

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-202

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

CLINICAL PHARMACOLOGY REVIEW

NDA 22-202:	Submission Date: September 21, 2007
Type:	505(b)(2)
Generic Name:	Diclofenac potassium
Brand Name:	Zipsor™ Soft Gelatin Capsules
Drug Class:	NSAID
Indication:	Relief of mild to moderate pain
Dosage Form:	Soft Gelatin capsule
Strength:	25 mg
Route of Administration:	Oral
Dosing regimen:	QID
Applicant:	Xanodyne Pharmaceuticals
OCP Division:	DCP2
Clinical Division:	DAARP (OND)
Reviewer:	Emmanuel O. Fadiran, R.Ph., Ph.D.
Team Leader:	Suresh Doddapeneni, Ph. D.

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1 EXECUTIVE SUMMARY

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology / Division of Clinical Pharmacology-2 (OCP / DCP-2) has reviewed NDA 22-202's Clinical Pharmacology information submitted on September 21, 2007 and finds it acceptable provided that a mutually acceptable agreement can be reached between the Agency and the Sponsor regarding the language in the package insert.

1.2 PHASE IV COMMITMENTS

None

1.3 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Zipsor™ (diclofenac potassium) Soft Gelatin Capsule (DPSGC) is a new 25 mg dose form of the existing reference listed drug, Cataflam® (diclofenac potassium immediate release tablets, 50 mg). Zipsor™ is indicated for the relief of mild to moderate pain. Zipsor™ is a liquid formulation of diclofenac potassium encapsulated in soft gelatin capsules. According to the Sponsor, the patented technology, ProSorb®, used in the formulation is designed to improve absorption characteristics and reduce time to onset of activity for pain relief which may be advantageous in the treatment of mild to moderate pain.

To support the efficacy and safety of DPSGC to treat mild to moderate pain, the Sponsor has submitted the following additional studies

- Four clinical pharmacokinetic Phase 1 studies using DPSGC. These studies establish the PK information (BA/BE, dose proportionality, food effect) for DPSGC.
- One Phase 2 PK/PD, one pediatric, and six adult Phase 3 safety and efficacy studies.

The Phase 2 trial investigated pain management in a postoperative model (bunionectomy) and provides both efficacy direction as well as PK/PD modeling data. The Phase 3 studies, including two postoperative bunionectomy pain studies, two postoperative dental pain studies, two postoperative knee pain studies, and the pediatric study utilized a variety of primary and secondary variables that are typical for pain investigations.

BA/BE Studies

Study OA170 examined the dose proportionality of DPSGC at 25 and 50 mg and compared the rate and extent of absorption of diclofenac at these doses with that of Cataflam 50 mg in healthy volunteers. The results from this study demonstrated dose proportionality for the two doses of DPSGC and showed that after administration of a 50 mg dose of Cataflam, the mean C_{max} was comparable to that of the 25 mg dose of DPSGC (1125 ng/ml for DPSGC versus 1169 ng/ml for Cataflam) although T_{max} was ~2-fold longer, and the mean AUC_{0-∞} was comparable to that of 50 mg dose of DPSGC (1232 ng.hr/ml for DPSGC versus 1144 ng.hr/ml for Cataflam). This indicates that the rate of absorption is greater from DPSGC than from Cataflam although the extent of absorption is comparable. The mean t_{1/2} was comparable for all treatments and ranged from 1.4 to 1.8 h.

Study AAI-US-142 compared the pharmacokinetics of diclofenac after single 50 mg doses of DPSGC and Cataflam in healthy volunteers. The results from the study indicated the rate of absorption diclofenac from DPSGC was about 80% greater than that from Cataflam tablets but the extent of absorption of diclofenac from DPSGC was equivalent to that from Cataflam (Table 1). The T_{max} of diclofenac from DPSGC is 0.6 h compared to 1.3 h for Cataflam tablet.

Table 1. Summary of the statistical comparison of diclofenac PK following administration of 50 mg DPSGC and Cataflam tablets.

PK Parameters ^a	Reference: 50 mg Cataflam tablet	Test: 50 mg DPSGC	Test : Reference ratio	
			Point estimate	90% Confidence Intervals
C _{max} (ng/mL)	992	1773	1.787	1.344 – 2.376
AUC _{0-t} (ng.hr/mL)	1078	1161	1.077	0.999 – 1.211
AUC _{0-∞} (ng.hr/mL)	1087	1195	1.099	0.982 – 1.181

^a Least-Squares (geometric) mean

BE Study on Formulations used in the Clinical trials

Study OA171 compared the bioavailability of the initial DPSGC 25 mg formulation used in several of the clinical trials (DPSGC old process or 1000 formulation series) to that of the intermediate DPSGC 25 mg formulation used for the pivotal bunionectomy studies (DPSGC new process or 1200 formulation series) and to a liquid formulation of 25 mg diclofenac potassium in healthy volunteers. The results from this study showed that C_{max} was reached earlier for the solution and the mean T_{max} was approximately 50% of that of either DPSGC formulation but all three formulations were bioequivalent with respect to rate and extent of absorption (Tables 2 & 3).

Table 2. Mean (SD) of diclofenac PK following administration of DPSGC formulations and diclofenac potassium liquid formulation[#]

PK Parameters	Treatment A [#]	Treatment B [#]	Treatment C [#]
C _{max} (ng/mL)	1087 (419)	958 (274)	1023 (400)
AUC _{0-∞} (ng.hr/mL)	597 (151)	606 (144)	607 (155)
T _{max} (h)	0.47 (0.17)	0.25 (0.09)	0.49 (0.19)
T _{1/2} (h)	1.07 (0.29)	1.07 (0.38)	1.45 (0.74)

[#]Treatment A: Diclofenac potassium, 25 mg soft gelatin capsule, (new process or 1200 formulation series)

[#]Treatment B: Diclofenac potassium, 25 mg/ml liquid

[#]Treatment C: Diclofenac potassium, 25 mg soft gelatin capsule, (old process or 1000

formulation series)

Table 3: Summary of the statistical comparison of diclofenac PK following administration of DPSGC formulations and diclofenac potassium liquid formulation[#]

Parameter	new vs. old		new vs. liquid		old vs. liquid	
	Ratio	90% CI	Ratio	90% CI	Ratio	90% CI
AUC _{0-t}	99.03%	(94%,104%)	98.23%	(93%,103%)	99.19%	(94%,104%)
AUC _{0-∞}	98.83%	(94%,103%)	97.88%	(93%,103%)	99.04%	(95%,104%)
C _{max}	107.43%	(94%,123%)	108.19%	(95%,124%)	100.71%	(88%,115%)
t _{max}	-0.02h ^x	(-0.08h,+0.04h) ^x	+0.23h ^x	(+0.17h,+0.29h) ^x	+0.25h ^x	(+0.19h,+0.31h) ^x

^x : difference CI : confidence interval

[#]Treatment A: Diclofenac potassium, 25 mg soft gelatin capsule, (new process or 1200 formulation series)

[#]Treatment B: Diclofenac potassium, 25 mg/ml liquid

[#]Treatment C: Diclofenac potassium, 25 mg soft gelatin capsule, (old process or 1000 formulation series)

Request for a Waiver of BE Study

There were three series of formulations used in the development of Zipsor Soft Gelatin Capsules, namely the old process or 1000 formulation series, the new process or 1200 formulation series and the to-be marketed or 1300/1400 formulation series. The changes in the formulation and capsule size between the 1000 series and the 1200 series were shown not to affect bioavailability, as evidenced by results of the bioequivalence Study OA171. The change (b) (4)

(b) (4)
based on the observation of the lack of effect of the change (b) (4) in the intermediate 1200 series as demonstrated by the results of BE study OA171.

In the Division's 74-day Letter, dated December 4, 2007, the Agency requested from the Sponsor "full dissolution profile (and corresponding f₂ data) comparison between the clinical formulation (series 1200) and to-be-marketed formulation (series 1300/1400)." The

Sponsor then provided dissolution profile data generated at the time of batch release for the registration batches (PDS1304, PDS1436, PDS1457) and compared these with batch PDS1218 (the 1200 series) used for BE Study OA171. Profiles of capsules were obtained at 10, 20, 30 and 45 minutes. (b) (4)

(b) (4)

Therefore it is reasonable to conclude that the two series have similar dissolution profiles.

Additionally batch 1304 (series 1300) was used for Bunionectomy Studies XP21L-301 and XP21L-302.

Based on this information the request for a bioequivalence waiver for the to-be-marketed formulation is granted.

Food Effect Study

Study AAI-US-119 examined the effect of food on the absorption of diclofenac from 25 mg and 50 mg DPSGC in healthy volunteers. Each subject received a dose of DPSGC after a 10-hour fast or after a standard high-fat breakfast according to a two-way crossover design. Co-administration of 25 mg or 50 mg DPSGC with high fat meal resulted in a decrease in C_{max} by approximately 47% and 53% respectively and T_{max} was increased ~2-fold, but no change in AUC (Table 4). The data indicate that a high-fat meal decreases the rate but not the extent of absorption of diclofenac from DPSGC. Under both fed and fasted conditions, dose proportional bioavailability was observed between the 25 mg and 50 mg doses.

The labeling for Cataflam tablet states that “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 peak plasma levels of approximately 30%”. But there is no restriction on dosing with meal. Zipsor is available in only one strength (25 mg) and no recommendation will be made regarding administration in relation to meal since the extent of absorption is not affected by food as observed for Cataflam tablet.

Table 4. Mean (SD) diclofenac PK parameters following oral administration of DPSGC to healthy volunteers under fed and fasted conditions

Treatment	C _{max} (ng/mL)	AUC _{0-t} (ng*hr/mL)	AUC _{0-inf} (ng*hr/mL)	T _{max} (hr)	T _{1/2} (hr)
25 mg (N=24)					
Fasted	1156 (482)	691 (195)	706 (199)	0.49 (0.16)	1.04 (0.42)
Fed	686 (411)	680 (184)	713 (182)	1.02 (0.55)	1.11 (0.42)
50 mg (N=23)					
Fasted	2365 (1034)	1521 (377)	1549 (384)	0.51 (0.19)	1.10 (0.25)
Fed	1154 (592)	1416 (366)	1457(373)	1.28 (0.71)	1.07 (0.25)

PK-PD Relationship

Study AAI-002000 compared diclofenac concentrations and pain relief efficacy in bunionectomy patients randomized to receive DPSGC 25 mg, DPSGC 50 mg, ProSorb-D™ liquid 12.5 mg, or Cataflam 50 mg every 8 hours for 8 days. The composition of ProSorb-D is (b) (4)

Pain scores and PK blood samples were obtained during the period following the initial dose of study drug on Day 1 and the morning dose on Day 4 at the following times: 0 (pre-dose), 10, 20, 30, 40, 50, 60 minutes and 1.5, 2, 3, 4, 5, 6, 7 and 8 hours post dose. Additional pain intensity scores were collected hourly if second dose was administered beyond 8 hours after initial dose on Day 1 and pre-dose pain intensity score was obtained prior to the second and third doses of study medication on Day 1. Patients who rescued prior to administration of the second dose on Day 1 recorded pain intensity score at the time of rescue but discontinued the remaining pain intensity assessments up until the pre-dose assessment for the second dose and the remaining PK blood samples were also discontinued.

A two-compartment model with first order absorption was fitted to the PK data for the DPSGC formulations. The PK for Cataflam dose were not included in the analysis because of the high variability in the data. Figure 1 shows that the PK model adequately describes the data for a typical patient in the study.

Graphs of the mean change from baseline in pain intensity versus the mean plasma diclofenac concentration at the same time demonstrated a counterclockwise hysteresis (Figure 2), consistent with a peripheral effect compartment. A modified E-max model with a component related to the baseline pain was fitted to the data for the pain relief and the concentration of diclofenac in the peripheral effect compartment. As shown in Figure 3, there was good agreement between the observed and model-predicted change from baseline in pain relief scores as a function of time. The results of the PK-PD analysis indicated that the PD appear to more closely match a relationship between relief and the peripheral concentration than between relief and plasma concentration which is in agreement with models previously utilized for analgesic. Sponsor acknowledges in the report that these results are not definitive, nor do they prove site-of- or mechanism of action and that the analysis was intended to give insight into the relationship of dose and effect. Given the different baseline pain on day 1 and day 4 (approximate average pain scores of 6 and 2, respectively), pain relief was represented with an absolute component and a component related to baseline pain (pain measured just prior to dose administration). There was also an arbitrary assumption that placebo effect is proportional to baseline pain. This model represented the pain relief data fairly well within the power of the model. As acknowledged by the sponsor, whether the addition of additional model structure improves model fidelity to data sufficiently justify additional model structure and parameters remains to be explored.

Figure 1: Graphical Output Showing Regressed Model (line) and Observed Plasma Concentrations (circles) Over Time for a Subject From day 4.

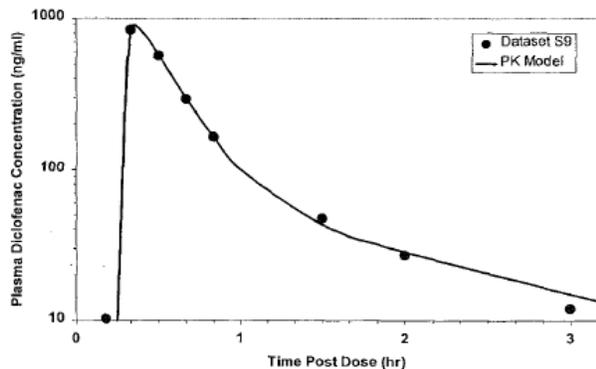


Figure 2: Relationship Between the Mean Change from Baseline in Pain Relief Score and the Mean Plasma Concentrations of Diclofenac on Day 4 During Oral Administration of DPSGC 25 mg, ProSorb-D 12.5 mg, and Cataflam 50 mg Every 8 Hours for 8 Days to Bunionectomy Patients

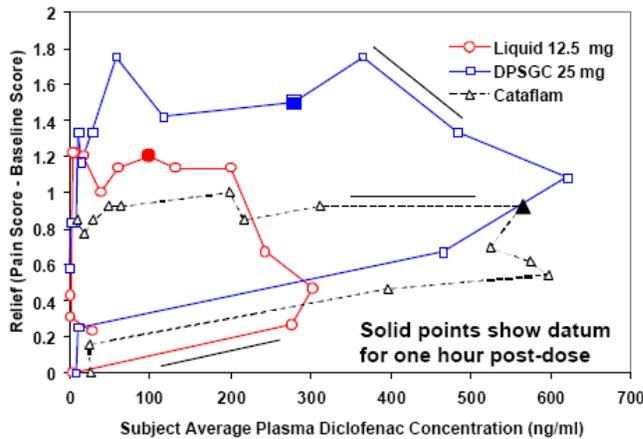
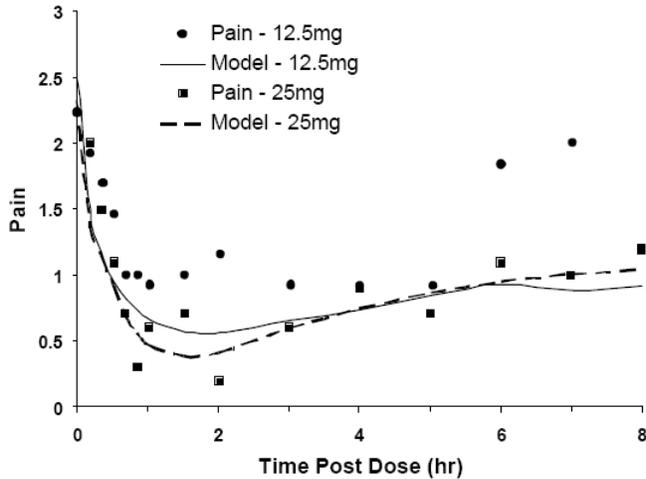


Figure 3: Observed and Model-Predicted Mean Change from Baseline in Pain Relief Scores During Oral Administration of DPSGC 25 mg and ProSorb-D 12.5 mg Every 8 Hours for 8 Days to Bunionectomy Patients



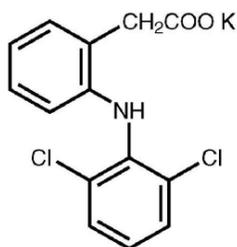
2 QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What are the general attributes of diclofenac potassium?

The chemical name of diclofenac potassium is 2-[(2,6-dichlorophenyl)amino] benzeneacetic acid monopotassium. The molecular weight is 334.24. Its molecular formula is $C_{14}H_{10}Cl_2NKO_2$, and it has the structural formula shown in Figure 1.

Figure 1: Diclofenac potassium Structural Formula



Mechanism of action:

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits antiinflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of diclofenac, like that of other NSAIDs, is not completely understood but may be related to regulation of prostaglandin synthesis via prostaglandin synthetase. The mechanism involves an inhibition of cyclooxygenase (COX-1 and COX-2) pathways. Diclofenac is a weak acid and is therefore relatively insoluble at acidic pH, resulting in poor solubility in gastric fluid. The initial phase of diclofenac absorption after oral administration may be dependent on factors with situational variability such as the degree of mechanical agitation in the stomach and the time required for passage of the drug from the stomach into the higher pH of the intestines. According to the labeling for Cataflam® tablet the maximum concentration of diclofenac occurs approximately 1 hour after dosing with a range of 0.33 to 2.0 hours.

Regulatory history:

The diclofenac products have been approved for marketing in the US since the 1980s. The Agency has approved numerous diclofenac products, including:

- Voltaren® (diclofenac sodium) 25, 50, and 75 mg Delayed Release Tablets (NDA 19-201, approved in 1988);
- Voltaren® (diclofenac sodium) 0.1% Ophthalmic Solution (NDA 20-037, approved in 1991);
- Cataflam® (diclofenac potassium) 25 and 50 mg Immediate Release Tablets (NDA 20-142, approved in 1993);
- Voltaren-XR® (diclofenac sodium) 100 mg Extended Release Tablets (NDA 20-254, approved in 1996);
- Arthrotec® (diclofenac sodium/misoprostol) 50, 75 mg/0.2 mg Delayed Release Tablets (NDA 20-607, approved in 1997);
- Solaraze® (diclofenac sodium) 3% Gel (NDA 21-005, approved in 2000); and

- Flector® (diclofenac epolamine) 1.3% patch (NDA 02-1234, approved in 2007).
- In addition, at least nine generic versions of Voltaren Delayed Release Tablets and six generic versions of Cataflam Immediate Release Tablets have been approved.

NDA 22-202 is therefore a 505(b)(2) application that relies on the Agency's prior findings of safety and effectiveness of diclofenac potassium in support of Cataflam 25 and 50 mg Immediate Release Tablets. By focusing on a 25 mg strength DPSGC product, Xanodyne has developed a product whose peak plasma levels closely match those of the approved 50 mg product, permitting direct reference to Cataflam's substantial evidence of efficacy in the treatment of mild to moderate pain. At the same time, the total exposure associated with DPSGC closely matches that of the approved 25 mg Cataflam product.

Formulation:

Zipsor™ (diclofenac potassium) Soft Gelatin Capsule (DPSGC) is a liquid formulation of 25 mg of diclofenac potassium encapsulated in a soft gelatin capsule. Diclofenac precipitates upon exposure to gastric fluid due to its relative insolubility at acidic pH. Thus, absorption characteristics are dependent on (1) mechanical agitation to disperse the drug in the stomach, and (2) passage of the drug from the stomach into the higher pH milieu of the intestines. The patented ProSorb technology used in DPSGC is designed to improve further the absorption characteristics of diclofenac potassium. According to the Sponsor, the principle behind the ProSorb technology is the use of selected dispersing agents designed to facilitate more rapid, consistent, and complete absorption of diclofenac from the gastrointestinal tract.

Indication (as per proposed label)

Zipsor is indicated for relief of mild to moderate pain.

Dosage and Administration (as per proposed label)

For treatment of pain the recommended dosage is 25 mg q.i.d.

2.2 General Clinical Pharmacology

The absorption, distribution, metabolism, and excretion of diclofenac as a molecular entity are described in the label for the reference listed drug (Cataflam Label, 2005).

To support the efficacy and safety of DPSGC to treat mild to moderate pain, the Sponsor has submitted the following additional studies:

- Four clinical pharmacokinetic Phase 1 studies using DPSGC. These studies establish the PK information (BA/BE, dose proportionality, food effect) for DPSGC.
- One Phase 2 PK/PD, one pediatric, and six adult Phase 3 safety and efficacy studies.

The Phase 2 trial investigated pain management in a postoperative model (bunionectomy) and provides both efficacy direction as well as PK/PD modeling data. The Phase 3 studies, including two postoperative bunionectomy pain studies, two postoperative dental pain studies, two postoperative knee pain studies, and the pediatric study utilized a variety of primary and secondary variables that are standard for pain investigations.

