CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-926

MEDICAL REVIEW(S)

M E M O R A N D U M
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 6, 2008

FROM: Eric Bastings, M.D.
Acting Deputy Director, Division of Neurology Products
HFD-120

TROUGH: Russell Katz, M.D.
Director, Division of Neurology Products
HFD-120

SUBJECT: Satisfaction of REMS requirement for approval action for Treximet for migraine

TO: File NDA 21-926

Risk Evaluation and Mitigation Strategy (REMS) Requirements – TREXIMET (sumatriptan and naproxen sodium)

Title IX, Subtitle A, Section 901 of FDAAA amends the FDCA to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if the Secretary determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)(1)). Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug
(F) Whether the drug is a new molecular entity.

We have determined that a REMS is necessary to ensure that the benefits of TREXIMET outweigh its risks. In reaching this determination, we considered the following:

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Treximet™ poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for

patients' safe and effective use of Treximet™. FDA has determined that Treximet™ is a product that has serious risks of which patients should be made aware because information concerning the risks could affect patients' decisions to use Treximet™. Specifically, nonsteroidal anti-inflammatory drugs (NSAIDs), including naproxen sodium, are associated with numerous safety risks, including an increased risk of cardiovascular events and gastrointestinal toxicity. For this reason, the Agency has determined that all prescription NSAIDs, including combination products in which an NSAID is a component (as is Treximet), must have Medication Guides.

Information needed for assessment of the REMS should include but may not be limited to:
a. Survey of patients' understanding of the serious risks of Treximet™
b. Report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
c. Report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

cc:
Orig NDA 21-926
HFD-120/RKatz/EBastings/RFarkas/LChen

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/s/

Russell Katz
7/1/2008 04:46:44 PM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Date:	June 15, 2007
From:	Eric Bastings, MD.
To:	File
Subject:	NDA 21-926 response to approvable letter

Pozen submitted a response to the approvable letter for Trexima issued June 8, 2006. Of note, the tradename Trexima was not found acceptable by FDA, but in the absence of an alternate name yet submitted to the Agency, I will use it in my memorandum to describe this new drug combination product.

In the approvable letter, the division agreed that Trexima is effective as an acute treatment for migraine headaches, but raised several safety issues which needed to be addressed before Trexima could be approved.

Issue 1: Serious cardiac adverse events

The division noted in the Trexima safety database the occurrence of a case of "acute coronary syndrome (ACS)" in a 47 year old woman with several risk factors for coronary artery disease and demonstrated narrowing (70%) of the left main coronary artery. This patient had chest discomfort and some shortness of breath two hours after taking Trexima, with ECG changes suggestive of ischemia in the lateral precordium, but no enzyme elevation during the acute event.

Cases of cardiac ischemia have been reported with triptans, and all triptans carry of prominent labeling regarding the risk for serious cardiac events, but the rate of these events is believed to be very low, and well justified by the efficacy of drugs of this class.

In the first review cycle, the division estimated that 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 the size of the original Trexima NDA, and that the incidence of serious cardiac events with Trexima may be considerably greater than that believed to be associated with sumatriptan.

Because GSK is now involved in this NDA, Pozen was able to provide a detailed comparative analysis of the Imitrex and Trexima NDA safety databases. The Trexima safety database also considerably increased since the original NDA, up to a total of 2999 patients treated with Trexima, most for short-term administration of the product. As noted by Dr. Farkas, no additional cardiac SAEs were reported in the additional 1679 subjects exposed since the original NDA.

The sponsor identified nine subjects who received sumatriptan 100 mg in the sumatriptan clinical database who experienced a cardiac SAE, out of a total of about 16,000 subjects

exposed. Dr. Farkas notes that only three of these cases are comparable to the cardiac SAE in the Trexima database. One of them in particular (S2CS01/2202) shares a similar temporal relationship, with ECG changes [plus mild enzyme elevation], and was attributed by a cardiologist to possible acute coronary ischemia. The other case with close temporal relationship (S2BT27/3018) was not reported to have any ECG or laboratory associated abnormality, and it is impossible to conclude that there was clearly cardiac ischemia involved. The seven other cases are not relevant, in my opinion, because of the long delay (2 weeks or more) between drug intake and the event.

The sponsor also provided comparative data based on labeling of all approved triptans:

Table 2.5.24 Estimated Incidence of Clinically Significant Cardiovascular Adverse Events among Triptans

Product	Estimated Incidence (%)	95% CI
Almotriptan tablets	0.03 (1/3865)	0.00, 0.14
Eletriptan tablets	0.03 (2/7143)	0.00, 0.11
Frovatriptan tablets	0.00 (0/3000)	0.00, 0.12
Naratriptan tablets	0.11 (4/3500)	0.03, 0.29
Rizatriptan tablets	0.03 (1/3700)	0.00, 0.15
Sumatriptan tablets	0.03 (2/6348)	0.00, 0.11
Zolmitriptan tablets	0.00 (0/2500)	0.00, 0.14
Trexima tablets	0.03 (1/2999)	0.00, 0.18

Source: Warnings Sections of current Prescribing Information for marketed Triptans

I reviewed the individual cases in labeling. For eletriptan, one of the cases was "atrial fibrillation", which is not clearly directly related to CAD. The other case occurred during a coronary angiographic study, and is not clearly similar to these of interest for the comparison. For naratriptan, three of the cases were for asymptomatic ECG changes. The fourth one was thought to be likely due to coronary vasospasm, but occurred after a dose three times higher than the highest recommended approved dose. I obtained the narrative from the original NDA review:

Associated events for which no other condition is listed which can be viewed as causal (5 Patients)

9-- (ID-B0904) 40 yo symptomless female had ECG showing variable T-wave flattening (Lead II) at 120 minutes after naratriptan 7.5mg dose and borderline ST segment sagging (Lateral Leads) with increased heart rate to 100 bpm at about 240 minutes post-treatment; pre-treatment ECG showed T-wave inversion (Lead III); hospitalized for investigation and for unresolved migraine; ECG was still abnormal the following morning and in the afternoon 2 days post treatment; cardiac enzymes remained normal; follow-up stress test normal; evaluation of ECG results by independent cardiologist considered T-wave changes related to drug with a likely cause of coronary spasm (Case: B0004718).

For rizatriptan, the case is reported in labeling as "chest pain with possible ischemic ECG changes". I obtained the narrative from Dr. Oliva's NDA review of rizatriptan:

Chest Pain: A 40 y/o F (022-026) taking rizatriptan 10mg in the extension phase was hospitalized for chest pain, which occurred during treatment in the emergency room for a worsening migraine 6 hours after a dose of rizatriptan 10mg. She had previously treated 14 migraine attacks with rizatriptan 10mg over a 4 month period. While in the emergency room, she developed non-pleuritic chest pain which was unrelieved by nitroglycerin. She had experienced similar episodes of exertional and non-exertional chest pain in the prior 2 months not associated with any medication use. She was admitted and serial ECG's showed sinus bradycardia (considered normal for the patient), clockwise axis rotation and nonspecific ST-T wave changes, but no acute changes. Cardiac enzymes were normal. A stress test 10 days later was unremarkable. The investigator felt that the headache and chest pain were unrelated to rizatriptan. I think a relationship between rizatriptan and the chest pain is possible.

The main difference between this case and the case of acute coronary syndrome on Trexima is the absence of demonstrated ECG changes with rizatriptan, and the occurrence of similar symptoms off drug prior to the event. The pain was not relieved by nitroglycerin, which also argues against a cardiac origin.

Overall, it appears that the cases described in the above table are not qualitatively similar (i.e. clearly of cardiac origin) to the case of acute coronary syndrome seen with Trexima, except for one of the two cases reported for sumatriptan.

Issue 2: Severe chest pain

The division also noted in the original NDA review four cases of severe chest pain in patients treated with Trexima in short term efficacy studies, compared to none in the other treatment groups (including sumatriptan), again suggesting possible important differences in the tolerability of Trexima compared to sumatriptan alone. The division also noted that a dog study suggested increased coronary constriction with the combination compared to sumatriptan given alone, although that study had methodological limitations.

As noted by Dr. Farkas, there were no new reports of "severe" chest pain or chest discomfort associated with Trexima in additional 1679 patients treated with Trexima since the original NDA submission. Thus, the incidence of severe chest pain in the entire Trexima database is 0.15% (4/2628), versus 0.11% (2/1785) reported by subjects on placebo. In sumatriptan studies, the incidence of severe chest pain ranged between 0.07% and 0.27% for the doses tested (50-100 mg).

Overall, I agree that the incidence of severe chest pain appears similar for Trexima and sumatriptan. This may have no relationship to the incidence of coronary vasospasm induced by the drugs, but it nevertheless provides some reassurance. The sponsor also provided data supporting that the number or type of withdrawals for cardiac adverse events were not different between Trexima and sumatriptan studies.

Issue 3: Hypertensive effects of Trexima

The division noted the complete absence of any blood pressure monitoring appropriately timed to dosing with the combination, or with chronic intermittent dosing, and the lack of reliable information about the maximal effects of Trexima on blood pressure either acutely or chronically.

As noted by Dr. Farkas, the sponsor conducted an inpatient, open-label, 2-way (Trexima and sumatriptan) cross-over study in 32 healthy adult volunteers to address this deficiency. The study did not show any acute hypertensive effect for either drug. The study, however, does not address the possible hypertensive effect of the chronic intermittent administration of the drug.

Issue 4: Tradename
The division rejected the proposed tradename, Trexima. Pozen however submitted additional arguments to support the name Trexima, which the division, in concurrence with DMETS, also rejected. The sponsor submitted a new proposed tradename, [redacted] at the end of June 2007, and this is under review.

Issue 5: Non clinical issues
The division also raised non clinical issues, and requested a repeat in vitro chromosomal aberration assay in CHO cells testing concentrations between those exhibiting minimal or no cytotoxicity and those resulting in substantial cytotoxicity, and an in vitro mouse lymphoma tk assay (with colony sizing) testing naproxen and sumatriptan alone and in combination. I refer to the non clinical reviews for a discussion of these issues.

Conclusions and Recommendation

1. In this response to approvable letter, the sponsor has provided additional information (i.e. larger Trexima database, data from Imitrex database) that provide sufficient reassurance regarding the cardiovascular risk of Trexima. My observation is that there were two cases suggestive of coronary ischemia in a database of about 16,000 patients treated with Imitrex, versus one case suggestive of coronary ischemia in about 3,000 patients treated with Trexima. Also, the single case reported in the Trexima database had a significant structural coronary lesion present, which makes it less relevant. Given the various differences between the databases (e.g. increased weight of patients in the Trexima database, which is more recent), this does not appear to represent a truly higher rate. In addition, the numbers of patients with severe chest pain or discomfort were similar for both drugs. There is also a possibility that the increased sustained relief provided by Trexima will lead to less use of rescue medication, which could lower the risk.

2. Considering the reassuring data obtained from the study looking at the acute hypertensive effect of Trexima, I agree with Dr. Farkas that the effect of chronic intermittent administration of Trexima on blood pressure could be characterized in phase IV. The sponsor is already proposing to conduct a randomized, double-blind, active-comparator study in adults with episodic migraine dosed with either Trexima, naproxen sodium 500mg or sumatriptan 85mg to further assess the hypertensive effect of Trexima. That study should be part of phase IV commitments.

3. If the non clinical issues have been adequately addressed, I recommend approval.

Eric P. Bastings, M.D.
Team Leader, Neurology

epb
cc:
HFD-120

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/s/

Eric Bastings
7/20/2007 05:42:54 PM
MEDICAL OFFICER

Review and Evaluation of Clinical Data

NDA (Serial Number)	**N21-926**
Sponsor:	**Pozen**
Drug:	**Trexima**
Proposed Indication:	**Acute Migraine**
Material Submitted:	**Approvable action Full Response**
Correspondence Date:	**January 31, 2007**
Reviewer:	**Ronald Farkas, MD, PhD. Medical Reviewer, DNP, ODE I**

1. Introduction

This submission is a Full Response to the Approvable Letter for Trexima issued June 8, 2006 (NDA 21946). The Approvable Letter noted Agency concern about the occurrence of a case of "acute coronary syndrome" in a subject in the chronic Trexima treatment study (MT400-303), and stated "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." The sponsor and Division in a meeting on July 26, 2006, agreed that a comparison of cardiac safety findings in the Trexima development program to cardiac safety findings in the original Imitrex development program could contribute to addressing if the cardiac safety of Trexima was different from that of sumatriptan alone.

The sponsor's first Full Response submission, in which a comparison of cardiac safety was made between Trexima and Imitrex was considered an Incomplete Response. The following deficiencies were noted in the Divisions Incomplete Response letter of December 8, 2006:

1. Comparison of Trexima and sumatriptan adverse events was presented without sufficient data and analysis. In particular, incidence calculation of adverse events did not adequately consider drug exposure.
2. Adverse events from the sumatriptan program were not described in sufficient detail to make comparisons with adverse events in the Trexima program.
3. Inadequate data and analysis was presented on the comparability of the sumatriptan and Trexima data, for example addressing differences in patient populations and methods of collecting adverse events.

Additionally, the Division noted that the tabulation of cardiac adverse events in the submission's summary tables appeared to be incorrect.

A teleconference was held with the sponsor January 4, 2007 to clarify deficiencies in the November 6, 2006 Full Response. [redacted]

2. Reviewer Conclusions

The major issues of concern in the Approvable Letter and previous Full Response have been adequately addressed by the sponsor. The new safety information supports the assertion that Trexima has a similar cardiac safety profile to sumatriptan alone. Approval of Trexima is recommended.

- Cardiac adverse events in the Trexima and sumatriptan databases were compared using adequately transparent and reasonable methods.
- Cardiac SAEs rarely (1 in several thousand patients) occurred in both Trexima and sumatriptan development. The relationship between drug and cardiac ischemia remained uncertain for events in both programs.
- The incidence of severe (non-serious) chest pain was similar for both programs.
- Dropouts due to cardiac adverse events were similar for both programs.
- Acute effects of both drugs on blood pressure were similar.
- An acceptable plan was submitted for gaining chronic blood pressure data post-approval.

Proposed labeling for Trexima adequately reflects cardiovascular risks of the combination of sumatriptan and naproxen.

3. Organization of Review

In the Approvable Letter, the Division found that Trexima was effective for acute migraine, but that the safety of Trexima had not been adequately demonstrated. Data addressing the cardiac safety of Trexima is discussed in the following sections:

The incidence of serious cardiac events associated with Trexima versus sumatriptan alone is addressed in *Section 4, Serious Cardiac Adverse Events.*

The Approvable letter also expressed concern at four cases of severe (non-serious) chest pain in the Trexima treated patients in studies 301 and 302, compared to none in the other treatment groups. Comparison of severe chest pain associated with Trexima versus sumatriptan alone is addressed in this review in *Section 5, Severe Chest Pain.* [Dropouts due to cardiac adverse events, while not specifically mentioned in the Approvable letter, are also addressed in this section]

A discussion of the methodology of the sponsor's comparison of the Trexima and sumatriptan databases is addressed in this review in *Section 6, Comparability of Trexima and Sumatriptan Databases.*

The Approvable letter also noted a study in dogs designed to assess the effects of the combination on coronary artery constriction that showed in five of the six dogs increased constriction with the combination compared to sumatriptan given alone. This is addressed in this review in *Section 8 Drug Combination Study: Dog Coronary Artery Constriction.*

The Approvable letter noted the absence of blood pressure monitoring during acute or chronic dosing with Trexima, with the result that no reliable information was presented about the maximal effects of Trexima on blood pressure either acutely or chronically. Acute blood pressure changes from Trexima are addressed in this review in *Section 9, Acute Blood Pressure Effects of Trexima.* The sponsor proposes a post-approval study to examine chronic effects of Trexima on blood pressure. This study proposal is discussed in *Section 10 , Proposed Post-Approval Chronic Blood Pressure Study*

This submission also includes a Safety Update, discussed in *Section 11, Full Response Safety Update.*

4. Serious Cardiac Adverse Events

The sponsor argues that the absence of any additional cardiac SAEs in studies of Trexima since the NDA submission suggests Trexima does not pose a cardiac risk. The sponsor states the following:

> "No serious cardiac adverse events were reported in any of the completed GSK Trexima studies [note: the new Trexima studies]. The single SAE reported in the NDA remains the only occurrence of a cardiac SAE considered related to Trexima in 2999 migraineurs dosed with Trexima."

Since the NDA submission, safety data from 5 additional controlled studies with Trexima has become available, more than doubling the number of subjects exposed to Trexima (Table 1).

Table 1: Trexima Safety Population

(from Table 2.5.1, Adverse Events Analysis Populations for the NDA Trexima Database and the GSK Trexima Database: Migraine Subjects Only)

Population Used for Comparison	**NDA Trexima Database**	**GSK Trexima Database**	**Trexima Full Response Database**
All migraineurs exposed to *single and multiple doses of Trexima*	**N=1320**	**N=1679**	**N=2999**
Migraineurs *who took a single dose of Trexima to treat the first attack*	**N=1162**	**N=1466**	**N=2628**

No additional cardiac SAEs were reported in the additional 1679 subjects exposed. The additional exposures to Trexima are from studies with up to 4 doses.

