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APPLICATION NUMBER:

204592Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	September 30, 2013
From	Joshua M. Lloyd, M.D. Clinical Team Leader, DAAAP
Subject	Cross-Discipline Team Leader Review
NDA#	204592
Applicant	Iroko Pharmaceuticals
Date of Submission	December 20, 2012
PDUFA Goal Date	October 20, 2013
Proprietary Name / Established (USAN) names	Zorvolex / Diclofenac
Dosage forms / Strength	Oral Capsules / 18 mg and 35 mg
Proposed Indication(s)	For treatment of mild to moderate acute pain
Recommended:	Approval

1. Introduction

Iroko Pharmaceuticals (“Applicant”) submitted this New Drug Application (NDA) for Zorvolex capsules, an immediate-release formulation of diclofenac, for the treatment of mild to moderate acute pain in adults. The Applicant conducted the clinical development program under IND 103,880 and proposes to market Zorvolex in two capsule strengths, 18 mg and 35 mg, to be taken by mouth three times daily on an empty stomach. Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities and is a potent inhibitor of both COX-1 and COX-2. Diclofenac is approved and marketed in the United States as various salt forms in oral (immediate-release and modified-release) and topical formulations for multiple painful conditions. The Applicant submitted this NDA under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act referencing the approved product Cataflam (diclofenac potassium; NDA 020142; Novartis Pharmaceuticals Corporation). Cataflam is approved for treatment of primary dysmenorrhea, relief of mild to moderate pain, and relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis; all in adults.

The NDA submission consists of chemistry, manufacturing, and controls (CMC) information, nonclinical information, biopharmaceutics data, and clinical pharmacology and clinical data from two Phase 1 pharmacokinetic (PK) studies (DIC1-08-01 and DIC1-12-07), one Phase 2 proof-of-concept study (DIC2-08-03), and one pivotal Phase 3 clinical trial (DIC3-08-04). The Phase 1 PK study DIC1-12-07 and the pivotal Phase 3 clinical trial were conducted with the commercial, to-be-marketed formulation of Zorvolex, whereas the Phase 1 PK study DIC1-08-01 and the Phase 2 study were conducted using the proof-of-concept formulation.

This NDA submission was given a standard review designation. I have concluded that this application should receive an Approval action and have discussed my reasons for this decision

in Section 13 below. This review will cover the safety and efficacy of Zorvolex for use in patients with mild to moderate acute pain, in addition to several issues that came up during the review cycle.

2. Background

The Applicant developed Zorvolex as a new formulation of diclofenac (in the acid form) with reduced particle size to, according to the Applicant, promote the dissolution and absorption of diclofenac. The Applicant further purported that the improved dissolution properties of Zorvolex are associated with rapid absorption resulting in comparable pain relief to Cataflam tablets at an approximately 20% lower dose and that the lower dose may have the potential for an improved safety profile compared to Cataflam. However, it is uncertain how any potentially improved dissolution properties of a new formulation will substantially improve upon the absorption of diclofenac as Cataflam is completely absorbed (100%) following oral administration, with mean peak concentrations appearing within one hour. In addition, the Applicant did not provide any data comparing Zorvolex to Cataflam upon which to make any comparative safety or efficacy claims or to substantiate their rationale.

During development, the Applicant designated their formulation as a (b) (4), (b) (4). The Division informed the Applicant, during the End-of-Phase 2 meeting, that their formulation does not meet the Agency's definition of a (b) (4). The Applicant subsequently referred to their formulation as (b) (4) formulation.

The Division held End-of-Phase 2 and Pre-NDA meetings with the Applicant during clinical development where agreement was reached on the overall design of the clinical development program. One positive adequate and well-controlled clinical efficacy trial in post-operative bunionectomy patients with acute pain was sufficient given that the Applicant was relying in part on previous findings of safety and efficacy for Cataflam for this 505(b)(2) application. A safety database of at least 350 patients is required. A discussion also took place regarding the labeling implications of a potential food effect on efficacy given the PK results. The Division advised that the Applicant conduct a food effect study on analgesic efficacy or include a food restriction in the clinical efficacy studies and the proposed labeling. Additionally, the Division issued a Special Protocol Assessment Agreement letter to the Applicant on January 29, 2010, for the pivotal clinical trial (Protocol DIC3-08-04) with agreement on the overall design, primary endpoint, and imputation methods and concurrence that the trial is acceptable to support an efficacy claim for the treatment of mild to moderate acute pain.

3. CMC/Device

The CMC review was conducted by Ying Wang, Ph.D., with secondary concurrence by Prasad Peri, Ph.D. There are no unresolved CMC issues. Dr. Wang noted in her review that "[t]his NDA is recommended for approval from a Chemistry, Manufacturing, and Controls (CMC) perspective" and that "24 months shelf life is proposed and granted when stored at 25°C

(77°F) with excursions permitted to 15°C-30°C (59°F-86°F).” The following information summarizes the CMC review.

Zorvolex capsules are provided in two strengths, 18 mg and 35 mg, which contain a (b) (4) white to off-white powder encapsulated in hard gelatin. The 18 mg capsules have a blue body imprinted with “IP-203” and a light green cap imprinted with “18 mg” in white ink. The 35 mg capsules have a blue body imprinted with “IP-204” and a green cap imprinted with “35 mg” in white ink. The commercial manufacturing process involves (b) (4)

Dose strength is achieved by fill weight. The drug product is packaged in high density polyethylene (HDPE) bottles. The submitted drug product stability data include 12 months at long term storage conditions of 25°C/60%RH and 6 months at accelerated storage conditions of 40°C/75%RH for 3 batches of each strength. Dr. Wang notes that “[t]he stability data support the proposed 24-month shelf life for the drug product when stored at the proposed 25°C (77°F), with excursions permitted between 15°C and 30°C (between 59°F and 86°F)” and that “[t]he drug product specifications as amended are adequate and meet ICH Q3B guideline.”

The drug substance, diclofenac, is a white to off-white (b) (4) powder. Dr. Wang notes that “[s]pecifications as amended are adequate and meet ICH Q3A guideline.”

An overall “Acceptable” recommendation was issued by the Office of Compliance on June 13, 2013.

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology review was conducted by Z. Alex Xu, Ph.D., DABT, with secondary concurrence by Adam Wasserman, Ph.D. According to the nonclinical pharmacology/toxicology team, there are no issues that preclude approval for Zorvolex for the proposed indication, and the following information summarizes their review.

There was limited nonclinical information submitted in support of Zorvolex as the Applicant is relying on findings of safety and efficacy for the reference drug. Zorvolex is a reformulation of diclofenac with reduced particle size, and Dr. Xu notes that “reduction of particle size does not appear to impose additional risk of toxicity since the particles will be dissolved in gastric fluid after administration.” The maximum recommended dose for Zorvolex is 35 mg taken three times daily for an acute pain indication. This dose is covered by the maximum dose for Cataflam (i.e., 50 mg three times daily) based on systemic exposure with a comparable treatment duration (i.e., acute pain), therefore, nonclinical toxicity studies are not required for the current application. The excipients in the drug product are not novel and are being used in amounts that do not exceed those in previously approved products.

Three diclofenac-related impurities were identified in the drug substance and drug product (i.e., impurities A, B, and C), and all are below the qualification threshold levels as required in

the ICH Q3A and Q3B guidelines. Therefore, additional nonclinical toxicity studies for impurity qualification are not required for this application. However, for impurities that are less than the qualification threshold but with a structural alert for genotoxicity, a computational genotoxicity assessment is required for qualification. Impurities B and C have structural alerts for genotoxicity. According to Dr. Xu's review:

The Applicant conducted a computational toxicity evaluation to assess the potential genotoxicity of impurity A, B, and C using the MC4PC system. MC4PC is a knowledge-based system using statistical correlation which is designed to evaluate/predict the associations between the structure of the chemicals and their potential activities in a specific biological assay such as Ames assay, in vitro chromosomal assay, and in vivo micronucleus assay, etc. MC4PC performs analysis using modules developed by the Informatics and Computational Safety Analysis Staff (ICSAS) group of the US FDA (b)(4) (b)(4). The results of the analysis predicted that all 3 impurities are negative in Ames assay, in vitro gene mutation assay, in vitro chromosomal assay, in vivo micronucleus assay, and in vivo gene mutation assay, suggesting these are non-genotoxic. Based on the current thinking of the Agency, only the Ames assay is considered for computational toxicology analysis because of the large variability and unreliability in the data of other assays. If the computational analysis for Ames assay is negative, there is no need to further investigate the genotoxicity potential of an impurity. Notably, the Applicant's evaluation did not incorporate an evaluation in an expert rule-based QSAR model. Evaluation in models with both statistical correlation and expert rules are considered necessary by the Agency. Therefore, the structures of these compounds were sent to CDER computational toxicity group (CTG) for analysis of the association of the structures with the potential activity in Ames assay using MC4PC system and another knowledge-based system, Leadscape Model Appliers (LMA). Both MC4PC and LMA systems use statistical correlations to make predictions. In addition, a Derek analysis system which uses human expert rules for prediction was also used in the analysis conducted by CTG. The results of the analysis predicted that all 3 known impurities of the Zorvolex are negative in Ames assay thus not considered to be mutagenic. Overall, the known impurities of Zorvolex were sufficiently qualified.

Regarding labeling, Dr. Xu notes that:

The current Cataflam label does not contain the Nonclinical toxicology section (13). In 2005, when revisions to all NSAID labeling was initiated, the Agency incorrectly informed sponsors to leave out the pregnancy or carcinogenicity data if toxic effects were not seen in their studies. In this submission, the Applicant cited Zipsor® (NDA 22-202, diclofenac potassium) for the Nonclinical toxicology section in the Zorvolex label. Of note, Zipsor was approved in 2009 as a 505 (b)(2) application which also referenced Cataflam. The language of Nonclinical Toxicology section in the original

Cataflam label will be retrieved and compared with the proposed language of this section in Zorvolex label. Revision will be made if necessary.

5. Clinical Pharmacology/Biopharmaceutics

Clinical Pharmacology

The clinical pharmacology review was conducted by Suresh B Narahariseti, Ph.D., with secondary concurrence by Yun Xu, Ph.D. According to the clinical pharmacology team, this NDA is acceptable provided that agreement can be reached between the Applicant and the Agency on the language in the package insert. The following information summarizes their review.

Zorvolex capsules represent a reformulation of diclofenac (in the acid form) with reduced particle size. Zorvolex capsules are 20% lower in the molar diclofenac dose as compared to the reference drug, Cataflam tablets (diclofenac potassium salt). The two 20% lower Zorvolex doses are 18 mg and 35 mg and were compared to the 25 mg and 50 mg strengths of Cataflam, respectively. However, the 25 mg strength of Cataflam is discontinued, but not for reasons of safety or effectiveness. Please refer to the clinical pharmacology review for more details on how these dose comparisons were calculated.

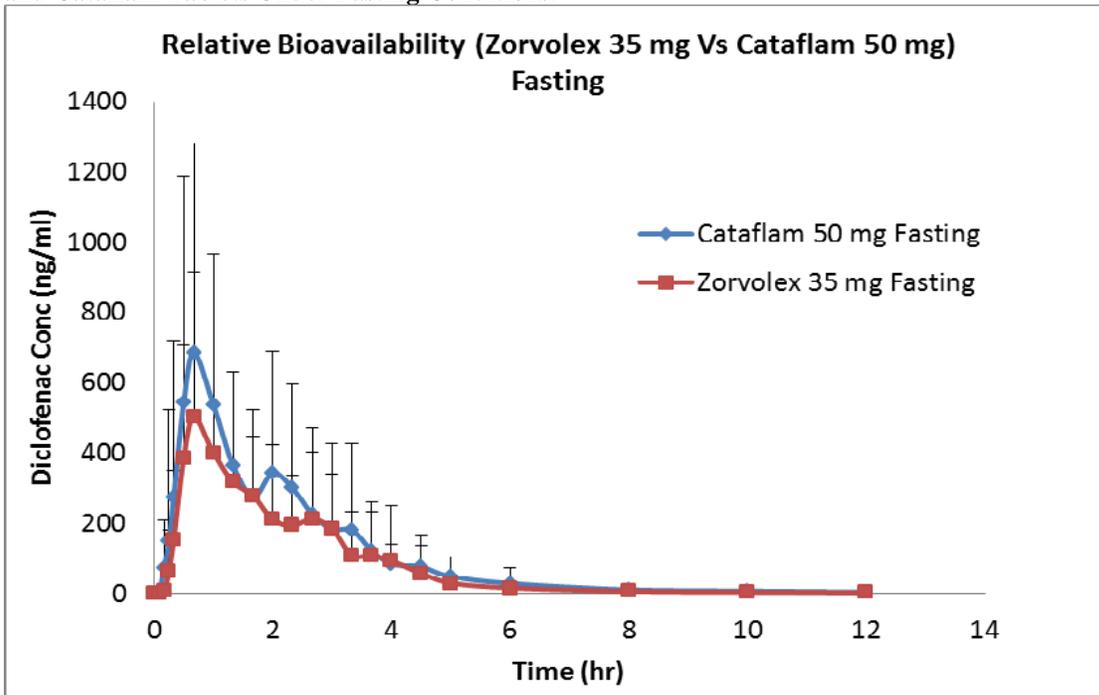
The Applicant submitted two clinical pharmacology studies in this application: DIC1-08-01 and DIC1-12-07. DIC1-08-01 was conducted with the proof-of-concept formulation and was not reviewed by the clinical pharmacology team except to evaluate the food effect for Cataflam. DIC1-12-07; a relative bioavailability (BA), dose proportionality, and food effect study; was conducted with the commercial formulation, and according to Dr. Narahariseti, fulfills the regulatory requirements to assess the clinical pharmacology information for this product.

The BA of Zorvolex 35 mg capsules was compared to Cataflam 50 mg tablets, under fasting and fed conditions, in 35 healthy subjects:

Under *fasted conditions*, the 20% lower dose of diclofenac in Zorvolex resulted in the following relative PK values compared to the reference drug, Cataflam:

- C_{max} (peak concentration; geometric mean): 26% lower
- AUC_{0-t} and AUC_{0-∞} (geometric mean): 23% lower
- T_{max} (time to reach peak concentration): no difference (approximately 1 hour for both)

Figure 1. Mean Diclofenac Plasma Concentration-Time Profiles After Administration of Zorvolex Capsules and Cataflam Tablets Under Fasting Conditions.

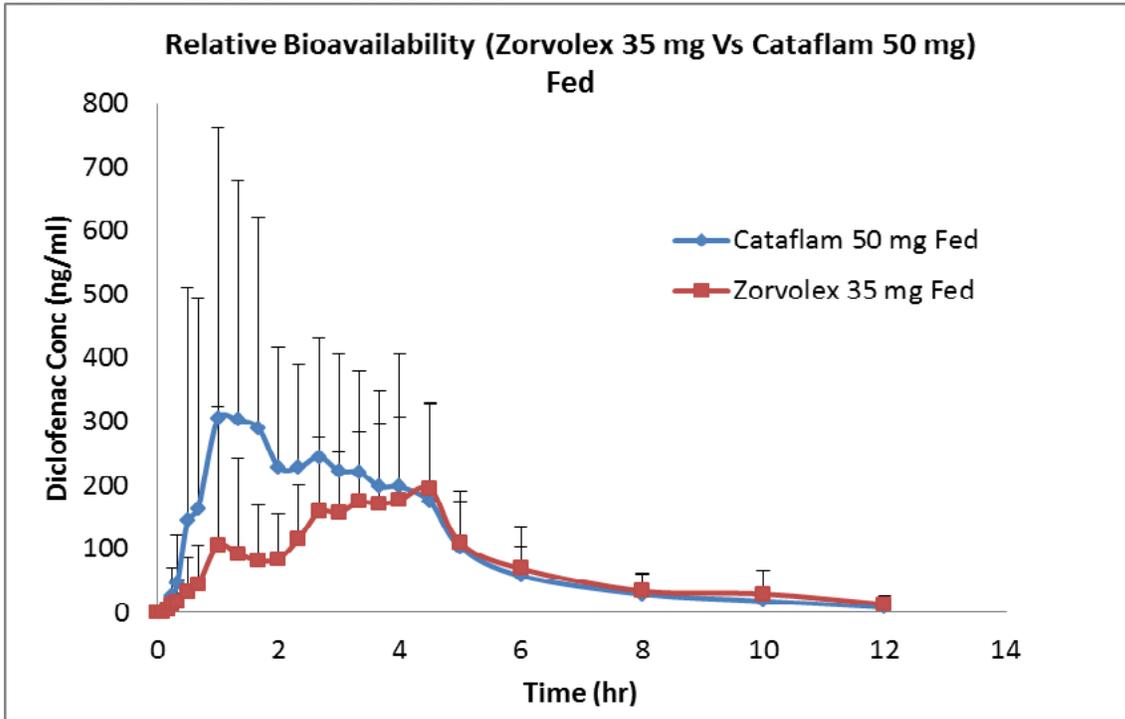


Source: Figure 2.4.1a from Dr. Naraharisetti's review

Under *fed conditions*, the 20% lower dose of diclofenac in Zorvolex resulted in the following relative PK values compared to the reference drug, Cataflam:

- C_{max} (peak concentration; geometric mean): 48% lower
- AUC_{0-t} and AUC_{0-∞} (geometric mean): 26% and 23% lower, respectively
- T_{max} (time to reach peak concentration): delayed by approximately 1 hour (Cataflam: 2.33 hours; Zorvolex: 3.32 hours)

Figure 2. Mean Diclofenac Plasma Concentration-Time Profiles After Administration of Zorvolex Capsules and Cataflam Tablets Under Fed Conditions.



Source: Figure 2.4.1b from Dr. Naraharisetti's review

There was no difference in the elimination half-life between Zorvolex and Cataflam under fasted or fed conditions.

Dr. Naraharisetti notes that:

The smaller particle size of Zorvolex capsules, as claimed by the sponsor has provided no additional advantage in either rate (C_{max} and T_{max}) 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 C_{max} and delayed T_{max}) of absorption compared to Cataflam.

As the particle size and use of the term (b) (4) to describe the formulation do not appear relevant to the performance of the drug product compared to the reference drug Cataflam, these terms should not appear in labeling or promotional materials.

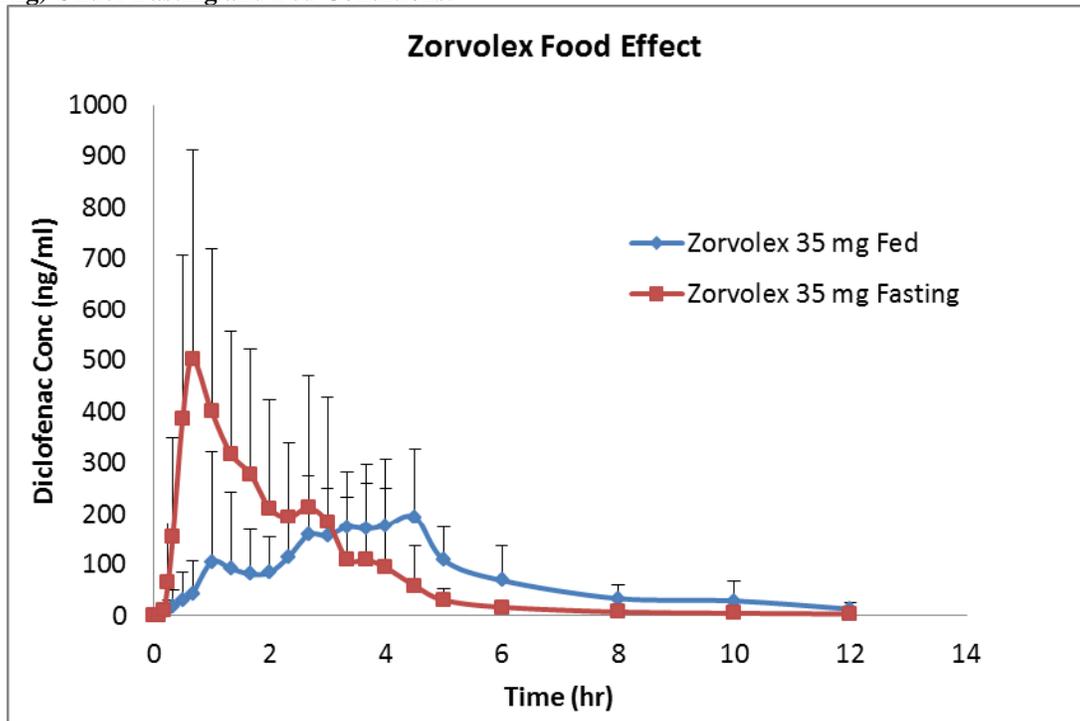
The two strengths of Zorvolex (i.e., 18 mg and 35 mg) are compositionally proportional and result in dose proportional PK for C_{max} and AUC under fasted conditions.

The food effect was assessed for Zorvolex 35 mg capsules and Cataflam 50 mg tablets in 35 healthy subjects:

The following relative PK parameters characterize Zorvolex in the fed state compared to Zorvolex in the fasted state:

- C_{max}: 60% lower
- AUC_{0-t}: 14% lower
- AUC_{0-∞}: 11% lower
- T_{max}: delayed by 2.32 hours (approximately 139 minutes; 1 hour fasted compared to 3.32 hours fed)

Figure 3. Mean Diclofenac Plasma Concentration-Time Profiles After Administration of Zorvolex Capsules (35 Mg) Under Fasting and Fed Conditions.



Source: Figure 2.4.2a from Dr. Naraharisetti's review

The following relative PK parameters characterize Cataflam in the fed state compared to Cataflam in the fasted state:

- C_{max}: 43% and 28% lower in studies DIC1-08-01 and DIC1-12-07, respectively
- AUC: no change

Dr. Naraharisetti notes that:

The observed 60% lower C_{max} 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.”*

I concur with Dr. Narahariseti’s conclusion regarding the potential clinical significance of the food effect seen with Zorvolex and the recommended labeling changes to address this issue.

Biopharmaceutics

The biopharmaceutics review was conducted by Banu S. Zolnik, Ph.D., with secondary concurrence by Sandra Suarez-Sharp, Ph.D. The biopharmaceutics team was consulted to review the dissolution method and acceptance criterion. The dissolution method and dissolution acceptance criterion for diclofenac acid capsules, 18 mg and 35 mg, have been accepted by the ONDQA Biopharmaceutics team. This application is recommended for approval from their perspective.

6. Clinical Microbiology

N/A

7. Clinical/Statistical- Efficacy

The efficacy portion of this NDA review was conducted by Steven Galati, M.D., with secondary concurrence by me. The statistical review was conducted by Feng Li, Ph.D., with secondary concurrence by Janice Derr, Ph.D.

The Applicant submitted the results of one pivotal Phase 3 clinical trial (DIC3-08-04) as evidence of efficacy for Zorvolex for the treatment of mild to moderate acute pain. They also submitted the results of one Phase 2, proof-of-concept study (DIC2-08-03) as supportive evidence. The Phase 2 study was conducted using the proof-of-concept formulation and not the commercial formulation.

Dr. Galati conducted a full review of Study DIC3-08-04, as this is the pivotal trial intended to demonstrate efficacy for Zorvolex. I will review the salient study design features and the results below.

Study DIC3-08-04

Title: 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

Primary Objective: To evaluate the analgesic efficacy of diclofenac capsules compared with placebo in subjects with acute postoperative pain after bunionectomy

Secondary Objectives:

- To evaluate the safety of diclofenac (b) (4) capsules compared with placebo in subjects with acute postoperative pain after bunionectomy
- To evaluate the time to onset of analgesia for diclofenac capsules compared with the standard formulation of celecoxib

Design: Phase 3, randomized, double-blind, multiple-dose, parallel group, active- and placebo-controlled, multicenter clinical trial

Duration: Study drug was administered for 48 hours after the first dose

Population: Adult patients (≥ 18 and ≤ 65 years of age) with acute postoperative pain after bunionectomy who had a pain intensity rating of ≥ 40 mm on a 100-mm visual analog scale (VAS) within 9 hours of discontinuing regional anesthesia

Treatment: Patients were randomized in a 1:1:1:1 fashion to the following treatment groups. Study drug (active or placebo) was administered four times daily to maintain the blind.

- Zorvolex 18 mg three times daily (TID)
- Zorvolex 35 mg TID
- Celecoxib 200 mg twice daily (BID)
- Placebo

Rescue Medication: Hydrocodone/acetaminophen 10 mg/325 mg, one tablet every 4 to 6 hours as needed for rescue; if patients were unable to tolerate hydrocodone/acetaminophen, oxycodone/acetaminophen 7.5 mg/325 mg, one tablet every 6 hours as needed could be used

Food Restriction: The Applicant did not include a food restriction in the protocol, and food intake was not formally monitored. During the review cycle, the Applicant clarified that the majority of subjects received their initial dose of study medication on an empty stomach due to the nature of when the first dose was given (i.e., postsurgical, pre-breakfast) without pre-specified food restrictions for subsequent dosing.

Primary Efficacy Variable: VAS summed pain intensity difference (calculated as time-weighted averages) over 0 to 48 hours (VAS SPID-48)

Secondary Efficacy Variables (none identified as key secondary variables):

- VAS pain intensity difference (VAS PID) at each scheduled time point after Time 0
- VAS pain intensity score at each scheduled time point
- VAS SPID-4, VAS SPID-8, and VAS SPID-24
- Total Pain Relief over 0 to 4 hours (TOTPAR-4), TOTPAR-8, TOTPAR-24, and TOTPAR-48
- Time to onset of analgesia (measured as time to perceptible pain relief confirmed by meaningful pain relief [double stopwatch method])
- Pain relief score on a 5-point categorical scale at each scheduled time point after Time 0

- Peak pain relief
- Time to peak pain relief
- Time to first perceptible pain relief
- Time to meaningful pain relief
- Proportion of subjects using rescue medication
- Time to first use of rescue medication
- Total use of opioid rescue analgesia over 0 to 24 hours and over 0 to 48 hours
- Patient's global evaluation of study drug

Statistical Analysis Plan: Dr. Li notes in his review that:

The primary efficacy variable was analyzed using an analysis of covariance (ANCOVA) model with baseline pain score as a covariate and treatment as a factor. The primary analysis population included all subjects who were randomized and received at least one dose of study medication. To control multiplicity, a sequential testing procedure was carried out for the comparisons of the two doses of diclofenac with placebo. Zorvolex 35 mg was compared to placebo first. Zorvolex 18 mg was compared to placebo only if Zorvolex 35 mg was significantly better than placebo. There were no comparisons between Zorvolex and celecoxib in the primary analysis.

Missing pain assessments for subjects who discontinued early due to lack of efficacy or adverse events were imputed using a baseline observation carried forward approach (BOCF). Missing pain assessments due to other reasons were imputed using a last observation carried forward approach (LOCF). For subjects who took any dose of rescue medication, subsequent pain assessments after the first dose of rescue medication were disregarded and imputed using a BOCF approach. Intermittent missing pain assessments were imputed using linear interpolation.

The applicant conducted a sensitivity analysis for the primary efficacy analysis by adding gender as a factor into the ANCOVA model. Sensitivity analyses for the methods to handling missing values were not conducted.

Time to onset of analgesia was right censored at 8 hours for subjects who did not experience both perceptible pain relief and meaningful pain relief during the 48-hour interval or who required rescue medication prior to achieving perceptible or meaningful pain relief.

Patient Disposition, Demographic and Baseline Characteristics:

As noted in Dr. Li's review:

A total of 428 subjects were randomized. All randomized subjects received the study medications...Overall, a total of 421 (98%) subjects completed the study. No subjects in the Zorvolex 18 mg group discontinued the study early.

Both the Zorvolex 35 mg and the celecoxib groups had one subject discontinued early due to investigator decision¹ and subject request, respectively. Five subjects (5%) in the placebo group discontinued the study early, three of which due to lack of efficacy.

The demographic and baseline characteristics were generally comparable across treatment groups. A summary of selected demographic and baseline characteristics is provided in [the] Table [below]. The summary for race was reproduced using the applicant’s dataset, which differed slightly from the clinical study report. The majority of the subjects were female and white. Overall, the mean age was about 40 years. Approximately 85% of the subjects were white.

Table 1. Summary of Demographics and Baseline Characteristics

	Zorvolex			
	35 mg TID	18 mg TID	Celecoxib BID	Placebo
	N=107	N=109	N=106	N=106
Mean age (SD)	39 (12)	39 (12)	40 (12)	40 (13)
Mean weight (SD) (kg)	77 (19)	75 (17)	72 (16)	73 (14)
Mean height (SD) (cm)	167 (9)	167 (9)	165 (8)	167 (8)
Mean BMI (SD) (kg/m ²)	27 (6)	27 (5)	26 (5)	26 (5)
Baseline pain - mean (SD)	74 (16)	77 (16)	74 (17)	76 (16)
- (Min, Max)	(44, 100)	(41, 100)	(40, 100)	(40, 100)
Gender, n (%)				
Male	18 (17%)	15 (14%)	10 (9%)	14 (13%)
Female	89 (83%)	94 (86%)	96 (91%)	92 (87%)
Ethnicity, n (%)				
Hispanic or Latino	19 (18%)	24 (22%)	18 (17%)	17 (16%)
Not Hispanic or Latino	88 (82%)	85 (78%)	88 (83%)	89 (84%)
Race, n(%)				
Black or African American	17 (16%)	19 (17%)	22 (21%)	19 (18%)
White or Caucasian	84 (78%)	86 (79%)	73 (69%)	79 (74%)
Other	6 (6%)	4 (4%)	11 (10%)	8 (8%)

Source: Table 2 from Dr. Li’s review; SD=standard deviation

The distribution seen in the study population with respect to demographics and baseline characteristics (i.e., predominantly White or Caucasian women) is expected given the epidemiology of the underlying disease process (i.e., bunions).

Baseline pain intensity was evenly balanced across treatment groups, as seen in the table below.

¹ Discontinued when the investigator learned that the subject did not meet inclusion/exclusion criteria for having a history of a gastric ulcer (i.e., protocol violation)

Table 2. Summary of Baseline Characteristics

Variable	Diclofenac (b) (4) formulation Capsule		Celecoxib Capsule	Placebo	Total
	35 mg (n = 107)	18 mg (n = 109)	200 mg ^a (n = 106)	(n = 106)	(N = 428)
Baseline pain intensity, mm					
n	107	109	106	106	428
Mean (SD)	74.1 (16.1)	76.7 (15.9)	74.2 (16.8)	76.3 (16.3)	75.4 (16.3)
Median	75.0	76.0	74.0	77.0	76.0
Minimum, maximum	(44, 100)	41, 100)	(40, 100)	(40, 100)	(40, 100)
Surgery duration, minutes					
n	107	109	106	106	428
Mean (SD)	28.2 (6.7)	28.9 (6.9)	29.7 (11.1)	29.9 (9.4)	29.2 (8.7)
Median	28.0	29.0	29.0	28.0	28.0
Minimum, maximum	(16, 48)	15, 52)	(16, 115)	(16, 72)	(15, 115)

Source of data: Section 14.1, Table 14.1.2

Abbreviations: SD = standard deviation.

^a The initial dose of celecoxib was 400 mg; subsequent doses were 200 mg.

Source: Table 9 from Dr. Galati's review

Results:

The results for the primary efficacy analysis are presented in the table below. The results were replicated by Dr. Li. Both Zorvolex 35 mg and 18 mg were superior to placebo on the primary efficacy endpoint.

Table 3. Primary Efficacy Analysis

Statistics	Zorvolex		Celecoxib BID	Placebo
	35 mg TID	18 mg TID		
n	107	109	106	106
LS Mean (SE)	524 (86)	393 (85)	390 (86)	77 (86)
95% CI	(355, 693)	(225, 561)	(220, 560)	(-93, 247)
Difference in LS mean(SE)	447 (122)	316 (121)	313 (122)	
95% CI for diff. in LS mean	(207, 687)	(77, 555)	(72, 554)	
p-value for treatment effect	<0.001	0.01	0.01	

Source: Table 3 from Dr. Li's review; SE=standard error; CI=confidence interval; LS=least square

The high and differential frequencies in rescue medication use and the imputation method for subsequent pain scores have the potential to substantially influence the comparisons among treatments. As noted in Dr. Li's review:

The applicant replaced all the pain scores after the first use of the rescue medication with the baseline observations. When the percentage of subjects who take rescue medications is high, the approach to handling the pain scores after rescue may substantially influence the comparisons among treatments. In the acute pain setting, it is often likely that subjects will take rescue medications. [The table [below] presents the percentage of subjects who took rescue medications for pain management during the study. For all treatment

