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APPLICATION NUMBER:
22511Orig1000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Donna Griebel, MD
Subject	Division Director Summary Review
NDA#	022511
Applicant Name	Pozen Inc.
Date of Submission	June 30, 2009 Received: July 7, 2009
PDUFA Goal Date	April 30, 2010
Proprietary Name / Established (USAN) Name	Vimovo naproxen and esomeprazole magnesium
Dosage Forms / Strength	Naproxen and esomeprazole magnesium tablets: 375 mg naproxen/20 mg esomeprazole magnesium AND 500 mg naproxen/ 20 mg esomeprazole magnesium
Proposed Indication(s)	Treatment of signs and symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis in patients at risk for developing NSAID-associated gastric ulcers
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Erica Wynn, MD/ Ruyi He, MD/Jin Chen, MD/Ellen Fields, MD
Biostatistical Review	Freda Cooner, PhD/Kate Meeker, MS/Mike Welch, PhD
Pharmacology Toxicology Review	Sushanta Chakder, PhD
CMC Review	Rajiv Agarwal/ Moo Jhong Rhee, PhD
Clinical Pharmacology Review	Jane Bai, PhD/Dilara Jappar, PhD/Sue-Chih Lee, PhD
Biopharmaceutics Review	Tien-Mien Chen, PhD/Patrick Marroum PhD
DDMAC	Katie Klemm/Lisa Hubbard/Shefali Doshi/Robert Dean
DSI	Sripal Mada, PhD/Sean Kassim, Ph.D./C.T. Viswanathan, PhD
CDTL Review	Ruyi He, MD
OSE/DMEPA	Kellie Taylor, PharmD, MPH/Denise Toyer, PharmD/Carol Holquist, RPh/Zachary Oleszczuk, Pharm D
SEALD	Debbie Beitzell, BSN
PMHS	Alyson Karesh, MD/Hari Cheryl Sachs, MD/Lisa Mathis, MD

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader
PMHS = Pediatric and Maternal Health Staff

Division Director Review

1. Introduction

This NDA, submitted under 505(b)(2) section of the Federal Food, Drug and Cosmetic Act and 21 CFR Part 314.50, seeks approval of two dosage strengths of a fixed combination of naproxen and immediate release esomeprazole. The inner enteric coated core of the tablet is one of two strengths of naproxen, either 375 mg or 500 mg. The tablet in both naproxen dosage strengths is coated in an outer immediate release film that contains 20 mg of esomeprazole. Two approved NDAs were referenced: NDA 020067 for EC-Naprosyn (375 mg and 500 mg) and NDA 021153 for Nexium capsules (20 mg and 40 mg). EC-Naprosyn is a delayed release naproxen tablet formulation approved for treatment of signs and symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis, at both dose strengths and dosed twice daily. Esomeprazole is approved for reducing the risk of developing NSAID-associated gastric ulcers, at doses of 20 mg and 40 mg, dosed once daily. The proposed dosing schedule for Vimovo is twice daily dosing.

The Applicant proposes the following indication for Vimovo:

VIMOVO is indicated for the relief of signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis in patients at risk of developing NSAID-associated gastric ulcers. (b) (4) VIMOVO is not recommended for initial treatment of acute pain because the absorption of naproxen is delayed compared to absorption from other naproxen containing products.

This indication does not clearly state the role/indication for the esomeprazole component of Vimovo and does not make clear that there are two component products, each with a separate indication. In addition, there are two deviations in the proposed indication from the reference drug Nexium:

(b) (4)

The Applicant conducted pharmacokinetic/bioavailability studies of each component of Vimovo (naproxen 375 mg, naproxen 500 mg and esomeprazole 20 mg) to establish a bridge between Vimovo and the two referenced NDAs. Bioequivalence was established for the two naproxen doses; however, the immediate release esomeprazole component of Vimovo was not bioequivalent to the referenced Nexium product. This was anticipated, due to the immediate release formulation of esomeprazole in Vimovo, which makes it subject to degradation by gastric acid.

