CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-202

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	June 8, 2009
To:	Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)
Through:	Claudia Karwoski, PharmD, Director (Acting) Division of Risk Management (DRISK)
From:	Mary Dempsey Risk Management Programs Coordinator Division of Risk Management (DRISK)
Subject:	DRISK Review of Proposed Risk Evaluation and Mitigation Strategy (REMS)
Drug Name(s):	Zipsor (diclofenac potassium) Soft Gelatin Capsules
Application Type/Number:	NDA 22-202
Submission Number:	N-000 submissions dated May 19, 2009 and June 2, 2009
Applicant/sponsor:	Xanodyne Pharmaceuticals, Inc
OSE RCM #:	2009-1061

1 INTRODUCTION

This review is written in response to a request from the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Risk Evaluation and Mitigation Strategy (REMS), which includes the draft Medication Guide (MG) and Timetable for Submission of Assessments of the effectiveness of the REMS. Comments on the draft Medication Guide were sent to DAARP in a separate memorandum dated June 23, 2008. Zipsor (diclofenac potassium) Soft Gelatin Capsules received an AE letter on July 21, 2008 due to chemistry and toxicology deficiencies.

2 MATERIAL REVIEWED

- Zipsor (diclofenac potassium) Soft Gelatin Capsules submission dated May 19, 2009 which responds to an email from Ms. Tanya Clayton dated May 7, 2009 which requests a reformatted proposed REMS
- Zipsor (diclofenac potassium) Soft Gelatin Capsules submission dated June 2, 2009 which responds to an email from Ms. Tanya Clayton dated May 26, 2009 which requests further formatting revisions to the proposed REMS

3 BACKGROUND

Zipsor (diclofenac potassium) Liquid Filled Capsule is a new 25 mg dose form of the existing reference listed drug, Cataflam® (diclofenac potassium) 50mg tablets. Cataflam is indicated for the relief of signs and symptoms of osteoarthritis and rheumatoid arthritis, for the treatment of primary dysmenorrhea, and for the relief of mild to moderate pain. Zipsor is a liquid formulation of diclofenac potassium encapsulated in liquid filled capsules. The formulation is designed to improve absorption characteristics and reduce time to onset of pain relief. This 505(b)(2) application for Zipsor seeks an indication only for the treatment of mild to moderate (b) (4) pain.

DRISK previously reviewed the Zipsor (diclofenac potassium) Soft Gelatin Capsules Medication Guide on June 23, 2008. Zipsor (diclofenac potassium) Soft Gelatin Capsules is a Non-Steroidal Anti-Inflammatory (NSAID) drug product and therefore requires the NSAID class Medication Guide.

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to provide FDA with new authorities to require applicants of approved drugs to develop and comply with REMS section 505-1 of the FDCA if FDA finds that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. These provisions took effect on March 25, 2008.

In an email dated May 7, 2009 DAARP informed Xanodyne Pharmaceuticals that a REMS is necessary for Zipsor (diclofenac potassium) Soft Gelatin Capsules. The only elements of the REMS will be a Medication Guide and a timetable of submission of assessments of the REMS.

The Applicant submitted a proposed REMS for Zipsor (diclofenac potassium) Soft Gelatin Capsules on May 19, 2009 and following an email from Ms. Tanya Clayton dated May 26, 2009 the sponsor submitted an amendment to the proposed REMS on June 2, 2009.

4 CONCLUSIONS AND RECOMMENDATIONS

DRISK believes that the Applicant's proposed REMS for Zipsor (diclofenac potassium) Soft Gelatin Capsules generally meets the statutory requirements outlined in 21 CFR 208 and in accordance with 505-1. However, we have the following comments and recommendations:

We have the following comments on the proposed REMS:

