CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-926

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-926

Pozen, Inc.
Attention: Paul Ossi
1414 Raleigh Road
Suite 400
Chapel Hill, NC 27517

Dear Mr. Ossi:

Please refer to your new drug application (NDA) dated August 5, 2005, received August 8, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Trexima (sumatriptan/naproxen) tablets.

We acknowledge receipt of your submissions dated the following:
January 31, 2007, March 8, 2007, June 21, 2007, July 2, 2007 and July 16, 2007.

The January 31, 2007 submission constituted a complete response to our June 8, 2006 action letter.

This new drug application provides for the use of Trexima (sumatriptan/naproxen) tablets for the acute treatment of migraine headaches.

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 adequately address the following issue:

We acknowledge that you have performed, as we had requested in our Approvable letter of June 8, 2006, a repeat *in vitro* chromosomal aberration assay in CHO cells, as well as an *in vitro* mouse lymphoma tk assay (MLA). We further acknowledge that the MLA was negative for sumatriptan and naproxen alone and in combination, up to the highest concentrations tested. We do note, however, that the results for naproxen alone in this study are at odds with the positive findings in the presence of metabolic activation, at lower concentrations, obtained in an earlier MLA conducted to support [redacted] The reasons for these discrepant findings are not clear, and we ask that you address this issue.

Of far greater concern, however, is the finding of a synergistic effect in the *in vitro* chromosomal aberration assay in CHO cells. Specifically, in this study, sumatriptan and naproxen alone were negative, both in the presence and absence of metabolic activation; however, the combination produced a concentration-related increase in the percentage of cells with aberrations, both with and without metabolic activation.

Cytotoxicity was expressed as reductions in mitotic index (% Mitotic Inhibition) and cell count

(% Reduction in Cell Count), as well as in population doubling (% Population Doubling Inhibition). Current guidelines (OECD, ICH) indicate that % reduction in cell count is the most appropriate measure of cytotoxicity for this assay. Population doubling has been proposed as an alternative measure (Greenwood SK et al. *Environ Mole Mutagen* 43:36-44, 2004); however, it has not been accepted as a more valid or more appropriate measure of cytotoxicity and should not be used to dismiss the positive responses observed.

In the absence of metabolic activation (S9), significant increases in the % of cells with chromosomal aberrations were obtained at concentrations of naproxen and sumatriptan in combination associated with 50-68% reductions in cell count. This degree of cytotoxicity is consistent with that recommended for the highest concentrations in this assay (ICH, OECD guidelines). In the presence of S9, increases in the % of cells with chromosomal aberrations were obtained at concentrations associated with only 32-52% decreases in cell count. It is notable that naproxen (at 2500 µg/mL) was negative in the presence of S9, whereas the combination of naproxen and sumatriptan (at 1745/1745 µg/mL) was positive, at the same degree of cytotoxicity (42% reduction in cell count); therefore, the positive response with the combination cannot be explained by a greater cytotoxic effect.

In our view, these findings cannot be dismissed, for the following reasons:

(a) Positive findings in the repeat *in vitro* CHO assay were not associated with excessive cytotoxicity and, as noted above, naproxen alone at a concentration producing a similar degree of cytotoxicity (as measured by reduction in cell count) was negative.

(b) Although it is true that the other *in vitro* and the *in vivo* genetic toxicology assays were negative, there is no apparent basis for dismissing a reproducible positive signal in one component of the standard battery of genetic toxicology assays based solely on negative findings in other assays comprising the battery.

(c) We acknowledge that sumatriptan was negative in carcinogenicity studies in mouse (78-week) and rat (104-week) and that naproxen was negative in a 2-year carcinogenicity study in rats (8-24 mg/kg/day) and, in combination with metoclopramide, in a 26-week p53 transgenic mouse assay (50 mg/kg). However, none of these studies tested the combination of sumatriptan and naproxen. In our opinion, rather than lessening the concern, it is the lack of a signal for carcinogenicity in these studies that heightens the concern regarding a possible synergistic effect of the combination of sumatriptan and naproxen. (It is of note that, due to the sensitivity of the rodent to the gastrointestinal effects of NSAIDs, naproxen could not be evaluated in any of the carcinogenicity studies at more than a fraction of clinically relevant doses or plasma exposures.)

The results of this study raise the possibility that the combination may be carcinogenic. We believe that you must adequately address this concern prior to the application being approved. We acknowledge that, were the application to be approved, the typical patient would not administer the drug daily; however, acute migraine treatments can be administered frequently, and for many years. For this reason, we consider an adequate assessment of carcinogenicity critical prior to the approval of any acute migraine treatment.

It appears to us unlikely that conducting additional *in vitro* or *in vivo* genetic toxicology studies would provide data that could be used to adequately address our concern about the positive finding in the *in vitro* CHO cell assays. It is also unlikely that lifetime carcinogenicity studies or shorter-term studies in transgenic animals (e.g., p53, TgHras2) would provide meaningful data, specifically because of the sensitivity of rodents to naproxen. It might be possible, however, to conduct a study in humans to assess the clastogenic potential of naproxen alone and in combination with sumatriptan. A number of studies have been published on the evaluation of clastogenic and/or mutagenic effects in circulating lymphocytes in various populations (e.g., smokers, industrial workers, military personnel). Studies have also been conducted in patients on therapeutic doses of various medications. For example, Saxena and Ahuja (Saxena R, Ahuja YR. *Hum Genet* 62(3):198-200, 1982) reported a significant increase in patients treated with thioridazine for 4 weeks. Ahuja et al. (Ahuja YR et al. *Arzneimittelforschung* 34(6):699-701, 1984) reported increases in chromosomal aberrations in patients on therapeutic doses of haloperidol. More recently, studies have been conducted to assess the effects of therapeutic doses of methylphenidate on circulating lymphocytes in children (El-Zein et al. *Cancer Lett* 230(2):284-291, 2005; Walitz S et al. *Environ Health Perspect* 115:936-940, 2007). Although we admit that the interpretation of a positive finding in such a study is not entirely clear, we do believe that the results of such a study would provide useful additional information that would affect our decision about the approvability of this combination.

In lieu of conducting such a clinical trial, you could also re-evaluate the conduct of the *in vitro* chromosomal aberration assays to investigate, for example, whether or not the apparent synergistic effect is an artifact of assay conditions.

We note your commitment to perform a post-approval study evaluating the effects of Trexima on blood pressure as described in your submission dated January 31, 2007. In your response to this approvable letter, please submit dates by which you will submit the final study protocol and final study report.

We also note that we are reviewing your current proposed tradenames of [redacted] Treximet, as submitted on July 16, 2007.

Labeling

We are including draft labeling with this letter. Although we have included language for the **Carcinogenesis, Mutagenesis, Impairment of Fertility** section, the language relating to carcinogenicity and mutagenicity should be regarded as a place holder; clearly, the specific language ultimately adopted will depend upon your response to the issue discussed above. Indeed, the approvability of the application itself will depend upon a satisfactory response to our concerns.

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:

- Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
- Present tabulations of the new safety data combined with the original NDA data.
- Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
- [redacted] 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.

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