2.2.1 What are the characteristics of the exposure-response relationship for efficacy?

Study AAI-002000 compared diclofenac concentrations and pain relief efficacy in bunionectomy patients randomized to receive DPSGC 25 mg, DPSGC 50 mg, ProSorb-D™ liquid 12.5 mg, or

Cataflam 50 mg every 8 hours for 8 days. The composition of ProSorb-D is (b) (4). Pain scores and PK blood samples were obtained during the period following the initial dose of study drug on Day 1 and the morning dose on Day 4 at the following times: 0 (pre-dose), 10, 20, 30, 40, 50, 60 minutes and 1.5, 2, 3, 4, 5, 6, 7 and 8 hours post dose. Additional pain intensity scores were collected hourly if second dose was administered beyond 8 hours after initial dose on Day 1 and pre-dose pain intensity score was obtained prior to the second and third doses of study medication on Day 1. Patients who rescued prior to administration of the second dose on Day 1 recorded pain intensity score at the time of rescue but discontinued the remaining pain intensity assessments up until the pre-dose assessment for the second dose and the remaining PK blood samples were also discontinued.

The mean plasma concentrations on Day 4 are shown in Figure 2, and the mean PK parameters on Day 4 are summarized in Table 1. The results indicate that there was a dose-related increase in C_{max} and AUC for the ProSorb-based formulations (DPSGC and ProSorb-D liquid) but the increases were less than dose-proportional. Although single dose studies in healthy volunteers showed an increase in C_{max} for 50 mg DPSGC compared to Cataflam (see Section 2.2.2 below), the mean for 50 mg Cataflam tablets (1086 ng/ml) and the 50 mg DPSGC (1126 ng/ml) were comparable. These observations are most likely due to the small numbers of subjects per group, the use of different subjects per group, and the fact that food consumption was not controlled in the study.

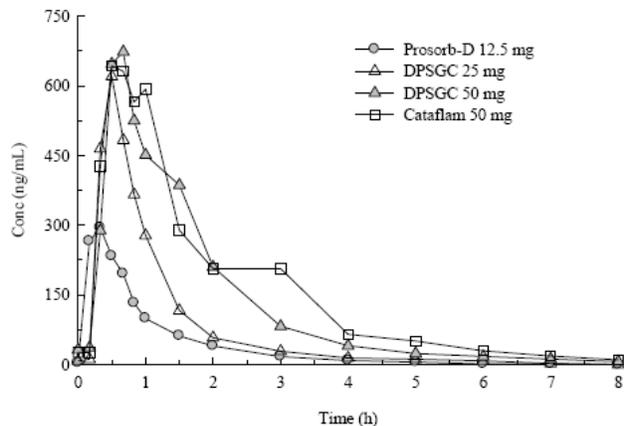
Table 1: Summary of Statistical Comparisons of Day 4 Diclofenac PK following the 4 treatments

Parameter	Means ¹				Statistical Significance ²
	12.5 mg (A)	25 mg (B)	50 mg (C)	Cataflam® (D)	
AUC 0-t (ng-hr/ml)	308	570	1033	1247	C, D > A D > B
AUC 0-8 (ng-hr/ml)	330	626	1040	1316	C, D > A D > B
AUCinf (ng-hr/ml)	334	642	1056	1380	C, D > A D > B
Cmax (ng/ml)	328	832	1126	1086	C, D > A
Tmax (hour)	0.49	0.63	0.95	1.26	D > A
Ke (1/hour)	0.683	0.482	0.368	0.452	A > C
T½ (hour)	1.19	1.87	2.22	1.64	C > A
Ln-Transformed:					
AUC 0-t (ng-hr/ml)	293	540	1022	1092	C, D > B > A
AUC 0-8 (ng-hr/ml)	316	595	1029	1166	C, D > B > A
AUCinf (ng-hr/ml)	319	609	1045	1208	C, D > B > A
Cmax (ng/ml)	302	749	1006	902	D, C, B > A

1. Geometric means for ln-transformed data.

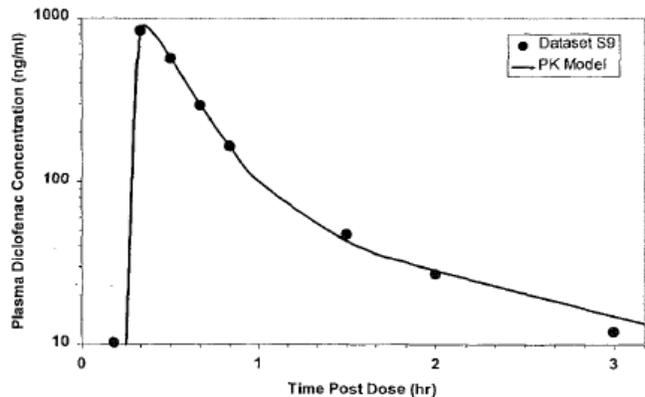
2. Results of the statistical evaluation by ANOVA ($\alpha=0.05$) for the hypothesis of equal treatment effects. When significance was detected ($p<0.05$), pair-wise comparisons were performed to determine if the significance could be attributed to differences between any two treatment means. C, D > A, B indicates that the 50 mg capsule and Cataflam® means were both statistically significantly different from the 12.5 mg and 25 mg means. None indicates that no difference was detected between treatment means ($p>0.05$).

Figure 2: Mean Plasma Concentrations of Diclofenac on Day 4 During Oral Administration of DPSGC 25 mg and 50 mg, ProSORB-D 12.5 mg, and Cataflam 50 mg Every 8 Hours for 8 Days to Bunionectomy Patients



A two-compartment model with first order absorption was fitted to the PK data for the DPSGC formulations. The PK for Cataflam dose were not included in the analysis because of the high variability in the data. Figure 3 shows that the PK model adequately describes the data for a typical patient in the study.

Figure 3: Graphical Output Showing Regressed Model (line) and Observed Plasma Concentrations (circles) Over Time for a Subject From day 4.



Graphs of the mean change from baseline in pain intensity versus the mean plasma diclofenac concentration at the same time demonstrated a counterclockwise hysteresis (Figure 4), consistent with a peripheral effect compartment. A modified E-max model with a component related to the baseline pain was fitted to the data for the pain relief and the concentration of diclofenac in the peripheral effect compartment. As shown in Figure 5, there was good agreement between the observed and model-predicted change from baseline in pain relief scores as a function of time. The results of the PK-PD analysis indicated that the PD appear to more closely match a relationship between relief and the peripheral concentration than between relief and plasma concentration which is in agreement with models previously utilized for analgesic. Sponsor acknowledges in the report that these results are not definitive, nor do they prove site-of- or mechanism of action and that the analysis was intended to give insight into the relationship of dose and effect. Given the different baseline pain on day 1 and day 4 (approximate average pain scores of 6 and 2, respectively), pain relief was represented with an absolute component and a component related to baseline pain (pain measured just prior to dose administration). There was also an arbitrary assumption that placebo effect is proportional to baseline pain. This model represented the pain relief data fairly well within the power of the model. As acknowledged by the sponsor, whether the addition of additional model structure improves model fidelity to data sufficiently justify additional model structure and parameters remains to be explored.

Figure 4: Relationship Between the Mean Change from Baseline in Pain Relief Score and the Mean Plasma Concentrations of Diclofenac on Day 4 During Oral Administration of DPSGC 25 mg, ProSorb-D 12.5 mg, and Cataflam 50 mg Every 8 Hours for 8 Days to Bunionectomy Patients

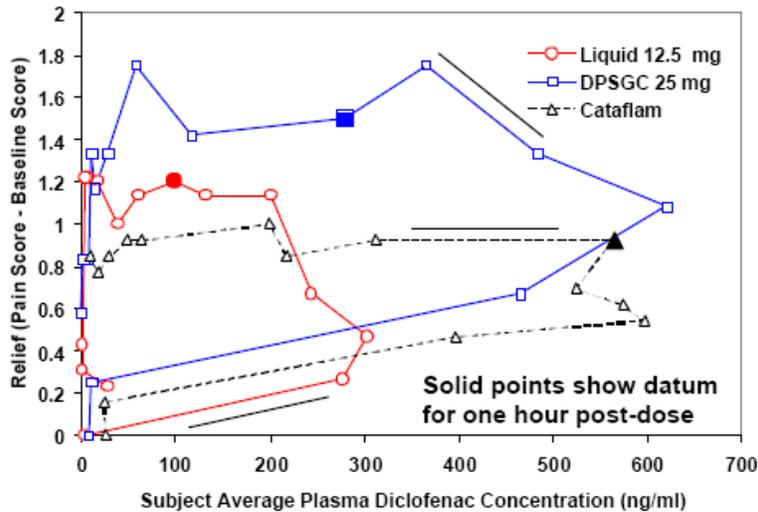
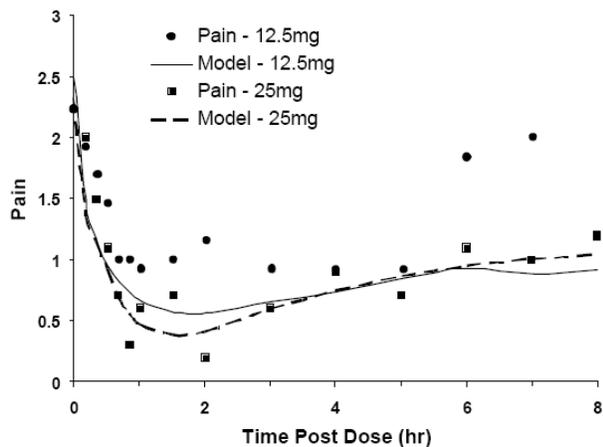


Figure 5: Observed and Model-Predicted Mean Change from Baseline in Pain Relief Scores During Oral Administration of DPSGC 25 mg and ProSorb-D 12.5 mg Every 8 Hours for 8 Days to Bunionectomy Patients



2.2.2 What is known about the pharmacokinetics of Zipsor™ Soft Gelatin Capsules?

Study OA170 examined the dose proportionality of 25 and 50 mg DPSGC and compared the rate and extent of absorption of diclofenac at these doses with that of Cataflam 50 mg in 54 healthy volunteers. The results from this study (Table 2, Figure 6) demonstrated dose proportionality for the two doses of DPSGC and showed that after administration of a 50 mg dose of Cataflam, the mean C_{max} was comparable to that of the 25 mg dose of DPSGC (1125 ng/ml for DPSGC versus 1169 ng/ml for Cataflam) although T_{max} was ~2-fold longer, and the mean AUC_{0-∞} was comparable to that of 50 mg dose of DPSGC (1232 ng.hr/ml for DPSGC versus 1144 ng.hr/ml

for Cataflam). This indicates that the rate of absorption is greater from DPSGC than from Cataflam although the extent of absorption is comparable. The mean $t_{1/2}$ was comparable for all treatments and ranged from 1.4 to 1.8 h.

Table 2. Mean (SD) of diclofenac PK following administration of Treatments A, B and C[#]

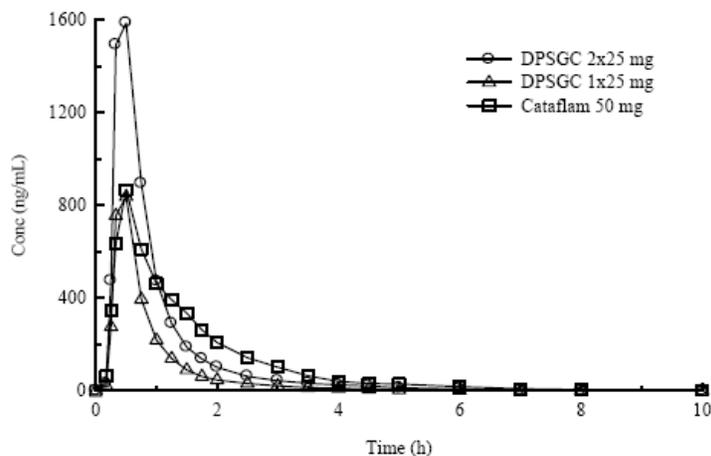
PK Parameters	Treatment A	Treatment B	Treatment C
C_{max} (ng/ml)	2035 (725)	1125 (486)	1169 (528)
AUC_{0-t} (ng.hr/ml)	1197 (300)	579 (168)	1133 (297)
$AUC_{0-\infty}$ (ng.hr/ml)	1232 (296)	603 (163)	1144 (282)
T_{max} (h)	0.48 (0.20)	0.45 (0.13)	0.93 (0.85)
$T_{1/2}$ (h)	1.84 (1.25)	1.35 (0.80)	1.45 (0.74)

[#]Treatment A: Diclofenac Potassium Soft gelatin Capsule, 2 x 25 mg

[#]Treatment B: Diclofenac Potassium Soft gelatin Capsule, 1 x 25 mg

[#]Treatment C: Cataflam[®] Tablet 1 x 50 mg

Figure 6: Mean Plasma Concentrations of Diclofenac After Oral Administration of DPSGC 1x25 mg and 2x25 mg and Cataflam 50 mg to Healthy Volunteers Under Fasted Conditions



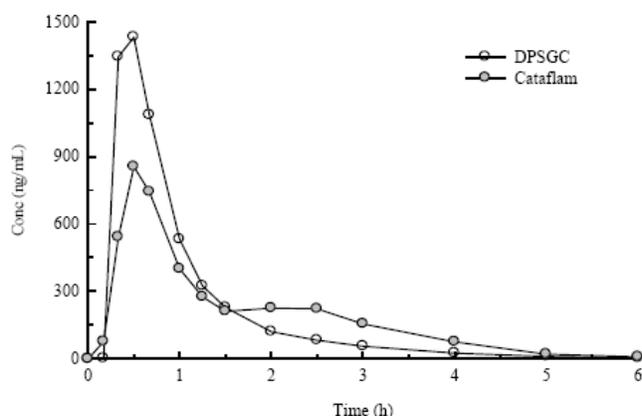
Study AAI-US-142 compared the pharmacokinetics of diclofenac after single 50 mg doses of DPSGC and Cataflam in 21 healthy volunteers. The results from the study indicated the rate of absorption diclofenac from DPSGC is about 80% greater that from Cataflam tablets but the extent of absorption of diclofenac from DPSGC was equivalent to that from Cataflam (Table 3, Figure 7). The T_{max} of diclofenac from DPSGC is 0.6 h compared to 1.28 h for Cataflam tablet. The $t_{1/2}$ for diclofenac was about 1 h for the two formulations.

Table 3. Summary of the statistical comparison of diclofenac PK following administration of test (DPSGC) and reference (Cataflam tablets) treatments.

PK Parameters ^a	Reference: 50 mg Cataflam tablet	Test: 50 mg DPSGC	Test : Reference ratio	
			Point estimate	90% Confidence Intervals
C _{max} (ng/mL)	992	1773	1.787	1.344 – 2.376
AUC _{0-t} (ng.hr/mL)	1078	1161	1.077	0.999 – 1.211
AUC _{0-∞} (ng.hr/mL)	1087	1195	1.099	0.982 – 1.181

^a Least-Squares (geometric) mean

Figure 7: Mean Plasma Concentrations of Diclofenac After Oral Administration of DPSGC 1×50 mg and Cataflam 1×50 mg to Healthy Volunteers Under Fasted Conditions



2.3 General Biopharmaceutics

2.3.1 What is the composition of the to-be-marketed formulation compared to other formulations used for the clinical studies?

For development and clinical evaluation, 3 DPSGC formulations were prepared: 1000 series (batches PDS1025, PDS1027, and PDS1029), an intermediate 1200 series (PDS1214, PDS1216, and PDS1218), and the to-be-marketed 1300/1400 series (PDS1304, PDS1436, and PDS1457). The compositions of these formulations are given in Table 4 below. All the batches of DPSGC 25 mg used for the Phase 1, 2 and 3 studies were manufactured at (b) (4) commercial scale (b) (4)

(b) (4)

Table 4: Compositions of the formulations

Ingredient	New Formulation	Intermediate Formulation	Old Formulation
	New Process	New Process	Old Process
	PDS-1304, PDS-1436, PDS-1457 %w/w	PDS-1214, PDS-1216 and PDS-1218 %w/w	PDS-1025, PDS-1027 and PDS-1029 %w/w
Diclofenac Potassium	6.3 (a)	6.3 (e)	6.3 (e)
PEG 400 NF	(b) (4)		
Glycerin	(b) (4)		
Sorbitol Solution	(b) (4)		
Povidone USP	(b) (4)		
Polysorbate 80	(b) (4)		
(b) HCl	(b) (4)		
(4) HCl	(b) (4)		
(b) (4)	(b) (4)		
Capsule Size	(b) (4)		

a: 6.25% rounded and recorded as 6.3%

b: (b) (4)

c:

d:

e:

f:

2.3.1.1 Can the request for a waiver of *in vivo* bioequivalence study between the 1200 formulation series and the 1300/1400 formulation series be granted?

The changes in the formulation and capsule size between the 1000 series and the 1200 series were shown not to affect bioavailability, as evidenced by bioequivalence between PDS-1027 and PDS-1218 (Study OA171, Section 2.3.3 below). The change (b) (4)

is not expected to

affect the BA of DPSGC based on the observation of the lack of effect of the change (b) (4) in the intermediate 1200 series as demonstrated by the results of BE study OA171 (Section 2.3.3 below). The Sponsor has requested for a waiver of *in vivo* BE study between the 1300/1400 series formulation (to-be-marketed) and the 1200 series formulation and in the Division’s 74-day Letter, dated December 4, 2007, the Agency requested from the Sponsor “full dissolution profile (and corresponding f_2 data) comparison between the clinical formulation (series 1200) and to-be-marketed formulation (series 1300/1400).” The Sponsor has provided dissolution profile data generated at the time of batch release for the registration batches (PDS1304, PDS1436, PDS1457) and compared these with the dissolution data from batch PDS1218 (1200 series) used for the BE Study OA171.

Dissolution Profile Comparison by Sublot:

Dissolution profiles from six capsules were obtained at 10, 20, 30 and 45 minutes. The Sponsor stated that the use of 12 units was not possible for comparison of PDS1218 to the 1300/1400 series because such data was not available as PDS1218 was manufactured in (b) (4)(b) (4)

Table 5 shows the summary of the dissolution data for the sublots. The f_2 comparison shows that sublots PDS1436A, PDS1436B, PDS1457, PDS1457Y, PDS1457Z failed to meet the f_2 criterion of greater than 50 (Table 6) but all the sublots had (b) (4) % dissolved at 30 minutes (Table 5).

Table 5: Summary Dissolution Profile Statistics by Sublot

(b) (4)

Table 6: Comparison of PDS1218 to Individual Sublots in the 1300/1400 Series.

Sublot PDS	1304	1436	1436A	1436B	1436C	1457	1457X	1457Y	1457Z	1458
f_2 comparison to PDS1218	(b) (4)									

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Table 10: Registration Stability Batches DGSGC

Batch Number	PDS1304	PDS1436	PDS1457
Batch Size	(b) (4)		
Capsule Strength	25 mg	25 mg	25 mg
Use	--	--	--
Phase III Bunionectomy Studies (XP21L-301 and XP21L-302)	X	--	--
Stability	X	X	X

Conclusions

Dissolution data from the 1300/1400 series have been compared to batch PDS1218. Profiles of capsules were obtained at 10, 20, 30 and 45 minutes.

(b) (4)

(b) (4)

Therefore it is reasonable to conclude that the two series have similar dissolution profiles.

Additionally, batch 1304 (series 1300) was used for Phase III Bunionectomy Studies XP21L-301 and XP21L-302.

All these information support the recommendation to grant the request for a bioequivalence waiver for the to-be-marketed formulation.

2.3.3 What is the comparative bioavailability of the to-be-marketed formulation to the formulation(s) used in the Phase 2 and 3 pivotal trials?

Study OA171 compared the bioavailability of the initial DPSGC 25 mg formulation used in several of the clinical trials (DPSGC old process or the 1000 formulation series) to that of the intermediate DPSGC 25 mg formulation used for the pivotal bunionectomy studies (DPSGC new process or the 1200 formulation series) and to a liquid formulation of 25 mg diclofenac potassium in 24 healthy male and female volunteers. The results from this study showed that Cmax was reached earlier for the solution and the mean Tmax was approximately 50% of that of either DPSGC formulation but all three formulations were bioequivalent with respect to rate and extent of absorption (Tables 11 & 12, Figure 10).

