CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204592Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 204-592	**Reviewer:** Banu S. Zolnik, Ph.D.	
Division:	Division of Anesthesia, Analgesia and Addiction Products		
Applicant:	Iroko Pharmaceuticals	**Biopharmaceutics Secondary Signature:** Sandra Suarez-Sharp, Ph.D.	
Trade Name:	Zorvolex	**Biopharmaceutics Supervisory Lead (Acting)**: Richard Lostritto, Ph.D.	
Generic Name:	Diclofenac Acid	**Date Assigned:**	February 5, 2013
Indication	For the treatment of acute pain of mild to moderate (b) (4) in adults.	**Date of Review:**	September 12, 2013
Formulation/ Strength	Capsules, 18 mg and 35 mg	**Route of Administration**	Oral

SUBMISSIONS REVIEWED IN THIS DOCUMENT		
Submission Dates	**Date of informal/Formal Consult**	**Primary Review due in DARRTS**
December 20, 2012 May 01, 2013	NA	September 17, 2013
Type of Submission:	Original 505 (b)(2) Standard Review	
Review Key Points:	▪ Dissolution method and acceptance criterion	

SUMMARY OF BIOPHARMACEUTICS FINDINGS:

In NDA 204-592, Iroko Pharmaceuticals seeks approval to market Diclofenac Acid Capsules for the treatment of mild to moderate acute pain in adults. The proposed commercial strengths of diclofenac acid are 18 mg and 35 mg. Diclofenac capsules (b) (4) . The applicant conducted BE studies on both strengths.

The development program supporting this submission consisted of two phase 1 PK studies (DIC1-08001 and DIC1-12-07), one phase 2 (DIC 2-08-03), and one phase 3 (DIC 3-08-04) efficacy study. The Phase 1 study DIC1-12-07 and the pivotal phase 3 efficacy studies were conducted using the commercial formulation of Zorvolex capsules 18 mg, and 35 mg. All the PK studies are being reviewed by Office of Clinical Pharmacology (OCP).

This review evaluates and makes recommendations on the acceptability of the dissolution method and acceptance criterion.

DISSOLUTION METHOD AND ACCEPTANCE CRITERION

The following dissolution method and acceptance criterion for diclofenac acid capsules, 18 mg and 35 mg originally proposed by the Applicant are deemed acceptable:

USP Apparatus	Rotation Speed	Temperature	Volume	Medium	Acceptance Criterion
USP Type I (basket)	100 rpm	37°C ± 0.5°C	900 mL	10 mM citric acid buffer (pH 5.5) with 0.05 % SLS	Q= (b) (4) % in 20 minutes

Discriminating ability of the dissolution method was assessed during development. It was shown that the dissolution method discriminates for batches manufactured using (b) (4) [redacted] The results of the bioavailability studies comparing the proposed product to the reference drug product showed that changes in particle size did not result in improved bioavailability, suggesting that particle size may not be a critical material attribute in this case. However, the outcome of these results should be interpreted with caution since there may be potential confounding formulation effects.

The dissolution acceptance criterion was based on the results of the performance of biobatches, clinical, commercial, and stability batches.

RECOMMENDATION:

The ONDQA/Biopharmaceutics team has reviewed NDA 204-592 and its amendments submitted on May 1, 2013. The above mentioned dissolution method and dissolution acceptance criterion for Diclofenac Acid Capsules, 18 mg and 35 mg have been accepted by the ONDQA-Biopharmaceutics team.

From the Biopharmaceutics perspective, NDA 204-592 for Diclofenac Acid Capsules, 18 mg and 35 mg is recommended for APPROVAL.

Banu S. Zolnik, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Sandra Suarez-Sharp, Ph. D.
Biopharmaceutics Secondary Signature
Office of New Drug Quality Assessment

cc: R. Lostritto

BIOPHARMACEUTICS ASSESSMENT

1. BACKGROUND

Submission: Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID). The Applicant is seeking approval to market Zorvolex capsules, 18 mg and 35 mg administered orally three times a day for the treatment of mild to moderate acute pain in adults.

The Applicant submitted this 505 (b) (2) Application to rely on the Agency's findings of the safety and effectiveness of the previously approved drug product, Cataflam® 50 mg (diclofenac potassium immediate release tablets, NDA 20-142). Diclofenac capsules 18 mg and 35 mg are [redacted] (b) (4) composition. The applicant conducted BE studies on both strengths.

The development program supporting this submission consisted of two phase 1 PK studies (DIC1-08001 and DIC1-12-07), one phase 2 (DIC 2-08-03), and one phase 3 (DIC 3-08-04) efficacy study. The Phase 1 study DIC1-12-07 and the pivotal phase 3 efficacy studies were conducted using the commercial formulation of Zorvolex capsules 18 mg, and 35 mg. All the PK studies are being reviewed by OCP.

Review: The Biopharmaceutics review is focused on the acceptability of the dissolution method and acceptance criterion.

Drug Substance

Drug substance solubility increases with the increase in pH. Solubility of diclofenac is 0.08060 mg/mL in pH 5.75 Citrate Buffer with 0.05% SLS. For 18 mg, and 35 mg strength capsules, the concentration of diclofenac in 900 mL media is 0.019 mg/mL and 0.037 mg/mL, respectively. Therefore, solubility of diclofenac in the proposed media is approximately 4.5 times the 18 mg dose, and 2.3 times the 35 mg dose. It is estimated that sink conditions are achieved for both strenghts.

Drug Product

Zorvolex capsules are a reformulation of diclofenac, in the acid form. The manufacturing process involves [redacted] (b) (4) are microcrystalline cellulose, croscarmellose sodium, sodium stearyl fumarate and sodium lauryl sulfate. Below tables summarize the formulation of Zorvolex Capsules, 18 mg and 35 mg.

Table 2.3.P.2-1 Overview of the Components of Zorvolex Capsules 18 mg Used in Clinical Studies

Study Phase	Initial Phase 1[b] and Phase 2[c]		Phase 1[d]		Phase 3[e]	
Component	**% w/w**	**mg**	**% w/w**	**mg**	**% w/w**	**mg**
Diclofenac	(b) (4)					
Lactose monohydrate, NF						
Microcrystalline cellulose, NF						
Croscarmellose sodium, NF						
Sodium lauryl sulfate, NF						
Sodium stearyl fumarate, NF						
Purified water, USP[a]						
Total (mg/capsule)						

Abbreviations: NF=National Formulary; USP = United States Pharmacopeia; %w/w = %weight/weight

[a] Used in POC Formulation for Initial Phase 1 and Phase 2 (b) (4)

(b) (4)

Table 2.3.P.2-2 Overview of the Components of Zorvolex Capsules 35 mg Used in Clinical Studies

Study Phase	Initial Phase 1[b] and Phase 2[c]		Phase 1[d]		Phase 3[e]	
Component	**% w/w**	**mg**	**% w/w**	**mg**	**% w/w**	**mg**
Diclofenac	(b) (4)					
Lactose monohydrate, NF						
Microcrystalline cellulose, NF						
Croscarmellose sodium, NF						
Sodium lauryl sulfate, NF						
Sodium stearyl fumarate, NF						
Purified water, USP[a]						
Total (mg/capsule)						

Abbreviations: NF=National Formulary; USP = United States Pharmacopeia; %w/w = %weight/weight

[a] Used in POC Formulation for Initial Phase 1 and Phase 2 (b) (4)

(b) (4)

Reviewer's Comments

18 mg and 35 mg strengths used in commercial studies are (b) (4).

As noted above, the pharmacokinetic and pivotal clinical studies were conducted using the 18 mg and 35 mg capsule strengths.

2. DISSOLUTION METHOD

Dissolution testing is performed at release and on stability. The dissolution method being proposed for Zorvolex capsules, 18 mg and 35 mg is summarized below:

USP Apparatus	Rotation Speed	Temperature	Volume	Medium
USP Type I (basket)	100 rpm	37°C ± 0.5°C	900 mL	10 mM citric acid buffer (pH 5.5) with 0.05 % SLS

Reviewer's Comments:

The Applicant conducted dissolution studies at different basket rotation speeds of (b) (4) 100, (b) (4) rpm and showed that dissolution rate (b) (4) basket speed of (b) (4) rpm. Additionally, the Applicant varied SLS concentrations of (b) (4) (b) (4) in the media and showed all dissolution profiles were similar.

The discriminating ability of the dissolution method was evaluated by varying (b) (4) Therefore, the IR comment listed below on page 7 was conveyed to the Applicant regarding the impact of particle size on dissolution.

Table 1: Particle Size Distribution (b) (4) Dissolution Method Characterization Method page 12)

(b) (4)

4 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

3. DISSOLUTION ACCEPTANCE CRITERION

Applicant's Originally Proposed Dissolution Acceptance Criterion

The proposed dissolution acceptance criterion for 18 mg and 35 mg is as follows:

The Applicant's Proposed Acceptance Criterion
Q= (b) (4) % in 20 minutes

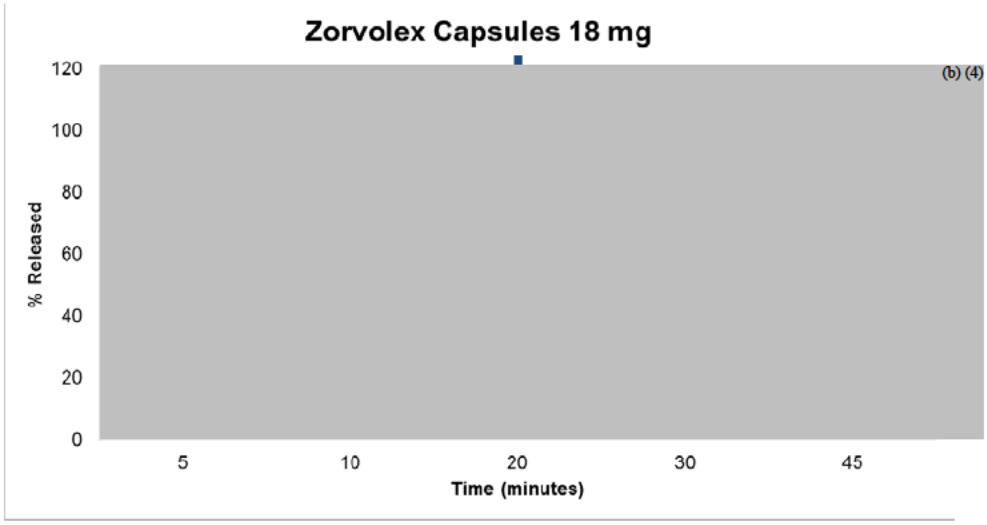

Figure 4: Comparative mean dissolution profiles plotted by the reviewer of three commercial stability batches of 18 mg strength

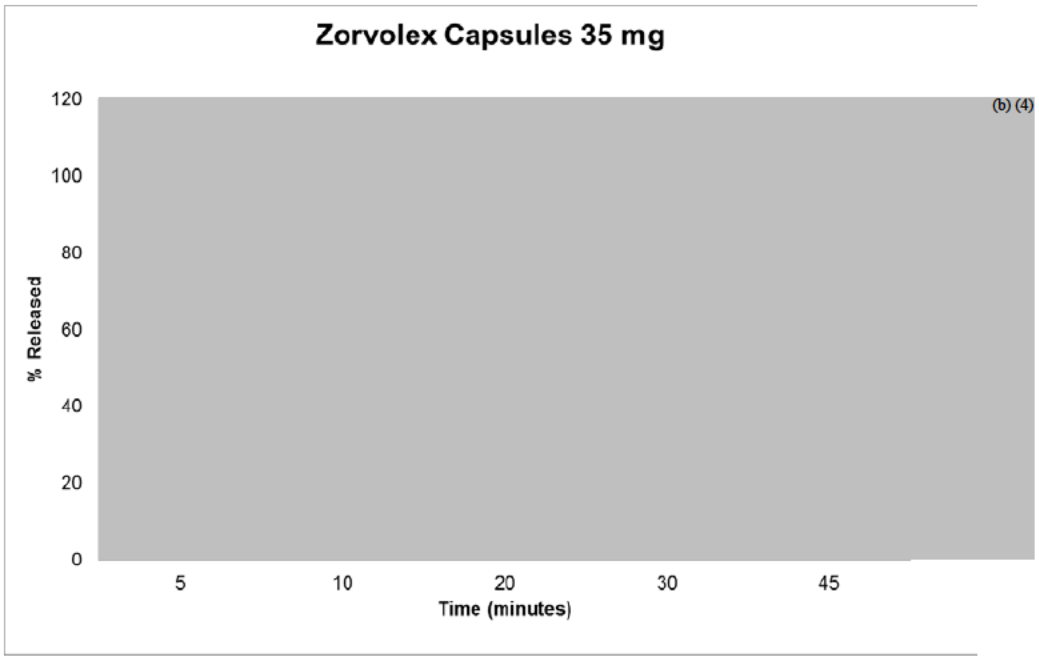

Figure 5: Comparative mean dissolution profiles plotted by the reviewer of three commercial stability batches of 35 mg strength

Reviewer's Comments:

Based on the figures above, the acceptance criterion proposed by the Applicant is found acceptable. It should be noted that for 18 mg (commercial batches L0309359, L0306589, L0306925, and L0306926) and 35 mg strength (commercial batches L0306590, L0306927 and L0306928) were used for the PK, the clinical and the stability studies.