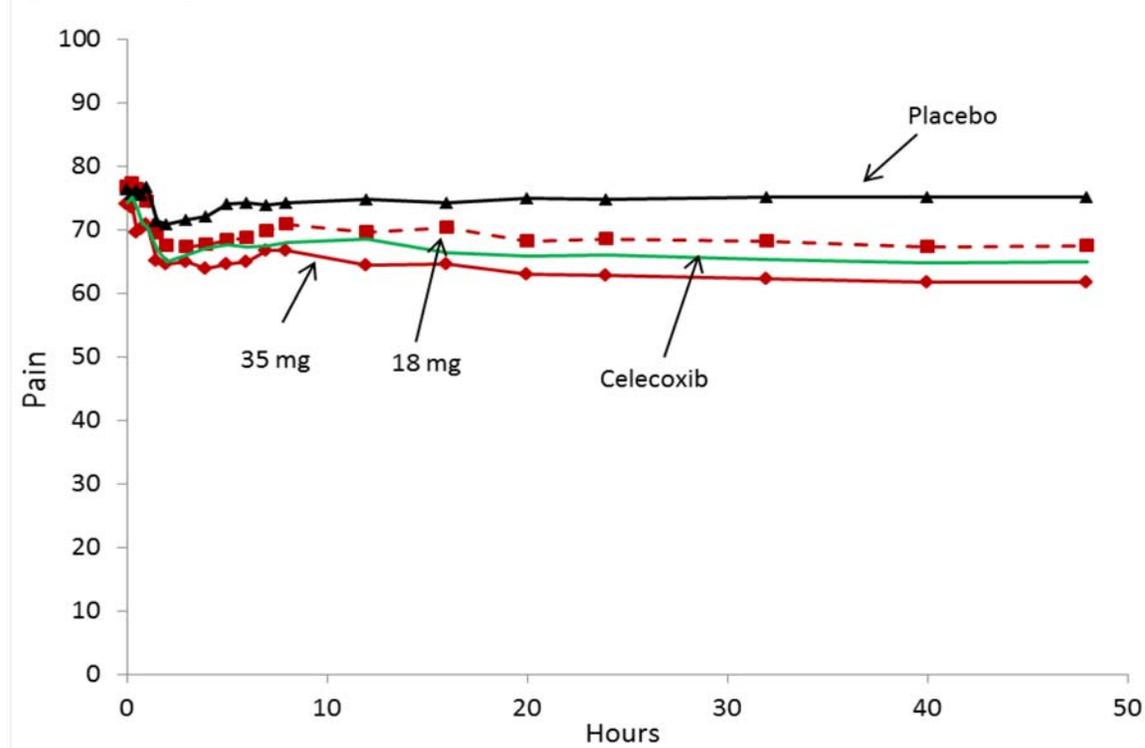
groups, more than 80% of the subjects took rescue. Placebo group had the highest percentage of subjects who took rescue. The majority of the subjects took their first rescue within 8 hours after the first dose, that is, before the second dose of the study medication. [The figure [below] depicts the average pain intensity over time for each treatment group during the 48 hours after the first dose with pain scores after rescue imputed using a BOCF approach. Although the placebo group had the worst pain on average, there was not much pain reduction for all treatment groups. All the pain curves are rather flat after 10 hours. This is because the majority of the subjects took rescue during the first 8 hours and their pain scores after the first rescue were replaced by the corresponding baseline values.

Table 4. Rescue Medication – Number (%) of Subjects

	Zorvolex		Celecoxib BID	Placebo
	35 mg TID	18 mg TID		
Randomized	107	109	106	106
Subjects who took rescue	88 (82%)	93 (85%)	90 (85%)	103 (97%)
Subjects who took rescue within 8 hours after first dose	84 (78%)	88 (81%)	87 (82%)	101 (95%)

Source: Table 4 from Dr. Li’s review

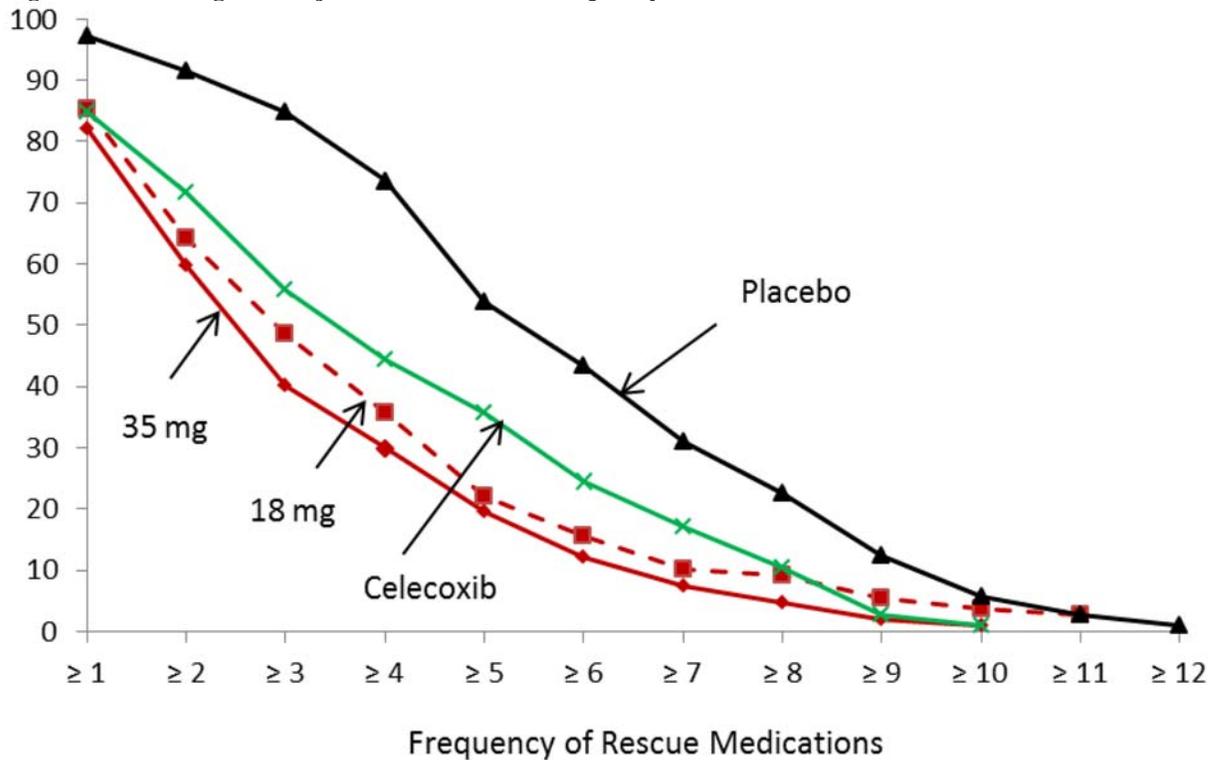
Figure 4. Average Pain Over Time – BOCF After Rescue



Source: Figure 1 from Dr. Li’s review

Additionally, a higher percentage of patients in the placebo group used rescue medication at each frequency level (see figure below).

Figure 5. Percentage of Subjects with Different Frequency of Rescue Use

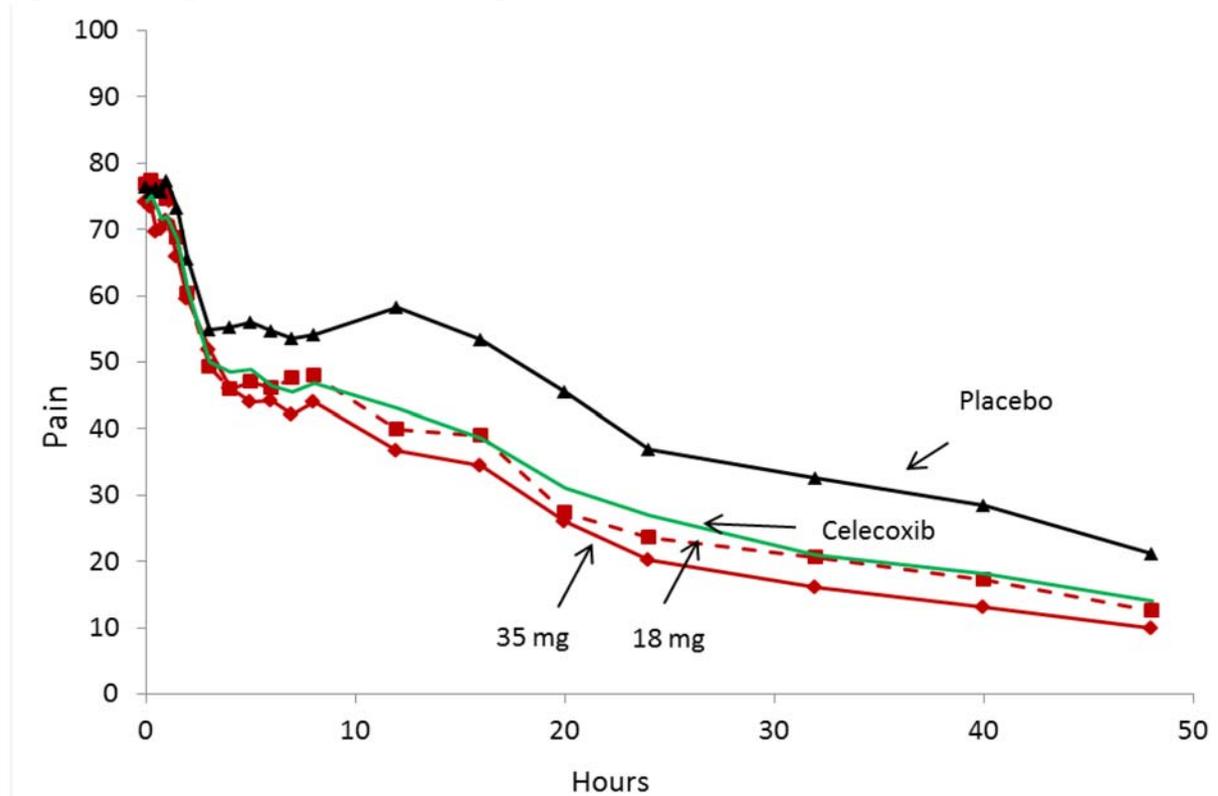


Source: Figure 3 from Dr. Li's review

Dr. Li calculated the primary efficacy endpoint using the observed pain scores after rescue and conducted an analysis using the same approach as the one in the primary analysis, and those results are described below.