Table 11. Mean (SD) of diclofenac PK following administration of Treatments A, B and C[#]

PK Parameters	Treatment A	Treatment B	Treatment C
C _{max} (ng/mL)	1087 (419)	958 (274)	1023 (400)
AUC _{0-∞} (ng.hr/mL)	597 (151)	606 (144)	607 (155)
T _{max} (h)	0.47 (0.17)	0.25 (0.09)	0.49 (0.19)
T _{1/2} (h)	1.07 (0.29)	1.07 (0.38)	1.45 (0.74)

[#]Treatment A: Diclofenac potassium, 25 mg soft gelatin capsule, (new process)

[#]Treatment B: Diclofenac potassium, 25 mg/ml liquid

[#]Treatment C: Diclofenac potassium, 25 mg soft gelatin capsule, (old process)

Table 12: Summary of the statistical comparison of diclofenac PK following administration of Treatments A, B and C

Parameter	new vs. old		new vs. liquid		old vs. liquid	
	Ratio	90% CI	Ratio	90% CI	Ratio	90% CI
AUC _{0-t}	99.03%	(94%,104%)	98.23%	(93%,103%)	99.19%	(94%,104%)
AUC _{0-∞}	98.83%	(94%,103%)	97.88%	(93%,103%)	99.04%	(95%,104%)
C _{max}	107.43%	(94%,123%)	108.19%	(95%,124%)	100.71%	(88%,115%)
t _{max}	-0.02h ^x	(-0.08h,+0.04h) ^x	+0.23h ^x	(+0.17h,+0.29h) ^x	+0.25h ^x	(+0.19h,+0.31h) ^x

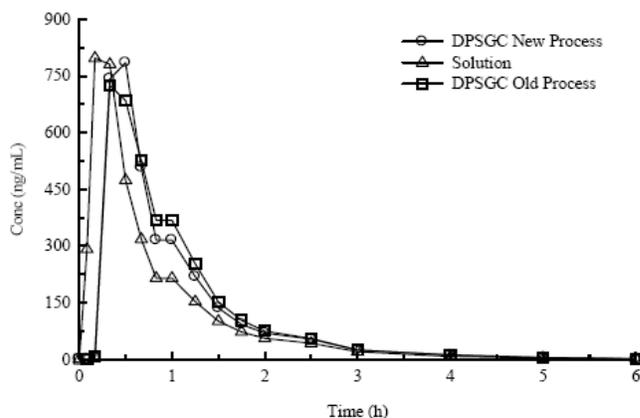
^x : difference CI : confidence interval

[#]Treatment A: Diclofenac potassium, 25 mg soft gelatin capsule, (new process)

[#]Treatment B: Diclofenac potassium, 25 mg/ml liquid

[#]Treatment C: Diclofenac potassium, 25 mg soft gelatin capsule, (old process)

Figure 10: Mean Plasma Concentrations of Diclofenac After Oral Administration of 25 mg of Diclofenac by the New and Old Process and as an Oral Solution to Healthy Volunteers Under Fasted Conditions



2.3.4 What is the effect of food on the bioavailability of diclofenac potassium from Zipsor and what dosing recommendation should be made regarding administration in relation to meals?

Study AAI-US-119 examined the effect of food on the absorption of diclofenac from 25 mg and 50 mg DPSGC in 47 healthy volunteers, (24 at 25 mg and 23 at 50 mg). Each subject received a dose of DPSGC after a 10-hour fast or after a standard high-fat breakfast according to a two-way crossover design. Co-administration of 25 mg or 50 mg DPSGC with high fat meal resulted in a decrease in C_{max} by approximately 47% and 53% respectively and T_{max} was increased ~2-fold, but no change in AUC (Tables 13-15, Figure 11). The data indicate that a high-fat meal decreases the rate but not the extent of absorption of diclofenac from DPSGC. Under both fed and fasted conditions, dose proportional bioavailability was observed between the 25 mg and 50 mg doses.

The labeling for Cataflam tablet states that “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 peak plasma levels of approximately 30%”. But there is no restriction on dosing with meal. Zipsor is available in only one strength (25 mg) and no recommendation will be made regarding administration in relation to meal since the extent of absorption is not affect by food as observed for Cataflam tablet.

Table 13. Mean (SD) diclofenac PK parameters following oral administration of DPSGC 1×25 mg and 1×50 mg to healthy volunteers under fed and fasted conditions

Treatment	C _{max} (ng/mL)	AUC _{0-t} (ng*hr/mL)	AUC _{0-inf} (ng*hr/mL)	T _{max} (hr)	T _{1/2} (hr)
25 mg (N=24)					
Fasted	1156 (482)	691 (195)	706 (199)	0.49 (0.16)	1.04 (0.42)
Fed	686 (411)	680 (184)	713 (182)	1.02 (0.55)	1.11 (0.42)
50 mg (N=23)					
Fasted	2365 (1034)	1521 (377)	1549 (384)	0.51 (0.19)	1.10 (0.25)
Fed	1154 (592)	1416 (366)	1457(373)	1.28 (0.71)	1.07 (0.25)

Table 14. Summary of the statistical comparison of diclofenac PK following oral administration of DPSGC 1×25 mg to healthy volunteers under fed and fasted conditions

PK Parameters ^a	Fed	Fasted	Fed : Fasted ratio	
			Point estimate	90% Confidence Intervals
C _{max} (ng/mL)	562	1069	0.526	0.41 – 0.68
AUC _{0-t} (ng.hr/mL)	656	665	0.987	0.92– 1.05
AUC _{0-∞} (ng.hr/mL)	700	667	1.035	0.99 – 1.08

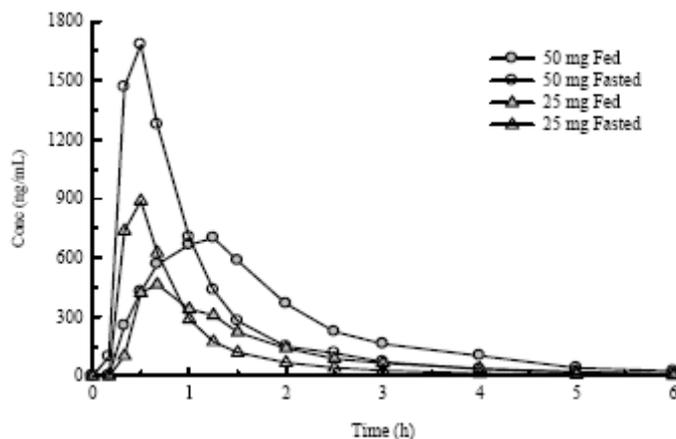
^aLeast-Squares (geometric) mean

Table 15. Summary of the statistical comparison of diclofenac PK following oral administration of DPSGC 1×50 mg to healthy volunteers under fed and fasted conditions

PK Parameters ^a	Fed	Fasted	Fed : Fasted ratio	
			Point estimate	90% Confidence Intervals
C _{max} (ng/mL)	1015	2155	0.471	0.39 – 0.57
AUC _{0-t} (ng.hr/mL)	1375	1479	0.929	0.89 – 0.98
AUC _{0-∞} (ng.hr/mL)	1415	1506	0.940	0.90 – 0.99

^aLeast-Squares (geometric) mean

Figure 11: Mean Plasma Concentrations of Diclofenac After Oral Administration of DPSGC 1×25 mg and 1×50 mg to Healthy Volunteers Under Fed and Fasted Conditions



2.4 Analytical Section

Were the analytical procedures used to determine drug concentrations in this NDA acceptable?

Yes. All bioanalytical assays fulfilled the regulatory criterion [FDA guidance for industry “Bioanalytical Method Validation (Final-May 2001)"] of not exceeding 15% (20% for the lowest QC samples) for precision and accuracy. Study samples were analyzed in runs containing calibrators and quality control samples, as recommended in the FDA guidance.

Table 16. Assay performance (in-study validation) for diclofenac



(b) (4)

3 DETAILED LABELING RECOMMENDATIONS

From Clinical Pharmacology perspective, the submitted label is acceptable besides the edits described below.

12.3 Pharmacokinetics

The pharmacokinetics of Zipsor was assessed in 24 healthy, normal volunteers who received 25 mg of Zipsor under fasting conditions. The mean pharmacokinetic parameters for Zipsor are shown in Table 2.

Table 2
Mean Pharmacokinetics of Zipsor

PK Parameter	Number of Subjects	Mean ± Standard Deviation
T _{max} (hr)	24	0.47 ± 0.17
Terminal Half-life (hr)	24	1.07 ± 0.29
C _{max} (ng/mL)	24	1087 ± 419
AUC(0-∞) (ng·h/mL)	24	597 ± 151

Absorption

Diclofenac is 100% absorbed after oral administration compared to IV administration as measured by urine recovery. However, due to first-pass metabolism, only about 50% of the absorbed dose is systemically available. After repeated oral administration, no accumulation of diclofenac in plasma occurred.

The extent of diclofenac absorption is not significantly affected when Zipsor is taken with food. However, the rate of absorption is reduced by food, as indicated by a two-fold increase in T_{max} and a 47% decrease in C_{max}.

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4.2. INDIVIDUAL STUDY REVIEW

Study AAI-US-142

Study Type: Single dose BA/BE study.

Title: An Open-Label, Randomized, Single Dose, Crossover Study in Healthy Volunteers to Investigate the Oral Bioavailability of Diclofenac Potassium Softgel Capsules and Cataflam[®] Tablets.

Clinical Investigator: Ralph Scallion, EE, MD, Medical Director, AAI Clinic, 6101 Quadrangle Dr, Chapel Hill, NC 27514.

Objectives: To characterize and compare the bioavailability of diclofenac from the investigational soft gelatin capsule 50 mg with that of the marketed Cataflam[®] Tablets 50 mg.

Study Design: This was an open-label, single dose, randomized, 2-way crossover study in 21 healthy subjects. Eligible subjects were randomized into one of two treatment groups shown below. There was a 7-day washout between the treatments.

- Treatment A (test): 50 mg Diclofenac Potassium Soft gelatin Capsule after an overnight fast (lot #PDS 1038)
- Treatment B (reference): 50 mg Diclofenac Potassium Tablet (Cataflam[®]) after an overnight fast (lot #CIH00481)

Blood sampling times: t = 0 (pre-dose), 10, 20, 30, 40, 60, 75, 90, 120, 150, 180, 240, 300 and 360 minutes post dose.

Criteria for Evaluation: PK parameters (AUC, C_{max}, T_{max}, Ke, t_{1/2}) of diclofenac.

Analytical Methodology

Assay Method: HPLC with UV detection

Calibration Range: 10-5000 ng/mL

LOQ: 10 ng/ml

Accuracy and Precision: Precision (CV%) ranged from 2.2 to 8.3%, and accuracy (bias %) ranged from 0.6 to 1.2%.

Data Analysis: PK parameters were calculated by non-compartmental or model-free methods. Descriptive statistics were computed for pertinent pharmacokinetic parameters for each treatment. An analysis of variance (ANOVA) was performed and the 90% confidence intervals were generated for the ratio of test/reference for C_{max}, AUC_{0-t} and AUC_{0-∞} (natural-log (ln) transformed prior to analysis).

Results:

Study Population: 24 subjects were enrolled but 21 subjects received both treatments and completed the study (15 males and 6 females). The mean age of the subjects was 29.0 years (range, 20-44 years).

Pharmacokinetics: Mean PK profiles of diclofenac following both treatments are shown in Figure 1. The PK results and statistical analysis for diclofenac are summarized in Tables 1 and 2.

Figure 1. Mean diclofenac plasma concentration-time profiles following administration of test (DPSGC) and reference (Cataflam tablets) treatments.

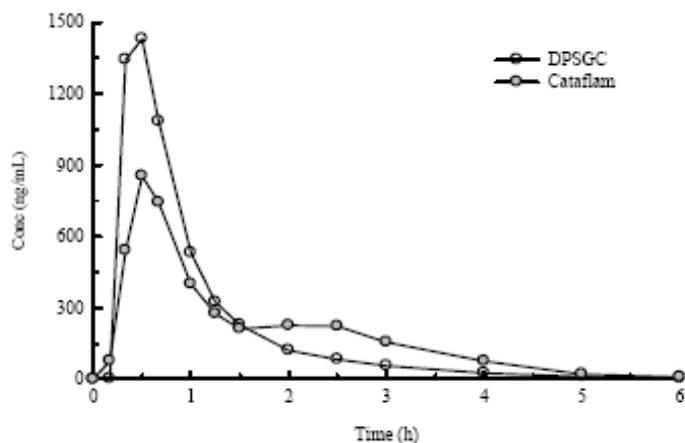


Table 1. Mean (SD) diclofenac PK parameters following administration of test (DPSGC) and reference (Cataflam tablets) treatments.

Pharmacokinetic Parameter (units)	Test	Reference
C_{max} (ng/mL)	1989 (921)	1168 (657)
t_{max} (h)	0.597 (0.467)	1.26 (0.991)
K_e (1/h) *	0.808 (0.269)	0.959 (0.309)
$t_{1/2}$ (h) *	0.965 (0.396)	0.853 (0.43)
AUC(0-t) (ng·h/mL)	1230 (459)	1131 (391)
AUC(0-∞) (ng·h/mL) *	1262 (473)	1175 (396)

* N=20

Table 2. Summary of the statistical comparison of diclofenac PK following administration of test (DPSGC) and reference (Cataflam tablets) treatments.

PK Parameters ^a	Reference: 50 mg Cataflam tablet	Test: 50 mg DPSGC	Test : Reference ratio	
			Point estimate	90% Confidence Intervals
C _{max} (ng/mL)	992	1773	1.787	1.344 – 2.376
AUC _{0-t} (ng.hr/mL)	1078	1161	1.077	0.999 – 1.211
AUC _{0-∞} (ng.hr/mL)	1087	1195	1.099	0.982 – 1.181

^a Least-Squares (geometric) mean

Comments: The mean C_{max} of DPSGC, 1,989 ± 921 ng/mL, was reached at an earlier time, 0.60 ± 0.47 h, compared to Cataflam, 1,168 ± 657 ng/mL at 1.26 ± 0.99 h and the 90% confidence interval for the geometric mean ratio fell outside the 0.80 to 1.25 equivalence window (Tables 1 & 2), indicating a more rapid absorption from DPSGC. The C_{max} of diclofenac from DPSGC is about 80% greater than that from Cataflam tablet. However, the 90% confidence intervals for the geometric mean ratios for AUC(0-t) and AUC(inf) of DPSGC and Cataflam tablet were within the 0.80 to 1.25 equivalence window, demonstrating that the extent of absorption of diclofenac from DPSGC was equivalent to that from Cataflam tablet.

Conclusions:

- The rate of absorption of diclofenac from DPSGC is about 80% greater than that from Cataflam tablet
- The t_{max} of diclofenac from DPSGC is about 50% lower than that from Cataflam tablet
- The extent of absorption of diclofenac from DPSGC was equivalent to that from Cataflam tablet

Study AAI-US-119

Study Type: Single dose food effect study.

Title: An Open-Label, Randomized, Single Dose, Crossover Study in Healthy Volunteers to Investigate the Oral Bioavailability of Two Different Strengths of Diclofenac Potassium Softgel Capsules.

Clinical Investigator: Ralph Scallion, EE, MD, Medical Director, AAI Clinic, 6101 Quadrangle Dr, Chapel Hill, NC 27514.

Objectives: To characterize and compare the bioavailability of diclofenac under fed and fasted conditions from two different strengths, 25 and 50 mg, of an investigational soft gelatin capsule.

Study Design: This was an open-label, single dose, randomized, 2-way crossover study in 47 healthy subjects. Eligible subjects were placed into two groups of 23 subjects for the 50 mg capsule and 24 subjects for the 25 mg capsule and then randomized into one of two treatment groups shown below. There was a 7-day washout between treatments.

- Treatment A: 1 Diclofenac Potassium Soft gelatin Capsule, 25 mg (lot #02252A) or 50 mg (lot #02253A), given after consumption of a high-fat breakfast.
- Treatment B: 1 Diclofenac Potassium Soft gelatin Capsule, 25 mg (lot #02252A) or 50 mg (lot #02253A) given after an overnight fast.

Blood sampling times: t = 0 (pre-dose), 10, 20, 30, 40, 60, 75, 90, 120, 150, 180, 240, 300 and 360 minutes post dose.

Criteria for Evaluation: PK parameters (AUC, C_{max}, T_{max}, t_{1/2}) of diclofenac.

Analytical Methodology

Assay Method: HPLC with UV detection

Calibration Range: 10-5000 ng/mL

LOQ: 10 ng/ml

Accuracy and Precision: Precision (CV%) ranged from 2.6 to 4.8%, and accuracy (bias %) ranged from 0.2 to 1.3%.

Data Analysis: PK parameters were calculated by non-compartmental or model-free methods. Descriptive statistics were computed for pertinent pharmacokinetic parameters for each treatment. An analysis of variance (ANOVA) was performed and the 90% confidence intervals were generated for the ratio of fed/fasted for C_{max}, AUC_{0-t} and AUC_{0-∞}, C_{max} and AUC_{0-∞} were natural-log (ln) transformed prior to analysis.

Results:

Study Population: 47 subjects were enrolled in the trial and all 47 subjects received their assigned doses and completed the study (38 males and 9 females). The mean age of the subjects was 28.6 years (range, 19-44 years).

Pharmacokinetics: Mean PK profiles of diclofenac following both treatments are shown in Figures 1 and 2. The PK results and statistical analysis for diclofenac are summarized in Tables 1 and 2.

Figure 1. Mean Plasma Concentrations of Diclofenac After Oral Administration of DPSGC 1×25 mg to Healthy Volunteers Under Fed and Fasted Condition.

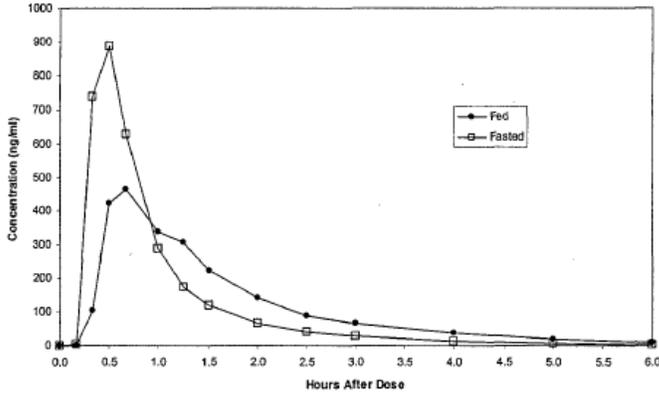


Figure 2. Mean Plasma Concentrations of Diclofenac After Oral Administration of DPSGC 1×50 mg to Healthy Volunteers Under Fed and Fasted Condition

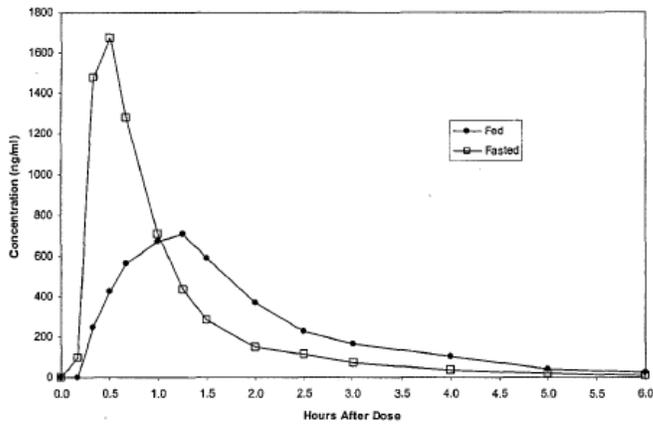


Table 1. Mean (SD) diclofenac PK parameters following oral administration of DPSGC 1×25 mg and 1×50 mg to healthy volunteers under fed and fasted conditions

Treatment	C _{max} (ng/mL)	AUC _{0-t} (ng*hr/mL)	AUC _{0-inf} (ng*hr/mL)	T _{max} (hr)	T _{1/2} (hr)
25 mg (N=24)					
Fasted	1156 (482)	691 (195)	706 (199)	0.49 (0.16)	1.04 (0.42)
Fed	686 (411)	680 (184)	713 (182)	1.02 (0.55)	1.11 (0.42)
50 mg (N=23)					
Fasted	2365 (1034)	1521 (377)	1549 (384)	0.51 (0.19)	1.10 (0.25)
Fed	1154 (592)	1416 (366)	1457(373)	1.28 (0.71)	1.07 (0.25)

Table 2. Summary of the statistical comparison of diclofenac PK following oral administration of DPSGC 1×25 mg to healthy volunteers under fed and fasted conditions

PK Parameters ^a	Fed	Fasted	Fed : Fasted ratio	
			Point estimate	90% Confidence Intervals
C _{max} (ng/mL)	562	1069	0.526	0.41 – 0.68
AUC _{0-t} (ng.hr/mL)	656	665	0.987	0.92– 1.05
AUC _{0-∞} (ng.hr/mL)	700	667	1.035	0.99 – 1.08

^aLeast-Squares (geometric) mean

Table 3. Summary of the statistical comparison of diclofenac PK following oral administration of DPSGC 1×50 mg to healthy volunteers under fed and fasted conditions

PK Parameters ^a	Fed	Fasted	Fed : Fasted ratio	
			Point estimate	90% Confidence Intervals
C _{max} (ng/mL)	1015	2155	0.471	0.39 – 0.57
AUC _{0-t} (ng.hr/mL)	1375	1479	0.929	0.89 – 0.98
AUC _{0-∞} (ng.hr/mL)	1415	1506	0.940	0.90 – 0.99

^aLeast-Squares (geometric) mean

Comments: Following administration of 25 mg or 50 mg DPSGC under fed conditions, C_{max} of diclofenac was decreased by 47% and 53% respectively and T_{max} was increased ~2-fold compared to under fasted conditions (Tables 1 and 2). Mean values for AUC(inf) were essentially the same under fed and fasted conditions. The data indicate that a high-fat meal decreases the rate but not the extent of absorption of diclofenac from DPSGC. Under both fed and fasted conditions, dose proportional bioavailability was observed between the 25 mg and 50 mg doses of DPSGC.

The labeling for Cataflam tablet states that “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 peak plasma levels of approximately 30%”. But there is no restriction on dosing with meal. Zipsor is available in only one strength (25 mg) and no recommendation will be made regarding administration in relation to meal since the extent of absorption is not affect by food as observed for Cataflam tablet.

