events were musculoskeletal system and general disorders. There were no differences between males and females in reporting events in cardiac disorders."

Age

No meaningful difference in adverse events were identified by comparing the older half of patients to the younger half in the controlled studies:

> "The effect of age was examined above and below the median age of 41 years. Younger subjects reported slightly more adverse events with Trexima than older subjects (30% versus 23% respectively), however the other treatment groups did not show an age differential. The increased reports in subjects <41 years were primary classified as nervous system disorders (dizziness and somnolence) and musculoskeletal disorders. Importantly, there were no differences in the reported incidences of cardiac disorders between the two age groups."

Few subjects were over the age of 55 (about 60-80 subjects/group in pivotal studies). No significant difference in adverse events was found in this 'oldest 1/3' compared to each younger 1/3 of subjects:

> "Further examination of age compared three groups of subjects, those 18-35 years, those 36 to 55 years, and those over 55 years. This examination needs to be interpreted with caution due to the lower numbers of subjects in the over 55 years age group. The general trend of adverse event reporting was again inversely related to age. The same trends in System Organ Classification reports were repeated. No differences were noted in the number of events in cardiac disorders among the age groups, however the oldest subjects reported more cardiac events following treatment with sumatriptan (6%; chest discomfort, cardiac flutter, chest pain and palpitations) than following treatment with Trexima (1%; chest discomfort)."

Race

About 70- to 80 subjects/arm were African American in the pivotal studies, with very few other races represented. No important differences in adverse event rates were found in African Americans.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Dog studies designed to asses possible additive cardiovascular effects of sumatriptan and naproxen in Trexima were performed (discussed in detail in Section 3.2, Animal Pharmacology/Toxicology). I find these studies suggest a possible increase in both vasoconstriction and blood pressure from Trexima that is greater than that from sumatriptan alone. Given the critical nature of these questions, the number of animals studied, 6 or fewer per arm, was not adequate. High experimental variability suggests that the studies might not have been conducted with adequately rigorous methodology or technique, and my review of the raw blood pressure datasets supports this.

7.2.5 Adequacy of Routine Clinical Testing

Monitoring of blood pressure, ECGs, and other vital signs was not carried out adequately at times when drug would be expected to be present in the body, or over the long-term safety study (see Sections 1.1, 7.1, 7.1.8.1, 7.1.9.1).

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Since both components of Trexima are currently approved, no studies were conducted examining metabolism, clearance, or drug interaction (other than preclinical studies examining cardiovascular effects in dog).

Metabolisms and Clearance

Sumatriptan:

Sumatriptan is rapidly but incompletely absorbed when given orally, and undergoes first-pass metabolism. Sumatriptan is extensively metabolised in the liver, predominantly by monoamine oxidase type A, and is excreted mainly in the urine as the inactive indole acetic acid derivative and its glucuronide. Sumatriptan and its metabolites also appear in the feces.

Naproxen

Naproxen is reported to be nearly 100% absorbed from the GI tract. About 95% of a dose is excreted in urine as naproxen and 6-*O*-desmethylnaproxen and their conjugates. Less than 5% of a dose appears in the feces.

Interaction

The Division, in pre-submission meetings, indicated that new studies would not be necessary examining the PK interaction of naproxen and sumatriptan. The effect of naproxen on sumatriptan pharmacokinetics had been examined by Srinivasu et al. ("Lack of Pharmacokinetic Interaction between Sumaptriptan and Naproxen," Clin. Pharmacol 2000;40:99-104). Twelve healthy volunteers were treated with 100 mg sumatriptan succinate either alone or with 500 mg naproxen orally. Naproxen had no statistically significant ($p > 0.05$) effect on any pharmacokinetic parameters of sumatriptan. The authors concluded that no alteration in sumatriptan dosage was necessary for migraine patients taking naproxen prophylactic therapy.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Cardiovascular safety of Trexima was not adequately addressed. See in particular sections 1.1 and 1.3.3

7.2.8 Assessment of Quality and Completeness of Data

The Trexima trials were either single-dose (controlled studies) or chronic intermittent dose (extension study) in migraine patients that were otherwise generally healthy. Most adverse effects were mild and reversible, and derived mainly from patient reported symptoms. Importantly, however, the trials provided insufficient evidence of cardiovascular safety.

7.2.9 Additional Submissions, Including Safety Update

The results of the 1-year open-label extension study were submitted with the 120-day safety update, and are integrated in the overall safety review.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Common Adverse Events
Common adverse events from Trexima generally reflect those encountered with sumatriptan. These common events could affect ability to drive or operate machinery, and I find this should be added to the Trexima label.

- Dizziness:
  - Generally of mild or moderate intensity, but sometimes severe
  - Brief duration (few hours), reverses spontaneously
- Somnolence:
  - Generally of mild or moderate intensity.
  - Brief duration (few hours), reverses spontaneously
- Paresthesia:
  - Generally mild intensity
  - Brief duration, reverses spontaneously.
- Nausea
  - Generally mild or moderate intensity, but can be severe.
  - Also a major symptom of the underlying migraine
- Dry Mouth
  - Generally mild intensity
  - Brief duration, reverses spontaneously
- Dyspepsia
  - Generally mild or moderate intensity, but less often severe
  - Brief duration, reverses spontaneously
- Chest pain
  - Generally mild or moderate, but can be severe
- throat pain/tightness
  - Generally mild or moderate, but can be severe
  - Brief duration, reverses spontaneously

Less common but serious adverse Events

Trexima is dosed intermittently, and is generally not present in the body between doses. Therefore, adverse events in close proximity to dosing could suggest causality.