The Applicant investigated the efficacy and safety of Vimovo for reduction of gastric ulcer in two phase 3 studies of 6 months duration in which the Vimovo 500 mg naproxen dosage form

(500 mg naproxen/immediate release esomeprazole 20 mg) was compared to EC-Naprasyn 500mg, both administered twice daily. Two additional phase 3 trials (active and placebo controlled) were conducted to evaluate the efficacy of the naproxen component of Vimovo for treatment of signs and symptoms of osteoarthritis.

The development program was a collaborative effort of two companies, Pozen and Astra Zeneca. Under a licensing agreement between the companies, the NDA will be transferred to Astra Zeneca upon approval.

No review issues preclude approval.

2. Background

Esomeprazole is a proton pump inhibitor that inhibits the H+/K+ ATPase enzyme system at the secretory surface of the gastric parietal cell. Esomeprazole is acid labile and is degraded by gastric acid to a cationic sulfonamide. The esomeprazole in Vimovo is an "immediate-release" formulation that exposes it to some degradation by gastric acid.

Naproxen is a marketed nonsteroidal anti-inflammatory drug. One of the marketed formulations of naproxen is enteric coated, EC-Naprosyn. EC-Naprosyn is approved for the indications of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis at both 375 mg and 500 mg doses, with twice daily administration. Esomeprazole is approved for risk reduction of NSAID-associated gastric ulcer at doses of 20 mg or 40 mg once daily for up to 6 months (controlled studies do not extend beyond 6 months).

3. CMC

I concur with the conclusions reached by the chemistry reviewers that the NDA has provided sufficient CMC information to assure the identity, strength, purity and quality of the drug product. An "acceptable" recommendation was received from the Office of Compliance on March 24, 2010.

The drug substance esomeprazole magnesium is manufactured in France by AstraZeneca Dunkerque Production. The naproxen drug substance is manufactured in (b) (4) The drug product, stability testing, bulk packaging and quality control testing is performed at Patheon Pharmaceuticals, Inc., in Cincinnati, Ohio. AstraZeneca Pharmaceuticals LP in Newark, Deleware performs packaging, labeling, quality control and batch release of drug product.

The drug product, Vimovo, was designed as a fixed combination tablet of two distinct formulations. The inner enteric coated (delayed release) component of naproxen contains either 375 mg or 500 mg of naproxen and the outer immediate release film coat of esomeprazole magnesium contains 20 mg of esomeprazole (present as 22.3 mg of esomeprazole magnesium). The CMC reviewer noted that "based on the qualitative and

quantitative formulation, the two strengths of [Vimovo] are dose proportional." Formulation changes made after the phase 3 batches were considered minor.

Biopharmaceutics

The Biopharmaceutics reviewer identified no approvability issues. He determined that the Applicant's proposed dissolution methodology should only be used on an interim basis and that the Applicant should submit, as a post-marketing commitment, additional dissolution testing data on the naproxen component of the tablets using the USP dissolution methodology for enteric coated drug products. The reason that the Applicant's dissolution methodology for naproxen was not considered optimal was that it lacked a pre-exposure in acid stage to test the enteric coating of naproxen. In addition, the reviewers recommended that the Applicant tighten its dissolution specifications for the esomeprazole in the buffer stage.

On February 24, 2010 FDA Biopharmaceutics review team requested a phase 4 commitment that the Applicant would implement by one year post-approval, transition from the proposed naproxen dissolution method in the NDA to the USP dissolution method for the naproxen component of the tablets. (See PMC in Approval Letter and in Section 13 of this review.) This agreement was documented in an amendment to the NDA on March 4, 2010. In an April 21, 2010 teleconference the FDA biopharmaceutics review team clarified that with reference to the post marketing commitment agreed to on March 4, the Applicant should generate new dissolution profile data utilizing the USP dissolution method and submit the data generated for both naproxen and esomeprazole. The FDA will reassess the interim specifications and consider if the new data generated are supportive of the interim specifications or if the data support revised specifications. The specifications selected and supported by data will then be adopted as the final specifications for naproxen and esomeprazole.