[Comment: The lack of cardiac SAEs, while reassuring, must be interpreted in the context of the relatively low power of this exposure to detect rare events.]

As discussed in the review of the original Trexima NDA, three subjects experienced cardiac SAEs in the Trexima long-term study.

One of these subjects was of particular concern to the Division, and was noted in the Approvable Letter (Study MT400-303, subject #2143).

- ***Subject 2143 / Site 030 / acute coronary syndrome***

The patient is a 47-year old female. During the course of her study participation, the subject treated 39 migraine headaches (54% with 2 tablets of study drug); an average of six headaches per month. Concurrently, she received, Excedrin migraine, ranitidine, Elavil, vitamins and a sleep-aid (OTC). Imitrex is listed as a concomitant medication in the ISS narrative, but in the CRF is noted as a medication the patient used for migraine before the study. During the study, Ultracet and Tylenol were used asmigraine rescue medications. The subject received the first dose of open-label study drug on August 2, 2004 and the last dose on [redacted] Approximately two hours after taking study drug on [redacted], the subject experienced chest discomfort and some shortness of breath. She presented to the emergency department and was given nitroglycerin, which provided some relief. An electrocardiogram showed ST-T wave changes in the lateral precordium. Troponin and CK levels were normal in the emergency room. Based on the subject's age and family history, the subject was admitted to the hospital for further evaluation. A cardiac catheterization, performed [redacted] showed a moderate dilation of the left ventricle with moderate mitral regurgitation, severe hypokinesis of the antero-apical wall of the left ventricle and a calculated ejection fraction of 27 percent. The left anterior descending coronary artery had a concentric discrete 70% narrowing of the ostium as it arose from the left main coronary artery. There was a post-stenotic filling defect suggestive of a thrombus. No significant disease was present in either the left main coronary artery or the right coronary artery. On [redacted] the subject underwent coronary artery bypass grafting surgery including the left internal mammary artery to left anterior descending artery. The subject was discharged from the hospital on [redacted] and treated with carvedilol, furosemide, and lisinopril for hypertension, aspirin for cardiac prophylaxis, potassium, Zocor for hypercholesterolemia and Percocet for postoperative pain.

Medical History:
The subject was a nonsmoker and reported that her father died of a myocardial infarction in his 50s. She had a history of tubal ligation, tension headaches, sinus headaches, seasonal allergies, obesity, mild rosacea, mild depression, insomnia, acid reflux, and two cesarean sections, BMI 35.7. At screening, her physical examination and

electrocardiogram were normal. Screening laboratory results revealed cholesterol of 200mg/dL and triglycerides of 386 mg/dL.

In the other two subjects, Trexima was unlikely related to the serious cardiac adverse events. Subject 2129, a 44 year old women, experienced chest pain and increased blood pressure (182/95 in the emergency room) more than 24 hours after her last dose of Trexima. ECG and cardiac lab tests were normal. The other case, subject 2709, was a 27 year old woman who presented to an emergency room with chest pain 5 days after her last dose of Trexima. She gave a history of chronic recurrent chest pain with radiation of pain to her left arm.

Thus, including all three of the above cases, with the additional Trexima exposure reported in this Full Response, there remain a total of 3 serious cardiac AEs in about 3000 total patients exposed to Trexima, including both single-dose and long-term studies.

The sponsor identified nine subjects who received sumatriptan 100mg in the sumatriptan clinical database who experienced a cardiac SAE (Table 2), out of a total of about 16,000 subjects exposed. The sponsor argues that the rate of cardiac SAEs is therefore similar for Trexima and sumatriptan.

Table 2: Sumatriptan Subjects with Cardiac SAEs

2.5.8.4.4 Narratives of All Sumatriptan Subjects with a "Chest and Cardiac" Serious Adverse Events

Patient ID Demographics (Age/Sex/Wt.Kg)	Treatment	Previous Doses*	Time to event after last dose	Acute Symptoms	Additional Information at Time of event	Other Information RE the Cardiovascular Event	With-drawal	SAE	Relationship to study drug judged by investigator
S2B308E/101 48/Female/95	Sumatriptan 100mg	5	1.5 months	Tachycardia	Severed vagal nerve during spinal surgery	Prolongation of hospitalization	No	Yes	Unlikely
S2B308E/501 52/Male/109	Sumatriptan 6mg (sc), 100mg 2 hours later	31 (tab and inj)	>24 hrs	Pain in arms and chest	2 vessel CAD discovered at angioplasty Baseline ECG with sinus bradycardia	ECG consistent with AMI; emergency angioplasty completed Subject is obese	Yes	Yes	Unlikely
S2B308E/525 41/Female/55	Sumatriptan 6mg (sc), 100mg	2	>2 months	Anterior myocardial infarction, angina		AMI occurred before first dose; angina occurred 2 months after only dose	Yes	Yes	Not recorded
S2BS70/100 60/Female/63	Sumatriptan 6mg (sc), 100mg	6	17 days	Tachycardia			No	Yes	Unrelated
S2BT21/3853 45/Female/64	Sumatriptan 100mg	4	2 weeks	Cerebro-vascular lesion, facial weakness, leg numbness		Investigator attributed SAE to ergotamine given 2 hours before onset	Yes	Yes	Unlikely

S2BT27/3018 43/Male/86	Sumatriptan 100mg	4	14 days	Atypical chest pain, bigeminy, diaphoresis	ECG at screen WNL; propranolol 80mg QD for prophylaxis of migraine	Follow-up EST consistent with ischemia; cardiac enzymes & echo normal	Yes	Yes	Not related
S2CS01/1599 37/Female/95	Sumatriptan 100mg	1	15 minutes	Chest pain/tightness, dry mouth, cyanotic lips, dry mouth, pallor, dilated pupils	No prior exposure to sumatriptan before this study	Duration of symptoms 45 - 60 minutes. ECG post event WNL	Yes	Yes	Almost certainly
S2CS01/1685 61/Female/55	Sumatriptan 100mg	4	44 days	Myocardial infarction		ECG showed "AMI"	Yes	Yes	Unlikely
S2WB3002/2202 33/Male/72	Sumatriptan 100mg	None	30 minutes	Chest pain, arm pain	CPK 8 hours after event was 94IU; 20 hours after 292IU. CK=MB and LDH in normal range	Negative stress test and normal echocardiogram 24 days later	Yes	Yes	Almost certainly

Only 3 of these cases, discussed below, appear to be possibly comparable to the cardiac SAE in the Trexima database:

S2B308E/501
On 12/04/92 the subject was given a 6mg sumatriptan injection at 10:15 am, followed with a 100mg sumatriptan tablet at 12:35 pm. On [redacted] the subject reported the development of arm and chest pain which became severe, and was sent to the hospital where an ECG was reportedly consistent with MI and the subject was admitted for emergency angioplasty and was subsequently noted to have 2 vessel CAD. Subject was withdrawn from the study and the investigator judged the event as probably related to underlying disease and unlikely to be related to study drug.

[Comment: The interval between dosing and onset of symptoms was more than 24 hours, arguing against an effect of sumatriptan in the event.]

S2CS01/1599
Narrative: This 37-year-old female patient received oral GR43175C to treat migraine. She experienced chest tightness 15 minutes after her first and only dose of study medication. She likened the pressure to a tight band squeezing across her chest and she could not breathe deeply. The symptoms lasted for 45 minutes to one hour. An attending physician described signs of blue lips, pallor and dilated pupils. The patient's migraine attack disappeared at the same time as the onset of the adverse event. An ECG trace was taken one day later. The investigator commented that there were no differences between post and pre-treatment ECG traces. The event was considered to be incapacitating to the patient and almost certainly related to the study drug, and the patient was withdrawn.

[Comment: This event might reflect the type of chest pain that, in varying severity, affects 1% or more of triptan users. Adverse events in the sumatriptan database were coded as SAEs on the basis of criteria different than used in the Trexima studies. This event was originally coded as "disabling or incapacitating" and was, for purposes of the current analysis, reclassified as a serious adverse event].

S2CS01/2202
This 33-year-old male patient had no previous cardiac history and no significant family history of coronary disease. His baseline ECG showed an RST pattern in lead V1 consistent with right bundle branch block, sinus bradycardia and normal left axis deviation. Thirty minutes after treating his first migraine attack with study medication (oral sumatriptan 100mg), he developed severe throat tightness and central chest pain which was described as feeling like a weight on his chest. The pain extended to the jaw and, about an hour after study treatment, there was severe pain in both arms. The patient also felt nauseated but there was no sweating. At two hours, the patient had difficulty expanding his chest, had pain in the fingertips and felt lightheaded. The arm pain and throat tightness resolved in seven hours and the chest pain in ten hours; all were reported as disabling or incapacitating. An ECG carried out later that day showed an RSR pattern which was similar to the pre-trial ECG but more prominent, particularly in leads V1 and V2. On the following day CK was elevated from 94IU/L at approximately eight hours after the event, to 292IU/L at approximately 20 hours after the event (normal range 23-235IU/L), but CK-MB and LDH were within the normal range. The patient was withdrawn from the study. Twenty-four days later, he saw a cardiologist and underwent an exercise treadmill test without any chest pain or significant ECG changes and an echocardiogram was normal. Furthermore, a resting ECG trace at this time was identical to that recorded pre-treatment. The cardiologist reported that, although not "Absolutely definitive", the chest pain may have been due to acute coronary ischaemia caused by coronary artery spasm triggered by the study medication. He further commented that stress may also have been a contributory factor and that there was no residual damage to the myocardium or any ongoing coronary ischaemia. The investigator considered that the events were almost certainly related to the study medication.

[Comment: This event might reflect the type of chest pain that, in varying severity, affects 1% or more of triptan users. Adverse events in the sumatriptan database were coded as SAEs on the basis of criteria different than used in the Trexima studies. This event was originally coded as "disabling or incapacitating" and was, for purposes of the current analysis, reclassified as a serious adverse event.

Reviewer Discussion: The sponsor's reanalysis of cardiac SAEs in the sumatriptan database revealed 2 cases that may represent serious cardiovascular adverse events related to sumatriptan (in the subject with myocardial infarction, the interval between sumatriptan dosing and the event was >24 hours, seemingly excluding the possibility of drug causation). Evidence is insufficient to determine if these two cases represent cardiac ischemic events, versus the apparently non-ischemic type of chest pain (albeit severe) of unknown origin that can occur in about 1/1000 of triptan users. The rarity of serious cardiac adverse events in both the Trexima and sumatriptan development programs precludes any convincing conclusions about relative incidence (and type) of severe cardiac adverse events in the two development programs.

5. Severe Chest Pain

The sponsor asserts that the additional data from Trexima studies demonstrates a lower incidence of severe chest pain then was found in the original Trexima NDA, arguing for the cardiovascular safety of Trexima:

> "There were no new reports of "severe" chest pain or chest discomfort associated with Trexima in the completed GSK Trexima studies. Thus, the three cases of "severe" chest discomfort and one case of "severe" chest pain identified in the original NDA remain the only cases in subjects treating their first migraine attack with a single tablet of Trexima for an incidence of 0.15% (4/2628); additionally, there were 2 incidences (0.11%; 2/1785) of severe chest pain/discomfort reported by subjects on placebo."

[Comment: These cases in placebo give some sense of 'assay sensitivity' to the studies, despite that fact that no cases were recorded in the active drug arm].

The sponsor states that the incidence of severe chest pain in Trexima controlled studies falls between the incidence of severe chest pain seen in the 50 and 100 mg sumatriptan studies:

> "[In] sumatriptan studies, 2/2793 subjects (0.07%) on 50mg sumatriptan, 10/3724 subjects (0.27%) on 100mg sumatriptan and 1/3632 subjects (0.03%) on placebo reported severe chest pain/discomfort. Thus, the overall Trexima incidence of 4/2628 (0.15%) is between the incidence rates for 50 and 100mg sumatriptan when larger sample sizes are compared."

Reviewer Discussion: The incidence of severe chest pain appears similar for Trexima and sumatriptan. While most chest pain associated with triptans is thought to be non-cardiac in origin, chest pain is often a symptom of cardiac ischemia. The apparent absence of 'excess' chest pain beyond that expected for sumatriptan is reassuring for the cardiac safety of Trexima.

6. Withdrawal due to cardiac adverse events

While withdrawal due to cardiac adverse events was not a specific concern identified in the review of the original Trexima NDA, as part of the comparison of cardiac adverse events in the Trexima and sumatriptan programs, withdrawals due to cardiac adverse events were also compared.

The rate of withdrawal due to cardiac adverse events was similar for sumatriptan and Trexima (Table 3).

Table 3: Withdrawal due to any cardiac adverse event, sumatriptan versus Trexima

Table 2.5.17 Incidence of Subject Withdrawal Due to Chest and Cardiac Adverse Events: All Causality

	GSK Sumatriptan Clinical Trials Database n/N (%)		Trexima Full Response Database n/N (%)
	50mg	100mg	Trexima
All Subjects Withdrawn Due to "Chest and Cardiac" Adverse Event in Placebo controlled Studies	2/2793 (0.1%)	10/3724 (0.3%)	8/2416 (0.3%)
All Subjects Withdrawn Due to "Chest and Cardiac" Adverse Event in LTS Studies	NA	6/562 (1.1%)	8/565 (1.4%)
All Subjects Withdrawn Due to "Chest and Cardiac" Adverse Event in All Other Studies	12/3716 (0.3%)	39/6070 (0.6%)	0/18
Total Subjects Withdrawn Due to "Chest and Cardiac" Adverse Event in All Studies	14/6509 (0.2%)	55/10,356 (0.5%)	16/2999 (0.5%)

Source: GSK sumatriptan Section 2.5.8.3.10, Listing T2.1.b
Trexima Full response Section 2.5.8.2.1.2

All withdrawals (N = 16) due to cardiac adverse events in Trexima development were in outpatient studies, without monitoring (other than AE reporting itself), and in most cases without follow-up ECG or other testing. In the context of the limited data, no case convincingly implicated cardiac involvement.

Reviewer discussion: There is no evidence that the number or type of withdrawals for cardiac adverse events were different for Trexima and sumatriptan studies.

7. Comparability of Trexima and Sumatriptan Databases

The comparisons above support that Trexima and sumatriptan were associated with similar rates of cardiac events. This section examines in more detail the methodology used to make the comparisons of adverse events between the two development programs.

7.1 Comparison scheme

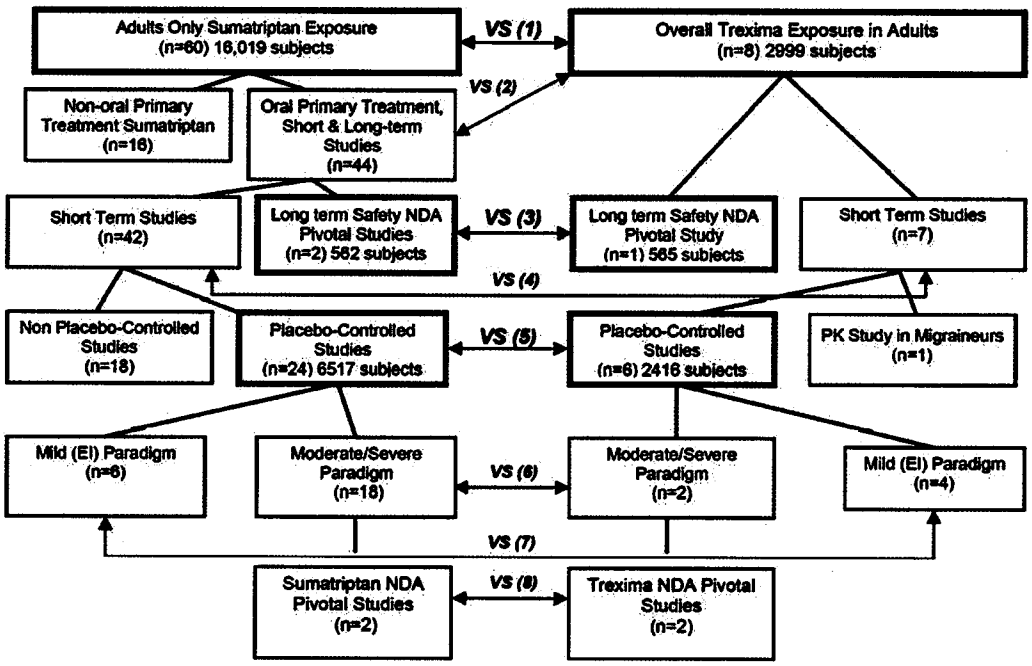
Figure 1 shows the scheme the sponsor used to select Trexima and sumatriptan studies to compare. Sixty sumatriptan studies were conducted with oral sumatriptan in adult migraine, and 8 studies were conducted with Trexima.

