that CYP2C8 > CYP2C19 approximately CYP2C18 >> CYP2B6 are the isoforms implicated in the 5-hydroxylation of diclofenac in vivo.

- Shen S, Marchick MR, Davis MR, Doss GA, Pohl LR. **Metabolic activation of diclofenac by human cytochrome P450 3A4: role of 5-hydroxydiclofenac.** *Chem Res Toxicol.* 1999 Feb;12(2):214-22.

Cytochrome P450 2C11 in rats was recently found to metabolize diclofenac into a highly reactive product that covalently bound to this enzyme before it could diffuse away and react with other proteins. To determine whether cytochromes P450 in human liver could catalyze a similar reaction, we have studied the covalent binding of diclofenac in vitro to liver microsomes of 16 individuals. Only three of 16 samples were found by immunoblot analysis to activate diclofenac appreciably to form protein adducts in a NADPH-dependent pathway. Cytochrome P450 2C9, which catalyzes the major route of oxidative metabolism of diclofenac to produce 4'-hydroxydiclofenac, did not appear to be responsible for the formation of the protein adducts, because sulfaphenazole, an inhibitor of this enzyme, did not affect protein adduct formation. In contrast, troleandomycin, an inhibitor of P450 3A4, inhibited both protein adduct formation and 5-hydroxylation of diclofenac. These findings were confirmed with the use of baculovirus-expressed human P450 2C9 and P450 3A4. One possible reactive intermediate that would be expected to bind covalently to liver proteins was the p-benzoquinone imine derivative of 5-hydroxydiclofenac. This product was formed by an apparent metal-catalyzed oxidation of 5-hydroxydiclofenac that was inhibited by EDTA, glutathione, and NADPH. The p-benzoquinone imine decomposition product bound covalently to human liver microsomes in vitro in a reaction that was inhibited by GSH. In contrast, GSH did not prevent the covalent binding of diclofenac to human liver microsomes. These results suggest that for appreciable P450-mediated bioactivation of diclofenac to occur in vivo, an individual may have to have both high activities of P450 3A4 and perhaps low activities of other enzymes that catalyze competing pathways of metabolism of diclofenac. Moreover, the p-benzoquinone imine derivative of 5-hydroxydiclofenac probably has a role in covalent binding in the liver only under the conditions where levels of NADPH, GSH, and other reducing agents would be expected to be low

Inhibition/Induction:

The sponsor reported that inconsistent literature reports were available on the inhibition/induction potential of diclofenac. There are some reports of diclofenac inhibitory activity of CYP2C9 and CYP3A4 in vitro; however, in vivo studies (quinidine and nateglinide) did not suggest the same.

Drug Interactions:

No new drug interaction information was found.

Hepatic Impairment:

Adequate assessment regarding the effect of hepatic impairment on diclofenac pharmacokinetics could not be made from the literature articles.

IV. DETAILED LABELING RECOMMENDATIONS

Much of the label is taken from the Cataflam® tablet labeling. Several changes are recommended to clarify or correct the sponsor's proposed label. Labeling recommendations are given by track changes to the relevant sections reviewed. Comments to the medical officer, chemist and project officer are **highlighted**.

V. INDIVIDUAL STUDY REVIEWS

5.1 ProEthics Study Number: PRO-513101

STUDY TITLE:

A Randomized, Single-dose, 4-period Crossover Trial Comparing the Relative Bioavailability of PRO-513 (diclofenac potassium powder for oral solution) and Cataflam® (diclofenac potassium) Tablets under Fed and Fasting Conditions

Investigational Product: PRO-513 (diclofenac potassium) sachet 50 mg

Sponsor: ProEthic Pharmaceuticals, Inc.
212 South Tryon Street, Suite 1280
Charlotte, NC 28281

Development Phase: I
Study Dates: 16 February -20 April 2006

CLINICAL STUDY:

Principal Investigator: Denis Audet, M.D.
Medical Director
Anapharm
2050, Boul. René-Lévesque Ouest
Sainte-Foy (Québec), Canada, G1V 2K8

Institution:

Bioanalytical Laboratory:

(b) (4)

Clinical Data Management, Clinical Data Analysis, and Medical Writing

(b) (4)

STUDY OBJECTIVES

The primary objectives of the study were:

1. To compare the bioavailability of diclofenac in PRO-513 (test formulation) to that of diclofenac in Cataflam® tablets (reference formulation) under fasting conditions; and
2. To compare the bioavailability of diclofenac in PRO-513 (test formulation) to that of diclofenac in Cataflam® tablets (reference formulation) under fed conditions (after eating a high fat breakfast).

Secondary objectives included an estimation of the food effect within formulation and an evaluation of the safety and tolerability of PRO-513 in healthy adult volunteers.

TREATMENTS:

Test: PRO-513 (diclofenac potassium powder for oral solution)
50 mg sachets (Lot/Batch # CO60123A)

Reference: Cataflam® (diclofenac potassium) 50 mg tablets (Lot # C5J00751)

Treatment Description

Fasted:

- A. PRO-513 (diclofenac potassium) sachet 50 mg x 1 fasting
- B. Cataflam® (diclofenac potassium) tablets 50 mg x 1 fasting

Fed:

- C. PRO-513 (diclofenac potassium) sachet 50 mg x 1 fed
- D. Cataflam® (diclofenac potassium) tablets 50 mg x 1 fed

STUDY DESIGN:

This was an open-label, randomized, 4-period, complete crossover pharmacokinetic study in 36 healthy male and female subjects, designed to study the relative bioavailability of PRO-513 in comparison to Cataflam® tablets under fasted and fed conditions. The study was also aimed at assessing the safety and tolerability of PRO-513 in healthy adult volunteers.

Subjects fasted for approximately 10 hours prior to administration of study medication during each treatment period. For administration of the PRO-513 sachet, study personnel measured 240 mL of room temperature water in a cylinder/flask. Immediately prior to dosing, the powder was dissolved in a glass with approximately 100 to 150 mL of the 240 mL of water. In order to prevent any powder remaining in the sachet, the study personnel rinsed the sachet with 5 mL of water (using a syringe or a pipette) and emptied the contents into the glass, ensuring that all powder was dissolved. The subject was then instructed to drink the contents of the glass. Immediately following dosing, the glass was rinsed twice with the remainder of the 240 mL of water, ensuring that any residual powder was dissolved. The subject immediately drank the remainder of the contents of the glass. Each treatment period was separated by a minimum of 7 days.

Fasting Arm: During administration of treatments A and B (fasting), subjects were not allowed any oral fluids for one (1) hour post-dose and any food until four (4) hours post-dose.

Fed Arm: During administration of treatments C and D (fed), subjects were administered a single oral dose of study drug immediately after a standard high fat, high-calorie breakfast. Subjects were not allowed any oral fluids for one (1) hour post-dose and any additional food until four (4) hours post-dose.

The high fat breakfast consisted of:

- 2 eggs fried in butter,
- 2 strips of bacon,
- 2 slices of buttered toast,
- 4 ounces of hash brown potatoes and
- 8 ounces of whole milk.

Protocol Deviations:

All subjects met the inclusion/exclusion criteria during the screening, but the following protocol deviations occurred during the study. During treatment periods 1, 2, 3 and 4, the quantity of milk served as part of the high-fat breakfast was 200 mL instead of 240 mL. The guidance suggests that 500-600 calories of the high-fat meal should come from fat. As this deviation resulted in a reduction of only 25

calories, it would not be expected to have a significant impact on the assessment of food effect. Blood samples collected from 11 subjects at various time points in the study were centrifuged beyond the specified time schedule by 1-23 minutes, resulting in delayed storage time. However, as stability data documents the stability of diclofenac for up to 290 minutes at 4°C, the short delay in time to storage almost certainly did not affect the sample stability or the validity of the resulting plasma data.

