

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-926

APPROVABLE LETTER

(% 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.
 - ~~_____~~ 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.

NDA 21-926
Page 5

If you have any questions, call Lana Chen, Regulatory Project Manager, at (301) 796-1056.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Russell Katz
8/1/2007 06:00:41 PM



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 applications (NDA) dated August 5, 2005, received August 8, 2005 and submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Trexima (sumatriptan and naproxen sodium) tablets.

We acknowledge receipt of your submissions to NDA 21-926 dated the following:

August 5, 2005	February 22, 2006
October 27, 2005	April 7, 2006
November 16, 2005	April 19, 2006
December 5, 2005	April 28, 2006
December 8, 2005	May 9, 2006
January 27, 2006	May 30, 2006

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 address the following issues:

Clinical

Although we have determined that Trexima is effective as an acute treatment for migraine headaches, there are several findings that raise serious questions about the safety of this combination.

First, we note the occurrence of a case of "acute coronary syndrome" in a 47 year old woman receiving chronic treatment in Study 303 (subject 2143, site 030). This woman experienced documented coronary ischemia about 2 hours after a dose of Trexima. Although this woman had several risk factors for coronary artery disease (obesity, family history), and was noted to have underlying coronary artery disease on angiography, clearly the investigator concluded that she was an appropriate candidate for treatment with a triptan. Current triptan labeling recommends that patients with risk factors not be treated unless a cardiac evaluation does not reveal underlying disease. A reasonable interpretation of such cardiac evaluation can be, as was apparently the case here, a normal EKG at baseline.

Although we are aware, of course, of cases of documented cardiac ischemia with triptans, the rate of these events is considered to be quite low. If the rate of such events with Trexima was similar to that of sumatriptan, it would be extraordinarily unlikely to see even one case in a database of this size. The occurrence of this case, then, at least suggests that the incidence of serious cardiac events with Trexima may be considerably greater than that believed to be associated with sumatriptan.

In addition, our concerns are increased by the finding of four cases of severe chest pain in the Trexima treated patients in Studies 301 and 302, compared to none in the other treatment groups. We acknowledge that we do not know if these cases represent cases of cardiac ischemia or not, but the disparity in the occurrence among the treatment groups in the incidence of severe chest pain again suggests that there may be important differences in the tolerability of the combination compared to the tolerability of the components.

Further, although we recognize the limitation of the study in dogs designed to assess the effects of the combination on coronary artery constriction, five of the six dogs showed increased constriction with the combination compared to sumatriptan given alone. The conclusion that this increased constriction was drug related is strengthened by the observation that this increased constriction was dose related, because it was not seen on Days 2 and 3, when levels of naproxen were diminishing. We also note that, based on its effects on prostaglandins, there is at least some reason to believe that naproxen itself can be a vasoconstrictor.

Finally, we note the complete absence in your application of any blood pressure monitoring appropriately timed to dosing with the combination, or with chronic dosing. For this reason, we have no reliable information about the maximal effects of this combination on blood pressure either acutely or chronically. Although we expect, were this drug to be approved, that few patients would dose themselves daily (when we would expect both the incidence, and the sequelae, of hypertension to be greatest), many patients may dose relatively frequently. In these cases, it is possible that important changes in blood pressure might occur. Obviously, chronic hypertension is dangerous in itself, but if such changes did occur with chronic dosing with Trexima, this might pose an additional risk if, as noted above, treatment with Trexima is associated with an increase in the incidence of coronary vasoconstriction.

These observations, taken as a whole, suggest that the cardiovascular risks of Trexima may be greater than those with sumatriptan or naproxen alone. If this is true, this would raise questions about the approvability of the combination. Therefore, you must address these concerns prior to the approval of this application.

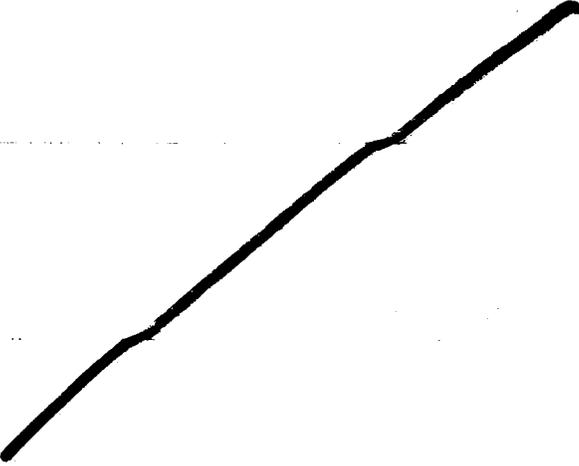
Regarding the risk of coronary vasoconstriction, a study comparing the effects of the combination to sumatriptan alone might be able to be performed in patients who are undergoing catheterization for other reasons, and who might consent to have these compounds administered. An adequate study of this sort that documents no important increased constriction of the combination might address our concerns. Alternatively, a trial comparing the incidence of adverse events of interest (perhaps severe chest pain [as a "surrogate" for ischemia] or actual chest pain accompanied by EKG changes consistent with ischemia) between patients treated with the combination and sumatriptan might be acceptable. Such a study would likely need to enroll several thousand patients per group followed for a reasonable duration (at least 3-6 months). Such a trial would also be an appropriate setting in which to obtain adequate blood pressure data. Whether such a large, relatively long trial is necessary to obtain