The studies were broken down into short-term and long-term studies for comparison across development programs (Figure 1).

Figure 1: Comparison Scheme, Trexima vs. Sumatriptan Studies

(from figure 2.5.1, clinical_overview.pdf)

Figure 2.5.1 Clinical Safety Analysis Populations – Trexima vs. Sumatriptan (n = number of studies)



[Comment: The sponsor provided data for comparisions 1, 3, and 5 (in bold). Analysis of smaller sub-groupings of studies seems unlikely to yield additional data, since there is no reason to believe, for instance, that meaningful differences exist between studies treating mild migraine discomfort versus moderate/severe migraine discomfort (comparison 6)].

The sponsor selected twenty-four sumatriptan double-blind, placebo-controlled trials (N=6517) as comparable to the 6 Trexima double-blind, placebo controlled trials (N=2416)[comparison 5 in Figure 1]. The sumatriptan trials included 2793 subjects who received 50mg, 3724 subjects who received 100mg, and 3632 who received placebo.

The sponsor compared data from the 2 long-term sumatriptan safety studies (N=562) included in the original Imitrex Tablets NDA (NDA 20-132) to the Trexima long-term safety trial (N= 565; comparison #3). The sumatriptan studies were conducted outside the US, whereas the Trexima studies were conducted in the US. The

Trexima long-term study did not include any subjects previously treated with Trexima, whereas, all sumatriptan subjects were rolled over from other oral sumatriptan trials.

[Comment: A large number of subjects in the Trexima studies were likely previously exposed to triptans due to their widespread use in treating migraine. However, the true percentage is unknown. This could be a source of enrollment bias for patients tolerant to potential cardiac adverse effects of triptans. Previous short-term exposure to sumatriptan of subjects in the

sumatriptan long-term studies could also have been a source of enrollment bias towards patients tolerant to any cardiovascular adverse effects of sumatriptan. Overall, enrollment bias for 'triptan tolerant' patients was likely similar in both development programs.]

The demographics of subjects in the sumatriptan and Trexima studies were similar, except the Trexima subjects had greater body weight, by 15-20 pounds.
[Comment: Importantly, the large increased body weight in the Trexima studies might have increased the chance of cardiac adverse events in the Trexima database, since obesity (presumably a major source of the weight difference) is a cardiovascular risk factor. The subject with the SAE of acute coronary syndrome in the Trexima program was obese.]

The occurrence of 'all cause' adverse events in the Trexima and Sumatriptan databases was similar, for both placebo controlled (Table 4) and long-term safety studies (Table 5),
[Comment: This suggests that comparison of cardiac adverse events across databases is valid (while some variation across studies existed for AEs in each system organ class, the breakdown of AEs was roughly similar in Trexima and sumatriptan studies)].

Table 4: All Causality Adverse Events, Controlled Studies

(from Table 2.5.11, All Causality Adverse Events by Body System: GSK Sumatriptan Placebo Controlled Studies vs. Trexima Placebo Controlled Studies, [clinical_overview.pdf]).

System Organ Class	GSK Sumatriptan Clinical Trials Database			Trexima Full Response Database	
	50 mg N=2793	100 mg N=3724	Placebo N=3632	Trexima N=2416	Placebo N=2159
Subjects with at least one AE	518 (18.6)	1148 (30.8)	595 (16.4)	561 (23.2)	214 (9.9)

Table 5: All Causality Adverse Events, Long Term Safety Studies

(from Table 2.5.12 All Causality Adverse Events by Body System: GSK Sumatriptan Long Term Safety Studies vs. Trexima Long Term Safety Study [clinical_overview.pdf]).

System Organ Class	GSK Sumatriptan Clinical Trials Database	Trexima Full Response Database
	100 mg N=562	Trexima N=565
Subjects with at least one AE	340 (60.5)	374 (66.2)

The occurrence of 'chest and cardiac' adverse events, was also similar in the *placebo* arms of sumatriptan and Trexima studies, both for 'all causality' events, and in the individual categorie of 'severe' adverse events.
[Comment: This argues that the comparison of drug arms was valid].

7.2 Coding Dictionaries

Coding dictionaries have evolved in the long interval between the sumatriptan and Trexima clinical programs. Comparison of adverse events between the two development programs was carried out by re-coding verbatim terms from the sumatriptan database to match the Trexima database.
[Comment: The sponsor's method for re-coding adverse events appears reasonable.]

Additional Discussion
The sponsor's comparison of severe chest pain/discomfort between the Trexima and sumatriptan controlled studies was based on verbatim terms such as 'chest pain' that would likely be reported roughly similarly even among different studies with somewhat different characteristics. The incidence of severe chest pain/discomfort from Trexima, which contains 85 mg sumatriptan, was actually about half that for 100 mg sumatriptan (0.15% vs. 0.27% for sumatriptan), suggesting that Trexima is not more likely to induce more severe chest pain than 100 mg sumatriptan. Furthermore, the exposure in the Trexima controlled trials was a single dose, while in the sumatriptan studies, exposure to sumatriptan was, in some studies, up to 4 doses. Therefore, comparing number of subjects instead of number of doses could not introduce bias for a lower adverse event rate in Trexima studies.

Reviewer Conclusions
The methodology used to compare adverse events between the two development programs was reasonable.

8. Drug Combination Study: Dog Coronary Artery Constriction

The Approvable Letter noted Agency concern about a study in dogs examining possible interaction between naproxen and sumatriptan on coronary artery constriction. The Agency noted that five of six dogs showed increased constriction with the combination versus sumatriptan given alone, with some evidence of dose-response effect. The Agency also noted that mechanistically, there was at least some reason to believe that naproxen might be a vasoconstrictor due to effects on prostaglandins.

Sponsor Response
The sponsor acknowledges that five of six dogs showed a 'mathematical' decrease in coronary artery diameter following exposure to sumatriptan and naproxen. The sponsor further states that when all six dogs are considered, the maximum reduction in coronary artery diameter following administration of sumatriptan followed by naproxen ranged from 3% to 8%. The sponsor argues that, as a guideline for coronary angiography, a 20% change in lumen diameter can be due to "vasomotion itself" and that coronary vasospasm is only present when a reduction in lumen diameter of 50% is present. The sponsor therefore asserts that the effect in dog is unremarkable, and indicative of no additive effect. The sponsor also notes that the coronary diameter of the dogs was highly variable (baseline coronary diameter varied for each dog from day to day; the coefficient of variation in daily baseline coronary diameter ranged from 2.26% to 11.29% of the mean for individual dogs).

[Comment: The guidelines for defining different types of vasoconstriction during coronary angiography would seem to have little or no bearing on the existence or clinical significance of a possible additive effect of sumatriptan and naproxen on coronary vasoconstriction. The most persuasive argument made by the sponsor is that the experiment showed a high degree of variation, and that while the results show a decrease in coronary artery diameter, this decrease is not interpretable in the context of the large variability. Repeating the experiment might likely also yield data that is difficult to interpret because of high variability.]

The sponsor additionally cites published studies from which they conclude that current scientific evidence does not support that naproxen could be a vasoconstrictor when administered concurrently with sumatriptan.

[Comment: Published studies appear inconclusive. One of the papers the sponsor cites is a meta-analysis by Aw et al. of clinical trial data on the cardiovascular effects of naproxen (Arch Int. Med. 2005;165:490-496). This paper appears to suggest that nonselective NSAIDs might, in fact, raise blood pressure and cause vasoconstriction:

> "A nonsignificantly increased risk of developing hypertension with coxib use compared with both placebo and nonselective NSAIDs. This risk was more pronounced when coxibs were compared with placebo (a 61% increase in RR) compared with nonselective NSAIDs (a 25% increase in RR). This is consistent with both coxibs and nonselective NSAIDs causing prostaglandin inhibition and possessing antinatriuretic and vasoconstrictor properties"[emphasis added].

9. Acute Blood Pressure Effects of Trexima

The Approvable letter noted the absence in the original NDA of blood pressure monitoring during acute dosing with Trexima, with the result that no reliable information was presented about the maximal effects of Trexima on blood pressure.

The sponsor conducted study TRX106396 to address this deficiency. The sponsor concludes from this study that blood pressure changes after a single dose of Trexima are similar to sumatriptan 100mg.

The acute blood pressure comparison was conducted as follows:

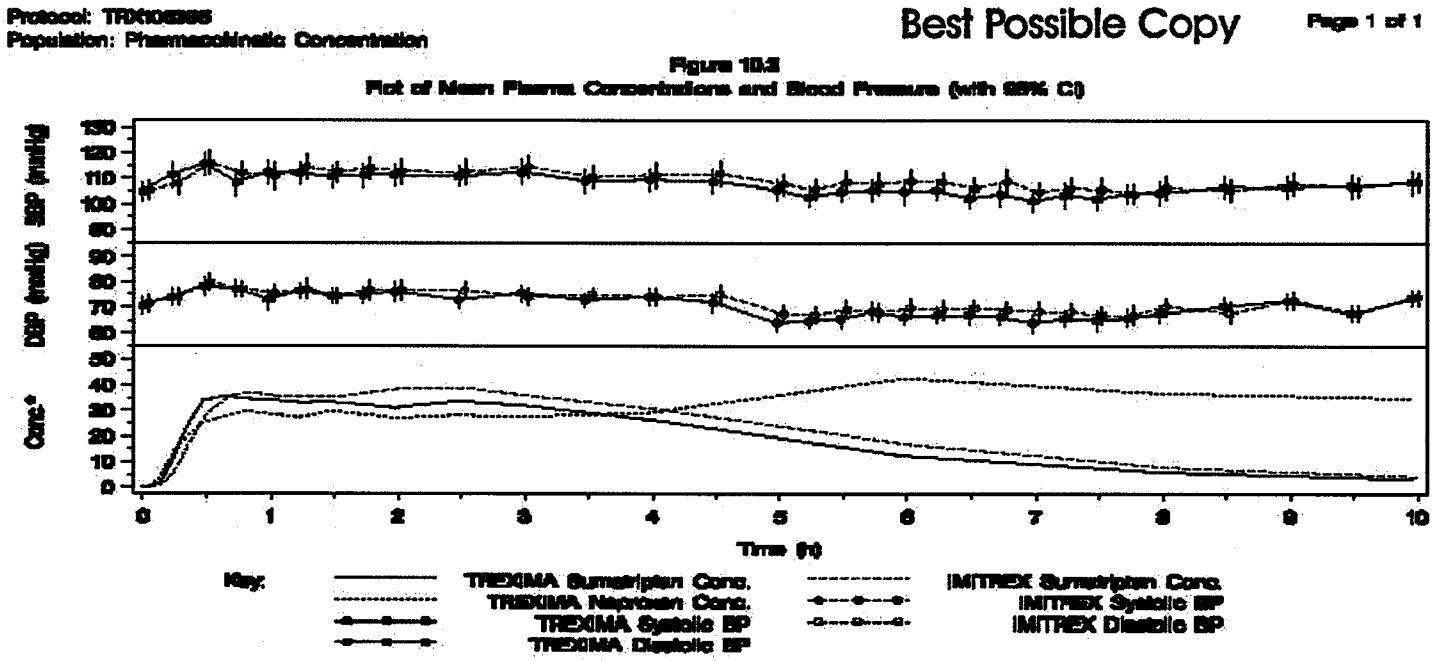
> "TRX106396 was an inpatient, open-label, 2-way cross-over study in 32 healthy adult volunteers primarily designed to compare the pharmacokinetic profile of a single dose of Trexima to that of a single dose of sumatriptan 100mg. Cardiovascular monitoring included continuous 5-lead ECG monitoring and serial blood pressure measurements obtained every 15 minutes around the expected Tmax of the components and every 30 minutes at all other times beginning one hour prior to dosing and continuing through 10 hours post-dose for both treatments."

[Comment: The study was open-label, with a higher potential for bias than if blinded.]

Figure 2 shows the average blood pressure for Trexima and sumatriptan from this study.

[Comment: The average blood pressure change is essentially the same for Trexima and sumatriptan (100 mg). At most time points, the blood pressure is higher for sumatriptan than for Trexima.]

Figure 2: Blood pressure, Trexima versus Sumatriptan, Study TRX106396



The sponsor also calculated mean blood pressure over 0-2 hours (near the sumatriptan Tmax) and 2.5-8 hours (near the naproxen Tmax). The blood pressure was similar for both, about 10 mm systolic (slightly higher for sumatriptan than Trexima) over these intervals (Table 6).

Table 6: Blood Pressure, Trexima-Imitrex, TRX106396

Summary of Analysis of Blood Pressure

Parameter	Point Estimate (TREXIMA-IMITREX)	95% CI
Blood Pressure assessments around Sumatriptan tmax		
Weighted Mean of Systolic BP over 0-2 hrs (mmHg)	-0.93	(-3.15, 1.29)
Weighted Mean of Diastolic BP over 0-2 hrs (mmHg)	-0.96	(-2.53, 0.61)
Blood Pressure assessments around Naproxen tmax		
Weighted Mean of Systolic BP over 2.5-8 hrs (mmHg)	-2.63	(-4.21, -1.05)
Weighted Mean of Diastolic BP over 2.5-8 hrs (mmHg)	-1.94	(-3.18, -0.71)

Sumatriptan blood levels were generally similar from Trexima and from Imitrex 100 mg. Cmax, AUC(0-t), and AUC(0-∞) of sumatriptan were completely contained within the equivalence interval 80 to 125%. Sumatriptan t_{max} occurred 53 minutes earlier for TREXIMA compared to IMITREX.

[Comment: This study compares acute effects of sumatriptan and Trexima on blood pressure in non-hypertensive subjects. Since NSAIDs are thought to antagonize the effect of several commonly used anti-hypertensive drugs, the effect of Trexima in controlled hypertensives is of concern, and would not be adequately addressed by this study. The chronic (chronic intermittent) effect of Trexima on blood pressure is not adequately addressed by this type of study.]

10. Proposed Post-Approval Chronic Blood Pressure Study

The sponsor proposes a post-approval study of Trexima to examine effects on blood pressure of chronic-intermittent dosing.

The sponsor proposes the following study question:

> *Does the addition of sumatriptan to naproxen sodium for chronic intermittent migraine treatment increase blood pressure over naproxen sodium alone?*

[Comment: This is a three arm study, including a sumatriptan arm. All three arms should be compared to each other.]

The following is the sponsor's description of the study design:

> "A randomized, double-blind, active-comparator study in adults with episodic IHS migraine dosed with either Trexima, naproxen sodium 500mg or sumatriptan 85mg will be conducted. The objective of this study is to determine the effects of sumatriptan when added to naproxen sodium on systolic and diastolic blood pressure. [redacted]

[redacted]

[Comment: This is a logical plan that should improve data from this type of study.]

[redacted]

Reviewer discussion:
The proposed 3-arm study could potentially be a valuable addition to knowledge about the comparative safety (and efficacy, if data collected) of sumatriptan, Trexima, and naproxen. To approximate ICH guidelines, [redacted]

11. Safety Update

This update of Clinical Safety is through September 29, 2006, and includes 5 new Trexima studies (Table 7).

TRX106396
This was a single center 2 period crossover trial assessing the pharmacokinetics of sumatriptan administered as Trexima versus sumatriptan 100mg. The acute effects of Trexima on 5-lead ECG, heart rate and blood pressure were compared to the effects of sumatriptan 100 mg in 32 healthy adults (mean age 29).

TRX101998 and TRX101999
These were identical randomized, double-blind, parallel group, placebo-controlled, multicenter trials evaluating single doses of Trexima administered during the mild pain phase of a migraine and within one hour of onset of head pain. Medication (Trexima or placebo) was taken by 580 subjects in study 998, and 542 subjects in study 999.

TRX103632 and TRX103635
These were identical randomized, double-blind, multicenter, placebo-controlled, 4-period cross-over, multi-attack (up to 4), out-patient trials in adult migraineurs who typically experienced moderate to severe migraine headache pain preceded by an identifiable mild pain phase. Subjects were asked to treat four migraine attacks during the mild pain phase and within one hour of onset of headache pain. Study 632 treated 670 subjects, and study 635 treated 565 subjects with at least one dose of Trexima or placebo.