4. Nonclinical Pharmacology/Toxicology

This is a 505(b)(2) application. The Applicant submitted a nonclinical pharmacokinetic study in which urinary and plasma metabolites of buffered and unbuffered omeprazole were determined in rats following 14 days of oral dosing. The metabolite profiles for omeprazole were similar for the two formulations. Dr. Chakder agreed that oral administration of the uncoated esomeprazole in Vimovo should not lead to exposure of humans to new metabolites. I concur with the conclusions reached by the pharmacology reviewer, Dr. Chakder, that there are no outstanding pharmacology/toxicology issues that preclude approval. I concur with his labeling recommendations.

5. Clinical Pharmacology

I concur with the conclusions reached by the clinical pharmacology reviewers that there are no outstanding clinical pharmacology and biopharmaceutics issues that preclude approval. Their labeling recommendations were incorporated in label negotiations. The Clinical Pharmacology reviewers recommended the Applicant should be required to conduct pharmacokinetic studies in a pediatric population ages 2 years to 17 years.

The Vimovo 500/20 mg tablet batches were tested in Phase 1 clinical pharmacology studies and in the clinical phase 3 pivotal studies. The lower naproxen dose tablet, Vimovo 375/20 mg, was not tested in Phase 3 clinical trials; however, a primary stability batch of the 375/20 mg tablet was tested in a phase 1 clinical pharmacology study. The reviewers determined that no biowaiver request was needed for this NDA. The excipients used in the two dose formulations of Vimovo are approximately dose proportional.

The clinical pharmacology reviewers found that both doses of the referenced naproxen product, EC-Naprosyn, were bioequivalent to their respective Vimovo dose levels. The reviewers determined that the AUC of the 20 mg immediate release esomeprazole component of Vimovo after a single dose was approximately half that of the Nexium 20 mg reference. This was anticipated because the immediate release without gastric protection allows for degradation of the product by gastric acid. However, the Cmax was only slightly lower. The data from the single dose study are summarized in the table below, which is reproduced from Dr. Bai's Clinical Pharmacology Review. (Vimovo is designated PN-400 in this table.)

Summary of Esomeprazole (20 mg) Pharmacokinetic Parameters by treatment:

Treatment	Statistics	C_{max} (ng/mL)	T_{max} (hr)	T_{lag} (hr)	AUC_{0-t} (hr*ng/mL)	AUC_{0-inf} (hr*ng/mL)	$t_{½}$ (hr)
A PN 400 (N = 38)	Mean	425	0.51	0.03	465	467	0.971
	%CV	81	49	234	91	91	45
B EC Naproxen +EC Eso (N = 39)	Mean	432	2.50	0.91	801	803	0.945
	%CV	48	54	134	79	79	49
D EC Esomeprazole (N = 39)	Mean	455	2.43	0.87	806	815	0.936
	%CV	40	34	47	78	81	44

Treatment A: PN 400 (500 mg naproxen/ 20 mg esomeprazole)
Treatment B: EC-NAPROSYN 500 mg tablet + EC-Esomeprazole 20 mg capsule (NEXIUM)
Treatment D: EC-Esomeprazole 20 mg capsule (Nexium®)

With repeat dosing (twice daily times 14 days) the AUC and Cmax were higher than after a single dose, especially with the morning dose. The PM dose was associated with lower esomeprazole concentrations than the morning dose. The esomeprazole repeat dose pharmacokinetic data for Vimovo (PN-400) are summarized in the table below, reproduced from Dr. Bai's clinical Pharmacology review. High inter-and intraindividual variability in pharmacokinetics was noted for the esomeprazole component of Vimovo.