Conclusions:

- The rate of absorption of diclofenac from DPSGC is about 50% lower following a high-fat meal compared to fasted condition.
- The t_{max} of diclofenac from DPSGC is about 50% lower following a high-fat

- meal compared to fasted condition.
- The extent of absorption of diclofenac from DPSGC is not affected following a high-fat meal compared to fasted condition.
 - Dose proportional bioavailability was observed between the 25 mg and 50 mg doses of DPSGC under fed and fasted conditions.
 - Zipsor is available in only one strength (25 mg) and no recommendation will be made regarding administration in relation to meal since the extent of absorption is not affected by food as observed for Cataflam tablet.

Study OA170

Study Type: Single dose BA/BE study.

Title: A comparative bioavailability study of two doses of Diclofenac Potassium Soft Gelatin Capsules (DPSGC) given as a single 25 mg or 50 mg oral dose with Cataflam[®] 50 mg tablet in healthy subjects.

Clinical Investigator: Michael Lissy, Physician, AAI Deutschland GmbH & Co KG, Wegenerstraße 13, 89231 Neu-Ulm, Germany.

Objectives: To compare the extent of absorption of the investigational capsule with that of the Cataflam[®] tablet when each was given at an equivalent 50 mg dose, and to compare the peak concentration of the investigational capsule given as a 25 mg dose to that of the 50 mg Cataflam[®] tablet.

Study Design : This was an open-label, single dose, randomized, 3-way crossover study in 54 healthy subjects treated in two consecutive subgroups of 27 subjects each. There was a 7-day washout between treatments. Each subject received the following treatments after an over night fast:

- Treatment A: Test Drug: Diclofenac Potassium Soft gelatin Capsule, 2 x 25 mg (batch #04117A)
- Treatment B: Test Drug: Diclofenac Potassium Soft gelatin Capsule, 1 x 25 mg (batch #04117B)
- Treatment C: Reference Drug: Cataflam[®] Tablet 1 x 50 mg (batch #C2002111)

Blood sampling times: t = 0 (pre-dose), 10, 15, 20, 30, 45, 60 minutes and 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, and 10 hours post dose.

Criteria for Evaluation: PK parameters (AUC, C_{max}, T_{max}, t_{1/2}) of diclofenac.

Analytical Methodology

Assay Method: HPLC with UV detection

Calibration Range: 10-5000 ng/mL

LOQ: 10 ng/ml

Accuracy and Precision: Precision (CV%) ranged from 2.3 to 8.4%, and accuracy (bias %) ranged from -4.1 to -1.3%.

Data Analysis: PK parameters were calculated by non-compartmental or model-free methods. Descriptive statistics were computed for pertinent pharmacokinetic parameters for each treatment. An analysis of variance (ANOVA) was performed and the 90% confidence intervals were generated for the ratio of test/reference for C_{max}, AUC_{0-t} and AUC_{0-∞} (natural-log (ln) transformed prior to analysis).

Results:

Study Population: 54 subjects were enrolled in the trial and all 54 subjects received their assigned doses and completed the study (29 males and 25 females). The mean age of the subjects was 30.8 years (range, 18-50 years).

Pharmacokinetics: Mean PK profiles of diclofenac following both treatments are shown in Figure 1. The PK results and statistical analysis for diclofenac are summarized in Tables 1-4.

Figure 1: Mean Plasma Concentrations of Diclofenac After Oral Administration of DPSGC 1×25 mg and 2×25 mg and Cataflam 50 mg to Healthy Volunteers Under Fasted Conditions

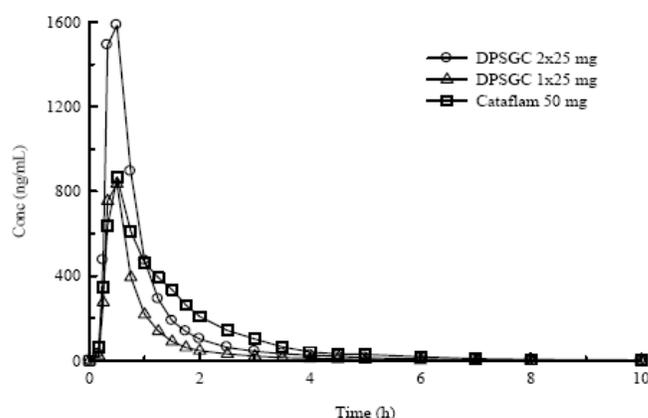


Table 1. Mean (SD) of diclofenac PK following administration of Treatments A, B and C[#]

PK Parameters	Treatment A	Treatment B	Treatment C
C _{max} (ng/mL)	2035 (725)	1125 (486)	1169 (528)
AUC _{0-t} (ng.hr/mL)	1197 (300)	579 (168)	1133 (297)
AUC _{0-∞} (ng.hr/mL)	1232 (296)	603 (163)	1144 (282)
T _{max} (h)	0.48 (0.20)	0.45 (0.13)	0.93 (0.85)
T _{1/2} (h)	1.84 (1.25)	1.35 (0.80)	1.45 (0.74)

[#]Treatment A: Diclofenac Potassium Soft gelatin Capsule, 2 x 25 mg

[#]Treatment B: Diclofenac Potassium Soft gelatin Capsule, 1 x 25 mg

[#]Treatment C: Cataflam[®] Tablet 1 x 50 mg

Table 2. Summary of the statistical comparison of diclofenac PK following administration of Treatments A and C

PK Parameters ^a	Treatment A	Treatment C	A/C	
			Point estimate	90% Confidence Intervals
C _{max} (ng/mL)	1882	1060	1.77	1.60 – 1.97
AUC _{0-t} (ng.hr/mL)	1161	1096	1.06	1.02 – 1.10
AUC _{0-∞} (ng.hr/mL)	1197	1111	1.06	1.02 – 1.10

^a Least-Squares (geometric) mean

Table 3. Summary of the statistical comparison of diclofenac PK following administration of Treatments B and C

PK Parameters ^a	Treatment B	Treatment C	B/C	
			Point estimate	90% Confidence Intervals
C _{max} (ng/mL)	1025	1060	0.97	0.87 – 1.07
AUC _{0-t} (ng.hr/mL)	557	1096	0.51	0.48 – 0.53
AUC _{0-∞} (ng.hr/mL)	582	1111	0.52	0.50 – 0.54

^a Least-Squares (geometric) mean

Table 4. Summary of the statistical comparison of diclofenac PK following administration of Treatments A and B.

PK Parameters ^a	Treatment A	Treatment B	A/B	
			Point estimate	90% Confidence Intervals
C _{max} (ng/mL)	1882	1025	1.84	1.65 – 2.04
AUC _{0-t} (ng.hr/mL)	1161	557	2.08	2.01 – 2.16
AUC _{0-∞} (ng.hr/mL)	1197	582	2.03	1.96 – 2.11

^a Least-Squares (geometric) mean

Comments: Mean plasma concentrations and mean values for C_{max} and AUC(inf) for the 2×25 mg dose of DPSGC were essentially twice those of the 1×25 mg dose with essentially the same T_{max}, demonstrating dose proportionality for the formulation. After administration of a 50 mg dose of Cataflam, the mean C_{max} was comparable to that of the 1×25 mg dose of DPSGC although T_{max} was ~2-fold longer, and the mean AUC(inf) was comparable to that of 2×25 mg dose of DPSGC. This indicates that the rate of absorption is greater from DPSGC than from Cataflam although the extent of absorption is comparable. The mean t_{1/2} was comparable for all treatments.

Conclusions:

- The t_{max} of diclofenac from DPSGC is about 50% lower than that from Cataflam[®] tablet
- After administration of a 50 mg dose of Cataflam, the mean C_{max} was comparable to that of the 1×25 mg dose of DPSGC although T_{max} was ~2-fold longer, and the mean AUC(inf) was comparable to that of 2×25 mg dose of DPSGC. This indicates that the rate of absorption is greater from DPSGC than from Cataflam although the extent of absorption is comparable. The mean t_{1/2} was comparable for all treatments.
- Dose proportional bioavailability was observed between the 25 mg and 50 mg doses of DPSGC under fasted conditions.

Study OA171

Study Type: Single dose BA/BE study.

Title: An Open-Label, Randomized, Single-Dose, Three-way, Cross-over, Comparative Bioavailability study in Healthy Volunteers with Three Different Diclofenac Potassium Formulations Dose in a Fasted State.

Clinical Investigator: Michael Lissy, Physician, AAI Deutschland GmbH & Co KG, Wegenerstraße 13, 89231 Neu-Ulm, Germany.

Objectives: To compare the pharmacokinetics of diclofenac potassium following administration of single 25 mg doses of a soft gelatin capsule (new process), diclofenac potassium liquid, and soft gelatin capsule (old process).

Study Design : This was an open-label, single dose, randomized, 3-way crossover study in 23 healthy subjects treated in three consecutive subgroups of 8 subjects each. There was a 3-day washout between treatments. Each subject received the following treatments after an over night fast:

- Treatment A: Test Drug: Diclofenac potassium, 25 mg soft gelatin capsule, (new process, batch #04117A)
- Treatment B: Reference Drug: Diclofenac potassium, 25 mg/ml liquid (batch #04117B)
- Treatment C: Reference Drug: Diclofenac potassium, 25 mg soft gelatin capsule, (old process, batch #04117A)

Blood sampling times: t = 0 (pre-dose), 5, 10, 20, 30, 40, 50 minutes and 1, 1.25, 1.5, 1.75, 2, 3, 4, , 5 and 6 hours post dose.

Criteria for Evaluation: PK parameters (AUC, C_{max}, T_{max}, t_{1/2}) of diclofenac.

Analytical Methodology

Assay Method: HPLC with UV detection

Calibration Range: 10-5000 ng/mL

LOQ: 10 ng/ml

Accuracy and Precision: Precision (CV%) ranged from 2.2 to 5.4%, and accuracy (bias %) ranged from -2.8 to -1.3% .

Data Analysis: PK parameters were calculated by non-compartmental or model-free methods. Descriptive statistics were computed for pertinent pharmacokinetic parameters for each treatment. An analysis of variance (ANOVA) was performed and the 90% confidence intervals were generated for the ratio of test/reference for C_{max}, AUC_{0-t} and AUC_{0-∞} (natural-log (ln) transformed prior to analysis).

Results:

Study Population: 24 subjects (15 males and 9 females) were enrolled in the trial and 23 subjects received their assigned doses and completed the study. The mean age of the subjects was 34.5 years (range, 19-47 years).

Pharmacokinetics: Mean PK profiles of diclofenac following both treatments are shown in Figure 1. The PK results and statistical analysis for diclofenac are summarized in Tables 1-3.

Figure 1: Mean Plasma Concentrations of Diclofenac After Oral Administration of 25 mg of Diclofenac by the New and Old Process and as an Oral Solution to Healthy Volunteers Under Fasted Conditions

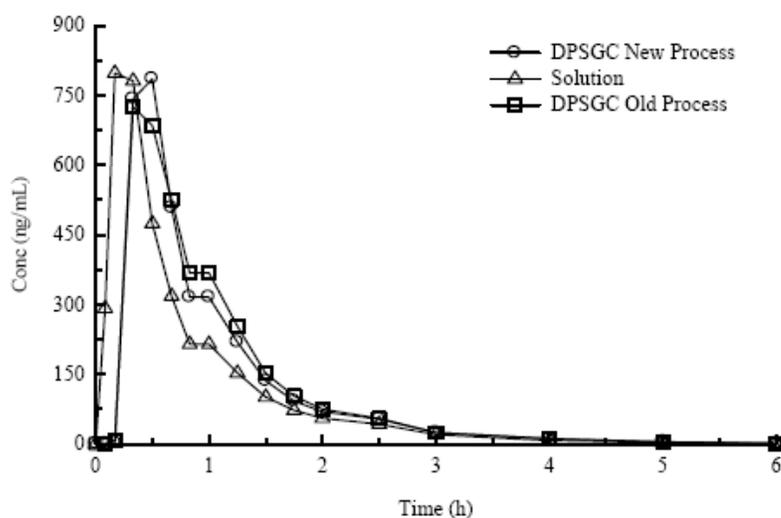


Table 1. Mean (SD) of diclofenac PK following administration of Treatments A, B and C[#]

PK Parameters	Treatment A	Treatment B	Treatment C
C _{max} (ng/mL)	1087 (419)	958 (274)	1023 (400)
AUC _{0-∞} (ng.hr/mL)	597 (151)	606 (144)	607 (155)
T _{max} (h)	0.47 (0.17)	0.25 (0.09)	0.49 (0.19)
T _{1/2} (h)	1.07 (0.29)	1.07 (0.38)	1.45 (0.74)

[#]Treatment A: Diclofenac potassium, 25 mg soft gelatin capsule, (new process)

[#]Treatment B: Diclofenac potassium, 25 mg/ml liquid

[#]Treatment C: Diclofenac potassium, 25 mg soft gelatin capsule, (old process)

Table 2: Geometric Mean (%CV) of diclofenac PK following administration of Treatments A, B and C

		A (new) (n=24)	B (liquid) (n=23)	C (old) (n=24)
Parameter	unit	geom mean geom %CV	geom mean geom %CV	geom mean geom %CV
AUC _{0-t}	h*ng/mL	561 (24%)	567 (25%)	566 (27%)
AUC _{0-∞}	h*ng/mL	581 (24%)	590 (24%)	588 (26%)
C _{max}	ng/mL	1019 (37%)	928 (25%)	949 (42%)
t _{max}	h	0.5 (0.33-1) ⁺	0.33 (0.17-0.33) ⁺	0.42 (0.33-1) ⁺
t _{1/2}	h	1.03 (28%)	1.01 (36%)	1.06 (28%)

⁺: median and range n=24 in all cases.

Table 3. Summary of the statistical comparison of diclofenac PK following administration of Treatments A, B and C

Parameter	new vs. old		new vs. liquid		old vs. liquid	
	Ratio	90% CI	Ratio	90% CI	Ratio	90% CI
AUC _{0-t}	99.03%	(94%,104%)	98.23%	(93%,103%)	99.19%	(94%,104%)
AUC _{0-∞}	98.83%	(94%,103%)	97.88%	(93%,103%)	99.04%	(95%,104%)
C _{max}	107.43%	(94%,123%)	108.19%	(95%,124%)	100.71%	(88%,115%)
t _{max}	-0.02h ^x	(-0.08h,+0.04h) ^x	+0.23h ^x	(+0.17h,+0.29h) ^x	+0.25h ^x	(+0.19h,+0.31h) ^x

^x: difference CI: confidence interval

Comments: Although mean plasma concentrations reached a maximum earlier for the solution (Figure 1) and the mean value for T_{max} was approximately 50% of that of either DPSGC formulation (Table 1), all three formulations were bioequivalent with respect to C_{max}, AUC(0-t), and AUC(inf).

Conclusions:

- The T_{max} of diclofenac from diclofenac liquid formulation is about 50% lower than that DPSGC
- The three formulations were bioequivalent with respect to C_{max}, AUC(0-t), and AUC(inf).

Study CL-002000

Study Type: Single dose / Multiple Dose PK-PD study.

Title: A Randomized, Open-Label, Active Comparator, PK-PD Study of Diclofenac Potassium (Prosorb-D™ Formulations drug product as liquid and Soft Gelatin Capsules) in Patients Undergoing Bunionectomy Surgery.

Clinical Investigator: Douglas G Stoker, D.P.M, JBA Research, Recovery Center, 1045 East 3900 South, Suite 100, Salt Lake City, Utah 84124.

Primary Objectives: To evaluate the single dose PK-PD relationship of diclofenac (as diclofenac potassium and Cataflam®) plasma concentrations and effects on pain intensity following bunionectomy surgery (osteotomy and internal fixation).

Study Design : This was a randomized, open-label, 24 hour in-patient study of the PK and PD of diclofenac potassium given at 3 dose levels (12.5, 25, 50 mg every 8 hours) and Cataflam® tablets given at 50 mg every 8 hours in patients undergoing bunionectomy surgery. This phase was followed by an open-label, out-patient study for 7 additional days during which patients continued to take their medication (as randomized in the in-patient phase) every 8 hours and take rescue medication (Lortab® 5/500, 1-2 tablets every 4-6 hours) as necessary. During the out-patient treatment period, patients returned to the study unit on Day 4 where the morning dose of the study drug was administered and a second PK-PD assessment period was carried out with pain intensity scores and PK blood samples obtained in the post-dose period.

Patients were randomized into 1 of the following 4 treatment groups:

- Group A (13 patients): one 25 mg Diclofenac Potassium Soft Gelatin Capsule, (Lot Number PDS1027)
- Group B (14 patients): one 50 mg Diclofenac Potassium Soft Gelatin Capsule, (Lot Number PDS1038)
- Group C (14 patients): 1 ml Diclofenac Potassium liquid (12.5 mg/ml, Lot Number 03159A)
- Group D (12 patients): one 50 mg Cataflam® tablet, (Lot Number C2D 02111)

PK and PD sampling times: Pain scores and PK blood samples were obtained during the period following the initial dose of study drug on Day 1 and the morning dose on Day 4 at the following times: 0 (pre-dose), 10, 20, 30, 40, 50, 60 minutes and 1.5, 2, 3, 4, 5, 6, 7 and 8 hours post dose. Additional pain intensity scores were collected hourly if second dose was administered beyond 8 hours after initial dose on Day 1 and pre-dose pain intensity score was obtained prior to the second and third doses of study medication on Day 1. Patients who rescued prior to administration of the second dose on Day 1 recorded pain intensity score at the time of rescue but discontinued the remaining pain intensity assessments up until the pre-dose assessment for the second dose and the remaining PK blood samples were also discontinued.

During the out-patient phase on days 2 to 8, patients called into an Interactive Voice Response System (IVRS) to record the time of each treatment dose, time and amount of

rescue medication and their pain scores daily at 8 AM (± 1 hour), 12 Noon (± 1 hour), 6 PM (± 1 hour), 10 PM (± 1 hour) and at the time of each rescue. An additional PK sample was obtained prior to the second dose on Day 8.

PK Criteria for Evaluation: PK parameters (AUC , C_{max} , T_{max} , Ke , $t_{1/2}$) of diclofenac.

PD Criteria for Evaluation: Pain intensity scores utilizing the Patient 11-point Numerical Pain rating Scale (NPRS) compared to plasma concentrations.

Analytical Methodology

Assay Method: HPLC with UV detection

Calibration Range: 10-5000 ng/mL

LOQ: 10 ng/ml

Accuracy and Precision: Precision (CV%) ranged from 1.8 to 7.3%, and accuracy (bias %) ranged from -1.6 to 1.7% .

Data Analysis: PK parameters were calculated by non-compartmental using SAS. Descriptive statistics were computed for pertinent PK parameters for each treatment. Compartmental PK analysis was performed using Kinetica 4.2.0.034 ((b) (4))

PK-PD model was developed by relating pain relief to the peripheral compartment of the PK model using the following equation:

$$f_{Drug}(t) = \frac{E_{MAX}C_p}{EC50 + C_p}$$

$$f_{Placebo}(t) = P(e^{-\gamma_1 t} - e^{-\gamma_2 t}) + (P_{Pain} t)^{P_v}$$

where C_p = concentration of diclofenac in the peripheral PK compartment

The model equations give relief in absolute terms. Given the different baseline pain on Day 1 and Day 4 (approximate average pain scores of 6 and 2 respectively), a need for the model to reflect relief related to pain was recognized. Analysis showed that relief was best represented with both an absolute component, and a component related to baseline pain. Therefore, following modified equations were used:

$$f_{Drug}(t) = \left(\frac{E_{MAX}C_p}{EC50 + C_p} \right) (1 + k_1 P_{BL})$$

$$f_{Placebo}(t) = k_2 P_{BL} (e^{-\gamma_1 t} - e^{-\gamma_2 t}) + P_{BL} (k_3 t)^{P_v}$$

$$P_{Measured}(t) = P_{BL} - f_{Drug}(t) - f_{Placebo}(t)$$

Where P_{BL} is the baseline pain, which is the pain measured prior to dose administration.

The equations allow for a component of pain relief to be proportional to P_{BL} and also assume, arbitrarily, that placebo effect is proportional to P_{BL} .

Results:

Study Population: 53 patients (4 males and 49 females) were enrolled in the trial and all patients completed the study. The mean age of the subjects was 39.8 years (range, 18.8 to 71.7 years).

Non-compartmental Pharmacokinetics: Mean PK profiles of diclofenac following both treatments are shown in Figure 1. The PK results and statistical analysis for diclofenac are summarized in Table 1.