Logically, adverse events in Trexima studies similar to those caused by sumatriptan or naproxen were likely caused by Trexima.

Many of the adverse effects of NSAIDs are similar or identical to those of sumatriptan, including heart attack, stroke, hypertension, and dizziness.

Due to the size and design of the Trexima database, it is not possible to determine if the risk from Trexima is greater than that from sumatriptan or naproxen alone.

I conclude that Trexima can cause serious cardiovascular adverse events, including acute coronary syndrome (two subjects in the safety study, one definite, one 'possible').

There were 2 cases of elevated liver enzymes in the long-term Trexima study, a known adverse event associated with naproxen (described fully in section 7.1.3, Dropouts and Other Significant Adverse Events).

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The safety database for Trexima was relatively small. Adverse events data was examined for each study individually, and for pooled data from controlled trials.

7.4.1.2 Combining data

Not applicable

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

See Section 8.1, Dosing Regimen and Administration.

7.4.2.2 Explorations for time dependency for adverse findings

The reported incidence of adverse events declined between the first and last treated migraine attack regardless of the use of one or two tablets of Trexima to treat the migraine. This might represent an actual decrease of adverse events with time, or a lower reporting rate for adverse events with time.

7.4.2.3 Explorations for drug-demographic interactions

Like sumatriptan, Trexima appears most likely to induce adverse cardiac events in demographic groups with the highest cardiovascular risk. Although the safety population for Trexima is small, obesity and a history of hypertension appear to be risk factors for adverse cardiac events proximate to Trexima dosing.

7.4.2.4 Explorations for drug-disease interactions

The migraine syndrome studied in this NDA was fairly narrowly defined, such that differences in efficacy or safety across subgroups were not found.

7.4.2.5 Explorations for drug-drug interactions

See Section 8.2, Drug-Drug Interactions

7.4.3 Causality Determination

See section 7.3, Summary of Selected Drug-Related Adverse Events

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Appropriateness of dose
Study MT400-204 evaluated the combination of Imitrex 50 mg non-RT and naproxen 500 mg, co-administered as separate pills. This represents about half the dose of sumatriptan in the final formulation of Trexima. Estimating dose/response by comparing separate studies is not usually productive, but I believe study MT400-204 can be cautiously compared to studies of Trexima. Table 67 and Table 68 show 2-hour and sustained pain efficacy results for studies MT100-204

and MT100-301/302, respectively. The response rates for placebo and naproxen are very similar across studies. In addition, sumatriptan 85 mg appeared more efficacious than 50 mg, as might be expected. Trexima, however, did not have any efficacy advantage over the lower dose combination used in study 204.

Table 67: Study MT400-204, 'Low' Dose Efficacy

	50 mg Sumatriptan + 500 mg naproxen 'MT-400' (%)	50 mg Sumatriptan (%)	500 mg Naproxen (%)	Placebo (%)
2-hour pain relief	65	49	46	27
Sustained pain free	25	11	12	5

Table 68: MT400-301/302, 'High' Dose Efficacy

	85mg Sumatriptan + 500 mg naproxen 'Trexima' (%) 301 /302	85 mg Sumatriptan (%) 301 / 302	500 mg Naproxen (%) 301 / 302	Placebo (%) 301 / 302
2-hour pain relief	57/65	50/55	43/44	29/28
Sustained pain free	23/25	14/16	10/10	7/8

Regardless of the strength of the above comparison, for many migraine patients 50 mg is an appropriate dose of sumatriptan based on the balance of safety and efficacy. Sumatriptan is known to have a dose-related increase in adverse events in the clinically prescribed dose range (from Imitrex label). Trexima would clearly ***not*** be an appropriate choice for most patients starting triptan therapy. For the subset of patients failing 50 mg sumatriptan, the next appropriate clinical step might be a combination of 50 mg sumatriptan and 500 mg naproxen, as was used in the proof-of-concept study for Trexima and shown to be effective. Thus, only for those patients failing the combination of 50 mg sumatriptan and 500 mg naproxen might an increase of sumatriptan to 85 mg, as in Trexima, be appropriate.

Repeat dosing of Trexima within 24 hours

Pozen proposes the following labeling for repeat dosing:

[redacted] Do not take more than 2 tablets in 24 hours.

The safety study did not suggest increased adverse events within 24 hours after a second dose of Trexima versus a single dose (Table 69). In fact, a lower rate of adverse events was reported in patients taking a second dose compared to those taking only 1 tablet. I reviewed the MedDRA terms (not shown) and found no evidence for excess adverse events in the second-dose group.

[Comment: the population that took a second tablet for the first attack might have been different from the population that took only one tablet. For example, patients with more experience using triptans might have been more likely to take a second tablet, and also more likely not to report adverse events that were familiar. This effect of decreased reporting with patient experience is similarly likely responsible for the decreased reporting rate of adverse events between first and last migraine attacks during the study (Table 69), although a biological explanation is also possible].

Table 69: Adverse Events, 1 vs. 2 tabs, first vs. last headache, MT400-303

POZEN, Inc. Study Number MT400-303

Table 14.2.8.1
Adverse Events Within 24 Hours after Dosing, First Attack versus Last Attack
By MedDRA System Organ Class and Preferred Term
Overall Safety Population (N=565)

	First Attack 1 Tab. Taken (N=407)	First Attack 2 Tab. Taken (N=158)	Last Attack 1 Tab. Taken (N=374)	Last Attack 2 Tab. Taken (N=169)
Subject Had at Least One Adverse Event				
No	328 (80.6%)	138 (87.3%)	348 (93.0%)	160 (94.7%)
Yes	79 (19.4%)	20 (12.7%)	26 (7.0%)	9 (5.3%)

8.2 Drug-Drug Interactions

Naproxen and antihypertensives

The interaction of naproxen on the action of antihypertensives is discussed here. I discuss the effect of naproxen on blood pressure in normotensives in Section 8.6, Literature Review.

