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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
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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, Leadscope 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) (b) (4) capsule 35 mg. The dose normalized C_{max} (↓ 4%) and AUC (↑8%) at 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

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