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/s/

BANU S ZOLNIK
09/12/2013

SANDRA SUAREZ
09/16/2013

CLINICAL PHARMACOLOGY REVIEW

NDA: 202080	Submission Date: 12/20/2012
Relevant IND(s):	103880
Submission Type; Code:	505 (b) (2)
Reference Drug:	Cataflam (NDA 020142)
Brand Name:	Zorvolex™ capsules
Generic Name:	Diclofenac
Formulation; Strength(s):	Immediate-release capsules; 18 and 35 mg
Clinical Pharmacology Reviewer:	Suresh B Naraharisetti, Ph.D.
Team Leader:	Yun, Xu, Ph.D.
OCP Division:	Division of Clinical Pharmacology II
OND Division:	Division of Anesthesia and Analgesia Products
Sponsor:	Iroko Pharmaceuticals, LLC
Proposed Indication:	Treatment of mild to moderate acute pain in adults
Proposed Dosage Regimen:	18 mg or 35 mg orally three times a day (b) (4)

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1.0 Executive Summary

1.1 Recommendation

From the Clinical Pharmacology perspective, NDA 204592 submitted on 03/12/2012 is acceptable provided an agreement can be reached between the sponsor and the Agency regarding the language in the package insert.

1.2 Phase 4 Commitments

None

1.3. Summary of Clinical Pharmacology Findings

Iroko Pharmaceuticals, LLC submitted a 505 (b) (2) application for Zorvolex capsules, an immediate-release (IR) formulation of Diclofenac for the treatment of mild to moderate acute pain in adults. The application is relying on the prior findings of safety and efficacy of the reference drug, Cataflam® (NDA 020142). The proposed dose strengths are 18 and 35 mg, (b) (4). The sponsor proposed dosage regimen is 18 mg or 35 mg orally three times a day (b) (4).

Diclofenac is approved and marketed in the United States as immediate release, modified release (both delayed and extended release) and topical formulations for the treatment for multiple pain indications. The proposed Zorvolex capsules are a reformulation of diclofenac (in acid form) with reduced particle size. Zorvolex capsules are 20% lower in 'molar' diclofenac dose compared to Cataflam tablets (diclofenac potassium salt). The calculation of 20% lower molar dose is described in the section 2.1.1. The two 20% lower strengths of Zorvolex capsules are 18 mg and 35 mg compared to 25 mg and 50 mg strengths of Cataflam. The 25 mg strength of Cataflam is however discontinued and the Federal Register determination is that the product was not discontinued or withdrawn for safety or efficacy reasons.

Sponsor's rationale for reduced particle size of the proposed formulation is to increase the surface area to-mass ratio and thereby facilitate the rapid absorption in the GI tract. However, the label for Cataflam indicates that diclofenac is completely absorbed (100%) following oral administration, with mean peak concentrations (Tmax) appearing within 1 hour. Therefore, there may be little room for a new formulation to improve on the absorption of the drug.

For this NDA, the safety, the end of Phase 2, the pre-NDA meetings were held on 04/01/2009, 11/ 09/2010 and 06/7/2012, respectively under IND 103880. The clinical development program includes two clinical pharmacology studies and two clinical studies.

Clinical Pharmacology Studies:

Two clinical pharmacology studies, DIC1-08-01 and DIC1-12-07 are conducted for this application. Out of these two studies, DIC1-08-01 was conducted with initial proof of concept formulation and hence not reviewed expect for the food effect data of Cataflam.

The study DIC1-12-07 was conducted with commercial scale formulation and serves for assessing clinical pharmacology information for this product.

- **DIC1-12-07** (Phase 1): Relative bioavailability (BA), dose-proportionality and food effect study. This study was conducted with commercial scale formulation and fulfills the clinical pharmacology information of the proposed product from regulatory requirement perspective.

Clinical Studies:
Sponsor conducted one Phase 2 and one Phase 3 clinical studies. The Phase 2 study, DIC2-08-03 was conducted with initial proof of concept formulation. The Phase 3 study, DIC3-08-04 conducted commercial scale formulation serves as pivotal clinical safety and efficacy study for this product.

- DIC2-08-03 (Phase 2 study): Single dose study conducted in patients following surgical removal of impacted third molars. This study was conducted with a POC formulation and hence only serves as support to efficacy and safety of the pivotal trial DIC3-08-04, but not as a primary source of data.
- **DIC3-08-04** (Phase 3 study): Multiple dose, pivotal safety and efficacy study in patients with acute postoperative pain following bunionectomy. This study was conducted with a commercial scale formulation.

Relative bioavailability of Zorvolex compared to reference drug Cataflam:
The relative bioavailability of Zorvolex 35 mg capsules was compared to Cataflam 50 mg tablets under fasting and fed conditions in 35 healthy subjects.

- When taken under fasted conditions, 20% lower dose of Zorvolex capsules (35 mg) compared to reference Cataflam tablets (50 mg) results in 26% lower (geometric mean) peak concentrations (Cmax) and 23% lower (geometric mean) AUC (AUC_{0-t} and $AUC_{0-\infty}$). There was no difference in time to reach peak concentrations (Tmax) between Zorvolex capsules and Cataflam tablets and it was ~1 hr for both.
- When taken under fed conditions, the 20% lower dose of Zorvolex capsules (35 mg) compared to the Cataflam tablets (50 mg) results in a 48% lower (geometric mean) Cmax and 26% and 23% lower (geometric mean) AUC_{0-t} and $AUC_{0-\infty}$, respectively. The Tmax for Zorvolex was delayed by ~1 hr compared to Cataflam (Cataflam-2.33 hr vs. Zorvolex-3.32 hr) under fed conditions.
- There were no differences in elimination half-life (T1/2) between Zorvolex and Cataflam under fasted or fed conditions.

Reviewer comments on formulation:
The smaller particle size of Zorvolex capsules, as claimed by the sponsor has provided no additional advantage in either rate (Cmax and Tmax) or the extent of absorption (AUC) compared to Cataflam when taken under fasted conditions. In contrast, when taken under fed conditions, Zorvolex capsules has delayed rate (decreased Cmax and delayed Tmax) of absorption compared to the Cataflam

Dose Proportionality between 18 and 35 Zorvolex capsules:

- The two strengths Zorvolex capsules,18 and 35 mg (b) (4) pharmacokinetics for Cmax and AUC under fasted conditions

Food Effect on Zorvolex capsules:

The food effect was assessed for Zorvolex 35 mg capsules as well as reference drug Cataflam 50 mg tablets under fasting and fed conditions in 35 healthy subjects.

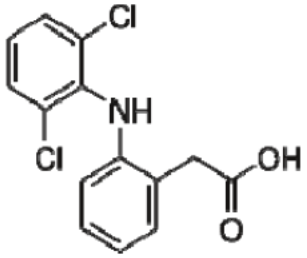
- When taken under fed conditions, Zorvolex capsules results in significant food effect in terms of reduced Cmax. Under fed conditions, Zorvolex capsules results in 60%, 14% and 11% lower Cmax, AUC_{0-t} and $AUC_{0-\infty}$, respectively compared to fasted conditions. Taking Zorvolex with food delayed the Tmax by 2.32 hr (~139 minutes) (1.0 hr fasted vs 3.32 hr fed).
- The reference drug Cataflam results in 43% and 28% lower Cmax under fed conditions without change in AUC, respectively in the studies DIC1-08-01 and DIC1-12-07. For food effect, the Cataflam label indicates 30% lower Cmax without change in AUC and can be dosed without regards to meals.
- The observed 60% lower Cmax for Zorvolex capsules in the food effect PK study is considered significant. Based on the single-oral-dose PK profile of Zorvolex capsules, the diclofenac is almost completely eliminated from the body by 8 hours (no accumulation). Since Zorvolex is administered TID (every 8 hr) and no accumulation from the previous dose, even after multiple dosing every-dose of Zorvolex capsules will have similar food effect as observed for a single dose. Hence, Zorvolex capsules are to be labeled as '*Taking Zorvolex with food may cause a reduction in effectiveness compared to taking Zorvolex on an empty stomach.*

Overall, adequate information has been provided characterizing the clinical pharmacology aspects of Zorvolex tablets.

2.0 Question Based Review

2.1 General Attributes of the Drug

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

Table 2.1.1: Physical-Chemical Properties of Diclofenac Acid	
Drug Name	Diclofenac Acid
Chemical Name	2-[2-(2,6-dichlorophenylamino)phenyl]acetic acid
Structure	
Molecular Formula	C14H11Cl2NO2
Molecular Weight	296.15
Appearance	white to slight yellowish (b) (4) powder

Formulation:
Zorvolex capsules are a reformulation of diclofenac with reduced particle size. Zorvolex capsules are 20% lower in diclofenac dose compared to Cataflam tablets (potassium salt). The two strengths of Zorvolex capsules are 18 mg and 35 mg compared to the 25 mg and 50 mg strengths of Cataflam. (b) (4)

(b) (4)

2.1.2. What is the regulatory history of diclofenac products?

Diclofenac is an approved drug that is already available and marketed in the United States as a treatment for multiple indications as shown in Table 2.1.2.

Table 2.1.2: Brand name diclofenac products and indications:

Drug Product	NDA	Approval Date	Dose Form	Indication
Zipsor	22202	06/16/2009	Capsule	Relief of mild to moderate pain
Pennsaid	20947	11/04/2009	Lotion	Treatment of signs and symptoms of osteoarthritis (OA)
Flector	21234	01/31/2007	Patch	Topical treatment of acute pain due to minor strains, sprains, and contusions.
Voltaren Gel	22122	10/17/2007	Gel	Treatment of OA of joints amenable to superficial treatment such as the hands and knees
Voltaren	19201	07/28/1988	Tablet	Relief of the signs and symptoms of OA and rheumatoid arthritis (RA),Acute or long-term use in the relief of signs and symptoms of ankylosing spondylitis
Cataflam	20142	11/24/1993	Tablet	Treatment of primary dysmenorrhea, Relief of mild to moderate pain; signs and symptoms of OA and RA
Voltaren XR	20254	03/8/1996	ER Tablet	Treatment of RA and OA

2.1.3 What is the composition of the to-be-marketed formulation of Zorvolex capsules?

The proposed commercial dosage forms of Zorvolex capsules include 18 mg and 35 mg strengths of diclofenac acid. Table 2.1.3 provides the quantitative composition for both tablet strengths and the function of each component.