Sumatriptan is contraindicated in patients with uncontrolled hypertension. Trexima might lead to poorer control of blood pressure in treated hypertensives. NSAIDs are thought to attenuate the antihypertensive effects of several common classes of antihypertensives, including diuretics, beta-blockers, and vasodilators (but probably not calcium channel blockers). For diuretics and beta-blockers, this is reflected in current naproxen labeling:

> "Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. The use of NSAIDs in patients who are receiving ACE-inhibitors may potentiate renal disease."
>
> "Naproxen and other nonsteroidal anti-inflammatory drugs can reduce the antihypertensive effect of propranalol and other beta-blockers."

Naproxen/sumatriptan interactions

The effect of naproxen on sumatriptan pharmacokinetics was examined by Srinivasu et al. ("Lack of Pharmacokinetic Interaction between Sumaptriptan and Naproxen," Clin. Pharmacol

2000;40:99-104). Twelve healthy volunteers were treated with 100 mg sumatriptan succinate either alone or with 500 mg naproxen orally. Naproxen had no statistically significant ($p > 0.05$) effect on any pharmacokinetic parameters of sumatriptan. The authors concluded that no alteration in sumatriptan dosage was necessary for migraine patients taking naproxen prophylactic therapy.

Known Drug-Drug Interactions of Trexima Components

Prescribing information for Trexima will include those interactions currently listed in the individual prescribing information for naproxen and sumatriptan. Additional modifications include:

- Co-administration of valproic acid and naproxen appears to affect the clearance of both drugs. A small (20%) but significant displacement of valproic acid from plasma proteins results in increased overall metabolic flux. A small decrease (10%) in plasma clearance of naproxen also occurred. Accordingly, Trexima should be used with caution in patients receiving valproic acid therapy.

8.3 Special Populations

Renal Failure

Naproxen pharmacokinetics has not been determined in subjects with renal insufficiency. Given that naproxen, its metabolites and conjugates are primarily excreted by the kidney, the potential exists for naproxen metabolites to accumulate in the presence of renal insufficiency. Elimination of naproxen is decreased in patients with severe renal impairment. Naproxen-containing products are not recommended for use in patients with moderate to severe and severe renal impairment (creatinine < 30 ml/min).

While the effect of renal impairment on the PK of sumatriptan has not been examined, little clinical effect is expected because sumatriptan is metabolized to an inactive substance.

Hepatic Insufficiency

From Imitrex label:

> "The liver plays an important role in the presystemic clearance of orally administered sumatriptan. Accordingly, the bioavailability of sumatriptan following oral administration may be markedly increased in patients with liver disease. In 1 small study of hepatically impaired patients (n = 8) matched for sex, age, and weight with healthy subjects, the hepatically impaired patients had an approximately 70% increase in AUC and C_{max} and a t_{max} 40 minutes earlier compared to the healthy subjects."

In chronic hepatic insufficiency, the clearance of naproxen is reduced and the dose should likely be reduced.

8.4 Pediatrics

See Section 1.2, Recommendation on Postmarketing Actions.

8.5 Advisory Committee Meeting

In February 2005, FDA held a joint meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee to address risk of COX-2 selective NSAIDs and related agents, including naproxen. The meeting transcript can be accessed through FDA Dockets Management: http://www.fda.gov/ohrms/dockets/default.htm

From the discussions, I conclude that the cardiovascular risk of naproxen has not been established.

- The ADAPT study data that was influential in specifically implicating naproxen in increased cardiovascular risk appears weak, and remains not publicly released or peer-reviewed.
- Meta-analysis of about a dozen studies using naproxen generally fails to find an increased cardiovascular risk from naproxen, although importantly the studies are methodologically weak. The studies can more confidently be interpreted to indicate that naproxen is unlikely to have a cardioprotective effect.
- Many of the advisory committee members thought that the cardiovascular risk posed by naproxen was probably less than that of other NSAIDs. However, the data is not strong enough to justify indicating this in labeling.

8.6 Literature Review

Hypertensive Effect of NSAIDs

NSAIDs appear to have small but significant effects on blood pressure (Frishman, Am J. Cardiol. 2002;89:18D-25D). This effect is largest in hypertensive patients on antihypertensive medication, but NSAIDs might also increase blood pressure to a lesser degree in normotensive subjects. For Trexima, a major safety concern is that the combination of NSAID-induced hypertension with sumatriptan-induced vasoconstriction could result in additive cardiovascular adverse effects.

I have included below brief summaries of selected publications examining the relationship between naproxen/NSAIDs and blood pressure in non-hypertensive subjects. Some studies have positive findings, and others negative. I conclude that the chance of an effect is high enough, and the risk great enough, that the effect should be considered in Trexima approval and labeling.