Figure 1: Logarithm of Mean Day 4 Diclofenac Plasma Concentrations following the 4 treatments

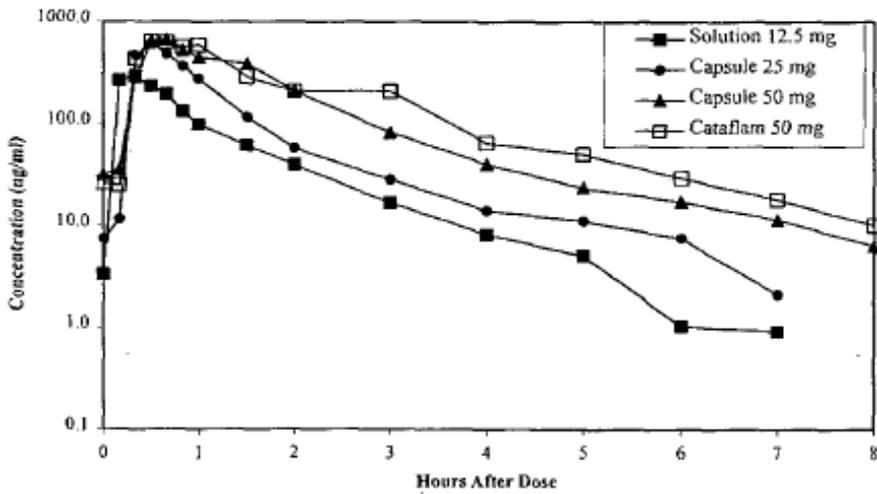


Table 1: Summary of Statistical Comparisons of Day 4 Diclofenac PK following the 4 treatments

Parameter	Means ¹				Statistical Significance ²
	12.5 mg (A)	25 mg (B)	50 mg (C)	Cataflam® (D)	
AUC 0-t (ng-hr/ml)	308	570	1033	1247	C, D > A D > B
AUC 0-8 (ng-hr/ml)	330	626	1040	1316	C, D > A D > B
AUCinf (ng-hr/ml)	334	642	1056	1380	C, D > A D > B
Cmax (ng/ml)	328	832	1126	1086	C, D > A
Tmax (hour)	0.49	0.63	0.95	1.26	D > A
Ke (1/hour)	0.683	0.482	0.368	0.452	A > C
T½ (hour)	1.19	1.87	2.22	1.64	C > A
Ln-Transformed:					
AUC 0-t (ng-hr/ml)	293	540	1022	1092	C, D > B > A
AUC 0-8 (ng-hr/ml)	316	595	1029	1166	C, D > B > A
AUCinf (ng-hr/ml)	319	609	1045	1208	C, D > B > A
Cmax (ng/ml)	302	749	1006	902	D, C, B > A

1. Geometric means for ln-transformed data.

2. Results of the statistical evaluation by ANOVA ($\alpha=0.05$) for the hypothesis of equal treatment effects. When significance was detected ($p<0.05$), pair-wise comparisons were performed to determine if the significance could be attributed to differences between any two treatment means. C, D > A, B indicates that the 50 mg capsule and Cataflam® means were both statistically significantly different from the 12.5 mg and 25 mg means. None indicates that no difference was detected between treatment means ($p>0.05$).

Compartmental Pharmacokinetics: A PK model with first-order absorption and two-compartment kinetics was used. The PK of Cataflam dose was not included in the analysis because they were highly variable (most likely due to non-uniform absorption) compared to DPSGC – Figures 2 and 3 show representative results from Day 1. Table 2 shows the median and upper- and lower-quartile for parameters identified for 12.5 and 25 mg DP dose on Day 4 and indicating a shorter lag time for the liquid formulation and 2 elimination phases needed for the two-compartment model. Figure 4 shows a representative result for a 25 mg DPSGC administered on Day 4 and indicating that the data were represented by the two-compartment model.

PK-PD analysis: A counter-clockwise hysteresis in the data relating pain to plasma concentrations (Figure 5) indicate that the model must consider the use of an effect compartment. The results of the PD modeling effort indicated a better relationship between relief and peripheral compartment concentration than between relief and plasma concentration, as demonstrated by the hysteresis curve (Figure 5) and the PD model (Figure 6). Table 3 shows the parameters resulting from regression of the model against the study data.

Figure 2: Plasma Concentrations for DPSGC 50 mg Patients (average is dashed line)

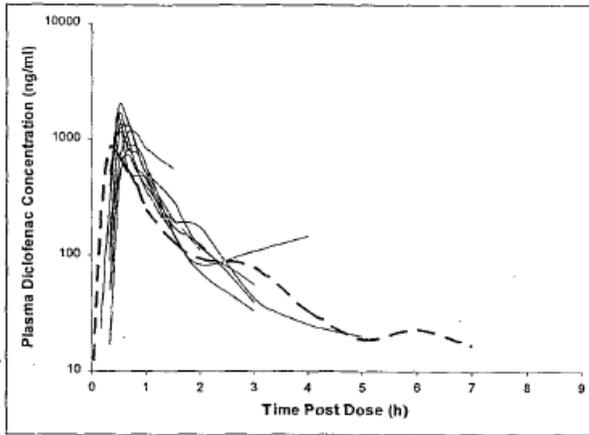


Figure 3: Plasma Concentrations for Cataflam 50 mg Patients (average is dashed line)

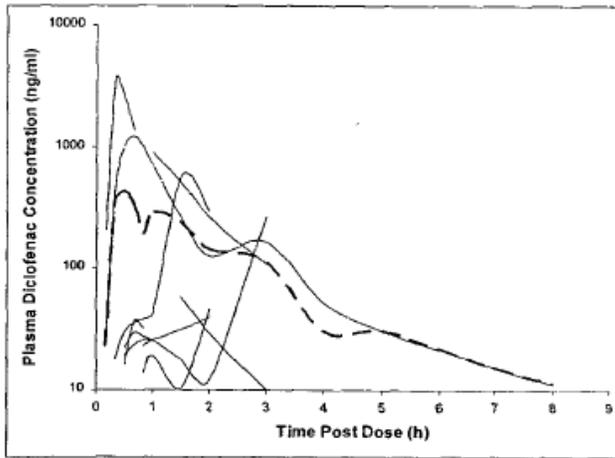


Table 2: Parameters From Compartmental PK analysis – Day 4

Parameter	12.5 mg Liquid Dose			25 mg DPSGC Dose		
	Median	Lower Quartile	Upper Quartile	Median	Lower Quartile	Upper Quartile
Time Lag (min)	4.12	0.64	5.88	22.58	17.12	36.98
Ka (1/hr)	3.99	2.49	5.38	6.01	2.71	21.47
Kel (1/hr)	2.96	2.00	5.93	7.10	2.33	23.73
K12 (1/hr)	1.55	1.00	2.77	2.91	0.78	10.87
K21(1/hr)	0.635	0.280	1.175	0.564	0.472	0.952
V(ml)	9.98	7.93	20.20	10.39	2.11	23.92
F (assumed)	50%	-	-	50%	-	-

Figure 4: Graphical Output Showing Regressed Model (line) and Observed Plasma Concentrations (circles) Over Time for a Representative Subject From day 4.

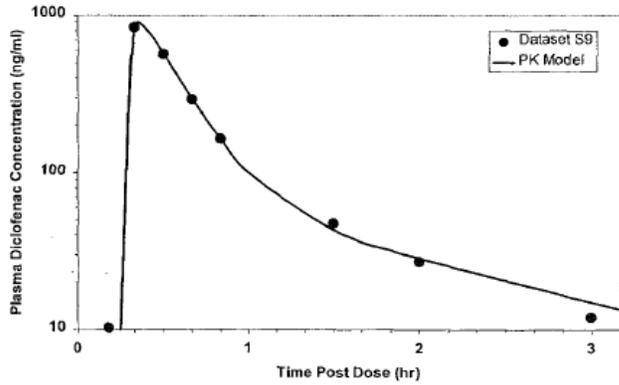


Figure 5: Hysteresis Effect Shown with PK and PD Data From day 4.

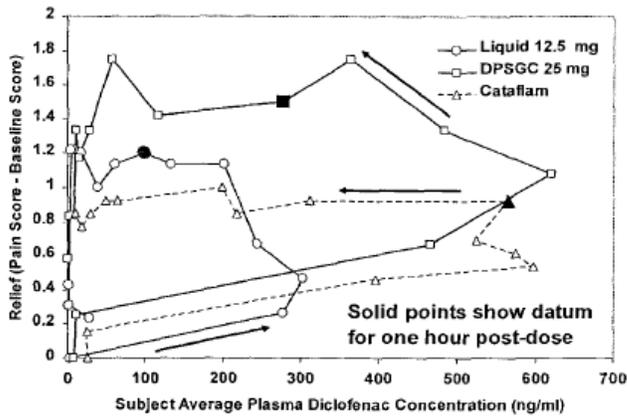
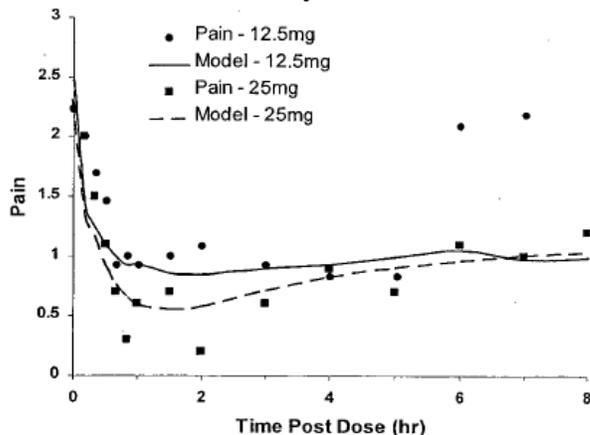


Table 3: PD Model Parameters for Day 4

Parameter	Value	Units
Emax	0.408	Pain units * ml/ng
EC50	559	Ng/ml
K1	0.0336	1/Pain units
K2	5.12	Dimensionless
γ_1	0.544	1/hours
γ_2	0.593	1/hours
K3	4.0E-05	1/hours
Pw	0.0826	Dimensionless

Figure 6: Average Pharmacodynamic Model Prediction Compared to Average Pain Score for Patients on Day 4.



Comments:

Sponsor acknowledges in the report that these results are not definitive, nor do they prove site-of- or mechanism of action and that the analysis was intended to give insight into the relationship of dose and effect. Given the different baseline pain on day 1 and day 4 (approximate average pain scores of 6 and 2, respectively), pain relief was represented with an absolute component and a component related to baseline pain (pain measured just prior to dose administration). There was also an arbitrary assumption that placebo effect is proportional to baseline pain. The PK analysis showed that there was a dose-related increase in systemic exposure from DPSGC formulations but the increases were less than dose proportional probably due to the small number of patients per group or because it was a parallel study design or due to the fact that food consumption was not controlled during the study. The variability in the PK of DPSGC formulations were less than those from Cataflam tablet. The PK-PD model is in agreement with models previously utilized for analgesics. Given the observed hysteresis and the bi-exponential clearance of diclofenac from plasma, drug effect was taken to relate to the amount of drug in the peripheral or effect compartment. This model represented the pain relief data fairly well within the power of the model. This model represented the pain relief data fairly well within the power of the model. As acknowledged by the sponsor, whether the addition of additional model structure improves model fidelity to data sufficiently justify additional model structure and parameters remains to be explored.

Conclusions:

- The extent of diclofenac absorption from all the formulations increased with dose but less than dose proportional when given as a single, steady-state dose to patients who have undergone bunionectomy surgery. The rate of absorption from the liquid is significantly faster than that of the capsule which is faster than that of the Cataflam tablet.
- For ProSORB-D dose forms, a PK-PD model based on the amount of drug in the peripheral compartment was fit to pain relief data. This model represented the pain relief data fairly well within the power of the model.

COMPARATIVE DISSOLUTION PROFILE DATA

In the Division’s 74-day Letter, dated December 4, 2007, the Agency requested from the Sponsor “full dissolution profile (and corresponding f_2 data) comparison between the clinical formulation (series 1200) and to-be-marketed formulation (series 1300/1400).” The Sponsor has provided dissolution profile data generated at the time of batch release for the registration batches (PDS1304, PDS1436, PDS1457) and supportive stability batches. Additional dissolution profile data was provided for the registration batch sublots (lots PDS1436A, PDS1436B, PDS1436C, PDS1457X, PDS1457Y, PDS 1457Z and PDS1458) as shown in Table 1. Dissolution data from four batches of diclofenac soft gelatin capsules were analyzed. One batch was from the 1200 series and three batches were from the 1300/1400 series (Table 1).

Table 1: Batches and Sublots Used in the f_2 Analysis

Series	Batch	Sublots
1200	PDS1218	PDS1218
1300/1400	PDS1304	PDS1304
1300/1400	PDS1436	PDS1436, PDS1436A, PDS1436B, PDS1436C
1300/1400	PDS1457	PDS1457, PDS1457X, PDS1457Y, PDS1457Z, PDS1458

Dissolution Profile Comparison by Sublot:

Dissolution profiles from six capsules were obtained at 10, 20, 30 and 45 minutes. The Sponsor stated that the use of 12 units was not possible for comparison of PDS1218 to the 1300/1400 series because such data was not available as PDS1218 was manufactured in 2003 and only 6 capsules for all batches were tested in dissolution for product release at the time of manufacture. Table 2 shows the summary of the dissolution data for the sublots. The f_2 comparison shows that sublots PDS1436A, PDS1436B, PDS1457, PDS1457Y, PDS1457Z failed to meet the f_2 criterion of greater than 50 (Table 3) but all the sublots had (b)
(4) % dissolved at 30 minutes (Table 2).

Table 2: Summary Dissolution Profile Statistics by Sublot

(b) (4)

Table 3: Comparison of PDS1218 to Individual Sublots in the 1300/1400 Series.

Sublot PDS	(b) (4)										
f₂ comparison to PDS1218											

Dissolution Profile Comparison by Batches:

Since a different number of capsules were tested for each batch in the 1300/1400 series (PDS1304 has results from six capsules, PDS1436 and its sublots had results from 24 capsules, and PDS1457 and its sublots had results from 30 capsules), and since it was desired to give equal weight to each of the three batches rather than to weight batches by the number of capsules tested, it was decided to use the average of the three batch means rather than the average of the 60 capsules. Table 4 shows the summary of the dissolution data for the batches while Table 5 shows the results of the f₂ comparison. Figure 1 shows the mean dissolution profiles by batch.

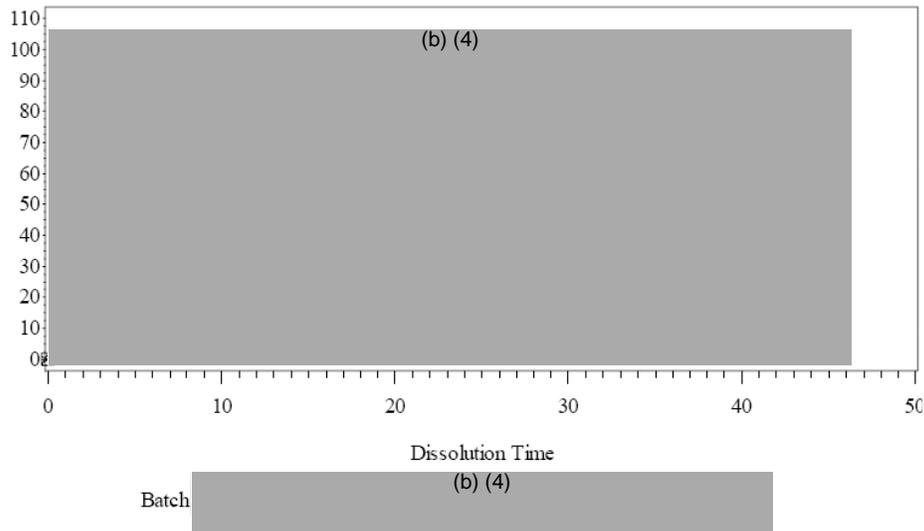
Table 4: Summary Dissolution Profile Statistics by Batch

Batch	Number Capsules	Mean 10 Min	Std.RSD 10 Min	Min.Max 10 Min	Mean 20 Min	Std.RSD 20 Min	Min.Max 20 Min	Mean 30 Min	Std.RSD 30 Min	Min.Max 30 Min	Mean 45 Min	Std.RSD 45 Min	Min.Max 45 Min
(b) (4)													

Table 5: Comparison of PDS1218 to Individual Batches in the 1300/1400 Series.

Batch Number	(b) (4)		
f₂ comparison to PDS1218			

Figure 1: Mean Dissolution Profiles by Batch



The results of the analysis showed that Batches PDS1304 and PDS1436 meet the acceptance criterion of f_2 greater than 50 but Batch PDS 1457 failed to meet this criterion. The 1200 and 1300/1400 series formulation series have similar release profiles (Figure 1).

Comparison of Clinical Formulation (series 1200) and the To-Be-Marketed Formulation (series 1300/1400)

Since a different number of capsules were tested for each batch in the 1300/1400 series (PDS1304 has results from six capsules, PDS1436 and its sublots had results from 24 capsules, and PDS1457 and its sublots had results from 30 capsules), and since it was

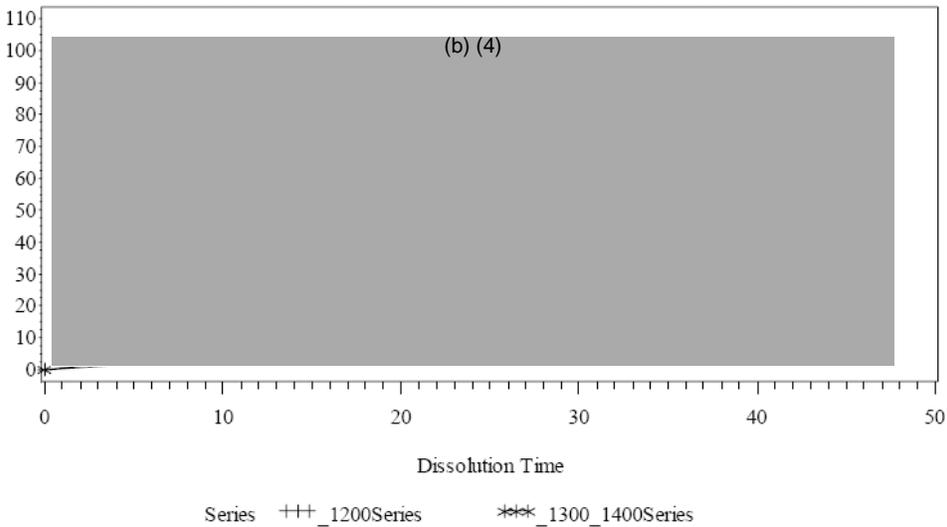
desired to give equal weight to each of the three batches rather than to weight batches by the number of capsules tested, the Sponsor decided to use the average of the three batch means rather than the average of the 60 capsules (Table 6). The f_2 value for the comparison of the 1200 series to the 1300/1400 series was (b) (4) indicating that the two series meet the usual acceptance criteria of f_2 greater than 50. Figure 2 shows the plot of mean profiles by series indicating that the 1200 and 1300/1400 series formulation series have similar release profiles.

Table 6: Summary Dissolution Profile Statistics by Series, Weight by Batch

(b) (4)



Figure 2: Mean Dissolution Profiles by Series



Conclusions

Dissolution data from the 1300/1400 series have been compared to batch PDS1218. Profiles of capsules were obtained at 10, 20, 30 and 45 minutes.

(b) (4)




(b) (4)

Therefore it is reasonable to conclude that the two series have similar dissolution profiles.

It is therefore recommended that the request for a bioequivalence waiver for the to-be-marketed formulation be granted.

4.3 OCP FILING/REVIEW FORM

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

6.1.1.1.1 General Information About the Submission

	Information		Information
NDA Number	22-202	Brand Name	Zipsor™ Soft Gelatin Capsule
OCP Division (1, 2, 3, 4, 5)	DCP 2	Generic Name	Diclofenac potassium
Medical Division	DAARP	Drug Class	NSAID
OCP Reviewer	Emmanuel Fadiran	Indication(s)	Relief of mild to moderate pain
OCP Team Leader	Suresh Doddapaneni	Dosage Form/Strength	Soft Gelatin Capsule, 25 mg
		Dosing Regimen	25 mg QID
Date of Submission	09/21/2007	Route of Administration	Oral
Estimated Due Date of OCP Review	05/21/2008	Sponsor	Xanodyne Pharmaceuticals
PDUFA Due Date	07/20/2008	Priority Classification	S
Division Due Date	05/21/2008		

6.1.1.1.1.1.1 Clin. Pharm. and Biopharm. Information

	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
6.2 Healthy Volunteers-				
single dose:	x	4		
multiple dose:	x	1		
6.2.1 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:	x	1		
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:	x	1		
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	x	1		
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				

capsules. According to the Sponsor, the patented technology, ProSorb[®], used in the formulation is designed to improve absorption characteristics and reduce time to onset of activity for pain relief. The principle behind the ProSorb technology is the use of selected dispersing agents that are designed to facilitate more rapid, consistent, and complete absorption of NSAIDs from the gastrointestinal tract which may be advantageous in the treatment of mild to moderate pain.

To support the efficacy and safety of DPSGC to treat mild to moderate pain, the Sponsor has submitted the following additional studies:

- One toxicology study was performed using (b) (4), the degradation product that is unique to DPSGC, to confirm the general safety of this compound in this new formulation.
- Four clinical pharmacokinetic Phase 1 studies using DPSGC. These studies establish the PK information (BA/BE, dose proportionality, food effect) for DPSGC.
- One Phase 2 PK/PD, one pediatric, and six adult Phase 3 safety and efficacy studies. The Phase 2 trial investigated pain management in a postoperative model (bunionectomy) and provides both efficacy direction as well as PK/PD modeling data. The Phase 3 studies, including two postoperative bunionectomy pain studies, two postoperative dental pain studies, two postoperative knee pain studies, and the pediatric study utilized a variety of primary and secondary variables that are standard for pain investigations as summarized in Table 1 below.