Table 2.1.3: Composition of Zorvolex capsules (18 and 35 mg)

Component	Quality Standard	Function	Strength	
			18	35
			Amount per Capsule (mg/capsule weight)	Amount per Capsule (mg/capsule weight)
Diclofenac acid		Active pharmaceutical ingredient	18	35.0
Lactose monohydrate	NF	[redacted] (b) (4)		
Microcrystalline cellulose	NF			
Croscarmellose sodium	NF			
Sodium lauryl sulfate	NF			
Sodium stearyl fumarate	NF			
Total capsule fill weight	-			
			1 capsule #	1 capsule $

NF - National Formulary

Size 2 capsule with a blue body with "IP-203" imprinted in white ink and a light green cap with "18 mg" printed in white ink.

$ Size 1 capsule with a blue body with "IP- 204" imprinted in white ink and a green cap with "35 mg" printed in white ink

2.1.4 What are the proposed mechanism(s) of action and therapeutic indication(s)?
Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, 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. The proposed indication for Zorvolex capsules is for treatment of mild to moderate acute pain in adults.

2.1.5 What are the proposed dosage and route of administration?
Zorvolex capsules are intended for oral administration. The proposed dosage is 18 mg or 35 mg orally three times a day. (b) (4)

2.1.6 What are the core studies submitted in this NDA?
The clinical development program includes one pivotal clinical pharmacology study and one clinical safety and efficacy study.

- **DIC1-12-07** (Phase 1 study using commercial scale formulation): Relative BA, dose proportionality and food effect study. This study is a randomized, single-dose, five-way crossover, relative bioavailability study of Zorvolex capsules 18 mg and 35 mg and Cataflam® 50 mg tablets, in healthy subjects under fed and fasting conditions. This study fulfills the clinical pharmacology requirements of the proposed product.
- **DIC3-08-04** (Phase 3 study using commercial scale formulation): A Phase 3, randomized, double-blind, multiple-dose, parallel-group, active- and placebo-controlled study of Zorvolex capsules for the treatment of acute postoperative pain after bunionectomy. This is the pivotal safety and efficacy study for this product.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The clinical efficacy study, DIC3-08-04 for treatment of acute postoperative pain after bunionectomy and the clinical pharmacology study characterizing the formulation form the basis to support the dosing for this NDA

For final assessment of the safety and efficacy findings, see Clinical review by Dr. Steven Galati (reviewing Medical Officer). Following is a brief summary of the Clinical Efficacy assessment provided by Dr. Dr. Steven Galati:

Design: Phase 3, multicenter, randomized, double-blind, multiple-dose, parallel-group, active- and placebo-controlled study to evaluate the safety and efficacy of 2 dosing regimens of Zorvolex Capsules (35 mg 3 times daily [TID] or 18 mg TID) in subjects with acute postoperative pain after bunionectomy. On Day 1 of the study, when subjects requested pain medication, a Visual Analog Scale (VAS) assessment was to be performed. Subjects with a pain intensity rating ≥ 40 mm on a 100-mm VAS within 9

hours of discontinuation of regional anesthesia were to be eligible. Pain intensity (VAS) and pain relief (5-point categorical scale) assessments were to be performed during the 48 hour period after Time 0. Safety was to be assessed by the incidence of treatment-emergent AEs (TEAEs) and changes in vital sign measurements. TEAEs were to be recorded during the inpatient portion of the study as well as 1 week after discharge. The TEAEs after discharge were to be reported to the investigator at a 1 week follow-up visit.

Treatment

Once the pain intensity entry criteria were to be met, subjects were to be randomly assigned to 1 of 4 treatment groups (Table 2.2.1): Zorvolex Capsules 35 mg TID (n=107) or 18 mg TID (n=109); placebo (n=106); or celecoxib capsules 200 mg BID (n=106). Study drug was to be administered in a QID regimen for 48 hours after the first dose, with a maximum of 4 doses (active and/or dummy) in a 24-hour period. One tablet of hydrocodone/acetaminophen 10 mg/325 mg was to be allowed every 4 to 6 hours as needed for rescue.

Table 2.2.1: Dosing of Treatment Groups DIC3-08-04

	DAY 1				DAY 2			
Treatment group	**Dose 1 (0 h)**	**Dose 2 (8 h)**	**Dose 3 (12 h)**	**Dose 4 (16 h)**	**Dose 5 (24 h)**	**Dose 6 (32 h)**	**Dose 7 (36 h)**	**Dose 8 (40 h)**
35 mg TID	35 mg + P	35 mg	P	35 mg	35 mg	35 mg	P	35 mg
18 mg TID	18 mg + P	18 mg	P	18 mg	18 mg	18 mg	P	18 mg
Placebo	P + P	P	P	P	P	P	P	P
Celecoxib	200 mg + 200 mg	P	200 mg	P	200 mg	P	200 mg	P

Abbreviation: P, placebo.
Note: First dose on Day 1 only includes 2 capsules for each treatment regimen.

Source: Applicant's Protocol p. 39

Efficacy

The primary efficacy analysis was based on the primary endpoint VAS summed pain intensity difference (VASSPID) over 0 to 48 hours (VASSPID0-48) in the ITT population. Baseline pain on to the VAS pain scale was a mean (SD) value of 75.4 (16.27) mm and was evenly balanced across treatment groups. The primary efficacy analysis was performed using an analysis of covariance (ANCOVA) model, which included treatment effect as the factor and baseline pain intensity as the covariate (Model 1). For Model 1, the LS mean (standard error [SE]) was used in the primary analysis. In comparison with the placebo group, the largest difference in squares mean (SE) was seen for the 35-mg diclofenac treatment group (446.946 [122.2935]) indicating a statistically significant difference ($P < 0.001$). Differences in the 18-mg diclofenac group 316.145 (121.5971) ($P < 0.010$) and the celecoxib treatment group 313.119 (122.5676) ($P <$

0.011) compared with the placebo group were of a lesser magnitude than the 35mg diclofenac.

Safety

- Deaths: No subjects died during the trial.
- Serious Adverse Events (SAEs): One subject experienced a serious AE during the trial. The subject was in the Celecoxib group.
- Discontinuations Due to Adverse Events: No subject discontinued due to an AE during the trial.
- Common Adverse Events: 77 (72%) and 84 (77.1%) subjects experienced at least 1 TEAE in the 35mg and 18mg diclofenac groups, respectively. 86 (81.1%) and 83 (78.3%) subjects experienced at least 1 TEAE in the Celecoxib and placebo groups, respectively. The most frequent AEs were nausea (23.4%, 31.2%), headache (10.3%, 15.6%) and dizziness (4.7%, 15/6%) in 35mg and 18mg diclofenac groups, respectively.

Conclusion

Diclofenac was evaluated at a dose of 18-35 mg, given three times per day, in one adequate and well-controlled trial. Both the 18mg and 35mg groups showed statistical significance in the primary analysis when compared to placebo. In general, there were supportive findings in both treatment groups through the secondary analyses as well. There is a trend towards improved efficacy and time to onset among the diclofenac 35mg subjects compared to the 18mg group. However, no clear dose response can be determined from the design and analyses performed.

2.2.2 What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology study data? How was it measured?

No biological biomarker was assessed in this NDA. In the randomized, double-blind, multiple-dose, parallel-group, active- and placebo-controlled study (DIC3-08-04), the primary efficacy end point was the s VAS summed pain intensity difference (VASSPID) over 0 to 48 hours (VASSPID0-48).

2.2.3. What are the general PK characteristics of the drug?

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).

2.2.4 Were the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Diclofenac analgesic activity is primarily due to the parent compound diclofenac; only the parent compound was measured to assess the PK parameters.

2.2.5. What are the characteristics of drug absorption? Are Zorvolex parameters dose proportional?

From the Cataflam package insert, it is known that 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. Hence its absolute bioavailability is 55%.

Dose proportionality of Zorvolex tablets:
The dose proportionality between two strengths, 18 and 35 mg Zorvolex capsules was assessed as part of study DIC1-12-07 under fasting conditions. Note that the two strengths Zorvolex, 18 and 35 mg (b) (4).

Treatments:

- Zorvolex capsules 18 mg Fasted (lot #L0309359)
- Zorvolex capsules 35 mg Fasted (lot #L0309360)

The mean ± SD concentration-time profiles and PK parameters for 18 and 35 mg Zorvolex capsules are shown in the Figures 2.2.5 and Table 2.2.5a, respectively. The dose proportionality for dose normalized diclofenac plasma PK parameters (35 mg vs. 18 mg) is shown in the Table 2.2.5b. The dose normalized PK parameters show that 18 and 35 mg Zorvolex capsules results in dose proportional pharmacokinetics for Cmax and AUC under fasted conditions

2.3. Intrinsic factors

2.3.1. What is the pediatric plan?

Zorvolex is a capsule formulation and this application triggers PREA because it is a new dosage form. For pediatric studies, Sponsor requested for a waiver from birth to (b) (4) and deferral for of pediatric studies for (b) (4) 17 years, however not acceptable to the Division.

Below is the pediatric studies requirement for this application, based on the discussion with Pediatric Review Committee (PeRC), on September 4, 2013.

- Partial waiver in pediatric patients aged birth to < one year
  - Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients of this age and is not likely to be used in a substantial number of pediatric patients in this age group.
- Deferral for pediatric patients aged 1 to < 18 years. Required pediatric studies as below:
  - Study 1: An open-label pharmacokinetic and safety study or studies of an age appropriate formulation of diclofenac in pediatric patients 6 to < 18 years of age with acute pain.

- Study 2: An open-label pharmacokinetic and safety study or studies of an age appropriate formulation of diclofenac in pediatric patients 2 to < 6 years of age with acute pain.
- Study 3: A pharmacokinetic, safety, and efficacy study or studies of an age appropriate formulation of diclofenac in pediatric patients 1 to < 2 years of age with acute pain.

Reviewer comments:
Based on the discussion with PeRC on September 4, 2013, the PeRC agreed with the Division to grant a deferral for pediatric patients aged 1 to less than 18 years because the product is ready for approval in adults. The PeRC recommended granting a partial waiver in pediatric patients aged birth to less than one year because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients of this age and is not likely to be used in a substantial number of pediatric patients in this age group. (b) (4)

[redacted]

2.4. General Biopharmaceutics

2.4.1. What is the relative bioavailability of Zorvolex® capsules compared to the reference drug, Cataflam tablets?

The relative bioavailability of Zorvolex® 35 mg capsules was compared to reference drug Cataflam 50 mg tablets under fasted and fed conditions as a part of study DIC1-12-07. This study was done using commercial scale formulation of Zorvolex. A total number of 35 healthy subjects completed the treatments.

Treatments:

• Test	Zorvolex capsules	18 mg (lot #L0309359)	Fasted
• Test	Zorvolex capsules	35 mg (lot #L0309360)	Fasted
• Test	Zorvolex capsules	35 mg	Fed
• Reference	Cataflam tablets	50 mg (lot #FXPB)	Fasted
• Reference	Cataflam tablets	50 mg	Fed

There was at least a 7-day washout interval between doses. Blood samples for PK were collected for 12 hours.