Table 7: Additional Trexima Trials

Table 2.7.53 Clinical Studies Providing Safety Data – Full Response Safety Update[1]

Study Reference Number	Study Objectives	Study Design	Treatments: Dose, Dosage Form	Subjects: Number, Sex (M/F), Median Age, Type
Phase 1 Studies				
TRX106396 Section 5.3.4.1.1	To evaluate sumatriptan & naproxen pharmacokinetics of a TREXIMA Tablet compared with an IMITREX® 100mg Tablet	Open-label randomized single dose 2-period crossover	Trexima tablets (sumatriptan 85 mg / naproxen sodium 500mg) Imitrex tablets (sumatriptan 100mg)	32 (6 M/26 F) treated, all evaluable 29 years, healthy volunteers
Phase 3 Studies				
TRX101998 Filed to IND 68,436	Placebo controlled safety and efficacy of Trexima when administered during the mild pain phase of a migraine	Double-blind, parallel-group single-dose, multicenter study	1) Trexima Tablets (sumatriptan 85 mg RT / naproxen sodium 500 mg) 2) Placebo Tablet	580 treated: 283 Trexima (36M/247F), 40 years 297 placebo (39M/258F), 41 years migraine subjects treated during the mild pain phase of a migraine
TRX101999 Filed to IND 68,436	Placebo controlled safety and efficacy of Trexima when administered during the mild pain phase of a migraine	Double-blind, parallel-group single-dose, multicenter study	1) Trexima Tablets (sumatriptan 85 mg RT / naproxen sodium 500 mg) 2) Placebo Tablet	542 treated: 278 Trexima (25M/253F), 42 years 264 placebo (27M/237F), 42 years migraine subjects treated during the mild pain phase of a migraine
TRX103632 Safety data only reported Protocol filed to IND 68,436 Serial #043 October 5, 2005	Determine the consistency of response for Trexima administered during the mild pain phase of multiple migraine attacks	Double blind placebo controlled parallel-group, multicenter, 4-period multi-attack study	1) Trexima Tablets (sumatriptan 85 mg RT / naproxen sodium 500 mg) 2) Placebo Tablet	Randomized: 646 Safety population: 570 (64M/506F), 43 years Exposure of Trexima by number of attacks: 1 attack: 30 2 attacks: 24 3 attacks: 409 4 attacks: 97 migraine subjects treated during the mild pain phase of a migraine
TRX103635 Safety data only reported Protocol filed to IND 68,436 Serial #043 October 5, 2005	Determine the consistency of response for Trexima administered during the mild pain phase of multiple migraine attacks	Double blind placebo controlled parallel-group, multicenter, 4-period multi-attack study	1) Trexima Tablets (sumatriptan 85 mg RT / naproxen sodium 500 mg) 2) Placebo Tablet	Randomized: 620 Safety population: 565 (54M/511F), 41 years Exposure of Trexima by number of attacks: 1 attack: 31 2 attacks: 25 3 attacks: 411 4 attacks: 91 migraine subjects treated during the mild pain phase of a migraine

Deaths

No deaths are associated with Trexima in these additional studies (one death in the original database was due to gunshot wound).

Serious Adverse Events
The sponsor asserts that none of the serious adverse events (SAEs) in the additional studies were treatment related.

There were three new SAEs reported in the safety update:

- Worsening menorrhagia
- Carcinoma in situ of breast
- Viral gastroenteritis

Reviewer Conclusions: All of the newly reported SAEs are unlikely related to drug (NDAIDs reduce blood loss in menorrhagia).

Premature Withdrawals
Study 998 and 999 were single attack studies, and by definition had no premature withdrawals.

Study 632
4-period, up to 4 migraine attacks
10 subjects prematurely withdrew due to an adverse event after taking Trexima.

Adverse events leading to withdrawal were the following (number experienced out of 560 exposed):

- Chest discomfort (3)
- Feeling hot (1)
- Dyspepsia (1)
- Nausea (1)
- Palpitations (1)
- Muscle tightness (1)
- Dizziness (1)
- Throat tightness (1)

[Comment: Subject 43 (site 018947) experienced hives more than 2 weeks after taking Trexima. This event is not likely drug related and not included above.]

Study 635
4-period, up to 4 migraine attacks
There were 10 subjects who prematurely withdrew due to an adverse event, 8 were after taking TREXIMA and 2 were after taking Placebo.

Adverse events leading to withdrawal were the following (number experienced out of 558 exposed):

- Nausea (3)
- Swollen tongue (1) [subject 515]
- Chest discomfort (2)
- Chest pain (1)
- Dizziness (1)

- Mental impairment (1)
- Hypersensitivity (1) [subject 661]
- Muscular weakness (1)
- Dyspnea (1)
- Throat tightness (1)

[Note: None of the symptoms of chest pain/discomfort in these two studies was 'severe,' and no additional diagnostic testing, such as ECG or cardiac enzyme tests, was performed.]

Reviewer conclusions
One case of swollen tongue and one case of 'allergic reaction' occurred in different patients in this study.

The subject that withdrew due to allergic reaction reported this event after 2 of the 3 doses of study medication taken. Both events were reported as mild in severity, resolving the same day.

The subject with tongue swelling experienced moderate symptoms that resolved the next day.

No cases of hypersensitivity or plausibly related events were reported previously in Trexima studies.

Rare hypersensitivity reactions can occur associated with both naproxen and sumatriptan. There is insufficient data to determine if the incidence of allergic reactions differs for Trexima versus its individual components. Anaphylactic/anaphylactoid reactions are in proposed labeling in both CONTRAINDICATIONS and WARNINGS. This labeling is adequate.

Common Adverse Events
Common adverse events in the newly reported studies were similar to those in the original NDA (Table 8)

Table 8: Common Adverse Events (>/=2%)

Adverse Event N=(%)	Trexima		Placebo		Sumatriptan[2]	Naproxen[2]
	NDA[1] N=1162	Full Response[2] N=2628	NDA[1] N=994	Full Response[2] N=1785	NDA N=735	NDA N=982
Subjects with at least 1 event	282 (24.3%)	533 (20.3%)	120 (12.1%)	197 (11.0%)	194 (26.4%)	142 (14.5%)
Nervous System	**118 (10.2%)**	**196 (7.5%)**	**46 (4.6%)**	**62 (3.5%)**	**63 (8.6%)**	**47 (4.8%)**
Dizziness	36 (3.1%)	71 (2.7%)	16 (1.6%)	20 (1.1%)	16 (2.2%)	11 (1.1%)
Somnolence	32 (2.8%)	54 (2.1%)	15 (1.5%)	20 (1.1%)	17 (2.3%)	14 (1.4%)
Paraesthesia	23 (2.0%)	38 (1.4%)	4 (0.4%)	6 (0.3%)	17 (2.3%)	3 (0.3%)
Gastrointestinal Disorders	**100 (8.6%)**	**193 (7.3%)**	**50 (5.0%)**	**80 (4.5%)**	**71 (9.7%)**	**52 (5.3%)**
Nausea	40 (3.4%)	88 (3.3%)	10 (1.0%)	22 (1.2%)	21 (2.9%)	7 (0.7%)
Dry Mouth	18 (1.5%)	45 (1.7%)	9 (0.9%)	20 (1.1%)	15 (2.0%)	4 (0.4%)

[1] Source: Section 2.7.4.7.2.1 120-Day Safety Update (Amendment 003, December 5, 2005)
[2] Source: Section 2.7.4.7.2.1 Full Response

Laboratory Studies
No post-enrollment laboratory testing was conducted for the newly reported studies

Vital Signs, physical findings, ECG
There were no clinically meaningful new findings.

Exposure in-utero
A total of 8 pregnancies occurred with exposure to Trexima. One patient experienced a tubal pregnancy.

[Comment: this event is unlikely drug-related]

12. Labeling

The proposed label generally follows the 'Proposed NSAID Package Insert Labeling Template' of FDA (http://www.fda.gov/cder/drug/infopage/COX2/default.htm#NSAIDletters). Some differences are noted and discussed, and some changes are recommended to conform to the FDA template.

29 Page(s) Withheld

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/s/

Ronald Farkas
6/22/2007 03:11:56 PM
MEDICAL OFFICER

Eric Bastings
7/20/2007 05:40:39 PM
MEDICAL OFFICER
Please refer to the action letter for final labeling.

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANALGESIA, ANESTHESIA, AND RHEUMATOLOGY PRODUCTS
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MEMORANDUM

Date: May 30, 2006

To: Eric Basting, MD
Neurology Team Leader
Division of Neurology Products

From: Jin Chen, M.D., Ph.D.
Medical Officer
Division of Anesthesia, Analgesia and Rheumatology Products

Through: Sharon Hertz, M.D.
Deputy Director
Division of Anesthesia, Analgesia and Rheumatology Products

Bob Rappaport, M.D.
Division Director
Division of Anesthesia, Analgesia and Rheumatology Products

Reference: Consult on cardiovascular risks of naproxen formulated with sumatriptan (Trexima): NDA 21-926

Background

This consult was requested by the Division of Neurology Products (DNP) on October 5, 2005, to assess the cardiovascular safety of Trexima (ND 21-916). Trexima is a combination tablet of sumatriptan succinate (85 mg) and naproxen sodium (500 mg) with **the proposed indication "for the** acute treatment of migraine attacks with or without aura **in adults". DNP seeks the fo**llowing inputs from our division:

- *Scientific and regulatory developments on cardiovascular risks of naproxen and*
- *Possible additive cardiovascular effects of naproxen combined with sumatriptan*

This memo will briefly summarize the cardiovascular risk of naproxen and its potential interaction with sumatriptan.

Proposed Dosing Regimen of Trexima

The dosing regimen proposed in the labeling of Trexima, as extracted below, suggests that Trexima may be used on an intermittent basis for acute treatment of migraine attack:

- [redacted]
- Do not take more than two tablets in 24 hours
- [redacted]

Cardiovascular Risk of Naproxen

Class Effect: The potential cardiovascular risk of naproxen was assessed along with the COX-2 selective and other non-selective NSAIDs as a class before and after the joint advisory committee meeting (the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee) in February 2005. It was concluded in the **CDER's Decision Memo [1] of April 6, 2005 (in FDA's internet) that all NSAIDs** (excluding aspirin) with reasonably prolonged use are associated with an increased risk of serious adverse cardiovascular events, and large long-term controlled trials did not clearly demonstrate the COX-2 selective agents confer a greater risk than non-selective NSAIDs.

Subsequently, the Agency made the following regulatory class actions for all non-aspirin NSAIDs:

- Revise professional labeling for all Rx NSAIDs by including a boxed warning highlighting the potential increased risk of serious cardiovascular events (the template was published in the FDA internet in July 2005)[2].

- Develop a class Medication Guide for Rx NSAIDs to inform patients of potential increased risk of serious cardiovascular events and serious GI bleeding (the template was published in the FDA internet in July 2005)[3].

- Revise NSAID OTC label with more specific information about potential CV and GI risks (the template was published in the FDA internet in July 18, 2005)[4]. It was **also conclude in the CDER's Decision Me**mo that short-term use of low dose of NSAIDs OTC product is not associated with an increased risk of serious adverse CV events.

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[1] Decision Memo - Analysis and Recommendations for Agency Action - COX-2 Selective and Non-selective NSAIDs http://www.fda.gov/cder/drug/infopage/COX2/NSAIDdecisionMemo.pdf
[2] NSAIDs Package Insert template: http://www.fda.gov/cder/drug/infopage/COX2/NSAIDRxTemplate.pdf
[3] Medication Guide for Rx NSAIDs: http://www.fda.gov/cder/drug/infopage/COX2/NSAIDmedguide.pdf
[4] OTC NSAIDs Label: http://www.fda.gov/cder/drug/infopage/COX2/NSAIDOTCSuppLTRrevised.pdf

- Conduct and submit a comprehensive review and analysis of available controlled clinical trial database (the request letter was sent to all NSAIDs sponsor on April 7, 2005, see below for detail).

Naproxen has been included in the above class actions, although naproxen as an active comparator in long-term COX-2 selective NSAIDs studies has shown mixed results in cardiovascular risk. For example, in VIGOR study (Vioxx GI Outcome Research)[5] the relative risk of MI in subjects treated with naproxen was 0.2 (95% CI: 0.1-0.7) as compared with rofecoxib (Vioxx); although the incidence of cardiovascular death was similar between naproxen and Vioxx. In TARGET study (Therapeutic Arthritis Research and Gastrointestinal Event Trial)[6], the primary cardiovascular endpoint (MI, stroke and cardiac death) between lumiracoxib (an investigational COX2 inhibitor) and naproxen showed less risk for naproxen at 1-year follow-up. However, lack of a placebo control in those long-term trials makes it difficult to adequately assess the relative cardiovascular risk of naproxen or other nonselective NSAIDs.

Long-term placebo-controlled RCT on naproxen: The only long-term, placebo-controlled trial including nonselective NSAIDs as an active control is the unpublished **Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT). This was a** randomized, placebo-controlled, multicenter trial to assess the efficacy of celecoxib (Celebrex, Pfizer) and naproxen (Aleve, Bayer) for the primary prevention of **Alzheimer's disease. The trial was sponsored** by NIH/NIA and conducted in the United States by the ADAPT Steering Committee[7]. The study was suspended approximately 3.5 years after the initial enrollment (projected duration was 7 years). The manuscript draft (with summary data) on the cardiovascular data analysis became recently available (submitted with NDA 20-204/C-000 by Bayer on July, 22, 2005).

The study population was cognitively normal males and females age ≥ 70 years with a family history of Alzheimer-like dementia. The known risk factors for NSAID treatment were excluded, such as pre-existing uncontrolled hypertension, anemia or a history of GI bleeding, perforation or obstruction [*extracted from the transcript of the joint Advisory Committee meeting of Feb 2005*]. Projected sample size was 2625 subjects with randomization ratio of 1:1:1.5 for celecoxib, naproxen and placebo. The subjects would be contacted by in-person visit (interview) every 6 months (started at month 1) and telephone interview in-between (every 6 month, started at month 3) for up to 7 years.

At the time of premature termination of the trial, 2,528 participants had been enrolled and 2,463 of them (704 on celecoxib, 702 on naproxen and 1057 on placebo) were followed up for an average duration of 20 months, which was contributed to 3,888 person-years. In

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[5] Bombardier C et al: Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Eng J Med* 343(21): 1520-8, 2000

[6] Farkouh ME et al: Comparison of lumiracoxib with naproxen and ibuprofen in The Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), cardiovascular outcomes: randomized Controlled trial. *Lancet* 364: 675-84, 2004

[7] Martin BK et al: Double placebo design in a prevention trial for Alzheimer's disease. *Controlled Clin Trials* 23: 93-99, 2002

the manuscript draft, the cardiovascular risk analysis was based on events reported from the 2,463 participants by using the composite cardiovascular (CV) outcome (MI, stroke and cardiac death) of APTC (Anti-**platelet Trialists' Collaboration)**[8].

The detailed summaries of CV events and data analyses were not presented in the manuscript. The relative risk of the APTC composite CV outcome was 1.50 (95% CI: 0.77-2.92; p=0.29) for celecoxib and 1.77 (95% CI: 0.93-3.36; p=0.09) for naproxen as compared to placebo (Table 1).

The ADAPT results suggest that long-term treatment with naproxen may increase cardiovascular risk as compared to placebo and the probability of this risk is at least as high as celecoxib. However, the differences in the relative risk and the estimated probability of the risk based on the APTC composite outcome between naproxen or celecoxib and placebo were not statistically significant. This was mainly due to the small sample size, the small number of CV event and the short duration of treatment (average 20 months) resulted from the early termination. It is unclear if covariates were adjusted during the data analyses, particularly cardiovascular history and conditions, cardiovascular risk factors, low-dose aspirin use and other baseline characteristics (BMI and gender).

Sponsor's Randomized Controlled Trials: On April 7, 2005, FDA issued a request letter to all primary NDA holders of non-selective non-aspirin NSAIDs products, requesting analysis of cardiovascular safety data reported in all previous randomized controlled trials (RCT) of NSAIDs (during the pre- and post-marketing period) with duration of treatment $\geq$ 28 days. There were two sponsors/primary NDA holders of naproxen products (naproxen as a single ingredient), Roche (naproxen IR and ER) [redacted] (naproxen ER). The sponsors identified 15 eligible placebo-controlled and/or active-controlled RCTs. The total patient exposure was 1033 patients on naproxen, 402 patients on placebo and 160 patients on aspirin for 4-16 weeks. There were a few unadjudicated serious cardiovascular events reported from some of those trials, but no meaningful risk assessment can be made due to additional limitations such as small sample size of each trial, high heterogeneity among trials, and short duration of exposure.

Current Regulatory Development on NSAIDs

The package insert of all NSAIDs Rx products indicated for chronic use has been updated **according to the FDA's template by including a boxed warning, revising CV risk** information under Warnings and the addition of a Medication Guide. This includes the naproxen products (three primary NDA holders).

There are three NSAIDs products (single or combination) indicated solely for acute use, Vicoprofen (ibuprofen + hydrocodone; NDA 20-716), Combunox (ibuprofen + oxycodone; NDA 21-378), and Toradol (ketorolac). Combunox and Toradol labeling will include the full NSAID warnings. Vicoprofen, when used according to the package

[8] Secondary prevention of vascular disease by prolonged antiplatelet treatment. Antiplatelet Trialists' Collaboration. *Br Med J* 296 (6618): 320-331, 1988

insert, has a maximum daily dose of ibuprofen of 1000 mg. While most of the NSAID warnings have been added to the package insert, discussion is ongoing with respect to the use of the medication guide.