Mean (CV%) of Esomeprazole Pharmacokinetic Parameters by Study Day and Dose Time for Treatment B (PN 400/E20)

Day, dose, N	Cmax (ng/mL)	Tmax (hr)	$AUC_{0-10,am}$ or $AUC_{0-14,pm}$ (hr*ng/mL)	AUC0-24 (hr*ng/mL)	T1/2 (hrs)
Day 1, am N=20	339 (84)	0.52 (34)	398 (88)	--	0.89 (26)
Day 1, pm N=20	246 (116)	0.60 (58)	384 (145)	781 (109)	1.06 (33)
Day 14, am N=19	1034 (35)	0.53 (44)	1874 (50)	--	1.24 (35)
Day 14, pm N=19	468 (81)	1.10 (84)	1120 (73)	2994 (57)	1.48 (36)

The Day 14 AM Cmax is 3 times higher than the Day 1 AM Cmax. The Day 14 PM Cmax is 1.9 times higher than the Day 1 PM Cmax. The AUC associated with the AM dose on Day 14 is 4.7 times higher than the AM dose AUC on Day 1. The Day 14 PM dose AUC is 2.9 times higher than the Day PM AUC. This is briefly summarized below:

Day 14 AM Cmax = 3x Day 1 Cmax
Day 14 PM Cmax = 1.9 x Day 1 Cmax
Day 14 AM AUC = 4.7 X Day 1 AUC
Day 14 PM AUC = 2.9 X Day 1 AUC

There are no head to head comparisons of multidose PK between the Vimovo esomeprazole and Nexium 20 mg. The Nexium NDA's Clinical Pharmacology review includes a summary of two PK studies of 5-day multi-dosing (less than half of the duration of exposure in the Vimovo multi-dosing study). In these studies, increased exposure over 5 days was also documented. In a Nexium 40 mg study, the Cmax increased 2 fold and the AUC increased 2.6 fold. In another study that utilized Nexium 20 mg, the AUC increased 1.8 fold.

The Nexium NDA's Clinical Pharmacology review also presents data from a study in which 20 mg and 40 mg of esomeprazole were administered. The Cmax of the 40 mg dose was double that of the 20 mg dose level and the AUC was 3 fold higher than the 20 mg dose. Based on the single day dosing head to head comparison of Vimovo with Nexium presented above, and what is known about increased exposure over time with Nexium, the reviewers concluded that patients who take Vimovo will not be exposed to the Cmax achieved with a 40 mg dose level of the approved Nexium product, and that the AUC would be similar to taking Nexium 20 mg BID, which would also not exceed the Nexium 40 mg once daily exposure.

A pharmacodynamic study of varying doses of immediate release esomeprazole in the fixed combination of Vimovo was conducted, utilizing the endpoint of percent time of intragastric pH >4.0 on Day 9 of administration. The study included an enteric coated esomeprazole + naproxen arm. Based on this study, the to be marketed dose combination resulted in median of 70% time with pH> 4.0 on Day 9, which exceeded the % time associated with the lower esomeprazole (10 mg) combination and compared favorably within the study to the enteric coated esomeprazole + naproxen arm. Those data are summarized in the table below, which is reproduced from Dr. Bai's Clinical Pharmacology review.

Treatment	A PN 400/E30	B PN 400/E20	C PN 400/E10	D EC E20 + Naproxen
	N=25	N=25	N=25	N=25
% Time pH >4.0				
Mean (SD)	76.50 (12.26)	71.35 (13.01)	40.85 (22.51)	56.85 (10.06)
Median	78.79	70.42	35.76	55.14
%CV	16	18	55	18
Range	49.79 – 95.32	51.76 – 97.61	10.30 – 85.26	40.63 – 75.51
LS Mean (SE)	76.75 (3.02)	71.46 (3.02)	41.09 (3.02)	57.23 (3.02)
	A vs. D	B vs. D	C vs. D	
LS Mean Difference (SE)	19.52 (3.25)	14.23 (3.25)	-16.14 (3.25)	--
95% Confidence Interval	13.04 – 26.01	7.75 – 20.71	-22.26 – -9.66	--

