

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204592Orig1s000**

**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**

Application number: 204-592  
Supporting document/s: 000/Original submission  
Applicant's letter date: 12/20/2012  
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

**Disclaimer**

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 204-592 are owned by Iroko Pharmaceuticals, LLC or are data for which Iroko Pharmaceuticals, LLC has obtained a written right of reference. Any information or data necessary for approval of NDA 204-592 that Iroko Pharmaceuticals, LLC does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 204-592.

## TABLE OF CONTENTS

<b>1</b>	<b>EXECUTIVE SUMMARY .....</b>	<b>3</b>
1.1	INTRODUCTION .....	3
1.2	BRIEF DISCUSSION OF NONCLINICAL FINDINGS .....	3
1.3	RECOMMENDATIONS .....	5
<b>2</b>	<b>DRUG INFORMATION .....</b>	<b>6</b>
2.1	DRUG .....	6
2.2	RELEVANT INDS, NDAs, BLAs AND DMFs .....	6
2.3	DRUG FORMULATION .....	7
2.4	COMMENTS ON NOVEL EXCIPIENTS .....	7
2.5	COMMENTS ON IMPURITIES/DEGRADANTS OF CONCERN .....	7
2.6	PROPOSED CLINICAL POPULATION AND DOSING REGIMEN .....	8
2.7	REGULATORY BACKGROUND .....	8
<b>3</b>	<b>STUDIES SUBMITTED .....</b>	<b>9</b>
3.1	STUDIES REVIEWED .....	9
3.2	STUDIES NOT REVIEWED .....	9
3.3	PREVIOUS REVIEWS REFERENCED .....	9
<b>4</b>	<b>PHARMACOKINETICS/ADME/TOXICOKINETICS .....</b>	<b>9</b>
<b>5</b>	<b>SPECIAL TOXICOLOGY STUDIES .....</b>	<b>11</b>
<b>6</b>	<b>LITERATURE SUBMISSION .....</b>	<b>14</b>
<b>7</b>	<b>APPENDIX/ATTACHMENTS .....</b>	<b>14</b>

# 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

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

## LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

## FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

## E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.