Subjects:

Thirty-six (36) healthy male (22=61.1%) and female (14=38.9%) subjects (all non-smokers) were enrolled and 9 subjects each were randomly assigned to one of the following four treatment sequences: ABCD, BADC, CDBA, and DCAB. The overall mean (SD) age of subjects in the study was 31.9 (7.62) years and the mean (SD) BMI was 24.8 (2.76) kg/m². Of the 36 subjects enrolled, 33 (91.7%) were White, 2 (5.6%) were Hispanic or Latino and one (2.8%) was African American. None of the subjects had clinically significant medical history findings at screening. No formal assessments of treatment compliance were conducted. All doses of study medication were administered under the supervision of site personnel.

Thirty-three (33) (91.7%) subjects completed all 4 treatment periods of the study. Subjects 001, 011 and 036 left the study after completing 3, 1 and 3 treatment periods, respectively. All subjects received at least one dose of study drug and were included in the safety population. Subjects 001 and 011 left the study early due to work and personal obligations, unrelated to study medication. Subject 036 left the study due to health reasons unrelated to study drug. It was estimated that a sample size of 33 subjects would be sufficient to provide 80% power to confirm equivalence for the products if the observed geometric mean ratio fell between 0.95 and 1.05 based on previously reported values for diclofenac AUC with a CV of 28%.

Sample Collection:

Blood samples (4 mL) were obtained for each treatment period at the following times: 0 (pre-dose) and at 0.08, 0.167, 0.25, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, and 12 hours post-dose.

Analytical:

The analysis of diclofenac in human EDTA plasma for Study Number PRO513-101 was determined using a validated High Performance Liquid Chromatography / Tandem Mass Spectrometry Method.

Bioanalytical Principal Investigator:

(b) (4)

Project Number:

Sponsor:

PRO513-101

(b) (4)

(b) (4)

Plasma samples (4 mL) were collected in EDTA K2 tubes and immediately mixed with anticoagulant. Plasma samples were processed and stored frozen (at -20°C) until they were transferred to the analytical facility. The internal standard (IS), diclofenac-d4, was added to the samples and the analyte diclofenac and its IS were extracted from a 0.100 mL aliquot of human EDTA plasma into 1-chlorobutane using a liquid-liquid extraction method. The samples were injected into a liquid chromatography equipped with a

Reverse Phase 4.6 x 50 mm, 3.5 µm column. The mobile phase was a mixture of methanol / water (75/25), ammonium formate 2 mM, pH 3.50. The detection method used was tandem mass spectrometry.

Reference Standard	Supplier	Lot Number	%Purity
Diclofenac Sodium	USP	H013150	100
Diclofenac-d ₄ (phenyl-d ₄)	(b) (4)	K109P25	99

Study samples were analyzed using a calibration curve and four sets of quality control samples (low, medium, intermediate and high) analyzed in duplicate. A summary of the method parameters are shown in Table 1. A total of 2612 study samples were analyzed.

Table 1: Summary of Bioanalytical Method Parameters		
Analyte	Diclofenac	
Matrix	Human EDTA Plasma	
Internal Standard	diclofenac-d ₄	
Method Peak Area	HPLC-MS/MS	
Analysis Dates	2006-03-23 to 2006-05-24	
Limit of Quantitation (LOQ)	5.09 ng/mL	
Upper Limit of Quantitation (ULOQ)	2546.40ng/mL	
Duration of Sample Storage	96 days (2006-02-17 to 2006-05-24)	
Calibration curve range	5.09 to 2546.40 ng/mL	
Linearity (Peak Area)	weighted (1/C ²) least squares linear regression analysis	
Correlation Coefficient n=39	0.9989	
Slope		
Recovery		
Intercept		
Inter-day precision (%CV)	1.61 to 3.98	
Inter-day accuracy (% bias)	-2.05 to 1.69	
Quality Control Samples		
Precision % CV (n=89)	14.80 ng/mL	44.39
Precision % CV (n=71)	246.64 ng/mL	2.32
Precision % CV (n=85)	739.92 ng/mL	14.39
Precision % CV (n=89)	1726.48 ng/mL	6.52
Accuracy % bias (n=89)	14.80 ng/mL	4.86
Accuracy % bias (n=71)	246.64 ng/mL	0.89
Accuracy % bias (n=85)	739.92 ng/mL	2.71
Accuracy % bias (n=89)	1726.48 ng/mL	0.20

The performance of the analytical method was successfully demonstrated. The analyte and the internal standard are stable under all conditions tested.

SAFETY EVALUATIONS:

The sponsor assed safety by monitoring of adverse events (AEs), vital signs (blood pressure, respiratory rate, pulse, and oral body temperature), clinical laboratory parameters, and physical examination. The study safety population included all 36 subjects who received at least one dose of the study medication. 33 subjects received all 4 doses. Subjects 001 received 3 treatments (C, D and B); Subject 011 received 1 treatment (B); and Subject 036 received 3 treatments (D, C and A). Each AE was evaluated for duration,

intensity, and putative relationship to (or association with) study treatment (or other causes). The relationship (or association) of each AE to the test medication was assessed by the investigator.

Brief Summary of Adverse Events

According to the sponsor, of the 36 subjects treated, 12 (33.3%) experienced at least one treatment-emergent AE during the study. Treatment-emergent AEs were experienced by 4 subjects (11.8%) following treatment with PRO-513 in the fasting state, 7 subjects (20.0%) following treatment with Cataflam® in the fasting state, 3 subjects (8.6%) following treatment with PRO-513 after a high fat breakfast, and 6 subjects (17.1%) following treatment with Cataflam® after a high-fat breakfast. Across all treatments, the most commonly reported treatment-emergent AEs were I.V. catheter site pain (reported by 4 subjects, 11.1%), presence of red blood cells in urine (reported by 3 subjects, 8.3%), decrease in heart rate (reported by 2 subjects, 5.6%) and prolongation of bleeding time (reported by 2 subjects (5.6%). Four subjects experienced 6 AEs that were considered to be possibly or probably related to study drug. By self report, 2 subjects stated that they “bled longer than usual,” which was reported as an AE of bleeding time prolonged following treatment with Cataflam®. One subject reported 3 treatment-related AEs that are consistent with the known effects of NSAID use, including red blood cells in urine, protein in urine, and hot flushes; 1 subject experienced pruritus. All AEs were mild or moderate, and none was serious or resulted in study discontinuation.

Safety Conclusions

According to the sponsor, single doses of PRO-513 and Cataflam® were well tolerated by all subjects. The safety profiles were typical for diclofenac treatment, and no treatment-related trends were observed in clinical laboratory results, vital sign measurements, or physical examination findings. Although the Cataflam® treatment had more reported adverse events, given the limited number of subjects exposed to each treatment, no definitive conclusions may be based on these results.

PHARMACOKINETIC ASSESSMENT:

The pharmacokinetic population included all subjects who completed the pharmacokinetic sampling period for a minimum of two treatment periods. Thirty-five (35) subjects (97.2%) were included in the PK and bioequivalence populations. Subject 011 discontinued after completing only one treatment period, and therefore, was excluded from the PK and bioequivalence populations.