Results:

The plasma concentration-time profiles comparing Zorvolex 35 mg capsules and Cataflam 50 mg tablets under fasted and fed conditions are shown in figures 2.4.1a and 2.4.1b, respectively. The corresponding PK parameters are shown in Table 2.4.1a. The geometric mean ratios and the 90% CIs for AUC_{0-t} and $AUC_{0-\infty}$ and Cmax are shown in the Table 2.4.1b. The summary of results is shown below:

- When taken under fasted conditions, 20% lower dose of Zorvolex capsules (35 mg) compared to reference Cataflam tablets (50 mg) results in 26% lower (geometric mean) peak concentrations (Cmax) and 23% lower (geometric mean) AUC (AUC_{0-t} and $AUC_{0-\infty}$). There was no difference in time to reach peak concentrations (Tmax) between Zorvolex capsules and Cataflam tablets and it was ~1 hr for both.
- When taken under fed conditions, the 20% lower dose of Zorvolex capsules (35 mg) compared to the Cataflam tablets (50 mg) results in 48% lower (geometric mean) Cmax and 26% and 23% lower (geometric mean) AUC_{0-t} and $AUC_{0-\infty}$, respectively. The Tmax for Zorvolex was delayed by ~1 hr compared to Cataflam (Cataflam-2.33 hr vs. Zorvolex-3.32 hr) under fed conditions.
- There were no differences in elimination half-life (T1/2) between Zorvolex and Cataflam under fasted or fed conditions.

Reviewer comments:
The smaller particle size of Zorvolex capsules, as claimed by the sponsor has provided no additional advantage in either rate (Cmax and Tmax) or the extent of absorption (AUC) compared to Cataflam when taken under fasted conditions. In contrast, when taken under fed conditions, Zorvolex capsules has delayed rate of absorption compared to the Cataflam (decreased Cmax and delayed Tmax).

Figure 2.4.1a: Mean diclofenac plasma concentration-time profiles after administration of Zorvolex capsules and Cataflam tablets under fasting conditions.

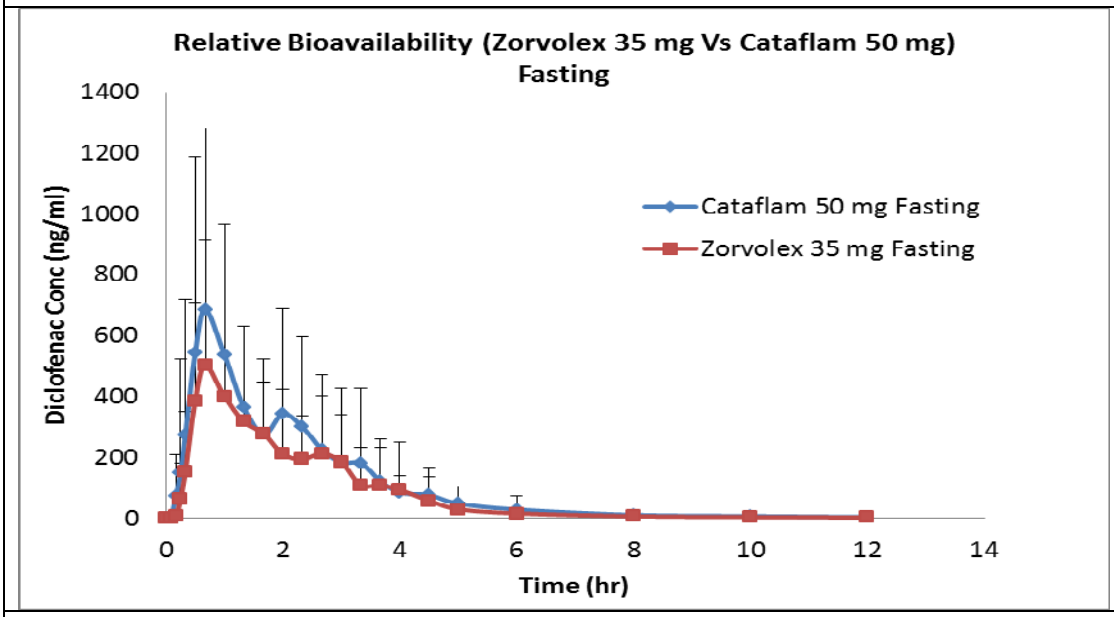


Figure 2.4.1b: Mean diclofenac plasma concentration-time profiles after administration of Zorvolex capsules and Cataflam tablets under fed conditions.

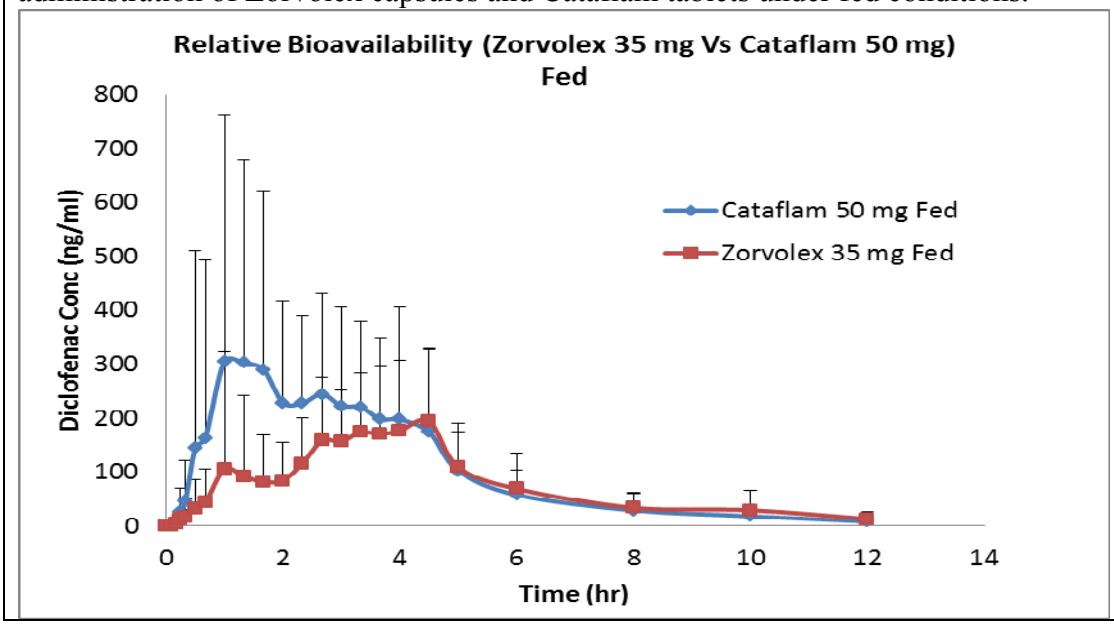


Table 2.4.1a. Pharmacokinetic parameters comparing Zorvolex and Cataflam under fasting and fed conditions.

Parameter Mean ± SD	**Zorvolex (35 mg) Fasting**	**Cataflam (50 mg) Fasting**	**Zorvolex (35 mg) Fed**	**Cataflam (50 mg) Fed**
Cmax (ng/mL)	868.7 ± 352.8	1194.2 ± 543.2	354.8 ± 169.9	712.5 ± 392.8
AUC_{0-t} (hr*ng/mL)	1004.7 ± 242.8	1318.8 ± 307.9	861.2 ± 209.9	1178.0 ± 271.4
$AUC_{0-\infty}$ (hr*ng/mL)	1001.1 ± 229.7	1334.1 ± 312.5	876.1 ± 211.5	1204.0 ± 275.7
Tmax (hr)*	1.00 (0.47 – 4)	1.00 (0.25-4.48)	3.32 (0.5-10.0)	2.33 (0.5- 4.53)
T1/2 (hr)	2.09 ± 0.49	2.26 ± 0.60	2.24 ± 0.82	2.27 ± 0.65
Tlast (hr)	10.70 ± 1.43	11.36 ± 1.24	11.74 ± 1.06	11.79 ± 0.78
Clast(ng/mL)	3.71 ± 0.99	4.62 ± 3.44	12.80 ± 13.28	8.09 ± 6.51

*Median (min-max)

Table 2.4.1b: Geometric LS mean ratios and 90% confidence intervals for Cmax AUC_{0-t} and $AUC_{0-\infty}$of Zorvolex versus Cataflam in fasted and fed conditions.

Parameter	**Geometric LS mean ratio (90% CI of ratio) [Zorvolex 35 mg / Cataflam 50 mg]**	
	Fasting	**Fed**
Cmax (ng/mL)	0.744 (0.628, 0.881)	0.518 (0.438, 0.612)
AUC_{0-t} (ng.h/mL)	0.767 (0.735, 0.799)	0.738 (0.707, 0.770)
$AUC_{0-\infty}$ (ng.h/mL)	0.768 (0.738, 0.800)	0.769 (0.737, 0.801)

2.4.2 What is the effect of food on the BA of Zorvolex?

For Zorvolex tablets food effect was evaluated as part of the study DIC1-12-07. The food effect on reference drug Cataflam was also evaluated in the study DIC1-12-07 This study was done using commercial scale formulation of Zorvolex. A total number of 35 healthy subjects completed the treatments.

Treatments:

- Test Zorvolex capsules 35 mg (lot #L0309360) Fasted
- Test Zorvolex capsules 35 mg Fed
- Reference Cataflam tablets 50 mg (lot #FXPB) Fasted
- Reference Cataflam tablets 50 mg Fed

There was at least a 7-day washout interval between doses. Blood samples for PK were collected for 12 hours.

Results:

The Figure 2.4.2a shows the plasma concentration-time profiles of Zorvolex under fasted and fed conditions. The figure 2.4.2b shows the plasma concentration-time profiles for Cataflam under fasted and fed conditions. The food effect PK parameters for diclofenac after Zorvolex and Cataflam are presented in Table 2.4.2a. The geometric mean ratios and the 90% CIs for AUC_{0-t} and $AUC_{0-\infty}$and Cmax are shown in the Table 2.4.2b. The summary of results is shown below:

- When taken under fed conditions, Zorvolex capsules results in significant food effect in terms of reduced Cmax. Under fed conditions, Zorvolex capsules results in 60%, 14% and 11% lower Cmax, AUC_{0-t} and $AUC_{0-\infty,}$ respectively compared to fasted conditions. Taking Zorvolex with food delayed the Tmax by 2.32 hr (~139 minutes) (1.0 hr fasted vs 3.32 hr fed).
- The reference drug Cataflam results in 43% and 28% lower Cmax under fed conditions without change in AUC, respectively in the studies, DIC1-08-01 and DIC1-12-07. For food effect, the Cataflam's label indicates 30% lower Cmax without change in AUC with food and can be dosed without regards to meals.
- In the conducted multiple dose bunionectomy clinical trial (DIC3-08-04) in which Zorvolex dosing regimen was 18 or 35 mg TID, as per the clinical review, both dose strengths of Zorvolex capsules are efficacious when compared to placebo. In this bunionectomy trial, the food intake in subjects with respect to drug-dosing was not monitored for all the doses administered. Only the initial dose was given on the empty stomach and for subsequent doses the food intake was not monitored. Hence the food effect on pain scores (efficacy) could not be determined from this trail.
- Even though food effect in the efficacy trail could not be assessed, the observed 60% lower peak concentrations for Zorvolex capsules in the food effect PK study is considered significant. In addition, based on the single-oral-dose PK profiles of Zorvolex capsules, the diclofenac is almost completely eliminated from the body by 8 hours (no accumulation). Since Zorvolex is administered TID (every 8 hr) and no accumulation from the previous dose, even after multiple dosing every-dose of Zorvolex capsules will have similar food effect as observed for a single dose. Hence, Zorvolex capsules are to be labeled as '*Taking Zorvolex with food may cause a reduction in effectiveness compared to taking Zorvolex on an empty stomach.*.

Figure 2.4.2a: Mean diclofenac plasma concentration-time profiles after administration of Zorvolex capsules (35 mg) under fasting and fed conditions.