[The figure below] displays the average pain intensity over time for each treatment group without imputation for taking rescue, that is, the actual observed pain scores after rescue were used. The overall trend of actual pain reduction over time is apparent for each treatment group. Among the treatments, subjects in the placebo group experienced the least pain reduction. The separation of the pain curve of the placebo from the three active treatments occurred after approximately 3 hours after dosing. To compare the treatment effects under the influence of rescue medications in terms of the primary efficacy endpoint, I calculated the summed pain intensity difference over 48 hours using the observed pain scores after rescue and conducted an analysis using the same ANCOVA model as the one used in the primary analysis. The analysis results are presented in [the table below]. The differences between the three active treatments and placebo were all statistically significant, which indicates that the active treatments in combination with the rescue medications produced superior analgesic effects to placebo in combination with the rescue medications.

Figure 6. Average Pain Over Time – No Imputation After Rescue



Source: Figure 2 from Dr. Li’s review

Table 5. Additional Efficacy Analysis for VAS SPID-48 – No Imputation After Rescue

Statistics	Zorvolex			
	35 mg TID	18 mg TID	Celecoxib BID	Placebo
n	107	109	106	106
LS Mean (SE)	2392 (82)	2293 (81)	2159 (82)	1661 (82)
95% CI	(2232,2553)	(2134,2452)	(1997,2320)	(1499,1823)
Difference in LS mean(SE)	731 (116)	632 (115)	498 (116)	
95% CI for diff. in LS mean	(503,960)	(405,859)	(269,726)	
p-value for treatment effect	<0.0001	<0.0001	<0.0001	

SE: standard error; CI: confidence interval; LS: least square.

Source: Table 5 from Dr. Li’s review

Dr. Li conducted an additional analysis in which the pain scores within 6 hours after rescue use were replaced with the pre-rescue pain score, and those results are summarized in the table below. Dr. Li also conducted similar analyses using different lengths of time for the window after rescue use (i.e., 4 or 8 hours), and he reports that these analyses yielded similar results.

Table 6. Additional Efficacy Analysis for VAS SPID-48 – Pre-rescue Score Carried Forward for 6 hours

Statistics	Zorvolex		Celecoxib BID	Placebo
	35 mg TID	18 mg TID		
n	107	109	106	106
LS Mean (SE)	2221(82)	2097(81)	1976(83)	1407(83)
95% CI	(2060,2383)	(1937,2257)	(1813,2138)	(1245,1569)
Difference in LS mean(SE)	814(117)	690(116)	569(117)	
95% CI for diff. in LS mean	(585,1043)	(462,918)	(339,798)	
p-value for treatment effect	<0.0001	<0.0001	<0.0001	

SE: standard error; CI: confidence interval; LS: least square.

Source: Table 6 from Dr. Li’s review

The results of the primary efficacy analysis were in favor of the active treatments. The review team was initially concerned about the Applicant’s imputation method for pain scores after rescue medication use, as the differences between treatment groups may have been largely driven by the differential and large percentages of subjects who took rescue. However, the results of Dr. Li’s multiple sensitivity analyses also yielded statistically significant results in favor of the active treatments.

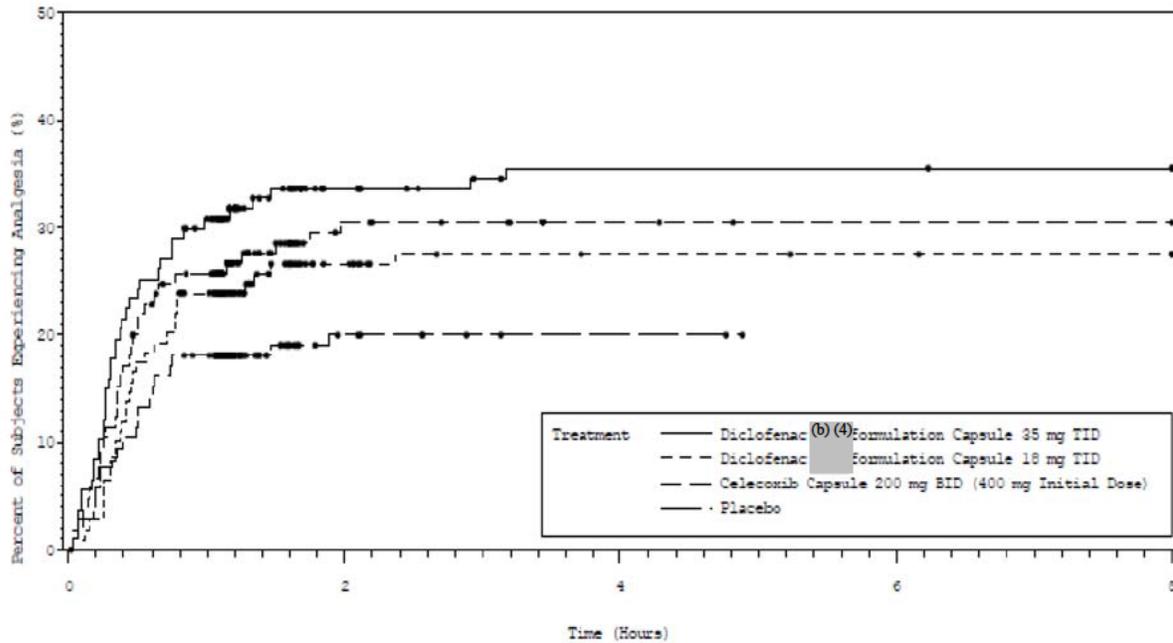
The mean times to onset of analgesia (measured as time to perceptible pain relief confirmed by meaningful pain relief) were 2.2 hours, 1.8 hours, and 1.5 hours for the Zorvolex 35 mg, Zorvolex 18 mg, and Celecoxib groups, respectively.

Dr. Li notes in his review that:

The cumulative distribution of time to onset of analgesia for each treatment group is shown in [the f]igure below. For all the treatment groups, onset of analgesia occurred in less than 40% of the subjects. Among the treatment groups, the Zorvolex 35 mg group had the highest percentage of subjects who experienced onset of analgesia whereas the placebo group had the lowest percentage. Approximately 31% of the subjects in the Zorvolex 35 mg group, 25% of the subjects in the celecoxib group, 24% of the subjects in the Zorvolex 18 mg group, and 18% of the subjects in the placebo group experienced onset of analgesia within 1 hour after the first dose.

The slow onset of analgesic action, that was apparent across all treatment groups, including the active control, may have contributed to the high frequency of rescue medication use seen in this trial.

Figure 7. Cumulative Distribution of Time to Onset of Analgesia



Source: Figure 4 from Dr. Li's review

Mean time to first rescue medication use was 5.9 hours and 9.1 hours for the Zorvolex 35 mg and 18 mg groups, respectively, and is generally supportive of the proposed dosing interval. This dosing interval is consistent with the dosing interval for the reference drug, Cataflam. The time to first use of rescue medication was similar between the Zorvolex and celecoxib groups; however, all active treatment groups had a longer time to first rescue medication use as compared to placebo. These results are summarized in the table below.