All pharmacokinetic results were summarized using appropriate descriptive statistics. Following log-transformation (natural log), AUC_{0-inf}, AUC_{0-t}, and C_{max} results were compared between treatment groups using the average bioequivalence approach. A linear mixed-effects model was used for the analysis of this crossover study for average bioequivalence (BE). PROC MIXED in SAS® version 8.2 was used with sequence, subject, period, and treatment variables in the model.

Comparative bioavailability assessments were performed for the following treatment pairs:

- Primary - Relative Bioavailability Fasting: A/B
- Primary - Relative Bioavailability Fed: C/D
- Secondary - Effect of Food on PRO-513: C/A
- Secondary - Effect of Food on Cataflam®: D/B

Pharmacokinetic variables were calculated from the plasma concentration data using standard, non-compartmental methods with calculated using WinNonlin® Version 4.1.

Pharmacokinetic Results

Mean plasma concentration-time profiles for diclofenac potassium following single doses of the two study drugs, PRO-513 and Cataflam®, under fasting and fed condition are shown in [Figure 11.4.1-1](#) and [11.4.1-2](#), respectively.

Figure 11.4.1-1: Mean Plasma Diclofenac Concentrations by Treatment and Time Under Fasting Conditions

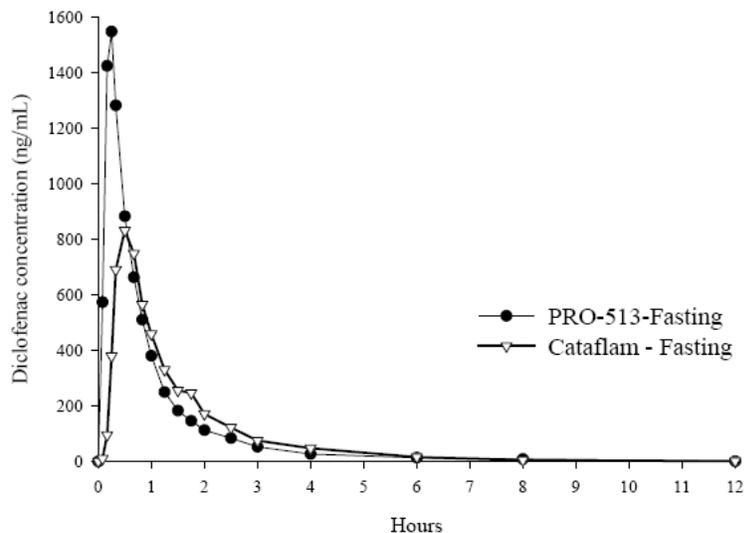
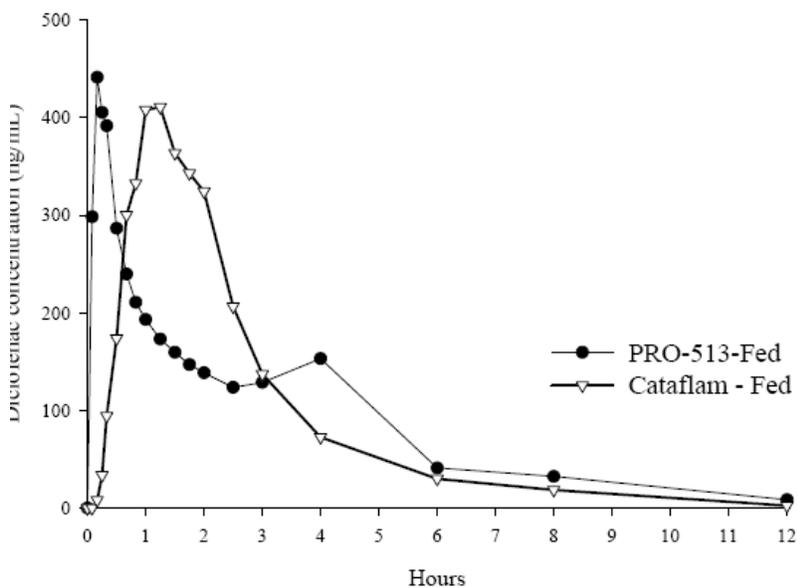


Figure 11.4.1-2: Mean Plasma Diclofenac Concentrations by Treatment and Time Under Fed Conditions



Under fasting conditions, plasma diclofenac concentrations increased rapidly following oral administration of both formulations followed by rapid and smooth declines. Peak plasma diclofenac concentrations from PRO-513 occurred sooner and plasma diclofenac concentrations were higher than those from Cataflam® until approximately one hour after dosing. The mean concentration versus time curves for PRO-513 and Cataflam® under fed conditions show that food decreased peak plasma diclofenac concentrations for both formulations compared to fasting conditions.

Peak plasma diclofenac concentrations of PRO-513 occurred sooner than with Cataflam® and declined over several hours with a secondary peak about 4 hours after dose administration. Plasma diclofenac concentrations following Cataflam® administration increased monotonically and reached a peak concentration between 1 and 2 hours following administration. The peak plasma diclofenac concentration following Cataflam® administration was lower and overall, slightly broader than with PRO-513 and declined monotonically after the peak with no evidence of a secondary peak.

Secondary peaks may be related to release of drug from the test formulation, administration of meals, or enterohepatic recirculation. Since PRO-513 is administered as an oral solution, the secondary peak was not due to release of drug from the formulation. Presence of food in the gastrointestinal (GI) tract decreases GI transit time and increases splanchnic blood flow, both of which may increase drug absorption from the GI tract. The secondary peak for PRO-513 is temporally coincident with a meal served 4 hours after drug administration, although a similar peak was not seen for Cataflam® under fed conditions. Secondary peaks were not observed for either formulation under fasting conditions. Diclofenac undergoes enterohepatic recirculation in animals, but only minimally in humans (AHFS, 2003). While the most likely explanation for the secondary peak for PRO-513 under fed conditions is the meal served 4 hours following drug administration, it is not clear why a similar effect was not observed with Cataflam®, although the absence of the effect could be related to diclofenac release characteristics of the Cataflam® formulation.

Pharmacokinetic Parameters

Non-transformed pharmacokinetic parameters for diclofenac potassium are summarized below in Table 11.4.2-1.

Table 11.4.2-1: Mean Pharmacokinetic Parameters by Treatment

PK Parameters	PRO-513-Fasting	Cataflam [®] -Fasting	PRO-513-Fed	Cataflam [®] -Fed
	Mean ± SD (N)			
AUC _{0-inf} [ng*hr/mL]	1254.6 ± 305.9 (33)	1097.9 ± 271.7 (33)	1084.2 ± 245.0 (28)	1071.4 ± 257.8 (33)
AUC _{0-t} [ng*hr/mL]	1236.9 ± 298.0 (34)	1078.5 ± 268.6 (34)	1054.6 ± 249.7 (35)	1062.2 ± 251.9 (35)
C _{max} [ng/mL]	1618.3 ± 538.4 (34)	1160.7 ± 451.6 (34)	505.5 ± 305.4 (35)	835.3 ± 448.9 (35)
T _{max} (hr) Median (Min, Max)	0.25 (0.17, 0.67) (34)	0.50 (0.25, 4.00) (34)	0.17 (0.08, 4.00) (35)	1.25 (0.33, 8.00) (35)
K _{el} [1/hr]	0.56 ± 0.17 (33)	0.59 ± 0.18 (33)	0.39 ± 0.16 (28)	0.49 ± 0.15 (33)
T _½ [hr]	1.35 ± 0.40 (33)	1.29 ± 0.37 (33)	2.15 ± 0.94 (28)	1.56 ± 0.55 (33)

Source Data: [Appendix 15.2.2](#).