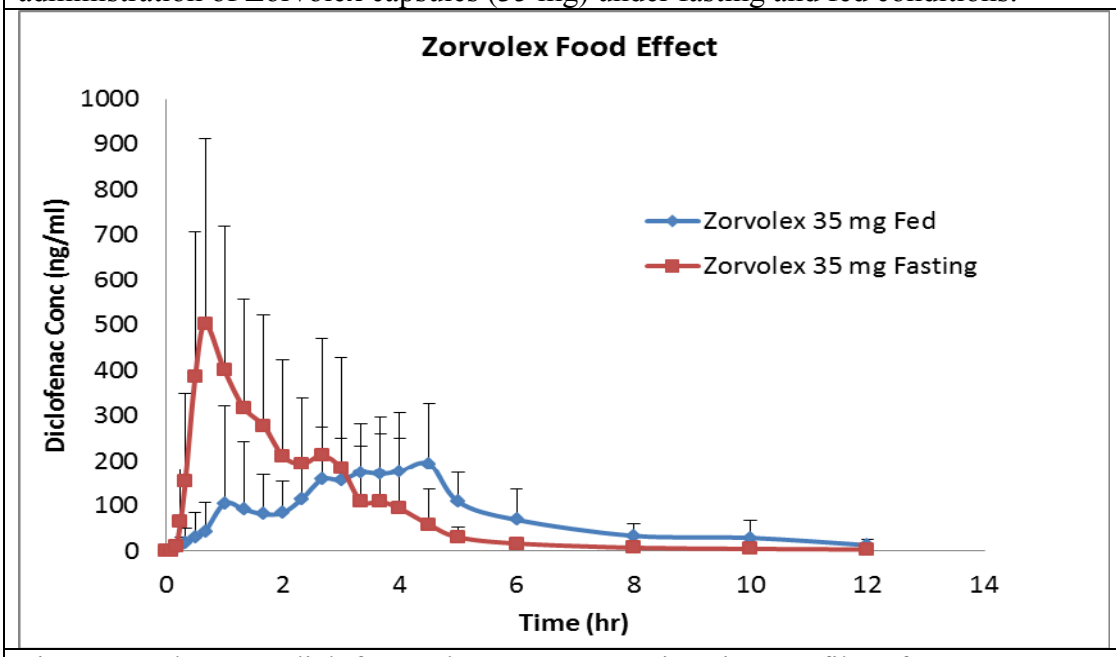


Figure 2.4.2b: Mean diclofenac plasma concentration-time profiles after administration of Cataflam (50 mg) under fasting and fed conditions.

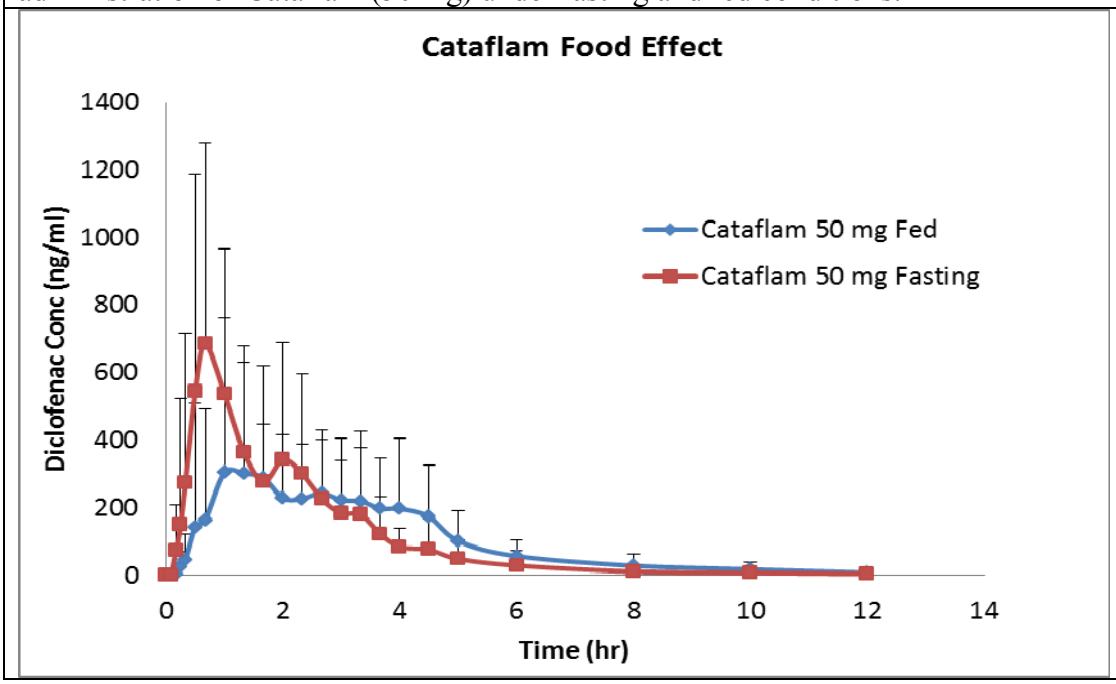


Table 2.4.2a. Pharmacokinetic parameters of diclofenac after administration of Zorvolex and Cataflam under fasting and fed conditions

Parameter Mean ± SD	Zorvolex		Cataflam	
	Fasting	**Fed**	**Fasting**	**Fed**
Cmax (ng/mL)	868.7 ± 352.8	354.8 ± 169.9	1194.2 ± 543.2	712.5 ± 392.8
AUC_{0-t} (hr*ng/mL)	1004.7 ± 242.8	861.2 ± 209.9	1318.8 ± 307.9	1178.0 ± 271.4
$AUC_{0-\infty}$ (hr*ng/mL)	1001.1 ± 229.7	876.1 ± 211.5	1334.1 ± 312.5	1204.0 ± 275.7
Tmax (hr)* (range)	1.00 (0.47 – 4)	3.32 (0.5-10.0)	1.00 (0.25-4.48)	2.33 (0.5- 4.53)

*median

Table 2.4.2b: Ratio of means and 90% CI of AUC and Cmax comparing Zorvolex fasted vs. fed conditions and Cataflam fasted vs. Cataflam fed.

PK parameter	Treatment Ratio (90% CI of ratio)	
	Zorvolex Fasted / Zorvolex Fed	**Cataflam Fasted / Cataflam Fed**
Cmax	0.399 (0.337, 0.473)	0.573 (0.484, 0.678)
AUC_{0-t}	0.858 (0.824, 0.895)	0.894 (0.858, 0.932)
$AUC_{0-\infty}$	0.892 (0.855, 0.931)	0.904 (0.869, 0.941)

Reviewer comments:
In the two studies (DIC1-08-01 and DIC1-12-07) conducted by sponsor, Cataflam food effect was evaluated, and it showed that taking Cataflam with food causes 43% and 28% lower Cmax, respectively without change in AUC. The Cataflam label shows 30% lower Cmax without change in AUC with food and is labeled to be taken without regards to meals.
The observed food effect for Zorvolex warrants labeling recommendation. The following labeling comments for the food effect are proposed by this reviewer. Deletion is shown by Strike-through text and addition is shown by underline text.

Food effect labeling language:
(b) (4) Taking ZORVOLEX with food causes a significant decrease in the rate but not the overall extent of systemic absorption of diclofenac compared with taking ZORVOLEX on an empty stomach. Zorvolex capsules shows 60% lower Cmax, 11% lower $AUC_{inf,}$ and 2.32 hr delayed Tmax (1.0 hr during fasted versus 3.32 hr during fed) under fed condition compared to fasted condition. Decreased Cmax may be associated to decreased effectiveness. Taking ZORVOLEX with food may cause a reduction in effectiveness compared to taking ZORVOLEX on an empty stomach.

2.5. Analytical Section

2.5.1 Are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies? What is the QC sample plan? What are the accuracy, precision and selectivity of the method?

Clinical Facility:
PAREXEL International LLC, 195 West Street, Waltham, MA 02451

- Clinical study DIC1-12-07 was conducted between 07/16/2012 (first subject) to 09/26/2012 (last subject).

Bio-analytcial Facility:
(b) (4)

- Assays were conducted between (b) (4).

The plasma concentrations of diclofenac were analyzed using validated LC-MS/MS assays.

Bio-analytcial Validation:
The range of calibrators and QCs used for studies were:

- Calibrators: 2.442, 4.884, 9.769, 19.54, 39.07, 78.15, 156.3, 312.6, 625.2, 1250 and 2501 ng/mL
- Quality controls: 2.442, 6.010, 12.02, 62.50, 125.0, 250.0, 500.0, 1000, 2000 and 4000 (dilution) ng/ml

Accuracy and Precision over the range:

- Accuracy (expressed as % bias): -6.9 – 1.4
- Precision (expressed as % CV): 2.9 – 10.5

Retention times:

- Diclofenac - ~ 1.64 minutes
- Indomethacin (internal standard) - ~ 1.70 minutes
- Total run time: 2.2 minutes

Recovery (mean extraction yields)

- Diclofenac: ~ 89 % (mean % CV = 8.7)
- Internal standard: ~ 93 % (% CV = 5.6)

Stability:

Stock solution stability:

- Diclofenac: 15 days at RT, at ~5 °C and at ~ -20 °C
- Indomethacin: 15 days at RT, at ~5 °C and at ~ -20 °C

Freeze and thaw stability:

- freeze-thaw cycles

Short-term matrix stability:

- 17 hours and 7 minutes at room temperature

Long-term matrix stability from a previous study*: 657 days when stored at ~ -20 ºC

**Determination of Diclofenac in Human Plasma by HPLC, Method Validation Report,* [redacted]

3. Detailed Labeling Recommendations

The following labeling comments are proposed by this reviewer. Deletion is shown by Strike-through text and addition is shown by underline text.

Reviewer Comments:

This labeling recommendation for hepatic impairment for Zorvolex is updated in comparison to previous diclofenac products. The updated sections are in 2.3 and 12.3. These recommendations are due to new requirements based on the SEALD LABELING high level comments.

2.2 Non-Interchangeability with Other Formulations of Diclofenac

Zorvolex (diclofenac [redacted]) capsules have not shown equivalent systemic exposure [redacted] to other formulations of oral diclofenac [redacted]. Other formulations contain salt forms of diclofenac, i.e. diclofenac potassium or sodium, while Zorvolex contains the [redacted]. Therefore, [redacted] to substitute similar dosing strengths of diclofenac for Zorvolex. [redacted]

2.3 Dosage Adjustments in Patients with Hepatic Impairment

Patients with hepatic disease may require reduced doses of ZORVOLEX compared to patients with normal hepatic function [*see Clinical Pharmacology*]. Start with the lowest effective dose for the shortest duration in patients with hepatic impairment, and monitor the patients carefully for adverse reactions.

USE IN SPECIAL POPULATIONS

12.3 Pharmacokinetics

[redacted]

[redacted]

27 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4.2 Individual Study Synopses:

Note: Study synopses in this section were extracted from the NDA submission

4.2.1 Study Designs:

DIC1-12-07 (Phase 1): Relative bioavailability (BA), dose-proportionality and food effect study. This study was conducted with commercial scale formulation and it fulfills the clinical pharmacology information of the proposed product from regulatory requirement perspective.