Potential Interaction between naproxen and sumatriptan:

Cardiovascular risk of Sumatriptan: Sumatriptan is an agonist of vascular serotonin receptor 5-HT1D subtype and stimulates vasoconstriction or vasospasm (coronary artery, cerebrovascular and peripheral vascular) through activation of this receptor. It has been reported that the sumatriptan-induced vasospasm can cause serious cardiovascular and cerebrovascular events, although the events seem to be rare. These include coronary vasospasm, rare cardiac arrhythmias (ventricular tachycardia, ventricular fibrillation, cardiac arrest, and death), angina, transient myocardial ischemia, myocardial infarction, cardiac arrest, hypertension, intracranial bleeding, subarachnoid hemorrhage, stroke and seizures. Patients with risk factors for cardiovascular disease are more susceptible to serious adverse events with use of sumatriptan.

Cardiovascular biology of NSAIDs: Substantial body of evident suggests that non-aspirin NSAIDs decrease PGI2 production through inhibition of the vascular COX-1 and, particularly, COX-2 (in endothelia and smooth muscle). The suppression of PGI2 (synthesis or PHI2 receptors) can enhance the vascular response to thrombotic stimuli (interaction of platelet and endothelium) and hypertensive stimuli, and initiate and accelerate atherogenesis[9].

Potential Synergistic Interaction: Potential drug-drug interactions between sumatriptan and naproxen may occur through different pharmacological mechanisms. This interaction may play a synergistic role in cardiovascular pathogenesis, particularly in patients with underlying cardiovascular disorders and risk factors. Cardiovascular insults (thrombotic and/or hemodynamic) from chronic or intermittent exposure to naproxen (or other NSAIDs) may become risk factors for adverse events from sumatriptan.

The potential pharmacodynamic interaction between naproxen and sumatriptan is supported by the cardiovascular safety pharmacology study (MT400-T15 and T17) submitted with this NDA, which showed that the intravenous co-administration of sumatriptan (80 ug/kg) and naproxen (20 mg/kg) tended to increase vasoconstriction of coronary artery and carotid artery and increase mean arterial pressure. However, there are no long-term, placebo-controlled and/or active-controlled clinical outcome trials to further support this interaction.

Clinical study in literature: co-therapy of a triptan (particularly sumatriptan) and nonselective NSAIDs (including naproxen) has been studied in patients with headache conditions such as migraine and cluster headache with no serious cardiovascular events reported. However, all these studies were single-dose with small sample size. There are

[9] Grosser T et al: Biological basis for the cardiovascular consequences of COX-2 inhibition: therapeutic challenges and opportunities. *J Clin Invest* 116: 4-15, 2006

no long-term, multiple-dose, controlled studies on sumatriptan and naproxen used in combination in the literature.

Safety trial on Trexima in this NDA: A total of 1,441 subjects from Phase 1 to 3 trials were exposed to Trexima tablets (85 mg sumatriptan and 500 mg naproxen); 60% (n=876) of them were treated with a single dose of Trexima, including two pivotal trials. The only multiple-dose, long-term assessment was from the open-label uncontrolled trial.

1. Two pivotal Phase 3 trials (MT400-301 and MT400-302) were randomized, placebo- and active-controlled, single dose trials in migraine patients. A total of 791 (55% of 1,441) patients were enrolled in the two trials and treated with a single dose of Trexima. A total of six SAEs were reported, two each on Trexima, sumatriptan and naproxen, none on placebo. The medical reviewer in DNP judged that only one SAE in sumatriptan **group "possibly related to drug".**

2. One long-term open-label safety trial (MT400-303) enrolled a total of 565 patients with migraine who received Trexima with an average of five doses (migraine attacks) per month and with a mean interval of seven days between the attacks (doses). Of the 565 patients enrolled, 414 completed the 6-month treatment and 362 stayed in the study for 12 months. A total of 20 SAEs were reported from 14 patients. Three of the SAEs were serious CV events which were judged by the **medical reviewer in DNP "*probably or possibly related to Trexima*" (as follows).**

   - Subject 030/2143: acute coronary syndrome (*the investigator judged "related to Trexima"*). This 47-year old female developed acute coronary syndrome after Trexima treatment for 6.5 months. The patient had an average of six headaches (doses) per month during the study, and experienced chest discomfort with some shortness of breath approximately two hours after taking the last dose at 6.5 months. Angiography showed single-vessel coronary artery disease. The patient was obese (BMI 35.7), with hypercholesterolemia and a family history of cardiovascular disease.

   - Subject 296/2129: acute coronary syndrome and hypertension (*the investigator judged "not related to Trexima"*). This 44-year old female developed acute coronary syndrome and hypertension after six migraine attacks with seven doses **of Trexima within six weeks. At the emergency room, the patient's BP was** 182/95 (baseline BP was 110/82) with a normal ECG. She responded to routine therapy. The patient had no significant medical history and cardiovascular risk factors.

   - Subject 296/2709: pleurisy chest wall pain syndrome (*the investigator judged "not related to Trexima"*). This 27-year old female experienced chronic recurrent chest pain with radiation to left arm after treatment with Trexima for five migraine attacks within one month. The patient had the following medical history: knee arthroscopy, cesarean section, appendectomy, laparoscopy, left eardrum rupture, and toxemia of pregnancy. Her BMI was 38.9 without other

cardiovascular risk factors. Concomitant medications were Singulair, Nasalcort, Advair, Allegra, hormonal contraceptive and Patanol.

The three serious cardiovascular events were acute coronary spasm, which was more likely associated with the sumatriptan in Trexima. However, it is hard to rule out if naproxen played a synergistic role in the cardiovascular events in the absence of controlled trials.

Comment and Conclusion

1. There is limited evidence that naproxen may increase cardiovascular risk following chronic systemic exposure.

2. Evidence from randomized placebo-controlled trials does not suggest that a short-term use of naproxen and other NSAIDs for an acute indication increase cardiovascular risk.

3. There is no data available to assess the cardiovascular risk of naproxen and other NSAIDs under long-term intermittent use.

4. Both naproxen and sumatriptan are known to have different associated cardiovascular risk and the possibility of a synergistic interaction is possible.

5. **The data from the sponsor's long-term**, open-label, multiple-dose (average 5 doses per month) uncontro**lled trial resulted in 3 "possibly Trexima-related"** serious cardiovascular events in 565 patients treated with Trexima for up to 12 months. However, it is not possible to assess if these cardiovascular SAEs were due to the synergistic cardiovascular effects of Trexima without a control group.

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/s/

Jin Chen
8/11/2006 02:49:54 PM
MEDICAL OFFICER

Sharon Hertz
8/14/2006 05:04:00 PM
MEDICAL OFFICER
I concur with this review

Bob Rappaport
8/14/2006 05:22:12 PM
MEDICAL OFFICER

MEMORANDUM

DATE: June 9, 2006

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 21-926

SUBJECT: Action Memo for NDA 21-926, for the use of Trexima (sumatriptan/naproxen tablets) as acute treatment of migraine headache

NDA 21-926, for the use of Trexima (sumatriptan/naproxen tablets) as acute treatment of migraine headache, was submitted by Pozen and Glaxo SmithKline on 8/5/05. It contains the results of two single dose, placebo controlled trials, as well as safety data and the requisite chemistry and manufacturing (CMC) and clinical pharmacology data. The application has been reviewed by Dr. Ron Farkas, medical officer, Dr. Kun He, statistician, Dr. David Hawver, pharmacologist, Dr. Chhagan Tele, chemist, Dr. Sally Yasuda, clinical pharmacologist, Dr. Laura Pincock, Division of Medication Errors and Technical Support (DMETS), Jeanine Best, Division of Surveillance, Research, and Communication Support (DSRCS), Sherbet Samuels, Division of Scientific Investigations, Dr. Shari Targum, cardiology consult, and Dr. Eric Bastings, neurology drugs team leader. The clinical team recommends that the sponsor be required to submit substantial additional evidence of safety before the application can be approved. I will very briefly review the relevant effectiveness and safety data, and offer the rationale for the division's action.

EFFECTIVENESS

As noted above, the sponsor has presented the results of two identically designed studies that examined the effectiveness of a single dose of the fixed combination of sumatriptan (85 mg) and naproxen (500 mg) in patients with an acute migraine headache. As with all recently approved acute migraine treatments, the sponsor demonstrated the effectiveness of the drug (in this case, of course, a fixed combination product) at two hours on pain, as well as the associated symptoms of nausea, photophobia, and phonophobia, compared to placebo. It should be noted that, in one study (301), the comparison between Trexima and placebo on the proportion of patients nausea-free at 2 hours did not reach statistical significance with the original protocol-specified analysis. However, as all reviewers note, the sponsor [redacted] to the statistical analysis plan prior to breaking the blind [redacted] that changed the analysis if there were baseline differences between the treatment group (there

were for nausea). On the amended analysis, the Trexima-placebo contrast for nausea at two hours reached statistical significance.

Because this is a fixed combination product, the requirement of 21 CFR 300.50 (fixed combination drug products) must be met; that is, each component must demonstrate a contribution to some meaningful effect of the drug. We had prospectively agreed with the sponsor that the contribution of each component could be shown on the proportion of patients who remained pain-free from 2-24 hours (so-called "sustained pain free"). On this outcome, Trexima was statistically significantly superior to each component. In this way, the contribution of each component was demonstrated, and 21 CFR 300.50 was satisfied.

SAFETY

As noted by Dr. Farkas, a total of 1405 patients received at least one dose of Trexima (a total of 737 patients received a single dose of Trexima in the two controlled trials described above). A total of 409 patients received at least 25 doses in the single, long-term, one year, open label study.

As described by Dr. Farkas, there were few serious adverse events in the controlled trials, and one death, which could not reasonably be related to treatment. There were also few serious adverse events in the open label experience, but Dr. Farkas notes one serious event of note.

A 47 year old woman experienced an "acute coronary syndrome" after her 39th treated headache. She experienced chest discomfort and shortness of breath about 2 hours after a dose of Trexima. An EKG in the Emergency Department showed ST changes in the lateral precordium, and nitroglycerin provided some relief. Troponin and CK levels were normal.

She underwent a cardiac catheterization that revealed a 70% narrowing of the ostium as it arose from the left main coronary artery with a post-stenotic filling defect consistent with a thrombus. She underwent coronary artery bypass surgery. This woman had a family history of cardiac disease and was overweight, with a BMI of 35.7. Her EKG at baseline was normal.

Dr. Farkas describes in detail the single dose, as well as the multiple dose, safety experience. In general, adverse events seen were consistent with those known to be associated with either component of the product.

However, as Dr. Farkas points out, in the two controlled trials, there were 4 cases of severe chest pain/discomfort in the Trexima group, and none in the other treatment groups (sumatriptan, naproxen, placebo). None of these patients had an EKG assessed in relation to these events, and none of the patients required additional medical intervention for these events.

Although there were few lab abnormalities or vital sign measurements of note, as Dr. Farkas points out, there is no blood pressure data timed appropriately to dosing with Trexima (blood pressure monitoring in the controlled studies was performed days after treatment). As Dr. Farkas notes, each component of Trexima is associated with elevations in blood pressure, and there is some reason to believe that naproxen may have a coronary vasoconstrictor effect (of course, sumatriptan is well known to have such an effect). Also, recently the Agency has determined that NSAIDs, including naproxen, may be associated with a risk for cardiovascular disease, although this is typically considered to be true in the setting of chronic treatment.

Because of our concerns about the possibility that Trexima may result in greater coronary artery constriction than sumatriptan alone, we had asked the sponsor to perform a nonclinical study looking at this possibility.

As described by Dr. Farkas, the sponsor performed a study in dogs that examined coronary artery constriction in animals given the combination of sumatriptan and naproxen compared to animals just given sumatriptan. Although this study was methodologically flawed, the combination produced greater constriction than sumatriptan individually in five of six animals, and the combination of sumatriptan and lower doses of naproxen did not show the increase in vasoconstriction seen with the combination using higher doses of naproxen. A similar pattern of findings was seen in the carotid artery.

Clinical Pharmacology

As noted by Dr. Yasuda, the Cmax of sumatriptan after ingestion of Trexima was about 20% greater than that when sumatriptan was given alone, and the Cmax of naproxen from the combination was about 30% lower than when naproxen was given alone. Although the AUCs for both components were essentially the same whether given alone or in the combination, the tmax for naproxen was considerably prolonged when given in the combination compared to when it was given alone (about 6 and 4 hours, respectively).

Pharmacology

There is evidence that the combination of sumatriptan and naproxen produces a clastogenic effect in the in vitro chromosomal aberration assay that is greater than that with naproxen alone. However, these effects were seen only at concentrations that produced substantial cytotoxicity. For this reason, Dr. Freed recommends that the in vitro chromosomal aberration assay in CHO cells be repeated at additional concentrations, and also that an in vitro mouse lymphoma tk assay testing naproxen and sumatriptan alone and in combination be performed.

Product Name

. For these reasons, we will reject the proposed name Trexima.

COMMENTS

The sponsor has submitted the results of two randomized controlled trials that document that Trexima is effective as an acute treatment for migraine. Further, the requirements of 21 CFR 300.50 have been satisfied, because they have provided evidence that each component of the combination makes a contribution to the effect, by demonstrating the superiority of the combination to each component on the proportion of patients who were pain-free from 2-24 hours after dosing.

Although there were few significant adverse events, there are some troubling findings in the safety database, as described by Drs. Farkas and Bastings. These findings are the occurrence of a single case of cardiac ischemia in a 46 year old woman, the occurrence of 4 cases of severe chest pain in the Trexima group (and no such cases in the other treatment groups), and the findings in the dog study that suggest a greater degree of coronary vasoconstriction with the combination than with sumaltriptan alone.

The woman who experienced cardiac ischemia did have risk factors (she was overweight and had a family history of cardiac disease), and she ultimately was shown to have coronary artery narrowing requiring surgery. According to current triptan labeling, such a patient should ordinarily not receive treatment with a triptan unless, "...a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of CAD and ischemic myocardial disease or other significant underlying cardiovascular disease.". In this case, of course, the investigator presumably considered this patient a candidate for treatment with a triptan, perhaps because the baseline EKG was normal. In any event, although we know that treatment with triptans can cause myocardial infarction, we believe that these events are quite rare. If the risk with Trexima was on the order of that seen with triptans, the occurrence of even a single case in a database of the size in this application would be extraordinarily unlikely. Therefore, this single occurrence (although not a case of myocardial infarction) is extremely worrisome. This is especially true in the face of the other evidence cited.

Specifically, there were four cases of severe chest pain in the Trexima group,

and none in the other treatment groups. Although the incidence is low, and it has to be acknowledged that we have no evidence that these cases represent cardiac ischemia, nonetheless the disparity in the incidence among treatment groups is also at least suggestive of a different process in the Trexima group compared to the other treatments. Again, if these cases (or even one of them) represented ischemia, this would be quite worrisome, given that we would not expect even a single case of ischemia in a database this size with sumatriptan alone. The dog findings, although perhaps not definitive, are also highly suggestive of an increase in coronary vasoconstriction with the combination compared to sumatriptan alone.

Finally, as noted above, we have no adequate information about the effects on blood pressure of this combination, given that no blood pressure measurements were appropriately timed to dosing. Although, if approved, we expect that few patients would take this treatment every day (when the risks both of the occurrence and sequelae of hypertension would be expected to be greatest), nonetheless many patients may take the treatment somewhat frequently, and, in any event, we do not know the effects on blood pressure even if the treatment were to be taken intermittently.

These findings, taken together, raise important questions about the safety of this combination that, in my view, need to be resolved before the application can be approved.

As Dr. Bastings suggests, the sponsor might be able to perform a cardiac angiography study comparing the vasoconstrictor effects of the combination to sumatriptan. An adequate study of this sort that demonstrated no additional constrictor effect of the naproxen would provide powerful evidence that this risk is no greater with the combination than with sumatriptan itself. Alternatively, the sponsor could expose a large cohort to the combination and sumatriptan (probably several thousand patients on each treatment for 6 months or so) with the hope that there was no increase in the incidence of events of interest (for example, EKG changes, severe chest pain, etc.) in the group treated with the combination. The exact design of either of these studies, or alternative approaches, should be discussed with the sponsor.

Finally, the sponsor must obtain adequate blood pressure data, appropriately timed to dosing. Whether a relatively short term study can adequately document the effects of the combination on blood pressure, or whether this should be done in the sort of clinical trial described in the above paragraph should also be discussed with the sponsor.

In addition, the pharmacology and DMETS comments will be conveyed to the sponsor.

For the reasons cited above, then, I will issue the attached Approvable letter with appended draft labeling.

Russell Katz, M.D.

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/s/

Russell Katz
6/9/2006 04:29:11 PM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Date:	June 1, 2006
From:	Eric Bastings, MD.
To:	Russell Katz, MD
Subject:	21-926 Trexima

NDA 21-926 received on August 5, 2005 contains information to support the marketing of Trexima (sumatriptan succinate/naproxen sodium) for the acute treatment of migraine with and without an aura in adults. I will the tradename "Trexima" throughout my memo. However, as discussed below, this tradename is not recommended by DMETS, and the sponsor will be asked to propose an alternate name proposal.

