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.

6. Clinical Microbiology

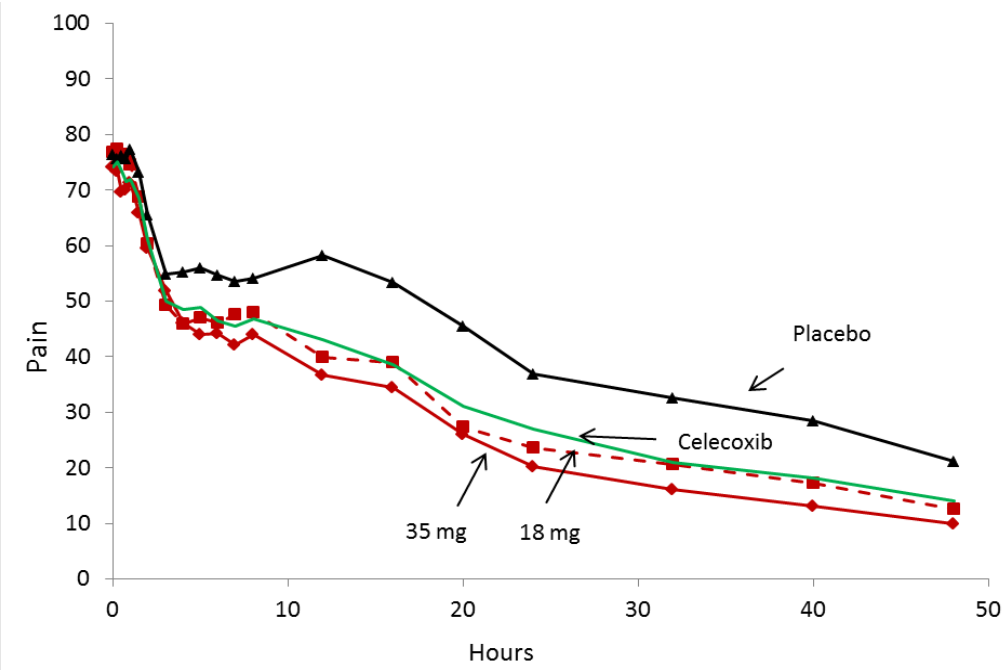
N/A

7. Clinical/Statistical-Efficacy

Efficacy is supported by one Phase 3 study. A single-dose Phase 2 study was conducted with an early formulation and will not be considered further. The Phase 3 study was a randomized, double-blind, multicenter, parallel, active and placebo-controlled study evaluating the efficacy and safety of two dosing regimens of Zorvolex capsules in subjects with acute postoperative pain after bunionectomy. Details of the study design can be found in Dr. Galati's review. Efficacy was demonstrated in this study based on the primary efficacy analysis of the summed pain intensity difference (SPID) over 48 hours. The Applicant's method of handling the effect of the use of rescue medication was unusual in that all efficacy results following the use of rescue were imputed using the baseline score, rather than the more common method of imputing the pre-rescue pain score for the period of time the rescue was expected to be active. As more than 80% of the study population used rescue medication, this masked much of the effect of Zorvolex. Dr. Li conducted several sensitivity analyses including an analysis of pain intensity over time without imputation and an analysis in which pain scores within a time window after taking rescue medication were replaced with the pre-rescue pain score. Both of these analyses demonstrated efficacy for both doses of Zorvolex as compared to placebo, as well as efficacy of an active comparator, celecoxib. No comparative claims with celecoxib are supported by this single efficacy study.

As shown in the analysis of data without imputation by Dr. Li, depicted in Figure 2 (page 11) from his review, Zorvolex had a statistically significant difference from placebo, indicating that in combination with the rescue medication, Zorvolex produced an analgesic effect superior to placebo in combination with the rescue medication. The high use of rescue also indicates that Zorvolex alone is not sufficient to manage the pain following bunionectomy, particularly in the first few hours following surgery, and is consistent with the indication for mild to moderate pain, (b) (4). As the purpose of the study was to confirm that the lower doses of Zorvolex were effective, and as studies of mild pain can be methodologically challenging, the use of the post-bunionectomy surgery study population is acceptable.

