CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204592Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, M.D.
Subject	Deputy Division Director Summary Review
NDA #	204592/000
Applicant Name	Iroko Pharmaceuticals
Date of Submission	December 20, 2012
PDUFA Goal Date	October 20. 2013
Proprietary Name / Established (USAN) Name	Zorvolex /Diclofenac
Dosage Forms / Strength	Capsules, 18 mg and 35 mg
Proposed Indication(s)	For the treatment of mild to moderate acute pain
Action/Recommended Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Steven Galati, M.D.
Statistical Review	Feng Li, Ph.D., Janice Derr, Ph.D.
Pharmacology Toxicology Review	Alex Xu, Ph.D., Adam Wasserman, Ph.D.
CMC Review	Ying Wang, Ph.D., Prasad Peri, Ph.D.
OBP Review	Banu S. Zolnik, Ph.D, Sandra Suarez, Ph.D.
Clinical Pharmacology Review	Suresh Naraharisetti, Ph.D., Yun Xu, Ph.D.
OSI	Cynthia F. Kleppinger, M.D., Janice Pohlman, M.D., M.P.H.
CDTL Review	Joshua Lloyd, M.D.
OSE/DMEPA	Vicky Borders-Hemphill, Pharm.D., Jamie Wilkins-Parker, Pharm.D.
OPDP/DCDP	Eunice Chung-Davies, Pharm.D., L. Shenee' Toombs, Pharm.D.
OMP/DMPP	LaShawn Griffiths, MSHS-PH, BSN, RN, Barbara Fuller, RN, MSN, CWOCN
CMC Microbiology	Stephen P. Donald, M.S.

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication ErrorsPrevention
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OPDP=Office of Prescription Drug Promotion
DCDP=Division of Consumer Drug Promotion
OMP=Office of Medical Policy Initiatives
DMPP=Division of Medical Policy Programs

Signatory Authority Review Template

1. Introduction

This is a 505(b)(2) new drug application for Zorvolex, a new immediate-release capsule formulation of diclofenac acid. The referenced product is NDA 020142, Cataflam Tablet, an immediate-release formulation of diclofenac potassium. The key issues that will be discussed in this review are the Applicant's theory about the effect of a smaller particle size of diclofenac in this formulation and the food effect.

2. Background

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 dosed three times daily. The application is supported by a relative bioavailability and food effect study, a Phase 2 single-dose study and a Phase 3 efficacy study that was the subject of a special protocol agreement, along with relying, in part, on the Agency's prior finding of efficacy and safety of Cataflam. The Applicant developed Zorvolex as a new formulation of diclofenac with reduced particle size, intended to promote the dissolution and absorption of diclofenac. However, the absorption of diclofenac from Cataflam is nearly 100% following oral administration. The Applicant claimed that the improved dissolution properties of Zorvolex would be associated with rapid absorption resulting in comparable pain relief to Cataflam at an approximately 20% lower dose, although they did not conduct any studies with Cataflam as an active comparator. For further details about the development program, refer to reviews by Drs. Lloyd and Galati.

3. CMC/Device

DMF (b) (4), held by (b) (4), supports the drug substance and was found to be acceptable. As noted by Dr. Wang:

> The Zorvolex Capsules commercial manufacturing process involves (b) (4)

The proposed dissolution method and dissolution acceptance criteria were found to be acceptable. The Applicant's request for elimination of bioburden and specified microorganism testing for product release and approval of the stability protocol was found acceptable.

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance, and with the categorization of the particle size (b) (4). Manufacturing site inspections were acceptable. The Applicant's request for a categorical exclusion (21CFR25.31(a)) is supported by the their argument that approval of Zorvolex will "not increase overall use" of diclofenac as Zorvolex will compete with existing approved applications. The Applicant also postulated that Zorvolex may reduce environmental introductions due to lower dosage levels, but this is speculative and without data to support that the lower dosage levels will provide comparable efficacy. Stability testing supports an expiry of 24 months. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

As noted by Dr. Xu, while three diclofenac-related impurities are below qualification threshold, two have structural alerts for genotoxicity. A computational toxicity evaluation of all three impurities predict that they are not mutagenic. I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

As noted by Dr. Naraharisetti:

> **Relative bioavailability of Zorvolex compared to reference drug Cataflam:**
> The relative bioavailability of Zorvolex 35 mg capsules was compared to Cataflam 50 mg tablets under fasting and fed conditions in 35 healthy subjects.
>
> - When taken under fasted conditions, 20% lower dose of Zorvolex capsules (35 mg) compared to reference Cataflam tablets (50 mg) results in 26% lower (geometric mean) peak concentrations (Cmax) and 23% lower (geometric mean) AUC (AUC_{0-t} and $AUC_{0-\infty}$). There was no difference in time to reach peak concentrations (Tmax) between Zorvolex capsules and Cataflam tablets and it was ~1 hr for both.
> - When taken under fed conditions, the 20% lower dose of Zorvolex capsules (35 mg) compared to the Cataflam tablets (50 mg) results in a 48% lower (geometric mean) Cmax and 26% and 23% lower (geometric mean) AUC_{0-t} and $AUC_{0-\infty}$, respectively. The Tmax for Zorvolex was delayed by ~1 hr compared to Cataflam (Cataflam-2.33 hr vs. Zorvolex-3.32 hr) under fed conditions.
> - There were no differences in elimination half-life (T1/2) between Zorvolex and Cataflam under fasted or fed conditions.

Dose Proportionality between 18 and 35 Zorvolex capsules:

- The two strengths Zorvolex capsules,18 and 35 mg are (b) (4) results in dose proportional pharmacokinetics for Cmax and AUC under fasted conditions

Food Effect on Zorvolex capsules:

- The food effect was assessed for Zorvolex 35 mg capsules as well as reference drug Cataflam 50 mg tablets under fasting and fed conditions in 35 healthy subjects. When taken under fed conditions, Zorvolex capsules results in significant food effect in terms of reduced Cmax. Under fed conditions, Zorvolex capsules results in 60%, 14% and 11% lower Cmax, AUC_{0-t} and $AUC_{0-\infty}$, respectively compared to fasted conditions. Taking Zorvolex with food delayed the Tmax by 2.32 hr (~139 minutes) (1.0 hr fasted vs 3.32 hr fed).
- The reference drug Cataflam results in 43% and 28% lower Cmax under fed conditions without change in AUC, respectively in the studies DIC1-08-01 and DIC1-12-07. For food effect, the Cataflam label indicates 30% lower Cmax without change in AUC and can be dosed without regards to meals.
- The observed 60% lower Cmax 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.*

Dr. Naraharisetti concludes:

> The smaller particle size of Zorvolex capsules, as claimed by the sponsor has provided no additional advantage in either rate (Cmax and Tmax) 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 Cmax and delayed Tmax) of absorption compared to the Cataflam.

The Applicant developed Zorvolex to have a greater extent of absorption than Cataflam and has failed to demonstrate this to be the case. The relative bioavailability study demonstrated bioequivalence when adjusted for dose, so that Zorvolex represents a smaller dose of diclofenac than is available with Cataflam, although the difference in weight of the salt vs. the free acid makes comparing the strengths confusing. I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

DOCKET ALARM

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.