Table 7. Time to First Use of Rescue Medication — Intent-to-Treat Population

Statistic	^{(b) (4)} Diclofenac formulation Capsule		Celecoxib Capsule	Placebo (n = 106)
	35 mg (n = 107)	18 mg (n = 109)	200 mg ^a (n = 106)	
Subjects analyzed, n (%)	88 (82.2%)	93 (85.3%)	93 (85.3%)	103 (97.2%)
Subjects censored, n (%)	19 (17.8%)	16 (14.7%)	16 (15.1%)	3 (2.8%)
Mean (SE) (hour) ^b	5.9 (0.78)	9.1 (1.56)	4.9 (0.68)	2.7 (0.45)
Log-rank <i>P</i> value ^c	<0.001			
Restricted model 1				
Log-rank <i>P</i> value ^d	0.423	0.873		
Cox proportional hazards model ^e				
Hazard ratio (95% CI)	0.9 (0.67, 1.21)	0.9 (0.70, 1.25)		
Treatment <i>P</i> value	0.488	0.664		
Gender <i>P</i> value	0.040	0.474		
Baseline pain intensity <i>P</i> value	0.059	<0.001		
Restricted model 2				
Log-rank <i>P</i> value ^f	<0.001	0.001	0.004	
Cox proportional hazards model ^g				
Hazard ratio (95% CI)	0.6 (0.44, 0.79)	0.7 (0.49, 0.87)	0.7 (0.52, 0.92)	
Treatment <i>P</i> value	<0.001	0.003	0.013	
Gender <i>P</i> value	0.286	0.671	0.456	
Baseline pain intensity <i>P</i> value	0.829	0.003	0.013	

Source of data: [Section 14.2, Table 14.2.10](#)

Source: Table 18 from Dr. Galati's review

The results from the secondary efficacy analyses were supportive of the primary analysis and generally indicated a treatment effect in favor of the active treatments. Please refer to Dr. Galati's review for more detail on the Applicant's results from the secondary analyses. Although the study was not designed to make comparative efficacy claims between Zorvolex and celecoxib, the results of the primary and secondary efficacy analyses suggest that Zorvolex is no worse or better than celecoxib.

Dr. Li conducted subgroup analyses by age, race, and gender for all randomized subjects. The findings from the subgroup analyses were consistent with those observed in the overall population, in that all of the active treatment subgroups were numerically better than placebo.

Dr. Li concluded that the pivotal Phase 3 clinical trial has demonstrated the superiority of both Zorvolex 35 mg and 18 mg, given three times daily, over placebo in pain intensity reduction, and I concur with his conclusion. As a high percentage of patients in the clinical trial also took rescue medication for pain management, information about the type of rescue medication that was available and the percentage of subjects who used rescue medication should be included in the clinical studies section of the labeling. No comparative efficacy claims with regard to celecoxib should be included in labeling, as the study was not designed to evaluate comparative efficacy between Zorvolex and celecoxib.

Furthermore, the Applicant did not evaluate comparative efficacy between the reference drug, Cataflam, and Zorvolex in their clinical development program. As such, they have not provided any support for the assertion that this reformulation of diclofenac can provide comparable pain relief to Cataflam tablets at an approximately 20% lower dose.

Dr. Galati noted in his review that:

Although the Applicant reported that most subjects were given their initial dose of study medication before 7 AM, and thus likely on an empty stomach, the pivotal study DIC3-08-04 did not specify the timing of study medication administration with regard to food intake. Given that efficacy for this product was demonstrated in this trial and that many patients are likely to have been dosed on a fed stomach after the initial dosing, I recommend removing any statement in the label with regard to taking the medication with or without food. Also, safety is not a concern with regard to taking the medication in a fasting or fed state.² In addition, I propose adding in language that efficacy may be decreased in patients who take this medication on a fed stomach, based on the fed/fasted PK findings for Zorvolex.

I concur with Dr. Galati's assessment. Please refer to Section 5, Clinical Pharmacology of this review for the specific labeling recommendations regarding this issue.

I also recommend adding additional detail about the pivotal clinical trial to the clinical studies section of the labeling to communicate to prescribers basic study population characteristics including a brief description of the study population and baseline characteristics and the inclusion criterion for baseline pain.

Study DIC2-08-03

The Applicant also submitted the results from a Phase 2, randomized, double-blind, single-dose, parallel-group, active- and placebo-controlled study of Zorvolex (18 mg or 35 mg) in 202 patients with acute pain following impacted third molar extraction. The Applicant's results showed a statistically significant treatment effect for both Zorvolex groups over placebo on the primary endpoint, sum of total pain relief over 0 to 12 hours (TOTPAR-12). However, this study utilized the proof-of-concept formulation and not the commercial formulation and is only supportive of the findings in the pivotal Phase 3 clinical trial. Therefore, the data from this study cannot be used to support any labeling claims and should not be referenced in product labeling.

² Although taking NSAIDs on an empty stomach may result in decreased tolerability of the medication, that in of itself does not cause an increased safety risk (i.e., gastric ulcers, etc).

8. Safety

The safety portion of this NDA review was conducted by Steven Galati, M.D., with secondary concurrence by me. Zorvolex 18 mg and 35 mg capsules appear to be relatively well-tolerated among patients in the clinical development program. No new or unexpected safety signals were observed for Zorvolex, as compared to what is already known about diclofenac. The following is a summary of Dr. Galati's review.

The safety evaluation of Zorvolex in patients with acute pain primarily consisted of data from the pivotal Phase 3 clinical trial (DIC3-08-04), and the safety results from this trial will be discussed further below. The Applicant also submitted safety data from two Phase 1 pharmacokinetic (PK) studies (DIC1-08-01 and DIC1-12-07) and one Phase 2 proof-of-concept study (DIC2-08-03) [REDACTED] (b) (4)

[REDACTED] The Phase 1 PK study DIC1-08-01 and the Phase 2 study were conducted using the proof-of-concept formulation. The safety data from the Phase 1 and 2 studies [REDACTED] (b) (4) were reviewed by Dr. Galati and did not provide any additional safety findings beyond that reported for the pivotal Phase 3 clinical trial and what is already known about diclofenac.

The pivotal Phase 3 clinical trial consisted of 428 subjects who were randomized to four treatment groups and received study medication. All of these subjects were included in the safety population. Two-hundred sixteen subjects received either Zorvolex 35 mg or Zorvolex 18 mg three times daily for 48 hours. The exposure to Zorvolex is adequate to assess safety for the intended acute pain population given the established safety profile for diclofenac.

There were no deaths in the Phase 3 trial, and there were no serious adverse events (SAEs) in the Zorvolex groups. No subjects discontinued due to an adverse event. Three-hundred thirty (77%) subjects reported at least one treatment-emergent adverse event (TEAE), and most TEAEs were reported as mild with 22% and 3% of subjects having moderate or severe TEAEs, respectively. A summary of TEAEs experienced by 5% or more subjects in any treatment group is reviewed below. Many of the AEs occurred more frequently in the placebo group, and this finding may be attributable to the higher frequency of rescue medication use in this group. Therefore, I recommend that the Applicant include a footnote to the adverse event table in the product labeling indicating the type and amount of rescue medication used by patients in each treatment group so clinicians will be able to more accurately understand the adverse event profile seen in this clinical trial.

Table 8. Summary of Most Frequent Treatment-Emergent Adverse Events (5% or More of Subjects in Any Treatment Group) by Preferred Term — Safety Population

Preferred term	^{(b) (4)} Diclofenac formulation Capsule		Celecoxib Capsule	Placebo (n = 106)	Total (N = 428)
	35 mg (n = 107)	18 mg (n = 109)	200 mg ^a (n = 106)		
ANY TEAE	77 (72.0%)	84 (77.1%)	86 (81.1%)	63 (78.3%)	330 (77.1%)
Postprocedural edema	35 (32.7%)	36 (33.0%)	35 (33.0%)	34 (32.1%)	140 (32.7%)
Nausea	25 (23.4%)	34 (31.2%)	29 (27.4%)	39 (36.8%)	127 (29.7%)
Headache	11 (10.3%)	17 (15.6%)	11 (10.4%)	16 (15.1%)	55 (12.9%)
Dizziness	5 (4.7%)	17 (15.6%)	11 (10.4%)	17 (16.0%)	50 (11.7%)
Vomiting	7 (6.5%)	13 (11.9%)	15 (14.2%)	13 (12.3%)	48 (11.2%)
Post-procedural hematoma	4 (3.7%)	12 (11.0%)	8 (7.5%)	11 (10.4%)	35 (8.2%)
Constipation	6 (5.6%)	12 (11.0%)	9 (8.5%)	4 (3.8%)	31 (7.2%)
Pruritus	6 (5.6%)	4 (3.7%)	4 (3.8%)	4 (3.8%)	18 (4.2%)
Paraesthesia	2 (1.9%)	2 (1.8%)	8 (7.5%)	3 (2.8%)	15 (3.5%)

Source of data: Section 14.3.1, Table 14.3.1.5

Abbreviations: TEAE = treatment-emergent adverse event.

NOTE: All data are presented as n (%). For each preferred term, subjects were only counted once.

^a The initial dose of celecoxib was 400 mg; subsequent doses were 200 mg.

^b Any subject who had AEs leading to discontinuation was counted.