For this application, Dr. Chhagan Tele provided the chemistry review. Dr. Dave Hawyer provided the Pharm/Tox review. Dr. Sally Yasuda provided the OCPB review. Sherbet Samuels, R.N., M.P.H. provided the DSI review. Dr. Ron Farkas provided the clinical review. Dr. Kun He provided the biostatistics review. Jeanine Best provided a review of the patient information section of labeling. Dr. Laura Pincock reviewed the proprietary name.

In this memo, I describe each component of the application below, along with the relevant conclusions from the respective reviewer.

CHEMISTRY:

Dr. Tele recommends approval from a CMC standpoint, with no phase 4 commitment.

Dr. Tele notes that Trexima tablets are [redacted] immediate release, film coated tablets and are intended for oral administration. Each [redacted] tablet contains 85 mg sumatriptan (as 119 mg sumatriptan succinate) and 500 mg naproxen sodium. Dr. Tele notes that this combination product is based on approved drug substances. Sumatriptan succinate is currently approved for use in GlaxoSmithKline's marketed products Imitrex Injection and Imitrex Tablets, and is provided by cross-reference to the parent NDA (Imitrex Injection NDA 20-080). Naproxen sodium is a USP material and is currently approved for use in various proprietary (Anaprox Tablets, Roche NDA 18-164) and over the counter medication (Aleve). Naproxen sodium is manufactured and supplied by [redacted] [redacted] according (DMF cross-referenced). Dr. Tele found no issues with the drug substance sumatriptan succinate and naproxen sodium.

Dr. Tele observes that conventional pharmaceutical excipients at typical levels are used in Trexima Tablets. The excipient selection was directed by the composition of Imitrex tablets and Anaprox DS (naproxen sodium 550 mg) tablets. Each tablet also contains the inactive ingredients croscarmellose sodium, dextrose monohydrate, dibasic calcium phosphate, FD&C Blue No. 2, lecithin, magnesium stearate, maltodextrin, microcrystalline cellulose, povidone, sodium bicarbonate, sodium carboxy-methylcellulose, talc, and titanium dioxide. Dr. Tele notes that [redacted] is the only non-compendial excipient used in Trexima tablets formulation.

Dr. Tele notes that batch analysis data were provided for three definitive NDA stability batches of Trexima Tablets [redacted] Dr. Tele notes that each of the batches was manufactured according to the proposed commercial process at the proposed commercial site of tablet manufacture and tested by the proposed commercial methods. Dr. Tele adds that validated analytical methods were provided in the submission.

Dr. Tele states that six months of primary stability data are presented for three batches of Trexima tablets identical to those proposed for marketing and packed in the proposed commercial pack. Accelerated and long-term stability studies demonstrate, according to Dr. Tele, an excellent chemical and physical stability of Trexima Tablets when stored for up to 6 months at 25° C/60% Relative Humidity (RH), and for up to 6 months at 40° C/75% RH. Eighteen months of supportive stability data were also presented for one batch of Trexima Tablets manufactured on a laboratory-scale, with no significant changes noted. Also, no significant changes were observed after short-term storage under the stress condition of exposure to light.

Dr. Tele notes that Trexima will be marketed into [redacted] with desiccant disk [redacted] Dr. Tele notes that the storage conditions for the drug product were recommended as "Store at 25° C (77° F); excursions permitted to 15-30° C (59-86° F) [see USP Controlled Room Temperature]. [redacted]

Finally, Dr. Tele observes that Pozen made the usual post-approval stability commitments with regards to stability studies indicating that the first three production batches and each container/closure system will continue according to the approved stability protocols through the expiration dating period. Dr Tele agrees that this application qualifies for categorical exclusion from environmental assessment under the provisions in 21 CFR § 25.31(a).

PHARMACOLOGY AND TOXICOLOGY

Dr. Freed recommends further genotoxicity testing before the drug can be approved. Please refer to her memo for further details.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

Dr. Yasuda recommends approval on an OCPB standpoint, with no phase 4 commitment.

Dr Yasuda notes that the formulation of sumatriptan contains sodium bicarbonate (referred to by the Sponsor as RT technology) that is the same technology used in the 25, 50, and 100 mg Imitrex tablets that are currently marketed, although not the same technology as in the Imitrex tablets available during the development program and to which the PK has been compared. However, since the RT sumatriptan replaced the non-RT formulation, it is expected that these have equivalent in vivo performance. Naproxen is currently available in comparable strengths of immediate release tablets as naproxen 500 mg and naproxen sodium 550 mg (Anaprox DS).

For the comparison of Trexima to the reference listed products (Imitrex 100 mg non-RT and Anaprox 550mg), Dr. Yasuda notes that for Cmax, neither naproxen nor sumatriptan fell within the BE limit of 80-125% when given as Trexima compared to the reference listed products (non-RT Imitrex or Anaprox 550 mg). Cmax values for sumatriptan were approximately 20% higher from Trexima than from Imitrex (90% CI 0.94-1.31). Cmax values for naproxen were approximately 36% lower from Trexima than from Anaprox 550 mg (90% CI 0.67-0.79). In addition, the median tmax for naproxen was delayed after administration of Trexima relative to Anaprox (approximately 6 hr vs 1 hr). The median tmax for sumatriptan was approximately 1-1.5 hr. For AUC the BE criteria were met for both sumatriptan and naproxen.

For the comparison of Trexima to its components (Sumatriptan 85mg RT and naproxen 500mg), Cmax for sumatriptan was approximately 17% greater (90% CI 1.02-1.34) from Trexima than from the individual sumatriptan 85 mg (RT) tablet (Study MT 400-102). The Cmax for naproxen from Trexima was 26% lower (90% CI 0.67-0.79) than from naproxen given alone (Study MT 400-101). There were no differences in AUCs.

Dr. Yasuda noted that pharmacokinetics were similar during or outside a migraine attack for Cmax and AUC, but Tmax was slightly earlier during a migraine (1.5h versus 2h). The only food effect that Dr. Yasuda noted is a 36 minutes delay in sumatriptan Tmax.

Dr. Yasuda found the sponsor's proposed dissolution methods and specifications acceptable, as follows:

Apparatus: USP Apparatus 1 (Basket)
Medium: USP Phosphate Buffer pH 6.8
Volume: 900 ml
Rotation Speed: 75 rpm
Specification:
Sumatriptan: 15 minutes: Q= [redacted]
Naproxen sodium: 30 minutes: Q= [redacted]

DIVISION OF SCIENTIFIC INVESTIGATIONS

Sherbet Samuels, R.N., M.P.H. conducted the DSI review. Two sites with high percentage of treatment responders, based on the primary efficacy measure, covering the two pivotal studies were inspected. For Study 301, Dr. Norman Garrrison's site, which enrolled 41 subjects, was inspected. For Study 302, Dr. Timothy Powell's site, which enrolled 26 subjects, was inspected. DSI found that data from both sites acceptable.

CLINICAL AND BIOSTATISTICS

I will first discuss the efficacy findings in these trials, and then discuss safety and dosing issues.

Efficacy

In order to be found effective, Trexima had to be meet two conditions:

1. To fulfill the combination policy requirement, Trexima had to be superior to its components on sustained pain-free (defined as no pain at 2 hours and no relapse of pain and no use of rescue medication during the 24-hour period after dosing)
2. To show efficacy as an acute migraine treatment, Trexima had to be superior to placebo on two hours post-dose pain relief (no or mild pain), and the incidence of photophobia, phonophobia, and nausea at 2 hours.

Dr. He concludes that Trexima was statistically significantly superior to placebo for 2-hour pain relief, 2-hour photophobia-free and 2-hour phonophobia-free, and that Trexima was statistically significantly superior to placebo for 2-hour nausea-free in Study 302. Dr. He also confirmed that Trexima was statistically significantly superior to the components for sustained pain free.

Pozen conducted two identical randomized, double-blind, parallel-group, placebo and active controlled single attack studies in patients with moderate or severe migraine headache. Both studies compared a single Trexima tablet with placebo for relief of migraine pain and associated symptoms at 2 hours and compared Trexima to the individual active components (85 mg sumatriptan RT and 500 mg naproxen sodium) for sustained pain relief through 24 hours. Each study enrolled approximately 1600 patients to each of the four treatment groups in a 1:1:1:1 ratio at approximately 60 centers in the United States.

The primary analysis for the superiority comparisons between Trexima and placebo for pain relief, photophobia and phonophobia was a Cochran-Mantel-Haenszel (CMH) test with two outcome categories and with pooled investigator sites as strata. The primary analysis for the superiority comparison between Trexima and placebo for incidence of nausea was a CMH test with two outcome categories and with pooled investigator sites as strata for Study 301, and a logistic regression with the baseline symptom and pooled investigator sites as covariates for Study 302. In the Statistical Analysis Plan dated March 21, 2005, the protocol stated that "if any of the baseline symptoms (i.e. pain, nausea, photophobia and phonophobia) suggest a treatment imbalance, as evidenced by a p-value

of <0.15 for overall treatment differences, then the primary analysis (Trexima versus placebo at 2 hours) for that symptom will be adjusted for baseline. Logistic Regression, with the baseline symptom and pooled investigator sites as covariates, will be done instead of the Cochran-Mantel-Haenszel test." Pozen provided documents to indicate that the database was locked on March 29, 2005 and the study unblinded to treatment assignments on March 30, 2005. Therefore, the change was done prospectively, according to Pozen. [redacted]

For both Studies, the primary analysis for the superiority comparison (sustained pain-free) between Trexima and its individual components used a CMH test with two outcome categories and with pooled investigator sites as strata.

Table 1 and Table 2 summarize the key analyses comparing Trexima to its components. Trexima clearly met the combination policy requirements by showing a contribution of each component to the rate of sustained pain-free outcome.

Table 1: Sustained pain-free comparison in Study 301 (Trexima versus components)

	Trexima N = 362	**Sumatriptan** N = 362	**Naproxen Sodium** N = 364	**Placebo** N = 382
Sustained Pain-Free – n (%)	83 (23)	51 (14)	37 (10)	25 (7)
p-value vs. Trexima	-	<0.001	<0.001	<0.001

Table 2: Sustained pain-free comparison in Study 302 (Trexima versus components)

	Trexima N = 364	**Sumatriptan** N = 361	**Naproxen Sodium** N = 356	**Placebo** N = 360
Sustained Pain-Free – n (%)	90 (25)	59 (16)	37 (10)	30 (8)
p-value vs. Trexima	-	0.009	<0.001	<0.001

Table 3 and Table 4 summarize the key analyses comparing Trexima to placebo. Trexima was clearly superior to placebo for all measures of pain relief, and rate of photophobia-free and phonophobia-free at 2 hours. However, the rate of nausea-free at 2 hours was not significantly better for Trexima than for placebo in Study 301, using the prospective CMH test stratified by pooled sites. That comparison was significantly in favor of Trexima in Study 302, using a logistic regression adjusted for baseline (see above for discussion on the difference of analysis method in the two studies).

Table 3: Primary efficacy analyses at 2 hours in Study 301 (Trexima versus placebo)

	Trexima N = 362	Placebo N = 382	p-Value
Pain Relief – n (%)	207 (57)	109 (29)	<0.001
Photophobia-free – n (%)	180 (50)	122 (32)	<0.001
Phonophobia-free – n (%)	204 (56)	128 (34)	<0.001
Nausea-free – n (%)	237 (65)	244 (64)	0.711

Table 4: Primary efficacy analyses at 2 hours in Study 302 (Trexima versus placebo)

	Trexima	Placebo	p-Value
	N = 364	N = 360	
Pain Relief – n (%)	237 (65)	102 (28)	<. 001
Photophobia-Free – n (%)	211 (58)	131 (36)	<. 001
Phonophobia-Free – n (%)	223 (61)	138 (38)	<. 001
Nausea-Free[1] – n (%)	260 (71)	233 (65)	0.007

[1] analysis adjusted for baseline nausea

Dr. He notes that an imbalance in incidence of nausea at baseline between Trexima and placebo was observed in Study 301 (56% in the Trexima group versus 49% in the placebo group), and that may have affected the results at 2-hours post-dose. Numerically, subjects treated with Trexima had a higher nausea-free rate at 2, 3 and 4 hours compared to placebo in Study 301. Also, using the prospective analysis, the comparison of nausea-free was significant at 4 hours (73% for Trexima versus 56% for placebo, p<0.001). Nausea-free rates were also very similar at 3 hours (72% versus 57%), but the p value was not calculated, because this was not a prospective comparison. It is possible that this difference was statistically significant.

Also, the difference of nausea free rate between 2 hours post-dose and baseline for Trexima was similar in both studies (21% in Study 301 and 19% in Study 302). The rate of nausea-free at 2 hours for Trexima was similar to that of sumatriptan in Study 301 (65% vs. 64%), and numerically higher than that of sumatriptan in Study 302 (71% vs. 66%). The rate of sustained nausea-free was also significantly higher for Trexima than for placebo in both studies. Overall, I believe that the requirements of the combination policy have been met, and that substantial evidence of efficacy has been provided.

Safety

Dr. Farkas has two concerns regarding the cardiovascular safety of Trexima.

1. Blood pressure

Dr. Farkas notes that Trexima contains sumatriptan and naproxen, both of which are known from previous studies to increase blood pressure. He emphasizes that the fact that both sumatriptan and naproxen are FDA approved individually is not, of itself, sufficient evidence that the drugs are equally safe when used in combination. I agree. Dr. Farkas also notes that a nonclinical (dog) study conducted by Pozen suggest that sumatriptan and naproxen might increase blood pressure in an additive fashion, although the study is essentially uninterpretable.

Dr. Farkas believes that to assess the cardiovascular safety of Trexima, blood pressure data should be presented in an adequate number of patients from two settings: 1) after a single Trexima dose, and 2) after long term, multiple dose exposure, reflective of clinical use. Dr. Farkas observes that throughout the clinical development program of Trexima, blood pressure and other vital signs were not monitored in either of these settings.

2. Cardiac risk

Dr. Farkas notes that sumatriptan alone induces some degree of coronary vasoconstriction in humans. Very rare but potentially very serious (including reports of death) adverse events have been reported with triptans, and with sumatriptan in particular. Dr. Farkas notes wisely that decreased myocardial oxygen supply from coronary vasoconstrictive coexistent with increased myocardial oxygen demand from increased blood pressure would be a potentially serious safety risk.

Dr. Farkas mentions an additional concern about coronary vasoconstriction from published reports that prostaglandins might regulate coronary blood flow, and that NSAIDs might have a coronary vasoconstrictor effect. He believes that even a small increase of vasoconstriction caused by the combination of sumatriptan and naproxen could be clinically significant, and result in an increase of rare but serious cardiovascular adverse events. He also emphasizes that sumatriptan levels from Trexima are at the high end of approved dosing for Imitrex, suggesting that any additive cardiovascular risk from the combination of sumatriptan and naproxen would increase the risk of Trexima above that of Imitrex.

Dr. Farkas also notes that the cardiovascular safety of Trexima must be reviewed in the context of recent data suggesting that NSAIDs as a class might pose greater cardiovascular risk than previously appreciated, and of the boxed warning of cardiovascular safety risk is currently in the label of all NSAIDs.

In the absence of specific ECG and vital signs monitoring in Trexima acute and long-term study, the only available information comes from the analysis of adverse events reported in Trexima clinical studies, with the caveat however that the serious cardiac adverse events with triptans are know to be very rare, and that even a multi-fold increase in the risk would not be expected to be captured in a typical NDA database. In that context, significant cardiac adverse events were not expected in the Trexima database. However, in the (uncontrolled) long-term safety study, there was two cases of 'acute coronary syndrome', including one in close temporal relationship to dosing with Trexima in a 47 year old woman (study MT400-303, subject 2143). This adverse event was

reported as probably related to Trexima by the study investigator. I refer to Dr. Farkas'es review for a narrative of the event. Briefly, this 47 year-old premenopausal female, who had a normal physical examination and electrocardiogram at screening, developed chest discomfort and some shortness of breath approximately two hours after taking Trexima. She presented to the emergency department and was given nitroglycerin, which provided some relief. An electrocardiogram showed ST-T wave changes in the lateral precordium. Troponin and CK levels were normal in the emergency room. A cardiac catheterization, showed a moderate dilation of the left ventricle with moderate mitral regurgitation, severe hypokinesis of the antero-apical wall of the left ventricle and a calculated ejection fraction of 27 percent. The left anterior descending coronary artery had a concentric discrete 70% narrowing of the ostium as it arose from the left main coronary artery. There was a post-stenotic filling defect suggestive of a thrombus. The subject underwent coronary artery bypass grafting surgery. The fact that the patient had undiagnosed coronary artery disease does not exonerate the drug, because the patient otherwise did not have any contraindication to Trexima or sumatriptan, and is representative of the patient population to whom the drug may be prescribed. This finding is obviously worrisome, since it is compatible with a true rate of acute coronary syndrome up to 0.52 % (0.18%, 95% CI up to 0.52%).