Articles finding an increased risk of hypertension from naproxen exposure

- Curhan et al., *Frequency of analgesic use and risk of hypertension in younger women*, Arch Intern Med. 2002 Oct 28;162(19):2204-8.
  - Prospective study of 80,020 women aged 31 to 50 years who participated in the Nurses' Health Study II and had no previous history of hypertension.
  - NSAIDs and acetaminophen (P<.001 for trend for both) were significantly associated with risk of hypertension. Compared with nonusers, the relative risk of hypertension for women taking NSAIDs 22 d/mo or more was 1.86 (95% confidence interval, 1.51-2.28) and for those taking acetaminophen 22 d/mo or more was 2.00 (95% confidence interval, 1.52-2.62).

- Johnson et al., *Do nonsteroidal anti-inflammatory drugs affect blood pressure? A meta-analysis.* Ann Intern Med 1994;121(4):289-300.
  - When pooled, NSAIDs elevated supine mean blood pressure by 5.0 mm Hg (95% CI, 1.2 to 8.7 mm Hg) but had no effect on variables other than blood pressure. Nonsteroidal anti-inflammatory drugs antagonized the antihypertensive effect of beta-blockers (blood pressure elevation, 6.2 mm Hg; CI, 1.1 to 11.4 mm Hg) more than did vasodilators and diuretics.

- Pope et al., *A meta-analysis of the effects of nonsteroidal anti-inflammatory drugs on blood pressure.* Arch Intern Med. 1993 Feb 22;153(4):477-84.
  - Fifty-four studies with 123 NSAID treatment arms met inclusion criteria. The mean age of subjects was 46 years. Of the 1324 participants, 1213 subjects (92%) were hypertensive. The effects of NSAIDs on blood pressure were found solely in hypertensive subjects.
  - The increase in mean arterial pressure (MAP) was 3.59 mm Hg for indomethacin (57 treatment arms), 3.74 mm Hg for naproxen (four arms), and 0.49 mm Hg for piroxicam (four arms). The MAP decreased by 2.59 mm Hg for placebo (10 arms), 0.83 mm Hg for ibuprofen (six arms), 1.76 mm Hg for aspirin (four arms), and 0.16 mm Hg for sulindac (23 arms).

Articles finding no increased risk of hypertension from naproxen exposure

- Kurth et al., *Analgesic use and risk of subsequent hypertension in apparently healthy men.* Arch Intern Med. 2005 Sep 12;165(16):1903-9.
  - Prospective cohort study of 8229 participants in the Physicians' Health Study who were free of hypertension and completed detailed analgesic questionnaires.
  - Apparently healthy male physicians who self-selected for analgesic use had no significantly increased risk of subsequent hypertension

- Sowers et al., *The Effects of cyclooxygenase-2 inhibitors and nonsteroidal anti-inflammatory therapy on 24-hour blood pressure in patients with hypertension, osteoarthritis, and type 2 diabetes mellitus.* Arch Intern Med. 2005 Jan 24;165(2):161-8.
    - Double-blind, randomized trial to evaluate the effects of celecoxib, rofecoxib, and naproxen on 24-hour blood pressure (BP) in patients with type 2 diabetes, hypertension, and osteoarthritis.
    - BP following 6 weeks of therapy was increased significantly by rofecoxib (from 130.3 +/- 1.2 to 134.5 +/- 1.4 mm Hg; P < .001) but not by celecoxib (132.0 +/- 1.3 to 131.9 +/- 1.3 mm Hg; P = .54) or naproxen (133.7 +/- 1.5 to 133.0 +/- 1.4 mm Hg; P = .74).

Myocardial Infarction and NSAIDs

No agreement exists in the literature about the degree naproxen might increase the risk of myocardial infarction. Risk from naproxen might be less than the risk from some other commonly used NSAIDs. I find that the chance of increased risk is great enough that it should be considered in Naproxen approval and labeling. A selection of informative papers are described below:

Articles finding increased risk of myocardial infarction from naproxen exposure

- Hippisley-Cox and Coupland, *Risk of myocardial infarction in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis.* BMJ 2005;330:1366
    - Nested case-control study
    - 9218 cases with a first myocardial infarction
    - Increased risks were associated with naproxen at < 0.05 rather than < 0.01 for current use but significant at < 0.01 in the tests for trend.
    - No evidence was found to support a reduction in risk of myocardial infarction associated with current use of naproxen.

- Johnsen et al., *Risk of hospitalization for myocardial infarction among users of rofecoxib, celecoxib, and other NSAIDs: a population-based case-control study.* Arch Intern Med 2005;165:978-84.
    - Nested case-control study.
    - 10,280 cases of first-time hospitalization for MI
    - Current users of rofecoxib had an elevated risk estimate for hospitalization for MI compared with nonusers of any category of nonaspirin NSAIDs (adjusted relative risk [ARR], 1.80; 95% confidence interval [CI], 1.47-2.21). Increased risk estimates were also found among current users of celecoxib (ARR, 1.25; 95% CI, 0.97-1.62), other cyclooxygenase-2 selective inhibitors (ARR, 1.45; 95% CI, 1.09-1.93), naproxen (ARR, 1.50; 95% CI, 0.99-2.29), and other conventional nonaspirin NSAIDs (ARR, 1.68; 95% CI, 1.52-1.85). The highest ARRs were found among new users of all examined drug categories.

- Graham et al., *Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study.* Lancet 2005;365:475-81.
    - Nested case-control study.
    - 8143 cases of serious coronary heart disease
    - Multivariate adjusted odds ratios versus celecoxib were: for rofecoxib (all doses), 1.59 (95% CI 1.10-2.32, p=0.015); for rofecoxib 25 mg/day or less, 1.47 (0.99-2.17, p=0.054); and for rofecoxib greater than 25 mg/day, 3.58 (1.27-10.11, p=0.016). For naproxen versus remote NSAID use the adjusted odds ratio was 1.14 (1.00-1.30, p=0.05).

