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APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

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CDER stamp date: 12/20/2012
Product: Zorvolex® (diclofenac acid)
Indication: Treatment of mild to moderate acute pain
Applicant: Iroko Pharmaceuticals, LLC, Philadelphia, PA
Review Division: Division of Anesthesia, Analgesia, and Addiction
Products (HFD-170)
Reviewer: Z. Alex Xu, PhD, DABT
Supervisor/Team Leader: Adam Wasserman, PhD
Division Director: Bob Rappaport, MD
Project Manager: Swati Patwardhan

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1 Executive Summary

1.1 Introduction

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) which has been approved by the Agency with various salt formula and different formulations including Cataflam® (NDA 20-142; Novartis Pharmaceuticals Corporation), a diclofenac potassium oral tablet, for treatment of primary dysmenorrhea, relief of mild to moderate pain, and relief of the signs and symptoms of OA and RA in adults. This submission is a 505(b)(2) application referencing Cataflam which seeks approval of Zorvolex (diclofenac acid (b)(4)) for treatment of mild to moderate acute pain.

The application relies on prior findings of safety and efficacy of the reference drug, Cataflam along with results of 4 clinical trials conducted by the Applicant. There is limited nonclinical information submitted to support the approval of Zorvolex. Zorvolex capsule is a reformulation of diclofenac with a reduced particle size which was hypothesized to improve bioavailability after oral administration. Of note, 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 Applicant proposed that with improved bioavailability, a 20% reduction in the diclofenac dose of Zorvolex could provide comparable pain relief to Cataflam 50 mg tablets, while offering the potential to improve the safety profile of this NSAID compound. However, clinical studies did not prove this hypothesis. Dose-normalized systemic exposure of diclofenac of Zorvolex was actually slightly lower than that of Cataflam in human at equivalent dose. The recommended maximum dosage is 35 mg TID which is covered by the recommended maximum dosage in Cataflam label (50 mg TID) based on systemic exposure. In addition, the treatment duration for Zorvolex does not appear to be longer than that of Cataflam as suggested by the indication. Therefore, nonclinical toxicity studies are not needed for Zorvolex NDA submission. The excipients in the drug formulation are not novel and the amounts of these excipients in the drug product do not exceed those of prior approved products by the Agency. All impurities in the drug substance and product are below the qualification level as required by the ICH Q3A and Q3B guidance. For impurities with structure alert for genotoxicity, computational toxicity analysis which is also known as quantitative structure-relationship analysis (QSAR) were conducted to investigate the potential for genotoxicity, which is consistent with the Agency's current thinking.

1.2 Brief Discussion of Nonclinical Findings

Three known diclofenac acid related impurities were identified in the drug substances and drug product (impurity A, B, and C). According to the specifications of drug substance, the level of these known impurities is no more than (NMT) (b)(4)% of the drug substance, which is lower than the qualification threshold level as required by ICH guidance Q3A: *impurities in new drug substances*. In addition, the levels of these impurities in the drug product are NMT (b)(4)% and (b)(4)% in the 18 mg and 35 mg strength capsule, respectively, according to the release and shelf-life specifications of

the drug product. These specifications are less than the qualification threshold levels required by the ICH guidance *Q3B: impurities in new drug products*, when the daily intake of drug product is 10-100 mg and 100 mg -2 g, respectively. Therefore, additional toxicity studies for impurity qualification as required by ICH Q3 guidance are not needed for the Zorvolex NDA. For impurities that are less than the qualification threshold but with a structure alert for genotoxicity, a computational genotoxicity assessment is required for qualification. According to Dr. Ying Wang, the CMC reviewer for this product, impurity B and C have structure alerts. 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). 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.

A pharmacokinetic study was included in this submission to compare the bioavailability between the diclofenac acid (b) (4) capsule formulation and Voltaren® immediate-release tablet (diclofenac potassium) in beagle dogs. In this study, 6 dogs/group were administered Voltaren 25 mg tablet, diclofenac acid (b) (4) capsule 18 mg and diclofenac acid (b) (4) capsule 35 mg. The diclofenac (b) (4) capsule 18 mg produced higher C_{max} (30% ↑) and AUC_{0-4hr} (16% ↑) as compared to Voltaren 25 mg after dose normalization. However, this effect was not seen with administration of (b) (4) capsule 35 mg. The dose normalized C_{max} (↓ 4%) and AUC (↑8%) at (b) (4) 35 mg were generally similar to those of Voltaren 25 mg tablet. In addition, there was no significant difference in T_{max} between the Voltaren 25 mg group and (b) (4) 18 mg group while T_{max} of (b) (4) 35 mg group was 45% higher than that of Voltaren 25 mg group. Overall, this study did not provide convincing evidence to

demonstrate that the reduction of particle size of diclofenac significantly improves absorption and systemic exposure. This study is not required for NDA approval since human PK data of Zorvolex are available.