The second case of acute coronary syndrome in the long-term safety study was less worrisome, because symptoms onset was almost 48 hours post-dose, and work-up was negative for cardiac ischemia. Patient was however noted to have a blood pressure of 182/95 in the ER, when her screening blood pressure was 110/82. This elevation of blood pressure is difficult to interpret in the context of an uncontrolled study, but it is suggestive of a possible elevation of blood pressure with chronic use of Trexima.

Dr. Farkas also looked at other possible safety signals suggesting an increased cardiovascular risk of Trexima compared to sumatriptan. He notes that in pivotal controlled trials (with 737 subjects on Trexima), there were four severe adverse events of chest pain with Trexima, while the sumatriptan and naproxen groups had none. The overall rate of chest discomfort (all intensities) was however slightly higher for Trexima than for sumatriptan in the single dose pivotal studies (1.8% vs. 1.4%). There is a general belief that most chest symptoms caused by triptans are not cardiac in nature. However, the imbalance in the cases of severe chest symptoms adds to the concerns created by the non clinical findings in the dog study and the case of acute coronary syndrome. Also, Pozen's argument that the risk of cardiovascular adverse events appears similar between Trexima and sumatriptan in the Trexima database is not compelling, because the database was too small to detect a difference (which makes the finding of one case of acute coronary syndrome more worrisome).

Dr. Farkas recommends that two additional studies be conducted before approval of Trexima: a multiple-dose, controlled trial to examine the effect of Trexima on blood pressure and cardiovascular adverse events over a period of at least 6 months, and safety assessments, including blood pressure, during the pharmacokinetic time course of a single Trexima dose. He also recommends that nonclinical studies should examine

possible additive effects of sumatriptan and naproxen on blood pressure and arterial vasoconstriction.

Dosing issues

Dr. Farkas notes that no dose-finding studies were conducted for Trexima, and that a phase 2 trial suggests that a lower dose of sumatriptan (50 mg) in combination with naproxen might have similar efficacy to the higher dose (85 mg) ultimately selected by the sponsor for development. Given the cardiovascular risk of Trexima, Dr. Farkas recommends that Trexima, if approved, should be used only by patients not experiencing adequate relief with lower sumatriptan doses, either alone or in combination with naproxen. I note however that Trexima has not been tested in that population. Also, based on anecdotal discussions with migraine experts, there appears to be a common practice to start migraine patients at the 100mg dose.

I recommend that the dosage and administration section includes language that Trexima contains a dose of sumatriptan higher than the lowest dose [redacted] approved, and that ordinarily the choice of the sumatriptan dose should be made on an individual basis, weighing the possible benefit of a higher dose with the potential for a greater risk of adverse events. [redacted]

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. However, in the absence of demonstration of efficacy of a second dose, and especially given the uncertainty related to the safety of the combination [redacted]

DIVISION OF SURVEILLANCE, RESEARCH, AND COMMUNICATION SUPPORT

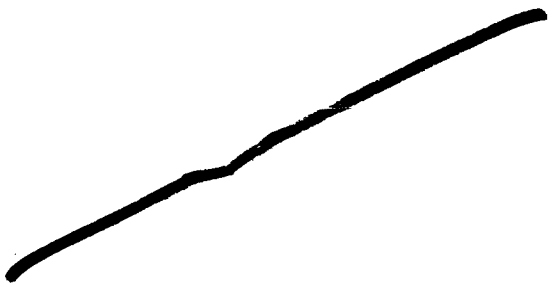
Jeanine Best notes that FDA sent supplement request letters on June 14, 2005, requiring class labeling language for all non-selective non-steroidal anti-inflammatory drugs (NSAIDs), to include a boxed warning to address possible cardiovascular risks as well as known gastrointestinal risks, revised CONTRAINDICATIONS, WARNINGS and PRECAUTIONS sections of the package insert, and a Med Guide for NSAIDS. This requirement included all prescription naproxen-containing products.

The required labeling, including the Medication Guide was approved on January 14, 2006, for the following naproxen innovator products:

- NDA 17-581 S-106 Naprosyn (naproxen tablets)
- NDA 18-164 S-056 Anaprox /Anaprox DS (naproxen sodium tablets)
- NDA 18-965 S-014 Naprosyn (naproxen suspension)
- NDA 20-067 S-011 EC Naprosyn (naproxen delayed-release tablets).

Ms. Best recommended that the sponsor should submit the required class labeling language for NSAID products including the Medication Guide. That request was forwarded to Pozen during the review cycle. Pozen objected to the request. A telecon with Pozen was held in May 2006. Pozen's argument was that their product was closer to the OTC naproxen product, for which there is no equivalent to a black box. The Agency noted at the time that the current policy was to require a black box for naproxen-containing prescription products, but that the issue would be revisited soon. It was unclear at the time if the issue could be resolved prior to the action date. As of today May 30, 2006), an Agency decision to change the current policy has not been taken, at my knowledge.

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT



RECOMMENDATION

I recommend an approvable action. The sponsor should be required to submit additional cardiovascular safety data. I am not convinced that repeating a non clinical cardiovascular safety study would provide sufficient information to address the safety risk. A major issue is that the rate of the serious adverse events we are concerned about is very small, and very difficult to be evaluated in a long-term clinical study of the typical size in migraine drug development programs.

The following data could potentially address our concerns:
1. Acute blood pressure data, in particular in subjects at higher risk (i.e. patients with controlled hypertension, and risk factors for coronary disease otherwise not contra-indicated to Imitrex), comparing Trexima to Imitrex.
2. Long-term blood pressure data in a population of subjects at higher risk (i.e. patients with controlled hypertension, and risk factors for coronary disease otherwise not contra-indicated to Imitrex). Ideally, that study should be controlled, comparing Trexima to Imitrex, and be powered to exclude a risk of uncontrolled hypertension higher than the risk with Imitrex by a reasonable margin, to be defined in further discussions with the sponsor. The study should also exclude an increased risk of serious cardiovascular events, and be powered to exclude a risk increase compared to sumatriptan higher than a margin to be discussed with Pozen. Because the rate of coronary events is thought to be very small, it would be very difficult to adequately assess if the risk of coronary events with Trexima is increased compared to sumatriptan (the study would have to be exceedingly large), but that study would cap the risk to a level in itself not necessarily acceptable, but to be interpreted in concert with the coronary study described below.
3. A clinical study comparing the vasoconstrictive effect of Trexima vs. Imitrex on the coronary vasculature in patients at risk, similar to studies conducted to support approval of Relpax. That study would complement the long-term safety study described under #2, and should provide a basis to conclude that Trexima is not associated to an increased cardiovascular risk, compared to sumatriptan.

Finally, the sponsor requested a waiver from pediatric studies. I believe that a partial waiver should be granted for patients age 1-11, but that pediatric studies in patients age 12-17 [redacted] There is no migraine drug currently approved for the pediatric population, and this drug combination could represent a meaningful therapeutic benefit. Unless there is strong evidence that this drug combination would be unsafe in the pediatric population, a pediatric development program should be required.

Eric P. Bastings, M.D.
Team leader, Neurology

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HFD-120

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/s/

Eric Bastings
6/8/2006 03:07:01 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA 21-926
Letter Date	August 5, 2005
PDUFA Goal Date	June 8, 2006
Reviewer Name	Ronald Farkas, M.D., Ph.D.
(Proposed) Trade Name	Trexima™
Applicant	Pozen Inc.
Priority Designation	S
Formulation	Sumatriptan succinate/naproxen sodium
Indication	Migraine with or without aura
Intended Population	Adults age 18 years or older

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

My clinical recommendation is that Trexima is approvable if additional evidence of cardiovascular safety can be presented. Efficacy of Trexima has been established.

A major deficiency regarding cardiovascular safety is insufficient data on blood pressure. In general, the effect of any drug on blood pressure is a necessary measure for assessing cardiovascular safety. Trexima contains sumatriptan and naproxen, both of which are known from previous studies to increase blood pressure. The fact that both sumatriptan and naproxen are FDA approved individually is not, of itself, sufficient evidence that the drugs are equally safe when used in combination, as in Trexima. To asses the cardiovascular safety of Trexima, blood pressure data should be presented in an adequate number of patients from two settings: 1) during the pharmacokinetic time course of a single Trexima dose, and 2) after long term, multiple dose exposure, reflective of clinical use. Throughout the clinical development program of Trexima, blood pressure and other vital signs were not monitored in either of these settings. The clinical information available for Trexima is so limited that the effect of Trexima on blood pressure can not be adequately addressed.

Obtaining blood pressure data for Trexima is particularly important because the drugs in combination might increase cardiovascular risk additively. Sumatriptan and naproxen are thought to increase blood pressure through different molecular mechanisms, suggesting that the effects of the two drugs on blood pressure could be additive. Nonclinical dog studies of Trexima provide direct evidence that sumatriptan and naproxen might indeed increase blood pressure in an additive fashion, although variability observed between dogs raises questions about study interpretability (see study MT400-T15, section 3.2, Animal Pharmacology/Toxicology).

It is important to know if, and how much, Trexima increases blood pressure. Sumatriptan alone induces some degree of coronary vasoconstriction in humans. This coronary artery vasoconstriction might underlie the rare cases of myocardial infarction related to sumatriptan. Decreased myocardial oxygen supply from coronary vasoconstrictive coexistent with increased myocardial oxygen demand from increased blood pressure would be a potentially serious safety risk.

Additional concern about coronary vasoconstriction arises from published reports that *prostaglandins* might regulate coronary blood flow, and that NSAIDs might have a coronary vasoconstrictor effect. While these reports do not specifically implicate naproxen, nonclinical dog studies conducted by Pozen at the Agency's request suggest that an adverse interaction between naproxen and sumatriptan might increase coronary and carotid artery vasoconstriction above that caused by sumatriptan alone (although, again, variability between dogs raises questions about study interpretability; see study MT400-T15, section 3.2 Animal Pharmacology/Toxicology). Even a small increase of vasoconstriction caused by the combination of sumatriptan and naproxen could be clinically significant, and result in an increase

of rare but serious cardiovascular adverse events. Importantly, sumatriptan levels from Trexima are at the high end of approved dosing for Imitrex, suggesting that any additive cardiovascular risk from the combination of sumatriptan and naproxen would increase the risk of Trexima above that of Imitrex.

The cardiovascular safety of Trexima must also be reviewed in the context of recent data suggesting that nonsteroidal anti-inflammatory agents (NSAIDs) as a class might pose greater cardiovascular risk than previously appreciated. A boxed warning of cardiovascular safety risk is currently in the label of all NSAIDs. I stress, however, that the potential cardiovascular safety risk of Trexima outlined above, and the lack of sufficient data for Trexima, can not be addressed by studies of naproxen alone.

The single-dose controlled trials of Trexima provide very little data on cardiovascular safety due to the very brief drug exposure and relatively small study population (800 subjects). The data obtained from the controlled trials, in fact, raises concerns that Trexima poses a greater cardiovascular risk than sumatriptan or naproxen alone. For example, Trexima had 4 severe adverse events of chest pain, while sumatriptan and naproxen had none. In the uncontrolled long-term safety study, several serious adverse cardiovascular event occurred, with one case of 'acute coronary syndrome' associated with severe cardiac injury in a 47 year old woman (study MT400-303, subject 2143). The incidence of such serious cardiac adverse events can not be determined from the data available.

I recommend that additional studies be conducted before approval of Trexima:

1. The effect of Trexima on blood pressure should be examined in human trials.

2. Possible additive effects of sumatriptan and naproxen on arterial vasoconstriction should be clarified.

3. Depending on the results of the above, additional human safety studies might be necessary to characterize cardiac risk.

Additional Safety Concerns: Dose Selection

No dose-finding studies were conducted for Trexima. However, a phase 2 trial suggests that a lower dose of sumatriptan (50 mg) in combination with naproxen might have similar efficacy to the higher dose (85 mg) ultimately selected by the sponsor for development (see Section 8.1, *Dosing Regimen and Administration*). Sumatriptan adverse effects are dose-related in this range. Given the cardiovascular risk of Trexima, I find that Trexima, if approved, should be used only by patients not experiencing adequate relief with lower sumatriptan doses, either alone or in combination with naproxen.

1.2 Recommendation on Postmarketing Actions

Pozen has submitted a formal request for a waiver to conduct pediatric studies, stating that pediatric studies are not warranted because:

- Previous studies of sumatriptan and other triptans have failed to demonstrate clear benefit in the pediatric population.
- In children, migraine attacks tend to be shorter duration, with less recurrence, such that the addition of naproxen, with its long half life, would be of no benefit.

I find that Trexima could represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is likely to be used in a substantial number of pediatric patients. While triptans have failed to demonstrate clear benefit in the pediatric population, the combination of drugs in Trexima might be of benefit. No existing evidence strongly suggests that Trexima would be ineffective or unsafe in all pediatric age groups. Trexima should be developed as an appropriate formulation(s) for pediatric patients, to allow individualization of dosing.

1.2.1 Risk Management Activity

None recommended.

1.2.2 Required Phase 4 Commitments

None recommended.

1.2.3 Other Phase 4 Requests

Trexima will be available as a single fixed dose combination. A phase 2 study suggested that 50mg sumatriptan, instead of the 85mg ultimately selected, might have similar efficacy in combination with naproxen. Previous studies of sumatriptan have shown that lower doses are associated with fewer adverse events. A significant number of patients who would respond to lower doses of sumatriptan in combination with naproxen will instead likely use Trexima, and as a result suffer adverse events that would not have occurred with lower drug doses. A lower-dose combination should therefore be developed to increase patient safety (The issue of appropriateness of Trexima dose is discussed further in Section 1.3.3, Safety; and in section 8.1, Dosing Regimen and Administration).

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

[overview adapted from Dr. Kevin Prohaska]
Migraine is a common disorder characterized by intermittent attacks of moderate- to severe, pulsating, unilateral head pain, often associated with nausea, photophobia, and phonophobia. An 'aura' (e.g. vision changes) precedes other symptoms in ≈10 to 20% of migraineurs. Each attack generally lasts from 4 to 72 hours. Migraine prevalence is between 3 to 8% of all men and 11 to 18% of all women. In general, migraine is most common in women of reproductive age. Approximately one-third of migraine attacks are disabling enough to require bed rest.

Drugs approved for acute migraine treatment include over-the-counter (OTC) analgesics, 5-hydroxytryptamine-1 ($5HT_1$) agonists, and ergot alkaloids. In the past decade, the $5HT_1$ agonists, called 'triptans,' have become a mainstay of therapy, and most clinicians believe that triptans are more effective than other migraine products. A major limitation triptans, including sumatriptan, is early efficacy followed by migraine recurrence in 25-78% of those treated. The reasons for recurrence are not known. Concomitant therapy with a triptan and NSAID might provide equal, or even greater initial efficacy combined with less recurrence.

Pozen therefore developed Trexima, a combination drug consisting of a single tablet containing sumatriptan succinate (85 mg) and naproxen sodium (500 mg). This single fixed dose was the only formulation fully developed (a 'proof-of-concept' study examined sumatriptan 50 mg/ naproxen 500 mg). Trexima tablets are [redacted], immediate release, film coated tablets intended for oral administration. The combination of the two active ingredients in a single tablet is thought by Pozen to provide increased patient convenience, decreased 'pill burden,' and enhanced compliance. Trexima was studied in, and is intended for, adults 18 years of age or older. Trexima, or similar combinations of sumatriptan and naproxen, is not approved in any foreign country.

Both drug components of Trexima are approved in the United States for migraine, and in most countries world-wide (naproxen: Advil Migraine, NDA 020402; sumatriptan: Imitrex, NDA 20-132). Naproxen is also approved for the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, juvenile arthritis, pain, primary dysmenorrhea, tendonitis and bursitis, and gout (Anaprox, NDA 18-164). The Trexima application was filed under Section 505(b)(2) of the FD&C Act.

The NDA is formatted according to the International Conference on Harmonization (ICH) Common Technical Document and has been submitted electronically at:
\\CDSESUB1\N21926\N_000\2005-08-05
The 120 day safety amendment is at:
\\CDSESUB1\N21926\N_000\2005-10-27

The following amendments were filed to the NDA:

Responses to issues raised in the 74 day filing letter:
\\CDSESUB1\N21926\N_000\2005-12-08

Response to request for more information:
\\CDSESUB1\N21926\N_000\2006-01-27

CMC stability update:
\\CDSESUB1\N21926\N_000\2006-02-22

Response to questions from OCPB:
\\CDSESUB1\N21926\N_000\2006-04-07

CMC: change in packaging configuration:
\\CDSESUB1\N21926\N_000\2006-04-19

Response to questions from OCPB:
\\CDSESUB1\N21926\N_000\2006-04-28

Table 1 lists the clinical trials conducted in support of the Trexima NDA. More detailed tabular listing of studies is in section 7.2.1.1, '*Study Type and Design/Patient Enumeration*' (Table 62, Table 63, and Table 64). A single phase II study (MT400-204) examined the combination of 50 mg sumatriptan non-RT [redacted]) with 500 mg naproxen, given as separate tablets. The dose combination was then changed to 85 mg sumatriptan-RT [redacted] with 500 mg naproxen for the later phase III trials with the final Trexima tablet. All studies were single dose, except for MT400-303, an open-label, repeat dose safety study conducted over 12 months.