Assessment of PK

The intra-subject variation (%CV derived from residual error) for fasting treatments A vs. B were 13.85% for AUC 0-inf 14.72% for AUC 0-t and 46.92% for Cmax. The results of the statistical analysis of Cmax and AUC0-t and AUC0-inf are summarized below in Table 11.4.3-1.

Table 11.4.3-1: Analysis of Relative Bioavailability Between the Test Treatments

Parameter	Test/Reference	Geometric LS Means		Geometric Mean ratio* (%)	90% Confidence Interval
		Test	Reference		
AUC _{0-inf} (ng*hr/mL)	A vs B	1203.19	1060.40	113	107.10, 120.21
AUC _{0-t} (ng*hr/mL)		1184.34	1043.87	113	106.86, 120.46
C _{max} (ng/mL)		1502.19	1033.32	145	121.12, 174.48
AUC _{0-inf} (ng*hr/mL)	C vs D	1078.28	1035.70	104	98.05, 110.55
AUC _{0-t} (ng*hr/mL)		1025.70	1032.38	99	93.75, 105.29
C _{max} (ng/mL)		433.22	714.33	61	50.83, 72.36
AUC _{0-inf} (ng*hr/mL)	C vs A	1076.34	1220.59	88	82.94, 93.75
AUC _{0-t} (ng*hr/mL)		1022.67	1200.63	85	80.29, 90.37
C _{max} (ng/mL)		432.76	1528.60	28	23.63, 33.92
AUC _{0-inf} (ng*hr/mL)	D vs B	1029.55	1065.97	97	91.22, 102.26
AUC _{0-t} (ng*hr/mL)		1026.23	1049.33	98	92.22, 103.72
C _{max} (ng/mL)		701.52	1044.38	67	56.20, 80.28

A: PRO-513 (diclofenac potassium) sachet 50 mg x 1 fasting

B: Cataflam® (diclofenac potassium) tablets 50 mg x 1 fasting

C: PRO-513 (diclofenac potassium) sachet 50 mg x 1 fed

D: Cataflam® (diclofenac potassium) tablets 50 mg x 1 fed

*Test/Reference

Source Data: [Appendix 15.2.3](#).

Note: Differences in tabulated geometric LS mean values for the Test/Reference comparisons may be attributed to the number of individual subjects in the respective pair-wise comparison. The source data table in [Appendix 15.2.3](#) provides details of the groupings for each analysis.

Inter-subject variability:

The inter-subject variability of the AUC, measured by CV, was similar for both formulations (PRO-513 and Cataflam® tablets). Inter-subject variability for C_{max} and t_{max} tended to be smaller for diclofenac-K sachets than for diclofenac-K tablets. For C_{max} the inter-subject CV for the reference diclofenac-K tablet was 38.91 compared to 33.27 for the sachet. For T_{max} the inter-subject CV for the diclofenac-K tablet was 96.24 compared to 36.9 for the sachets.

Statistical/Analytical Issues

Handling of Dropouts or Missing Data

Subject 011 withdrew from the study after the first treatment period and received only Treatment B. This subject was not included in the PK analysis due to the minimum requirement of two treatment periods for the analysis of bioequivalence as specified in the Study Analysis Plan. Subjects 001 and 036 withdrew from the study after completing three treatment periods, C, D, B and D, C, A respectively. These two subjects were included in the PK analysis where data were available for comparison between two treatments.

DISCUSSION AND OVERALL CONCLUSIONS

The primary objective of this open-label, randomized, four period, crossover study was to compare the relative bioavailability of PRO-513 sachet and Cataflam® tablets under fasting and fed conditions in healthy male and female adult volunteers. There was a difference in relative bioavailability between PRO-513 and Cataflam® under both fasting and fed conditions as follows:

- **PRO-513 versus Cataflam® Tablets under Fasting Conditions:** Following single oral doses administered under fasting conditions, PRO-513 and Cataflam® had similar AUCs (total amount of diclofenac absorbed). However, peak diclofenac concentrations following administration of PRO-513 were 46% higher than peak concentrations following administration of Cataflam® and the median Tmax for PRO-513 was shorter than Cataflam® (0.25 hours versus 0.50 hours). Therefore, while the total amounts of diclofenac absorbed from PRO-513 and Cataflam® differed insignificantly (and latter met FDA bioequivalence criteria) under fasting conditions, diclofenac was more rapidly absorbed from PRO-513 and reached significantly higher concentrations that occurred earlier post-dosing.
- **PRO-513 versus Cataflam® Tablets under Fed Conditions:** Following single oral doses administered under fed conditions, PRO-513 and Cataflam® had similar AUCs (total amount of diclofenac absorbed). However, food decreased the mean diclofenac Cmax for both PRO-513 and Cataflam® compared to the fasted state. Food had a more pronounced effect on peak diclofenac concentrations for PRO-513, producing a Cmax that was 39% lower than for Cataflam®. Further, food increased the diclofenac Tmax for Cataflam®. The median Tmax value for Cataflam® was significantly longer than for PRO-513 (1.25 hours versus 0.17 hours), thus, while food decreased the diclofenac Cmax for PRO-513, food did not lengthen the diclofenac Tmax for PRO513. Thus, PRO-513 was more rapidly absorbed than Cataflam® following a high-fat meal.
- **Effect of Food on PRO-513:** Administration of PRO-513 following a high-fat meal was associated with a shorter Tmax and a significant reduction in mean diclofenac Cmax. The median Tmax value for PRO-513 following a high-fat meal decreased from insignificantly 0.25 hour to 0.17 hours. A secondary diclofenac concentration peak 4 hours after drug administration was temporally related to a meal served 4 hours following drug administration. The mean fed-to-fasted ratio (90% confidence interval) for diclofenac Cmax was 28% (23.63-33.92) indicating a 72% reduction in peak diclofenac concentrations when PRO-513 is administered with food. There was no significant decrease in mean bioavailability (AUC) when PRO-513 was administered with food.
- **Effect of Food on Cataflam® Tablets:** Administration of Cataflam® following a high-fat meal was associated with a prolonged diclofenac Tmax and a significant reduction in mean Cmax. The median Tmax value for Cataflam® following a high-fat meal increased insignificantly from 0.50 hour to 1.25 hours. The mean fed-to-fasted ratio (90% confidence interval) for diclofenac Cmax was 67% (56.20-80.28), indicating a 33% reduction when Cataflam® is administered with food. There was no significant decrease in mean bioavailability (AUC) when Cataflam® was administered with food.

CONCLUSION

Pharmacokinetic Conclusions

- PRO-513 was similar to Cataflam® with respect to extent of absorption when the drugs were administered in single oral doses under both fasting and fed conditions.
- PRO-513 produces significantly higher peak plasma diclofenac concentrations in the fasted state than Cataflam®.
- Absorption of PRO-513 appears more rapid than Cataflam® under fasting and fed conditions.

- Food does not appear to affect the total amount of diclofenac potassium absorbed from either PRO-513 or Cataflam®.
- Food decreases peak plasma diclofenac concentrations from both PRO-513 and Cataflam®, but to a greater extent with PRO-513.
- Food delays the time to peak plasma diclofenac concentration for Cataflam® but not for PRO-513.

Safety Conclusions:

- All treatments were well tolerated by the study subjects.