PN 400/E30 = naproxen 500 mg/esomeprazole 30 mg bid
PN 400/E20 = naproxen 500 mg/esomeprazole 20 mg bid
PN 400/E10 = naproxen 500 mg/esomeprazole 10 mg bid
EC E20 + naproxen = EC esomeprazole 20 mg + naproxen 500 mg in AM, naproxen 500 mg in PM. SD = standard deviation; LS = least-squares; SE = standard error; CV = coefficient of variation

The Clinical Reviewer expressed concerns that the Applicant did not study a 10 mg esomeprazole combination formulation in phase 3 efficacy trials. However, the Clinical Pharmacology reviewer states in her review that the 20 mg esomeprazole dose was selected based on the higher percentage of time with intragastric pH>4 associated with the 20 mg dose (71%) relative to the 10 mg esomeprazole dose (41%).

No drug drug interaction between esomeprazole and naproxen was observed with coadministration. High fat meals reduced esomeprazole bioavailability by 50% and substantially delayed naproxen absorption (note shifts in Tmax in table below). Administration 30 to 60 minute prior to a meal decreased the impact of food. The summary food effects PK for naproxen are summarized in the table below, which is reproduced from Dr. Bai's review (PN400 = Vimovo).

Summary of Naproxen PK parameters by treatment:

Treatment	N	Statistics	Cmax (µg/mL)	Tmax (hr)	Tlag (hr)	AUC0-t (hr*µg/mL)	AUC0-inf (hr*µg/mL)	$t_{½}$ (hr)
A PN 400 with Food	22	Mean	55.9	16.5	10.2	1089	1201	17.5
		%CV	27	47	51	13	14	13
B PN 400 30 min before Food	23	Mean	55.5	10.4	5.09	1075	1166	18.1
		%CV	30	78	127	22	22	12
C PN 400 60 min before Food	24	Mean	65.1	6.8	2.87	1093	1178	18.2
		%CV	29	106	158	12	13	12
D PN 400 Fasted	23	Mean	62.4	6.1	2.00	1135	1220	18.8
		%CV	19	55	49	10	12	10

6. Clinical Microbiology

Not applicable.

7. Clinical-Efficacy

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Two identical phase 3 studies (Study 301 and 302) were submitted to support the efficacy of Vimovo in reducing the risk of developing NSAID-associated gastric ulcers (evaluation of the immediate release esomeprazole component of Vimovo). The 500 mg naproxen dose of the fixed combination Vimovo was studied in both studies. A third trial (Study 303) was initiated in a high risk population, but was terminated early due to insufficient enrollment (n=20). The Applicant also conducted two phase 3 trials, Study 307 and Study 309, to evaluate the efficacy of Vimovo (its naproxen component) for treating the signs and symptoms of osteoarthritis. Both studies enrolled patients with osteoarthritis of the knee and were designed to evaluate noninferiority to celecoxib. Reviewers from the Division of Gastroenterology Products (DGP) reviewed Studies 301 and 302, and reviewers from the Division of Anesthesia and Analgesia Products (DAAP) were consulted to review Studies 307 and 309. (DAARP had been previously consulted regarding the study design of these two trials at the post-end of Phase 2 meeting in June 2008 and at the pre-NDA meetings.)