4.2.2 Study Synopses

Study DIC1-12-07

Name of Sponsor/Company: Iroko Pharmaceuticals, LLC	**Individual Study Table Referring to Part of the Dossier**		**(For National Authority Use Only)**
Name of Finished Product: Zorvolex™ (diclofenac [redacted] (b) (4)) Capsules 18 mg and 35 mg	**Volume:** **Page:**		
Name of Active Ingredient: Diclofenac			
Title of Study:	A Randomized, Single-Dose, Five-Way Crossover, Relative Bioavailability Study of Zorvolex™ (diclofenac [redacted] (b) (4)) Capsules 18 mg and 35 mg and Cataflam® 50 mg Tablets, in Healthy Subjects under Fed and Fasting Conditions		
Principal Investigator:	Olukemi Olugemo, MD		
Study Center(s):	PAREXEL Early Phase Clinical Unit, 3001 South Hanover Street, Baltimore, Maryland 21225, United States of America		
Publication:	None at the time of writing this clinical study report.		
Development Phase:	Phase 1 – Bioavailability, food-effect, dose proportionality		
Studied Period:	**First subject enrolled:**	16 July 2012	
	Last subject completed:	26 September 2012	

Study Objective(s):

The primary objectives of this study were:

- To determine the relative bioavailability of diclofenac following administration of 35 mg Test capsules [Zorvolex™ (diclofenac [redacted] (b) (4)) Capsules] versus the 50 mg Reference (Cataflam®) tablet when administered to healthy subjects under fasting conditions,
- To determine the effect of food on the rate and extent of absorption of a single dose of the 35 mg (Test) capsule formulation of Zorvolex administered to healthy subjects under fed and fasting conditions,
- To determine the effect of food on the rate and extent of absorption of a single dose of the 50 mg Cataflam (Reference) tablet formulation of diclofenac potassium administered to healthy subjects under fed and fasting conditions,
- To evaluate the dose proportionality between 18 mg and 35 mg Test capsule formulations of Zorvolex administered to healthy subjects under fasting conditions

Study Design:

This was a single-center, randomized, open-label, 5-period, 5-treatment, 5-sequence, single-dose crossover PK study in which 40 healthy adult subjects were scheduled to receive 5 separate single-dose administrations of diclofenac. The treatments under investigation were:

- Treatment A: Zorvolex Capsules 18 mg Single Dose: 1 x 18 mg capsule given after a fast on an empty stomach
- Treatment B: Zorvolex Capsules 35 mg Single Dose: 1 x 35 mg capsule given after a fast on an empty stomach
- Treatment C: Zorvolex Capsules 35 mg Single Dose: 1 x 35 mg capsule given 30 minutes after a Standard Food and Drug Administration (FDA) High Fat breakfast
- Treatment D: Cataflam (diclofenac potassium) 50 mg tablet Single Dose: 1 x 50 mg tablet given after a fast on an empty stomach
- Treatment E: Cataflam (diclofenac potassium) 50 mg tablet Single Dose: 1 x 50 mg tablet given 30 minutes after a Standard FDA High Fat breakfast

Name of Sponsor/Company: Iroko Pharmaceuticals, LLC	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: Zorvolex™ (diclofenac (b) (4) Capsules 18 mg and 35 mg	Volume:	
Name of Active Ingredient: Diclofenac	Page:	

Methodology:

Healthy adult male and female subjects who met all study eligibility criteria were randomized equally to 1 of 5 predetermined sequences of treatment administration. Subjects were administered the investigational medicinal products (IMPs) in the order of their assigned sequence. There was at least a 7-day washout interval between administrations. The study was divided into a Screening Phase followed by 5 sequential Treatment Periods with intervening Washout Periods scheduled between administrations.

Study Plan

Assignment	Study Day	Washout Period
Screening Phase	Days -28 to -1	Not applicable
Treatment Period 1	Day 1	Days 2 to 7
Treatment Period 2	Day 8	Days 9 to 14
Treatment Period 3	Day 15	Days 16 to 21
Treatment Period 4	Day 22	Days 23 to 28
Treatment Period 5	Day 29	End of Treatment

The Screening phase took place within 28 days before the administration of the first dose of IMP. Subjects were required to provide written informed consent to participate in the study before any protocol-specified procedures or evaluations were completed. During the Screening phase, subjects were evaluated against the protocol-specific inclusion and exclusion criteria to determine their eligibility for participation in the study.

In Treatment Period 1, subjects who met eligibility requirements were admitted to the clinical research unit (CRU) the evening before the scheduled morning dose. All subjects underwent at least a 10-hour overnight fast. The following morning, subjects randomized to receive Treatments A, B, and D were administered a single oral dose of IMP with 240 mL of water on an empty stomach. Subjects randomized to receive Treatments C and E were administered a single oral dose of IMP with 240 mL of water 30 minutes after starting the FDA high-fat breakfast.

Subjects were confined to the CRU until at least 12 hours after IMP administration. Blood samples (approximately 4 mL each) for PK analysis were collected at the following times: pre-dose (time 0) and 5, 10, 15, 20, 30, 40 min, 1 hr, 1 hr 20 min, 1 hr 40 min, 2 hr, 2 hr 20 min, 2 hr 40 min, 3 hr, 3 hr 20 min, 3 hr 40 min, 4 hr, 4 hr 30 min, 5, 6, 8, 10 and 12 hrs after dosing. Blood samples for safety assessments were performed at specified times throughout confinement.

In Treatment Periods 2, 3, 4, and 5, subjects returned to the CRU after a 7-day Washout Period (from dose to dose). The same study procedures were performed as in Treatment Period 1; however, the subjects followed the order of their randomly assigned sequences and "crossed over" to a different treatment. A blood sample for safety assessments was collected with the last PK sample in Treatment Period 5.

Subjects who required follow-up for adverse events (AEs), additional physical examinations, or additional vital signs, electrocardiogram (ECG), or clinical laboratory assessments, were to return to the CRU as deemed appropriate by the investigator.

Number of Study Subjects (Planned and Analyzed):

Planned for completion	40
Enrolled and randomized:	40
Completed:	35
Analyzed:	40

Name of Sponsor/Company: Iroko Pharmaceuticals, LLC	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: Zorvolex™ (diclofenac (b) (4) Capsules 18 mg and 35 mg	Volume:	
	Page:	
Name of Active Ingredient: Diclofenac		

Diagnosis and Main Criteria for Inclusion:

The study population consisted of healthy adult males or females between 18 and 55 years of age (inclusive), with a body mass index between 18 and 30 kg/m^2 (inclusive). Subjects were in good health, as determined by lack of clinically significant abnormalities in health and/or laboratory assessments. Acceptable forms of contraception were to be used during the study until at least 7 days after study completion.

Test Product, Treatment A, Dose and Mode of Administration, Batch Number:

Treatment A:	Zorvolex Capsules
Batch number:	L0309359
Mode of administration:	Oral
Strength:	18 mg
Dose:	1 Capsule

Test Product, Treatments B and C, Dose and Mode of Administration, Batch Number:

Treatment B and C:	Zorvolex Capsules
Batch number:	L0309360
Mode of administration:	Oral
Strength:	35 mg
Dose:	1 Capsule

Reference Product, Treatments D and E, Dose and Mode of Administration, Batch Number:

Treatment D:	Cataflam (diclofenac potassium) Tablet
Lot number:	FXPB
Mode of administration:	Oral
Strength:	50 mg
Dose:	1 Tablet

Duration of Treatment: For an individual subject, the duration of the clinical study was up to approximately 10 weeks (including a Screening phase up to 28 days).

Criteria for Evaluation:

Pharmacokinetics:

The following PK parameters were calculated from the concentrations of diclofenac determined in plasma following single dose administration in each Treatment Period:

- Area under the concentration-time curve from time zero to the time of last sample with a quantifiable concentration (AUC_{0-t})
- Area under the concentration-time curve from time 0 extrapolated to infinity ($AUC_{0-\infty}$)
- Maximum measured plasma concentration (C_{max})
- Time to maximum measured concentration (t_{max})
- Apparent terminal elimination rate constant (λ_z)
- Apparent terminal elimination half-life ($t_{½}$)

Safety:

- Incidence of treatment-emergent adverse events (TEAEs)
- Change in physical examination findings
- Change in clinical laboratory test results
- Change in vital signs measurements

Name of Sponsor/Company: Iroko Pharmaceuticals, LLC	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: Zorvolex™ (diclofenac (b) (4) Capsules 18 mg and 35 mg	Volume: Page:	
Name of Active Ingredient: Diclofenac		

Statistical Methods:

All original and derived parameters as well as demographic data are listed and described using summary statistics.

Frequency counts (number of subjects [n] and percentages) were made for each qualitative variable. Descriptive statistics (n, mean, standard deviation [SD], median, minimum and maximum) were calculated for each quantitative variable (unless otherwise stated) and are presented by treatment (if applicable).

If not otherwise specified, 'baseline' refers to the last non-missing observation before IMP administration. All statistical tests were two-sided and were performed at the 0.05 level of significance, unless otherwise stated.

All listings were sorted by subject (randomization number), treatment period, parameter (if applicable) and time-point (if applicable). All tables were sorted by ascending treatment, i.e., A, B, C, D then E (if applicable).

For changes from baseline, only changes subsequent to the defined baseline are shown in the listings and tabulations; in the listings any repeat/unscheduled measurements are included in chronological order with the scheduled measurements, no unscheduled and or repeated measurements (unless used as the baseline measurement) are included in the tables.

Summary of Results:

Demographic Characteristics of Subjects:

Forty (40) subjects were randomized into treatment and 35 subjects (87.5%) completed all 5 study periods. Five subjects discontinued before study completion. The 40 subjects who received at least one dose of study drug were included in the full analysis set and ranged in age from 18 to 52 years, with a mean age of 33.4 years. There were 21 male subjects (52.5%) and 19 female subjects (47.5%). With regard to race, 30 subjects (75.0%) were Black or African American and 10 subjects (25.0%) were White. The mean height was 171.8 cm, with a range of 154 to 191 cm. The mean body weight was 74.09 kg, with a range of 53.4 to 96.4 kg. The mean BMI was 25.02 kg/m^2, with a range of 20.6 to 30.0 kg/m^2. Demographic findings were reflective of a healthy adult population.

Name of Sponsor/Company: Iroko Pharmaceuticals, LLC	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: Zorvolex™ (diclofenac [redacted] (b) (4) Capsules 18 mg and 35 mg	Volume: Page:	
Name of Active Ingredient: Diclofenac		

Pharmacokinetic Results:

Consistent with the Statistical Analysis Plan, all subjects who received any amount of study drug and had at least 1 non-zero concentration after dosing were used in the pharmacokinetic analyses. A summary of the descriptive statistics for the five treatments is presented in the table below. Statistical test results for the pharmacokinetic parameters for diclofenac are also summarized in the tables that follow.