In addition, the Applicant conducted nonclinical literature search using National Library of Medicine (NLM, PUBMED) as the search engine with publication period from 1978 – 2012, attempting to support the efficacy and safety of diclofenac . The publications which were found by literature search are listed in Appendix 1. Since the safety of Zorvolex is covered in dosage and duration by the referenced FDA approved drug product, Cataflam, information from these publications will not be included in the label of Zorvolex. These publications were not evaluated.

In summary, Zorvolex NDA referenced Cataflam to support the safety of dosage and duration; therefore, nonclinical toxicity studies are not needed. There are no safety issues for excipients. In addition, the impurities of Zorvolex drug substance and drug products were appropriately qualified.

1.3 Recommendations

1.3.1 Approvability

Zorvolex may be approved for the proposed indication from the nonclinical perspective

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

Labeling of Zorvolex is still ongoing. Topics that will be addressed from nonclinical perspective include: 1) Converting the pregnancy (8.1), Labor and Delivery (8.2), and Nursing mother (8.3) section into PLLR format; 2) Revision of Nonclinical Toxicology section (13) if necessary.

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

2 Drug Information

2.1 Drug

CAS Registry Number (Optional)

Generic Name Diclofenac

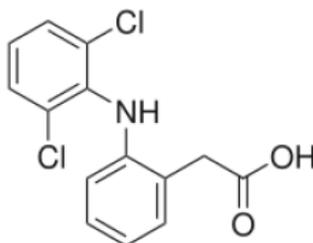
Code Name Diclofenac acid

Chemical Name: 2-(2-(2,6-dichlorophenylamino)phenyl) acetic acid

Molecular Formula/Molecular Weight

C₁₄H₁₁Cl₂NO₂; MW = 296.15

Structure or Biochemical Description



Pharmacologic Class: Nonsteroidal Anti-inflammatory Drug

2.2 Relevant INDs, NDAs, BLAs and DMFs

Zorvolex was developed under IND 103,880. Diclofenac has been approved by the Agency with various salt formula and formulations as shown in the below table.

List of Approved diclofenac drug products

NDA No.	Drug name	Active ingredient	Date of approval	Formulation	Indication
20-607	Arthrotec	Diclofenac Na ⁺ misoprostol	12/1997	Oral tablet	Treatment of the signs and symptoms of OA or RA in patients at high risk of developing NSAID-induced gastric and duodenal ulcers and their complications
22-165	Cambia	Diclofenac K ⁺	06/2009	Oral solution	Acute treatment of migraine attacks with or without aura
20-809	Diclofenac Sodium	Diclofenac Na ⁺	05/1998	Ophthalmic solution	Postoperative inflammation in cataract extraction
21-234	Flector	Diclofenac epolamine	01/2007	Patch	Treatment of acute pain due to minor strains, sprains, and contusions
20-947	Pennsaid	Diclofenac Na ⁺	11/2009	Topical solution	Treatment of signs and symptoms of osteoarthritis
21-005	Solaraze	Diclofenac Na ⁺	11/2000	Topical gel (3%)	Treatment of actinic keratoses

22-202	Zipsor	Diclofenac K ⁺	06/2009	Oral capsule	Relief of mild to moderate acute pain in adults
20-142	Cataflam	Diclofenac K ⁺	11/1993	Tablet	Treatment of primary dysmenorrhea; relief of mild to moderate pain, the signs and symptoms of OA and RA
19-201	Voltaren	Diclofenac Na ⁺	07/1988	Enteric-coated tablets	Relief of the signs and symptoms of OA, RA and ankylosing spondylitis

2.3 Drug Formulation

The composition of the drug product is shown below as extracted from the submission

Table 2.3.P.1-1 Composition of Zorvolex Capsules 18 mg

Component	Amount per Capsule (mg/capsule weight)	Function
Diclofenac acid	18.0	Active pharmaceutical ingredient
Lactose monohydrate	(b) (4)	(b) (4)
Microcrystalline cellulose		
Croscarmellose sodium		
Sodium lauryl sulfate		
Sodium stearyl fumarate		
Total capsule fill weight		
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		