1. The format and content of the REMS and the REMS Supporting Documents should be revised. Please see Appendix A and B.
2. We remind the Applicant of their requirement to comply with 21 CFR 208.24
    - A required statement alerting the dispenser to provide the Medication Guide with the product must be on the carton and container of all strengths and formulations. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):
        "Dispense the enclosed Medication Guide to each patient." or
        "Dispense the accompanying Medication Guide to each patient."
    - Sufficient numbers of Medication Guides should be provided with the product such that a dispenser can provide one Medication Guide with each new or refilled prescription. We recommend that each packaging configuration contain enough Medication Guides so that one is provided for each "usual" or average dose. For example:
        - A minimum of four Medication Guides would be provided with a bottle of 100 for a product where the usual or average dose is 1 capsule/tablet daily, thus a monthly supply is 30 tablets.
        - A minimum of one Medication Guide would be provided with unit of use where it is expected that all tablets/capsules would be supplied to the patient.
3. The Applicant's proposed timetable for assessments is acceptable; it is also acceptable to include only the month and year that the REMS Assessment is due.
4. The Applicant should submit for review a detailed plan to evaluate patients' understanding about the safe use of Zipsor (diclofenac potassium) Soft Gelatin Capsules at least 90 days before they plan to conduct the evaluation. The submission should include:
    - All methodology and instruments that will be used to evaluate the patients' understanding about the safe use of Zipsor (diclofenac

potassium) Soft Gelatin Capsules. This should include, but not be limited to:

- Sample size and confidence associated with that sample size
- How the sample will be determined (selection criteria)
- The expected number of patients to be surveyed
- How the participants will be recruited
- How and how often the surveys will be administered
- Explain controls used to minimize bias
- Explain controls used to compensate for the limitations associated with the methodology

- The survey instruments (questionnaires and/or moderator's guide).
- Any background information on testing survey questions and correlation to the messages in the Medication Guide.

4. Your REMS assessment plan will need to assess the effectiveness of the REMS including:

a. An evaluation of patients' understanding of the serious risks of Zipsor (diclofenac potassium) Soft Gelatin Capsules.
b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

For products that are not unit of use, you must assess whether patients are receiving the Medication Guide. This requirement stems not from Part 208 of the regulations, but rather from 505-1(d) of FDAAA which requires that the Applicant assess the strategy at designated intervals. When requiring a Medication Guide through a REMS, the strategy is to mitigate the risks of the drug through the use of a Medication Guide that patients both understand and receive. Therefore, each assessment must include information on whether patients understand the information in the Medication Guide as well as the distribution and dispensing of the Medication Guide.

Please let us know if you have any questions.

Appendix A:

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

NDA 22-202 Zipsor™ (diclofenac potassium)

Non-Steroidal Anti-Inflammatory Drug (NSAIDs)

Xanodyne Pharmaceuticals, Inc.
One Riverfront Place
Newport, KY 41071-4563

I. GOAL(S):

The goal of this REMS is to communicate the key safety information on Zipsor™ (diclofenac potassium) Liquid Filled Capsule.

II. REMS ELEMENTS:

A. Medication Guide

A Medication Guide will be dispensed with each Zipsor prescription.

Pursuant to 21 CFR 208.24, the Medication Guide will be made available in sufficient numbers to US Zipsor™ distributors. US distributors will provide the Medication Guide with every pharmacy shelf container of Zipsor™ to ensure its availability for dispensing to patients who are dispensed Zipsor™. The label of each container or package of Zipsor™ will include a prominent instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and state how the Medication Guide is provided.

In addition, the Medication Guide will be included with all samples and trade packets intended for direct distribution to patients.

B. Timetable for Submission of Assessments

The assessment interval period will close no earlier than 60 days prior to the date the respective assessment is due as noted below:

- 1st Assessment: 18 months after NDA approval
- 2nd Assessment: 3 years after NDA approval
- 3rd Assessment: 7 years after NDA approval

The assessments will include an evaluation of the effectiveness of the Medication Guide in communicating the risks of Zipsor.

APPENDIX B:

REMS SUPPORTING DOCUMENT MEDICATION GUIDE REMS

1. Background

Xanodyne Pharmaceuticals is submitting this Risk Evaluation Mitigation Strategy (REMS) for Zipsor (diclofenac potassium) Liquid Filled Capsules for the relief of mild to moderate acute pain. The submission responds to FDA's request for further formatting revision to our proposed REMS (email dated May 26, 2009 from Ms. Tanya Clayton to Arthur Ilse).