Pharmacokinetic Parameters of Diclofenac by Treatment (PK Population)

Parameter	Statistics	Treatment				
		Treatment A Zorvolex Capsules 18 mg (fast)	Treatment B Zorvolex Capsules 35 mg (fast)	Treatment C Zorvolex Capsules 35 mg (fed)	Treatment D Cataflam 50 mg (fast)	Treatment E Cataflam 50 mg (fed)
C_{max} (ng/mL)	n	39	37	38	37	38
	Mean	495.79	868.72	354.76	1194.21	712.52
	SD	202.928	352.833	169.906	543.147	392.817
	CV (%)	40.9	40.6	47.9	45.5	55.1
	Geometric Mean	454.34	803.72	321.12	1087.06	620.82
t_{max} (h)	n	39	37	38	37	38
	Median	1.000	1.000	3.320	1.000	2.330
	Minimum	0.50	0.47	0.50	0.25	0.50
	Maximum	4.50	4.00	10.00	4.48	4.53
λ_z (1/h)	n	39	36	32	37	38
	Mean	0.399	0.349	0.371	0.333	0.332
	SD	0.1170	0.0854	0.2482	0.1194	0.1063
	CV (%)	29.3	24.4	67.0	35.8	32.0
	Geometric Mean	0.384	0.340	0.333	0.318	0.318
$t_{½}$ (h)	n	39	36	32	37	38
	Mean	1.872	2.096	2.243	2.265	2.267
	SD	0.5012	0.4926	0.8235	0.5973	0.6448
	CV (%)	26.8	23.5	36.7	26.4	28.4
AUC_{0-t} (h.ng/mL)	n	39	37	38	37	38
	Mean	490.224	1004.656	861.199	1318.841	1178.007
	SD	105.0911	242.7496	209.9178	307.8542	271.3502
	CV (%)	21.4	24.2	24.4	23.3	23.0
	Geometric Mean	478.358	979.751	837.294	1287.310	1150.399
$AUC_{0-\infty}$ (h.ng/mL)	n	39	36	32	37	38
	Mean	499.213	1001.130	876.144	1334.061	1204.032
	SD	105.5112	229.7418	211.4453	312.5063	275.6847
	CV (%)	21.1	22.9	24.1	23.4	22.9
	Geometric Mean	487.466	978.937	851.956	1301.961	1175.869

AUC = Area under the curve; C_{max} = Maximum concentration; t_{max} = Time of maximum concentration; * t_{max} is summarized by Median and range; $t_{½}$ = half-life

Name of Sponsor/Company: Iroko Pharmaceuticals, LLC	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: Zorvolex™ (diclofenac (b) (4) Capsules 18 mg and 35 mg	Volume:	
Name of Active Ingredient: Diclofenac	Page:	

Under fasting conditions, the AUC_{0-t} and $AUC_{0-\infty}$ for the Test Product, Zorvolex (diclofenac (b) (4) (b) (4) Capsules 35 mg, were approximately 23% lower than that observed for the Reference product, Cataflam (diclofenac potassium) 50 mg tablets. Similarly, the C_{max} for the Zorvolex Capsules 35 mg (Test Product) was 26% lower than Cataflam 50 mg tablets (Reference Product). The 90% confidence intervals for the geometric mean ratios for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ between these two treatments were below the equivalence limits (0.8 to 1.25). Median t_{max} values, 1.00 hour, for Zorvolex 35 mg and Cataflam 50 mg were identical. As expected, $t_{½}$ values were also comparable for the Zorvolex 35 mg and Cataflam 50 mg products.

Statistical Analysis of Relative Bioavailability of Diclofenac Plasma Pharmacokinetic Parameters (PK Population) for Treatments B:D (35 mg Test product vs. 50 mg Reference product [fasting conditions])

Parameter (unit)	Treatment	N*	Geometric LS Mean	Geometric LS Mean 95% CI	Treatment Ratio (B/D) (%)	90% CI of Ratio
C_{max} (ng/mL)	B	37	808.35	700.03, 933.44	0.744	0.628, 0.881
	D	37	1086.53	940.71, 1254.94		
AUC_{0-t} (ng.h/mL)	B	37	976.99	907.95, 1051.27	0.767	0.735, 0.799
	D	37	1274.22	1184.14, 1371.16		
$AUC_{0-\infty}$ (ng.h/mL)	B	36	989.65	919.22, 1065.48	0.768	0.738, 0.800
	D	37	1288.35	1196.92, 1386.76		

CI = confidence interval; LS: least squares; N = number of subjects in the pharmacokinetic population; % = percentage

Treatment B: Zorvolex Capsules 35 mg Single Dose: 1 x 35 mg capsule (Fasting).
Treatment D: Cataflam (diclofenac potassium) 50 mg tablet Single Dose: 1 x 50 mg tablet (Fasting).
Mixed model ANOVA with fixed effects for treatment, period and sequence, and random effect for subject nested within sequence was utilized.
Least squares (LS) means, Ratio of LS means, and their confidence intervals (CI) were transformed back to the original scale.
* Shows the number of subjects exposed to the treatment.
Subject 6, randomized to sequence 'DCAEB' never received treatment B. Subject 7, randomized to sequence 'ABCDE' never received treatments B, C, D, E.
Subject 25, randomized to sequence 'ABCDE' never received treatments D and E. Subject 35, randomized to sequence 'EADBC' never received treatments D, B, C.

Name of Sponsor/Company: Iroko Pharmaceuticals, LLC	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: Zorvolex™ (diclofenac (b) (4) Capsules 18 mg and 35 mg	Volume: Page:	
Name of Active Ingredient: Diclofenac		

For the treatments of 18 mg and 35 mg doses of Zorvolex Capsules under fasting conditions, dose proportional increases in AUC_{0-t} and $AUC_{0-\infty}$ were confirmed by comparison of dose-normalized ln transformed AUC_{0-t} and $AUC_{0-\infty}$. The 90% CI of the ratios of the dose-normalized geometric means were within the range 0.8 to 1.25, and the dose-normalized geometric mean ratios between the 18 mg and 35 mg Zorvolex Capsules (Test Product) were 1.041 and 1.031, respectively, close to the value of 1.00. The 90% CI of the ratio of the dose-normalized geometric means of C_{max} fell just outside the lower limit of the 0.8 to 1.25 range; the dose-normalized geometric mean ratio between the 18 mg and 35 mg Zorvolex Capsules (Test Product) was 0.904 for C_{max}.

Statistical Analysis of Dose Proportionality for Dose Normalized Diclofenac Plasma Pharmacokinetic Parameters (PK Population) for Treatments B:A (35 mg vs. 18 mg Test Product [Fasted Subjects])

Parameter (unit)	Treatment	N*	Geometric LS Mean	Geometric LS Mean 95% CI	Treatment Ratio (B/A) (%)	90% CI of Ratio
C_{max} (ng/mL)	A	39	25.41	22.18, 29.12		
	B	37	22.96	19.96, 26.41	0.904	0.777, 1.050
AUC_{0-t} (ng.h/mL)	A	39	26.80	24.82, 28.93		
	B	37	27.90	25.82, 30.15	1.041	0.995, 1.089
$AUC_{0-\infty}$ (ng.h/mL)	A	39	27.06	25.13, 29.15		
	B	36	27.90	25.88, 30.09	1.031	0.987, 1.077

CI = confidence interval; LS: least squares; N = number of subjects in the pharmacokinetic population; % = percentage

Treatment A: Zorvolex Capsules 18 mg Single Dose: 1 x 18 mg capsule (Fasting).
Treatment B: Zorvolex Capsules 35 mg Single Dose: 1 x 35 mg capsule (Fasting).
Mixed model ANOVA with fixed effects for treatment, period and sequence, and random effect for subject nested within sequence was utilized.
Least squares (LS) means, Ratio of LS means, and their confidence intervals (CI) were transformed back to the original scale. Dependent variable in the analysis was the natural logarithm of the dose normalized PK parameter.
The ANOVA was subset on treatments A and B.
* Shows the number of subjects exposed to the treatment.
Subject 6, randomized to sequence 'DCAEB' never received treatment B. Subject 7, randomized to sequence 'ABCDE' never received treatments B, C, D, E.
Subject 32, randomized to sequence 'BDECA' never received treatment A. Subject 35, randomized to sequence 'EADBC' never received treatments D, B, C.
Evidence of dose proportionality holds if the estimated ratio of geometric means is close to 1 and if the 90% CI for the ratio of geometric means are within the range 0.8 to 1.25.

Name of Sponsor/Company: Iroko Pharmaceuticals, LLC	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: Zorvolex™ (diclofenac (b) (4) Capsules 18 mg and 35 mg	Volume:	
Name of Active Ingredient: Diclofenac	Page:	

Similar to the dose normalized results, non-dose normalized AUC_{0-t} and $AUC_{0-\infty}$ demonstrated a dose proportional increase in overall systemic absorption, as the ratios of non-dose normalized geometric means between the 18 mg and 35 mg Zorvolex Capsules were 2.024 and 2.005, respectively, close to the value of 1.94 used to define a linear dose-effect. The ratio of non-dose normalized geometric means between the 18 mg and 35 mg Zorvolex Capsules was 1.757 for C_{max}.

Statistical Analysis of Dose Proportionality for Non-Dose Normalized Diclofenac Plasma Pharmacokinetic Parameters (PK Population) for Treatments B:A (35 mg vs. 18 mg Test Product [Fasted Subjects])

Parameter (unit)	Treatment	N*	Geometric LS Mean	Geometric LS Mean 95% CI	Treatment Ratio (B/A) (%)	90% CI of Ratio
C_{max} (ng/mL)	A	39	457.43	399.16, 524.22		
	B	37	803.63	698.68, 924.33	1.757	1.512, 2.042
AUC_{0-t} (ng.h/mL)	A	39	482.34	446.72, 520.79		
	B	37	976.41	903.53, 1055.16	2.024	1.935, 2.117
$AUC_{0-\infty}$ (ng.h/mL)	A	39	487.17	452.36, 524.65		
	B	36	976.65	905.70, 1053.15	2.005	1.918, 2.095

CI = confidence interval; LS: least squares; N = number of subjects in the pharmacokinetic population; % = percentage

Treatment A: Zorvolex Capsules 18 mg Single Dose: 1 x 18 mg capsule (Fasting).
Treatment B: Zorvolex Capsule 35 mg Single Dose: 1 x 35 mg capsule (Fasting).
Mixed model ANOVA with fixed effects for treatment, period and sequence, and random effect for subject nested within sequence was utilized.
Least squares (LS) means, Ratio of LS means, and their confidence intervals (CI) were transformed back to the original scale. Dependent variable in the analysis was the natural logarithm of the PK parameter.
The ANOVA was subset on treatments A and B.
* Shows the number of subjects exposed to the treatment.
Subject 6, randomized to sequence 'DCAEB' never received treatment B. Subject 7, randomized to sequence 'ABCDE' never received treatments B, C, D, E.
Subject 32, randomized to sequence 'BDECA' never received treatment A. Subject 35, randomized to sequence 'EADBC' never received treatments D, B, C.
Evidence of dose proportionality holds if the estimated ratio of geometric means is close to 1.94.

Name of Sponsor/Company: Iroko Pharmaceuticals, LLC	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: Zorvolex™ (diclofenac [redacted] (b) (4)) Capsules 18 mg and 35 mg	Volume: Page:	
Name of Active Ingredient: Diclofenac		

As described for diclofenac, food decreased the rate but not the extent of absorption. Administration of Zorvolex Capsules 35 mg under fasted and fed conditions showed that food decreased AUC_{0-t} and $AUC_{0-\infty}$ values by 11% and 14% respectively. The 90% CI on the geometric mean ratios for AUC_{0-t} and $AUC_{0-\infty}$ for Zorvolex Capsules 35 mg administered under fed versus fasting conditions were contained within the interval 0.8 to 1.25.

In contrast, C_{max} was decreased by 60% after administration under fed conditions compared to fasted. Median t_{max} was 3.32 hours when Zorvolex Capsules 35 mg was administered under fed conditions compared to 1.00 hour when administered under fasting conditions. The difference (90% CI) in median t_{max} values was 1.67 (1.26, 2.01) hours for the fed vs. fasting comparison. These results indicate a definite food effect on the rate (C_{max} and t_{max}) but not the overall extent (AUC_{0-t} and $AUC_{0-\infty}$) of absorption for Zorvolex (diclofenac [redacted] (b) (4)) Capsules 35 mg.

Similarly, administration of Cataflam 50 mg under fasted and fed conditions showed that food had minimal effect on overall systemic absorption of diclofenac. AUC_{0-t} and $AUC_{0-\infty}$ values were reduced by 11% and 10%, respectively, following administration with food. The 90% confidence intervals (CI) for the geometric mean ratios for AUC_{0-t} and $AUC_{0-\infty}$ for Cataflam administered under fed and fasting condition were contained within the interval 0.8 to 1.25).