Table 2.3.P.1-2 Composition of Zorvolex Capsules 35 mg

Component	Amount per Capsule (mg/capsule weight)	Function
Diclofenac acid	35.0	Active pharmaceutical ingredient
Lactose monohydrate	(b) (4)	(b) (4)
Microcrystalline cellulose		
Croscarmellose sodium		
Sodium lauryl sulfate		
Sodium stearyl fumarate		
Total capsule fill weight		
Size 1 capsule consisting of a blue body with "IP-204" imprinted in white ink and a green cap with "35 mg" printed in white ink		

Abbreviations: NF=National Formulary

2.4 Comments on Novel Excipients

There are no novel excipients in the drug product. The amounts of the excipients used in the drug product are below those in approved oral products by the Agency as shown in the Inactive Ingredients for FDA Approved Drugs database.

2.5 Comments on Impurities/Degradants of Concern

For the drug substance, the acceptance criterion for each diclofenac acid known related substance A, B and C (impurity A, B, and C), was set at not more than (NMT) (b) (4)%

based on the ICH qualification threshold. Based on the ICH Q3A guidance, if the drug substance is administered ≤ 2 g/day, the qualification threshold of a drug substance impurity is 0.15% of the drug substance or 1 mg per day intake of the impurity, whichever is lower. In this case, the total intake per day of an impurity is (b) (4) (b) (4) which is significantly lower than the qualification threshold based on mg amount. The unknown impurities are NMT (b) (4) % which is less than the identification threshold required by the ICHQ3A guidance. For the drug product, the reported impurity levels (NMT) are shown in tables of release specifications and shelf-life specifications of the drug product with same acceptance criteria, as in the table below.

Impurity levels (NMT) in Zorvolex product	Known (%)			Unknown (%)	Total (%)
	Impurity A	Impurity B	Impurity C		
18 mg capsule	(b) (4)				(b) (4)
35 mg capsule					

The impurities in the drug product (also known as degradants) are regulated according to ICH Q3B: Impurities in New Drug Products. The impurity levels in Zorvolex are below the required threshold for identification and qualification as required by ICH Q3B.

Of note, if an impurity possesses a structure alert for genotoxicity, qualification is needed even the level of this impurity is below the ICH Q3 qualification threshold. Based the Agency's current policy, computational toxicity assessments are needed to investigate the potential of genotoxicity. For computational toxicology analysis, only Ames is considered because of the large variability and unreliability in the data of other assays. If QSAR for Ames assay is negative, there is no need to further investigate the genotoxicity potential of an impurity (if \leq ICH Q3 qualification threshold). The Applicant submitted computational genotoxicity studies (QSAR analysis) of the 3 known impurities and the results indicated that the all 3 impurities are not genotoxic. Analysis from the CDER Computational Toxicology Consultation Service for a QSAR analysis of genetic toxicity confirmed that these compounds are not mutagenic. Overall, the impurities in the drug substance and drug product of Zorvolex area considered to be qualified. There are no impurity issues for Zorvolex.

2.6 Proposed Clinical Population and Dosing Regimen

ZORVOLEX is indicated for acute treatment of mild to moderate pain in adults

2.7 Regulatory Background

The sponsor submitted the IND (IND 103,880) for the development of diclofenac (b) (4) capsules in March, 2009. In an advice letter sent to the Sponsor in response to the questions included in the IND submission, the Division stated that "additional nonclinical safety studies are not required to support the safety of diclofenac for an NDA provided clinical exposure to diclofenac is within the approved limits of the RLD". However, the Division indicated that the safety of any novel excipient, as well as any

impurities which exceed ICH thresholds must be adequately qualified for safety. Similar information was conveyed to the Sponsor in the EOP2 and pre-NDA meeting.

3 Studies Submitted

3.1 Studies Reviewed

Title	Report Designation	Location
<i>Pharmacokinetics Study Reports</i>		
Diclofenac: A comparative bioavailability study in non-naïve beagle dogs	1609-002	eCTD
<i>Toxicology Study Reports</i>		
Computational assessment and evaluation of potential genotoxicity of 3 diclofenac degradation products using MC4PC	11455-21237	eCTD

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

None

4 Pharmacokinetics/ADME/Toxicokinetics

Study Title: Diclofenac: A comparative bioavailability study in non-naïve beagle dogs

Study no.: 1609-002
 Study report location: eCTD
 Conducting laboratory and location: (b) (4)
 Date of study initiation: 09/2008
 GLP compliance: Yes
 QA statement: Yes

Non-naïve female beagle dogs at 9 months to 3 years of age were used in the study. The experiment design is shown below as extracted from the study report. Voltaren® tablet 25 mg (diclofenac potassium salt tablet which is similar to Catflam), and capsules of 35 mg (diclofenac (b) (4) or 18 mg (diclofenac (b) (4) diclofenac acid (b) (4) particles were administered orally once on day 1 during the study.