Articles finding no increased risk of myocardial infarction from naproxen exposure

- Fischer et al., *Current use of nonsteroidal antiinflammatory drugs and the risk of acute myocardial infarction.* Pharmacotherapy. 2005 Apr;25(4):503-10.
    - Retrospective case-control analysis of 8688 case patients with a first-time acute myocardial infarction and 33,923 matched control subjects.
    - The relative risk (expressed as odds ratio [OR]) of acute myocardial infarction was 1.07 (95% confidence interval [CI] 0.96-1.19) for subjects with current NSAID exposure compared with those not taking NSAIDs. The adjusted OR for current diclofenac use was 1.23 (95% CI 1.00-1.51), for current ibuprofen use 1.16 (95% CI 0.92-1.46), and for current naproxen use 0.96 (95% CI 0.66-1.38) compared with those not taking NSAIDs. Current aspirin use combined with current NSAID use was associated with a statistically significant risk reduction (adjusted OR 0.74, 95% CI 0.57-0.97), compared with nonuse of NSAIDs and aspirin.

- Garcia Rodriguez et al., *Nonsteroidal antiinflammatory drugs and the risk of myocardial infarction in the general population.* Circulation. 2004 Jun 22;109(24):3000-6.
    - Nested case-control analysis.
    - 4975 cases of acute myocardial infarction (MI) and death from coronary heart disease (CHD) were identified.
    - The multivariate-adjusted OR for current NSAID use compared with nonuse was 1.07 (95% CI, 0.95 to 1.20). Treatment duration or daily dose did not change the results. The effect was similar among patients free of CHD history (1.04; 95% CI, 0.90 to 1.20) and patients with previous history (1.12; 95% CI, 0.91 to 1.38). Estimates for individual NSAIDs were all comparable, with no major effect on the risk of acute MI. Naproxen was associated with an OR of 0.89 (95% CI, 0.64 to 1.24).

- Levesque et al., *The risk for myocardial infarction with cyclooxygenase-2 inhibitors: a population study of elderly adults.* Ann Intern Med 2005;142:481-9.
    - Nested case-control approach.
    - NSAID exposure and occurrence of MI assessed by using Quebec's administrative health databases.
    - Compared with no use of NSAIDs in the year preceding the event, current use of rofecoxib was associated with an increased risk for an acute MI (rate ratio [RR], 1.24 [95% CI, 1.05 to 1.46]) that was more pronounced at higher doses (RR, 1.73 [CI, 1.09 to 2.76]). The concomitant use of aspirin appears to decrease the risk associated with low-dose rofecoxib (RR, 1.00 [CI, 0.77 to 1.28]) but not with high-dose rofecoxib (RR, 2.36 [CI, 1.27 to 4.39]). No increased risks were observed with celecoxib (RR, 0.99 [CI, 0.85 to 1.16]) or the other NSAIDs.

- Rahme et al., *Association between naproxen use and protection against acute myocardial infarction.* Arch Intern Med 2002;162:1111-5.
    - Nested case-control study
    - 4163 cases
    - Determinants (adjusted odds ratios [95% confidence intervals]) of AMI included use in the prior year of anticoagulants (0.76 [0.64-0.90]), nitrates (2.01 [1.86-2.17]), antidiabetic agents (1.72 [1.56-1.90]), antihypertensive agents (1.36 [1.28-1.45]), and lipid-lowering agents (0.83 [0.75-0.91]), as well as concurrent exposure to naproxen vs other NSAIDs (0.79 [0.63-0.99]).
    - Compared with other NSAIDs, concurrent exposure to naproxen has a protective effect against AMI.

- Mamdani M et al., *Effect of selective cyclooxygenase 2 inhibitors and naproxen on short-term risk of acute myocardial infarction in the elderly.* Arch Intern Med. 2003 Feb 24;163(4):481-6.
    - Retrospective cohort study using administrative health care data from Ontario, Canada
    - No significant differences in AMI risk for new users of celecoxib (adjusted rate ratio [aRR], 0.9; 95% confidence interval [CI], 0.7-1.2), rofecoxib (aRR, 1.0; 95% CI, 0.8-1.4), naproxen (aRR, 1.0; 95% CI, 0.6-1.7), or nonnaproxen nonselective NSAIDs (aRR, 1.2; 95% CI, 0.9-1.4).
    - No increase in the short-term risk of AMI among users of selective cyclooxygenase 2 inhibitors as commonly used in clinical practice. Furthermore, the findings do not support a short-term reduced risk of AMI with naproxen.

Other articles finding no increased risk of first-time myocardial infarction from naproxen:

- Fischer et al., 2005, *Current use of nonsteroidal antiinflammatory drugs and the risk of acute myocardial infarction.* Pharmacotherapy. 2005 Apr;25(4):503-10.

Coronary Artery Constriction and NSAIDs

Evidence is conflicting regarding the effect of COX inhibitors on coronary artery constriction. Studies examining the effect of naproxen specifically have apparently not been conducted.

