

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-202**

**SUMMARY REVIEW**

## Deputy Director Memo and Cross-Discipline Team Leader Review

<b>Date</b>	June 3, 2009
<b>From</b>	Sharon Hertz, M.D.
<b>Subject</b>	Cross Discipline Team Leader Review and Deputy Director Memo
<b>NDA#</b>	22-202 N000 AZ 505(b)(2)
<b>Applicant</b>	Xanodyne Pharmaceuticals, Inc.
<b>Date of Submission</b>	December 16, 2008
<b>PDUFA Goal Date</b>	June 15, 2009
<b>Proprietary Name / Established (USAN) names</b>	Zipsor Diclofenac Potassium
<b>Dosage forms / Strength</b>	Liquid Filled Capsule, 25 mg
<b>Proposed Indication(s)</b>	For the relief of mild to moderate pain.
<b>Recommended:</b>	Approval

<b>Material Reviewed/Consulted</b>	
OND Action Package, including:	
Pharmacology Toxicology Review	Marcus Delatte, Ph.D./ R. Daniel Mellon, Ph.D.

### 1. Introduction

Zipsor (diclofenac potassium) Liquid Filled Capsules are liquid-filled, soft gelatin capsules containing 25 mg of diclofenac potassium for oral administration. The related IND for this NDA is 63,308. This is a 505(b)(2) application referencing the Agency's prior findings of safety and efficacy for Cataflam (NDA 20-142). The current submission represents a complete response to an approvable action taken on July 21, 2008.

### 2. Background

Diclofenac is a non-selective nonsteroidal anti-inflammatory drug (NSAID) currently marketed in several oral formulations; as a potassium salt (Cataflam, approved November 24, 1993) for mild to moderate pain and as a sodium salt (Voltaren, NDA 19-201, approved July 28, 1988 and Voltaren XR, NDA 20-254, approved March 8, 1996)) for the relief of the signs and symptoms of osteoarthritis, the signs and symptoms of rheumatoid arthritis, acute or long-term use in the relief of the signs and symptoms of ankylosing spondylitis. Other diclofenac products include one combination product with diclofenac sodium and misoprostol, Arthrotec, NDA 20-607, three topical formulations of diclofenac, Flector Patch, Voltaren Gel and Solaraze and an ophthalmic solution under the tradename Voltaren.

The deficiencies cited in the action letter from the first cycle review were:

The overall clinical risk to benefit evaluation appears to favor approval of Zipsor 25 mg, dosed every 6 hours for mild to moderate acute pain. However, there are impurities specific to this formulation of diclofenac that must first be assessed for safety in nonclinical toxicology tests and genetic toxicology tests prior to completion of the risk to benefit assessment.

1. Submit the final study reports for the ongoing safety qualification studies for the following drug product impurities that exceed ICHQ3B(R) qualification thresholds:

- a. Impurity (b) (4)
- b. Impurity
- c. Impurity

2. Your ongoing adequate qualification studies include:

- a. Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
- b. Repeat dose toxicology of appropriate duration to support the proposed indication. For an acute pain indication, a 28-day repeat dose toxicology study would be acceptable.

3. Since these impurities contain a structural alert for mutagenicity, if the results in either of the two genetic toxicology assays for an individual impurity are positive, you must reduce the impurity to not more than (b) (4) mcg/day unless otherwise justified. Justification may require an assessment for carcinogenic potential in either a standard 2-year rodent bioassay or in an appropriate transgenic mouse model.

### 3. CMC

There were no outstanding CMC issues from the first cycle and no additional CMC review was conducted.

### 4. Nonclinical Pharmacology/Toxicology

Dr. Marcus Delatte performed the review of the nonclinical data submitted in this complete response. While the Applicant referenced the Agency's prior findings for Cataflam, there were drug product impurities specific to the formulation of Zipsor that required qualification since the levels exceeded the ICHQ3B(R) qualification threshold of NMT 0.5% for drug products with a maximum daily dose of 10 mg to 100 mg. Dr. Delatte reviewed five studies submitted to address the deficiencies. The studies were of adequate design and conduct.