Group Assignments		
Group Number	Test Article	Number of Female Animals
1	Voltaren® Rapid 25 mg (Diclofenac potassium salt)	6
2	Diclofenac (b) (4) 35 mg (acid)	6
3	Diclofenac (b) (4) 18 mg (acid)	6

Animals were observed for mortality and clinical signs. The body weight was recorded on the day of dosing. Blood samples were collected prior to dosing, and post-dosing at 10, 20, 30, and 45 minutes, and 1, 1.5, 2, 4, 6, 8, 12, 24, 30, 36, and 48 hours. PK parameters were calculated.

Results:

The dose normalized C_{max} and AUC are shown in the table below. At 18 mg, the diclofenac acid (b) (4) particles appeared to produce higher than Voltaren 25 mg in C_{max} (30% ↑) and AUC_{0-4hr} (16% ↑). However, this was not seen at 35 mg diclofenac acid (b) (4) group. This may be because of the ratio of available area for absorption versus the amount of drug substance. Nevertheless, these data did not suggest that absorption may be increased by reduction of particle size of the drug substance.

Comparison of C_{max} and AUC with dosing correction

PK parameters normalized by dose	Voltaren 25 mg	Diclofenac acid (b) (4) 35 mg	Diclofenac acid (b) (4) 18 mg
C_{max}/mg (ng/ml)	472	455	617
AUC_{0-4hr}/mg (ng•hr/ml)	692	753	801
AUC_{0-24hr}/mg (ng•hr/ml)	1164	1262	1205

In addition, there was no significant difference in T_{max} between the Voltaren 25 mg group and (b) (4) group while T_{max} of (b) (4) group was 45% higher than that of Voltaren 25 mg group as shown in the table below (extracted from the study report). Overall, reduction of particle size may not play an important role in diclofenac drug substance absorption and systemic exposure.

Table 2. Summary Statistics for Pharmacokinetic Parameters for Diclofenac in Dogs

Parameter	Group	Formulation	Mean ± SD	%CV	Median	Range
C_{max} (ng/mL)	1	VR	11,793 ± 4,631	39%	14,000	4,920 - 15,500
	2	(b) (4)	15,920 ± 6,293	40%	14,200	8,020 - 24,100
	3	(b) (4)	11,107 ± 3,127	28%	10,900	8,080 - 16,900
		(b) (4)/VR	135%		101%	
		(b) (4)/VR	94%		78%	
T_{max} (hr)	1	VR	0.708 ± 0.488	69%	0.625	0.167 - 1.50
	2	(b) (4)	1.03 ± 0.65	64%	1.00	0.333 - 2.00
	3	(b) (4)	0.681 ± 0.232	34%	0.750	0.333 - 1.00
		(b) (4)/VR	145%		160%	
		(b) (4)/VR	96%		120%	
AUC_{0-4} (ng•hr/mL)	1	VR	17,296 ± 3,239	19%	17,898	13,483 - 21,686
	2	(b) (4)	26,356 ± 4,104	16%	25,812	22,373 - 32,814
	3	(b) (4)	14,428 ± 2,223	15%	14,038	12,494 - 18,367
		(b) (4)/VR	152%		144%	
		(b) (4)/VR	83%		78%	
AUC_{0-24} (ng•hr/mL)	1	VR	29,107 ± 8,342	29%	27,660	21,764 - 44,800
	2	(b) (4)	44,186 ± 11,560	26%	40,584	36,410 - 67,384
	3	(b) (4)	21,703 ± 3,213	15%	20,524	18,935 - 27,255
		(b) (4)/VR	152%		147%	
		(b) (4)/VR	75%		74%	
$AUC_{0-\infty}$ (ng•hr/mL)	1	VR	35,030 ± 9,999 ^a	29%	33,233 ^a	23,867 - 49,925 ^a
	2	(b) (4)	48,813 ± 14,220 ^b	29%	42,868 ^b	39,517 - 69,999 ^b
	3	(b) (4)	23,086 ± 4,116	18%	22,461	19,005 - 30,182
		(b) (4)/VR	139%		129%	
		(b) (4)/VR	66%		68%	
$t_{1/2}$ (hr)	1	VR	10.9 ± 6.1 ^a	56%	8.78 ^a	7.02 - 21.7 ^a
	2	(b) (4)	6.06 ± 0.70 ^b	12%	6.10 ^b	5.35 - 6.70 ^b
	3	(b) (4)	6.78 ± 2.82	42%	6.77	3.57 - 10.0
		(b) (4)/VR	56%		69%	
		(b) (4)/VR	62%		77%	

