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APPLICATION NUMBER:
22-202

OTHER ACTION LETTER(s)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-202

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

Attention: Arthur C. Ilse
Director, Regulatory Affairs

Dear Mr. Ilse:

Please refer to your new drug application (NDA) dated September 21, 2007, received September 21, 2007, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Zipsor (diclofenac potassium) Soft Gelatin Capsules.

We acknowledge receipt of your submissions dated January 23, March 24, April 10, and April 18, 2008.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to:

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

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.

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) 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.

In addition, it will be necessary for you to submit draft labeling revised as follows:

1. Submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that incorporates the revisions listed in the enclosed draft labeling (text for the package insert, Medication Guide).

2. Soft gelatin capsule is not a recognized USP dosage form. Revise all labels to indicate capsules as the dosage form.

3. Retail Container Label

a. Decrease the prominence of the company name and accompanying logo on the container label so that it does not compete with the prominence of the drug name.

Appears this way on original

b. Remove the graphics (red dots) above the letter 'p' in the proprietary name.

c. Left justify the lines containing the established name and formulation to begin at the same position as the proprietary name.

d. Increase the prominence of the product strength with use of larger font or color.

4. Physician Sample Blister Label

a. Remove the graphics (red dots) above the letter 'p' in the proprietary name.

b. Left justify the lines containing the established name and formulation to begin at the same position as the proprietary name.

c. Increase the prominence of the product strength with use of larger font or color.

d. It is possible that a patient will interpret the four capsules in the blister pack to be one dose instead of four. To avoid a patient taking all four capsules at one time, a statement should be added that each individual capsule in the blister is 25 mg.

5. Physician Sample Carton Label

a. Remove the graphics (red dots) above the letter 'p' in the proprietary name.

b. Left justify the lines containing the established name and formulation to begin at the same position as the proprietary name.

c. Increase the prominence of the product strength with use of larger font or color.

- d. It is possible that a patient will interpret the four capsules in the blister pack to be one dose instead of four. To avoid a patient taking all four capsules at one time, a statement should be added to the principle display panel that each individual capsule in the blister is 25 mg.

The draft package insert, Medication Guide, and carton and container labels should be modified to reflect the above comments, and the revisions noted in the attached marked-up draft labeling. Further labeling comments will be provided once the aforementioned deficiencies are adequately addressed.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - a. Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - b. Present tabulations of the new safety data combined with the original NDA data.
 - c. Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - d. For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Tanya Clayton, Regulatory Project Manager, at (301) 796-0871.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, M.D.
Deputy Director
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure