

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-926

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA#	21-926 amendment 025
Submission Date:	10/11/2007 & e-mail response of 3/19/08
Consult to OCP:	3/12/2008
Drug and dosage form:	Treximet tablets (sumatriptan 85 mg/naproxen 500 mg)
Indication:	Migraine
Sponsor:	Pozen Pharmaceuticals
Reviewer:	Ramana Uppoor, PhD
Submission Type:	Response to the second Approvable letter

BACKGROUND

This NDA for a combination product of sumatriptan and naproxen was originally submitted on 8/5/2005 and the Clinical Pharmacology section was reviewed by Dr. Sally Yasuda as the primary reviewer. An approvable letter was sent in June 2006. There were no major issues from Clinical Pharmacology except labeling comments. The responses to this first approvable letter did not involve Clinical Pharmacology.

CURRENT SUBMISSION

From a Clinical Pharmacology perspective, this submission (response to 2nd approvable letter) contains the sponsor's modifications to the label (see attachment 1 for the Clin. Pharm. section of the label). The sponsor made the following changes to the label:

1. Trade name was replaced by 'Treximet' (this has been provided in the most recent version of the label on 1/15/2008), and MAO was expanded to Monoamine oxidase. This is acceptable.
2. In the PK section, the following sentence was previously recommended by the FDA reviewer:



This second change above is not supported by the data reviewed in the original NDA i.e. study MT400-101. The sponsor states that this is obtained from a new study # TRX106396 submitted on 1/31/2007 to the FDA as amendment # 016. The sponsor provided the following justification to use this study instead of MT400-101. This justification seems reasonable. However, this study was not previously reviewed by OCP. Therefore, this study is being reviewed here.

Sponsor's justification: At the time of the original NDA submission, MT400-101 was the only pharmacokinetic study that directly compared the pharmacokinetic profile of

sumatriptan, when administered as [TRADENAME] to that of sumatriptan when administered as IMITREX 100 mg. However, several design aspects of this study limit the utility of data from MT400-101 to support labeling statements. A more recently completed study, TRX106396 (submitted to FDA in the January 31, 2007 Full Response, NDA 21-926, Amendment 016) provides a more scientifically robust comparison of the pharmacokinetic profile of sumatriptan when administered as [TRADENAME] and when administered as IMITREX 100 mg. TRX106396 is a more appropriate study from which to draw data for inclusion in the package insert because:

- TRX106396 employed a crossover study design with 32 subjects that compared the commercial formulation of Treximet to the current commercial Imitrex 100mg, which includes RT technology, while MT400-101 was an exploratory study that employed the Treximet tablet formulation made in the RTP pilot plant, which was not a proposed commercial batch manufactured in Ware (GSK UK site).

-

Thus, we think the comparisons in TRX106396 would be more relevant.

- The size of study TRX106396 makes the data more robust than study MT400-101, in which only 8 of the 24 subjects received both a dose of Imitrex 100mg (non-RT) and Treximet, as this study used an uneven block study design (not a balanced crossover design).
- So, using data from TRX106396: the arithmetic mean for Treximet = 46ng/ml vs 53ng/ml for Imitrex 100mg (RT). The average sumatriptan Cmax for Imitrex 100mg is 15% greater than the average Cmax for Treximet (Table 9.3, page 103 of 937, Study # TRX106396). The statistical analysis performed in TRX106396 shows there is no statistical difference between these formulations with regards to sumatriptan Cmax (ratio is 0.90 and 90% CI is 0.804 - 1.00).
- The data from Study TRX106396 are more consistent with those generated in the 3 other Treximet NDA studies (MT400-102, MT400-104 and MT400-105) that employed the proposed commercial formulation.

STUDY TRX106396 (submitted on 1/31/07)
(Note: Treximet is same as Trexima)

Study Title: An open-label, randomized, single-dose, 2-period crossover study to evaluate sumatriptan pharmacokinetics from a TREXIMA (sumatriptan 85mg/naproxen sodium 500mg) Tablet compared with an IMITREX (sumatriptan) 100mg Tablet.

Investigator(s): _____

Study center(s): _____

Study Period: 10 Feb 2006 – 18 Mar 2006

Objectives: The primary objective was to evaluate sumatriptan exposure (as measured by AUC(0-2) and Cmax) during the first 2 hours following administration of a single TREXIMA tablet and a single IMITREX 100mg tablet. The secondary objectives were to

evaluate sumatriptan AUC(0-∞), AUC(0-t), tmax, and %Cmax at 15, 20, 25, and 30 minutes postdose; to assess the time required to achieve sumatriptan concentrations of 5, 10, and 20 ng/mL following administration of a TREXIMA tablet and a single IMITREX 100mg tablet; to evaluate naproxen pharmacokinetics following administration of a single TREXIMA tablet; and to assess the safety and tolerability of a single TREXIMA tablet and a single IMITREX 100mg tablet.

Note: Given the focus of this review, this reviewer is focusing only on Cmax, AUC and Tmax for sumatriptan and naproxen.

Methodology: This was a single-center, randomized, open-label, single-dose, 2-period crossover pharmacokinetic study in healthy adult males and females, ages 18 to 55 years. A minimum of 7 days separated the dosing sessions to allow for complete washout of residual drugs from the previous dosing session.

Number of subjects: Thirty-two subjects (26 females and 6 males) were enrolled, received both treatments, and completed the study.

Investigational products: Subjects received the following treatments in a crossover fashion, administered as single doses with 240 ml of water following a minimum 8 hour fast:

Treatment A: TREXIMA tablets – an investigational product containing 119mg of sumatriptan succinate, equivalent to 85mg of sumatriptan, and 500mg of naproxen sodium (Batch B916681)

Treatment B: IMITREX tablets – an approved, marketed product containing 140mg of sumatriptan succinate, equivalent to 100mg of sumatriptan (commercially available product purchased by the site)

BLOOD SAMPLING AND SAFETY ASSESSMENTS: Blood samples were collected predose and at specified time points up to 72 hours (0, 5, 10, 15, 20, 25, 30, 40, 50, 60, 75, 90 minutes and 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 48 and 72 hours) following a single dose of TREXIMA and for up to 24 hours (0, 5, 10, 15, 20, 25, 30, 40, 50, 60, 75, 90 minutes and 2, 2.5, 3, 4, 6, 8, 10, 12, 16 and 24 hours) following a single dose of IMITREX 100mg.

Continuous cardiovascular monitoring (5-lead ECG telemetry monitoring and serial blood pressure measurements) was performed for both treatments, beginning 1 hour prior to treatment administration and until 10 hours postdose.

PK endpoints:

- Sumatriptan AUC(0-2) and Cmax
- Sumatriptan AUC(0-t), AUC (0-∞), and tmax
- Naproxen AUC(0-t), AUC (0-∞), Cmax, and tmax
- Sumatriptan: %Cmax at 15, 20, 25, and 30 minutes postdose
- Times to achieve sumatriptan concentrations of 5, 10, and 20ng/mL

Statistical analysis: The point estimate and 90% confidence interval for the ratio between a single TREXIMA tablet and a single IMITREX 100mg tablet (TREXIMA-IMITREX) were determined for sumatriptan pharmacokinetic parameters. This analysis used log transformed PK parameters and were analysed by mixed model ANOVA fitting subject(sequence) as a random effect and period, sequence, and regimen as fixed effect terms.

Results:

Assay: Plasma samples were analyzed for sumatriptan (GR43175) by [REDACTED] using a validated analytical method based on [REDACTED] followed by HPLC-MS/MS analysis. The lower limit of quantification (LLQ) was 0.1 ng/mL for sumatriptan, using a 100 µL aliquot of EDTA plasma. The higher limit of quantification (HLQ) was 100 ng/mL for sumatriptan (GlaxoSmithKline Document number FD2006/00077/00).

Plasma samples were analyzed for naproxen (BRL-19255) using a validated analytical method based on [REDACTED] followed by HPLC-MS/MS analysis. The LLQ for naproxen was 2.5 µg/mL, using a 25 µL aliquot of plasma with a HLQ of 250 µg/mL (GlaxoSmithKline Document number WD2005/00471/00).

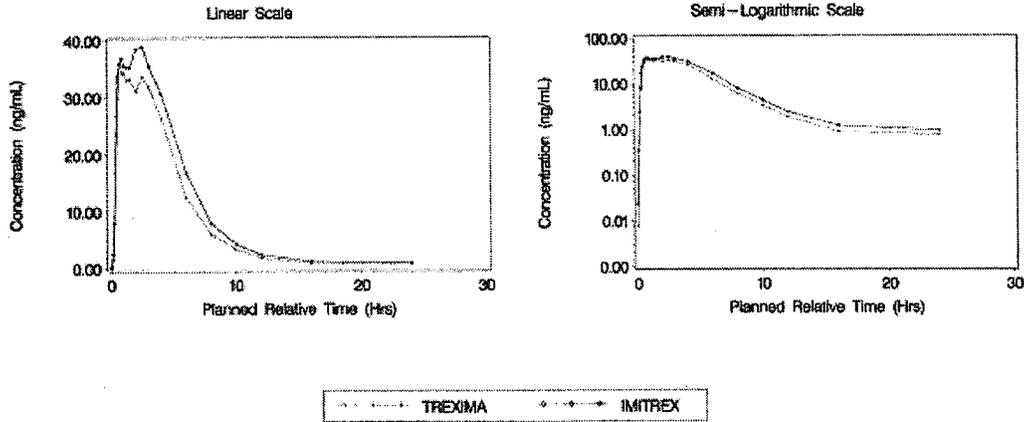
The method validation for sumatriptan and naproxen looks reasonable, and the detailed reports can be found in the NDA 21-926 submission date 01/31/07, module 5, under study TRX106396.

For each analytical method, Quality Control (QC) samples, containing the relevant analytes at 3 different concentrations and stored with study samples, were analyzed with each batch of samples against separately prepared calibration standards. For the analysis to be acceptable, no more than one-third of the QC results had to deviate from the nominal concentration by more than 15%, and at least 50% of the results from each QC concentration had to be within 15% of nominal. According to the sponsor, the applicable analytical runs met all predefined run acceptance criteria.

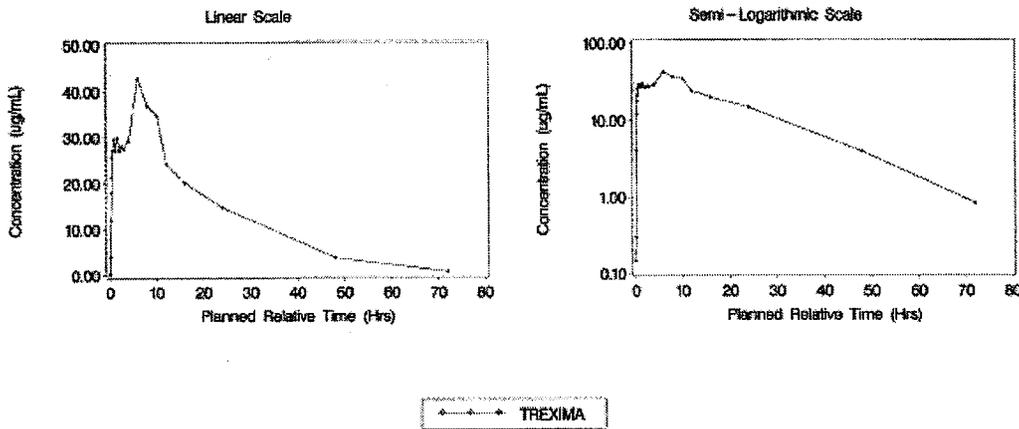
WITHIN STUDY ASSAY PERFORMANCE: A set of 8 calibration standards ranging from 0.1 ng/mL to 100 ng/mL and Quality Control (QC) samples at three different concentrations (0.4, 4.0, and 80 ng/mL) of the analyte were prepared and stored at -20°C. Between-batch precision and accuracy for analysis of the QC samples were determined from batch analyses of clinical samples in this study. The inter-assay precision of the quality controls for the sumatriptan runs ranged from 10.2% to 20.2% (20.2% at the lowest QC), with accuracy ranging from -4.9% to 4.1%. The back-calculated calibration curve values expressed as a percent of the nominal value ranged from 96.2% to 102.3%.

PK results: The results from PK analyses of sumatriptan and naproxen and the statistical comparisons of sumatriptan parameters are presented in the following figures and tables. Plasma concentration time profiles for sumatriptan and naproxen as shown below:

SUMATRIPTAN:



NAPROXEN:



Arithmetic mean PK parameters are provided in the following table.

PK parameters	Trexima	Imitrex
Sumatriptan		
AUC (0-2), ng*hr/mL	Mean: 56.05 SD: 19.78 Range: 24.12 – 116.29	Mean: 59.16 SD: 26.79 Range: 27.56 – 167.20
AUC (0-inf), ng*hr/mL	Mean: 201.07 SD: 60.44 Range: 95.66 – 349.05	Mean: 241.07 SD: 76.18 Range: 93.98 – 455.95
Cmax, ng/mL	Mean: 45.98 SD: 13.24 Range: 27.07 – 82.68	Mean: 52.70 SD: 20.99 Range: 24.27 – 124.86
Tmax, hr	Median: 0.83	Median: 1.50

	Range: 0.35 – 4.00	Range: 0.42 – 6.00
Naproxen		
AUC (0-inf), µg*hr/mL	Mean: 944.86 SD: 308.44 Range: 523.38 – 1740.86	NA
Cmax, µg/mL	Mean: 54.86 SD: 18.82 Range: 28.58 – 96.19	NA
Tmax, hr	Median: 6.00 Range: 0.17 – 10.02	NA

Geometric Mean (CVb%) Sumatriptan PK Parameters					
Treatment	N	AUC(0-2) (ng hr/mL)	AUC(0-t) (ng hr/mL)	AUC(0-∞) (ng hr/mL)	Cmax (ng/mL)
TREXIMA	32	52.8 (36.6)	190 (29.6)	192 (31.2) ¹	44.3 (27.9)
IMITREX	32	54.8 (39.5)	222 (33.7)	230 (33.2)	49.4 (36.2)

¹ N=28

Median (Range) Sumatriptan tmax Parameters					
Treatment	N	tmax (hr)	T5 (hr)	T10 (hr)	T20 (hr)
TREXIMA	32	0.83 (0.35-4.00)	0.20 (0.1-0.4)	0.30 (0.2-0.5)	0.40 (0.2-1.9)
IMITREX	32	1.56 (0.42-6.00)	0.20 (0.1-0.3)	0.30 (0.1-0.5)	0.40 (0.2-1.0)

Median (Range) Sumatriptan %Cmax Parameters					
Treatment	N	C15 (%)	C20 (%)	C25 (%)	C30 (%)
TREXIMA	32	18.0 (2.54-70.4)	42.6 (10.1-100)	57.2 (19.7-98.9) ²	77.3 (27.2-100)
IMITREX	32	13.8 (2.03-68.0) ¹	30.6 (8.23-76.0)	42.0 (11.6-100)	53.0 (26.5-100) ²

¹ N=29

² N=31

90% confidence intervals:

Statistical Analysis of Sumatriptan PK Parameters				
Parameter	Comparison	Ratio	90% CI	CVw(%)
AUC(0-2)	TREXIMA : IMITREX	0.96	(0.86, 1.08)	27.11%
Cmax	TREXIMA : IMITREX	0.90	(0.80, 1.00)	25.76%
AUC(0-t)	TREXIMA : IMITREX	0.86	(0.81, 0.91)	13.23%
AUC(0-∞)	TREXIMA : IMITREX	0.85	(0.80, 0.89)	11.58%
tmax (hr) ¹	TREXIMA – IMITREX	-0.88	(-0.88, -0.2†)	

¹ Represents estimated median of the differences between regimens

Geometric Mean (CVb%) Naproxen Pharmacokinetic Parameters					
Treatment	N	AUC(0-t) (µg hr/mL)	AUC(0-∞) (µg hr/mL)	Cmax (µg/mL)	tmax (hr) ¹
TREXIMA	32	765 (35.3)	900 (32.1) ²	51.8 (35.9)	6.00 (0.17-10.02)

Source Data: Tables 9.13 and 9.14

¹ Median (range)

² N=29

CONCLUSIONS: The arithmetic mean Cmax of sumatriptan from Treximet tablets is 46 ng/ml with a range of 27 to 83 ng/ml, and is similar between the two treatments (Treximet and Imitrex). The median of the differences indicated that the sumatriptan tmax occurred 53 minutes earlier for TREXIMA, as compared to IMITREX.

LABELING COMMENTS

1. From Clinical Pharmacology perspective, the minor changes such as ‘trade name’ and ‘MAO to Monoamine oxidase’ are acceptable.
 2. Use of study TRX 106396 for labeling statements related to sumatriptan is acceptable.
-

RECOMMENDATIONS

Please forward the above comments to the medical reviewer and the sponsor as appropriate.

Ramana Uppoor, PhD
Deputy Director/Neurology CP Team Leader
Division of Clinical Pharmacology 1

Date

Mehul Mehta, PhD
Director
Division of Clinical Pharmacology 1

Date

cc: HFD-120 NDA 21-926
HFD-860 Mehul Mehta, Ramana Uppoor

3 Page(s) Withheld

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/s/

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Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-926 (505(b)(2))
Brand Name:	Trexima
Generic Name:	Sumatriptan Succinate/Naproxen Sodium
Type of Dosage Form:	Tablet
Strengths:	85 mg sumatriptan/500 mg naproxen sodium
Indications:	Acute Migraine
Type of Submission:	Standard
Sponsor:	Pozen
Submission Date:	August 5, 2005 October 27, 2005 November 16, 2005 December 12, 2005 December 8, 2005 January 27, 2006 February 22, 2006 April 7, 2006 April 14, 2006 April 28, 2006
OCPB Division:	DCP-I
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OCPB Team Leader:	Ramana Uppoor, PhD

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1 Executive Summary

1.1 Recommendations

- 1) The clinical pharmacology and biopharmaceutics information submitted to NDA 21926 is acceptable provided that satisfactory agreement is reached between the Sponsor and the Agency regarding labeling (Please refer to **Section 3** of this review)
- 2) The Sponsor proposed the following dissolution method and specifications:

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

The Office of Clinical Pharmacology finds the proposed dissolution method and specification acceptable.

1.2 Phase 4 Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

NDA 21-926 has been submitted to support the approval of TREXIMA (sumatriptan 85 mg /naproxen sodium 500 mg) for acute treatment of migraine attacks with or without aura in adults. (Sumatriptan is given as 119 mg sumatriptan succinate). The proposed dose is 1 tablet given orally.

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

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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).

The following clinical pharmacology studies have been submitted and reviewed:

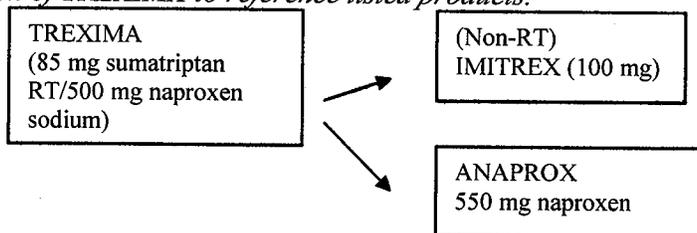
Study	Description
MT400-101	BA of TREXIMA, each component, and marketed versions of components
MT400-102	Food Effect Study
MT400-103	BA of TREXIMA and combinations of various formulations
MT400-104	Effect of Migraine on PK
MT400-105	PK of 2 single tablets given 2 hours apart

The Sponsor states that the to-be-marketed formulation was used in each of the clinical pharmacology and pivotal clinical studies. However, the clinical trial batch was not debossed, whereas the to-be-marketed tablet is debossed **XXXXXXXXXX**

The key findings with respect to the Clinical Pharmacology and Biopharmaceutics of TREXIMA are as follows:

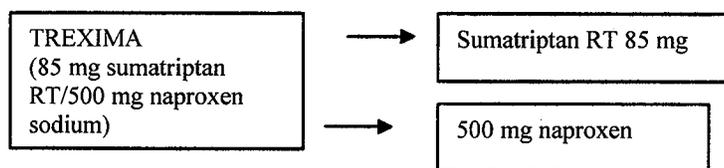
Pharmacokinetics

Comparison of TREXIMA to reference listed products:



For C_{max}, 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). C_{max} values for sumatriptan were approximately 20% higher from TREXIMA than from IMITREX (90% CI 0.94-1.31). C_{max} values for naproxen were approximately 36% lower from TREXIMA than from ANAPROX 550 mg (90% CI 0.67-0.79). In addition, the median t_{max} for naproxen was delayed after administration of TREXIMA relative to ANAPROX (approximately 6 hr vs 1 hr). The median t_{max} for sumatriptan was approximately 1-1.5 hr. For AUC the BE criteria were met for either analyte.

Comparison of TREXIMA to individual components given separately:



For sumatriptan, C_{max} 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 C_{max} 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.

TREXIMA PK in Migraine:

PK of naproxen and sumatriptan were similar in terms of C_{max} and AUC for naproxen or sumatriptan when TREXIMA was given during or outside of a migraine. Median T_{max} was slightly earlier during a migraine (1.5 hr, range 0.5-4.0) than outside of a migraine (2.0 hr, range 0.5-4.1).

Food Effect:

After TREXIMA administration with a high fat meal, there was no difference (90% CI within 80-125% BE criteria) in C_{max} or AUC or in T_{max} for naproxen compared to TREXIMA given in a fasted state in 21 healthy subjects. For sumatriptan, there was no difference (90% CI within 80-125% BE criteria) in C_{max} or AUC, although food delayed the sumatriptan T_{max} by approximately 36 minutes. The labeling may state that TREXIMA can be given without regard to food. The fasting PK parameters from this study are in agreement with the PK parameters for other Phase I studies in NDA 21926.

Other relevant aspects of the clinical pharmacology of sumatriptan and naproxen are described in the current labels for the approved marketed products and can be extended to the labeling for TREXIMA.

Biopharmaceutics

The Sponsor proposed the following dissolution method and specifications:

Apparatus: USP Apparatus 1 (Basket)
Medium: USP Phosphate Buffer pH 6.8
Volume: 900 ml
Rotation Speed: 75 rpm
Specification:

Sumatriptan: 15 minutes:
Naproxen sodium: 30 minutes:

Q=
Q=

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TREXIMA

The Office of Clinical Pharmacology finds the proposed dissolution method and specifications acceptable.

In addition, the dissolution profile of the debossed tablet that is the to-be-marketed tablet is similar to that of the biobatch/clinical trial tablet.

Sally Usdin Yasuda, MS, PharmD
Reviewer, Neurology Drug Products, DCP I
Office of Clinical Pharmacology

Concurrence: Ramana Uppoor, PhD
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2 Question-Based Review

2.1 General Attributes

Sumatriptan succinate and naproxen sodium have been previously approved for use under NDAs 20132 (Imitrex) and 18164 (Anaprox), respectively. Imitrex is indicated for acute treatment of migraine. Anaprox does not have an indication for migraine. Sumatriptan succinate is marketed as Imitrex tablets (GlaxoSmithKline) and for migraine it is given as single doses up to 25mg-100 mg that may be repeated after 2 hours, not to exceed a total daily dose of 200 mg. NDA 21,926 has been submitted as a 505(b)(2) and the Sponsor references Imitrex (sumatriptan) and Anaprox DS (550 mg of naproxen sodium). The current IMITREX tablet has sumatriptan in a formulation that uses the same "rapid release technology" (RT) as the sumatriptan in the TREXIMA tablet (contains sodium bicarbonate). However, the IMITREX tablet (non-RT) used in the Phase I studies did not have this technology.

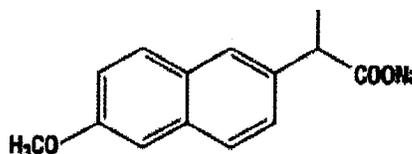
2.1.1 What are the highlights of the chemistry and physical-chemical properties of TREXIMA, and the formulation of the drug product?

TREXIMA contains sumatriptan (as the succinate) and naproxen sodium. Sumatriptan succinate has an empirical formula of $C_{14}H_{21}N_3O_2S \cdot C_4H_6O_4$ and is designated as 3-[2-dimethylamino)ethyl]-N-methyl-indole-5-methanesulfonamide succinate (1:1) with a molecular weight of 413.5. Naproxen sodium has an empirical formula of $C_{14}H_{13}O_3Na$ and is designated as (-)-sodium (S)-6-methoxy- α -methyl-2-naphthaleneacetic acid with a molecular weight of 252.24. The structures are shown below:

Sumatriptan succinate



Naproxen sodium



TREXIMA tablets are  immediate release, film coated tablets. Each tablet contains 85 mg sumatriptan (as 119 mg sumatriptan succinate) and 500 mg naproxen sodium. The composition of the TREXIMA formulation used in all of the Phase 1 and Phase 3 clinical studies is shown in the table below, as provided by the Sponsor.

Component	Function	Quantity per Tablet (mg)
Sumatriptan Succinate Layer		
Sumatriptan succinate ¹	Active	119.0
dibasic calcium phosphate		
Microcrystalline cellulose		
Sodium bicarbonate		
Croscarmellose sodium		
Magnesium stearate		
Naproxen Sodium Layer		
Naproxen sodium	Active	500.0
Microcrystalline cellulose		
Povidone		
Croscarmellose sodium		
Talc		
Magnesium stearate		
Total (film coated tablet)		1107

¹ 119 mg sumatriptan succinate is equivalent to 85 mg sumatriptan.

Source: Section 3.2.P.2, Table 1

The Sponsor states that the to-be-marketed formulation was used in each of the studies. Batch 916681 was used in the PK studies MT 400-102, MT 400-104, and MT 400-105 and the Phase III clinical studies MT 400-301, MT 400-302, and MT 400-303. This batch was manufactured at the site of commercial manufacture (Glaxo, UK) according to the commercial process. Additional PK studies MT 400-101 and MT 400-103 also used Trexima tablets prepared according to the commercial process but from a pilot scale batch. The biobatch was not debossed, although the commercial tablet will be debossed on 1 side. The dissolution profiles of the debossed tablet and the biobatch are similar.

Imitrex is currently available as 25, 50, and 100 mg of sumatriptan (base) as the succinate. The current formulation that incorporates the RT Technology was approved in June 2003 under NDA 20-132/S-015. Since the RT formulation replaced the non-RT formulation, bioequivalence of this formulation to the standard sumatriptan tablet for the 50 mg and 100 mg tablets is assumed. In the present submission, TREXIMA was evaluated against Imitrex 50 mg (non-RT) and Imitrex 100 mg (non-RT) as they were the marketed products at the time of the beginning of the

development program. Other comparators were Anaprox 550 mg, naproxen sodium 500 mg, sumatriptan 85 mg (RT), and sumatriptan 85 mg (non-RT).

2.1.2 *What is the proposed mechanism of drug action and what is the proposed therapeutic indication?*

Sumatriptan is a 5-HT receptor agonist that blocks the release of vasodilating neuromodulators and blocks the transmission of pain. Naproxen is an NSAID that inhibits synthesis of inflammatory mediators of pain (via inhibition of cyclooxygenase). The proposed indication for TREXIMA is for the acute treatment of migraine attacks with or without aura in adults.

2.1.3 *What is the proposed dosage and route of administration?*

The proposed recommended dose is 1 tablet given orally.

2.2 General Clinical Pharmacology

2.2.1 *What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?*

The two pivotal efficacy studies were identical studies that 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 or 500 mg naproxen sodium for sustained pain relief through 24 hours. The long-term safety study was a multiple-attack, open label study, that allowed for a second dose of study medication to treat the same migraine attack at least 2 hours after taking the first dose if needed, with no more than 2 tablets allowed in any 24 hour period.

2.2.2 *What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (collectively called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?*

The primary pharmacodynamic endpoints, that are typical for migraine studies, were pain relief and incidence of photophobia, phonophobia, and nausea at 2 hours post-dose, and sustained pain free over 24 hours.

2.2.3 *Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?*

The active moieties are considered to be naproxen and sumatriptan, and these were appropriately determined in the pharmacokinetic studies.

2.2.4 *Exposure-response*

2.2.4.1 *What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.*

Only 1 dosage strength (85 mg sumatriptan succinate/500 mg naproxen sodium) was evaluated in the pivotal efficacy studies. The primary endpoint for efficacy was pain free at 2 hours. TREXIMA was superior to placebo in 2-hour relief of pain and for relief of associated symptoms

of photophobia and phonophobia. Knowing that sumatriptan is effective in doses as low as 25 mg (as labeled), ideally lower dose combinations should be studied.

2.2.4.1.1 What is the rationale for this combination and what is the rationale for this combination of doses?

The Sponsor states that the symptom complex in migraine may result from more than 1 mechanism, and that headache recurrence occurs in patients treated with sumatriptan. Therefore, the rationale for developing the combination of sumatriptan and naproxen sodium was to provide rapid and sustained relief of migraine pain and associated symptoms, reducing headache recurrence and the need for rescue medication. The rationale for selecting the 85 mg sumatriptan dose was to produce a PK profile during the first 2-3 hours that is generally similar to that following 100 mg Imitrex. The naproxen dose was chosen based on efficacy of a combination of Imitrex 50 mg and naproxen sodium 500 mg in a proof of concept study.

Imitrex tablets are given for migraine as 25, 50, or 100 mg single doses that may be repeated after 2 hours, not to exceed a total daily dose of 200 mg. Naproxen sodium is given in doses up to 550 mg twice daily for management of pain, and the initial total daily dose should not exceed 1375 mg naproxen sodium, and thereafter the total daily dose should not exceed 1100 mg of naproxen sodium.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

Exposure-response relationships for safety were not evaluated in this submission. The labeling of Anaprox refers to more frequent and severe gastrointestinal reactions in rheumatoid arthritis patients taking daily doses of 1500 mg naproxen compared to 750 mg naproxen. However, these adverse effects, including GI ulceration and bleeding, can occur with low doses and the Anaprox labeling provides specific warnings regarding these adverse effects. In addition, a risk of cardiac adverse events in patients taking NSAIDs has been identified. Other serious adverse effects of NSAIDs including naproxen are anaphylactoid reactions, hepatotoxicity, and nephrotoxicity. For sumatriptan, serious adverse cardiac events have been reported as well as increases in blood pressure and the labeling for Imitrex includes contraindications to use in patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes, or patients with other significant underlying cardiovascular disease.

2.2.4.3 Does this drug prolong the QT or QTc interval?

QT prolongation is not identified in the labels of either Imitrex or Anaprox and has not been addressed in the present submission.

2.2.4.4. Is the dose and dosing regimen selected by the Sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues? (In some cases it may be possible to combine with 2.2.4.2 and 2.2.4.3)

The proposed dose and dosing regimen is the same as evaluated in the pivotal clinical studies.

2.2.5 What are PK characteristics of the drug and its major metabolites?

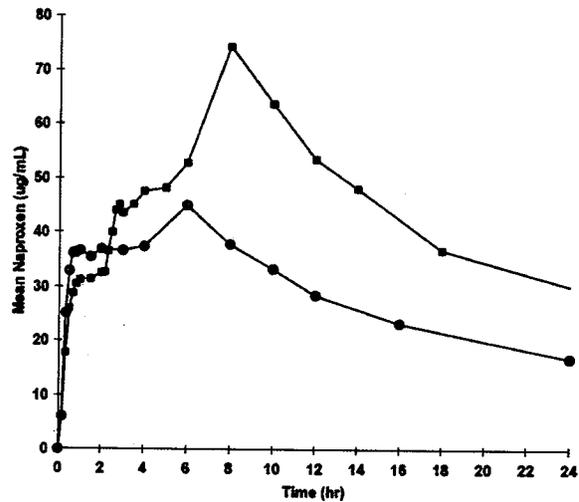
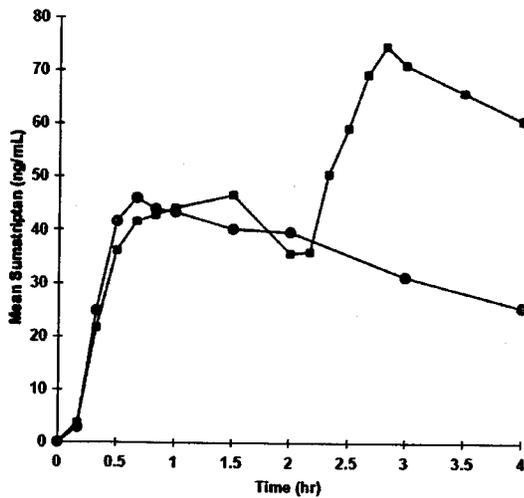
2.2.5.1 What are the single dose and multiple dose PK parameters?

Single dose PK has been evaluated in several studies and the results are similar across studies. The following data show the PK parameters after a single dose of TREXIMA in Study MT 400-105 in 24 healthy volunteers. In addition, the table below shows PK parameters following administration of a single TREXIMA tablet followed by a second TREXIMA tablet that was given 2 hours later in that study. Due to the rapid elimination of sumatriptan, a second peak can be seen after administration of the second TREXIMA tablet. The less than proportional increase in AUC for naproxen may be due to saturable protein binding, discussed in Section 2.2.5.4.

Pharmacokinetic parameters (arithmetic mean) for Naproxen and for Sumatriptan (Study MT 400-105)

	One TREXIMA Tablet (% CV)	Two TREXIMA Tablets (2 hours apart) (% CV)
Naproxen	<i>(n=24)</i>	<i>(n=23)</i>
t _{max} (h) ^a	5.0 (0.5-10.0)	8.0 (2.5-10.0)
C _{max} (µg/mL)	54.5 (24)	81.5 (16)
AUC _{0-t} (µg*h/h)	1111.0 (16)	1773.3 (13)
AUC _{0-∞} (µg*h/mL)	1186.4 (17)	1882.9 (14)
λ _z (hr ⁻¹)	0.039 (12)	0.040 (14)
t _{1/2} (h)	18.0 (13)	17.6 (14)
Sumatriptan	<i>(n=24)</i>	<i>(n=23)</i>
t _{max1} (h) ^a	0.9 (0.3-2.0)	1.0 (0.5-1.5)
C _{max1} (ng/ml)	57.4 (37)	53.1 (29)
t _{max2} (h) ^a	NA	2.8 (2.7-5.0)
C _{max2} (ng/ml)	NA	81.4 (20)
AUC _{0-t} (ng*h/mL)	216.2 (24)	458.3 (14)
AUC _{0-∞} (ng*h/mL)	223.7 (23)	473.6 (15)
λ _z (hr ⁻¹) ^b	.345 (12)	0.347 (17)
t _{1/2} (h) ^b	2.04 (15)	2.06 (19)

The mean plasma sumatriptan and naproxen concentrations from the single dose and repeat dose regimens are shown in the figures below. The open symbols represent 1 TREXIMA tablet and the Closed symbols represent 2 TREXIMA tablets taken 2 hours apart.



2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

PK of naproxen and sumatriptan have been evaluated in migraineurs in Study MT 400-104 during and outside of a migraine. It was confirmed at dosing that subjects continued to have a moderate to severe headache. There was no difference in C_{max} or AUC for either naproxen or sumatriptan when given during or outside of a migraine (the 90% CI for the ratio of geometric means was within the BE interval of 80-125%). For sumatriptan, the median t_{max} occurred slightly earlier during a migraine (1.5 hr, range 0.5-4.0) than outside of a migraine (2.0 hr, range 0.5-4.1).

2.2.5.3 How do the pharmacokinetics of naproxen and sumatriptan from TREXIMA compare to the PK of those analytes from the reference listed products?

For C_{max}, neither naproxen nor sumatriptan fell within the BE limit of 80-125% when given as TREXIMA compared to the reference listed products. Study MT400-101, a Phase I study in healthy subjects compared the PK parameters for naproxen when given as TREXIMA to ANAPROX 550 mg and compared the PK parameters for sumatriptan when given as TREXIMA to IMITREX 100 mg (non RT). (The IMITREX nonRT was the formulation approved and marketed at the time of these studies. Since that time, the RT formulation of IMITREX was approved and is now the marketed product). Following administration of TREXIMA, C_{max} values for naproxen were approximately 36% lower than from Anaprox 550 mg and C_{max} values for sumatriptan were approximately 20% higher than from Imitrex. C_{max} fell outside of the BE interval of 80-125% (90% CI for naproxen C_{max} 0.67, 0.79; 90% CI for sumatriptan C_{max} 0.94, 1.31). In addition, the median t_{max} for naproxen was delayed after administration of TREXIMA relative to ANAPROX. The median t_{max} for sumatriptan was only slightly changed. For AUC the BE criteria were met. Results are shown in the table below.

Pharmacokinetic parameters (arithmetic mean) for Naproxen and for Sumatriptan (Study MT 400-101)

	Naproxen (% CV) n=23	Sumatriptan (% CV) n=23
TREXIMA		
t _{max} (h) ^a	6.0 (0.5-8.0)	1.0 (0.5-2.0)
C _{max} (µg/mL)	69.5 (24)	76.2 (35)
AUC _{0-t} (µg*h/mL)	1446.1 (13)	275.5 (23)
AUC _{0-∞} (µg*h/mL)	1492.8 (14)	282.7 (23)
λz (hr ⁻¹)	0.037 (13)	0.305 (36)
t _{1/2} (h)	19.3 (14)	2.6 (43)
Imitrex 100 mg		
t _{max} (h) ^a		1.5 (0.7-4.0)
C _{max} (ng/mL)		63.8 (30)
AUC _{0-t} (ng*h/mL)		300.9 (28)
AUC _{0-∞} (ng*h/mL)		308.6 (28)
λz (hr ⁻¹)		0.263 (27)
t _{1/2} (h)		2.8 (25)
Anaprox 550 mg		
t _{max} (h) ^a	1.0 (0.5-3.0)	

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C_{max} (ng/mL)	99.6 (18)
AUC _{0-t} (ng*h/mL)	1443.6 (15)
AUC _{0-∞} (ng*h/mL)	1487.7 (16)
λ_z (hr ⁻¹)	0.036 (12)
$t_{1/2}$ (h)	19.5 (12)

2.2.5.4. How do the PK characteristics of TREXIMA compare to the individual components given separately?

In the pivotal efficacy studies, TREXIMA was compared to sumatriptan 85 mg RT or naproxen sodium 500 mg given individually. The PK of the individual components have been compared to the PK when given as TREXIMA. For sumatriptan, C_{max} 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 C_{max} 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. The differences could be due to a drug - drug interaction between the 2 moieties or due to a formulation effect.

2.2.5.4.1 Is there a drug interaction between sumatriptan and naproxen?

Please refer to section 2.4.2.1.

2.2.5.5. What are the characteristics of drug absorption? (This may include discussion of transporter or pH effect).

According to the sumatriptan (Imitrex) label, the bioavailability of sumatriptan is approximately 15%, primarily due to pre-systemic metabolism. According to the labeling of Anaprox (naproxen sodium), naproxen is rapidly and completely absorbed from the GI tract with an in vivo bioavailability of 95%.

2.2.5.6. What are the characteristics of drug distribution? (Include protein binding)

According to the Imitrex labeling, protein binding of sumatriptan is approximately 14-21%.

According to the Anaprox label, naproxen has a volume of distribution of 0.16 L/kg. At therapeutic levels, naproxen is greater than 99% albumin-bound. At doses of naproxen greater than 500 mg/day there is less than proportional increase in plasma levels due to an increase in clearance caused by saturation of plasma protein binding at higher doses. According to the OCPB review of IND 60669 (8/30/00), the unbound fraction increases proportionally with dose. The naproxen anion has been found in the milk of lactating women at a concentration equivalent to approximately 1% of the maximum naproxen concentration in plasma.

2.2.5.7 Does the mass balance study suggest renal or hepatic as the major route of elimination? (This may include table with results of mass balance study)

According to the Imitrex labeling, 60% of ¹⁴C-sumatriptan administered orally is renally excreted (with about 40% found in feces). Most of the radiolabeled compound in the urine is the major metabolite, indole acetic acid, which is inactive, or the indole acetic acid glucuronide. Only 3% of the dose was recovered as unchanged sumatriptan.

According to the Anaprox label, naproxen is extensively metabolized. Approximately 95% of the naproxen from any dose is excreted in the urine, primarily as naproxen (less than 1%), 6-O-desmethylnaproxen (less than 1%), or their conjugates (66% to 92%).

2.2.5.8 What are the characteristics of drug metabolism? (This may include data on extraction ratio; metabolic scheme; enzymes responsible for metabolism; fractional clearance of drug).

According to the Imitrex label, *in vitro* studies with human liver microsomes suggest that sumatriptan is metabolized by monoamine oxidase (MAO), predominantly the MAO A isozyme.

According to the Anaprox label, naproxen is extensively metabolized to 6-O-desmethyl naproxen and to conjugates of naproxen and the desmethyl metabolite.

2.2.5.9 What are the characteristics of drug excretion?

As discussed above, sumatriptan is extensively metabolized, and the major metabolite is renally eliminated. The elimination half-life of sumatriptan, as described in the Imitrex labeling, is approximately 2.5 hours. This is in agreement with the data in the present submission.

According to the Anaprox label, the clearance of naproxen is 0.13 ml/min/kg. The plasma half-life in humans ranges from 12-17 hours. This is in agreement with the data in the present submission. The corresponding half-lives of naproxen metabolites are shorter than 12 hours. Conjugates account for 66% to 92% of a dose that is found in the urine, with naproxen and the desmethyl metabolite each accounting for < 1%. Metabolites may accumulate in renal failure.

2.2.5.10 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Dose linearity was not evaluated in NDA 21-926. According to the Imitrex label, when given as a single dose, sumatriptan displays dose proportionality in AUC over the dose range of 25 to 200 mg, but C_{max} after 100 mg is approximately 25% less than expected based on the 25 mg dose.

For naproxen, exposure increases less than dose proportionately, as described above (Section 2.2.5.4), due to saturation of protein binding resulting in increased clearance.

2.2.5.11 How do the PK parameters change with time following chronic dosing?

This was not evaluated in the present submission and is not described in the labeling of either Imitrex or Anaprox.

2.2.5.12 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Intra-subject variability was not assessed. Inter-subject variability for naproxen across studies was approximately 13-24% for C_{max} and AUC. Inter-subject variability for sumatriptan across studies was approximately 22-40% for C_{max} and AUC. This could be due to variability in absorption as well as metabolism.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on efficacy or safety responses?

Age – The effect of age (pediatric or elderly) on sumatriptan or naproxen PK was not evaluated in the present submission. The Phase I studies only included subjects 18-55 years of age.

According to Imitrex labeling, PK of oral sumatriptan in the elderly (mean age 72 years) was similar to PK in healthy males (mean age 30 years). Imitrex is not recommended for use in children less than 18 years of age; PK in that age group is not described in the Imitrex label.

According to the Anaprox label, pediatric patients with arthritis aged 5-16 years given a 5 mg/kg single dose of naproxen suspension had naproxen plasma concentrations similar to those found in normal adults following a 500 mg dose, and the elimination half-life appears to be similar in pediatric and adult patients. For the elderly, the Anaprox label states that unbound trough naproxen concentrations are 0.12%-0.19% of total naproxen concentration, compared with 0.05% to 0.75% in younger subjects, and the clinical significance of this is unclear.

Gender – In study MT 400-012, males (n=12) had approximately 15% lower naproxen AUC values than females (n=11) in the fed and fasted state, and approximately 30% lower sumatriptan C_{max} and AUC than did females. The Sponsor speculates that some of the difference may have been due to the difference in weight. However, the Reviewer has corrected the sumatriptan C_{max} and AUC for weight, and the difference was not corrected for by weight. Across all studies, the Sponsor has compared naproxen and sumatriptan C_{max} and AUCs for males and females, and the results that suggest that bioavailability is 6-14% lower for males compared to females. This is consistent with the lack of gender effect on PK described in the labeling of IMITREX.

Race – According to the Imitrex label, systemic clearance and C_{max} of sumatriptan were similar in black and Caucasian healthy male subjects. According to the Anaprox label, the effect of race on PK has not been studied. The effect of race on PK was not evaluated in NDA 21926.

Weight – Not evaluated.

Height – Not evaluated.

Disease – The PK of sumatriptan and naproxen after administration of TREXIMA were evaluated inside and outside of migraine. Please refer to *Section 2.2.5.2*.

Genetic Polymorphism – Not evaluated.

Pregnancy – Not evaluated.

Organ Dysfunction –

Renal Impairment – Based on the label for Imitrex, the effect of renal impairment on the PK of sumatriptan has not been evaluated. The Anaprox label states that elimination of naproxen is decreased in patients with severe renal impairment.

Hepatic impairment – According to the labeling of Imitrex, hepatically impaired patients had an approximate 70% increase in sumatriptan AUC and Cmax and a Tmax 40 minutes earlier compared to healthy subjects.

According to the Anaprox label, naproxen PK has not been determined in hepatic insufficiency.

2.3.2 Based upon what is known about exposure-response relationships and their variability, and the groups studied, healthy volunteers vs patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Elderly - The ANAPROX label, that allows for initial total daily doses of 550 mg of naproxen sodium twice daily for rheumatoid arthritis, states that caution is advised when high doses are required in geriatric patients, that some adjustment of dosage may be required in elderly patients, and that as with other drugs used in the elderly, it is prudent to use the lowest effective dose. The current IMITREX label states that use of sumatriptan in elderly patients is not recommended because elderly patients are more likely to have decreased hepatic function, they are at higher risk for CAD, and blood pressure increases may be more pronounced.

The recommendation regarding the use of sumatriptan in the elderly has been extended to the proposed TREXIMA labeling.

2.3.2.2 Pediatric patients. Also, what is the status of pediatric studies and/or any pediatric plan for study?

The pediatric population was not evaluated in the present submission. The Imitrex label states that Imitrex is not recommended for use in patients under 18 years of age.

2.3.2.3 Gender - None.

2.3.2.4 Race – None

2.3.2.5 Renal Impairment – **No recommendation regarding use in renal impairment is made in the Imitrex label.** The Anaprox label states that naproxen-containing products are not recommended for use in patients with moderate to severe and severe renal impairment (creatinine clearance < 30 ml/min). This is extended to the TREXIMA label.

2.3.2.6 Hepatic Impairment - The Imitrex label states that in the presence of liver disease, the maximum single dose of Imitrex should not exceed 50 mg. There is no recommendation regarding the use of Anaprox in hepatic impairment. Since sumatriptan is contraindicated in patients with severe hepatic impairment and the dose is limited to 50 mg in liver disease, the Sponsor plans to contraindicate administration of TREXIMA in patients with hepatic impairment.

2.3.2.7 What pharmacogenetics information is there in the application and is it important or not?

There is no pharmacogenetics information in the application.

2.3.2.8 What pregnancy and lactation use information is there in the application?

There is no pregnancy and lactation information in humans in this application.

2.3.2.9 Other human factors that are important to understanding the drug's efficacy and safety

None.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on response?

According to the Imitrex label, alcohol consumed 30 minutes prior to sumatriptan ingestion had no effect on the pharmacokinetics of sumatriptan. The effects on sumatriptan PK of other extrinsic factors such as herbal products, diet, and smoking have not been evaluated. The effect of such factors has not been described in the Anaprox label or in the present submission.

Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

No recommendations.

2.4.2 Drug-Drug Interactions

2.4.2.1 Since TREXIMA is a combination of sumatriptan (85 mg as the succinate, RT formulation) and naproxen sodium (500 mg) has the interaction potential between these drugs been evaluated?

What is the effect of naproxen on sumatriptan PK?

The potential for this interaction has been evaluated in the literature in 12 healthy male volunteers who received sumatriptan succinate 100 mg as an immediate release capsule along with or without a single dose of naproxen 500 mg.¹ Neither C_{max}, AUC, or t_{max} appeared to be substantially different after a single dose of sumatriptan 100 mg with or without naproxen 500 mg (and no statistically significant effect was observed, P > 0.05).

¹ Srinivasu P, Rahbhau D, Rao BR, Rao YM. Lack of pharmacokinetic interaction between sumatriptan and naproxen. J Clin Pharmacol 2000; 40:99-104.

Note: In the present submission, this interaction could potentially be addressed by evaluating sumatriptan 85 mg (RT) vs TREXIMA if sumatriptan from TREXIMA were BE to sumatriptan from a combination of the individual components (sumatriptan 85 mg RT plus naproxen sodium 500 mg). In that case an interaction could be assumed to be due to a drug interaction, rather than an effect of the formulation. However, TREXIMA and the combination of sumatriptan 85 mg with bicarb (RT) plus naproxen 500 mg given as individual components were not bioequivalent in Study MT 400-103, a Phase I study in healthy subjects, with TREXIMA having an approximately 16% lower C_{max} than the combination. Therefore, we must rely on the available literature, described above, for information on this interaction, since the studies conducted under the present NDA cannot rule out a formulation effect.

What is the effect of sumatriptan on naproxen PK?

This could be addressed by evaluating naproxen 500 mg vs TREXIMA, if naproxen from TREXIMA were BE to naproxen from a combination of the individual components (sumatriptan 85 mg RT plus naproxen sodium 500 mg). In that case, an interaction could be assumed to be due to a drug interaction, rather than an effect of the formulation. Using this approach, in Study MT400-103 (TREXIMA vs the combination of sumatriptan 85 mg RT plus naproxen sodium 500 mg given as individual tablets), the ratios of the geometric means for C_{max} and AUC for naproxen from either treatment were within the BE range of 80-125%. Thus the 2 treatments were BE in terms of naproxen, thus a formulation effect can be ruled out. This allows for examination of naproxen from TEXIMA vs naproxen sodium 500 mg in Study MT 400-101. In that study, naproxen from Trexima had a 26% lower C_{max} than naproxen given alone (90% CI for the ratio of geometric means was 0.67 to 0.79) but no effect on the AUC, suggesting that sumatriptan reduces the rate of absorption of naproxen.

2.4.2.2 Is there an in vitro basis to suspect in vivo drug-drug- interactions?

According to the Imitrex label, *in vitro* studies suggest that sumatriptan is metabolized by MAO, and that pretreatment with an MAO-A inhibitor decreased the clearance of sumatriptan, resulting in a 2-fold increase in sumatriptan AUC after subcutaneous administration and a 7-fold increase in systemic exposure following oral administration of sumatriptan 25 mg. The use of MAO inhibitors with sumatriptan is contraindicated in the Imitrex label.

According to the Anaprox label, concomitant administration of naproxen and aspirin is not recommended because naproxen is displaced from binding sites, resulting in lower exposure. In addition, probenecid given with naproxen increases naproxen exposure. The label also describes the potential effects of naproxen on other drugs including the possibility of reduced tubular secretion of methotrexate that could increase toxicity of methotrexate, diminished activity of the antihypertensive effect of ACE-inhibitors, reduced natriuretic effect of furosemide and thiazides, inhibition of renal lithium clearance, protein-binding based interactions with coumarin-type anticoagulants, sulfonyleureas, hydantoins, other NSAIDS, and aspirin, reduced antihypertensive effect of propranolol and other beta-blockers.

2.4.2.3 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?
Sumatriptan is not known to be a substrate of CYP enzymes.

Based on a review of the literature provided by the Sponsor, the primary metabolic pathway for naproxen is glucuronidation. Approximately 58% of an oral dose of naproxen is recovered in the urine as the acyl glucuronide of naproxen. Naproxen also undergoes Phase I metabolism resulting in the formation of 6-O-desmethyl naproxen. Approximately 30-36% of a dose of naproxen can be accounted for by O-demethylation, based on urine recovery of the O-demethyl metabolite or its conjugates. There is published literature that identifies CYP1A2, CYP2C8, and CYP2C9 as being involved in this pathway, with 2C9 being the predominant form.² CYP2C9-mediated demethylation was reduced by 47% by sulfaphenazole, a CYP2C9 inhibitor and 28% by the CYP1A2 inhibitor furafylline *in vitro*. There has been no direct evaluation of the role of genetics in naproxen metabolism.

2.4.2.4 Is the drug and inhibitor and/or an inducer of CYP enzymes?

The role of sumatriptan as an inhibitor or inducer of P450s is not identified in the IMITREX label or in the literature. The Anaprox label states that neither naproxen nor its metabolites induce drug metabolizing enzyme. Their effects as inhibitors are not discussed.

2.4.2.5 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

This is not described in the current labeling of either IMITREX or ANAPROX.

2.4.2.6 Are there other metabolic/transporter pathways that may be important in the pharmacokinetics of TREXIMA?

NSAIDs inhibit renal tubular secretion of methotrexate as outlined in the labeling.

2.4.2.7 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

No co-administration specified.

2.4.2.8 What other co-medications are likely to be administered to the target patient population?

Propranolol is given for migraine prophylaxis. Propranolol had no significant effect on the PK of sumatriptan in 10 healthy male volunteers who received propranolol 80 mg twice daily plus a single dose of sumatriptan 300 mg orally (Scott et al, Br J Clin Pharmacol 1991; 32:581-584). This is not addressed in the IMITREX label. (A pharmacodynamic interaction between naproxen and propranolol regarding the antihypertensive effect of propranolol is described in the labeling.) According to the Topamax labeling, "multiple dosing of topiramate (100 mg every 12 hrs) in 24 healthy volunteers (14 M, 10 F) did not affect the pharmacokinetics of single dose sumatriptan either orally (100 mg) or subcutaneously (6 mg)".

2.4.2.9 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

² Tracy TS, Marra C, Wrighton SA, Gonzalez FJ, Korzekwa KR. Involvement of multiple cytochrome P450 isoforms in naproxen O-demethylation. Eur J Clin Pharmacol 1997; 52(4):293-8.

The Sponsor has submitted literature regarding potential for drug interactions (summarized in Appendix 4.2.10) and has not identified clinically relevant drug interactions that have not been described in the labeling for either Imitrex or ANAPROX.

2.4.2.10 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

It is recommended in the Imitrex label that the use of ergotamine-containing or ergot-type medications and sumatriptan within 24 hours of each other should be avoided, due to the potential for additive vasospastic effects. In addition, SSRIs have been reported to cause weakness, hyperreflexia, and incoordination when coadministered with sumatriptan. If concomitant treatment is clinically warranted, appropriate observation of the patient is advised, according to the Imitrex label.

The effects of warfarin and NSAIDs on GI bleeding are synergistic.

2.4.2.11 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?

None.

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved, and represent significant omissions?

None.

2.5 General Biopharmaceutics

2.5.1 Based on the biopharmaceutics classification system (BCS principles), in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

There is not enough information in the present submission to determine BCS class of either naproxen or sumatriptan. The pH *solubility* profiles have not been provided. *Permeability* considerations are as follows. When the extent of absorption in humans is determined to be 90% or more of an administered dose based on a mass balance determination, a drug substance is considered to be highly permeable. For sumatriptan in the mass balance study only 60% was excreted in the urine, and therefore the extent of absorption is considered to be about 60% (it is not known whether if sumatriptan is stable in the gastrointestinal tract). Whether oral absorption 60% or less has not been determined. Based on the available data, sumatriptan cannot be considered highly permeable. According to the labeling of Anaprox (naproxen sodium), naproxen is rapidly and completely absorbed from the GI tract with an in vivo bioavailability of 95%, and therefore naproxen meets the criteria for highly permeable.

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?

The to-be-marketed formulation differs from the pivotal clinical trial formulation and the Phase I formulations only in that it is debossed on 1 side. BE comparison is not required. Dissolution profile comparisons between the biobatch and the to-be-marketed (debossed tablet) show that these profiles are similar.

2.5.2.1 What data support or do not support a waiver of in vivo BE data?

Not applicable.

2.5.2.2 What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125% .

Not applicable.

2.5.2.3 If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?

Not applicable.

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

After TREXIMA administration with a high fat meal in Study MT 400-102, there was no difference (90% CI within 80-125% BE criteria) in Cmax or AUC or in Tmax for naproxen compared to TREXIMA given in a fasted state in 21 healthy subjects. For sumatriptan, there was no difference (90% CI within 80-125% BE criteria) in Cmax or AUC, although food delayed the sumatriptan Tmax by approximately 36 minutes. The labeling may state that TREXIMA can be given without regard to food. The fasting PK parameters from this study are in agreement with the PK parameters for other Phase I studies in NDA 21926.

2.5.4 When would a fed BE study be appropriate and was one conducted?

Not required in this case.

2.5.5 How do the dissolution conditions and specifications assure in vivo performance and quality of the product?

The Sponsor has provided information to determine the adequacy of the conditions (rotation speed, apparatus, and dissolution media) and has shown the discriminatory ability of the proposed method. For sumatriptan, more than 85% is dissolved in 15 minutes in all four media evaluated (0.1 N HCl, USP Acetate Buffer pH 4.5, water, and USP Phosphate Buffer pH 6.8); the minimum dissolved in 5 minutes was 85%. Naproxen dissolution was greater than 85% (minimum) at 30 minutes in either pH 6.8 or water, but not greater than 7% in acidic media.

The Sponsor proposed the following dissolution method and specifications based on the biobatch (Batch B916681):

Apparatus: USP Apparatus 1 (Basket)
Medium: USP Phosphate Buffer pH 6.8
Volume: 900 ml
Rotation Speed: 75 rpm
Specification:

Sumatriptan: 15 minutes: Q=
Naproxen sodium: 30 minutes: Q=

The Office of Clinical Pharmacology finds the proposed dissolution method and specifications acceptable.

2.5.6 *If different-strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?*

Not applicable.

2.5.7 *If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?*

Not applicable.

2.5.8 *If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either in vitro or in vivo data to evaluate BE?*

Not applicable.

2.5.9 *What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?*

None.

2.6 Analytical Section

2.6.1 *How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?*

Naproxen was measured using HPLC. Sumatriptan was measured using HPLC with MS detection.

2.6.2 *Which metabolites have been selected for analysis and why?*

The analytes that have been measured are sumatriptan and naproxen. Sumatriptan is considered to be the active moiety after administration of sumatriptan. Naproxen is considered to have pharmacologic activity. Activity of its metabolites is not described in the ANAPROX labeling.

2.6.3 *For all moieties measured, is free, bound or total measured? What is the basis for that decision, if any, and is it appropriate?*

Total naproxen and total sumatriptan are measured. This is consistent with studies supporting other NDAs with naproxen and sumatriptan products, and with pharmacokinetic information found in the labels of those products.

2.6.4 *What bioanalytical methods are used to assess concentrations?*

2.6.4.1 *What is the range of the standard curve and how does it relate to the requirements for the clinical studies? What curve fitting techniques are used?*

Bioanalytical methods are summarized below. The calibration range was adequate to cover the range of plasma concentrations observed in most cases, and otherwise, dilution integrity was shown.

Analyte	Method	Study	Calibration Range	LOQ	Linearity
Naproxen	Method LC 72.2 (HPLC)	MT 400-102 MT 400-104 MT 400-105	0.1 ug/ml to 100 ug/ml	0.1 ug/ml	1/x ² , least squares regression, linear
	Project 54076 (HPLC)	MT 400-101 MT 400-103	0.5 ug/ml to 99/96 ug/ml	0.5 ug/ml	1/x, linear regression, linear
Sumatriptan	LMS-M-6410-00	MT 400-101 MT 400-103	1.0-140 ng/ml	1.0 ng/ml	1/x, sum of squares regression, linear
	LCMS 174	MT 400-102 MT 400-105 MT 400-104	0.2 to 100 ng/ml	0.2 ng/ml	1/x, least squares regression, linear

2.6.4.2 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

See Section 2.6.4.1 above.

2.6.4.3 What are the accuracy, precision, and selectivity at these limits?

Selectivity was demonstrated with respect to interfering endogenous peaks, internal standard, and naproxen or sumatriptan. Precision and accuracy were acceptable (< 15%).

2.6.4.4 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

	Naproxen Method LC 72.2	Naproxen Project 54076	Sumatriptan LMS-M-6410-00	Sumatriptan LCMS 174
Freeze-thaw In process	3 cycles 21 hours (benchtop)	3 cycles	3 cycles 12.5 hours (room temperature)	3 cycles 26 hours at room temperature
Autosampler	155 hours at room temperature	39.2 hours at 4 ° C	146 hours at 5° C	127 hours at room temperature
Long-term stability	189 days at -20° C	79 days at -22° C	65 days at -20° C	852 days at -20 ° C

2.6.4.5 What is the QC sample plan?

Duplicate or triplicate QC standard replicates were run with each batch of naproxen samples and duplicate or 4 or 6 replicate QC samples were run with each sumatriptan batch of study samples analyzed.

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 Trade Secret / Confidential

✓ Draft Labeling

 Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 9

4.2 Clinical Pharmacology and Biopharmaceutics Individual Study Reviews

4.2.1 BIOANALYTICAL METHOD FOR NAPROXEN ([REDACTED] PROJECT 54076)

Bioanalytical Method ([REDACTED] Project 54076) for Naproxen in Human Plasma Used in Study MT400-101 and in Study MT 400-103

A high performance liquid chromatography (HPLC) assay was developed and validated for analysis of Naproxen. Aliquots of human plasma (EDTA) containing the analyte and internal standard [REDACTED] are extracted [REDACTED]. Reference standards for naproxen [REDACTED]

Extracted samples are analyzed using HPLC. Chromatography was carried out using a C-18 analytical column [REDACTED]

Standard operating procedures (SOPs) were in place for sample preparation, the analytical procedure, and for acceptance of the bioanalytical run (acceptance of calibration standards and quality control (QC) samples).

Selectivity, Accuracy, Precision, and Recovery

Selectivity was determined by analysis of blank samples from 25 independent sources of blank human plasma for presence of interfering endogenous peaks with respect to naproxen or internal standard. It is stated that there was no significant interference in 23 of 25 blanks screened, although the reason for interference of 2 was not described. In addition, during the performance of the Assay for Study MT400-101, selectivity against sumatriptan was demonstrated. Ranges of the calibration curves, LOQ for each analyte, and nominal values for the QC samples are shown in Table 1 below.

Table 1. Summary of standard curves and QC samples

Analyte	Range of Calibration Curve	LOQ	QC Samples
Naproxen	0.5 µg/ml to 99.96 µg/ml	0.5 µg/ml	0.5 µg/ml 1.501 µg/ml 35.014 µg/ml 75.030 µg/ml

A calibration curve included 7 non-zero standards (as well as a zero and a blank). Four sets of calibration curves (in singlicate) were performed. Linearity was established ($r > 0.998$, weighted 1/concentration linear regression analysis). The precision (%CV) for each nonzero standard ranged from 0.2 to 4.6% and is acceptable. The accuracy for each nonzero standard ranged from -7.42 to 9.91 %, as calculated by the reviewer, and is therefore acceptable.

Intra-assay precision and accuracy were analyzed for 10 replicates of each of 4 quality control (QC) concentrations and ranged from 1.6-5.5% and from -9.06 to 3.62%, respectively. Inter-

assay precision and accuracy, with 4 separate sets of analysis (in duplicate) performed ranged from 2.0 to 6.4% and from -9.58 to -0.13, respectively. These values are acceptable.

Stability

Stability of naproxen was demonstrated as follows. Freeze-thaw stability in plasma was demonstrated for 10 aliquots of low and high concentrations after three freeze/thaw cycles. Autosampler stability of extracted samples was demonstrated for 39.2 hours at 4° C. Long term stability in plasma was demonstrated for 79 days at -22° C. Dilution integrity was demonstrated for dilution with plasma by a factor of 10-fold.

The validation report states that in-process (bench top) stability was demonstrated in human plasma prior to extraction at -22 °C for 6.5 hours and at bench-top light conditions for a designated period, although that period was not provided. However, the Sponsor states that the temperature of -22 °C was incorrectly reported, since the extraction procedure in the SOP states that the extraction is performed at room temperature and it is therefore believed that the short term stability evaluation was performed at room temperature.

Stability of stock solutions of internal standard and naproxen were demonstrated in methanol at -22 °C for 113 and 664 days, respectively.

Conclusion

The bioanalytical method used for analysis of human plasma samples with respect to naproxen in clinical study MT400-101 and MT 400-103 is considered adequately documented and validated (although there is a question of the determination of bench-top stability).

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4.12 to 8.90% and from -1.49 to 2.2%, respectively in ██████████ plasma (3 sets of analyses) or ██████████ (2 sets of analyses). These values are acceptable.

Stability

Stability of naproxen was demonstrated as follows. Freeze-thaw stability in plasma was demonstrated for 6 aliquots of low and high concentrations after three freeze/thaw cycles. In-process (bench top) stability was demonstrated in human plasma prior to extraction for 21 hours at room temperature. Autosampler stability of extracted samples was demonstrated for 155 hours at room temperature. Long term stability in plasma was demonstrated for 189 days at -20° C. Dilution integrity was evaluated and demonstrated in performance of the analysis for study MT 400-105 by diluting aliquots of the 70 µg/ml QC sample in runs where subject samples were diluted.

Stability of stock solutions of internal standard and naproxen were demonstrated in methanol for 13 days for naproxen, and 137 days for internal standard at 2-8° C.

Conclusion

The bioanalytical method used for analysis of human plasma samples with respect to naproxen in clinical study MT400-102 is considered adequately documented and validated.

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4.2.3 BIOANALYTICAL METHOD FOR SUMATRIPTAN (LMS-M-6410-00)

Bioanalytical Method (LMS-M-6410-00) for Sumatriptan in Human Plasma Used in Study MT400-101 and MTT 400-103

A high performance liquid chromatography (HPLC) assay [REDACTED] developed and validated [REDACTED] for analysis of sumatriptan in plasma. An aliquot of plasma (EDTA) containing analyte and internal standard [REDACTED], was extracted [REDACTED]. The extracted samples were analyzed by an HPLC mass spectrometer. [REDACTED]

Standard operating procedures (SOPs) were in place.

Selectivity, Accuracy, Precision, and Recovery

Selectivity was determined by analysis of blank samples from 6 independent sources of blank human plasma (EDTA) for presence of interfering endogenous peaks with respect to sumatriptan or internal standard. No significant interference was observed from endogenous components. No significant matrix effect was observed near the concentration of the LLOQ and near the concentration of the high QC sample.

For MT 400-103 and MT 400-101, the validation was updated to show that naproxen did not interfere with analysis of sumatriptan or internal standard.

Ranges of the calibration curves, LOQ, and nominal values for the QC samples are shown in Table 1 below.

Table 1. Summary of standard curves and QC samples

Analyte	Range of Calibration Curve	LOQ	QC Samples
Sumatriptan	1.00-140 ng/ml	1.00 ng/ml	1.00 ng/ml 3.00 ng/ml 40.0 ng/ml 110 ng/ml

A calibration curve included 10 non-zero standards. Three sets of calibration curves were performed. Linearity was established ($r > 0.999$, $1/\text{concentration}$, sum of squares). The precision (%CV) for each nonzero standard ranged from 0.7 to 6.0% and is acceptable. The accuracy for each nonzero standard ranged from -2.2 to 2.9 % and is therefore acceptable.

Intra-assay precision and accuracy were analyzed for 12 replicates of each of 4 quality control (QC) concentrations and ranged from 3.1-6.3% and from -5.45 to 8.67%, respectively. Inter-assay precision and accuracy, with 3 separate sets of analysis (in 6 replicates each) ranged from 1.60 to 7.9% and from 1.00 to 8.00, respectively. These values are acceptable.

Stability

Stability of sumatriptan was demonstrated as follows. Freeze-thaw stability in plasma was demonstrated for 6 aliquots of low and high concentrations after three freeze/thaw cycles (-20° C). In process (bench top) stability of plasma samples was demonstrated at room temperature for 12.5 hours. Autosampler stability of extracted samples was demonstrated for 146.1 hours at 5° C. Long term stability in plasma was demonstrated for 8 days at -20° C, and later was shown for 65 days at -20° C. Dilution integrity was demonstrated for dilution with plasma for up to 500 ng/ml.

Stability of stock solutions of sumatriptan in methanol was demonstrated at -20 °C for 195 days.

Conclusion

The bioanalytical method used for analysis of human plasma samples with respect to sumatriptan in clinical study MT400-101 (and MT 400-103) is considered adequately documented and validated. (*Note:* a later partial validation by [REDACTED] showed long term stability for 130 days and a later revision of the [REDACTED] method (for MT400-103) showed long term stability for 65 days).

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4.2.4 BIOANALYTICAL METHOD FOR SUMATRIPTAN (LCMS 174)

Bioanalytical Method (LCMS 174) for Sumatriptan in Human Plasma Used in Study MT400-102, MT 400-105, and MT 400-104

A high performance liquid chromatography (HPLC) assay [redacted] was partially validated by [redacted] for analysis of sumatriptan. A sample aliquot is fortified with internal standard [redacted]. The Analytes [redacted]

[redacted] The final extract is analyzed vial HPLC with MS/MS detection.

Standard operating procedures (SOPs) were in place.

Selectivity, Accuracy, Precision, and Recovery

Selectivity was determined by analysis of blank samples from 6 independent sources of blank human plasma (EDTA) for presence of interfering endogenous peaks with respect to sumatriptan or internal standard. No significant interference was observed from endogenous components. Matrix suppression effects were also evaluated with the low QC sample and results indicate that matrix suppression effects do not compromise the accuracy of the assay.

Low and high QC samples fortified with 150000 ng/ml naproxen did not show assay interference.

Ranges of the calibration curves, LOQ, and nominal values for the QC samples are shown in Table 1 below.

Table 1. Summary of standard curves and QC samples

Analyte	Range of Calibration Curve	LOQ	QC Samples
Sumatriptan	0.200-100 ng/ml	0.2 ng/ml	0.5 ng/ml 7.5 ng/ml 75.0 ng/ml

A calibration curve included 9 non-zero standards in duplicate. Two sets of calibration curves were performed. Linearity was established ($r > 0.990$, linear weighted, $1/\text{concentration}$, least-squares regression). The precision (%CV) for each nonzero standard ranged from 0.917 to 5.51% and is acceptable. The accuracy for each nonzero standard ranged from -6.56 to 3.36 % and is therefore acceptable.

Intra-assay precision and accuracy were analyzed for 6 replicates of each of 3 quality control (QC) concentrations and ranged from 0.733 to 2.64% and from -2.61 to 1.40%, respectively. Inter-assay precision and accuracy, with 2 separate sets of analysis (in 6 replicates each) ranged from 1.46 to 2.12% and from -1.98 to 0.377, respectively. These values are acceptable.

Stability

Stability of sumatriptan was demonstrated as follows. Long term stability in plasma was demonstrated for 130 days at -20° C. (This was updated for study MT 400-105 that showed long term stability for 852 days). Freeze thaw stability was demonstrated for 3 cycles. In process stability showed analyte stability in thawed matrix for 26 hours at room temperature. Autosampler stability was demonstrated for 127 hours at room temperature. Dilution integrity was demonstrated for diluted high QC samples in the performance of the assay for MT 100-105.

Conclusion

The bioanalytical method used for analysis of human plasma samples with respect to sumatriptan in clinical study MT400-102 (and MT 400-104 and MT400-105) is considered adequately documented and validated. (Stability measures other than long term stability have been shown in other methods provided by the Sponsor).

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4.2.5 BIOAVAILABILITY STUDY MT 400-101

**A STUDY TO EVALUATE THE BIOAVAILABILITY OF COMBO FORMULATION,
EACH OF ITS COMPONENTS AND CURRENTLY MARKETED VERSIONS OF THE
COMPONENTS IN HEALTHY VOLUNTEERS**

Study Investigators and Site:

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Protocol Number: MT 400-101

OBJECTIVES:

To determine the bioavailability of sumatriptan (as the succinate) and naproxen sodium following single oral doses of the following:

- a combination tablet formulation containing sumatriptan 85 mg with sodium bicarbonate and naproxen sodium 500 mg (TREXIMA)
- a sumatriptan 85 mg tablet (with no sodium bicarbonate) (non-RT)
- a naproxen sodium 500 mg component of TREXIMA
- IMITREX 100 mg (with no sodium bicarbonate) (non-RT)
- ANAPROX 550 mg in healthy volunteers.

FORMULATIONS:

Table 1. Products used in MT400-101

	Batch No.	Exp. Date (Dates of Study)
Trexima 85mg/500mg GlaxoSmithKline	031000304	Man. Date is 6/26/03 (9/9/03-10/22/03) (24 months stability data)
Sumatriptan 85 mg GlaxoSmithKline	031000305	Man. Date 6/20/03 (9/9/03-10/22/03) (12 months stability data)
Naproxen sodium 500 mg GlaxoSmithKline	031000306	Man. Date 7/22/03 (9/9/03-10/22/03)
Imitrex 100 mg GlaxoSmithKline	3ZP1113	Exp Date 3/31/06 (9/9/03-10/22/03)
Anaprox 550 mg Roche	E3204	(9/9/03-10/22/03) Exp Date 2/28/06

STUDY DESIGN:

This was a Phase I, randomized, incomplete block, 3-way crossover, open-label, single center study. Subjects were randomized to receive 3 of the following treatments:

TREATMENT GROUP	STUDY MEDICATION
A	Trexima (sumatriptan 85 mg with sodium bicarbonate/ naproxen sodium 500 mg)
B	Sumatriptan (contains no sodium bicarbonate) 85 mg
C	Imitrex 100 mg
D	Anaprox 550 mg
E	Naproxen Sodium 500 mg

Four subjects were randomized to each sequence listed below, so that 24 subjects received each treatment. There was at least an 8-day washout period between doses.

Sequence	Period 1	Period 2	Period 3
I	E	C	D
II	A	D	E
III	B	E	A
IV	C	A	B
V	D	B	C
VI	E	B	A
VII	A	C	B
VIII	B	D	C
IX	C	E	D
X	D	A	E

Inclusion criteria included nonsmoking males or females of non-childbearing potential (surgically sterile or post-menopausal), age 18-55 years. Exclusion criteria included significant medical or psychiatric condition that may have affected interpretation of the PK data or otherwise contraindicated participation in a clinical trial, recent history in the past year suggestive of alcohol or drug abuse or dependence, history of cerebrovascular pathology, history of evidence of ischemic abdominal syndromes, **peripheral vascular disease or Reynaud's syndrome**, uncontrolled hypertension at screening, ingestion of any prescription or OTC medications within 72 hours prior to each study dose, ingestion of any triptan or naproxen-containing products one week before the first dose through 96- hours following the last dose, use of MAO inhibitors within 2 weeks of screening.

All subjects entered the clinical research facility for baseline evaluations by 9PM the day; prior to dosing. On the day of study drug administration, following overnight fast of at least 10 hours, subjects were administered drug product with 240 ml of water. No food was allowed for at least 4 hours post-dose. Water was allowed as desired except for 1 hour before and 1 hour after drug administration. Subjects received standardized meals scheduled at the same time in each period of the study. On the day of dosing, Subjects remained in the Phase I unit until after the 24 hour blood draw had been completed, and returned to the clinic on Days 3, 4, and 5 for the 48-, 72- and 96-hour PK blood draw and review of adverse events and concurrent medications. Blood

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TREXIMA**

samples for determination of plasma naproxen and sumatriptan concentrations were collected prior to dosing and at 10, 20, 30, 40, 50, 60, and 90 minutes and 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours post dose. Subjects who received TREXIMA, naproxen sodium 500 mg, or ANAPROX 550 mg had additional PK samples collected at 48, 72, and 96 hours after the dose. The 96-hour time point could be obtained at any time between 96 and 100 hours post-dose. Each study period was separated by at least an 8-day washout.

Plasma from blood samples were frozen at -20° C or lower and shipped frozen [REDACTED] for analysis.

ASSAY:

Plasma concentrations for naproxen and for sumatriptan were measured using validated methods.

Table 3. Performance of Analytical Methods for MT 400-101

Analyte	Method	Range	Linearity	LOQ	QC	Inter-assay CV (%)	Inter-assay Accuracy (%)
Naproxen	HPLC	0.5-100 µg/ml	r > 0.997	(µg/ml) 0.5	(µg/ml) 1.50	4.1	7.3
	[REDACTED]				35.0	3.7	5.43
	Project				80.0	3.8	3.87
	54076)				80.0	2.3	4.5
Sumatriptan	LC/MS/MS	1-140 ng/ml	r > 0.997	(ng/ml) 1.0	(ng/ml) 3.0	5.5	3.3
	(LCMS				40.0	3.9	3.5
	174)				110.0	3.1	3.6

For naproxen analysis, a set of 8 non-zero calibration standards and duplicate QC standards were run with each batch of study samples. Sample analysis was performed within the period for which the samples are stable. The Sponsor requested that only time points of 0 hours, 10 minutes and 20 minutes were to be analyzed from treatments B and C (that were sumatriptan formulations).

For sumatriptan analysis, samples were stored at a nominal temperature of -20 °C for a duration not exceeding 30 days. This was within the time period in which they are stable. A set of calibration standards (including at least 6 different non zero standards) and 2 replicate QC standards were included in each batch. The Sponsor requested that only the 0, 10 minutes and 20 minutes time points were to be analyzed from Treatments D and E (that were naproxen formulations), although, in fact, all sampling times were analyzed. However, the concentration results were not provided.

The performance of the assays for all analytes is considered acceptable.

RESULTS:

Demographics

Forty subjects were enrolled and completed the study. Demographics are shown in the table below.

Table 4. Demographics of Subjects Completing Study MT 400-101

Mean Age (Range)	Gender	Weight (mean \pm SD)	Race
44 (25-55)	15 males	72 \pm 12 kg (n=40)	Caucasian 19
	25 females	80 \pm 13 kg (male)	Black/African American 4
		67 \pm 9 kg (female)	Other 17 (Ethnic origin reported as Hispanic or Latino in 39 subjects)

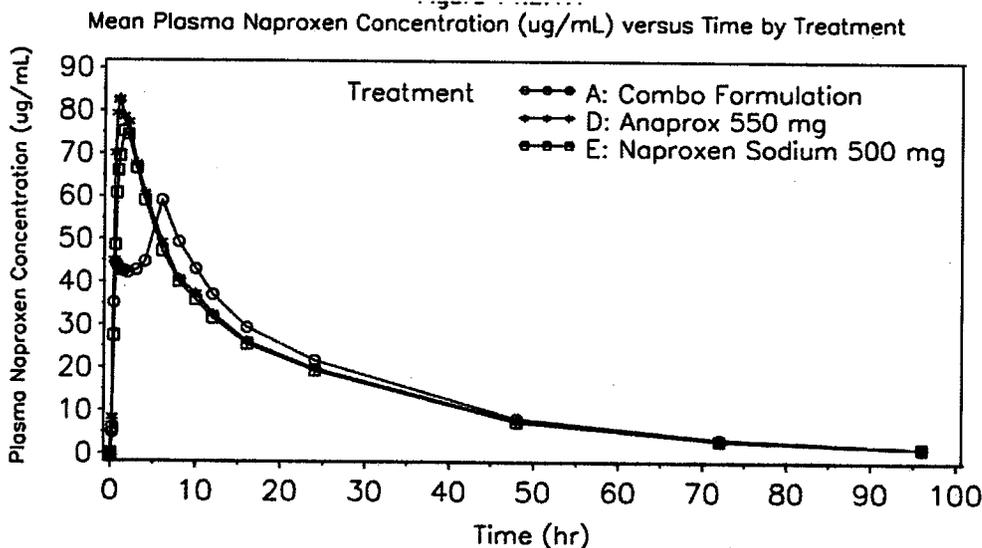
There were no concurrent medications taken during the course of the study.

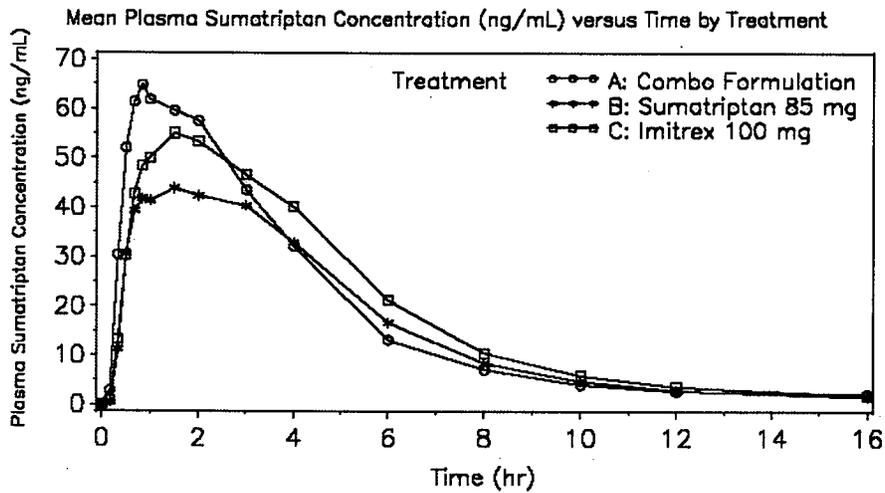
Pharmacokinetics

Pharmacokinetic parameters were determined using noncompartmental analysis. The primary and secondary comparisons are identified in the table below, as provided by the Sponsor.

Primary Objective	n
A vs. B = Trexima vs. Sumatriptan 85 mg	16
A vs. E = Trexima vs. Naproxen Sodium 500 mg	16
Secondary Objective	
B vs. C = Sumatriptan 85 mg vs. Imitrex 100 mg	16
E vs. D = Naproxen Sodium 500 mg vs. Anaprox 550 mg	16
A vs. C = Trexima vs. Imitrex 100 mg	8
A vs. D = Trexima vs. Anaprox 550 mg	8

The mean plasma concentration time course for naproxen (from Treatments A, D and E) and for sumatriptan (From Treatments A, B, and C) are shown in the figures below, as provided by the Sponsor.





For naproxen from Trexima, the C_{max} was lower and delayed relative to naproxen from either Anaprox or naproxen sodium 500 mg. For sumatriptan from Trexima, sumatriptan concentrations were higher than either those from sumatriptan 85 mg or from 100 mg Imitrex, although the shape of the curve was similar.

The pertinent pharmacokinetic parameters for naproxen and for sumatriptan from the specific formulations are shown in the table below, as calculated by the reviewer. The values are generally in agreement with those reported by the Sponsor.

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Table 5. Pharmacokinetic parameters (arithmetic mean) for Naproxen and for Sumatriptan (Study MT 400-101)

	Naproxen (% CV) n=23	Sumatriptan (% CV) n=23
TREXIMA		
t _{max} (h) ^a	6.0 (0.5-8.0)	1.0 (0.5-2.0)
C _{max} (µg/mL)	69.5 (24)	76.2 (35)
AUC _{0-t} (µg*h/mL)	1446.1 (13)	275.5 (23)
AUC _{0-∞} (µg*h/mL)	1492.8 (14)	282.7 (23)
λ _z (hr ⁻¹)	0.037 (13)	0.305 (36)
t _{1/2} (h)	19.3 (14)	2.6 (43)
Sumatriptan 85 mg		
t _{max} (h) ^a		1.5 (0.5-4.0)
C _{max} (µg/mL)		54.3 (31)
AUC _{0-t} (µg*h/mL)		244.9 (28)
AUC _{0-∞} (µg*h/mL)		251.1 (26)
λ _z (hr ⁻¹)		0.292 (26)
t _{1/2} (h)		2.5 (27)
Imitrex 100 mg		
t _{max} (h) ^a		1.5 (0.7-4.0)
C _{max} (ng/mL)		63.8 (30)
AUC _{0-t} (ng*h/mL)		300.9 (28)
AUC _{0-∞} (ng*h/mL)		308.6 (28)
λ _z (hr ⁻¹)		0.263 (27)
t _{1/2} (h)		2.8 (25)
Anaprox 550 mg		
t _{max} (h) ^a	1.0 (0.5-3.0)	
C _{max} (ng/mL)	99.6 (18)	
AUC _{0-t} (ng*h/mL)	1443.6 (15)	
AUC _{0-∞} (ng*h/mL)	1487.7 (16)	
λ _z (hr ⁻¹)	0.036 (12)	
t _{1/2} (h)	19.5 (12)	
Naproxen Sodium 500 mg		
t _{max} (h) ^a	1.0 (0.5-4.0)	
C _{max} (ng/mL)	92.4 (18)	
AUC _{0-t} (ng*h/mL)	1382.8 (17)	
AUC _{0-∞} (ng*h/mL)	1426.6 (18)	
λ _z (hr ⁻¹)	0.037 (14)	
t _{1/2} (h)	19.1 (14)	

^a median (range)

The ratios for determination of bioavailability of naproxen and of sumatriptan from TREXIMA relative to those analytes from the individual formulations are shown in the table below, as determined by the Sponsor. These results confirm the approximate 30% decrease in C_{max} for naproxen from TREXIMA relative to NAPROXEN given at similar doses alone, although the extent of exposure was similar. Sumatriptan C_{max} from TREXIMA was slightly higher (10-30%) than from either Sumatriptan 85 mg or from IMITREX 500 mg given alone, with similar AUCs.

Table 6. Bioavailability Ratios for Study MT400-101

	Geometric Mean for subjects receiving TREXIMA and Reference (B)		Ratio of Geometric Means	90% CI for the Ratio of Geometric Means
	Treatment A	Treatment B		
Naproxen	TREXIMA	ANAPROX 550 mg		
C _{max} (µg/ml)	69.7	109.2	0.65	(0.60,0.72)
AUC _{0-t} (µg*h/ml)	1499.4	1528.9	0.98	(0.94, 1.02)
AUC _{0-∞} (µg*h/mL)	1547.6	1577.2	0.98	(0.94, 1.03)
Naproxen	TREXIMA	NAPROXEN 500 mg		
C _{max} (µg/ml)	69.9	95.4	0.73	(0.67, 0.79)
AUC _{0-t} (µg*h/ml)	1470.9	1408.4	1.04	(1.01, 1.08)
AUC _{0-∞} (µg*h/mL)	1512.1	1448.5	1.04	(1.08, 1.08)
Sumatriptan	TREXIMA	SUMATRIPTAN 85 mg		
C _{max} (ng/ml)	69.6	53.1	1.3	(1.14, 1.50)
AUC _{0-t} (ng*h/ml)	259.3	234.7	1.1	(1.02, 1.19)
AUC _{0-∞} (ng*h/mL)	265.7	240.6	1.1	(1.02, 1.18)
Sumatriptan	TREXIMA	IMITREX 100 mg		
C _{max} (ng/ml)	74.9	69.1	1.11	(0.94, 1.31)
AUC _{0-t} (ng*h/ml)	262.7	298.5	0.90	(0.82, 0.98)
AUC _{0-∞} (ng*h/mL)	269.5	304.9	0.90	(0.83, 0.98)

Gender

The effect of gender on pharmacokinetics of the TREXIMA product was evaluated by the reviewer. The means by gender for selected PK parameters are shown in the table below. PK parameters were similar for men and women.

	Male (n=8)	Female (n=16)
	(% CV)	(% CV)
Naproxen		
t _{max} (h) ^a	2.75 (0.5-8.0)	6.0 (0.5-8.0)
C _{max} (µg/mL)	65.8 (15)	71.3 (27)
AUC _{0-∞} (µg*h/mL)	1411.6 (14)	1533.4 (13)
t _{1/2} (h)	19.3 (20)	19.3 (11)
Sumatriptan		
t _{max} (h) ^a	0.7 (0.5-1.5)	1.0 (0.5-2.0)
C _{max} (ng/mL)	72.4 (38)	78.2 (34)
AUC _{0-∞} (ng*h/mL)	273.8 (21)	287.1 (24)
t _{1/2} (h)	2.7 (47)	2.6 (42)

^a median (range)

Safety

There were no serious adverse events or deaths reported. Four subjects (17%) reported 5 adverse events with TREXIMA. Two subjects (8%) reported 3 adverse events in both sumatriptan 85 mg and Imitrex 100 mg treatment. Two subjects (8%) reported 6 adverse events with Anaprox and none for naproxen sodium 500 mg. The only event occurring in more than 1 subject in any treatment group was dizziness occurring in 3 subjects (13%) in the Trexima group. Other

adverse events included headache (Trexima and Anaprox), nausea (Imitrex and Anaprox), tinnitus (naproxen sodium) and pruritus (Anaprox).

CONCLUSIONS:

1. Administration of naproxen with sumatriptan in TREXIMA resulted in a reduction in C_{max} and a 5-hour delay in T_{max} for TREXIMA compared to naproxen sodium alone. AUC values were similar for naproxen when given with sumatriptan or when given alone.
2. Sumatriptan C_{max} was higher when given as TREXIMA than when given as either sumatriptan 85 mg or Imitrex 100 mg. T_{max} occurred slightly earlier (median 1.0 vs 1.5 hours) for sumatriptan when given as TREXIMA compared to sumatriptan from either sumatriptan 85 mg or Imitrex 100 mg given alone.

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4.2.6 FOOD EFFECT STUDY MT 400-102

**A STUDY TO EVALUATE THE EFFECT OF FOOD ON THE BIOAVAILABILITY OF
A SUMATRIPTAN SUCCINATE AND NAPROXEN SODIUM COMBINATION
TABLET IN HEALTHY VOLUNTEERS**

Study Investigators and Site:

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SFBC International
11190 Biscayne Boulevard
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Protocol Number: MT 400-102

OBJECTIVE:

The primary objective was to determine effects of a high-fat meal on the bioavailability of naproxen sodium and sumatriptan succinate (hereafter sumatriptan) following a single oral dose of TREXIMA (Combo Formulation: sumatriptan 85 mg rapid release technology [RRT] formulation/naproxen sodium 500 mg) in healthy volunteers. An additional objective was to compare the bioavailability of the sumatriptan in TREXIMA (fasted) with the single entity sumatriptan 85 mg RRT (fasted).

FORMULATIONS:

Table 1. Products used in MT400-102

	Batch No.	Exp. Date (Dates of Study)
Trexima 85mg/500mg GlaxoSmithKline	B916681	Man. Date is 11/121/03 (4/7/04-7/8/04) (18 month stability data)
Sumatriptan 85 mg GlaxoSmithKline	031006060	Man. Date is 6/26/03 (4/7/04-7/8/04) (24 month stability data)

STUDY DESIGN:

This was a Phase I, randomized, 3-way crossover, open-label, single center study. Subjects were randomized to one of six sequences for receiving each of the following treatments: TREXIMA (fasted), TREXIMA (fed) and sumatriptan 85 (fasted).

Number of Subjects	Treatment Sequences
4	1 Trexima Tablet (Fasted) 1 Trexima Tablet (Fed) 1 Sumatriptan 85 mg Tablet (Fasted)
4	1 Sumatriptan 85 mg Tablet (Fasted) 1 Trexima Tablet (Fasted) 1 Trexima Tablet (Fed)
4	1 Trexima Tablet (Fed) 1 Trexima Tablet (Fasted) 1 Sumatriptan 85 mg Tablet (Fasted)
4	1 Trexima Tablet (Fasted) 1 Sumatriptan 85 mg Tablet (Fasted) 1 Trexima Tablet (Fed)
4	1 Sumatriptan 85 mg Tablet (Fasted) 1 Trexima Tablet (Fed) 1 Trexima Tablet (Fasted)
4	1 Trexima Tablet (Fed) 1 Sumatriptan 85 mg Tablet (Fasted) 1 Trexima Tablet (Fasted)

Inclusion criteria included males or females (not pregnant or lactating), age 18-55 years that were not currently smokers. Females must have been of non-childbearing potential or of child-bearing potential with abstinence, sterilization, or contraception (including oral contraception). Exclusion criteria included significant medical or psychiatric condition that may have affected interpretation or otherwise contraindicated participation in a clinical trial, recent history in the past year suggestive of alcohol or drug abuse or dependence, history of cerebrovascular pathology, confirmed or suspected ischemic heart disease or ischemic abdominal syndromes, **peripheral vascular disease or Reynaud's syndrome**, uncontrolled hypertension at screening, ingestion of any prescription or OTC medications within 72 hours prior to each study dose, ingestion of any triptan or naproxen-containing products one week before the first dose through 96- hours following the last dose, use of MAO inhibitors within 2 weeks of screening, and any subject with a known allergy or intolerance to naproxen sodium or sumatriptan.

Subjects were admitted to the inpatient unit the evening prior to dosing in each study period. Study periods were separated by a washout period of at least 8 days. Each subject received one dose of study medication on the first day of each of the three treatment periods after an overnight fast of at least 10 hours. Subjects receiving the fed TREXIMA treatment were served a high fat meal (800-1000 calories, with 50% of the calories from fat and was in accordance with the Food Effect Guidance) 30 minutes prior to receiving the study drug. The meal was to be consumed over 30 minutes with administration of study drug immediately after the meal. The study drug was administered with 240 ml water. For the fasted periods, no food was allowed for at least 4 hours post-dose. For both fed and fasted treatments, water was allowed as desired except for 1 hour before and 1 hour after drug administration. Subjects received other standardized meals scheduled at the same time in each period of the study. Blood was collected for plasma naproxen and sumatriptan analysis at pre-dose and at 10, 20, 30, 40, 50, 60, and 90 minutes and at 2, 3, 4, 6, 8, 10, 12, 16, 24, 48, and 72 hours following the dose.

Plasma from blood samples were frozen at -20° C or lower and shipped frozen to [REDACTED] for analysis.

ASSAY:

Plasma concentrations for naproxen and for sumatriptan were measured using validated methods.

Table 3. Performance of Analytical Methods for MT 400-102

Analyte	Method	Range	Linearity	LOQ	QC	Inter-assay CV (%)	Inter-assay Accuracy (%)
Naproxen	HPLC (LC 72.2)	0.1-100 µg/ml	r > 0.998	(µg/ml) 0.1	(µg/ml) 0.25	10.6	0.039
					3.0	2.32	0.663
					70.0	1.98	-3.22
Sumatriptan	LC/MS/MS (Method LCMS 174)	0.2-100 ng/ml	r > 0.999	(ng/ml) 0.2	(ng/ml) 0.5	3.17	-0.176
					7.5	1.53	-0.379
					75.0	1.40	-0.831

For naproxen analysis, a set of 10 non-zero calibration standards in duplicate and triplicate QC standards were run with each batch of study samples. Sample analysis was performed within the period for which the samples are stable.

For sumatriptan analysis a set of 9 non-zero calibration standards in duplicate and 6 replicate QC standards were included in each batch. Sample analysis was performed within the period for which the samples are stable.

The performance of the assays for all analytes is considered acceptable.

RESULTS:

Demographics

Twenty-four subjects were enrolled in the study and 21 subjects completed the study. The demographics of the subjects completing the study are shown below.

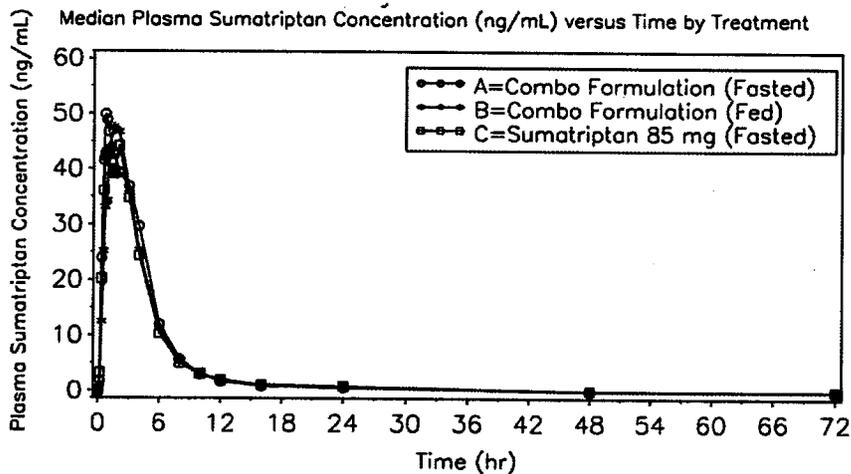
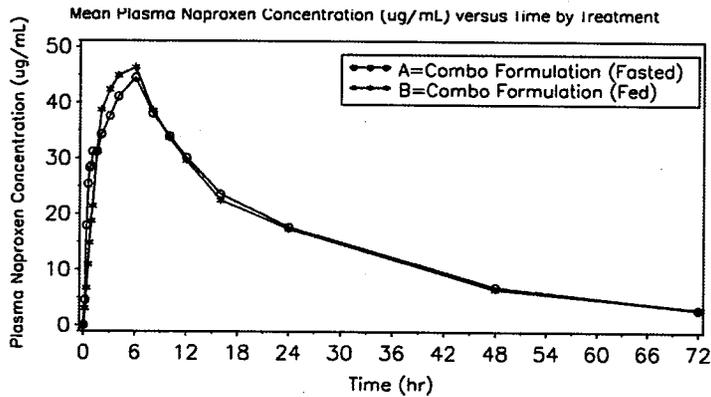
Table 4. Demographics of Subjects Completing Study MT 400-105

Mean Age (Range)	Gender	Weight (mean ± SD)	Race
46.2 (21-55)	10 males	71 ± 10 kg (n=24)	Caucasian 21
	11 females	77 ± 10 kg (male)	
		67 ± 8 kg (female)	

The only concurrent medication taken by any subject was ibuprofen for back pain. This occurred during a between treatment 8-day washout period by subject 1019.

Pharmacokinetics

The mean plasma concentration time course from each treatment for naproxen (fed or fasted with the Combo Formulation (TREXIMA)) and for sumatriptan (fed or fasted with the Combo Formulation (TREXIMA) or fasted with sumatriptan 85 mg) are shown in the figures below, as provided by the Sponsor.



Pharmacokinetic parameters were determined using noncompartmental analysis. The pertinent pharmacokinetic parameters for naproxen and for sumatriptan from the specific treatments are shown in the table below, as calculated by the Sponsor. The values are generally in agreement with those calculated by the reviewer.

Table 5. Pharmacokinetic parameters (arithmetic mean) for Naproxen and for Sumatriptan (Study MT 400-102)

	Fed (TREXIMA) (% CV)	Fasted (TREXIMA) (% CV)	Fasted (SUMATRIPTAN 85 mg) (% CV)
Naproxen	<i>(n=23)</i>	<i>(n=22)</i>	NA
t _{max} (h) ^a	4.0 (1.5-6.0)	4.0 (0.33-12.0)	
C _{max} (µg/mL)	54.7 (16)	54.2 (19)	
AUC _{0-t} (µg*h)	1095.3 (16)	1120.6 (18)	
AUC _{0-∞} (µg*h/mL)	1169.4 (17)	1202.7 (20)	
t _{1/2} (h)	17.7 (14)	18.2 (13)	
Sumatriptan	<i>(n=23)</i>	<i>(n=22)</i>	<i>(n=23)</i>
t _{max} (h) ^a	1.5 (0.8-4.0)	0.9 (0.5-3.0)	0.8 (0.5-4.0)
C _{max} (ng/ml)	57.9 (37)	58.5 (40)	51.5 (39)
AUC _{0-t} (ng*h/mL)	225.9 (30)	223.3 (36)	205.2 (32)
AUC _{0-∞} (ng*h/mL)	229.9 (30)	227.3 (36)	210.4(32)
t _{1/2} (h) ^b	2.6 (16)	2.6 (21)	2.9 (17)

^a median (range)
NA = not applicable

The bioavailability comparisons for fed vs fasted for TREXIMA are shown in the Table below, as calculated by the Sponsor, and in agreement with that calculated by the Reviewer.

Table 6. Bioavailability Ratios for TREXIMA Fed and Fasting in Study MT400-102

	Geometric Mean for subjects receiving both fed and fasted treatments (n=22)		Ratio of Geometric Means	90% CI for the Ratio of Geometric Means
	Treatment A Fasted (REFERENCE)	Treatment B Fed (TEST)		
Naproxen				
C _{max} (µg/ml)	53.1	54.1	1.02	(0.96, 1.08)
AUC _{0-t} (µg*h/ml)	1098.0	1081.6	0.98	(0.96, 1.01)
AUC _{0-∞} (µg*h/mL)	1175.2	1152.7	0.98	(0.95, 1.01)
Sumatriptan				
C _{max} (ng/ml)	55.7	54.4	0.98	(0.85, 1.12)
AUC _{0-t} (ng*h/ml)	211.6	213.8	1.01	(0.94, 1.08)
AUC _{0-∞} (ng*h/mL)	215.2	271.5	1.01	(0.95, 1.08)

For naproxen, after administration of TREXIMA there was no difference in C_{max} or AUC or in T_{max} between fed or fasted. For sumatriptan, after administration of TREXIMA there was no difference in C_{max} or AUC, although food delayed the T_{max} by approximately 36 minutes.

A comparison of sumatriptan from TREXIMA and from Sumatriptan 85 mg tablets (n=21 subjects who received each treatment) showed no difference in AUC, although C_{max} from TREXIMA was approximately 17% greater than from the individual sumatriptan 85 mg tablet. The bioequivalence comparison is shown in the table below.

Table 7. Bioavailability Ratios for Sumatriptan from TREXIMA vs Sumatriptan 85 mg RT in Study MT400-102

	Geometric Mean for subjects receiving both treatments (n=21)		Ratio of Geometric Means	90% CI for the Ratio of Geometric Means
	Treatment C Sumatriptan 85 mg RT (REFERENCE)	Treatment A TREXIMA (TEST)		
Sumatriptan				
C _{max} (ng/ml)	47.5	55.7	1.17	(1.02,1.34)
AUC _{0-t} (ng*h/ml)	193.42	211.62	1.09	(1.02-1.17)
AUC _{0-∞} (ng*h/mL)	198.43	215.17	1.08	(1.01-1.16)

Gender

Pharmacokinetic parameters following administration of TREXIMA are shown by gender (data as provided by Sponsor).

Table 7. Pharmacokinetic parameters (arithmetic mean) for Naproxen and for Sumatriptan (Study MT 400-102) by gender after administration of TREXIMA

	Fed (TREXIMA) (% CV)		Fasted (TREXIMA) (% CV)	
	Females (n=11)	Males (n=12)	Females (n=11)	Males (n=12)
Naproxen				
t _{max} (h) ^a	6.0 (2.0-6.0)	3.5 (1.5-6.0)	5.03 (0.33-12.00)	4.00 (0.67-6.00)
C _{max} (µg/mL)	58.6 (16)	51.0 (14)	54.0 (13)	54.5 (23)
AUC _{0-t} (µg*h/h)	1198.4 (15)	1000.8 (12)	1209.5 (19)	1031.8 (12)
AUC _{0-∞} (µg*h/mL)	1279.8 (16)	1068.2 (14)	1305.0 (22)	1100.4 (13)
t _{1/2} (h)	17.4 (17)	18.0 (12)	18.4 (14)	18.0 (12)
Sumatriptan				
t _{max} (h) ^a	1.5 (0.8-4.0)	1.5 (0.8-3.0)	1.0 (0.5-3.0)	0.7 (0.5-2.0)
C _{max} (ng/ml)	67.3 (31)	49.2 (39)	66.5 (34)	50.6 (43)
AUC _{0-t} (ng*h/mL)	263.4 (17)	191.5 (36)	262.6 (32)	184.1 (31)
AUC _{0-∞} (ng*h/mL)	267.9 (18)	195.0 (36)	267.0 (32)	187.7 (31)
t _{1/2} (h) ^b	2.5 (17)	2.7 (14)	2.7 (20)	2.6 (23)

^a median (range)

For naproxen, males had an approximate 13% lower C_{max} than females in the fed state and an approximate 15% lower AUC in either fed or fasted conditions. T_{max} occurred slightly earlier in males. There was no difference in half-life. For sumatriptan, the C_{max} in males was approximately 25% lower than in females and AUC was approximately 30% lower in males than in females, with no difference in half-life. When C_{max} and AUC_{inf} were corrected for weight by the reviewer, the mean (%CV) sumatriptan C_{max} and AUC for males and females are as follows:

	Male		Female	
	Fed	Fasted	Fed	Fasted
C _{max} (ng/(kg*ml))	0.66 (43)	0.67 (46)	1.04 (44)	1.02 (39)
AUC _{0-∞} (ng*h/(kg*mL))	2.59 (39)	2.44 (30)	4.09(21)	4.08 (33)

It can be seen that the difference still exists.

Safety

There were no serious adverse events or deaths reported. Fifty percent of subjects reported adverse events with TREXIMA (fasted) and 39% reported adverse events with TREXIMA (fed). Thirty-five percent of subjects reported adverse events with sumatriptan. One subject discontinued the study due to continuous elevated high blood pressure. Adverse events judged by the investigator to be drug related included headache, dizziness, and nausea.

CONCLUSIONS:

1. For naproxen, after administration of TREXIMA there was no difference in Cmax or AUC or in Tmax between fed or fasted.
2. For sumatriptan, after administration of TREXIMA there was no difference in Cmax or AUC between fed or fasted, although food delayed the Tmax by approximately 36 minutes.
3. A comparison of sumatriptan from TREXIMA and from Sumatriptan 85 mg tablets (n=21) showed no difference in AUC, although Cmax from TREXIMA was approximately 17% greater than from the individual sumatriptan 85 mg tablet.
4. Males had lower exposure to either sumatriptan or naproxen than did females after administration of TREXIMA.

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4.2.7 BIOAVAILABILITY STUDY MT 400-103

A STUDY TO EVALUATE THE BIOAVAILABILITY OF DIFFERENT DOSE COMBINATIONS OF SUMATRIPTAN SUCCINATE AND NAPROXEN SODIUM 500 MG IN HEALTHY VOLUNTEERS

Study Investigators and Site:

Gilbert Weiner, DO
SFBC International
11190 Biscayne Boulevard
Miami, FL 33181

Protocol Number: MT 400-103

OBJECTIVE:

To accurately characterize the pharmacokinetic profiles of naproxen and sumatriptan when co-administered.

FORMULATIONS:

Table 1. Products used in MT400-103

	Batch No.	Exp. Date (Dates of Study)
Trexima 85mg/500mg GlaxoSmithKline	031000304	Man. Date is 6/26/03 (1/8/04-2/26/04) (24 month stability data)
Sumatriptan 85 mg with sodium bicarbonate GlaxoSmithKline	031006060	Man. Date 6/20/03 (1/8/04-2/26/04) (24 month stability data)
Naproxen sodium 500 mg GlaxoSmithKline	031000306	Man. Date 7/22/03 (1/8/04-2/26/04) (24 month stability data)
Imitrex 50 mg GlaxoSmithKline	3ZP1687	(1/8/04-2/26/04) Exp Date 3/3/06
Sumatriptan 85 mg (without sodium bicarbonate) GlaxoSmithKline	31000305	Man. Date 6/20/03 (1/8/04-2/26/04) (12 month stability data)

STUDY DESIGN:

This was a Phase I, randomized, 3-way incomplete crossover, open-label, single center study. Subjects were randomized to receive 3 of the following treatments (table as provided by Sponsor):

Treatment	Study Medication
A	One Sumatriptan 85 mg with sodium bicarbonate tablet and One naproxen sodium 500 mg tablet
B	One Imitrex 50 mg tablet and One naproxen sodium 500 mg tablet
C	One Sumatriptan 85 mg with sodium bicarbonate/naproxen sodium 500 mg tablet (Trexima tablet)
D	One Sumatriptan 85 mg tablet and One naproxen sodium 500 mg tablet

Subjects were randomized to one of four sequences shown in the table below, as provided by the Sponsor. This resulted in all subjects receiving A and B, 15 subjects receiving C and 15 receiving D.

Table 4: Treatment Sequences

Sequence	Period 1	Period 2	Period 3
I	A	B	C
II	A	B	D
III	B	A	C
IV	B	A	D

Inclusion criteria included males or females, age 18-55 years that were not currently smokers. Females must have been of non-childbearing potential or of child-bearing potential with abstinence, sterilization, or contraception (including oral contraception). Exclusion criteria included significant medical or psychiatric condition that may have affected interpretation or otherwise contraindicated participation in a clinical trial, recent history in the past year suggestive of alcohol or drug abuse or dependence, history of cerebrovascular pathology, history of evidence of ischemic heart disease or ischemic abdominal syndromes, peripheral vascular disease or **Reynaud's syndrome, uncontrolled hypertension** at screening, ingestion of any prescription or OTC medications within 72 hours prior to each study dose, ingestion of any triptan or naproxen-containing products one week before the first dose through 72- hours following the last dose, use of MAO inhibitors within 2 weeks of screening, and any subject with a known allergy or intolerance to naproxen sodium or sumatriptan.

Each subject received 1 dose of study medication with 120 ml of water on the morning of Day 1 of each of 3 treatment periods after an overnight fast of at least 10 hours. No food was allowed for at least 4 hours post-dose. Water was allowed as desired except for 1 hour before and 1 hour after study drug administration. Subjects received standardized meals scheduled at the same time in each period of the study. Blood samples were collected at pre-dose and at 10, 20, 30, 45, 60, and 90 minutes and at 2, 3, 4, 6, 9, 12, 16, 24, 48, and 72 hours after the dose. There was a washout period of at least 8 days between treatment periods.

Plasma from blood samples were frozen at -20° C or lower and shipped frozen to [REDACTED] for analysis.

ASSAY:

Plasma concentrations for naproxen and for sumatriptan were measured using validated methods.

Table 3. Performance of Analytical Methods for MT 400-103

Analyte	Method	Range	Linearity	LOQ	QC	Inter-assay CV (%)	Inter-assay Accuracy (%)
Naproxen	HPLC	0.5-100 µg/ml	r > 0.994	(µg/ml) 0.5	(µg/ml)	2.9	4.7
					1.50		
	Project 54076)				35.0		
					80.0		
					80.0	2.3	0.5
Sumatriptan	LC/MS/MS	1-140 ng/ml	r > 0.997	(ng/ml) 1.0	(ng/ml)	2.9	-0.7
					3.0		
	(LCMS 174)				40.0		
					110.0		
					2.9	-0.9	

For naproxen analysis, a set of 8 non-zero calibration standards and duplicate QC standards were run with each batch of study samples. Sample analysis was performed within the period for which the samples are stable.

For sumatriptan analysis, samples were stored at a nominal temperature of -20 °C for a duration not exceeding 20 days after receipt from the study site. Sample analysis was performed within the period for which the samples are stable. A set of calibration standards (including at 10 different non zero standards) and 4 replicate QC standards were included in each batch.

The performance of the assays for all analytes is considered acceptable.

RESULTS:

Demographics

Thirty-one subjects were randomized and 27 completed all three study treatments. Twenty-nine subjects were evaluable for pharmacokinetics. Demographics are shown in the table below for the subjects evaluable for pharmacokinetic analysis.

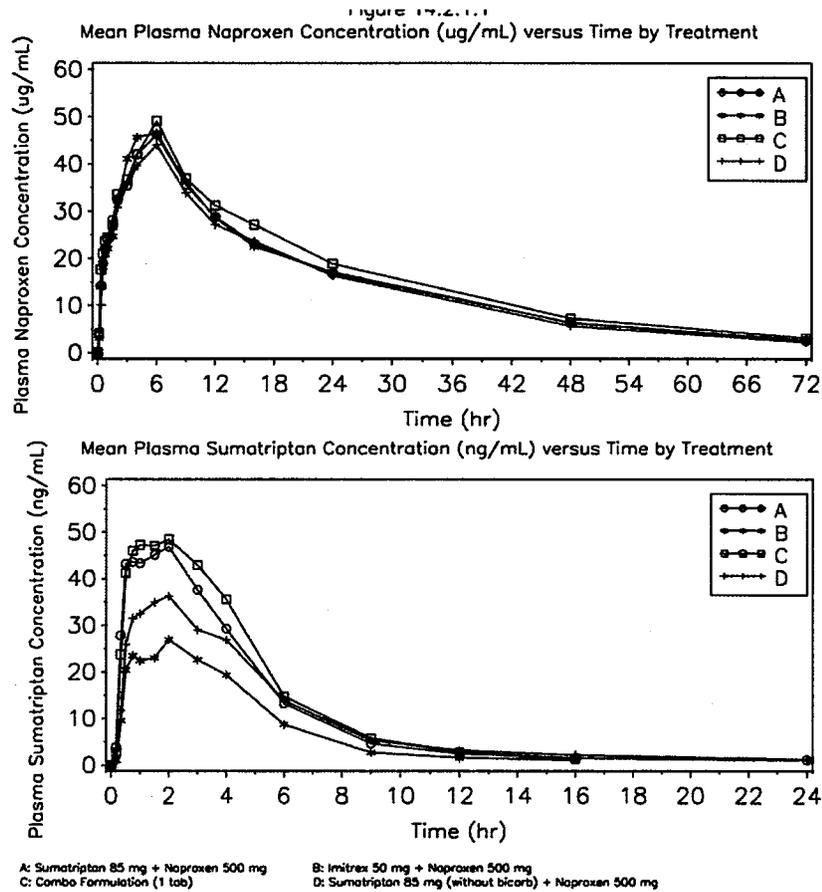
Table 4. Demographics of Subjects Completing Study MT 400-103

Mean Age (Range)	Gender	Weight (mean ± SD)	Race
40 (19-54)	14 males	75 ± 15 kg (n=29)	Caucasian 8
	15 females	84 ± 12 kg (male)	Black/African American 1
		67 ± 12 kg (female)	Other 20 (Ethnic origin reported as Hispanic or Central or South American Indian in 20 subjects)

Two subjects took concurrent medications during the study. One subject took propoxyphene for joint pain and one subject took Tylenol for a headache, and both were taken for 1 day.

Pharmacokinetics

The mean plasma concentration time course from each treatment for naproxen and for sumatriptan are shown in the figures below, as provided by the Sponsor.



Pharmacokinetic parameters were determined using noncompartmental analysis. The pertinent pharmacokinetic parameters for naproxen and for sumatriptan from the specific formulations are shown in the table below, as calculated by the reviewer. The values are generally in agreement with those reported by the Sponsor.

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Table 5. Pharmacokinetic parameters (arithmetic mean) for Naproxen and for Sumatriptan (Study MT 400-103)

	Naproxen (% CV)	Sumatriptan (% CV)
(A) Sumatriptan 85 mg (with bicarb) + Naproxen 500 mg		
t_{max} (h) ^a	(<i>n</i> =29) 4.0 (0.5-9.0)	(<i>n</i> =29) 1.5 (0.5-4.0)
C_{max} (µg/mL for Naproxen, ng/ml for Sumatriptan)	56.8 (21)	58.4 (38)
AUC _{0-t} (µg*h/mL for Naproxen, ng*h/mL for Sumatriptan)	1058.0 (18)	237.7 (31)
AUC _{0-∞} (µg*h/mL for Naproxen, ng*h/mL for Sumatriptan)	1148.5 (19)	244.2 (30)
λ_z (hr ⁻¹)	0.040 (16)	0.261 (33)
$t_{1/2}$ (h)	17.7 (17)	3.0 (33)
(B) Imitrex 50 mg + Naproxen 500 mg		
t_{max} (h) ^a	(<i>n</i> =29) 4.0 (1.5-6.0)	(<i>n</i> =29) 2.0 (0.5-4.0)
C_{max} (µg/mL for Naproxen, ng/ml for Sumatriptan)	56.6 (22)	32.0 (28)
AUC _{0-t} (µg*h/mL for Naproxen, ng*h/mL for Sumatriptan)	1080.3 (17)	134.5 (29)
AUC _{0-∞} (µg*h/mL for Naproxen, ng*h/mL for Sumatriptan)	1147.4 (19)	139.4 (28)
λ_z (hr ⁻¹)	0.041 (15)	0.349 (27)
$t_{1/2}$ (h)	17.2 (14)	2.2 (43)
(C) TREXIMA		
t_{max} (h) ^a	(<i>n</i> =14) 6.0 (0.5-6.0)	(<i>n</i> =14) 1.75 (0.5-4.0)
C_{max} (µg/mL for Naproxen, ng/ml for Sumatriptan)	57.9 (20)	56.0 (36)
AUC _{0-t} (µg*h/mL for Naproxen, ng*h/mL for Sumatriptan)	1178.2 (21)	262.2 (37)
AUC _{0-∞} (µg*h/mL for Naproxen, ng*h/mL for Sumatriptan)	1263.3 (22)	268.5 (36)
λ_z (hr ⁻¹)	0.039 (17)	0.276 (26)
$t_{1/2}$ (h)	18.1 (15)	2.7 (27)
(D) Sumatriptan 85 mg (without bicarb) + Naproxen 500 mg		
t_{max} (h) ^a	(<i>n</i> =13) 4.0 (0.75-6.0)	(<i>n</i> =13) 1.5 (0.5-3.0)
C_{max} (µg/mL for Naproxen, ng/ml for Sumatriptan)	54.0 (20)	42.7 (38)
AUC _{0-t} (µg*h/mL for Naproxen, ng*h/mL for Sumatriptan)	1025.6 (13)	205.0 (32)
AUC _{0-∞} (µg*h/mL for Naproxen, ng*h/mL for Sumatriptan)	1081.5 (13)	213.5 (30)
λ_z (hr ⁻¹)	0.042 (11)	0.256 (39)
$t_{1/2}$ (h)	16.7 (12)	3.2 (42)

^a median (range)

The ratios for determination of bioavailability of naproxen and of sumatriptan from TREXIMA (C) relative to those analytes from the other combinations are shown in the table below, as determined by the Sponsor. This analysis also includes comparisons of the other combinations to each other.

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Table 6. Bioavailability Ratios for Study MT400-103

		Geometric Mean		Ratio of Geometric Means	90% CI for the Ratio of Geometric Means	
PK Parameter	Comparison	Test	Reference			
Naproxen	C _{max} (µg/ml)	A vs B	55.6	55.5	1.00	(0.94, 1.07)
		A vs C	60.9	56.9	1.07	(0.95, 1.21)
		B vs C	60.9	56.9	1.07	(0.96, 1.20)
		A vs D	48.7	53.1	0.92	(0.84, 1.00)
		B vs D	51.6	53.2	0.97	(0.87, 1.08)
		C vs D	56.9	53.0	1.07	(0.94, 1.22)
	AUC _{0-t} (µg*h/ml)	A vs B	1042.8	1064.1	0.98	(0.95, 1.01)
		A vs C	1136.3	1154.8	0.98	(0.95, 1.02)
		B vs C	1139.8	1154.8	0.99	(0.95, 1.03)
		A vs D	977.0	1017.6	0.96	(0.92, 1.00)
		B vs D	985.4	1017.5	0.97	(0.91, 1.03)
		C vs D	1154.8	1017.9	1.13	(1.01, 1.27)
	AUC _{0-∞} (µg*h/mL)	A vs B	1130.11	1127.51	1.00	(0.97, 1.03)
		A vs C	1214.27	1234.48	0.98	(0.95, 1.02)
		B vs C	1212.62	1234.48	0.98	(0.94, 1.03)
		A vs D	1029.89	1072.72	0.96	(0.92, 1.00)
		B vs D	1036.02	1072.58	0.97	(0.90, 1.03)
		C vs D	1234.48	1073.53	1.15	(1.02, 1.30)
Sumatriptan	C _{max} (ng/ml)	A vs B	54.7	30.8	1.78	(1.60, 1.98)
		A vs C	61.2	52.8	1.16	(1.01, 1.34))
		B vs C	32.2	52.8	0.61	(0.53, 0.70)
		A vs D	49.5	40.3	1.23	(1.02, 1.48)
		B vs D	30.3	40.2	0.75	(0.65, 0.87)
		C vs D	52.8	40.1	1.32	(1.04, 1.68)
	AUC _{0-t} (ng*h/ml)	A vs B	227.04	128.98	1.76	(1.66, 1.86)
		A vs C	240.83	245.65	0.98	(0.90, 1.07)
		B vs C	132.85	245.65	0.54	(0.49, 0.59)
		A vs D	212.86	195.63	1.09	(0.99, 1.19)
		B vs D	123.59	195.90	0.63	(0.57, 0.7)
		C vs D	245.65	194.94	1.26	(0.99, 1.60)
	AUC _{0-∞} (ng*h/mL)	A vs B	233.78	134.09	1.74	(1.65, 1.84)
		A vs C	246.44	252.25	0.98	(0.89, 1.07)
		B vs C	137.69	252.25	0.55	(0.50, 0.60)
		A vs D	219.51	204.6	1.07	(0.99, 1.17)
		B vs D	128.98	204.9	0.63	(0.57, 0.69)
		C vs D	252.25	203.96	1.24	(0.98, 1.56)

There were no differences in naproxen C_{max} observed among the different combinations (all containing 500 mg naproxen sodium). There were no differences in AUC among the different combinations, except for TREXIMA vs Treatment D (Sumatriptan 85 mg (without bicarb) + Naproxen 500 mg) , in which an approximate 16% higher AUC for TREXIMA is observed.

For sumatriptan, there was a lower C_{max} from TREXIMA compared to Treatment A (sumatriptan with bicarb + naproxen given separately), but no difference in AUC was observed. Both TREXIMA and Treatment A showed higher C_{max} compared to Treatment D that had

sumatriptan without bicarb. TREXIMA but not Treatment A had a higher sumatriptan AUC than did Treatment D (approximately 26%). Exposure after administration of Treatment B (Imitrex 50 mg plus 500 mg naproxen) was lower compared to all other treatments (that had higher doses of sumatriptan).

Safety

There were no serious adverse events or deaths reported. Adverse event rates ranged from 28% to 38% across treatments (29% for TREXIMA). The most frequent adverse event reported with each of the treatments was headache in 17-31% (21% for TREXIMA). Other adverse events with TREXIMA included nausea, diarrhea, and vomiting. All events were mild or moderate in severity. One subject was discontinued due to adverse events following administration of Treatment A. These were reported as headache, tension in neck, nausea, and chest pressure on inhalation of which headache and nausea were considered by the investigator to be related to study medication, and all of which resolved.

CONCLUSIONS:

1. Naproxen C_{max} (when naproxen was given in combination with sumatriptan) was not dependent on sumatriptan dose or formulation.
2. Naproxen T_{max} was later (6 hr vs 4 hr) when given as TREXIMA than when given in other naproxen/sumatriptan formulations.
3. Naproxen AUC was similar (within the BE interval of 0.8 to 1.25) for TREXIMA compared to the other naproxen/sumatriptan formulations except for Treatment D in which TREXIMA had an approximate 16% higher AUC.
4. C_{max} for sumatriptan when given with sodium bicarb (Treatments A and C (TREXIMA)) was higher than when given without sodium bicarb.
5. Sumatriptan AUC was approximately 26% higher when given as TREXIMA than as Treatment D.
6. Based on conclusions #3 and 5, naproxen and sumatriptan were both more bioavailable from TREXIMA than from Treatment D (sumatriptan and naproxen given together as individual components), so that there is a formulation effect
7. Sumatriptan exposure (AUC and C_{max}) was dependent on dose.

4.2.8 EFFECT OF MIGRAINE ON TREXIMA PK (Study MT 400-104)

**AN OPEN-LABEL STUDY TO INVESTIGATE THE EFFECT OF MIGRAINE
ATTACKS ON THE PHARMACOKINETICS OF A SINGLE DOSE OF TREXIMA
ADMINISTERED BOTH DURING AND OUTSIDE OF A MIGRAINE ATTACK**

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Protocol Number: MT 400-104

OBJECTIVE:

To investigate the effect of migraine attacks on the PK of sumatriptan succinate and naproxen sodium following a single dose of TREXIMA administered both during and outside of migraine attacks.

FORMULATIONS:

Table 1. Products used in MT400-104

	Tablet Description	Batch No.	Exp. Date (Dates of Study)
Trexima 85mg/500mg GlaxoSmithKline	Medium blue film coated tablet	B916681	Man. Date is 11/12/03 (9/23/04-1/5/05) (18 month stability data)

STUDY DESIGN:

This was a Phase I, single dose, open-label, nonrandomized, one-sequence cross-over study. Subjects received a single TREXIMA tablet in each of 2 dosing periods. In the first treatment period, each subject received a single TREXIMA tablet with 240 ml water as soon as possible after onset of a moderate to severe migraine, and after a fast of at least 4 hours (determined at screening). It was confirmed at dosing that subjects continued to have a moderate to severe headache. In the second period (control), subjects received the same treatment during a time when they were not experiencing a migraine, and this was to be at the same time of day as their initial dosing. No food was allowed for at least 4 hours post-dose, and water was allowed as desired except for 1 hour before and 1 hour after study drug administration. Blood samples were collected prior to dosing and at 10, 20, 30, 40, 50, 60, and 90 minutes and at 2, 3, 4, 6, 8, 10, 12, 16, 24, 48 and 72 hours post dosing. If the subject vomited within 1 hour of taking study drug, the procedures were terminated and the subject was withdrawn from the study.

Inclusion criteria included males or females (not pregnant or lactating), age 18-55 years that were not currently smokers. Females must have been of non-childbearing potential or of child-bearing potential with abstinence, sterilization, or contraception (including oral contraception). Subjects must have had their first migraine prior to the age of 50 years and had at least a 6-month history of migraine with or without aura, and an average migraine headache frequency of 2-8 moderate or severe attacks per month in the previous 3 months. Exclusion criteria included significant medical or psychiatric condition that may have affected interpretation or otherwise contraindicated participation in a clinical trial, history of impaired renal or hepatic function, uncontrolled hypertension at screening, currently taking an MAO inhibitor (or within 2 weeks of screening or 2 weeks after treatment), currently taking any anti-coagulant or NSAID on a regular basis (except for aspirin \leq 325 mg per day for cardiovascular prophylaxis), having taken in the previous 4 weeks herbal preparations containing St. John's wort. Alcohol, NSAIDs, analgesics containing morphine, codeine, or opioid derivative, or any 5-HT agonist were not to have been taken within 24 hours prior to treatment in this study. Rescue medications were allowed after the 4-hour blood sample had been drawn but were not to include NSAIDs, ergot-type medication, and 5HT1 agonists.

Plasma from blood samples were frozen at -20° C or lower and shipped frozen to [REDACTED] for analysis.

ASSAY:

Plasma concentrations for naproxen and for sumatriptan were measured using validated methods.

Table 3. Performance of Analytical Methods for MT 400-104

Analyte	Method	Range	Linearity	LOQ	QC	Inter-assay CV (%)	Inter-assay Accuracy (%)		
Naproxen	HPLC	0.1-100 μ g/ml	$r > 0.998$	$(\mu$ g/ml)	$(\mu$ g/ml)				
	[REDACTED]					0.1	0.25	13.5	1.32
	LC 72.2)						3.0	5.39	-3.44
						70.0	2.61	-2.19	
Sumatriptan	LC/MS/MS	0.2-100 ng/ml	$r > 0.999$	(ng/ml)	(ng/ml)				
	(Method					0.2	0.5	4.93	1.42
	LCMS 174)						7.5	2.62	-0.539
						75.0	2.47	-2.10	

For naproxen analysis, a set of 10 non-zero calibration standards in duplicate and triplicate QC standards were run with each batch of study samples. Sample analysis was performed within the period for which the samples are stable.

For sumatriptan analysis a set of 9 non-zero calibration standards in duplicate and 6 replicate QC standards were included in each batch. Sample analysis was performed within the period for which the samples are stable.

The performance of the assays for all analytes is considered acceptable.

RESULTS:

Demographics

Eighteen subjects enrolled and completed both study periods and were evaluable for pharmacokinetic evaluation. However, 1 subject was excluded from analysis as a result of vomiting 1 hour after taking Treatment A (during migraine), and another subject was excluded from the naproxen analysis due to protocol violation (taking naproxen as a concurrent treatment) during Treatment B (outside of a migraine). Demographics for the subjects completing the study are shown below.

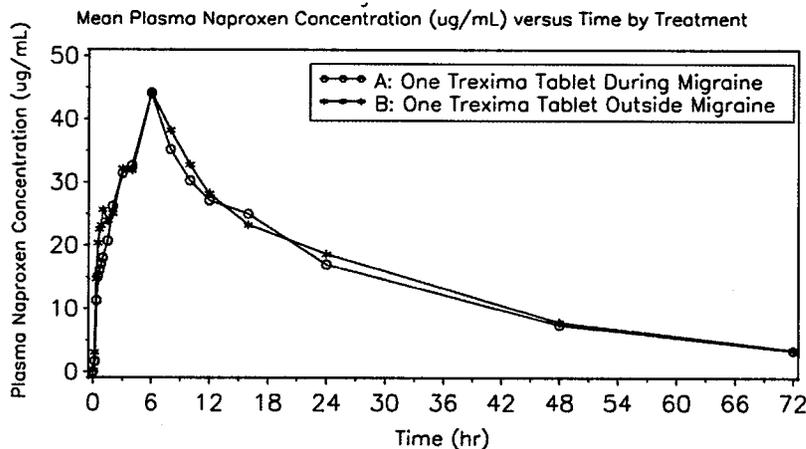
Table 4. Demographics of Subjects Completing Study MT 400-104

Mean Age (Range)	Gender	Weight (mean \pm SD)	Race
42.0 (21-55)	4 males	75 \pm 15 kg (n=16)	Caucasian 11
	13 females	80 \pm 8 kg (male)	Asian 1
		74 \pm 16 kg (female)	Black/African American 1

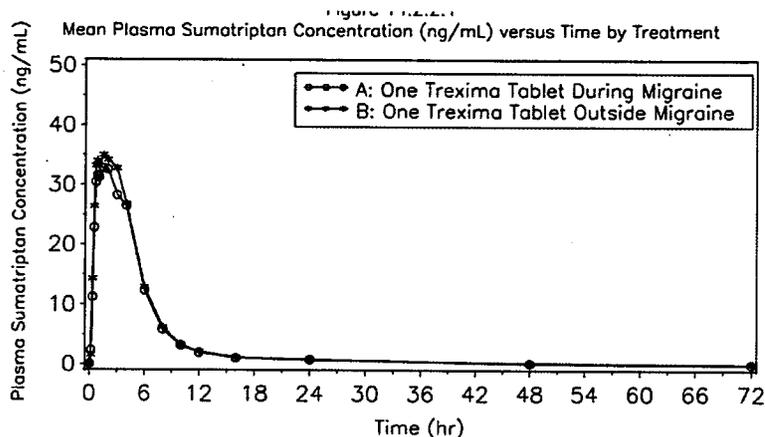
Fifteen subjects took at least 1 concurrent medication during the study. These included vitamins, psyllium, glycerin, acetaminophen, prochlorperazine, acetaminophen with codeine, ibuprofen, Imitrex, hormonal contraceptive (not identified), albuterol, pseudoephedrine, naproxen, Depo-Provera, Pepto Bismol, zolmitriptan, tramadol, Emetrol (glucose, fructose, phosphoric acid), and an unidentified herbal preparation.

Pharmacokinetics

The mean plasma concentration time course from each period (during and outside migraine) for naproxen and for sumatriptan are shown in the figures below, as provided by the Sponsor.



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TREXIMA



Pharmacokinetic parameters were determined using noncompartmental analysis. The pertinent pharmacokinetic parameters for naproxen and for sumatriptan from the specific treatments are shown in the table below, as calculated by the Sponsor. (Note: the sumatriptan half-life estimates were obtained by using post-absorption plasma concentration time data through 12-16 hours). The values are generally in agreement with those calculated by the reviewer.

The Sponsor also evaluated the T_{lag} , defined as the time of the first measurable plasma concentration for naproxen or sumatriptan. For naproxen, no lag time was observed for either treatment. For sumatriptan, there were 4 subjects with a T_{lag} for each treatment, all of which were 0.17 hours (10 minutes).

Table 5. Pharmacokinetic parameters (arithmetic mean) for Naproxen and for Sumatriptan (Study MT 400-102)

	Treatment A During Migraine (% CV)	Treatment B Outside of Migraine (% CV)
Naproxen	<i>(n=16)</i>	<i>(n=16)</i>
t_{max} (h) ^a	6.0 (3.0-16.0)	6.0 (0.7-8.0)
C_{max} (µg/mL)	50.2 (17)	49.2 (18)
AUC _{0-t} (µg*h)	1074.9 (14)	1118.0 (13)
AUC _{0-∞} (µg*h/mL)	1175.2 (16)	1220.9 (15)
$t_{1/2}$ (h)	19.9 (13)	19.8 (13)
Sumatriptan	<i>(n=17)</i>	<i>(n=17)</i>
t_{max} (h) ^a	1.5 (0.5-4.0)	2.0 (0.5-4.1)
C_{max} (ng/ml)	40.5 (19)	43.1 (24)
AUC _{0-t} (ng*h/mL)	198.9 (30)	214.8 (22)
AUC _{0-∞} (ng*h/mL)	200.44 (30)	216.2 (22)
$t_{1/2}$ (h) ^b	2.1 (19)	2.1 (15)

^a median (range)

The ratios of PK parameters during and outside of a migraine are shown in the table below, as provided by the Sponsor.

Table 6. Bioavailability Ratios for TREXIMA During and Outside of Migraine in MT 400-104

	Geometric Mean		Ratio of Geometric Means	90% CI for the Ratio of Geometric Means
	Treatment A During (REFERENCE)	Treatment B Outside (TEST)		
Naproxen				
C _{max} (µg/ml)	49.4	48.4	1.02	(0.95,1.098)
AUC _{0-t} (µg*h/ml)	1065.4	1109.3	0.96	(0.92, 1.001)
AUC _{0-∞} (µg*h/mL)	1161.6	1208.4	0.96	(0.92, 1.004)
Sumatriptan				
C _{max} (ng/ml)	39.8	42.0	0.95	(0.85, 1.05)
AUC _{0-t} (ng*h/ml)	191.31	209.97	0.91	(0.85, 0.98)
AUC _{0-∞} (ng*h/mL)	192.9	211.4	0.93	(0.81-1.08)

There was no difference in C_{max} or AUC for either naproxen or sumatriptan when given during or outside of a migraine. For sumatriptan, the median t_{max} occurred slightly earlier during a migraine than outside of a migraine.

Safety

There were no serious adverse events reported. The incidence of adverse events was 33% after treatment during a migraine and 22% outside of a migraine. The most frequent adverse event in both periods was somnolence.

CONCLUSIONS:

There was no difference in C_{max} or AUC for either naproxen or sumatriptan when given during or outside of a migraine. For sumatriptan, the median t_{max} occurred slightly earlier during a migraine than outside of a migraine.

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4.2.9 REPEAT DOSE STUDY MT 400-105

A STUDY TO EVALUATE THE PHARMACOKINETICS AND TOLERABILITY OF TWO SINGLE TREXIMA TABLETS (ADMINISTERED TWO HOURS APART) IN HEALTHY VOLUNTEERS

Study Investigators and Site:

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Protocol Number: MT 400-105

OBJECTIVE:

To evaluate the pharmacokinetics and tolerability of sumatriptan and naproxen following a single oral dose of TREXIMA (sumatriptan as the succinate [hereafter sumatriptan] 85 mg/naproxen sodium [hereafter naproxen] 500 mg) and two single oral doses of a TREXIMA tablet taken 2 hours apart in healthy volunteers.

FORMULATIONS:

Table 1. Products used in MT400-105

	Tablet Description	Batch No.	Exp. Date (Dates of Study)
Trexima 85mg/500mg GlaxoSmithKline	Medium blue film coated tablet	B916681	Man. Date is 11/12/03 (10/12/04-12/1/04) (18 month stability data)

The batch size was approximately [REDACTED] and was manufactured at full commercial scale at the proposed commercial facility.

STUDY DESIGN:

This was a Phase I, randomized, 2-way crossover, open-label, single center study. Subjects were randomized to receive one TREXIMA tablet in one study period and two TREXIMA tablets 2 hours apart in the other study period as follows (with each sequence specifying an equal number of males and females).

Treatment	Number of Subjects	Treatment/Sequence
AB	12	1 Trexima tablet (A)/ 2 Trexima tablets (2 hours apart)(B)
BA	12	2 Trexima tablets (2 hours apart)(B) / 1 Trexima tablet (A)

Inclusion criteria included males or females (not pregnant or lactating), age 18-55 years that were not currently smokers. Females must have been of non-childbearing potential or of child-

bearing potential with abstinence, sterilization, or contraception (including oral contraception). Exclusion criteria included significant medical or psychiatric condition that may have affected interpretation or otherwise contraindicated participation in a clinical trial, recent history in the past year suggestive of alcohol or drug abuse or dependence, history of cerebrovascular pathology, confirmed or suspected ischemic heart disease or ischemic abdominal syndromes, **peripheral vascular disease or Reynaud's syndrome**, uncontrolled hypertension at screening, ingestion of any prescription or OTC medications within 72 hours prior to each study dose, ingestion of any triptan or naproxen-containing products one week before the first dose through 72- hours following the last dose, use of MAO inhibitors within 2 weeks of screening, and any subject with a known allergy or intolerance to naproxen sodium or sumatriptan.

Subjects were admitted to the inpatient unit the evening prior to dosing in each study period. Study periods were separated by a washout period of at least 8 days. Subjects were housed in the Phase 1 unit until after the 24 hour post-dosing blood sample had been drawn. An overnight fast of at least 10 hours preceded each of the two treatment periods. Study medication was taken with 240 ml of water. No food was allowed for at least 4 hours post-dose. No food or water was allowed during the 2 hours in between the first and second TREXIMA dose. Otherwise, water was allowed except for 1 hour before and 1 hour after study drug administration. Subjects received standardized meals scheduled at the same time in each period of the study. In the single TREXIMA tablet period, blood samples for naproxen and sumatriptan were collected prior to dosing and at 10, 20, 30, 40, 50, 60, and 90 minutes and 2, 3, 4, 6, 8, 10, 12, 16, 24, 48, and 72 hours following dosing. In the 2 tablet period, blood samples for naproxen and sumatriptan were collected prior to dosing and at the following times post-dosing: 10, 20, 30, 40, 50, 60, and 90 minutes and 2 hours after the first dose (collected prior to the second dose) and at 10, 20, 30, 40, 50, 60, 90 minutes and 2, 3, 4, 6,8, 10, 12, 16, 24, 48, and 72 hours after the second dose.

Plasma from blood samples were frozen at -20° C or lower and shipped frozen to [REDACTED] for analysis.

ASSAY:

Plasma concentrations for naproxen and for sumatriptan were measured using validated methods.

Table 3. Performance of Analytical Methods for MT 400-105

Analyte	Method	Range	Linearity	LOQ	QC	Inter-assay CV (%)	Inter-assay Accuracy (%)
Naproxen	HPLC	0.1-100	r > 0.997	(µg/ml)	(µg/ml)		
	[REDACTED] Method	µg/ml		0.1	0.25	13.0	0.322
	LC 72.2)				3.0	2.86	-1.48
					70.0	2.43	-2.79
Sumatriptan	LC/MS/MS	0.2-100	r > 0.997	(ng/ml)	(ng/ml)		
	(Method	ng/ml		0.2	0.5	4.48	2.15
	LCMS 174)				7.5	2.41	-0.0596
					75.0	3.13	-0.622

For naproxen analysis, a set of 10 non-zero calibration standards in duplicate and triplicate QC standards were run with each batch of study samples. Sample analysis was performed within the period for which the samples are stable.

For sumatriptan analysis, sample analysis was performed within the period for which the samples are stable. A set of calibration standards (including 9 different non zero standards in duplicate) and 4 replicate QC standards were included in each batch.

The performance of the assays for all analytes is considered acceptable.

RESULTS:

Demographics

Twenty-four subjects were randomized and completed the study. Demographics are shown in the table below.

Table 4. Demographics of Subjects Completing Study MT 400-105

Mean Age (Range)	Gender	Weight (mean \pm SD)	Race
32.7 (19-55)	12 males	80 \pm 14 kg (n=24)	Caucasian 23
	12 females	85 \pm 14 kg (male)	Black/African American 1
		76 \pm 14 kg (female)	

Four subjects took concurrent medications. Two subjects took birth control pills, one took a single dose of allergy medication, and the other applied a topical analgesic once. The subject that took the allergy medication was #1006 and took Allegra-D approximately 24 hours after the 2nd dose of study drug in period 2 and it is stated that it was administered for an AE.

Pharmacokinetics

The PK population included all 24 subjects. However, subject #1023 did not have adequate blood sampling for the two-TREXIMA tablet period.

The mean plasma concentration time course from each treatment for naproxen and for sumatriptan are shown in the figures below, as provided by the Sponsor.

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Figure 1. Mean Plasma Naproxen Concentrations for the Single Dose and Repeat Dose Trexima Regimen.

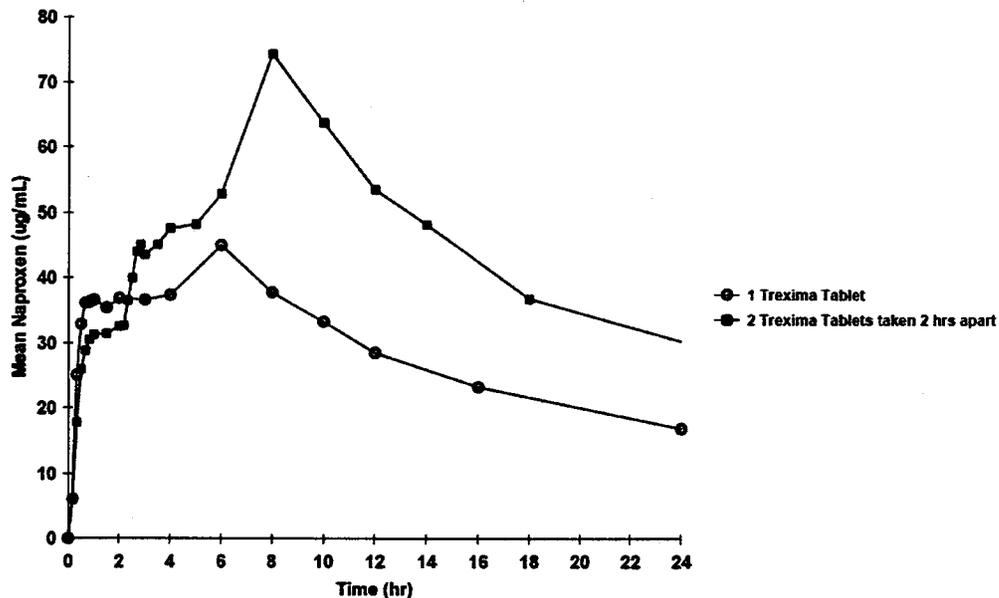
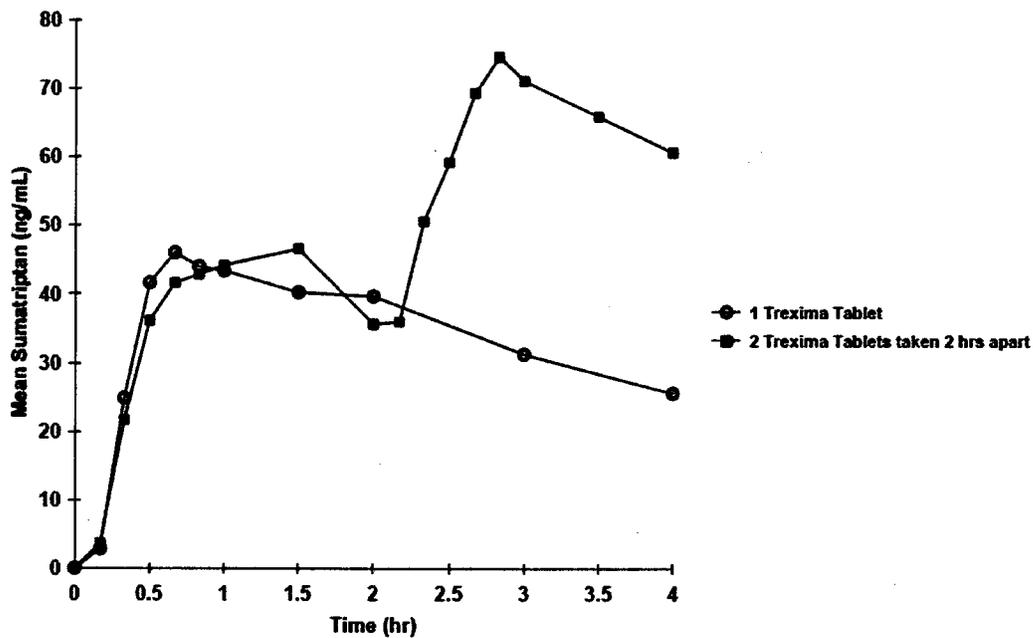


Figure 2. Mean Plasma Sumatriptan Concentrations for the Single Dose and Repeat Dose Trexima Regimen



Pharmacokinetic parameters were determined using noncompartmental analysis. The pertinent pharmacokinetic parameters for naproxen and for sumatriptan from the specific formulations are shown in the table below, as calculated by the reviewer. The values are generally in agreement with those reported by the Sponsor. Since the Tmax for naproxen extended beyond the 2 hour time point of the second dose of TREXIMA, only 1 Cmax and Tmax value for naproxen is presented for the repeat dose regimen.

Table 5. Pharmacokinetic parameters (arithmetic mean) for Naproxen and for Sumatriptan (Study MT 400-105)

	One TREXIMA Tablet (% CV)	Two TREXIMA Tablets (2 hours apart) (% CV)
Naproxen	<i>(n=24)</i>	<i>(n=23)</i>
t _{max} (h) ^a	5.0 (0.5-10.0)	8.0 (2.5-10.0)
C _{max} (µg/mL)	54.5 (24)	81.5 (16)
AUC _{0-t} (µg*h)	1111.0 (16)	1773.3 (13)
AUC _{0-∞} (µg*h/mL)	1186.4 (17)	1882.9 (14)
λz (hr ⁻¹)	0.039 (12)	0.040 (14)
t _{1/2} (h)	18.0 (13)	17.6 (14)
Sumatriptan	<i>(n=24)</i>	<i>(n=23)</i>
t _{max1} (h) ^a	0.9 (0.3-2.0)	1.0 (0.5-1.5)
C _{max1} (ng/ml)	57.4 (37)	53.1 (29)
t _{max2} (h) ^a	NA	2.8 (2.7-5.0)
C _{max2} (ng/ml)	NA	81.4 (20)
AUC _{0-t} (ng*h/mL)	216.2 (24)	458.3 (14)
AUC _{0-∞} (ng*h/mL)	223.7 (23)	473.6 (15)
λz (hr ⁻¹) ^b	.345 (12)	0.347 (17)
t _{1/2} (h) ^b	2.04 (15)	2.06 (19)

^a median (range)

^b as provided by the Sponsor

NA = not applicable

PK parameters after a single dose of naproxen were generally in agreement with the parameters that have been observed in other single dose TREXIMA studies (MT 400-101 and MT 400-103). Tmax for naproxen was 5 hours after a single dose, generally in agreement with data from other TREXIMA studies. Tmax was delayed by 3 hours in the repeat dose group, occurring at 8 hours after the initial dose, and approximately 6 hours after the 2nd dose. The naproxen Cmax and AUC after two TREXIMA tablets given 2 hours apart were approximately 1.5 fold greater than after a single dose. Elimination half-life was consistent between both treatment periods. The highest naproxen concentration observed was 100 µg/ml and was observed in a subject in the Two Tablet regimen, approximately 6 hours after the second TREXIMA dose.

For sumatriptan, the tmax, Cmax, AUC, and half-life after a single dose were generally in agreement with those observed in Studies MT 400-101 and MT 400-103. In some subjects sumatriptan appeared to be eliminated very slowly at concentrations less than approximately 1 ng/ml and beyond the 18 hour time point. The elimination half-life reported reflects the initial elimination half-life and is in agreement with that reported for the earlier studies. For the 2 dose regimen, the elimination half-life was in agreement with that after a single dose. In the 2-dose regimen, there were two distinguishable sumatriptan Cmax peaks, the first of which shows Cmax in agreement with a single dose, and the second of which shows concentrations approximately

1.5-fold higher than the first. Sumatriptan AUC is approximately 2-fold higher in the 2-dose regimen than in the 1 dose regimen.

Safety

The most frequent adverse event after the first dose in both periods was headache (21% in single tablet, 8% from first dose of repeat dose and none in the second dose of the repeat dose treatment). All events were mild in severity except for 2 moderate headaches and 1 severe headache. Other adverse events included dizziness in 2 (8%) subjects after Treatment B and 1 subject after treatment A. Hot flush was listed as a drug-related adverse event that occurred in 1 subject after the second dose of TREXIMA.

CONCLUSIONS:

1. Mean C_{max} and AUC for naproxen increased by approximately 1.5-fold following the 2nd dose of the repeat dose regimen compared to following a single dose.
2. The mean C_{max} for sumatriptan was approximately 1.5-fold greater following the 2nd dose of the repeat dose regimen compared to following a single dose, and the mean AUC was approximately 2 fold greater (e.g. dose proportional increase).
3. The half-life values for either naproxen or sumatriptan were similar whether after a single dose or after 2 doses of TREXIMA.

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4.2.10 LITERATURE REVIEW OF DRUG INTERACTIONS

As requested, the Sponsor has reviewed the literature regarding the potential for drug interactions with TREXIMA.

1. Interaction studies with naproxen are reviewed below. The sponsor also provided a publication to support a methotrexate interaction; that will not be reviewed here as it is already described in the naproxen label.

Valproic Acid – Addison et al evaluated the effects of co-administration of valproic acid and naproxen on their relative dispositions in 7 healthy males.(1) Each subject received each drug alone (naproxen 500 mg, valproic acid sodium 500 mg) and then in combination (orally twice daily for 7 days). Plasma and urine samples were collected for analysis on Day 7 of each dosing period. Co-administration of naproxen resulted in an approximate 20% increase in apparent plasma clearance of total valproic acid and in the unbound fraction of VPA in the plasma, and reduced exposure to valproic acid. These data come from steady state administration of naproxen, and the relevance to acute administration of TREXIMA in migraine is unknown. For naproxen, co-administration with valproic acid led to an approximate 7% increase in naproxen exposure (AUC_{0-t}). This is not likely to be clinically significant.

Cimetidine, ranitidine, famotidine – Vree et al evaluated the effect of cimetidine, ranitidine, and famotidine on naproxen PK in 6 healthy volunteers (3 men, 3 women ages 20-50 years).(2) In the first period all subjects took 500 mg naproxen orally with 1 glass of water after overnight fast. A low fat standard breakfast was taken 3 hours after drug administration. On separate occasions subjects took 500 mg naproxen with cimetidine 400 mg twice daily, ranitidine 150 mg twice daily, and famotidine 20 mg once daily for 6 days (starting 2 days before naproxen administration), and given 2 hours after naproxen on the study day. Blood samples were collected at 1, 2, 4, 6, and 8 hours on the first day of administration of naproxen and every 12 hours for the next 4 days. Urine was collected for 140 hours and urinary pH was kept acidic by oral intake of ammonium chloride. The H₂ antagonists all reduced the elimination half-life from approximately 26 hours after naproxen alone to approximately 18 to 21 hours in the presence of H₂ antagonist; these results were statistically significant. A statistically significant decrease in AUC (approximately 20%) was seen for naproxen plus cimetidine compared to naproxen alone, and the V_{ss} was decreased by all three H₂ antagonists. There was no change in C_{max}. The authors attribute these changes to a pH-mediated alteration in the rate of enterohepatic circulation. These changes are not likely to be clinically relevant in the context of TREXIMA administration for acute treatment of migraine.

Sucralfate – Caille et al evaluated the effect of sucralfate 2 g on naproxen pharmacokinetics in 12 healthy male volunteers, 18-27 y.o in an open label crossover study.(3) The two regimens were naproxen 500 mg given alone or naproxen 500 mg given 30 minutes after sucralfate 2 g. At the beginning of each study period, study medication was given as a single dose on Day 1 (either naproxen 500 mg given alone or naproxen 500 mg given 30 minutes after a single dose of sucralfate 2 g. Blood was collected for single dose PK parameters on Days 1, 2, and 3. After the last sample was obtained on the morning of Day 3, multiple dose administration of naproxen was started. Subjects took naproxen 500 mg twice daily at 12-hour intervals for 10 doses, 30

minutes after administration of sucralfate 2 g (when taken). Blood samples were collected pre dose on Days 4, 5, 6, and 7 pre-dose and on Day 8, with full PK curve after the dose on Day 8. After a 40 day washout, patients received the alternate regimen. A standardized breakfast was given 1 hour before study drug administration on Days 1 and 8 of each period. PK parameters were compared using 2-way ANOVA with a fixed source of variation. The authors state there was non significant effect of treatment, period, or subject. Following a single dose (that is pertinent to TREXIMA), There was an 8.13% decrease in naproxen C_{max}, a 7.8% decrease in half-life, and 1.65 % decrease in AUC, and an approximate 0.8 hour (mean 1.4 ± 0.2 hr vs 2.2 ± 0.4hr) delay in t_{max} when naproxen was given alone or with sucralfate. These changes were not statistically significant.

Cholestyramine – Cholestyramine is an anion exchange resin clinically used to reduce lipid and cholesterol levels. It decreases intestinal absorption of some drugs, presumably due to an interaction in the GI tract between the resin and the interacting drug. Calvo and Dominguez-Gil evaluated the PK of naproxen in 8 healthy subjects after concurrent oral administration in a single dose of 250 mg naproxen and 4 g of cholestyramine (a clinically relevant dose) given in 100 ml of orange juice.(4) The average age was 28 years; demographic details were not provided. The publication shows only average values for plasma concentrations (with no indication of variability) and suggests a reduction in exposure. The authors state that the average values for t_{max} and C_{max} were 4 h and 34.5 µg/ml, respectively in the presence of cholestyramine compared to a t_{max} of 2 hours and a C_{max} of 52.63 µg/ml after administration of naproxen alone. The authors have not provided details of the analytical methodology or details of the results. The t_{max} given for naproxen alone does not agree with the data provided in the present submission. These data are difficult to interpret.

2. Potential for interactions with sumatriptan are reviewed below. The sponsor also provided publications reviewing the potential for interaction with propranolol, topiramate, and ethanol that will not be reviewed here as that potential is already described in the sumatriptan label. Finally, the Sponsor provided a publication regarding the potential for interaction with flunarazine that will not be reviewed here since that is not an approved drug in the United States.

Oral contraceptives – Moore et al evaluated the effects on PK of both medications when a single dose of sumatriptan 50 mg is coadministered with an oral contraceptive (norethindrone 1 mg/ethinyl estradiol 0.035 mg) in an open-label, 1 sequence, crossover study in 26 healthy women (age range 18-44 years) who had received the oral contraceptive (OC) for at least 3 months.(5) The 90% CIs for the AUC_{inf} of sumatriptan and of the OC components were within the BE interval of 80-125%. For sumatriptan there was a 17% increase in C_{max} (90% CI 1.05-1.3) when given with OC. For norethindrone there was an 18% mean decrease in C_{max} (90% CI 0.76 to 0.88), with no effect on ethinyl estradiol. These changes are not likely to be clinically significant.

Clarithromycin – Moore et al evaluated the effect of coadministration of clarithromycin 500 mg every 12 hours, dosed to steady state, on the PK of a single dose of sumatriptan 50 mg in 24 healthy subjects (12 men, 12 women) 18-45 years old.(6) This was a randomized, open label, 2-way crossover study. Mean sumatriptan AUC_{inf} and C_{max} values were 9% and 14% higher, respectively, after administration with clarithromycin than when sumatriptan was given alone.

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TREXIMA

The 90% CI for the ratio of reference to test geometric mean for AUC was 1.03-1.15 and for Cmax was 1.03-1.26. This change is not likely to be clinically significant.

Paroxetine – **Wing et al** studied the effects of paroxetine 20 mg daily for 16 days on the neuroendocrine, cardiovascular, thermic, and subjective responses to a single dose of sumatriptan 6 mg given subcutaneously in 11 healthy volunteers, aged 21-45 years old. The measured pharmacodynamic effects of sumatriptan were not altered by administration of paroxetine. Blood samples were collected every 15 minutes for 180 minutes following sumatriptan injection, and it is reported that neither the mean peak concentration nor AUC for sumatriptan were different before or during paroxetine administration. (7)

Butorphanol – **Srinivas et al** evaluated the PK of butorphanol after administration of nasal spray alone and in combination with sumatriptan 6 mg given subcutaneously in 24 subjects (17 men, 7 women) with a mean age of 27.2 years.(1) This was a randomized 2-way crossover study. PK parameters for butorphanol were not statistically different in the presence or absence of sumatriptan.

3. Interaction between naproxen and sumatriptan

The effect of naproxen on sumatriptan PK has been evaluated by Srinivasu et al.(8) Twelve healthy male volunteers received sumatriptan succinate 100 mg as an immediate release capsule along with or without a single dose of naproxen 500 mg (Naproxyn tablet, Searle) after a 10-hour fast and a standard breakfast at either 1000 hours or 2200 hours. Blood samples were collected at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, and 12 hours after drug administration. Serum samples were analyzed for sumatriptan using an HPLC method with ofloxacin as the internal standard. A calibration curve included 6 nonzero concentrations from 1.56 to 50 ng/ml. Reproducibility was checked by analyzing spiked serum samples with different concentrations of drug 5 times during the analysis, and resulted in a coefficient of variation of less than 7.4% at all concentrations. Comparisons were made between values in the presence or absence of naproxen by a two-tailed paired t-test at the probability level of 95%. Raw data were not available. The results (mean, SD), adapted from the data in the publication, are shown in the table below. No statistically significant difference was observed in any sumatriptan pharmacokinetic parameter in the presence or absence of naproxen.

	1000 hours		2200 hours	
	Sumatriptan Alone	Sumatriptan +Naproxen	Sumatriptan Alone	Sumatriptan +Naproxen
Cmax (ng/ml)	41.81 ± 10.8	44.54 ± 17.6	37.98 ± 6.96	39.32 ± 10.9
Tmax (h)	2.0 ± 0.83	1.96 ± 0.94	2.04 ± 1.23	1.88 ± 1.17
T1/2 (h)	2.34 ± 0.56	2.61 ± 0.41	2.24 ± 0.57	2.17 ± 0.53
AUC 0-t (ng*h/ml)	255 ± 47	274 ± 52	242 ± 39	242 ± 59
AUC0-inf (ng*h/ml)	273 ± 48	308 ± 74	257 ± 37	258 ± 67

Conclusions:

1. A single dose of naproxen 500 mg did not have an effect on sumatriptan pharmacokinetics when sumatriptan was given as 100 mg orally alone or with naproxen.
2. The literature references provided by the Sponsor do not indicate the potential for previously unreported drug interactions and do not need to be included in the labeling.

References

- (1) Srinivas NR, Shyu WC, Upmalis D, Lee JS, Barbhैया RH. Lack of pharmacokinetic interaction between butorphanol tartrate nasal spray and sumatriptan succinate. *J Clin Pharmacol* 1995; 35(4):432-7.
- (2) Vree TB, van den Biggelaar-Martea M, Verwey-Van Wissen CPWGM, Vree ML, Guelen PJM. The effects of cimetidine, ranitidine and famotidine on the single-dose pharmacokinetics of naproxen and its metabolites in humans. *Int.J.of clinical Pharmacology, Therapy and Toxicology* 31[12], 597-601. 1993.
- (3) Caelle G, du Souich PGP, Besner JG, Vezina M. Effects of concurrent sucralfate administration on pharmacokinetics of naproxen. *Am.J.Med.* 83[suppl 38], 67-73. 1987.
- (4) Calvo MV, Dominguez-Gil A. Interaction of naproxen with cholestyramine. *Biopharm.Drug Dispos.* 5, 33-42. 1984.
- (5) Moore KH, McNeal S, Britto MR, Bye C, Sale M, Richardson MS. The pharmacokinetics of sumatriptan when administered with norethindrone 1 mg/ethinyl estradiol 0.035 mg in healthy volunteers. *Clin Ther* 2002; 24(11):1887-901.
- (6) Moore KH, Leese PT, McNeal S, Gray P, O'Quinn S, Bye C et al. The pharmacokinetics of sumatriptan when administered with clarithromycin in healthy volunteers. *Clin Ther* 2002; 24(4):583-94.
- (7) Wing YK, Clifford EM, Sheehan BD, Campling GM, Hockney RA, Cowen PJ. Paroxetine treatment and the prolactin response to sumatriptan. *Psychopharmacology (Berl)* 1996; 124(4):377-9.
- (8) Srinivasu P, Rahbhau D, Rao BR, Rao YM. Lack of pharmacokinetic interaction between sumatriptan and naproxen. *J Clin Pharmacol* 2000; 40:99-104.

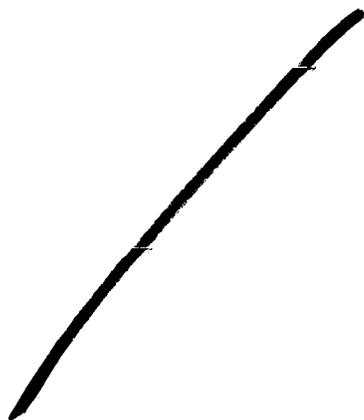
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Trade Secret / Confidential

Draft Labeling

Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 10



RECOMMENDATION:

The Office of Clinical Pharmacology finds the proposed dissolution method and specifications acceptable. In addition, the dissolution profiles of the debossed tablet (the to-be-marketed tablet) are similar to that of the biobatch/clinical trials formulation.

4.3 Consult Reviews

None.

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4.4 Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21926	Brand Name	Trexima
OCPB Division (I, II, III)	DPE-1	Generic Name	Sumatriptan&Naproxen
Medical Division	HFD-120	Drug Class	5-HT _{1B/1D} agonist (triptan) & NSAID
OCPB Reviewer	Sally Usdin Yasuda, MS, PharmD	Indication(s)	Migraine
OCPB Team Leader	Ramana Uppoor, PhD	Dosage Form	film-coated tablet containing 85 mg sumatriptan (as 119 mg sumatriptan succinate) and naproxen sodium 500 mg
		Dosing Regimen	1 tablet early in migraine; NTE 2 tablets in 24 hours
Date of Submission	August 5, 2005	Route of Administration	Oral
Estimated Due Date of OCPB Review	4/20/06	Sponsor	Pozen
PDUFA Due Date	6/8/06	Priority Classification	Standard
Division Due Date	5/7/06		

Clin. Pharm. and Biopharm. Information

Summary: This NDA, submitted under section 505 (b)(2) is for a combination product comprised of 2 drugs currently approved and marketed for oral administration, sumatriptan succinate (IMITREX) and naproxen (ANAPROX DS). The to-be-marketed formulation was used in each of the studies. Batch B916681 was used in PK studies MT400-102, MT400-104, and MT400-105, and Phase III clinical studies MT400-301, MT400-302, and MT400-303. This batch was manufactured at the site of commercial manufacture according to the commercial process. Additional PK studies MT400-101 and MT400-103 also used Trexima tablets that were prepared according to the commercial process but from a pilot scale batch. The pivotal efficacy trials MT400-301 and MT400-302 compared Trexima to each active component alone: endpoints were pain relief and incidence of photophobia, phonophobia, and nausea at 2 hrs. The

be reviewed. (*Note: this was not submitted during the review cycle.*)

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			

NDA 21,926
TREXIMA

Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			Only available as PDF
Reference Bioanalytical and Analytical Methods	X	4		
I. Clinical Pharmacology				
Mass balance:	-	-	-	
Isozyme characterization:				
Blood/plasma ratio:		-	-	
Plasma protein binding:		-		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	3	3	MT400-101 (BA of Sumatriptan and Naproxen from TREXIMA vs sumatriptan or naproxen alone MT400-103(BA of Sumatriptan and naproxen from Trexima or from sumatriptan tablets and naproxen tablets given together; also 2 different doses of sumatriptan) MT400-105 (single dose vs 2 single doses taken 2 hrs apart)
multiple dose:	-	-	-	
Patients-				
single dose:	X	1	1	MT400-104 effect of migraine on PK
multiple dose:			-	
Dose proportionality -				
fasting / non-fasting single dose:	X			
fasting / non-fasting multiple dose:	-	-	-	
Drug-drug interaction studies -				
In-vivo effects on primary drug:		-		
In-vivo effects of primary drug:	-	-		
In-vitro:			-	
Subpopulation studies -				
ethnicity:		-	-	Literature and cross reference to current FDA approved labels
gender:	X	1	-	considered in MT400-102 & pooled data from Phase I studies
pediatrics:	-	-	-	
geriatrics:	-	-	-	
renal impairment:	-	-	-	
hepatic impairment:	-	-	-	
PD:				
Phase 2:	-	-	-	
Phase 3:	-	-	-	
PK/PD:				
Phase 1 and/or 2, proof of concept:	-	-	-	
Phase 3 clinical trial:	-	-	-	

NDA 21,926
 TREXIMA

Population Analyses -				
Data rich:	-	-		
Data sparse:	-	-		
II. Biopharmaceutics				
Absolute bioavailability:	-	-	-	
Relative bioavailability -				
solution as reference:	-	-	-	
alternate formulation as reference:	X	2	2	MT400-101 (BA from Trexima vs currently marketed components) & MT400-103
Bioequivalence studies -				
traditional design; single / multi dose:	-	-	-	
replicate design; single / multi dose:	-	-	-	
Food-drug interaction studies:	X	1	1	MT400-102
Dissolution:	X	1	1	
(IVIVC):	-	-	-	
Bio-waiver request based on BCS	-	-	-	
BCS class	-			
III. Other CPB Studies				
Genotype/phenotype studies:	-	-	-	
Chronopharmacokinetics	-	-	-	
Pediatric development plan	-	-	-	
Literature References	X			
Total Number of Studies		9	9	
<i>Filability and QBR comments</i>				

NDA 21,926
TREXIMA

	"X" if yes	Comments
Application filable ?	X	Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable. Please forward to sponsor : Please send raw data and supporting figures to justify dissolution method development and dissolution specifications, including data showing the ability of the dissolution method to discriminate poorly performing tablets.
QBR questions (key issues to be considered)		What information is available that contributes to assessment of clinical pharmacology/dose response/exposure-response? Are the bioanalytical methods adequate to assess concentrations? Have the pharmacokinetics been adequately characterized to support safety and efficacy? Has the combination product been adequately linked to the individual components in terms of PK? Is drug metabolism and potential for drug interactions adequately characterized? Have appropriate in vivo drug interaction studies been done? Do the dissolution conditions and specifications assure in vivo performance and quality of the product?
Other comments or information not included above		Comments to the Project Manager: 1. Please ask the Sponsor to send raw data and supporting figures to justify dissolution method development and dissolution specifications, including data showing the ability of the dissolution method to discriminate poorly performing tablets. 2. It would be helpful to have a word document for the labeling
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-926, HFD-850(Electronic Entry or Lee), HFD-120(Chen), HFD-860 (R. Uppoor, N.A.M. Rahman, M. Mehta)

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/s/

Sally Yasuda
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Ramana S. Uppoor
5/16/2006 01:21:23 PM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21926	Brand Name	Trexima
OCPB Division (I, II, III)	DPE-I	Generic Name	Sumatriptan&Naproxen
Medical Division	HFD-120	Drug Class	5-HT _{1B/1D} agonist (triptan) & NSAID
OCPB Reviewer	Sally Usdin Yasuda, MS, PharmD	Indication(s)	Migraine
OCPB Team Leader	Ramana Uppoor, PhD	Dosage Form	film-coated tablet containing 85 mg sumatriptan (as 119 mg sumatriptan succinate) and naproxen sodium 500 mg
		Dosing Regimen	1 tablet early in migraine; NTE 2 tablets in 24 hours
Date of Submission	August 5, 2005	Route of Administration	Oral
Estimated Due Date of OCPB Review	4/20/06	Sponsor	Pozen
PDUFA Due Date	6/8/06	Priority Classification	Standard
Division Due Date	5/7/06		

Clin. Pharm. and Biopharm. Information

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	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			Only available as PDF
Reference Bioanalytical and Analytical Methods	X	4		
I. Clinical Pharmacology				
Mass balance:	-	-	-	
Isozyme characterization:			-	
Blood/plasma ratio:		-	-	
Plasma protein binding:	-	-		
Pharmacokinetics (e.g., Phase I) -				

Healthy Volunteers-				
single dose:	X	3	-	MT400-101 (BA of Sumatriptan and Naproxen from TREXIMA vs sumatriptan or naproxen alone MT400-103(BA of Sumatriptan and naproxen from Trexima or from sumatriptan tablets and naproxen tablets given together; also 2 different doses of sumatriptan) MT400-105 (single dose vs 2 single doses taken 2 hrs apart)
multiple dose:	-	-	-	
Patients-				
single dose:	X	1	-	MT400-104 effect of migraine on PK
multiple dose:			-	
Dose proportionality -				
fasting / non-fasting single dose:	X	1	-	Study MT400-103 had 2 different doses of sumatriptan
fasting / non-fasting multiple dose:	-	-	-	
Drug-drug interaction studies -				
In-vivo effects on primary drug:	-	-		
In-vivo effects of primary drug:	-	-		
In-vitro:			-	
Subpopulation studies -				
ethnicity:		-	-	Literature and cross reference to current FDA approved labels
gender:	X	1	-	considered in MT400-102 & pooled data from Phase I studies
pediatrics:	-	-	-	
geriatrics:	-	-	-	
renal impairment:	-	-	-	
hepatic impairment:	-	-	-	
PD:				
Phase 2:	-	-	-	
Phase 3:	-	-	-	
PK/PD:				
Phase 1 and/or 2, proof of concept:	-	-	-	
Phase 3 clinical trial:	-	-	-	
Population Analyses -				
Data rich:	-	-		
Data sparse:	-	-		
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:	-	-	-	
alternate formulation as reference:	X	2	-	MT400-101 (BA from Trexima vs currently marketed components) & MT400-103
Bioequivalence studies -				
traditional design; single / multi dose:	-	-		
replicate design; single / multi dose:	-	-		
Food-drug interaction studies:	X	1	-	MT400-102

Dissolution:	X	1		
(IVVC):	-	-	-	
Bio-waiver request based on BCS	-	-		
BCS class	-			
III. Other CPB Studies				
Genotype/phenotype studies:	-	-	-	
Chronopharmacokinetics	-	-	-	
Pediatric development plan	-	-	-	
Literature References	X			
Total Number of Studies		10		
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	X	Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable. Please forward to sponsor : Please send raw data and supporting figures to justify dissolution method development and dissolution specifications, including data showing the ability of the dissolution method to discriminate poorly performing tablets.		
QBR questions (key issues to be considered)		<p>What information is available that contributes to assessment of clinical pharmacology/dose response/exposure-response?</p> <p>Are the bioanalytical methods adequate to assess concentrations?</p> <p>Have the pharmacokinetics been adequately characterized to support safety and efficacy?</p> <p>Has the combination product been adequately linked to the individual components in terms of PK?</p> <p>Is drug metabolism and potential for drug interactions adequately characterized? Have appropriate in vivo drug interaction studies been done?</p> <p>Do the dissolution conditions and specifications assure in vivo performance and quality of the product?</p>		
Other comments or information not included above		<p>Comments to the Project Manager:</p> <ol style="list-style-type: none"> 1. Please ask the Sponsor to send raw data and supporting figures to justify dissolution method development and dissolution specifications, including data showing the ability of the dissolution method to discriminate poorly performing tablets. 2. It would be helpful to have a word document for the labeling 		
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

CC: NDA 21-926, HFD-850(Electronic Entry or Lee), HFD-120(Chen), HFD-860 (R. Uppoor, N.A.M. Rahman, M. Mehta)

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Sally Yasuda
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Ramana S. Uppoor
9/26/2005 01:48:52 PM
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