Table 1: Overall Clinical Development Program for Trexima

(Modified from NDA table 2.7.6.1, Listing of Clinical Studies, synopses-indiv-studies)

Study Number	Objectives	Treatments	N
Phase 1			
MT400-101	Bioavailability: Trexima and its components	Trexima sumatriptan 85mg/naproxen 500mg Sumatriptan 85mg non-RT* Naproxen 500mg Imitrex 100mg Anaprox DS 550mg	40
MT400-102	Bioavailability: Food effect	Trexima sumatriptan 85mg/naproxen 500mg Sumatriptan 85mg RT	24
MT400-103	Bioavailability: Dose combinations	Trexima sumatriptan 85mg/naproxen 500mg Sumatriptan 85 mg RT Naproxen 500 mg Sumatriptan 85 mg non-RT Imitrex 50 mg	31
MT400-104	PK: During and outside migraine	Trexima sumatriptan 85 mg/naproxen 500mg	18
MT400-105	PK: 2 doses, 2 hours apart	Trexima sumatriptan 85 mg/naproxen 500mg	24
Phase 2			
MT400-204	'Proof of concept'	MT400 Imitrex 50mg + Naproxen 500mg Naproxen/Imitrex 500 mg/50 mg Placebo tablets Placebo capsules	972
Phase 3			
MT400-301	Safety/efficacy	Trexima sumatriptan 85 mg RT/naproxen 500mg Sumatriptan 85 mg RT Naproxen 500 mg Placebo	1495
MT400-302	Safety/efficacy	Trexima sumatriptan 85 mg RT/naproxen 500mg Sumatriptan 85 mg RT Naproxen 500 mg Placebo	1462
MT400-303	Open label 12 month safety	Trexima sumatriptan 85 mg RT/naproxen 500mg	561

*During early development of Trexima, the formulation of sumatriptan used as a comparator was 'non-RT,' which has a [redacted] than 'RT' formulations used in phase III studies. It is important to consider these differences in interpreting and comparing study results.

Phase I Studies

Pharmacokinetic studies of Trexima examined:

- Absorption of sumatriptan and naproxen in Trexima, compared to absorption of each component administered individually, and to commercially available Imitrex and Anaprox tablets.
- Effect of food on absorption.
- Effect on PK of dosing during a migraine.
- PK of two tablets of Trexima dosed 2 hours apart.

Phase II Studies
A single 'proof-of-concept' study (MT400-204) compared the efficacy of co-administered naproxen (500 mg) plus over-encapsulated Imitrex (50 mg, non-RT) versus a single dose of naproxen (500 mg) alone, over-encapsulated Imitrex (50 mg non-RT) alone, or placebo.

Phase III Studies
Two identical Phase III efficacy studies were conducted. Both were randomized, double-blind, parallel-group, placebocontrolled single attack studies in adult patients with moderate or severe migraine headache. Both studies compared a single Trexima tablet (85 mg sumatriptan RT and 500 mg naproxen sodium) with placebo for relief of migraine pain and associated symptoms at 2 hours, and compared Trexima to the individual active components for 'sustained pain-free through 24 hours.' Each study enrolled approximately 1600 patients to each of the four treatment groups in a 1:1:1:1 ratio, at approximately 60 centers in the United States.

Overall Safety Database
In nine clinical studies 1,441 subjects were exposed to Trexima. Including the multiple-dose open-label safety study (MT400-303) about 24,000 individual exposures to Trexima occurred. The phase II study exposed an additional 251 subjects to a combination of sumatriptan 50 mg (non-RT; a lower amount than in Trexima) and naproxen 500 mg in individual tablets.

Subjects were to treat an average of at least two migraine attacks per month for up to twelve months in the safety study. About 500 patients were enrolled at 40 centers in the U.S. Patients in the safety study were permitted to take a second dose of study medication, if needed, to treat the same migraine attack after waiting at least 2 hours after the first dose. No more than 2 Trexima tablets were allowed in any 24-hour period.

The initial NDA submission contained data from about 400 patients treated for at least 6 months in study MT400-303. Data for 12 months of treatment was presented in the 120-day safety update.

[redacted]

1.3.2 Efficacy

Overall Conclusion

- Trexima was shown to be superior to its components at the time point of 'sustained pain free 2-24 hours*' thereby fulfilling the combination drug rule for marketing approval.

* 'Sustained pain free 2-24 hours' was defined as no pain at 2 hours after dosing, with no recurrence of pain through 24 hours after dosing.

- To fulfill the combination drug rule, Trexima was compared to an 'equal oral milligram' amount of its components, sumatriptan and naproxen. Trexima resulted in a higher C_{max} (17% higher) for sumatriptan than the comparator sumatriptan tablet, with a similar AUC. The cause of this pharmacokinetic difference is not known, but might have occurred due an interaction between naproxen and sumatriptan, from formulation differences in the Trexima tablet, or some combination of these and other factors. It is my clinical opinion that the higher C_{max} for sumatriptan in Trexima is small enough that it does not significantly confound the primary efficacy findings of Trexima versus its constituents.

Trexima claims efficacy as a combination product of sumatriptan and naproxen. Efficacy data was provided by two multicenter, randomized, controlled, U.S. studies (MT400-301 and MT400-302) in acute, moderate to severe migraine. Per CFR § 300.50, in order to claim efficacy as a combination product, Trexima was required to be statistically superior to each component alone. This was demonstrated for the endpoint of 'sustained pain free 2-24 hours': patients taking Trexima who were pain free at 2 hours had a ≈25% chance of being pain free through 24 hours, while for sumatriptan (85 mg RT), Naproxen (500 mg), and placebo, this chance was statistically significantly lower, respectively ≈15%, ≈10%, and ≈8%. The Division also expected at least equivalence of Trexima versus its components for the key symptoms of pain, nausea, photo- and phonophobia at *2 hours*, the standard point at which migraine treatments are usually evaluated for efficacy. This was to rule out a "pathological" outcome, i.e. that the combination was *worse* than its components at 2 hours. Trexima fulfilled these 2 hour outcomes, showing statistical or numerical (nausea in study 301) superiority for the standard migraine symptoms.

Secondary endpoints
There were 10 secondary endpoints, analyzed as ordered below by a hierarchical stepdown procedure to control for multiplicity. Once a test exceeded $p = 0.05$, subsequent endpoints were not considered to be significant.

1) Pain-free at 2 hours for Trexima vs. placebo [achieved]
2) Sustained pain relief for Trexima vs. placebo [achieved]
3) Sustained pain relief for Trexima vs. sumatriptan [achieved]

4) Sustained symptom-free (photophobia-free, phonophobia-free, or nausea-free) for Trexima vs. sumatriptan [this was not achieved statistically. I consider endpoints that follow to be 'not significant']
5) Use of rescue medication for Trexima vs. sumatriptan
6) Time to rescue for Trexima vs. sumatriptan
7) Pain-relief at 4 hours for Trexima vs. sumatriptan
8) Symptom-free (photophobia-free, phonophobia-free, or nausea-free) at 4 hours for Trexima vs. sumatriptan
9) Pain relief at 2 hours Trexima vs. sumatriptan
10) Symptom-free (photophobia-free, phonophobia-free, or nausea-free) at 2 hours for Trexima vs. sumatriptan

Summary of Major Efficacy Outcomes

2 hour endpoints

Pain (Table 27)
- Trexima was superior to placebo, naproxen, and sumatriptan, in two studies.

- **Nausea:** (Table 29, Figure 5, Figure 6)
  - Trexima was *not* statistically superior to placebo in study 301, but it was numerically superior; it was statistically superior in study 302
  - Trexima was statistically superior to placebo in both study 301 and 302 at 4 hours
  - Trexima was *not* statistically superior to sumatriptan at 2 hours, in either study
  - Trexima was approximately as efficacious as sumatriptan and naproxen at 2 hours
- **Photophobia**: (Table 30 and Table 31,)
  - Trexima was statistically superior to placebo in both study 301 and 302.
  - Trexima was statistically superior to sumatriptan in only study 302.
- **Phonophobia:** (Table 32 and Table 33)
  - Trexima was statistically superior to placebo for phonophobia in both study 301 and 302
  - Trexima was statistically superior to sumatriptan only in study 302.

24 hour endpoints
- **'Sustained pain-free, 2-24 hours'** (Table 34)
  - Trexima was statistically superior, in a clinically meaningful difference, to its components [Thereby satisfying the combination drug]
- **Nausea, Photophobia, Phonophobia** (Table 35; Table 36)
  - Trexima was statistically superior to placebo, both in studies 301 and 302
  - Trexima was *not* statistically superior to sumatriptan for associated symptoms in 2 studies, solely due to miss in nausea in study 301 (Trexima was, though, numerically superior)
  - Trexima was superior to naproxen for associated symptoms in both studies

Secondary endpoints
By the hierarchical stepdown procedure used for secondary endpoints, only endpoints 1-3 achieved statistical significance. Endpoint 4 (Sustained symptom-free [photophobia-free, phonophobia-free, or nausea-free] for Trexima vs. sumatriptan), failed at showing the nausea-free component.

Of the three statistically significant secondary outcomes, the third was addressed by the Division in pre-filling correspondence, and found to be so closely related to the primary outcome that it would not qualify as an independent secondary outcome. I also consider secondary outcome #1 to be a component of the primary outcome variable.

As discussed in more detail in Section 6, *Integrated Review of Efficacy*, I believe that to best communicate the efficacy of Trexima to patients, data describing the time course of use of rescue medication should be allowed to remain in labeling, despite the fact that it was not specified as a secondary outcome variable.

1.3.3 Safety

Overall Conclusion (see also discussion in Section 1.1 and section 7.3, *Summary of Selected Drug-Related Adverse Events*)

- For the majority of patients, Trexima was generally well-tolerated.
- The cardiovascular safety of Trexima was not adequately demonstrated.
- Only a single dose combination was developed for Trexima, containing 85 mg sumatriptan RT and 500 mg naproxen. Data submitted by Pozen (study MT400-204) suggest that a lower dose of sumatriptan in combination with naproxen may provide similar efficacy to Trexima (see Section 8.1, Dosing Regimen and Administration), with theoretically fewer adverse effects due to the lower sumatriptan exposure.

Cardiovascular Risk of Naproxen (see also section 1.1)
Recent data suggests that NSAIDs as a class, including possibly naproxen, could have previously unappreciated cardiovascular risk. Unlike for COX-2 selective agents, the cardiovascular risk from naproxen is not well-defined. A position of caution has been adopted by the FDA, as reflected by the following statement, released 12/20/04:

> *The Food and Drug Administration (FDA) is working with the National Institutes of Health to review the available scientific information on naproxen following the decision of the National Institute on Aging to halt a clinical trial studying non-steroidal anti-inflammatory drugs in patients at risk of developing Alzheimer's disease. Preliminary information from the study showed some evidence of increased risk of cardiovascular events, when compared to placebo, to patients taking naproxen.*
>
> *In the meantime, FDA advises patients who are currently taking over-the-counter naproxen products to carefully follow the instructions on the label. Patients should not exceed the recommended doses for naproxen (220 milligrams twice daily) and should not take naproxen for longer than ten days unless a physician directs otherwise. Patients with questions about naproxen should consult their physicians.*

In addition, FDA announced on April 7, 2005 that manufacturers of all prescription nonsteroidal anti-inflammatory drugs (NSAIDs), including naproxen, revise drug labeling to include a "boxed" warning about potential increased risk of cardiovascular events, including heart attack and stroke (and of serious and potentially life-threatening gastrointestinal (GI) bleeding associated with their use):

> *Based on a review of available data from long-term placebo- and active-controlled clinical trials of non-steroidal anti-inflammatory drugs (NSAIDs), FDA has concluded that an increased risk of serious adverse cardiovascular (CV) events may be a class effect for NSAIDs (excluding aspirin). FDA has requested that the package insert for all NSAIDs be revised to include a boxed warning*

to highlight the potential increased risk of CV events and the well described risk of serious, and potentially life-threatening, GI bleeding. FDA has also requested that the package insert for all NSAIDs include a contraindication for use in patients immediately post-operative from coronary artery bypass graft (CABG) surgery.

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 Committee specifically addressed the possibility that naproxen posed less cardiovascular risk than other NSAIDs, but found, in my interpretation, that data was not strong enough to justify a difference in labeling (see Section 8.5, *Advisory Committee Meeting*)

1.3.4 Dosing Regimen and Administration

The recommended dose of Trexima is 1 tablet. Efficacy of a second dose was not evaluated. In the long-term safety study (MT400-303) Trexima was generally well-tolerated when a second tablet was administered at least 2 hours after the initial dose.

Current Imitrex labeling limits intake to not more than 200 mg/24 hours, such that 2 doses of Trexima/24 hours falls within this range.

The initial recommended dosing for chronic treatment with naproxen is about 500 mg, with a total daily chronic dose that generally should not exceed 1100 mg. Under some conditions (arthritides), up to 1500 mg/day is indicated for up to 6 months. The dose of naproxen in Trexima is within this dose recommendation.

1.3.5 Drug-Drug Interactions

No formal drug interaction studies were conducted with Trexima because such interactions were not expected to be different from those described for its individual components, sumatriptan and naproxen.

Prescribing information for Trexima will include those interactions currently listed in the individual component prescribing information, with a few additions, as described in Section 8.2, *Drug-Drug Interactions.*

1.3.6 Special Populations

Although data is limited, no important differences were found in safety or efficacy based on gender, age, or race. Trexima should be used with caution in renal and hepatic insufficiency (See Sections 7.2.3, *Adequacy of Overall Clinical Experience*, and 8.3, *Special Population.*).

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Trexima contain sumatriptan succinate, a selective 5-hydroxytryptamine$_1$ ($5HT_1$) receptor agonist, and naproxen sodium, a member of the arylacetic acid group of NSAIDs. Trexima is intended for the acute treatment of migraine, with and without aura, in adults 18 years of age or older.

2.2 Currently Available Treatment for Indications

[redacted]

There are currently 16 approved drug products for treatment of acute migraine, including both prescription and OTC preparations. Most of the prescription products are 5- hydroxytryptamine 1B/1D receptor agonists, or "triptans". These include Amerge (naratriptan), Axert (almotriptan), Frova (frovatriptan), Imitrex (sumatriptan), Maxalt (rizatriptan), Relpax (elatriptan) and Zomig (zolmitriptan). Many triptans are available in several formulations (Table 2). Although simple analgesics and triptans are usually considered the treatment of choice, dihydroergotamines are also available by prescription for use in patients unresponsive to other treatments.

OTC treatments for acute migraine include Advil Migraine Liquidgels (ibuprofen), Motrin Migraine Pain Caplets (ibuprofen) and Excedrin Migraine Caplets/Gelcaps/Tablets (acetaminophen, aspirin and caffeine). In addition, Bayer Aspirin is approved for pain of migraine only. Isometheptene (Midrin) is labeled as "possibly effective in migraine." Many general analgesics are used off label in the treatment of migraine.

Table 2: Migraine Products

Drug Product	NDA	Sponsor	FDA Approval	Approved Strengths
Imitrex Injection	20-080	Glaxo Wellcome	12/28/1992	6 mg
Imitrex Tablets	20-132	Glaxo Wellcome	6/1/1995	25 and 50 mg
Imitrex Nasal Spray	20-626	Glaxo Wellcome	8/26/1997	5, 10, and 20 mg/spray
Zomig Tablets	20-768	IPR	11/25/1997	2.5 and 5.0 mg
Zomig-ZMT	21-231	Astra Zeneca	2/13/2001	2.5 mg
Zomig Nasal Spray	21-450	Astra Zeneca	9/30/03	5.0 mg
Amerge Tablets	20-763	Glaxo Wellcome	2/10/1998	1 and 2.5 mg
Maxalt Tablet	20-864	Merck	6/29/1998	5 and 10 mg
Maxalt-MLT Tablets	20-865	Merck	6/29/1998	5 and 10 mg
Axert Tablets	21-001	Pharmacia and Upjohn	5/7/2001	6.25 and 12.5 mg
Relpax Tablets	21-016	Pfizer	12/26/2002	20 and 40 mg

2.3 Availability of Proposed Active Ingredient in the United States

Sumatriptan is marketed in the United States by Glaxo-Wellcome. Naproxen is available generically and is manufactured by several pharmaceutical firms.