A summary of current knowledge is provided by Duffy SJ et al.(*Contribution of vasodilator prostanoids and nitric oxide to resting flow, metabolic vasodilation, and flow-mediated dilation in human coronary circulation.* Circulation. 1999;100:1951-7):

> "Previous studies have shown that cyclooxygenase inhibition with indomethacin reduces resting CBF in patients with coronary artery disease. Although it has been confirmed by others, some have speculated that the effects of indomethacin are not due to PG inhibition. However, experimental studies have suggested that PGs are not essential for coronary metabolic vasodilation. In humans, there has been conflicting evidence regarding the effect of cyclooxygenase inhibition on metabolic vasodilation. Although experimental studies have not demonstrated a reduction of resting CBF after cyclooxygenase inhibition, in models of coronary artery disease, PG inhibition significantly decreased coronary diameter and CBF. In humans with atherosclerosis, indomethacin has been shown to reduce resting CBF and increase CVR; these effects are associated with increased MABP, estimated myocardial oxygen demand, and arteriovenous oxygen extraction. Although estimated myocardial workload did not increase in the present study, our findings are otherwise consistent with these previous investigations."

I find that this increases concern regarding the cardiovascular safety of Trexima.

8.7 Postmarketing Risk Management Plan

None recommended

8.8 Other Relevant Materials

None

9 OVERALL ASSESSMENT

9.1 Conclusions

See Section 1.1

9.2 Recommendation on Regulatory Action

See Section 1.1

9.3 Recommendation on Postmarketing Actions

See Section 1.2 and subheadings.

9.3.1 Risk Management Activity

None

9.3.2 Required Phase 4 Commitments

None

9.3.3 Other Phase 4 Requests

See Section 1.2.3

9.4 Labeling Review

The nonclinical dog study of possible cardiovascular interactions between sumatriptan and naproxen is not adequately conclusive [redacted]

Adverse events related to chest pain should be combined and added to common adverse events.

The adverse events 'neck/throat/jaw-pain/tightness/pressure' should be combined and added to common adverse events.

9.5 Comments to Applicant

See DNP letter to sponsor.

10 APPENDICES

10.1 Review of Individual Study Reports

Reviews of all studies are contained in main review sections.

10.2 Line-by-Line Labeling Review

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/s/

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Shari L. Targum, M.D.
Division of Cardio-Renal Products, HFD-110

Food and Drug Administration
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Memorandum

DATE: April 17, 2006

FROM: Shari L. Targum, M.D., Team Leader
Division of Cardio-Renal Products, HFD-110

THROUGH:
Norman Stockbridge, M.D., Ph.D., Director, Division of Cardio-Renal Products, HFD-110

TO: Eric Bastings, M.D., Neurology Team Leader,
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SUBJECT: Address cardiac safety questions pertaining to NDA #21,926

NAME OF DRUG: sumatriptan succinate/ naproxen
TRADE NAME: Trexima
FORMULATION: Oral
RELATED APPLICATIONS: Sumatriptan and naproxen are approved products.
PROPOSED INDICATION: Migraine with or without aura
APPROVED INDICATIONS: The sumatriptan-naproxen combination is not approved.
SPONSOR: Pozen Inc.

DOCUMENTS AVAILABLE FOR REVIEW: 1. Consultation request; 2. Draft clinical review for NDA 21-926; 3. electronic submission (edr); 4. References (see footnotes).

DATE CONSULT RECEIVED: January 24, 2006
DATE DUE: April 10, 2006
DATE CONSULT COMPLETED: April 14, 2006

BACKGROUND & RATIONALE:

Trexima, a combination of sumatriptan and naproxen, has been developed by the sponsor for the acute treatment of migraine in adults. This division has been consulted to address the question of cardiovascular risk of Trexima relative to the cardiovascular risk of the individual active ingredients. Six additional related questions have been posed by the primary medical reviewer (see Your Questions section).

Both sumatriptan and naproxen are approved drugs. Sumatriptan is approved for the acute treatment of migraines (except for hemiplegic or basilar migraine): sumatriptan is not indicated for prophylaxis. In the labeling for sumatriptan, there is an extensive warning concerning

cardiovascular events. According to labeling, sumatriptan has been associated with coronary vasospasm or increased blood pressure in certain patients and "should not be given to patients with documented ischemic or vasospastic coronary artery disease." Naproxen is available over the counter and indicated for pain due to headache (with other indications as well)[1].

In December, 2004, the Agency issued a Public Health Advisory stating that preliminary results from a long-term placebo-controlled clinical study suggested that long term use of naproxen may be associated with an increased cardiovascular (CV) risk. The ADAPT study randomized about 2400 patients ≥70 years old with a family history of Alzheimer's disease to naproxen 220 mg bid, celecoxib, or placebo; the study was halted because of an NCI celecoxib colon cancer study that showed increased cardiovascular events in patients taking celecoxib. According to Agency reports, preliminary data from ADAPT indicated an apparent increase in cardiovascular/cerebrovascular events on naproxen vs. placebo.[2] In April, 2005, the Agency requested a black box warning on all non-selective nonsteroidal anti-inflammatory drugs (NSAIDs) regarding the potential serious adverse CV events and the serious, and potentially life-threatening GI adverse events associated with the use of this class of drugs. Naproxen labeling also includes a warning concerning new onset or worsening or pre-existing hypertension.

Other than ADAPT, there is no placebo-controlled long-term naproxen study that has demonstrated adverse effects on cardiovascular events. There are several epidemiologic studies of NSAIDs that have not shown consistent findings for naproxen.

Development program for Trexima (sumatriptan-naproxen):

The development program for Trexima included nine clinical studies (two pivotal studies, an open-label 12 month study, a phase 2 proof-of-concept study, and five smaller phase 1 trials). The two pivotal trials were each about 1500 patient, double-blind, parallel-group, placebo and active-controlled trials that compared a single Trexima (85 mg sumatriptan RT and 500 mg naproxen sodium) dose vs. placebo for the relief of migraine pain and symptoms at 2 hours, in addition to Trexima vs. the individual components for pain at 24 hours.