n = 6, except as noted.

^a n = 5^b n = 4

5 Special Toxicology Studies

Study title: Computational assessment and evaluation of potential genotoxicity of 3 diclofenac degradation products using MC4PC

Study no.: 11455-21237
 Study report location: eCTD
 Conducting laboratory and location: (b) (4)
 GLP compliance: No

The purpose of this study was to perform a hazard assessment of the potential genotoxicity of three known impurities identified in diclofenac drug substance and drug

product. These included (b) (4)
impurity A), (b) (4)
impurity B), and (b) (4)
impurity C). The structures of these compounds are as
follow.



The assessment was performed with a computer-based expert system consisting of the MC4PC software and 4 sets of carefully designed expert modules, i.e., two sets for rodent carcinogenicity (public domain and proprietary), one set for cardiotoxicity, and one regulatory relevant set for genotoxic potential. The modules were developed by the ICSAS group of the US FDA (b) (4). MC4PC is a knowledge-based system designed to evaluate the associations between the structure of the chemicals and their potential activities in a specific biological assay. Its main goal is to find the structural entities that discriminate active molecules from inactive ones and its success is dependent on the validity of the working hypothesis that a relationship exists between chemical structure and activity. The results of the assessment were summarized in the following tables as extracted from the study report. The RCA (Research Cooperative Agreement with ICSAS FDA) method expert analysis is a protocol currently used by FDA/CDER ICSAS to perform human expert prediction of toxicity for test chemicals by processing MC4PC output data and identify structural alerts across multiple toxicologically related endpoints. The process typically involves combining data obtained from a module set consisting of modules representing 3-6 (as many as 20) closely related endpoints. Based on the RCA analysis, all 3 compounds were predicted to be negative in Ames assay, in vitro gene mutation assay (MA in vitro), in vitro chromosomal assay (CA in vitro), in vivo micronucleus assay (MN in vivo), and in vivo gene mutation assay (MA in vivo) except "inclusive" for (b) (4) B in MA in vitro and CA in vitro. In addition, although it was predicted to be negative in Ames for (b) (4) A and in MA in vivo for (b) (4) B, there were possible structure coverage problems as shown below. However, the final conclusion represented the conclusion from the review expert in (b) (4) taking into account all the available evidence, including the (b) (4) and available experimental results.

Table 3. Summary of results and overall conclusions for the genotoxicity tests

Compound	Ames		MA <i>in vitro</i>		CA <i>in vitro</i>		MN <i>in vivo</i>		MA <i>in vivo</i>		FINAL CONCLUSION
	RCA Method Expert Call	Review Expert									
(b) (4) A	-*	-	-	-	-	-	-	-	-	-	-
(b) (4) B	-	-	?	-	?	-	-	-	-*	-	-
(b) (4) C	-	-	-	-	-	-	-	-	-	-	-

AMES = bacterial mutation assay; MA = mammalian; CA = chromosomal aberration; MN = mouse micronucleus

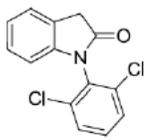
+ positive; (+) potentially positive; - negative; (-) potentially negative. ? -inconclusive † possible structural coverage problems

Based on these results, it was concluded in the study report that, overall, the 3 compounds (b) (4) A, (b) (4) B, and (b) (4) C did not demonstrate convincing evidence of activity in genotoxicity test assessments.