Table 1: Summary of Efficacy and Safety Studies of DPSGC in the Treatment of Pain

Study Number/ Study Dates	No. of sites	Treatment Arms	N/Total Enrolled/ Completed	Study Population	Study Design	Dosing Regimen and Duration	Demographics, Baseline Characteristics	Primary Endpoint
XP21L-301 Aug 2006- Oct 2006 Completed	7	DPSGC 25 mg Placebo	102/101 99/98 Total 201/199	Postbunionectomy pain	Randomized, double-blind, parallel, placebo-controlled	Initial dosing on Day 1 as needed (PRN) or q8 (2 oral [PO] doses), then q6 hour PO dosing for 4 days	27 M/174 F Mean age 45.2 y (18.0-65.0)	Average pain intensity over a 48-hour multidose period using the 11-pt numerical pain rating scale (NPRS)
XP21L-302 Sept 2006- Jan 2007 Completed	4	DPSGC 25 mg Placebo	99/96 101/95 Total 200/191	Postbunionectomy pain	Randomized, double-blind, parallel, placebo-controlled	Initial dosing on Day 1 PRN or q8 (2 PO doses), then q6 hour PO dosing for 4 days	28 M/ 172 F Mean age 40.4 y (18.0-65.0)	Average pain intensity over a 48-hour multidose period using the 11-pt NPRS
CL-000395 Dec 2001- March 2002 Completed	6	DPSGC 25 mg DPSGC 50 mg DPSGC 100 mg Placebo	63/63 68/68 66/66 68/67 Total 265/264	Postoperative dental pain	Randomized, double-blind, parallel, placebo-controlled	Single dose, 6-hour follow-up	111 M/154 F Mean age 23.3 y (18.0-46.2)	Time-weighted sum of pain intensity differences over 6 hours (SPID6)

Table 1: Summary of Efficacy and Safety Studies of DPSGC in the Treatment of Pain (Cont.)

Study Number/ Study Dates	No. of sites	Treatment Arms	N/Total Enrolled/ Completed	Study Population	Study Design	Dosing Regimen and Duration	Demographics, Baseline Characteristics	Primary Endpoint
CL-000400 Jan 2002-Apr 2002 Completed	7	DPSGC 25 mg DPSGC 50 mg DPSGC 100 mg Placebo	63/63 62/62 63/63 61/61 Total 249/249	Postoperative dental pain	Randomized, double-blind, parallel, placebo-controlled	Single dose, 6-hour follow-up	115 M/134 F Mean age 24.4 y (18.0-46.8)	SPID6
CL-000396 Feb 2002-July 2002 Completed	13	DPSGC 25 mg DPSGC 50 mg Placebo	67/64 61/60 62/59 Total 190/183	Postarthroscopy knee pain	Randomized, double-blind, parallel, placebo-controlled	5 days dosing (2 doses on Day 1, 3 doses/day on Days 2-5) 7-day follow-up	122 M/67 F Mean age 45.6 y (18.5-78.6)	Time-weighted sum of pain intensity differences over first 8 hours (SPID8)
CL-000401 Apr 2002-Sept 2002 Completed	13	DPSGC 25 mg DPSGC 50 mg Placebo	64/64 63/60 65/64 Total 192/188	Postarthroscopy knee pain	Randomized, double-blind, parallel, placebo-controlled	5 days dosing (2 doses on Day 1, 3 doses/day on Days 2-5) 7-day follow-up	112 M/80 F Mean age 46.4 y (18.3-82.1)	SPID8

Table 1: Summary of Efficacy and Safety Studies of DPSGC in the Treatment of Pain (Cont.)

Study Number/ Study Dates	No. of sites	Treatment Arms	N/Total Enrolled/ Completed	Study Population	Study Design	Dosing Regimen and Duration	Demographics, Baseline Characteristics	Primary Endpoint
CL-002000 July 2003-Sept 2003 Completed	1	Diclofenac (Proscrub-D) 12.5 mg liquid DPSGC 25 mg DPSGC 50 mg Cataflam 50 mg	14/14 13/13 14/14 12/12 Total 53/53	Postbunionectomy pain	Randomized, open-label, parallel	In-patient: 1 capsule/tablet or 1 mL liquid PO q8h for 24 h Out-patient: 1 capsule/tablet or 1 mL liquid PO q8h for 7 days	4 M/ 49 F Mean age 39.8 y (18.8-71.7)	Pain intensity scores (NPRS) compared with plasma concentrations
CL-000424 March 2002-June 2002 Completed	2	DPSGC 25 mg DPSGC 50 mg	47/47 50/49 Total 97/96	Pediatric orthodontal discomfort	Randomized, parallel group, double-blind, single-dose	Single dose	41 M/ 56 F Mean age 13.3 y (8.1-16.9)	Safety/tolerability, Time to onset of analgesia, duration of analgesia

Formulations used for clinical studies: For development and clinical evaluation, 3 DPSGC formulations were prepared: 1000 series (batches PDS1025, PDS1027, and PDS1029), an intermediate 1200 series (PDS1214, PDS1216, and PDS1218), and the to-be-marketed 1300/1400 series (PDS1304, PDS1436, and PDS1457). The compositions of these formulations are given in Table 2 below. All the batches of DPSGC 25 mg used for the Phase 1, 2 and 3 studies were manufactured at (b) (4) commercial scale (b) (4)



Table 2: Compositions of the formulations

	New Formulation	Intermediate Formulation	Old Formulation
	New Process	New Process	Old Process
Ingredient	PDS-1304, PDS-1436, PDS-1457 %w/w	PDS-1214, PDS-1216 and PDS-1218 %w/w	PDS-1025, PDS-1027 and PDS-1029 %w/w
Diclofenac Potassium	6.3 (a)	6.3 (e)	6.3 (e)
PEG 400 NF	(b) (4)		
Glycerin	(b) (4)		
Sorbitol Solution	(b) (4)		
Povidone USP	(b) (4)		
Polysorbate 80	(b) (4)		
(b) HCl	(b) (4)		
(4) HCl	(b) (4)		
(b) (4)	(b) (4)		
Capsule Size	(b) (4)		

a: 6.25% rounded and recorded as 6.3%
b: (b) (4)
c:
d:
e:
f:

Request for Waiver of In Vivo Bioequivalence Study

As discussed above, the changes in the formulation and capsule size between the 1000 series and the 1200 series were shown not to affect bioavailability, as evidenced by bioequivalence between PDS-1027 and PDS-1218 (Study OA171). The change (b) (4) based on the observation of the lack of effect of the change (b) (4) in the intermediate 1200 series as demonstrated by the results of BE study OA171. The Sponsor has requested for a waiver of *in vivo* bioequivalence study between the 1300/1400 series formulation (to-be-marketed) and the 1200 series formulation and this request will be reviewed by the chemistry reviewer.

Summary of Results of Individual Phase 1 and 2 Studies

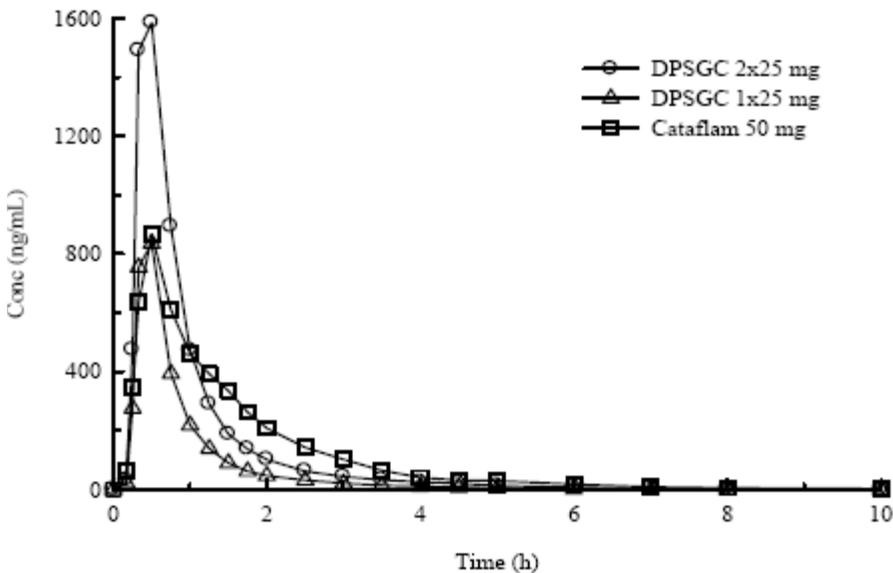
Study OA170 : The objective of this study was to examine the dose proportionality of DPSGC at two doses of the 25 mg capsule, 1×25 and 2×25 mg and to compare the rate and extent of absorption of diclofenac at these doses with that of Cataflam 50 mg. Fifty-four (54) healthy male and female volunteers received each of the three treatments according to a three-way crossover design. Doses were administered after a 10-hour fast and there was a washout period of at least 7 days between treatments.

RESULTS: Mean C_{max} and AUC(inf) for the 2×25 mg dose of DPSGC were essentially twice those of the 1×25 mg dose with essentially the same T_{max} (Table 3), demonstrating dose proportionality for the formulation. After administration of a 50 mg dose of Cataflam, the mean C_{max} was comparable to that of the 1×25 mg dose of DPSGC although T_{max} was ~2-fold longer, and the mean AUC(inf) was comparable to that of 2×25 mg dose of DPSGC (Table 3). This indicates that the rate of absorption is greater from DPSGC than from Cataflam although the extent of absorption is comparable. The mean t_{1/2} was comparable for all treatments. Figure 1 summarizes the mean concentration-time profiles following the three treatments.

Table 3: PK data from Study OA170

Study Ref. No.	Study Objective	Dose Route Formulation Lot/ Batch No.	Subjects No. (M/F) Type Age: Mean (Range)	Pharmacokinetic Parameters (a)					
				Treatment	C _{max} (ng/mL)	T _{max} (h)	AUC (b) (h·ng/mL)	C _{min} (ng/mL)	t _{1/2} (h)
OA170	Dose proportionality and comparison with Cataflam	25 mg Oral DPSGC Cap 04117B PDS-1027	54 (29/25) Healthy Volunteers 31 (18-50)	1×25 mg DPSGC	1,125 ± 486	0.45 ± 0.13	603 ± 163	--	1.35 ± 0.80
		50 mg Oral DPSGC Cap 04117A PDS-1027		2×25 mg DPSGC	2,035 ± 725	.48 ± 0.20	1,232 ± 296		1.84 ± 1.25
		50 mg Oral Cataflam Tab C2D02111		1×50 mg Cataflam	1,169 ± 528.0	0.93 ± 0.85	1,144 ± 282		1.45 ± 0.74

Figure 1: Mean Plasma Concentrations of Diclofenac After Oral Administration of DPSGC 1×25 mg and 2×25 mg and Cataflam 50 mg to Healthy Volunteers Under Fasted Conditions



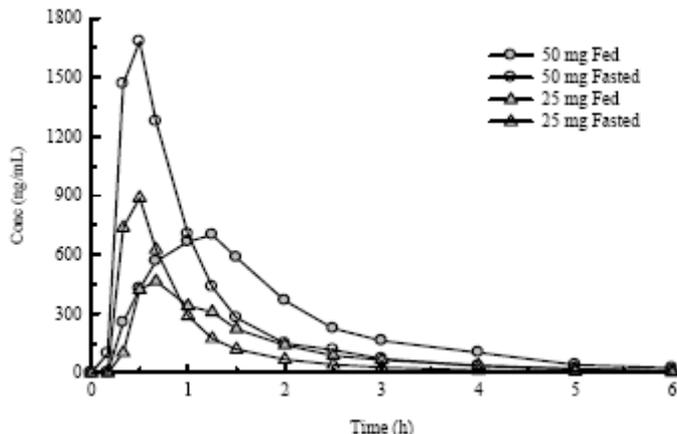
Study AAI-US-119 (food effect): The objective of this study was to examine the effect of food on the absorption of diclofenac from 25 mg and 50 mg DPSGC. Forty-seven (47) healthy male and female volunteers, 24 at 25 mg and 23 at 50 mg, received a dose of DPSGC after a 10-hour fast or after a standard high-fat breakfast according to a two-way crossover design. There was a washout period of at least 7 days between treatments.

RESULTS: As shown in Figure 2, following administration of 25 mg or 50 mg DPSGC under fed conditions, was decreased by approximately 40% to 50% respectively and Tmax was increased ~2-fold (Table 4). Mean values for AUC(inf) were essentially the same under fed and fasted conditions (Table 4). The data indicate that a high-fat meal decreases the rate but not the extent of absorption of diclofenac from DPSGC. Under both fed and fasted conditions, dose proportional bioavailability was observed between the 25 mg and 50 mg doses.

Table 4: PK data from Study AAI-US-119 & Study AAI-US-142

Study Ref. No.	Study Objective	Dose Route Formulation Lot No.	Subjects No. (M/F) Type Age: Mean (Range)	Pharmacokinetic Parameters (a)						Study Report Location
				Treatment	Cmax (ng/mL)	Tmax (h)	AUC (b) (h·ng/mL)	Cmin (ng/mL)	t½ (h)	
AAI-US-119	Effect of food on DPSGC	25 mg Oral DPSGC Cap 02252A PDS-1027	24 (21/3) Healthy Volunteers 29 (19-44)	Fasted	1,156 ± 482	0.49 ± 0.16	706 ± 199	--	1.04 ± 0.42	Module 5 Section 5.3.1.1.2
				Fed	686 ± 411	1.02 ± 0.55	713 ± 182	1.11 ± 0.42		
		50 mg Oral DPSGC Cap 02253A PDS-1038	23 (17/6) Healthy Volunteers 29 (20-40)	Fasted	2,365 ± 1,034	0.51 ± 0.19	1,549 ± 384	1.10 ± 0.25		
				Fed	1,154 ± 592	1.28 ± 0.71	1,457 ± 373	1.07 ± 0.25		

Figure 2: Mean Plasma Concentrations of Diclofenac After Oral Administration of DPSGC 1×25 mg and 1×50 mg to Healthy Volunteers Under Fed and Fasted Conditions



Study AAI-US-142: The objective of this study was to compare the pharmacokinetics of diclofenac after single 50 mg doses of DPSGC and Cataflam. Twenty-one (21) healthy male and female volunteers received a dose of each diclofenac formulation after a 10-hour fast according to a two-way crossover design. There was a washout period of at least 7 days between treatments.

RESULTS: The mean C_{max}, 1,989 ± 921 ng/mL, was reached at an earlier time, 0.60 ± 0.47 h, compared to Cataflam, 1,168 ± 657 ng/mL at 1.26 ± 0.99 h and the 90% confidence interval for the geometric mean ratio fell outside the 0.80 to 1.25 equivalence window (Table 5), indicating a more rapid absorption from DPSGC. However, the 90% confidence intervals for the geometric mean ratios for AUC(0-t) and AUC(inf) were within the 0.80 to 1.25 equivalence window, demonstrating that the extent of absorption of diclofenac from DPSGC was equivalent to that from Cataflam.

Table 5: Statistical analysis of PK data form Study Study AAI-US-142

Parameter	Least-Squares (Geometric) Means ¹			90% Confidence Interval ³	
	Test	Reference	Ratio ²	Lower	Upper
From Analysis of Ln-Transformed Parameters					
AUC(0-t) (ng h/mL)	1161	1078	1.077	0.982	1.181
AUC(0-∞) (ng h/mL)	1195	1087	1.099	0.999	1.211
C _{max} (ng/mL)	1773	992	1.787*	1.344	2.376
From Analysis of Untransformed Parameters					
t _{max} (h)	0.60	1.28	0.470*	-	-
Ke (1/h)	0.8142	0.9645	0.844	-	-
t1/2 (h)	0.96	0.85	1.130	-	-
1. Least-squares geometric means for ln-transformed data and least-squares means for untransformed parameters. 2. Ratio calculated as Test least-squares mean divided by the Reference least-squares mean. 3. Confidence interval of the ratio <ul style="list-style-type: none"> • Comparison was detected as statistically significant by ANOVA ($\alpha=0.05$). 					
Source: Appendix 14.3.					

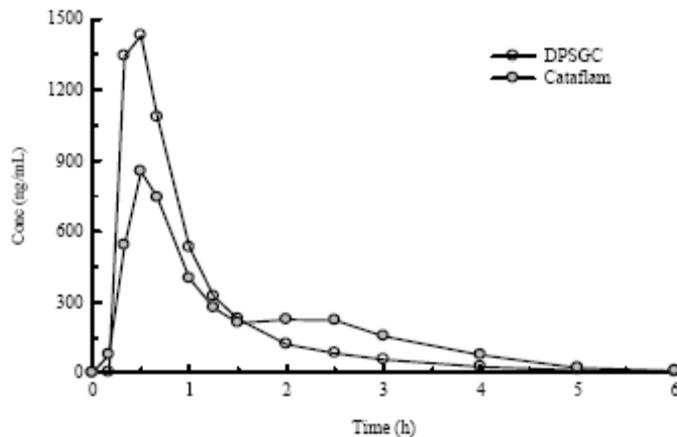
A historical comparison of the exposure to diclofenac from 25 mg DPSGC that from 25 mg Cataflam (not commercially available) as shown in Table 4 below shows that the AUC from both formulations are similar (Table 6).

Table 6: Comparative Bioavailability of DPSGC and Cataflam (a)

	AUC (ng-hr/mL)	C _{max} (ng/mL)	T _{max} (hr)
Cataflam® 25 mg	628	666	1.007
DPSGC 25 mg	603-706	1,023-1,156	0.45-0.49
Cataflam® 50 mg	1,144-1,175	1,168-1,169	1.26

a: The table shows the range of PK values for DPSGC 25 mg and Cataflam 50 mg that are from single dose PK studies conducted by the Sponsor. As Cataflam 25 mg is not commercially available, these results are abstracted from the Cataflam Summary Basis for Approval from Study CPD#91001, a single dose, crossover study in healthy volunteers.

Figure 3: Mean Plasma Concentrations of Diclofenac After Oral Administration of DPSGC 1×50 mg and Cataflam 1×50 mg to Healthy Volunteers Under Fasted Conditions



Study OA171: The objective of this study was to compare the bioavailability of the initial DPSGC 25 mg formulation used in several of the clinical trials (DPSGC old process) to that of the intermediate DPSGC 25 mg formulation used for the pivotal bunionectomy studies (DPSGC new process) and to a liquid formulation of 25 mg diclofenac potassium. Twenty-four (24) healthy male and female volunteers received each of the three treatments according to a three-way crossover design. Doses were administered after an overnight fast and there was a wash-out period of at least 3 days between treatments.

RESULTS: Although mean plasma concentrations reached a maximum earlier for the solution (Figure 4) and the mean value for T_{max} was approximately 50% of that of either DPSGC formulation (Table 7), all three formulations were bioequivalent with respect to C_{max}, AUC(0-t), and AUC(inf) as shown on Table 8.

Table 7: PK data from Study OA171

Study Ref. No.	Study Objective	Dose Route Formulation Lot No.	Subjects No. (M/F) Type Age: Mean (Range)	Pharmacokinetic Parameters (a)					
				Treatment	C _{max} (ng/mL)	T _{max} (h)	AUC (b) (h·ng/mL)	C _{min} (ng/mL)	t _{1/2} (h)
OA171	Comparison of a clinical trial formulation of DPSGC with a new process DPSGC and an oral solution	25 mg Oral DPSGC Cap PDS-1027	24 (15/9) Healthy Volunteers 35 (19-47)	1×25 mg DPSGC	1,023 ± 400	0.49 ± 0.19	607 ± 155	--	1.10 ± 0.27
		25 mg Oral DPSGC Cap PDS-1218		1×25 mg DPSGC	1,087 ± 419	0.47 ± 0.17	597 ± 151		1.07 ± 0.29
		25 mg Oral Solution 03160B		1×25 mg Solution	958 ± 274	0.25 ± 0.09	606 ± 144		1.07 ± 0.38

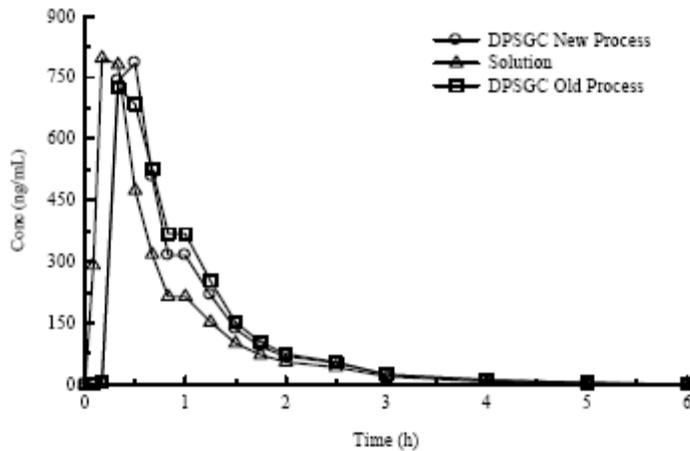
Table 8: Statistical analysis of the PK data from Study OA171

Parameter	new vs. old		new vs. liquid		old vs. liquid	
	Ratio	90% CI	Ratio	90% CI	Ratio	90% CI
AUC ₀₋₄	99.03%	(94%,104%)	98.23%	(93%,103%)	99.19%	(94%,104%)
AUC _{0-∞}	98.83%	(94%,103%)	97.88%	(93%,103%)	99.04%	(95%,104%)
C _{max}	107.43%	(94%,123%)	108.19%	(95%,124%)	100.71%	(88%,115%)
t _{max}	-0.02h ^x	(-0.08h,+0.04h) ^x	+0.23h ^x	(+0.17h,+0.29h) ^x	+0.25h ^x	(+0.19h,+0.31h) ^x

^x: difference CI: confidence interval

Source of data: Table 14.2.4.2

Figure 4: Mean Plasma Concentrations of Diclofenac After Oral Administration of 25 mg of Diclofenac by the New and Old Process and as an Oral Solution to Healthy Volunteers Under Fasted Conditions



Study AAI-002000: The objective of this study was to compare plasma drug concentrations (PK) and pain relief efficacy (PD) in bunionectomy patients randomized to receive DPSGC 25 mg, DPSGC 50 mg, ProSorb-D™ liquid 12.5 mg, or Cataflam 50 mg every 8 hours for 8 days. The composition of ProSorb-D (b) (4) Plasma samples were collected on Study Day 1 after the first dose, on Study Day 4 for up to 8 hours after the first daily dose, and on Study Day 8 prior to the second dose. PK sampling was discontinued on Day 1 in the majority of patients once rescue medication was administered and therefore no PK analysis was possible.