In the long-term study, patients were to treat an average of at least two migraine attacks per month for up to twelve months. Patients were permitted to take a second dose of study medication for the same migraine attack if needed after waiting at least 2 hours after the first dose. No more than 2 Trexima tablets were allowed in any 24-hour period.

The pivotal and open-label 12 month studies included a baseline 12-lead ECG; a second ECG to be performed only if symptoms suggestive of a cardiac abnormality occurred. For the 12-month study, vital signs were planned only at baseline.

Table 1. Clinical Studies and Timing of Vital Signs

Study	Design	Duration of treatment	Population	N treated	Vital signs (BP/HR)
MT400-101	Phase I, randomized, open, crossover	Single dose	Healthy subjects	40	At screening and Day 3-5 post-dosing
MT400-102	Phase I,	Single dose	Healthy	24	At screening

[1] Source: labeling for Aleve.

[2] Results from the ADAPT study could not be found in a Pubmed search.

	randomized, open, crossover		subjects		only
MT400-103	Phase I, randomized, open, 3-way incomplete crossover	Single dose	Healthy subjects	24	At screening and Day 3-4 post-dosing
MT400-104	Phase I, open, one-sequence crossover	Single dose	Migraine patients	18	At screening only
MT400-105	Phase I, randomized, open, two-way crossover, PK	Single dose (single vs. two tablet)	Healthy subjects	24	At screening only
MT400-204	Phase II, proof of concept, randomized, double-blind, placebo and active-controlled	Single dose	Migraine patients	972	At screening only
MT400-301	Phase III, randomized, double-blind, placebo and active-controlled, parallel-group	Single dose	Migraine patients	1495	At screening and follow-up visit (1-5 Days post-dosing)
MT400-302	Phase III, randomized, double-blind, placebo and active-controlled, parallel-group	Single dose	Migraine patients	1461	At screening and follow-up visit (1-5 Days post-dosing)
MT400-303	Phase III, multicenter, open-label, (12 month) safety follow-up	Single dose with option of second dose 2 hours later (for same attack)	Migraine patients	561 treated (ongoing)	At screening only

Thus, vital sign (blood pressure/heart rate) information post-dosing is available for studies MT400-301, MT400-302, MT400-101 and MT400-103 only. This reviewer focused on the two pivotal studies because of the larger sample sizes and similar dosing (i.e., the Phase I studies with post-dosing vital signs did not use higher drug doses).

Vital sign results for the two pivotal studies, MT400-301 and MT400-302, are shown below:

Table 2. Study MT400-301: Vital sign results

Mean (SD) vital sign results	Trexima (N=367)	Sumatriptan (N=370)	Naproxen (N=371)	Placebo (N=387)
Screening:				
Heart rate (bpm)	71.2 (9.2)	71.7 (9.9)	71.6 (9.9)	72.1 (10.0)
Systolic BP (mmHg)	115.4 (12.1)	115.8 (13.3)	115.8 (14.1)	116.7 (13.2)
Diastolic BP (mmHg)	74.7 (8.6)	74.8 (9.1)	74.5 (8.4)	75.4 (8.8)
Follow-up:				
Heart rate (bpm)	73.3 (9.6)	74.3 (10.0)	72.9 (10.3)	74.8 (10.6)
Systolic BP (mmHg)	116.0 (13.4)	115.9 (13.1)	115.6 (13.0)	117.2 (12.6)
Diastolic BP (mmHg)	75.2 (8.8)	75.0 (9.2)	74.3 (8.7)	75.1 (8.2)

For Trexima, the increase is mean systolic BP (0.6 mmHg) is comparable to the increase in the placebo group (0.5 mmHg). While this reviewer did not specifically perform the calculation, it is unlikely that the 0.5 mmHg increase in mean diastolic BP will be statistically significant.

Table 3. Study MT400-302: Vital sign results

Mean (SD) vital sign results	Trexima (N=370)	Sumatriptan (N=365)	Naproxen (N=361)	Placebo (N=365)
Screening:				
Heart rate (bpm)	72.5 (10.0)	72.2 (9.9)	72.2 (10.2)	72.5 (9.4)
Systolic BP (mmHg)	117.4 (13.2)	118.9 (12.8)	118.3 (13.0)	118.0 (12.9)
Diastolic BP (mmHg)	75.3 (8.5)	75.8 (9.5)	75.2 (9.3)	75.2 (8.8)
Follow-up:				
Heart rate (bpm)	75.1 (9.9)	75.6 (11.0)	74.9 (10.3)	74.2 (9.8)
Systolic BP (mmHg)	117.0 (13.1)	119.0 (13.8)	118.6 (13.4)	117.9 (13.1)
Diastolic BP (mmHg)	74.8 (8.6)	75.8 (9.3)	75.0 (8.8)	75.2 (8.8)

In study MT400-302, there do not appear to be any change in the mean vital sign results that are distinguishable from placebo.

Cardiovascular Adverse Events:

In the safety summary of NDA 21-926, the most common treatment-emergent adverse event (> 2% of subjects) in the safety population (combined MT400-301 and MT400-302) was chest discomfort (13 (2%) patients receiving Trexima, 10 (1%) patients receiving sumatriptan, and < 1% in patients receiving placebo (1 patient) or naproxen (3 patients)).

Deaths: There was one death that appeared non-cardiovascular (gunshot wound).