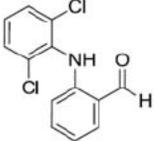
Based on the current thinking of the Agency, only Ames is considered right now for computational toxicology analysis because of the large variability and unreliability in the data of other assays. If the computational analysis for Ames assay is negative, there is no need to further investigate the genotoxicity potential of an impurity. The structures of these compounds were also sent to the CDER Computational Toxicology Group (CTG) for evaluation of Ames assay in order to confirm the results from the Applicant. All 3 compounds were determined to be no structure alerts using Derek Nexus software, an analysis system based on human expert rules for toxicity prediction. However, (b) (4) B and (b) (4) C were identified to contain structure alerts by Dr. Ying Wang, the CMC reviewer of the drug product. Using MC4PC as well as LMA (Leadscope Model Appliers) system, all 3 compounds were predicted to be non-mutagenic as shown below (extracted from CTG report). Predictions were made using statistical correlations in MC4PC and LMA systems.

Table 1. Results of CDER *in silico* analysis¹

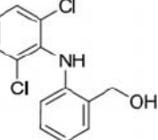
Substance A

	Software	Salmonella Mutagenicity
	Derek Nexus	NSA
	Leadscope	-
	MC4PC	-
	Overall Prediction	-

Substance B

	Software	Salmonella Mutagenicity
	Derek Nexus	NSA
	Leadscope	-
	MC4PC	-
	Overall Prediction	-

Substance C

	Software	Salmonella Mutagenicity
	Derek Nexus	NSA
	Leadscope	-
	MC4PC	-
	Overall Prediction	-

¹ + = positive; - = negative; Eqv = equivocal; NSA = no structural alerts are identified by DX (Derek Nexus cannot differentiate between a negative call and the inability to make a call because of no coverage); NC = test chemical features are not adequately represented in the model training data set, leading to a no call

Of note, the analysis from the CTG group was conducted based on only dataset of salmonella bacterial strains. E. coli strain models were not included. According to Dr. Mark Powley, an expert of computational toxicity assessment in CDER, the currently available E.coli models are based on small training sets and are not very useful. He also indicated that very few bacterial mutagens were only positive in E. coli and the inclusion of E. Coli strains is not critical.

6 Literature submission

The Applicant conducted nonclinical literature search using National Library of Medicine (NLM, PUBMED) as the search engine with publication period from 1978 - 2012. Since the safety of Zorvolex is covered by the referenced FDA approved drug product, Cataflam, and the information from these publications will not be included in the label of Zorvolex. These publications were not fully reviewed and evaluated by this reviewer.

7 Appendix/Attachments

Appendix 1 list of nonclinical publications included in this submission

1. Ahmad M, Iqbal M, Murtaza G. Comparison of bioavailability and pharmacokinetics of diclofenac sodium and diclofenac potassium in normal and alloxan-diabetic rabbits. Pak J Pharm Sci. 2012; 25(2):301-306.
2. Brambilla G, Mattioli F, Robbiano L, Martilli A. Update of carcinogenicity studies in animals and humans of 535 marketed pharmaceuticals. Mutation Research 2012; 750:1-51.
3. Buvanendran A, Reuben SS. Nonsteroidal anti-inflammatory drugs, Acetaminophen, and COX-2 inhibitors. In Raj's Practical Management of Pain, Edition 2008; Chapter 35; 671-692.
4. Cataflam [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2011.
5. Chan LY, Chiu PY, Sui SSN, Lau TK. A study of diclofenac-induced teratogenicity during organogenesis using a whole rat embryo culture model. Human Repro 2001; 16(11):2390-2393.
6. Chan LY, Chiu PY, Siu SSN, Wang CC, Lau TK. Diclofenac-induced embryotoxicity is associated with increased embryonic 8-isoprostaglandin F2 α level in rat whole embryo culture. Reprod Tox 2002; 16:841-844.
7. ChemIDPlus Advanced [Internet]. Bethesda (MD): United States National Library of Medicine's Chem SIS System; [cited 2012 April 05]. Diclofenac. CAS Registry Number 15307-86-5 [about 4 p]. Available from: <http://chem.sis.nlm.nih.gov/chemidplus>
8. ChemIDPlus Advanced [Internet]. Bethesda (MD): United States National Library of Medicine's Chem SIS System; [cited 2012 April 05]. Diclofenac Sodium. CAS Registry Number 15307-79-6 [about 5 p]. Available from: <http://chem.sis.nlm.nih.gov/chemidplus>