RESULTS: The mean plasma concentrations on Day 4 are compared in Figure 5, and the mean PK parameters on Day 4 are compared in Table 9. While there was a dose-related increase in mean plasma concentrations (Figure 5) and C_{max} and AUC (Table 9) for the ProSorb-based formulations (DPSGC and ProSorb-D liquid), the increases were somewhat less than dose-proportional. Although single dose studies in healthy volunteers showed an increase in C_{max} for 50 mg DPSGC compared to Cataflam

the mean for Cataflam tablets and the 50 mg DPSGC were comparable. These observations may be a consequence of the small numbers of subjects per group, the use of different subjects per group, and the fact that food consumption was not controlled.

Figure 5: Mean Plasma Concentrations of Diclofenac on Day 4 During Oral Administration of DPSGC 25 mg and 50 mg, ProSorb-D 12.5 mg, and Cataflam 50 mg Every 8 Hours for 8 Days to Bunionectomy Patients

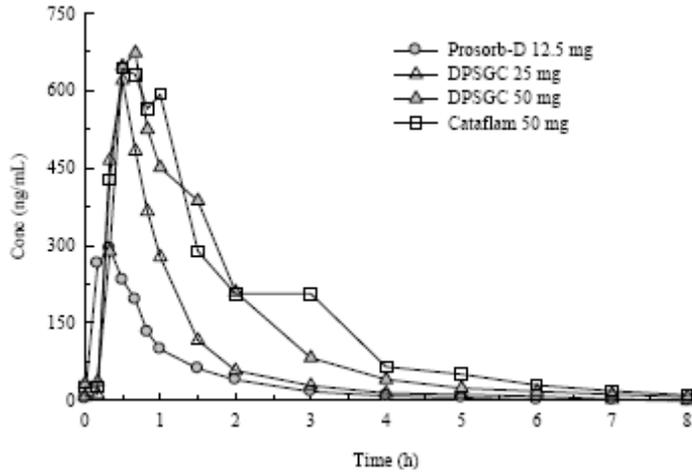


Table 9: PK data from Study AAI-002000

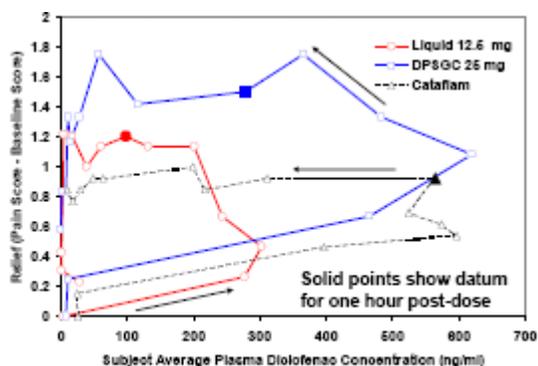
Study Ref. No.	Study Objective	Dose Route Formulation Lot No.	Subjects No. (M/F) Type Age: Mean (Range)	Pharmacokinetic Parameters (a)					
				Treatment	C _{max} (ng/mL)	T _{max} (h)	AUC (b) (h·ng/mL)	C _{min} (ng/mL)	t _{1/2} (h)
AAI-002000	PK/PD comparison of DPSGC, ProSorb-D™, and Cataflam	25 mg Oral DPSGC Cap PDS-1027	13 (0/13) Bunionectomy Patients 42 (22-67)	Day 4 Day 8	832 ± 365	0.63 ± 0.33	642 ± 223	7 ± 8 1 ± 3	1.87 ± 0.87
		50 mg Oral DPSGC Cap PDS-1038	14 (1/13) Bunionectomy Patients 33 (19-51)	Day 4 Day 8	1,126 ± 565	0.95 ± 0.51	1,056 ± 165	32 ± 38 10 ± 18	2.22 ± 1.11
		12.5 mg Oral ProSorb-D Liquid 03159A	14 (1/13) Bunionectomy Patients 40 (22-72)	Day 4 Day 8	328 ± 119	0.49 ± 0.36	334 ± 116	3 ± 7 0 ± 0	1.19 ± 0.52
		50 mg Oral Cataflam Tab C2D 02111	12 (2/10) Bunionectomy Patients 45 (21-71)	Day 4 Day 8	1,086 ± 749	1.26 ± 0.94	1,380 ± 1,012	26 ± 33 21 ± 37	1.64 ± 0.37

Graphs of the mean change from baseline in pain intensity versus the mean plasma diclofenac concentration demonstrated a counterclockwise hysteresis, consistent with a “peripheral” effect compartment (Figure 6).

Pharmacodynamic modeling with a pain model reported in the literature was used to

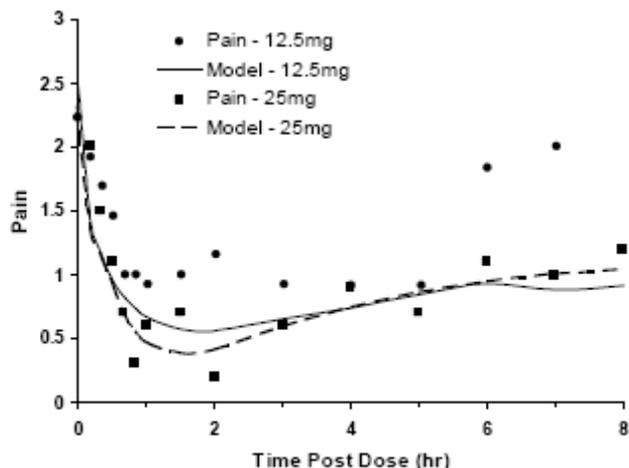
relate pain relief to the predicted effect compartment concentration, using a two compartment model to describe diclofenac pharmacokinetics. As shown in Figure 7, there was good agreement between the observed and model-predicted change from baseline in pain relief scores as a function of time.

Figure 6: Relationship Between the Mean Change from Baseline in Pain Relief Score and the Mean Plasma Concentrations of Diclofenac on Day 4 During Oral Administration of DPSGC 25 mg, ProSorb-D 12.5 mg, and Cataflam 50 mg



Note: Drug administration every 8 hours for 8 days to postbunionectomy patients

Figure 7: Observed and Model-Predicted Mean Change from Baseline in Pain Relief Scores During Oral Administration of DPSGC 25 mg and ProSorb-D 12.5 mg.



Note: Drug administration every 8 hours for 8 days to postbunionectomy patients

Comments to be sent to the sponsor:

- Submit the data files (as SAS transport files) and the input and output file for the PK-PD analysis for Study AAI-002000. Please specify the program that was used for the PK-PD analysis.
- Submit the full dissolution profile comparison between the clinical formulation series 1200 and to-be marketed formulation (series 1300/1400) with f-2 comparison.

Recommendation: The Office of Clinical Pharmacology, Division of Clinical Pharmacology 2 has reviewed of NDA 22-202 submitted on September 21, 2007 for filing and finds it filable from clinical pharmacology perspective.

Conclusion: The application is FILABLE. Please forward the above requests to the Sponsor.

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/s/

Emmanuel Fadiran
6/20/2008 03:27:11 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
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BIOPHARMACEUTICS

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-202	Brand Name	Zipsor™ Soft Gelatin Capsule
OCP Division (1, 2, 3, 4, 5)	DCP 2	Generic Name	Diclofenac potassium
Medical Division	DAARP	Drug Class	NSAID
OCP Reviewer	Emmanuel Fadiran	Indication(s)	Relief of mild to moderate pain
OCP Team Leader	Suresh Doddapaneni	Dosage Form/Strength	Soft Gelatin Capsule, 25 mg
		Dosing Regimen	25 mg QID
Date of Submission	09/21/2007	Route of Administration	Oral
Estimated Due Date of OCP Review	05/21/2008	Sponsor	Xadodyne Pharmaceuticals
PDUFA Due Date	07/20/2008	Priority Classification	S
Division Due Date	05/21/2008		

Clin. Pharm. and Biopharm. Information

	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<u>Healthy Volunteers-</u>				
single dose:	x	4		
multiple dose:	x	1		
<u>Patients-</u>				
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:	x	1		
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:	x	1		
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	x	1		
Phase 3 clinical trial:				
Population Analyses -				

Data rich:			
Data sparse:			
II. Biopharmaceutics			
Absolute bioavailability:			
Relative bioavailability -			
solution as reference:			
alternate formulation as reference:			
Bioequivalence studies -			
traditional design; single / multi dose:	x	1	2 (SD and MD) pivotal studies
replicate design; single / multi dose:			
Food-drug interaction studies:	x	1	1 pivotal and 1 pilot studies
Dissolution:			
(IVIVC):			
Bio-wavier request based on BCS			
BCS class			
III. Other CPB Studies			
Genotype/phenotype studies:			
Chronopharmacokinetics			
Pediatric development plan			
Literature References			
Total Number of Studies		6	4 studies are pivotal
Filability and QBR comments			
	"X" if yes	Comments	
Application filable?	x	<ul style="list-style-type: none"> See below. 	
Comments sent to firm?		<ul style="list-style-type: none"> Submit the data files (as SAS transport files) and the input and output file for the PK-PD analysis for Study AAI-002000. Please specify the program that was used for the PK-PD analysis. Submit the full dissolution profile comparison between the clinical formulation series 1200 and to-be marketed formulation (series 1300/1400) with f-2 comparison. 	
QBR questions (key issues to be considered)		<ul style="list-style-type: none"> What are the formulations used for the clinical development of DPSGC? Is the clinical formulation bioequivalent to the to-be marketed formulation? How does the PK profile of DPSGC compare to that of Cataflam tablet What is the effect of food on the BA of DPSGC? What role does the PK-PD analysis play in the approval of DPSGC? 	

Background:

Zipsor™ (diclofenac potassium) Soft Gelatin Capsule (DPSGC) is a new 25 mg dose form of the existing reference listed drug, Cataflam® (diclofenac potassium immediate release tablets, 50 mg, NDA 20-142). Cataflam is indicated for the relief of signs and symptoms of osteoarthritis and rheumatoid arthritis, for the treatment of primary dysmenorrhea, and for the relief of mild to moderate pain. This is therefore a 505(b)(2) application. Diclofenac, like most NSAIDs, precipitates upon exposure to gastric fluid due to its relative insolubility at acidic pH. Thus, absorption characteristics may be dependent on (1) mechanical agitation to disperse the drug in the stomach, and (2) passage of the drug from the stomach into the higher pH milieu of the intestines. This

may result in highly variable absorption among individuals following oral administration. Zipsor is a liquid formulation of diclofenac potassium encapsulated in soft gelatin capsules. According to the Sponsor, the patented technology, ProSorb®, used in the formulation is designed to improve absorption characteristics and reduce time to onset of activity for pain relief. The principle behind the ProSorb technology is the use of selected dispersing agents that are designed to facilitate more rapid, consistent, and complete absorption of NSAIDs from the gastrointestinal tract which may be advantageous in the treatment of mild to moderate pain.

To support the efficacy and safety of DPSGC to treat mild to moderate pain, the Sponsor has submitted the following additional studies:

- One toxicology study was performed using (b) (4) the degradation product that is unique to DPSGC, to confirm the general safety of this compound in this new formulation.
- Four clinical pharmacokinetic Phase 1 studies using DPSGC. These studies establish the PK information (BA/BE, dose proportionality, food effect) for DPSGC.
- One Phase 2 PK/PD, one pediatric, and six adult Phase 3 safety and efficacy studies. The Phase 2 trial investigated pain management in a postoperative model (bunionectomy) and provides both efficacy direction as well as PK/PD modeling data. The Phase 3 studies, including two postoperative bunionectomy pain studies, two postoperative dental pain studies, two postoperative knee pain studies, and the pediatric study utilized a variety of primary and secondary variables that are standard for pain investigations as summarized in Table 1 below.

Table 1: Summary of Efficacy and Safety Studies of DPSGC in the Treatment of Pain

Study Number/ Study Dates	No. of sites	Treatment Arms	N/Total Enrolled/ Completed	Study Population	Study Design	Dosing Regimen and Duration	Demographics, Baseline Characteristics	Primary Endpoint
XP21L-301 Aug 2006- Oct 2006 Completed	7	DPSGC 25 mg Placebo	102/101 99/98 Total 201/199	Postbunionectomy pain	Randomized, double-blind, parallel, placebo-controlled	Initial dosing on Day 1 as needed (PRN) or q8 (2 oral [PO] doses), then q6 hour PO dosing for 4 days	27 M/174 F Mean age 45.2 y (18.0-65.0)	Average pain intensity over a 48-hour multidose period using the 11-pt numerical pain rating scale (NPRS)
XP21L-302 Sept 2006- Jan 2007 Completed	4	DPSGC 25 mg Placebo	99/96 101/95 Total 200/191	Postbunionectomy pain	Randomized, double-blind, parallel, placebo-controlled	Initial dosing on Day 1 PRN or q8 (2 PO doses), then q6 hour PO dosing for 4 days	28 M/ 172 F Mean age 40.4 y (18.0-65.0)	Average pain intensity over a 48-hour multidose period using the 11-pt NPRS
CL-000395 Dec 2001- March 2002 Completed	6	DPSGC 25 mg DPSGC 50 mg DPSGC 100 mg Placebo	63/63 68/68 66/66 68/67 Total 265/264	Postoperative dental pain	Randomized, double-blind, parallel, placebo-controlled	Single dose, 6-hour follow-up	111 M/154 F Mean age 23.3 y (18.0-46.2)	Time-weighted sum of pain intensity differences over 6 hours (SPID6)

Table 1: Summary of Efficacy and Safety Studies of DPSGC in the Treatment of Pain (Cont.)

Study Number/ Study Dates	No. of sites	Treatment Arms	N/Total Enrolled/ Completed	Study Population	Study Design	Dosing Regimen and Duration	Demographics, Baseline Characteristics	Primary Endpoint
CL-000400 Jan 2002- Apr 2002 Completed	7	DPSGC 25 mg DPSGC 50 mg DPSGC 100 mg Placebo	63/63 62/62 63/63 61/61 Total 249/249	Postoperative dental pain	Randomized, double-blind, parallel, placebo-controlled	Single dose, 6-hour follow-up	115 M/134 F Mean age 24.4 y (18.0-46.8)	SPID6
CL-000396 Feb 2002- July 2002 Completed	13	DPSGC 25 mg DPSGC 50 mg Placebo	67/64 61/60 62/59 Total 190/183	Postarthroscopy knee pain	Randomized, double-blind, parallel, placebo-controlled	5 days dosing (2 doses on Day 1, 3 doses/day on Days 2-5) 7-day follow-up	122 M/67 F Mean age 45.6 y (18.5-78.6)	Time-weighted sum of pain intensity differences over first 8 hours (SPID8)
CL-000401 Apr 2002- Sept 2002 Completed	13	DPSGC 25 mg DPSGC 50 mg Placebo	64/64 63/60 65/64 Total 192/188	Postarthroscopy knee pain	Randomized, double-blind, parallel, placebo-controlled	5 days dosing (2 doses on Day 1, 3 doses/day on Days 2-5) 7-day follow-up	112 M/80 F Mean age 46.4 y (18.3-82.1)	SPID8

Table 1: Summary of Efficacy and Safety Studies of DPSGC in the Treatment of Pain (Cont.)

Study Number/ Study Dates	No. of sites	Treatment Arms	N/Total Enrolled/ Completed	Study Population	Study Design	Dosing Regimen and Duration	Demographics, Baseline Characteristics	Primary Endpoint
CL-002000 July 2003- Sept 2003 Completed	1	Diclofenac (Prosorb-D) 12.5 mg liquid DPSGC 25 mg DPSGC 50 mg Cataflam 50 mg	14/14 13/13 14/14 12/12 Total 53/53	Posttraumatic pain	Randomized, open-label, parallel	In-patient: 1 capsule/tablet or 1 mL liquid PO q8h for 24 h Out-patient: 1 capsule/tablet or 1 mL liquid PO q8h for 7 days	4 M/ 49 F Mean age 39.8 y (18.8-71.7)	Pain intensity scores (NPRS) compared with plasma concentrations
CL-000424 March 2002-June 2002 Completed	2	DPSGC 25 mg DPSGC 50 mg	47/47 50/49 Total 97/96	Pediatric orthodontal discomfort	Randomized, parallel group, double-blind, single-dose	Single dose	41 M/ 56 F Mean age 13.3 y (8.1-16.9)	Safety/tolerability, Time to onset of analgesia, duration of analgesia

Formulations used for clinical studies: For development and clinical evaluation, 3 DPSGC formulations were prepared: 1000 series (batches PDS1025, PDS1027, and PDS1029), an intermediate 1200 series (PDS1214, PDS1216, and PDS1218), and the to-be-marketed 1300/1400 series (PDS1304, PDS1436, and PDS1457). The compositions of these formulations are given in Table 2 below. All the batches of DPSGC 25 mg used for the

Phase 1, 2 and 3 studies were manufactured at (b) (4) commercial scale (b) (4)

(b) (4)



(b) (4)

Table 2: Compositions of the formulations

	New Formulation	Intermediate Formulation	Old Formulation
	New Process	New Process	Old Process
Ingredient	PDS-1304, PDS-1436, PDS-1457 %w/w	PDS-1214, PDS-1216 and PDS-1218 %w/w	PDS-1025, PDS-1027 and PDS-1029 %w/w
Diclofenac Potassium	6.3 (a)	6.3 (e)	6.3 (e)
PEG 400 NF	[REDACTED]		
Glycerin			
Sorbitol Solution (b) (4)			
Povidone USP			
Polysorbate 80			
(b) (4) HCl			
(4) HCl			
(b) (4)			
Capsule Size			

a: 6.25% rounded and recorded as 6.3%

b: (b) (4)

c:

d:

e:

f:

Request for Waiver of In Vivo Bioequivalence Study

As discussed above, the changes in the formulation and capsule size between the 1000 series and the 1200 series were shown not to affect bioavailability, as evidenced by bioequivalence between PDS-1027 and PDS-1218 (Study OA171). The change (b) (4) [REDACTED] based on the observation (b) (4) of the lack of effect of the change (b) (4) in the intermediate 1200 series as demonstrated by the results of BE study OA171. The Sponsor has requested for a waiver of *in vivo* bioequivalence study between the 1300/1400 series formulation (to-be-marketed) and the 1200 series formulation and this request will be reviewed by the chemistry reviewer.

Summary of Results of Individual Phase 1 and 2 Studies

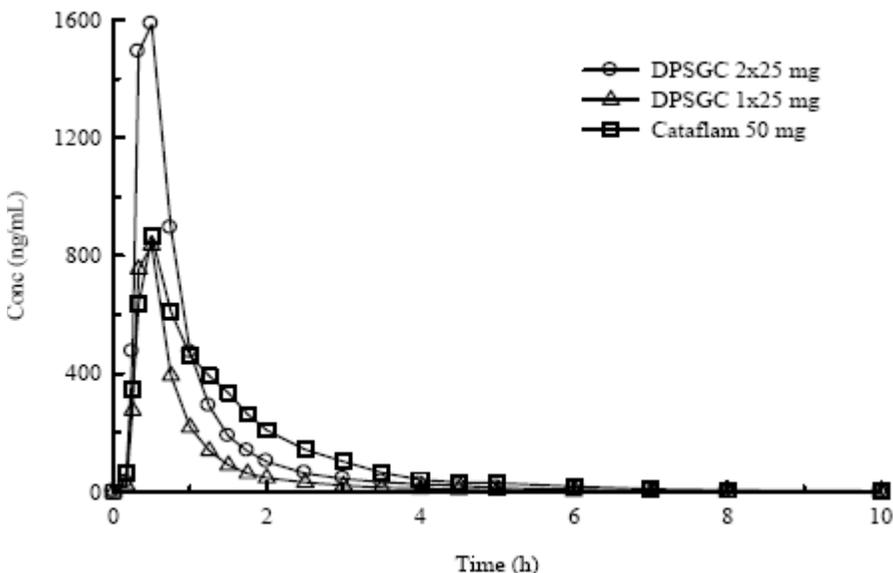
Study OA170 : The objective of this study was to examine the dose proportionality of DPSGC at two doses of the 25 mg capsule, 1×25 and 2×25 mg and to compare the rate and extent of absorption of diclofenac at these doses with that of Cataflam 50 mg. Fifty-four (54) healthy male and female volunteers received each of the three treatments according to a three-way crossover design. Doses were administered after a 10-hour fast and there was a washout period of at least 7 days between treatments.