Serious adverse events: In the two pivotal studies, there was one serious cardiovascular adverse event (palpitations) in the sumatriptan group. No serious adverse events were reported in

patients receiving Trexima. In MT400-303 (summary of clinical safety), the incidence of serious cardiac adverse events was <1%.

Withdrawals due to adverse events: According to the sponsor, no subject withdrew from studies MT400-101, MT400-105, MT400-204, MT400-301 or MT400-302 due to adverse events. One 54 year old male subject (292/#1024, MT400-102) withdrew due to "continuously elevated blood pressure." A 20 year old female (292/#1009, MT400-103) withdrew due to headache, neck tension, nausea and chest pressure on inhalation.

Your Questions:

1. Is the cardiovascular risk of Trexima greater than that of the individual active ingredients?

   Response: Your Division should carefully analyze the safety database for NDA 21-926. From a review of the summary of clinical safety, this reviewer did not detect a clinical cardiovascular safety signal suggesting an increased risk with Trexima compared to sumatriptan. One limitation is that the controlled clinical studies utilized single doses of Trexima. While Trexima is being developed for acute treatment of migraine, this reviewer does not know how frequently Trexima will be used, or whether more frequent use of Trexima will change the safety profile.

2. Do you think additional data are necessary to address Trexima's cardiovascular risk?

   Response: The answer will depend on how Trexima will be labeled and used. If the study population inadequately reflects how Trexima will be labeled and used, then additional data may be necessary. If clear instructions for use can be communicated based on the study population, then additional data may not be necessary.

3. Is Trexima likely to increase blood pressure, either acutely or chronically, above that caused by the individual drugs? Would this effect be clinically significant?

   Response: The available data from the pivotal studies do not show a clinically meaningful or statistically significant increase in diastolic or systolic blood pressure in patients treated with Trexima compared to sumatriptan. However, these data were not specifically obtained at peak pharmacodynamic blood pressure effect for Trexima. This reviewer was unable to find any data that specifically addressed blood pressure effects following a single dose of naproxen[3] Any potential cardiovascular issue with nonsteroidal anti-inflammatory drugs has surfaced in studies using chronic dosing (e.g., the ADAPT study). For Trexima, this reviewer simply does not have data to answer your question for chronic dosing; furthermore, it is

[3] A phone call to [redacted] of Roche did not reveal any information concerning blood pressure effects following a single dose of naproxen.

unclear whether Trexima "chronic dosing" will approach the chronic daily dosing seen with naproxen in studies like ADAPT.

4. Sumatriptan is contraindicated in patients with uncontrolled hypertension, but not in patients with hypertension controlled by medications. Do you think the naproxen in Trexima will have a significant negative effect on blood pressure in medication-controlled hypertensives?

   Response: There are no data available to directly answer this question. One could design a study in treated hypertensives comparing blood pressure effects with Trexima, naproxen and sumatriptan (perhaps as a Phase IV commitment)[4].

5. Is Trexima likely to cause clinically significant coronary artery vasoconstriction greater than that caused by sumatriptan alone? Does current evidence support a significant effect of NSAIDs such as naproxen on coronary artery tone (for example, how pertinent are studies of indomethacin showing an effect on coronary artery blood flow)?

   Response: The safety database does not show an increase in angina or myocardial infarction in patients receiving Trexima compared to sumatriptan alone; however, it is possible that the study population did not include enough susceptible patients (sumatriptan-containing products would probably be contraindicated in "at risk" patients). With regard to studies of indomethacin and effects on coronary artery blood flow, one would need to assume a "class effect" if one were to generalize findings with indomethacin to include naproxen use. In at least one paper, coronary vascular resistance and oxygen extraction was elevated with indomethacin but not with aspirin, naproxen, or ibuprofen use[5]; these data suggest that indomethacin's effects on coronary blood flow should not be generalized. Another paper has also supported that view that indomethacin has different cardiovascular effects than other nonsteroidal anti-inflammatory drugs.[6] Thus, this reviewer would argue that the indomethacin studies are not pertinent to the discussion of naproxen.

6. FDA announced in April 2005 that NSAIDs including naproxen should include boxed warnings about the potential for increased risk of cardiovascular (and bleeding) adverse events. Do you think a black box would be warranted for the Trexima label based on cardiovascular risk?

   Response: Naproxen is available without prescription for acute use. The available data do not support the use of a boxed warning for a single use of naproxen. However,

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[4] In designing such a trial, one would, of course, need to keep in mind potential drug interactions with NSAIDs and certain antihypertensives such as ACE inhibitors.

[5] Edlund A et. al. Coronary flow regulation in patients with ischemic heart disease: release of purines and prostacyclin and the effect of inhibitors of prostaglandin formation. Circulation 1985 Jun; 71 (6): 1113-20.

[6] Wennmalm A et. a. Central and peripheral haemodynamic effects of non-steroidal anti-inflammatory drugs in man. Arch Toxicol Suppl 1984;7: 350-9.

Trexima should be appropriately labeled with cardiovascular warnings in the current sumatriptan label and it is assumed that Trexima will be used in a similar fashion as seen in the study population for the NDA.

7. How are the above questions likely to be affected by the 'chronic-intermittent' dosing of Trexima?

   Response: Chronic-intermittent dosing, however this term is defined, was not studied in controlled clinical trials; therefore, this reviewer does not have the data to answer this question. One needs to keep in mind the possibility that a different dosing regimen might alter the safety profile of Trexima.

If you have any further questions, please feel free to contact me or the Division.

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/s/

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