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***APPLICATION NUMBER:***

# 204592Orig1s000

# CROSS DISCIPLINE TEAM LEADER REVIEW

# Cross-Discipline Team Leader Review

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| **Date** | September 30, 2013 |
| **From** | Joshua M. Lloyd, M.D.<br>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 /<br>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) (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, 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.

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

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