adequate blood pressure data can be a matter of discussion, but we will require that adequate blood pressure data be obtained.

Product Name

The Division of Medication Errors and Technical Support (DMETS) has recommended that the propriety name Trexima not be used for the following reasons:

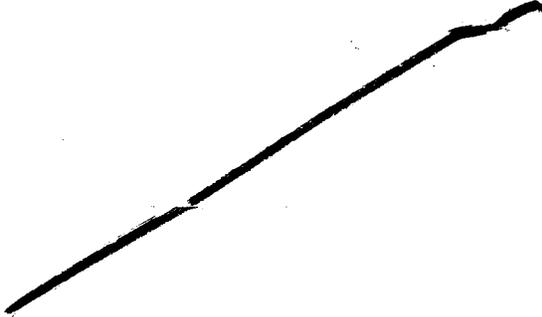
[Redacted content]

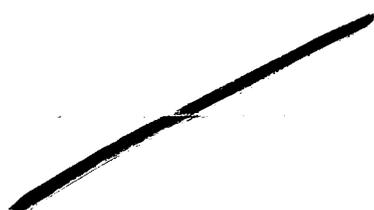


3. In review of the labels and labeling, DMETS has identified the following areas of possible improvement, which might minimize potential user error.

a) GENERAL COMMENTS

1





Product Labeling

We have included draft product labeling with this letter. Of course, the clinical issues described above will need to be resolved before this application may be approved. Obviously, then, the label we have included must be considered relatively preliminary at this point. We do wish to note two points, however.

As you know, we had discussed in a phone conversation on May 25, 2006 the possibility that labeling for this product might not be required to include a Boxed Warning, and we acknowledge your arguments to support this view. As we noted in that conversation, however, the inclusion of a Boxed Warning for all naproxen-containing products was a matter for internal Agency discussion beyond the division. Such a discussion has taken place, and the decision was made to require these products to include a Boxed Warning in their package insert. Therefore, we have included such a Warning.

Also, all naproxen-containing products are required to include a Medication Guide, the language for which can be found at the Website referred to in the attached draft labeling. For this reason, the product must be made available in unit of use packaging.

Preclinical

1. The results of the in vitro chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells (Study MT400/T07, #0735/0736-3110) demonstrated clastogenic effects of naproxen alone and in combination with sumatriptan. The magnitude of the clastogenic effect was greater with the combination of naproxen and sumatriptan than with naproxen alone, both in the absence and presence of metabolic activation. (Sumatriptan was negative in this assay.) These results raise the concern that naproxen and sumatriptan in combination may have carcinogenic effects not observed with either drug alone. However, since the clastogenic effects were observed only at concentrations producing substantial cytotoxicity, the biological significance of these effects is unclear, but cannot be dismissed. Therefore, you need to conduct the following additional studies:

- a. a repeat in vitro chromosomal aberration assay in CHO cells testing concentrations between those exhibiting minimal or no cytotoxicity (i.e., 1250/1250 µg/mL naproxen/sumatriptan) and those resulting in substantial cytotoxicity (i.e., 2500/2500 and 2000/2000 naproxen/sumatriptan in the absence and presence of metabolic activation, respectively).
- b. an in vitro mouse lymphoma tk assay (with colony sizing) testing naproxen and sumatriptan alone and in combination.

The results of these studies will determine the need for additional nonclinical studies.

2. You need to include the results of the in vitro mouse lymphoma tk assays (Studies MT 100 T25, MT100 T26) and the carcinogenicity study in p53^{+/-} heterozygous mice (Study MT 100 T35) for naproxen in product labeling.

Safety Update

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.
 - _____, 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 these products. 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 these applications, notify us of your intent to file amendments, 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 an informal meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug products may not be legally marketed until you have been notified in writing that the applications are approved.

If you have any questions, call Lana Chen, Regulatory Project Manager, at (301) 796-1056.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Russell Katz
6/8/2006 04:44:23 PM