RESULTS: Mean Cmax and AUC(inf) for the 2×25 mg dose of DPSGC were essentially twice those of the 1×25 mg dose with essentially the same Tmax (Table 3), demonstrating dose proportionality for the formulation. After administration of a 50 mg dose of Cataflam, the mean Cmax was comparable to that of the 1×25 mg dose of DPSGC although Tmax was ~2-fold longer, and the mean AUC(inf) was comparable to that of 2×25 mg dose of DPSGC (Table 3). This indicates that the rate of absorption is greater from DPSGC than from Cataflam although the extent of absorption is comparable. The mean t½ was comparable for all treatments. Figure 1 summarizes the mean concentration-time profiles following the three treatments.

Table 3: PK data from Study OA170

Study Ref. No.	Study Objective	Dose Route Formulation Lot/Batch No.	Subjects No. (M/F) Type Age: Mean (Range)	Pharmacokinetic Parameters (a)					
				Treatment	Cmax (ng/mL)	Tmax (h)	AUC (b) (h*ng/mL)	Cmin (ng/mL)	t½ (h)
OA170	Dose proportionality and comparison with Cataflam	25 mg Oral DPSGC Cap 04117B PDS-1027	54 (29/25) Healthy Volunteers 31 (18-50)	1×25 mg DPSGC	1,125 ± 486	0.45 ± 0.13	603 ± 163	--	1.35 ± 0.80
		50 mg Oral DPSGC Cap 04117A PDS-1027		2×25 mg DPSGC	2,035 ± 725	.48 ± 0.20	1,232 ± 296		1.84 ± 1.25
		50 mg Oral Cataflam Tab C2D02111		1×50 mg Cataflam	1,169 ± 528.0	0.93 ± 0.85	1,144 ± 282		1.45 ± 0.74

Figure 1: Mean Plasma Concentrations of Diclofenac After Oral Administration of DPSGC 1×25 mg and 2×25 mg and Cataflam 50 mg to Healthy Volunteers Under Fasted Conditions



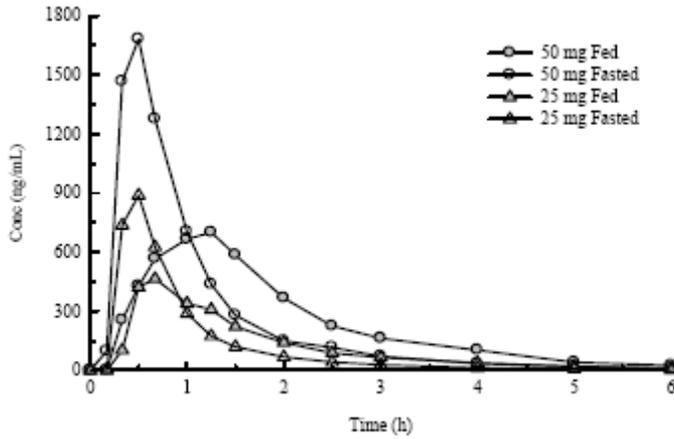
Study AAI-US-119 (food effect): The objective of this study was to examine the effect of food on the absorption of diclofenac from 25 mg and 50 mg DPSGC. Forty-seven (47) healthy male and female volunteers, 24 at 25 mg and 23 at 50 mg, received a dose of DPSGC after a 10-hour fast or after a standard high-fat breakfast according to a two-way crossover design. There was a washout period of at least 7 days between treatments.

RESULTS: As shown in Figure 2, following administration of 25 mg or 50 mg DPSGC under fed conditions, was decreased by approximately 40% to 50% respectively and T_{max} was increased ~2-fold (Table 4). Mean values for $AUC_{(inf)}$ were essentially the same under fed and fasted conditions (Table 4). The data indicate that a high-fat meal decreases the rate but not the extent of absorption of diclofenac from DPSGC. Under both fed and fasted conditions, dose proportional bioavailability was observed between the 25 mg and 50 mg doses.

Table 4: PK data from Study AAI-US-119 & Study AAI-US-142

Study Ref. No.	Study Objective	Dose Route Formulation Lot No.	Subjects No. (M/F) Type Age: Mean (Range)	Pharmacokinetic Parameters (a)						Study Report Location
				Treatment	C _{max} (ng/mL)	T _{max} (h)	AUC (h) (h·ng/mL)	C _{min} (ng/mL)	t _{1/2} (h)	
AAI-US-119	Effect of food on DPSGC	25 mg Oral DPSGC Cap 02252A PDS-1027	24 (21/3) Healthy Volunteers 29 (19-44)	Fasted	1,156 ± 482	0.49 ± 0.16	706 ± 199	--	1.04 ± 0.42	Module 5 Section 5.3.1.1.2
				Fed	686 ± 411	1.02 ± 0.55	713 ± 182	1.11 ± 0.42		
		50 mg Oral DPSGC Cap 02253A PDS-1038	23 (17/6) Healthy Volunteers 29 (20-40)	Fasted	2,365 ± 1,034	0.51 ± 0.19	1,549 ± 384	1.10 ± 0.25		
				Fed	1,154 ± 592	1.28 ± 0.71	1,457 ± 373	1.07 ± 0.25		

Figure 2: Mean Plasma Concentrations of Diclofenac After Oral Administration of DPSGC 1×25 mg and 1×50 mg to Healthy Volunteers Under Fed and Fasted Conditions



Study AAI-US-142: The objective of this study was to compare the pharmacokinetics of diclofenac after single 50 mg doses of DPSGC and Cataflam. Twenty-one (21) healthy male and female volunteers received a dose of each diclofenac formulation after a 10-hour fast according to a two-way crossover design. There was a washout period of at least 7 days between treatments.

RESULTS: The mean C_{max}, 1,989 ± 921 ng/mL, was reached at an earlier time, 0.60 ± 0.47 h, compared to Cataflam, 1,168 ± 657 ng/mL at 1.26 ± 0.99 h and the 90% confidence interval for the geometric mean ratio fell outside the 0.80 to 1.25 equivalence window (Table 5), indicating a more rapid absorption from DPSGC. However, the 90% confidence intervals for the geometric mean ratios for AUC(0-t) and AUC(inf) were within the 0.80 to 1.25 equivalence window, demonstrating that the extent of absorption of diclofenac from DPSGC was equivalent to that from Cataflam.

Table 5: Statistical analysis of PK data form Study Study AAI-US-142

Parameter	Least-Squares (Geometric) Means ¹		Ratio ²	90% Confidence Interval ³	
	Test	Reference		Lower	Upper
From Analysis of Ln-Transformed Parameters					
AUC(0-t) (ng h/mL)	1161	1078	1.077	0.982	1.181
AUC(0-∞) (ng h/mL)	1195	1087	1.099	0.999	1.211
C _{max} (ng/mL)	1773	992	1.787*	1.344	2.376
From Analysis of Untransformed Parameters					
t _{max} (h)	0.60	1.28	0.470*	-	-
K _e (1/h)	0.8142	0.9645	0.844	-	-
t _{1/2} (h)	0.96	0.85	1.130	-	-
1. Least-squares geometric means for ln-transformed data and least-squares means for untransformed parameters. 2. Ratio calculated as Test least-squares mean divided by the Reference least-squares mean. 3. Confidence interval of the ratio <ul style="list-style-type: none"> • Comparison was detected as statistically significant by ANOVA (α=0.05). 					
Source: Appendix 14.3.					

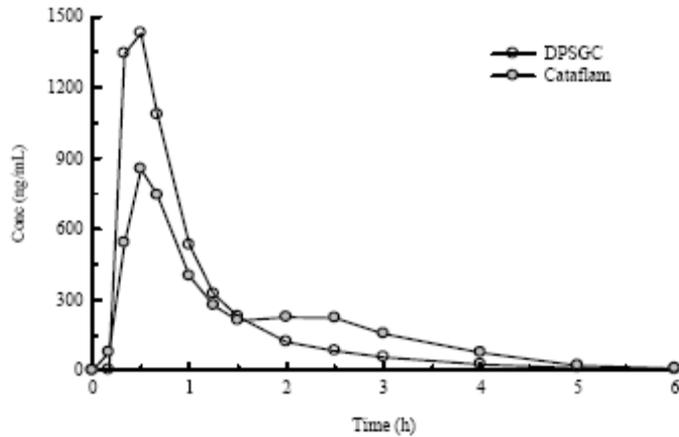
A historical comparison of the exposure to diclofenac from 25 mg DPSGC that from 25 mg Cataflam (not commercially available) as shown in Table 4 below shows that the AUC from both formulations are similar (Table 6).

Table 6: Comparative Bioavailability of DPSGC and Cataflam (a)

	AUC (ng-hr/mL)	C _{max} (ng/mL)	T _{max} (hr)
Cataflam® 25 mg	628	666	1.007
DPSGC 25 mg	603-706	1,023-1,156	0.45-0.49
Cataflam® 50 mg	1,144-1,175	1,168-1,169	1.26

a: The table shows the range of PK values for DPSGC 25 mg and Cataflam 50 mg that are from single dose PK studies conducted by the Sponsor. As Cataflam 25 mg is not commercially available, these results are abstracted from the Cataflam Summary Basis for Approval from Study CPD#91001, a single dose, crossover study in healthy volunteers.

Figure 3: Mean Plasma Concentrations of Diclofenac After Oral Administration of DPSGC 1×50 mg and Cataflam 1×50 mg to Healthy Volunteers Under Fasted Conditions



Study OA171: The objective of this study was to compare the bioavailability of the initial DPSGC 25 mg formulation used in several of the clinical trials (DPSGC old process) to that of the intermediate DPSGC 25 mg formulation used for the pivotal bunionectomy studies (DPSGC new process) and to a liquid formulation of 25 mg diclofenac potassium. Twenty-four (24) healthy male and female volunteers received each of the three treatments according to a three-way crossover design. Doses were administered after an overnight fast and there was a wash-out period of at least 3 days between treatments.

RESULTS: Although mean plasma concentrations reached a maximum earlier for the solution (Figure 4) and the mean value for T_{max} was approximately 50% of that of either DPSGC formulation (Table 7), all three formulations were bioequivalent with respect to C_{max}, AUC(0-t), and AUC(inf) as shown on Table 8.

Table 7: PK data from Study OA171

Study Ref. No.	Study Objective	Dose Route Formulation Lot No.	Subjects No. (M/F) Type Age: Mean (Range)	Pharmacokinetic Parameters (a)					
				Treatment	C _{max} (ng/mL)	T _{max} (h)	AUC (b) (h·ng/mL)	C _{min} (ng/mL)	t _{1/2} (h)
OA171	Comparison of a clinical trial formulation of DPSGC with a new process DPSGC and an oral solution	25 mg Oral DPSGC Cap PDS-1027	24 (15/9) Healthy Volunteers 35 (19-47)	1×25 mg DPSGC	1,023 ± 400	0.49 ± 0.19	607 ± 155	--	1.10 ± 0.27
		25 mg Oral DPSGC Cap PDS-1218		1×25 mg DPSGC	1,087 ± 419	0.47 ± 0.17	597 ± 151		1.07 ± 0.29
		25 mg Oral Solution 03160B		1×25 mg Solution	958 ± 274	0.25 ± 0.09	606 ± 144		1.07 ± 0.38

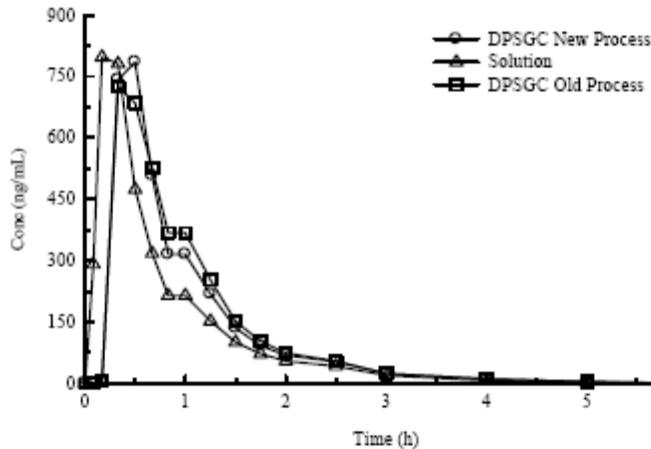
Table 8: Statistical analysis of the PK data from Study OA171

Parameter	new vs. old		new vs. liquid		old vs. liquid	
	Ratio	90% CI	Ratio	90% CI	Ratio	90% CI
AUC ₀₋₄	99.03%	(94%,104%)	98.23%	(93%,103%)	99.19%	(94%,104%)
AUC _{0-∞}	98.83%	(94%,103%)	97.88%	(93%,103%)	99.04%	(95%,104%)
C _{max}	107.43%	(94%,123%)	108.19%	(95%,124%)	100.71%	(88%,115%)
t _{max}	-0.02h ^x	(-0.08h,+0.04h) ^x	+0.23h ^x	(+0.17h,+0.29h) ^x	+0.25h ^x	(+0.19h,+0.31h) ^x

^x: difference CI: confidence interval

Source of data: Table 14.2.4.2

Figure 4: Mean Plasma Concentrations of Diclofenac After Oral Administration of 25 mg of Diclofenac by the New and Old Process and as an Oral Solution to Healthy Volunteers Under Fasted Conditions



Study AAI-002000: The objective of this study was to compare plasma drug concentrations (PK) and pain relief efficacy (PD) in bunionectomy patients randomized to receive DPSGC 25 mg, DPSGC 50 mg, ProSorb-D™ liquid 12.5 mg, or Cataflam 50 mg every 8 hours for 8 days. The composition of ProSorb-D is essentially the same as the solution component of DPSGC. Plasma samples were collected on Study Day 1 after the first dose, on Study Day 4 for up to 8 hours after the first daily dose, and on Study Day 8 prior to the second dose. PK sampling was discontinued on Day 1 in the majority of patients once rescue medication was administered and therefore no PK analysis was possible.

RESULTS: The mean plasma concentrations on Day 4 are compared in Figure 5, and the mean PK parameters on Day 4 are compared in Table 9. While there was a dose-related increase in mean plasma concentrations (Figure 5) and C_{max} and AUC (Table 9) for the ProSorb-based formulations (DPSGC and ProSorb-D liquid), the increases were somewhat less than dose-proportional. Although single dose studies in healthy volunteers showed an increase in C_{max} for 50 mg DPSGC compared to Cataflam

the mean for Cataflam tablets and the 50 mg DPSGC were comparable. These observations may be a consequence of the small numbers of subjects per group, the use of different subjects per group, and the fact that food consumption was not controlled.

Figure 5: Mean Plasma Concentrations of Diclofenac on Day 4 During Oral Administration of DPSGC 25 mg and 50 mg, ProSorb-D 12.5 mg, and Cataflam 50 mg Every 8 Hours for 8 Days to Bunionectomy Patients

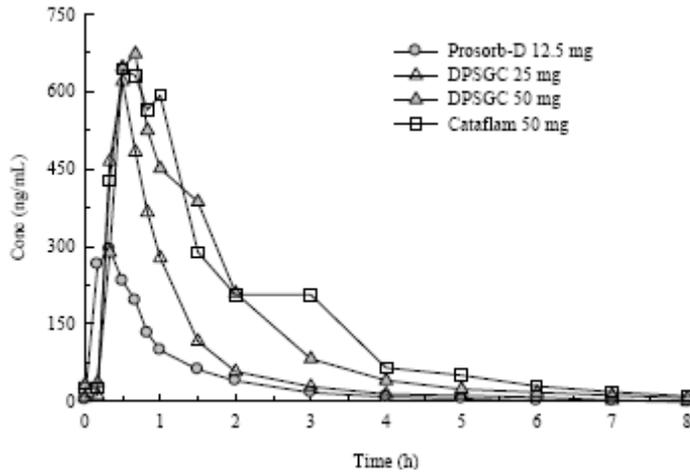


Table 9: PK data from Study AAI-002000

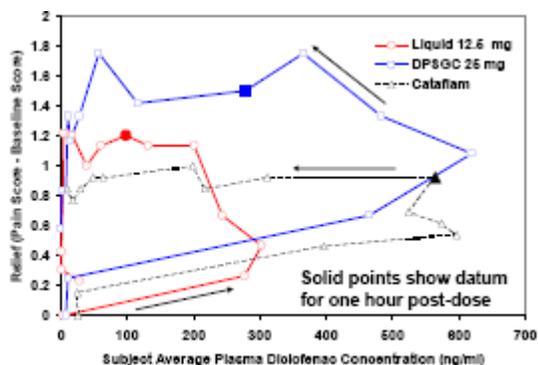
Study Ref. No.	Study Objective	Dose Route Formulation Lot No.	Subjects No. (M/F) Type Age: Mean (Range)	Pharmacokinetic Parameters (a)					
				Treatment	C _{max} (ng/mL)	T _{max} (h)	AUC (h·ng/mL)	C _{min} (ng/mL)	t _{1/2} (h)
AAI-002000	PK/PD comparison of DPSGC, ProSorb-D™, and Cataflam	25 mg Oral DPSGC Cap PDS-1027	13 (0/13) Bunionectomy Patients 42 (22-67)	Day 4 Day 8	832 ± 365	0.63 ± 0.33	642 ± 223	7 ± 8 1 ± 3	1.87 ± 0.87
		50 mg Oral DPSGC Cap PDS-1038	14 (1/13) Bunionectomy Patients 33 (19-51)	Day 4 Day 8	1,126 ± 565	0.95 ± 0.51	1,056 ± 165	32 ± 38 10 ± 18	2.22 ± 1.11
		12.5 mg Oral ProSorb-D Liquid 03159A	14 (1/13) Bunionectomy Patients 40 (22-72)	Day 4 Day 8	328 ± 119	0.49 ± 0.36	334 ± 116	3 ± 7 0 ± 0	1.19 ± 0.52
		50 mg Oral Cataflam Tab C2D 02111	12 (2/10) Bunionectomy Patients 45 (21-71)	Day 4 Day 8	1,086 ± 749	1.26 ± 0.94	1,380 ± 1,012	26 ± 33 21 ± 37	1.64 ± 0.37

Graphs of the mean change from baseline in pain intensity versus the mean plasma diclofenac concentration demonstrated a counterclockwise hysteresis, consistent with a “peripheral” effect compartment (Figure 6).

Pharmacodynamic modeling with a pain model reported in the literature was used to

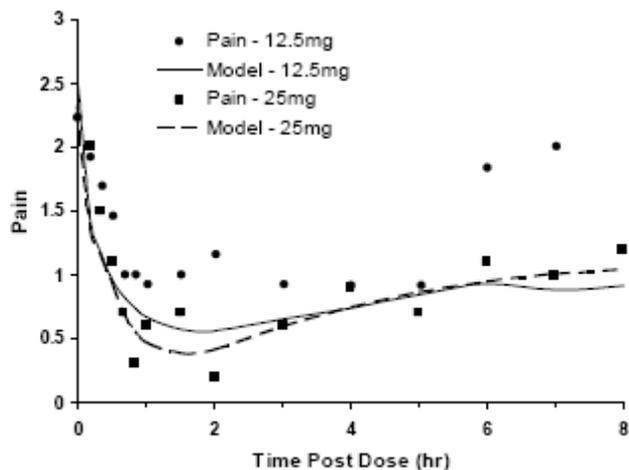
relate pain relief to the predicted effect compartment concentration, using a two compartment model to describe diclofenac pharmacokinetics. As shown in Figure 7, there was good agreement between the observed and model-predicted change from baseline in pain relief scores as a function of time.

Figure 6: Relationship Between the Mean Change from Baseline in Pain Relief Score and the Mean Plasma Concentrations of Diclofenac on Day 4 During Oral Administration of DPSGC 25 mg, ProSorb-D 12.5 mg, and Cataflam 50 mg



Note: Drug administration every 8 hours for 8 days to postbunionectomy patients

Figure 7: Observed and Model-Predicted Mean Change from Baseline in Pain Relief Scores During Oral Administration of DPSGC 25 mg and ProSorb-D 12.5 mg.



Note: Drug administration every 8 hours for 8 days to postbunionectomy patients

Comments to be sent to the sponsor:

- Submit the data files (as SAS transport files) and the input and output file for the PK-PD analysis for Study AAI-002000. Please specify the program that was used for the PK-PD analysis.
- Submit the full dissolution profile comparison between the clinical formulation series 1200 and to-be marketed formulation (series 1300/1400) with f-2 comparison.

Recommendation: The Office of Clinical Pharmacology, Division of Clinical Pharmacology 2 has reviewed of NDA 22-202 submitted on September 21, 2007 for filing and finds it filable from clinical pharmacology perspective.

Conclusion: The application is FILABLE. Please forward the above requests to the Sponsor.

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/s/

Emmanuel Fadiran
10/30/2007 08:54:43 AM
BIOPHARMACEUTICS

Suresh Doddapaneni
10/31/2007 08:04:26 AM
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