Figure 2: Average Pain Over Time – No Imputation After Rescue



Although an active comparator arm of Cataflam would have enabled the Applicant to evaluate whether their initial hypothesis of greater absorption leading to greater efficacy with a lower dose had merit, as well as providing early evidence of any differences in safety due to the different doses, the Applicant chose not to include a head-to-head comparison with Cataflam. Therefore, no comparative claims against Cataflam may be made in labeling or in promotional materials.

8. Safety

The assessment of safety is based primarily on data from the Phase 3 efficacy study. The overall exposure to Zorvolex was 216 subjects who received at least one dose of diclofenac (35mg and 18mg groups). As noted by Dr. Galati, no new significant safety concerns were identified. There were no deaths or serious adverse events in patients treated with Zorvolex.

It is difficult to assess the adverse events specific to Zorvolex in this population as more than 80% of subjects received rescue doses of an opioid during the study. Therefore, the reporting of adverse reactions in the package insert includes some events that were more frequent in placebo patients who relied on opioids for analgesia in the postoperative periods in order to provide some information about the frequency of adverse events with Zorvolex. The most frequent treatment emergent adverse events occurring in at least 5% of patients in a Zorvolex or placebo treatment group were edema, nausea, headache, dizziness vomiting, hematoma, constipation, and pruritus.

Zorvolex will have the class language in the package insert including all of the same warnings as Cataflam and will have the NSAID class medication guide.

9. Advisory Committee Meeting

No advisory committee was convened for this application.

10. Pediatrics

A deferral for pediatric studies was granted and the Applicant will perform following studies according to the requirements under the Pediatric Research Equity Act. Studies under the age of 1 year have been waived for diclofenac products due to immaturity of relevant metabolic pathways.

The following pediatric studies are required:

Study 1: An open-label pharmacokinetic and safety study or studies of an age-appropriate formulation of diclofenac in pediatric patients 6 to < 17 years of age with acute pain

Study 2: An open-label pharmacokinetic and safety study or studies of an age-appropriate formulation of diclofenac in pediatric patients 2 to < 6 years of age with acute pain

Study 3: A pharmacokinetic, safety, and efficacy study or studies of an age-appropriate formulation of diclofenac in pediatric patients 1 to < 2 years of age with acute pain

11. Other Relevant Regulatory Issues

Inspection of two clinical sites were conducted. Inclusion of a patient with a history of gastric ulcer and missed pain assessments were noted at one site that enrolled 143 subjects resulting in issuance of a Form FDA 483 and Voluntary Actions Indicated, the response by the investigator were adequate, and a conclusion, based on review of the full Establishment Inspection Report (EIR) was that the data from this site appear acceptable and the deviations noted do not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

There are no other unresolved relevant regulatory issues.

12. Labeling

The proprietary name of Zorvolex was found acceptable. Reviews of the package insert, medication guide, and carton and container labels were conducted, as appropriate by OSE's Division of Medication Error Prevention and Analysis, OMP's Division of Medical Policy Programs, and OPDP's Division of Consumer Drug Promotion and comments were conveyed to the Applicant for inclusion in labeling.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action - Approval

- Risk Benefit Assessment

Zorvolex is a novel formulation of diclofenac, in this case the free acid, intended for the management of mild to moderate pain. There is evidence of efficacy from one adequate and well-controlled trial. There is evidence of safety from the same clinical trial as well as through reliance on the Agency's prior findings of efficacy and safety for Cataflam. The primary differences between Zorvolex and Cataflam is that the former uses the free acid form of diclofenac, while the latter uses the potassium salt of diclofenac, and when corrected for differences related to the weights of the free acid and salt, the 18 mg and 35 mg strengths of Zorvolex are 20% lower than the 25 mg and 50 mg strengths of Cataflam.

- Recommendation for Postmarketing Risk Management Activities

None

- Recommendation for other Postmarketing Study Commitments

The only post marketing requirements are those required under the Pediatric Research Equity Act:

Study 1: An open-label pharmacokinetic and safety study or studies of an age-appropriate formulation of diclofenac in pediatric patients 6 to < 17 years of age with acute pain

Study 2: An open-label pharmacokinetic and safety study or studies of an age-appropriate formulation of diclofenac in pediatric patients 2 to < 6 years of age with acute pain

Study 3: A pharmacokinetic, safety, and efficacy study or studies of an age-appropriate formulation of diclofenac in pediatric patients 1 to < 2 years of age with acute pain

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/s/

SHARON H HERTZ
10/18/2013