The Bacterial Reverse Mutation Assays demonstrated no positive mutagenic responses for Impurities (b) (4). In the In Vitro Mammalian Chromosome Aberration Tests, Impurities (b) (4) were negative for induction of structural and numerical chromosomal aberrations. Repeat dose, 28-day oral toxicity studies in rats were conducted with Impurities (b) (4). For Impurity (b) (4) there was a 69-fold safety margin based on the NOAEL for alterations observed in organ weights, hemolytic, macroscopic and microscopic endpoints in both

genders, alterations in clinical signs (postured hunch, discolored hair, and piloerection) and clinical chemistry endpoints measured in females were reported and an increase in urine volume found in males. For Impurity (b) there was a 243-fold safety margin at the requested drug product specification of NMT (b) (4) % at the maximum daily dose of Zipsor of 100 mg/day, with few findings of note. For Impurity (b) there was a 243-fold safety margin at the requested drug product specification of NMT (b) (4) % at the maximum daily dose of Zipsor of 100 mg/day. This was based on gender-related differences with regard to the toxicokinetic profile. Biologically significant alterations were observed across various endpoints detailed in Dr. Delatte's review and included changes in food consumption, organ weights, hematology, clinical chemistry, and macroscopic and microscopic endpoints.

## **5. Clinical Pharmacology/Biopharmaceutics**

There was no new clinical pharmacology data submitted in this complete response. As noted from my review of the original submission:

Dose proportionality was demonstrated for the 25 mg and 50 mg doses of Zipsor. Zipsor is not bioequivalent to Cataflam. The C<sub>max</sub> following a 50 mg dose of Zipsor is nearly twice the C<sub>max</sub> following a 50 mg dose of Cataflam, although the values for the AUC<sub>0-∞</sub> were comparable. A high fat meal decreases the rate, but not the extent, of absorption of Zipsor, so that the PK profile is more similar to Cataflam. However, as only one strength is proposed and the change does not present any safety concerns, no dosing instructions with regard to food are recommended.

## **6. Clinical Microbiology**

Not Applicable

## **7. Clinical/Statistical- Efficacy**

There was no new clinical data submitted in this complete response. Adequate evidence of efficacy has been demonstrated and there is sufficient data to support the proposed every six hour dosing interval for Zipsor.

## **8. Safety**

No new safety data was submitted in this complete response. The safety profile of Zipsor was reviewed with the original NDA submission and no new safety concerns were identified.

## **9. Advisory Committee Meeting**

Not applicable.

## **10. Pediatrics**

A Pediatric Plan was submitted during the first review cycle that is adequate to address the requirements of PREA.

## **11. Other Relevant Regulatory Issues**

There will be a medication guide-only REMS as the labeling includes a the NSAID class medication guide.

## **12. Labeling**

The package insert will include the boxed warning, the NSAID class language regarding risk, and the NSAID Medication Guide.

## **13. Recommendations/Risk Benefit Assessment**

Recommended regulatory action: Approval

### **Risk Benefit Assessment**

The overall clinical risk to benefit evaluation appears to favor approval of Zipsor 25 mg, dosed every 6 hours for mild to moderate acute pain. Concerns about the presence of impurities specific to this formulation of diclofenac have been adequately addressed through appropriate nonclinical studies.

### **Recommendation for Postmarketing Risk Management Activities**

There will be a medication guide-only REMS as the labeling includes a the NSAID class medication guide.

### **Recommendation for other Postmarketing Study Commitments**

Pediatric studies will be required to address the requirements of PREA. These will include studies of the pharmacokinetics, efficacy and safety of Zipsor in pediatric patients with mild to moderate acute pain.

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Sharon Hertz  
6/16/2009 01:15:19 PM  
MEDICAL OFFICER