5.2. ProEthics Bioanalytical Method Validation

Title:

Validation of High Performance Liquid Chromatographic Method using Tandem Mass Spectrometry Detection for the Determination of Diclofenac in Human EDTA Plasma

(b) (4)

Method Validated by: (b) (4)

(b) (4)

(b) (4)

Reference Standard	Supplier	Lot Number	%Purity
Diclofenac Sodium	USP	H013150	100
Diclofenac-d4 (phenyl-d4)	(b) (4)	K109P25	99

Human EDTA K₂ plasma was obtained from (b) (4) No significant interference with the analyte and the internal standard was observed in the pooled human EDTA K₂ plasma used for the preparation of calibration standards and quality control samples.

Between-run accuracy and precision was assessed by the repeated analysis of human EDTA K₂ plasma samples containing different concentrations of diclofenac on separate occasions. (b) (4)

Within-run accuracy and precision evaluations were performed by analyzing the run's replicates consisting of a (b) (4)



(b) (4)

Potentially interfering drugs were spiked at therapeutic concentrations in the low quality control samples, and were processed and analyzed. Acetaminophen, caffeine, dextromethorphan, diphenhydramine, dimenhydrinate, heparin, ibuprofen, nicotine, pseudoephedrine and acetylsalicylic acid were analyzed and no effect on diclofenac in the QC samples was observed.

Hemolysis effect was determined by (b) (4)



The calculated concentrations yielded coefficients of variation of 2.07 and 3.13% for the low and high QC samples, respectively. Percentages of nominal concentrations are 103.47 and 97.50% for low and high QC samples respectively. It was shown that 2% of hemolysis did not affect the determination of diclofenac in human EDTA K₂ plasma.

A summary of the validation parameters are shown in the following table.

Table 1: Bioanalytical Method Validation Parameters		
Analyte	Diclofenac	
Matrix	Human EDTA Plasma	
Internal Standard	diclofenac-d4	
Method Peak Area	HPLC-MS/MS	
Limit of Quantitation (LOQ)	5.09 ng/mL	
Upper Limit of Quantitation (ULOQ)	2546.40ng/mL	
Calibration curve range	5.09 to 2546.40 ng/mL	
Linearity (Peak Area)	weighted (1/C ²) least squares linear regression	
Correlation Coefficient n=7	0.9989	
Slope (n=7)	0.89	
Intercept (n=7)	0.1823	
Inter-day precision (%CV)	1.61 to 3.98	
Inter-day accuracy (% bias)	-2.05 to 1.69	
Quality Control Samples n=28		
Between-run Precision % CV	4.22 to 6.20%	
Between-run Accuracy	97.87 to 100.17%	
Within run Accuracy	100.06% to 107.50%	
Within run Precision	0.96 to 3.865	
Recovery-Analyte	82.57, 83.86 and 86.59%	
Recovery-Internal Standard n=18	Mean 83.85%	
Stability		
Analyte in matrix % change in 24 hrs	Low	-3.51
Analyte in matrix % change in 24 hrs	High	-1.46
Room Temperature	40 hours	99.68-103.94%
-20 °C	486 days	Mean change 2.23%
Thaw/Freeze cycles - 4cycles		
% CV	Low	2.76
% CV	High	1.37

% Nominal	Low	98.27
% Nominal	High	98.19%

Conclusion:

The method is acceptable for the analysis of diclofenac from human plasma samples from study PRO513-101 where the minimum level of diclofenac is approximately 500 ng/mL.

5.3. Novartis Study Number: CAT 458C2101

STUDY TITLE:

An open-label, randomized, single oral dose, two-way comparative crossover study of the bioavailability of diclofenac-K sachets (powder for oral solution) vs. diclofenac-K tablets (Cataflam®, a marketed tablet) in 24 healthy subjects.

Investigational Product: (b) (4) Diclofenac-K (potassium) sachets
(powder for oral solution)

Sponsor: Novartis Pharma AG
4002 Basel, Switzerland

Development Phase: I
Study Dates: 29-Apr-2003 - 04-Jun-2003

CLINICAL STUDY:

Principal Investigator: Vets E., M.D.

Co-investigator:
Institution:

(b) (4)



Bioanalytical Laboratory:

STUDY OBJECTIVES

The primary objectives of the study were:

1. The primary objective of this study was to compare the bioavailability of diclofenac-K after a single oral dose of 50 mg diclofenac-K sachets (powder for oral solution) with 50 mg diclofenac-K sugar-coated tablets.

2. The secondary objective was to compare the general tolerability of the two treatments.

STUDY DESIGN:

This study was conducted using an open, randomized, two-way, single oral dose, two treatment crossover design in 24 healthy male and female subjects, designed to study the relative bioavailability of diclofenac-K sachets with the marketed diclofenac-K tablet formulation, using the same recommended dosage (50 mg) as the marketed product. Diclofenac-K sachets for oral solution (powder) is an alternative formulation of the already marketed product diclofenac-K tablets (Cataflam®), and was developed in order to have a faster absorption rate (Reiner et al 2001). During each of the two study periods, fasted (at least 10 hours) subjects were administered a single oral dose of either diclofenac-K sachets 50 mg or diclofenac-K tablets 50 mg with 240 mL of water at room temperature. The powder was dissolved in a glass with 100 mL water taken with a syringe from another glass containing 240 mL tap water at room temperature. In order to avoid any powder remaining in the sachet, the sachet was rinsed once with 5 ml water taken with a syringe and added to the contents of the glass to be drunk. The glass was rinsed twice with 50 mL water from the other glass. The volunteer then drank the water remaining in the glass. A wash-out period of at least 7 days separated the two periods.

Protocol Deviations:

None of the protocol deviations were considered to invalidate a subject's safety or pharmacokinetic data.

Formulations:

Test (Treatment B): Diclofenac potassium (50 mg) sachet (powder for oral solution), manufactured by (b) (4); batch number X325 1202, expiry date 07/2004.

Reference (Treatment A): Diclofenac potassium (50 mg) sugar coated tablet, marketed by Novartis; batch number X318 1102, expiry date 11/2007.

<i>Sequence no.</i>	<i>Period 1</i>	<i>Period 2</i>
1	A	B
2	B	A

Treatment A : Diclofenac-K 50 mg tablet (Reference formulation)
Treatment B: Diclofenac-K 50 mg sachet (Test formulation)

Subjects:

24 healthy subjects entered and completed the study (12 males and 12 females). Demographic characteristics were generally similar between males and females.

Sample Collection:

Blood collection (7 mL blood per sample, heparin tubes) were obtained for each treatment period at the following times: 0 pre-dose, 5 min, 10 min, 15 min, 20 min, 30 min, 45 min, 60 min, 75 min, 90 min, 105 min, 2 h, 2 h 30, 3 h, 4 h, 6 h, 8 h, 12 hours post-dose.

