CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-926

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	April 15, 2007
From	Eric Bastings, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	21926
Applicant	Pozen
Date of Submission	October 11, 2007
PDUFA Goal Date	April 15, 2008
Proprietary Name / Established (USAN) names	Treximet/sumatriptan and naproxen sodium
Dosage forms / Strength	85mg sumatriptan/ 500mg naproxen sodium
Proposed Indication(s)	Acute treatment of Migraine
Recommended:	*Approval*

1. Introduction

This submission is a response to the approvable letter of August 1, 2007 for a combination product of sumatriptan and naproxen sodium. The remaining issue in this application was related to potential carcinogenicity of the combination, which had been inadequately addressed by the sponsor. The sponsor was also requested to provide a safety update.

2. Background

I reproduce below the relevant section from the August 1, 2007 approvable letter, which is the key issue to be addressed in this submission:

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 teste. 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 pg/mL) was negative in the presence of S9, whereas the combination of naproxen and sumatriptan (at 1745/1745 pg/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 (EI-Zein et al, Cancer Lett 230(2):284-291, 200S; 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.

As discussed during the first review cycle, the sponsor committed to perform a post-approval study evaluating the effects of Trexima on blood pressure. The sponsor was requested to submit dates by which they will submit the final study protocol and final study report.

3. CMC/Device

There were no outstanding CMC issues from the previous review cycle.

4. Nonclinical Pharmacology/Toxicology

As noted by Dr. Freed in her supervisory memorandum, the sponsor submitted an open-label, placebo-controlled, parallel group study in healthy volunteers to assess the effects of MT 400 tablets or naproxen sodium on the frequency of chromosomal aberrations in peripheral lymphocytes, and data from three in vitro cell cycle analysis studies in CHO cells treated with various NSAIDs, or naproxen sodium and sumatriptan succinate. Although Dr. Freed concludes that the sponsor did not adequately address all the issues in the Agency's AE letter (see her memorandum for a detailed discussion), she believes that the data from the clinical

trial demonstrating no genotoxic effects of naproxen either alone or in combination with sumatriptan is sufficient to support approval of the application.

5. Clinical Pharmacology/Biopharmaceutics

There were no outstanding Clinical Pharmacology/Biopharmaceutics from the previous review cycle. Dr. R. Uppoor reviewed minor labeling changes proposed by the sponsor, and reviewed a pharmacokinetic study which provided a comparison of the pharmacokinetic profile of sumatriptan when administered as Treximet and when administered as IMITREX 100 mg, in support of the labeling changes. Dr. Uppoor essentially agreed to the changes, with minor edits, which were incorporated in the label.

6. Clinical Microbiology

N/A.

7. Clinical/Statistical- Efficacy

Efficacy of the combination product was established in earlier cycles. There was no outstanding efficacy issue.

8. Safety

The sponsor provided a safety update. The sponsor added two studies to the NDA database: Study TRX105850 and Study TRX105852, which were conducted in women with menstrual migraine (single attack). As a result of the addition of these two studies, the database increased from 2999 subjects to 3302 migraine patients. In addition, there were 117 healthy volunteers exposed during the drug development program (number unchanged from the full response).

The overall incidence of adverse events in the update was similar to that reported in the NDA and the Full Response. There is no new case of significant cardiac adverse event. There is no new death, adverse dropout, or treatment emergent serious adverse event. The additional safety data led to some minor changes in the adverse event section of labeling, which are acceptable.

The sponsor agreed to set up a pregnancy registry for this product, as recommended by the Pediatric and Maternal Health Staff.

Regarding the post-approval commitment for a chronic blood pressure study, the sponsor proposed that, following NDA approval, the protocol for the blood pressure study will be submitted to the Agency within 2 months. The sponsor anticipates that the final study protocol

will be submitted and the study will start within approximately 4 months after that, and that the final study report will be submitted to the Agency 18 months after initiation. In my opinion, this proposal is acceptable.

9. Advisory Committee Meeting

There was no need for an Advisory Committee Meeting, because this product is a combination of two currently marketed products, and there is ample experience for the indication being sought.

10. Pediatrics

A written request was sent to the sponsor on 06/29/2007. The request was for a PK study, an efficacy study in patients age 12-17, and a long-term safety study. On April 9, 2008, PERC recommended that the division grant a waiver for study in children under the age of 6, and a deferral for children age 6-17. PERC recommended that the sponsor be required to study the population age 6-11, if studies in that population are believed to be practicable. In the opinion of Dr. V. Elgin, a pediatric neurologist member of PERC, studies in that age group are possible. The division will further discuss the issue with outside migraine experts. Based on the outcome of these discussions, studies in the age group 6-11 may later be either required, or waived if believed not practicable.

11. Other Relevant Regulatory Issues

There is no other relevant regulatory issue.

12. Labeling

In a 12/21/2007 review document, OSE (DMETS) and DDMAC found the names [redacted] and "Treximet" acceptable. The Treximet name was re-evaluated by OSE (DMEP) in this review cycle, and its acceptability was confirmed.

There were only minor changes to the Professional Insert sent with the last approvable letter, and labeling negotiations with the sponsor resulted in an agreed upon labeling.

This product has a Medication Guide, as it contains an NSAID, naproxen. The sponsor proposed rather extensive changes to the Medication Guide sent with the last approvable letter. DNP and OSE (DRISK) reviewed the proposed language, and agreement was reached with the sponsor after labeling negotiations.

13. Recommendations/Risk Benefit Assessment

The sponsor has adequately addressed the remaining issue (potential carcinogenicity of the combination). I therefore recommend approval of Treximet.

As the combination contains an NSAID, this product must have a medication guide.
The sponsor has agreed to conduct a post-marketing safety study to assess the effect of the chronic intermittent administration of Trexima on blood pressure. The study will be randomized, double-blind, active-comparator study in adults with episodic migraine dosed with either Treximet, naproxen sodium 500mg or sumatriptan 85mg. Both active ingredients have the potential to increase blood pressure. We have sufficient short-term data to approve Treximet with the current labeling, which includes a contraindication for use in patients with uncontrolled hypertension, and a warning that Treximet should be used with caution in patients with controlled hypertension. The study is intended to better characterize if the chronic intermittent administration of Treximet may lead to new or worsened hypertension, which would need to be described in labeling.

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/s/

Eric Bastings
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