9. ChemIDPlus Advanced [Internet]. Bethesda (MD): United States National Library of Medicine's Chem SIS System; [cited 2012 April 05]. Diclofenac Related Compound A. CAS Registry Number 15362-40-0 [about 2 p]. Available from: <http://chem.sis.nlm.nih.gov/chemidplus>
10. Chung MC, Leandro dos Santos J, Oliveira EV, Blau L, Menegon RF, Peccinini RG. Synthesis, ex vivo and in vitro hydrolysis study of an indoline derivative designed as an anti-inflammatory with reduced gastric ulceration properties. *Molecules*. 2009; 14:3187-3197.
11. Evanson NK [Internet]. Diclofenac. xPharm: The Comprehensive Pharmacology Reference. Elsevier Inc. 2007; 1-7. Available from: <http://dx.doi.org/10.1016/B978-008055232-3.61588-0>
12. European Pharmacopoeia fifth Edition. European Directorate for Medicines and Healthcare, Strasbourg, France. Diclofenac potassium and diclofenac sodium. 2005; 1419-1422.
13. Gan TJ. Diclofenac: an update on its mechanism of action and safety profile. *Current Medical Research and Opinion*. 2010; 26(7):1715-1731.
14. GENETOX [Internet]. Bethesda (MD): United States National Library of Medicine; [cited 2012 May 05] Diclofenac, Genetox 15307-86-5 [about 1 p]. Available from: <http://toxnet.nlm.nih.gov>
15. Gökçimen A, Rağbetli MC, Baş O, Tunc AT, Aslan H, Yazici AC, Kaplan S. Effect of prenatal exposure to an anti-inflammatory drug on neuron number in cornu ammonis and dentate gyrus of the rat hippocampus: A stereological study. *Brain Research*. 2007;1127:185-192.
16. Grosser T, Smyth E, FitzGerald GA. Anti-inflammatory, antipyretic and analgesic agents; Pharmacotherapy of Gout. In Goodman and Gilman's *Pharmacological Basis of Therapeutics*, 12th Edition 2011; Chapter 34; 959-1004.
17. "HSDB" Hazardous Substances Data Bank [Internet]. Bethesda (MD): United States National Library of Medicine; [cited 2012 August 10]. Diclofenac, CAS Registry Number 15307-86-5 [50 p]. Last Revision Date 20120426. Available from: <http://toxnet.nlm.nih.gov>
- (b) (4)
20. Kenji T, Kiyoshi Y, Hiroyuki Y, Takako F, Terumichi N. Influence of pentobarbitone on in-vivo local disposition of diclofenac in rat liver. *J Pharm Pharmacol* 1996; 48:866-869.
21. Kudo C, Kori M, Matsuzaki K, Yamai K, Nakajima A, Shibuya A, Niwa H, Kamisaki Y, Wada K. Diclofenac inhibits proliferation and differentiation of neural stem cells. *Biochem.Pharmacol*. 2003; 66:289-295.
22. Kumar S, Samuel K, Subramanian R, Braun MP, Stearns RA, Chiu SL, Evans DC, Baillie TA. Extrapolation of diclofenac clearance from in vitro microsomal metabolism data: role of acyl glucuronidation and sequential oxidative metabolism of the acyl glucuronide. *J Pharm Exp Therapeu*. 2002; 303(3):969-978.
23. "LACT" Drug and Lactation Database [Internet]. Bethesda (MD): United States National Library of Medicine's ToxNet System; [cited 2012 April 05]. Diclofenac, CAS Registry Number 15307-86-5 [about 2 p]. Available from: <http://toxnet.nlm.nih.gov>
24. Lauer B, Tuschl G, Kling M, Mueller SO. Species-specific toxicity of diclofenac and troglitazone in primary human and rat hepatocytes. *Chemico-Biol Interac*. 2009; 179:17- 24.
25. León-Reyes MR, Castañeda-Hernández G, Ortiz MI. Pharmacokinetic of diclofenac in the presence and absence of glibenclamide in the rat. *J Pharm Pharmaceut Sci* 2009; 12(3):280-287.
26. LGC Standards MSDS. Wessel (United Kingdom). Diclofenac Related Compound C. 28 May 2010; 1-5