Analytical:

The analysis of diclofenac in human EDTA plasma was determined using a validated High Performance Liquid Chromatography / Tandem Mass Spectrometry Method. (b) (4)

(b) (4)

Table 1: Bioanalytical Method Parameters

Analyte	Diclofenac	
Matrix	Plasma	
Internal Standard	(b) (4)	
Method Peak Area	HPLC-MS/MS	
Analysis Dates	May 14, 2003 - June 13, 2003.	
Limit of Quantitation (LOQ)	0.5 ng/mL	
Calibration curve range	0.5 - 2 - 10 - 20 - 50 - 100 - 150 - 200 ng/mL	
Linearity	least-squares regression weighting factor of 1/C ²	
Correlation Coefficient	0.99800	
Slope	0.00123	
Recovery	80.7 (SD=4.99)	
Intercept	0.0000162	
Inter-day precision	1.79 to 7.02	
Inter-day accuracy	-1.09 to 2.03	
Quality Control Samples n=28		
Precision % CV	1 ng/mL	13.6 %
	40 ng/mL	7.70 %
	160 ng/mL	8.70 %
Accuracy % Rel. error	1 ng/mL	-7.08 %
	40 ng/mL	-8.22 %
	160 ng/mL	-7.79 %

SAFETY EVALUATIONS:

Safety and tolerability assessments

All subjects who received at least one treatment were to be included in the safety and tolerability evaluation. Safety and tolerability assessments included the monitoring and recording of all adverse events and of concomitant medications. Checks at screening and at study completion were made of routine clinical chemistry and hematology values, ECG recordings, and measurement of vital signs. A physical examination was performed at screening, pre-dose and at study completion.

Brief Summary of Adverse Events

According to the sponsor, there were no serious adverse events. Eleven subjects (46%) reported a total of 15 adverse events after drug administration, all of mild intensity. After diclofenac-K

sachets, 4 subjects (17%) reported 4 adverse events. For three of the adverse events, no relationship to the study drug was suspected. For one adverse event, a case of somnolence, a relationship to the study drug was suspected. After diclofenac-K tablets, 9 subjects (37.5%) reported 11 adverse events, and no relationship to the study drug was suspected for any of these events. The following table shows the incidence of AEs with diclofenac sachet and Cataflam®.

Table 2. Incidence of Adverse Events after Drug Administration

System organ class Preferred term	Number (%) of adverse events	
	Diclofenac-K sachets (N = 24)	Diclofenac-K tablets (N = 24)
Gastrointestinal disorders		
Loose stools	0	1 (4.2%)
General disorders and administration site conditions		
Influenza-like illness	0	2 (8.3%)
Musculoskeletal and connective tissue disorders		
Flank pain	1 (4.2%)	0
Nervous system disorders		
Headache	2 (8.3%)	2 (8.3%)
Somnolence	1 (4.2%)	1 (4.2%)
Syncope vasovagal	0	1 (4.2%)
Psychiatric disorders		
Insomnia	0	1 (4.2%)
Respiratory, thoracic and mediastinal disorders		
Cough	0	1 (4.2%)
Skin and subcutaneous tissue disorders		
Echymosis	0	1 (4.2%)
Pruritus	0	1 (4.2%)
Total	4	11

Source: Appendix 3, Table 5.4

Electrocardiographic findings

According to the sponsor, there were no clinically relevant ECG abnormalities after drug administration. There were no significant changes in ECGs between selection and discharge.

PHARMACOKINETIC ASSESSMENT:

Sample size

A previous study (Reiner et al. 2001) indicated that the intra-volunteer variability of the bioavailability of diclofenac was moderate for the area-under the concentration-time curve (AUC: coefficient of variation of the residual error, CV_{res} of about 10%), but large for C_{max} (CV_{res} of 40 %). In this case, 24 volunteers were required to reach a sufficient power using the confidence interval approach, if limits of 0.8-1.25 were used for AUC and if both study

formulations did not differ by more than 16%. Twenty-four subjects were entered: 12 males and 12 females. All completed the study.

Statistical methods:

Pharmacokinetic parameters were determined using non-compartmental method(s) using WinNonlin (Version 4.0 or later). Descriptive statistics of pharmacokinetic parameters included mean, SD, and CV. For continuous pharmacokinetic parameters: ANOVA (model: treatments, sequences, subjects, gender and periods of administration) after log transformation. Standard 90% confidence interval (90% CI) for the ratio test/reference (test = 50 mg diclofenac-K sachet; reference = 50 mg diclofenac-K tablet). Equivalent non-parametric methods were used for determining t_{max} and t_{lag}. All completed subjects were included in the pharmacokinetic data analysis.

Pharmacokinetic Parameters

Pharmacokinetic parameters are summarized in Table 3 below.

Table 3. Summary Statistics on Pharmacokinetic Parameters

Table 7-3 Summary statistics on pharmacokinetic parameters

Treatment	Parameter	Diclofenac-K tablets				Diclofenac-K sachets			
		N	Mean*	SD	Median (Range)	N	Mean*	SD	Median (Range)
C _{max}	ng/mL	24	855	580	782 (148-2430)	24	1620	872	1510 (367-3610)
t _{max}	h	24	0.864	0.624	0.50 (0.33-2.50)	24	0.233	0.0751	0.25 (0.08-0.37)
	(min)	24	51.8	37.4	30.0 (20.0-150)	24	14.0	4.51	15.0 (5.00-22.2)
t _{lag}	h	24	0.0925	0.0473	0.08 (0.00-0.18)	24	NE	NE	0.00 (0.00-0.00)
	(min)	24	5.55	2.84	5.00 (0.00-10.0)	24	NE	NE	0.00 (0.00-0.00)
AUC ₀₋₄	ng.h/mL	24	945	384	910 (440-1650)	24	1010	429	1040 (447-1970)
AUC _{0-∞}	ng.h/mL	24	952	384	913 (453-1660)	24	1020	430	1050 (451-1980)
t _{1/2}	h	24	2.07	0.435	2.07 (1.25-2.94)	24	2.20	0.494	2.16 (1.00-3.36)

*Arithmetic means

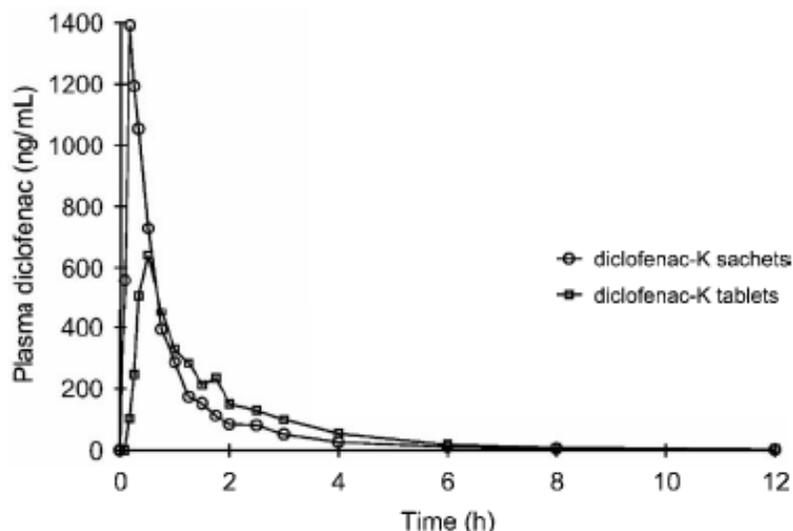
SD: Standard deviation

NE: not estimable

The plasma concentration-time profile for the sachet and Cataflam® tablets is given below:

Figure 7-1 Average diclofenac plasma concentration versus time, by treatment

Values are arithmetic means. Top: linear coordinates. Bottom: semi-logarithmic coordinates.



The statistical analysis of the PK results is given in the following table.