C_{max} was decreased by 43% after administration of Cataflam 50 mg tablets under fed conditions compared to fasted. The lower limit of the 90% CI for C_{max} following Cataflam 50 mg tablets administration to fed subjects was well below the lower limit of the interval for fasted subjects. Median t_{max} was 2.33 hours following Cataflam administration under fed conditions compared with 1.00 hour when administered under fasting conditions. The difference (90% CI) in median t_{max} values was 1.15 (0.67, 1.59) hours for the fed vs. fasting comparison. These results indicate a definite food effect on the rate of absorption (t_{max} and C_{max}) for the Cataflam (diclofenac potassium) 50 mg tablets.

Statistical Analysis of Food-Effect for Diclofenac Plasma Pharmacokinetic Parameters (PK Population)

Parameter (unit)	Treatment	N*	Geometric LS Mean	Geometric LS Mean 95% CI	Treatment Ratio (%)	90% CI of ratio
C_{max} (ng/mL)	B	37	808.35	(700.03, 933.44)	0.399	(0.337, 0.473)
	C	38	322.79	(280.07, 372.03)		
	D	37	1086.53	(940.71, 1254.94)	0.573	(0.484, 0.678)
	E	38	622.07	(539.62, 717.12)		
AUC_{0-t} (ng.h/mL)	B	37	976.99	(907.95, 1051.27)	0.858	(0.824, 0.895)
	C	38	838.63	(779.59, 902.14)		
	D	37	1274.22	(1184.14, 1371.16)	0.894	(0.858, 0.932)
	E	38	1139.46	(1059.26, 1225.74)		
$AUC_{0-\infty}$ (ng.h/mL)	B	36	989.65	(919.22, 1065.48)	0.892	(0.855, 0.931)
	C	32	883.03	(819.14, 951.89)		
	D	37	1288.35	(1196.92, 1386.76)	0.904	(0.869, 0.941)
	E	38	1164.76	(1082.42, 1253.35)		

Parameter (unit)	Treatment Comparison	N*	Hodges-Lehmann Estimate Median Difference	90% CI for Estimate of Median Difference
t_{max} (h)	C vs B	37	1.67	(1.26, 2.01)
	E vs D	37	1.15	(0.67, 1.59)

CI = confidence interval; LS: least squares; N = number of subjects in the pharmacokinetic population; % = percentage

Treatment B: Zorvolex Capsules 35 mg Single Dose: 1 x 35 mg capsule (Fasting). Treatment C: Zorvolex Capsules 35 mg Single Dose: 1 x 35 mg capsule (Fed).
Treatment D: Cataflam (diclofenac potassium) 50 mg tablet Single Dose: 1 x 50 mg tablet (Fasting). Treatment E: Cataflam

Name of Sponsor/Company: Iroko Pharmaceuticals, LLC	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: Zorvolex™ (diclofenac [redacted] (b)(4)) Capsules 18 mg and 35 mg	Volume: Page:	
Name of Active Ingredient: Diclofenac		

(diclofenac potassium) 50 mg tablet Single Dose: 1 x 50 mg tablet (Fed).
Mixed model ANOVA with fixed effects for treatment, period and sequence, and random effect for subject nested within sequence was utilized.
Least squares (LS) means, Ratio of LS means, and their confidence intervals (CI) were transformed back to the original scale. Dependent variable in the analysis was the natural logarithm of the PK parameter.
In all comparisons the fasting treatment was used as the reference treatment.
* Shows the number of subjects exposed to the treatment.
Subject 6, randomized to sequence 'DCAEB' never received treatment B. Subject 7, randomized to sequence 'ABCDE' never received treatments B, C, D, E.
Subject 25, randomized to sequence 'ABCDE' never received treatments D, E. Subject 35, randomized to sequence 'EADBC' never received treatments D, B, C.
In addition for t_{max}: The difference in medians and its 90% confidence interval was estimated using the methodology of Hodges-Lehmann for paired samples.
In addition for t_{max}: The CI of the median difference was obtained by applying a normal approximation to the Wilcoxon Signed-Rank distribution.
In addition for t_{max}: 'N' is the number of subjects used in the analysis. This is the number of subjects with complete data for both treatments.

Safety Results:

Six (6) subjects (15%) each reported one (1) AE during the study. There were four (4) TEAEs reported by 2 subjects (12.5%) who received the Zorvolex Capsules (Test Product) and 2 TEAEs reported by 2 subjects (12.5%) who received the Cataflam tablets (Reference Product). The other 2 AEs were reported by 2 subjects and occurred prior to first dosing. Five (5) of the 6 AEs reported were assessed by the Investigator as not related to study drug administration, and one (1) as unlikely to be related to study medication (Subject 37, headache, Reference Product). No subject discontinued before study completion due to an AE and there were no deaths or SAEs.

Conclusion:

Results from this study showed that overall systemic exposure to diclofenac from the Test Product, Zorvolex Capsules 35 mg was more than 20% lower (compared to the overall systemic exposure from the Reference Product, Cataflam 50 mg tablets), and supported the development rationale.

The C_{max} for the Zorvolex Capsules 35 mg (Test Product) was 26% lower than Cataflam 50 mg tablets (Reference Product).

Consistent with published diclofenac studies, food decreased the rate but not the extent of absorption of Zorvolex Capsules 35 mg and Cataflam 50 mg tablets when administered under fed conditions. The magnitude of the diclofenac decrease in C_{max} following administration of Zorvolex Capsules 35 mg was somewhat greater than the decrease observed for Cataflam 50 mg tablets under fed conditions.

The overall analysis of Zorvolex Capsules 18 mg and 35 mg showed dose proportionality based on the assessment of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, however, there were some analyses where the ratios of C_{max} did not fulfill the targeted ratio that defined dose proportional pharmacokinetics. This was not surprising based on the variability of diclofenac C_{max} described in published studies.

Based on review of published pharmacokinetic studies performed on diclofenac, the results of this study for C_{max} and t_{max} for Zorvolex Capsules (Test Product) and Cataflam tablets (Reference Product) are considered to be consistent with the variable absorption kinetics that have previously been described for diclofenac.

Zorvolex Capsules and Cataflam tablets were generally well tolerated. There were no withdrawals due to AEs and no deaths or serious adverse events occurred.

Date of Report: Final 1.0, 03 December 2012

This study was conducted in compliance with International Conference on Harmonization (ICH) Good Clinical Practice guidelines (GCP) and the Declaration of Helsinki.

4.3 Cover Sheet and OCPB Filing/Review Form

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	*NDA-204592*	Brand Name	*Zorvolex™*
OCP Division (I, II, III, IV, V)	*II*	Generic Name	*Diclofenac*
Medical Division	*DAAAP*	Drug Class	*NSAID*
OCP Reviewer	*Suresh B Naraharisetti*	Indication(s)	*Acute pain*
OCP Team Leader	*Yun Xu*	Dosage Form	*Immediate- release Capsule*
Pharmacometrics Reviewer		Dosing Regimen	*TID*
Date of Submission		Route of Administration	*Oral*
Estimated Due Date of OCP Review		Sponsor	Iroko Pharma
Medical Division Due Date		Priority Classification	
PDUFA Due Date	October 20, 2013		

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.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods	X	1		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -		1		
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:				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**	**1**		**Cataflam as reference**
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**1**		
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				**Yes**
Literature References				
Total Number of Studies		**4**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Comments to be communicated to the Sponsor in the Day-74 letter

- ***Zorvolex has two strengths, 35 mg and 18 mg based on diclofenac acid. The listed drug you relied on, Cataflam, has a strength of 50 mg based on diclofenac potassium salt. Provide clear justification with detail calculation on how Zorvolex Capsules have a 20% reduction in the diclofenac dose compared to the Cataflam 50 mg tablets. The calculation should be based on free base of diclofenac.***

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

BACKGROUND

Iroko Pharmaceuticals submitted a 505 (b) (2) NDA (204592) for Zorvolex™ for the indication of the treatment of acute pain of mild to moderate (b) (4) in adults. Per Sponsor, Zorvolex is formulation of diclofenac with reduced particle size (b) (4) The smaller particle size results in an increased surface area to- mass ratio, facilitates rapid absorption in the GI tract. Per Sponsor it offers the potential to improve the safety profile while providing comparable pain relief to Cataflam 50 mg tablets.

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  - This study was conducted with proof-of concept formulation. The study was repeated with similar design using commercial scale formulation in the DIC1-12-07. The PK information of cataflam from this study will be reviewed

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  - This study was conducted with commercial scale formulation. The study is pivotal study assessing relative bioavailability, dose proportionality and food effect of Zorvolex™ capsules.

Clinical Studies:

- **Phase 2 DIC2-08-03:**
  - Design: A phase 2, randomized, double-blind, single-dose, parallel-group, active- and placebo-controlled study of diclofenac (b) (4) formulation capsules for the treatment of pain after surgical removal of impacted third molars (n=202)
  - This study was conducted with proof-of concept formulation.

- **Phase 3 DIC3-08-04:** Pivotal trail
  - Design: A phase 3, randomized, double-blind, multiple-dose, parallel-group, active- and placebo-controlled study of diclofenac (b) (4) formulation capsules for the treatment of acute postoperative pain after bunionectomy (n= 428)
  - This study was conducted with a commercial scale formulation
  - Treatment duration: QID regimen for 48 hours after the first dose, with a maximum of 4

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doses (active and/or dummy) in a 24-hour period. The timing of trial drug dosing was based on the current dosage and administration recommendations for Cataflam

(b) (4)

Food effect Labelling: This product has a significant food effect and is labeled to be taken 1 hour before or 2 hours after a meal. This is different from the listed drug, Cataflam, which does not have recommendation on food in dose and administration.

20 % dose reduction claim:
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The conducted clinical pharmacology studies meet the regulatory requirements for filing and this application is filable from the clinical pharmacology perspective. Based on the preliminary review, the following comment needs to be communicated to the sponsor in 74-day letter.

Comments to be communicated to the Sponsor in the Day-74 letter

- ***Zorvolex has two strengths, 35 mg and 18 mg based on diclofenac acid. The listed drug you relied on, Cataflam, has a strength of 50 mg based on diclofenac potassium salt. Provide clear justification with detail calculation on how Zorvolex Capsules have a 20% reduction in the diclofenac dose compared to the Cataflam 50 mg tablets. The calculation should be based on free base of diclofenac.***

Suresh Babu Naraharisetti	February 1, 2013
Reviewing Clinical Pharmacologist	Date
Xu Yun	February 1, 2013
Team Leader/Supervisor	Date

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

/s/

SURESH B NARAHARISETTI
09/16/2013

YUN XU
09/16/2013

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	***NDA*-204592**	**Brand Name**	*Zorvolex™*
OCP Division (I, II, III, IV, V)	***II***	**Generic Name**	***Diclofenac***
Medical Division	***DAAAP***	**Drug Class**	***NSAID***
OCP Reviewer	***Suresh B Naraharisetti***	**Indication(s)**	***Acute pain***
OCP Team Leader	***Yun Xu***	**Dosage Form**	***Immediate- release Capsule***
Pharmacometrics Reviewer		**Dosing Regimen**	***TID***
Date of Submission		**Route of Administration**	***Oral***
Estimated Due Date of OCP Review		**Sponsor**	**Iroko Pharma**
Medical Division Due Date		**Priority Classification**	
PDUFA Due Date	**October 20, 2013**		

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.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods	**X**	**1**		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -		**1**		
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:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**	**1**		**Cataflam as reference**
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**1**		
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				**Yes**
Literature References				
Total Number of Studies		**4**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)						
	Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
	General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

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/s/

SURESH B NARAHARISETTI
02/10/2013

YUN XU
02/11/2013