27. Masubuchi Y, Ose A, Horie T. Mechanism-based inactivation of CYP2C11 by diclofenac. *Drug Metab and Disposition*. 2001; 29(9):1190-1195.
28. Menassé R, Hedwall PR, Kraetz J, Pericin C, Riesterer L, Sallmann A, Ziel R, Jaques R. Pharmacological properties of diclofenac sodium and its metabolites. *Scand J Rheumatology*, 1978; Suppl. 22:5-16.
29. Meyler's Side Effects of Drugs. The International Encyclopedia of Adverse Drug Reactions and Interactions. Fifteenth Edition, Elsevier Science, Amsterdam, Netherlands. 2006;1109-1113
30. Mikromol MSDS. Luckenwalde (Germany). Diclofenac Related Compound C. 06 October 2004; 1-4.
31. Odaci E, Cihan OF, Aslan H, Rağbetli MC, Kaplan S. Prenatal diclofenac sodium administration increases the number of Purkinje cells in female rats: a stereological study. *Int J Dev Neurosci*. 2010; 28(2); 145-151.
32. Özyurt B, Kesici H, Alici SK, Yilmaz S, Odaci E, Aslan H, Rağbetli MC, Kaplan S. Prenatal exposure to diclofenac sodium changes the morphology of the male rat cervical spinal cord: A stereological and histopathological study. *Neurotoxicology and Teratology*. 2011; 33: 282-287.
33. Peris-Ribera J-E, Torres-Molina F, Garcia-Carbonell MC, Aristorena JC, Pla-Delfina JM. Pharmacokinetics and bioavailability of diclofenac in the rat. *J Pharmacol and Biopharmaceutics*. 1991; 19(6);647-665.
34. PubChem [Internet]. Bethesda (MD): United States National Library of Medicine's National Center for Biotechnology Information; [cited 2012 August 03]. 1-(2,6-dichlorophenyl)indolin-2-one - Compound Summary. BioAssay Results [about 6 p]. Available from: <http://pubchem.ncbi.nlm.nih.gov>
35. Rağbetli MC, Özyurt B, Aslan H, Odaci E, Gökcimen A, Sahin B, Kaplan S. Effect of prenatal exposure to diclofenac sodium on purkinje cell numbers in the rat cerebellum: A stereological study. *Brain Research*. 2007; 1174: 130-135.
36. Schweitzer A, Hasler-Nguyen N, Zijlstra J. Preferential uptake of the non steroid anti-inflammatory drug diclofenac into inflamed tissues after a single oral dose in rats. *BMC Pharmacology*. 2009; 9(5):1-9.
37. Siu SSN, Yeung JHK, Lau TK. A study on the placental transfer of diclofenac in first trimester of human pregnancy. *Human Reprod*. 2000; 15(11):2423-2425.
38. Stacy ZA, Dobesh PP, Trujillo TC. Cardiovascular risks of cyclooxygenase inhibition. *Pharmacotherapy*. 2006; 26(7):919-938.
39. Stierlin H, Faigle JW. Biotransformation of diclofenac sodium (Voltaren®) in animals and in man. II. Quantitative determination of the unchanged drug and principal phenolic metabolites in urine and bile. *Xenobiotica*. 1979; 9(10):611-621.
40. Tajiri S, Kanamaru T, Yoshida K, Hosoi Y, Konno T, Yada S, Nakagami H. The relationship between the drug concentration profiles in plasma and the drug doses in the colon. *Chem Pharm Bull* 2010; 58(10):1295-1300.
41. Thomson Micromedex™. Drug Information for the Health Care Professional. USP DI. : Micromedex, Greenwood Village, CO; 2004. 374-391.
42. USP Material Safety Data Sheet. United States Pharmacopeia. Rockville (MD). Diclofenac Related Compound A. 22 June 2010; 1-4.

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/s/

ZENGJUN XU
09/16/2013

ADAM M WASSERMAN
09/17/2013

I concur with the approval recommendation from the nonclinical perspective.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA/BLA Number: 204592 Applicant: Iroko Pharmaceutical, Stamp Date: 12/20/2012
LLC**

**Drug Name: Zorvolex™ NDA/BLA Type: 505 (b)(2)
Capsule (Diclofenac acid)**

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

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	√		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	√		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	√		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	√		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	NA		No animal toxicity studies are required for the approval of this drug product
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	√		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	NA		No animal toxicity studies are required for the approval of this drug product
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	√		

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	√		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	√		
11	Has the applicant addressed any abuse potential issues in the submission?	NA		
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?		X	This NDA is not to support a Rx to OTC switch

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? _____yes_____

If the NDA/BLA is not fileable from the pharmacology/toxicology 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. None

Z. Alex Xu	02/01/2013
_____ Reviewing Pharmacologist	_____ Date
Adam Wasserman	02/01/2013
_____ Team Leader/Supervisor	_____ Date

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/s/

ZENGJUN XU
02/01/2013

ADAM M WASSERMAN
02/01/2013