Table 7-4 Statistical comparison of pharmacokinetic parameters

	P	CV (%)	Diclofenac-K tablets		Diclofenac-K sachets		PE**	90%CI
			Mean*	Median	Mean*	Median		
C_{max} ng/mL	<.0001	55.7	660		1380		209.2	162, 271
t_{max} h	<.0001	-		0.50		0.25	-0.500	-0.775, -0.330
$t_{1/2}$ h	<.0001	-		0.08		NE	-0.080	-0.125, -0.080
AUC_{0-4} ng.h/mL	0.29	22.0	865		926		107	96.1, 119
$AUC_{0-\infty}$ ng.h/mL	0.31	21.7	874		933		107	95.9, 119
$t_{1/2}$ h	0.38	21.0	2.03		2.14		106	95.2, 117

p: probability of no influence of treatment (ANOVA), or, for t_{max} and $t_{1/2}$, method of Koch for two-way crossover.

CV: Residual (intra-subject) coefficient of variation derived from the ANOVA

*: Least square geometric means

** : medians for t_{max} and $t_{1/2}$

NE: not estimable

PE: point estimate; CI: confidence interval (using the method of Moses for t_{max} and $t_{1/2}$)

Exposure:

The extent of exposure (AUC) was similar for the two formulations, with a p-value of 0.29 for AUC0-t and 0.31 for AUC0-inf. The 90% confidence intervals of the test/reference ratios (PE) were 96.1-119 % and 95.9-119 %, respectively, within the bioequivalence interval range of 80-125%.

Mean peak plasma concentrations (C_{max}) were 1620 ± 872 ng/mL for diclofenac-K sachets and 855 ± 580 ng/mL for diclofenac-K tablets. C_{max} was significantly higher with the diclofenac-K

sachets than with diclofenac-K tablets ($p < 0.0001$), with an estimate of the test/reference ratio of 209%, and a 90% CI ratio of 162 to 271%. The mean time to peak plasma concentration (mean t_{max}) was also significantly shorter with diclofenac-K sachets than with diclofenac-K tablets ($p < 0.0001$). Peak plasma concentration was reached in 14 min and 52 min, respectively. No lag time was observed with diclofenac-K sachets (all values at 0 h), whereas a median tlag of 5 min (mean tlag= 5.6 min was observed for diclofenac-K tablets. The difference in the two formulations was significant ($p < 0.0001$).

Terminal half-lives ($t_{1/2}$) did not differ significantly between formulations ($p = 0.38$). The estimate of test/reference ratio was 106%.

Gender: Novartis reported no significant gender effect was found for the various pharmacokinetic parameters.

Inter-subject variability:

The inter-subject variability of the AUC and C_{max} , measured by %CV, was similar for both formulations. Inter-subject variability for t_{max} tended to be smaller for diclofenac-K sachets than for diclofenac-K tablets (Table 5).

Table 5: Intra-and Inter-subject Variability of C_{max} , T_{max} and AUC 0-t
(Study CAT458C2101)

Parameter	No. of Subjects	CV (%)	CV (%)	
		Intra-subject (Residual)*	Sachet	Tablet
AUC _{0-t}	24	22	42.4	40.6
AUC _{0-∞}	24	21.7	42.2	40.3
C_{max}	24	55.7	53.8	67.8
t_{max}	24	—	32.2	72.3

CV: coefficient of variation

* Residual error from ANOVA

DISCUSSION AND OVERALL CONCLUSIONS

According to the sponsor, no serious adverse events were reported. Very few adverse events were reported for diclofenac-K sachets and all were of mild intensity. There were no significant changes in clinical laboratory results, vital signs, ECGs, physical examinations and body weight after drug treatment.

The extent of exposure, in terms of AUC_{0-t} or AUC_{0-∞} was equivalent for both diclofenac-K sachets and diclofenac-K tablets, and terminal half-lives were also similar with both formulations.

Diclofenac was more rapidly absorbed from diclofenac-K sachets than from diclofenac-K tablets, with higher peak plasma concentrations achieved with the sachet formulation, and no lag. No gender differences were detected for any of the pharmacokinetic parameters. More rapid absorption of diclofenac from the sachet formulation compared with the tablet formulation was achieved as expected, without any increase in the incidence, nature or severity of adverse events.

CONCLUSION

The extent of absorption was equivalent between both formulations as indicated by the test/reference ratio for AUC_{inf}. As indicated by shorter lag, t_{max}, and increased C_{max}, the rate of absorption of diclofenac was markedly faster with diclofenac-K sachets (powder dissolved in water) than with the reference diclofenac-K tablet.

5.4. Novartis Bioanalytical Method Report

**Novartis Analytical Method
Study No: CAT458C2101
Bioanalytical Data Report**

Compound Code:

(b) (4)
Diclofenac-K (potassium) sachets
(powder for oral solution)

Study Code Novartis:

CCAT458C2101

Study Code SGS:

SGS BIO3508

Analysis of biological samples and reporting:

Name and address of center:

(b) (4)

Lead Analyst:

(b) (4)

Sample processing:

(b) (4)



A summary of the method parameters are shown in the following table.

Bioanalytical Method Parameters

Analyte	Diclofenac	
Matrix	Plasma	
Internal Standard	(b) (4)	
Method Peak Area	HPLC-MS/MS	
Anaysis Dates	May 14, 2003 and June 13, 2003.	
Limit of Quantitation (LOQ)	0.5 ng/mL	
Calibration curve range	0.5 - 2 - 10 - 20 - 50 - 100 - 150 - 200 ng/mL	
Linearity	least-squares regression weighting factor of 1/C ²	
Correlation Coefficient	0.99800	
Slope	0.00123	
Recovery	80.7 (SD=4.99)	
Intercept	0.0000162	
Inter-day precision	1.79 to 7.02	
Inter-day accuracy	-1.09 to 2.03	
Quality Control Samples n=28		
Precision % CV	1 ng/mL	13.6 %
	40 ng/mL	7.70 %
	160 ng/mL	8.70 %
Accuracy % Rel. error	1 ng/mL	-7.08 %
	40 ng/mL	-8.22 %
	160 ng/mL	-7.79 %
Stability		
Room Temperature	24 hours	No significant degradation
-20 °C	3 months	No significant degradation
Thaw/Freeze cycles	3 cycles	No significant degradation

VI. SPONSOR'S PROPOSED LABELING

65 pages withheld after this page as B4 (draft labeling)



VII. FILING FORM

<i>Office of Clinical Pharmacology New Drug Application Filing and Review Form</i>			
General Information About the Submission			
	Information		Information
NDA Number	N22-165	Brand Name	(b) (4)
OCP Division (I, II, III)	DCP-I	Generic Name	Diclofenac potassium
Medical Division	HFD-120	Drug Class	NSAID
OCP Reviewer	Veneeta Tandon	Indication(s)	Migraine with or without aura
OCPB Team Leader	Ramana Uppoor	Dosage Form	50 mg powder for solution
		Dosing Regimen	Single dose 50 mg with 1or 2 ounces of water
Date of Submission	9/27/07	Route of Administration	Oral
Estimated Due Date of OCP Review	5/1/08	Sponsor	Proethic
PDUFA Due Date	7/27/08	Priority Classification	Standard
Division Due Date	5/27/08		

Clin. Pharm. and Biopharm. Information

Summary:

The NDA is a resubmission, as the original NDA submitted on 6/25/07 was not filed due to non-clinical issues. In terms of clinical pharmacology and Biopharmaceutics, the application remains the same.

Diclofenac is available worldwide in a number of dosage forms for oral, rectal, intramuscular or topical administration. In the United States, diclofenac is available in two different salts, diclofenac sodium (VOLTAREN) and diclofenac potassium (CATAFLAM), which are both marketed by Novartis Pharmaceuticals. An extended-release form of diclofenac sodium (VOLTAREN XR) is also available.