Source: Table 26 from Dr. Galati's review

The review of safety demonstrated that Zorvolex 18 mg and 35 mg given three times daily appears well-tolerated by patients with acute postsurgical pain. Dr. Galati concluded that no new or unexpected safety signals were detected during this review, and I concur with his conclusion.

No comparative safety claims with regard to celecoxib should be included in labeling, as the study was not designed to evaluate comparative safety between Zorvolex and celecoxib nor were the findings replicated. Additionally, the Applicant did not evaluate comparative safety between the reference drug, Cataflam, and Zorvolex in their clinical development program. As such, they have not provided any support for the assertion that this reformulation of diclofenac at a lower dose may have the potential for an improved safety profile compared to Cataflam.

9. Advisory Committee Meeting

An Advisory Committee meeting was not convened for this application.

10. Pediatrics

No studies have been carried out in pediatric patients. The Applicant submitted a pediatric study plan with this submission that was not consistent with advice provided during the End-of-Phase 2 meeting. After a subsequent information request and teleconference, the Applicant submitted a pediatric study plan consistent with Divisional requirements. Specifically, the pediatric study plan included a deferral request for studies in patients 1 to <17 years of age, citing reasons that the product is ready for approval in adults, and a partial waiver request for patients birth to <1 year of age, citing reasons that the product would be ineffective and/or unsafe in this age group due to immaturity of the enzymes required to metabolize diclofenac (i.e., CYP2C9). The following studies were included:

- **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

The Applicant's proposed timeline for completion of pediatric studies is presented in the table below.

Table 9. Proposed Timeline for Pediatric Studies

Studies	Final Protocol Submission Date	Study Start Date	Final Report Submission
6 years - < 18 years (Study 1)	November 1, 2014	May 3, 2015	May 3, 2017
2 years - < 6 years (Study 2)	June 6, 2015	January 6, 2016	January 6, 2018
1 year to < 2 years (Study 3)	January 6, 2018	July 30, 2018	July 30, 2020

Source: Table 29 from Dr. Galati's review

Efficacy may be extrapolated from adults to pediatric patients two years of age and older for NSAIDs, consistent with the Division's current policy. Granting a partial waiver request on the basis that the product would be ineffective and/or unsafe in this age group due to immaturity of the enzymes required for metabolism would be consistent with the Division's approach to pediatric study requirements for other diclofenac products.

The Applicant's pediatric study plan was discussed at a meeting of the Pediatric Research Committee (PeRC) on September 4, 2013. The PeRC agreed with granting the deferral request for patients 1 to <17 years of age because the product is ready for approval in adults.

Although the PeRC agreed with granting a partial waiver request for patients birth to <1 year of age, the PeRC did not agree with the Division's reason for granting the waiver request. PeRC recommended granting the partial waiver request because the product does not represent a meaningful therapeutic benefit over existing therapies. PeRC was concerned that granting a waiver request based on immaturity of metabolic pathways would set an unwanted precedent that could stifle pediatric drug development in the future. It was decided at the meeting that this issue requires further discussion between the Division and the PeRC/pediatric maternal health staff. There was consensus, however, that a partial waiver request should be granted in this age group. I recommend granting the partial waiver request in pediatric patients birth to <1 year of age for the reason that the product would be ineffective and/or unsafe in this age group, consistent with what the Division has done previously for diclofenac products, pending further discussion and consultation with the PeRC/pediatric maternal health staff. The pediatric postmarketing study requirements are listed in Section 13 of this review.

11. Other Relevant Regulatory Issues

Inspections by the Office of Scientific Investigations (OSI)

Cynthia F. Kleppinger, M.D., completed the Clinical Inspection Summary for this NDA, with secondary concurrence by Janice Pohlman, M.D., M.P.H., and Susan D. Thompson, M.D. for Kassa Ayalew, M.D., M.P.H.

According to Dr. Kleppinger's review, the overall assessment of the inspectional findings was that:

In general, based on the inspection of the two clinical study sites, the inspectional findings support validity of data as reported by the sponsor under this NDA.

Observations noted...for Dr. Golf are based on the review of the Establishment Inspection Report (EIR), Form FDA 483, and communications with the field investigator. Observations noted...for Dr. Schiffgen are based on communications from the field investigator and review of a draft EIR. An inspection summary addendum will be generated if conclusions change upon OSI final classification.

The following two study sites for DIC3-08-04, the pivotal clinical trial, were inspected due to high enrollment numbers:

Name of CI/ Site #	Protocol # and # of Subjects Randomized	Inspection Date	Final Classification
Michael Golf, DPM, PA Premier Research Group Limited Site # 001	Study DIC3-08-04 143 enrolled	May 14-20, 2013	VAI
Thomas Schiffgen, DPM Premier Research Group Limited Site # 002	Study DIC3-08-04 117 enrolled	June 10-12, 2013	NAI- preliminary

Key to Classifications

NAI = No deviation from regulations

VAI = Deviation(s) from regulations

Pending = Preliminary classification based on information in Form FDA 483, preliminary communication with the field, and review of EIR; final classification is pending.

Source: Dr. Kleppinger's review, pp. 2-3.

Dr. Kleppinger notes that:

Data from [site 001] appear acceptable. Although the inspection resulted in a Form FDA 483, the deviations noted do not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

Financial Disclosures

The Applicant submitted certification that 44 of the 45 investigators listed in the study reports had no financial interests or arrangements to disclose. The remaining investigator was listed as being out of the office and would be sent a copy of the financial interests form to sign at a later date.

505(b)(2) Committee

This application was presented at a 505(b)(2) clearance meeting on September 16, 2013, and it was cleared for action from their perspective.

12. Labeling

The proprietary name, Zorvolex, was found acceptable following review by the Division of Medication Error Prevention and Analysis (DMEPA). DMEPA also concluded that the proposed container label and blister and carton labeling can be improved to increase the readability and prominence of important information on the label to promote safe use of these products. DMEPA made recommendations for improving the container label and blister and carton labeling and requested that these recommendations be communicated to the Applicant prior to approval. DMEPA's recommendations were communicated to the Applicant on September 26, 2013 via mail.

Labeling is ongoing at the time of this writing, and specific recommendations have been made in the relevant sections of this review.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Approval

- Risk Benefit Assessment

The Applicant developed Zorvolex 18 mg and 35 mg capsules as a new formulation of diclofenac with reduced particle size to, according to the Applicant, promote the dissolution and absorption of diclofenac. The Applicant further purported that the improved dissolution properties of Zorvolex are associated with rapid absorption resulting in comparable pain relief to Cataflam tablets at an approximately 20% lower dose and that the lower dose may have the potential for an improved safety profile compared to Cataflam. From a PK perspective, the Applicant failed to show an enhanced rate or extent of absorption, as compared to the reference drug, Cataflam. As such, the overall relevance of this formulation is questionable. Additionally, the Applicant has not presented any evidence that the properties of their formulation result in comparable pain relief or an improved safety profile as compared to the reference product. The Applicant did not evaluate comparative efficacy or safety between their product and the reference product, Cataflam, during the clinical development program. Because of this, no claims can be made based on the Applicant's rationale for developing this product or aspects of the formulation such as particle size.

The Applicant did, however, demonstrate evidence of efficacy for their product in one Phase 3, randomized, double-blind, multiple-dose, parallel group, active- and placebo-controlled, multicenter clinical trial in 428 adult patients with acute postoperative pain after bunionectomy, on the primary efficacy endpoint, VAS SPID-48. Although patients were required to have a pain intensity rating of ≥ 40 mm on a 100-mm visual analog scale (VAS) within 9 hours of discontinuation of regional anesthesia to be included in the study, the vast majority of patients required rescue medication. Therefore, this study population appears reasonable for supporting the proposed, previously agreed upon, indication (i.e., for the treatment of mild to moderate acute pain in adults). The safety review demonstrated that Zorvolex 18 mg and 35 mg given three times daily appears well-tolerated by patients with acute postsurgical pain and that no new or unexpected safety signals were detected for diclofenac. The results of this clinical trial, in combination with the Agency's previous findings of safety and efficacy for the reference product (i.e., Cataflam) are acceptable to satisfy the regulatory

requirements for approval of this product with the recommended labeling changes documented throughout this review.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None

- Recommendation for other Postmarketing Requirements and Commitments

The following pediatric studies are required:

- **Study 1:** An open-label pharmacokinetic and safety study or studies of an age-appropriate formulation of diclofenac in pediatric patients 6 to < 17 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
- Recommended Comments to Applicant

None

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

/s/

JOSHUA M LLOYD
09/30/2013