2. Goals

The goal of this REMS is to communicate the key safety information on

Zipsor™ (diclofenac potassium) Liquid Filled Capsule via a Medication Guide.

3. Supporting Information on Proposed REMS Elements

a. Medication Guide

Medication Guide for Non-Steroidal Anti-Inflammatory (NSAID) drug product should be attached

b. Timetable for Submission of Assessments of the REMS (for products approved under an NDA or BLA)

1st Assessment: 18 months after NDA approval

2nd Assessment: 3 years after NDA approval

3rd Assessment: 7 years after NDA approval

4. REMS Assessment Plan (for products approved under an NDA or BLA)
   A. The Information Needed for Assessment should be detailed in the REMS Supporting Document only and removed from the REMS.
   B. Information Needed for Assessment (REMS Assessment Plan) will include, but is not limited to the following:
      i. **An evaluation of patients' and prescribers' understanding of the serious risks of Zipsor (diclofenac potassium) Liquid Filled Capsules**
      ii. **A report on periodic assessments of the dispensing of the Medication Guide in accordance with 21 CFR 208.24.**
      iii. **A report on failures to adhere to MG dispensing requirements and corrective actions taken to address noncompliance.**
      iv. **A description of specific measures that would be taken to increase awareness if surveys of healthcare prescribers indicate that prescriber awareness is not adequate.**
      v. **Periodic summaries of adverse event reports of Zipsor**

vi. Based on the information reported, an assessment of and conclusion of whether the REMS is meeting its goal and whether modifications to the REMS are needed.

C. Patient/Provider/ Pharmacist Survey:

Survey Requests: ***Submit for review a detailed plan to evaluate the [provider/patient/pharmacist]s' understanding about the safe use of Zipsor to FDA 60 days prior to conducting the survey. The submission should include, but is not limited to:***

- *Sample size and confidence interval associated with that sample size*
- *How the sample will be determined (selection criteria)*
- *The expected number of patients surveyed*
- *How the participants will be recruited*
- *How and how often the surveys will be administered*
- *Explain controls used to minimize bias*
- *Explain controls used to compensate for the limitations associated with their methodology*
- *The Sponsor should submit the survey instruments (questionnaires and moderator's guide) for review.*
- *Provide any background information on testing survey questions and the correlation to the educational materials, and explain what will be done with the resulting data from the surveys.*

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/s/

Mary Dempsey
6/8/2009 01:56:47 PM
DRUG SAFETY OFFICE REVIEWER

Claudia Karwoski
6/8/2009 03:58:13 PM
DRUG SAFETY OFFICE REVIEWER

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	June 23, 2008
To:	Bob A. Rappaport, M.D., Director Division of Anesthesia, Analgesia, and Rheumatology Products
Through:	Jodi Duckhorn, M.A., Team Leader Patient Labeling and Education Team Division of Risk Management (DRISK)
From:	Sharon R. Mills, BSN, RN, CCRP Patient Product Information Specialist Patient Labeling and Education Team Division of Risk Management (DRISK)
Subject:	Review of Patient Labeling (Medication Guide)
Drug Name(s):	Zipsor (diclofenac potassium) Soft Gelatin Capsules
Application Type/Number:	NDA 22-202
Applicant/sponsor:	Xanodyne Pharmaceuticals, Inc.
OSE RCM #:	2007-2321

Xanodyne Pharmaceuticals, Incorporated submitted an original New Drug Application, NDA 22-202 for Zipsor (diclofenac potassium) Soft Gelatin Capsules, on September 21, 2007. The sponsor's submission includes a proposed Medication Guide. Zipsor (diclofenac potassium) Soft Gelatin Capsules is a Non-Steroidal Anti-Inflammatory (NSAID) drug product and therefore requires the NSAID class Medication Guide.

We reviewed the sponsor's Medication Guide and it is consistent with the NSAID class MG template. The sponsor has added Zipsor to the list of NSAID medicines that need a prescription, in the Medication Guide. The sponsor's proposed Medication Guide is acceptable.

Please let us know if you have any questions.


APPEARS THIS WAY ON ORIGINAL

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/s/

Sharon Mills
6/23/2008 07:34:39 PM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
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