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The safety database includes these three studies and the two relative bioavailability studies.

	"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	2		
I. Clinical Pharmacology				
Mass balance:	-	-		
Isozyme characterization:	-	-		
Blood/plasma ratio:	-	-		
Plasma protein binding:	-	-		

Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X			
multiple dose:	-			
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:	X			
PK/PD:				
Phase 1 and/or 2, proof of concept:	-			
Phase 3 clinical trial:	X			
Population Analyses -				
Data rich:	X			
Data sparse:	X			
II. Biopharmaceutics				
Absolute bioavailability:	-			
Relative bioavailability -				
solution as reference:	X			
alternate formulation as reference:	X	2		one European study (CAT458C2101) and one US study (PRO-513101). This study also looks at food effect
Bioequivalence studies -				
traditional design; single / multi dose:	-			
replicate design; single / multi dose:	-			
Food-drug interaction studies:	X			
Dissolution:	X			Will be reviewed by CMC
(IVIVC):				
Bio-waiver request based on BCS	-			
BCS class	-			
III. Other CPB Studies				
Genotype/phenotype studies:	-			
Chronopharmacokinetics	-			
Pediatric development plan	-			

Literature References	16		6 on use in hepatic disease and 10 on CYP enzymes involved in the metabolism of diclofenac. The label has been updated
Total Number of Studies	2 PK 2 assay reports +16 literature articles that affect label		
Filability and QBR comments			
	"X" if yes	Comments	
Application filable?	X	Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?	
Comments sent to firm?	none		
QBR questions (key issues to be considered)	<ul style="list-style-type: none"> • What is the relative bioavailability of PRO 513 to Cataflam? • Is there a food effect with the PRO 513? • Are the CYP enzymes involved in the metabolism and inhibition/induction potential of diclofenac adequately established based on literature reports. • Is there adequate information on use of diclofenac in hepatic impaired subjects in the literature articles provided? 		
Other comments or information not included above	Reviewer's aid (Summary as requested) provided.		
Primary reviewer Signature and Date	Veneeta Tandon		
Secondary reviewer Signature and Date	Ramana Uppoor		

Table 2.5.3-1: PRO-513 Clinical Pharmacology Studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s), Dosage Regimen, Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status, Type of Report
PK	PRO-513101	Module 5.3	Assess relative bioavailability of test and reference treatments and the effect of food on test and reference treatments	Open-label, Randomized, 4-period Crossover	A) PRO-513 sachet 50 mg fasting B) CATAFLAM tablets 50 mg fasting C) PRO-513 sachet 50 mg fed D) CATAFLAM tablets 50 mg fed	36	Healthy Male and Female Volunteers	Single oral doses under fed and fasting conditions	Full, Complete
PK	CAT458C2101	Module 5.3	Assess relative bioavailability of test and reference treatments under fasting conditions	Open-label, Randomized, 2-period Crossover	A) Diclofenac potassium sachet 50 mg fasting B) CATAFLAM tablets 50 mg fasting	24	Healthy Male and Female Volunteers	Single oral doses under fasting conditions	Full, Complete

Table 2.5.4-1: Pivotal Studies Conducted in the Development of PRO-513

Study ID	No. of Study Centers (Location)	Study Period Total Random (Target Random)	Study Design	Study Treatment	Objective	No. of Subjects by Arm	Duration of Treatment	Gender Mean Age (Range)	Diagnosis	Primary Efficacy Endpoint(s)
CAT458C2301	21 (5-Germany, 5-Hungary, 4-Italy, 5-Poland, 2-The Netherlands)	July 5, 2003 – November 14, 2003 328 (300) ^a	Phase III, double-blind, double dummy, randomized, multi-center, crossover, safety and efficacy study	(b) (30 mg diclofenac-K sachet [powder for oral solution]) 50 mg diclofenac-K sugar-coated tablets (CATAFLAM) Placebo	To evaluate (b) relative to placebo (superiority) and diclofenac-K tablets (non-inferiority) in the acute treatment of migraine attacks	291 (b) 298 (CATAFLAM) 299 (Placebo)	Single dose treatment of up to 3 migraines over a 2-month period (each eligible subject used each treatment once)	46 Male, 271 Female 39.2 (18-64)	Subjects 18-65 years of age with histories of 2-6 migraine attacks (with and without aura) per month over the last 3 months with a disease duration of ≥ 1 year	Percentage of subjects who were pain free at 2 hours post-dose

^a 328 subjects were randomized for this study and 317 subjects actually dosed. The number of subjects by treatment arm and gender includes only those who used the study medication.

^b (b) is the name used for the PRO-513 formulation in the Novartis-conducted studies.

Table 2.5.4-1: Clinical Safety and Efficacy Studies Conducted in the Development of PRO-513
(Page 2 of 2)

Study ID	No. of Study Centers (Location)	Study Period Total Random (Target Random)	Study Design	Study Treatment	Objective	No. of Subjects by Arm	Duration of Treatment	Gender Mean Age (Range)	Diagnosis	Primary Efficacy Endpoint(s)
PRO-513301	25 (US)	May 18, 2006 – December 21, 2006 807 (650) ^a	Phase III, prospective, randomized, double-blind, parallel group, single-dose, placebo-controlled, multi-center, safety and efficacy study	PRO-513 (50 mg diclofenac-K sachet [powder for oral solution]) Placebo	To demonstrate safety and efficacy of PRO-513 relative to placebo in the treatment of a single migraine attack	343 (PRO-513) 347 (Placebo)	Single dose treatment of 1 migraine attack over 8 weeks	105 Male, 585 Female 40.7 (18-65)	Subjects 18-65 years of age with histories of 1-6 migraines per month for at least 1 year	4 co-primary endpoints: Percent of subjects who had no headache pain, nausea, photophobia, and phonophobia at 2 hours post-dose (Subjects could not have used rescue medication prior to 2 hours)

^a The plan was to enroll sufficient numbers to ensure that 650 subjects dosed with the study medication. 807 subjects were randomized and 690 subjects dosed. The number of subjects by treatment arm and gender includes only those who used the study medication. Note: One subject in the placebo group was lost to follow-up and it is not known whether the subject dosed. This subject was not included in the ITT or PP datasets and is not included in the tabulation here.

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/s/

Carol Noory
9/24/2008 11:51:31 AM
BIOPHARMACEUTICS

Veneeta Tandon
9/24/2008 01:23:52 PM
BIOPHARMACEUTICS

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

General Information About the Submission

	Information		Information
NDA Number	N22-165	Brand Name	(b) (4)
OCP Division (I, II, III)	DCP-I	Generic Name	Diclofenac potassium
Medical Division	HFD-120	Drug Class	NSAID
OCP Reviewer	Veneeta Tandon	Indication(s)	Migraine with or without aura
OCPB Team Leader	Ramana Upoor	Dosage Form	50 mg powder for solution
		Dosing Regimen	Single dose 50 mg with 1 or 2 ounces of water
Date of Submission	9/27/07	Route of Administration	Oral
Estimated Due Date of OCP Review	5/1/08	Sponsor	Proethic
PDUFA Due Date	7/27/08	Priority Classification	Standard
Division Due Date	5/27/08		

Clin. Pharm. and Biopharm. Information

Summary:

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/s/

Veneeta Tandon
11/7/2007 11:36:06 AM
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Ramana S. Uppoor
11/7/2007 12:49:00 PM
BIOPHARMACEUTICS