Gastric Ulcer Risk Reduction Trials

Studies 301 and 302 were identical randomized, double blind, parallel-group, multicenter clinical trials of 6 months duration. They were conducted in the United States. Patients were eligible for inclusion if they had a history of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, or other medical condition expected to require daily NSAID therapy for at least six months. In addition, there were specific eligibility criteria based on age. Patients could be under the age of 50 if they had a history of documented gastric or duodenal ulcer within the

past 5 years. If patients were 50 years of age or older, they were not required to have a history of documented ulcer. Patients were randomized (1:1) between naproxen 500 mg twice daily or Vimovo (500 mg naproxen dose formulation) twice daily. Randomization was stratified based on low dose aspirin use. Endoscopies were performed at screening, one month, 3 months and 6 months. Patients who discontinued prematurely returned for a final visit endoscopy.

The primary endpoint was proportion of patients who developed gastric ulcer at any time throughout 6 months of treatment. An ulcer was defined as a mucosal break of at least 3 mm diameter with unequivocal crater depth. Sample size was determined based on an assumption that 15% of patients treated with naproxen would develop a gastric ulcer over the six months study, compared to 5% of patients treated with Vimovo. Key secondary endpoints included duodenal ulcers, expressed as a "tolerability" endpoint. In the submission, the Applicant proposed two efficacy endpoints that the Statistical reviewer concluded could only be viewed as exploratory: 1) incidence of gastroduodenal ulcers at any time throughout 6 months of treatment by low-dose aspirin use, and 2) incidence of gastroduodenal ulcers at any time throughout 6 months of treatment.

The demographic analysis revealed that more than half of the population in both studies was female. The median age was 59 years. In Study 301, approximately 24% of patients used low dose aspirin and approximately 6% of patients had a history of ulcer. (Treatment arms were balanced). In Study 302, a similar proportion of patients were taking low dose aspirin (22% in the Vimovo arm and 24% in the naproxen arm), compared to Study 301; however a higher proportion had a history of ulcer (13% on the Vimovo arm and 9% on naproxen).

The primary efficacy endpoint was analyzed using a CMH test stratified by use of low dose aspirin at randomization. The Applicant also conducted Kaplan-Meier estimates of the proportion of patients who developed ulcers. Time to documentation of gastric ulcer was calculated from the first day of study drug. Censoring occurred at the last day of endoscopic evaluation or date of withdrawal from the study if no gastric ulcer developed. The Applicant conducted sensitivity analyses classifying premature withdrawals without a confirmed gastric ulcer as having developed an ulcer at 6 months if they had discontinued from the trial due to a pre-specified upper gastrointestinal adverse event or if they developed a duodenal ulcer. The Applicant conducted additional exploratory analyses.

FDA's Statistical reviewer noted an imbalance in missing data between the studies and within Study 301. There was a higher premature discontinuation rate for Vimovo in Study 302 than 301 (29% vs. 17%), and a higher premature discontinuation rate for naproxen in Study 301 than in 302 (30.5% vs. 27.5%). The premature withdrawal rate was higher in the naproxen arm of Study 301 (30.5%) than the Vimovo arm (17%). She pointed out that missing efficacy data would conventionally be imputed as treatment failures for primary analyses; however, the higher missing data for the naproxen arm of Study 301 would significantly favor Vimovo in that approach. She concluded that the Applicant's approach of imputing missing data as treatment success was the more conservative analysis from a regulatory perspective. The following table, which summarizes the primary efficacy results for the two studies, is reproduced from the Statistical review. Both studies resulted in a statistically significantly smaller proportion of patients who developed gastric ulcers over the 6 month period. The

proportion of patients developing an ulcer in the naproxen arm exceeded the assumption upon which the sample size was based.

Table 3.2. Proportion of ITT Subjects with Gastric Ulcers by 6 Months

		PN400-301		PN400-302	
		PN 400	EC naproxen	PN 400	EC naproxen
N		218	216	210	210
Gastric Ulcer		9 (4.1%)	50 (23.1%)	15 (7.1%)	51 (24.3%)
Gastric Ulcer Free		209 (95.9%)	166 (76.9%)	195 (92.9%)	159 (75.7%)
Maintained gastric ulcer free		171 (78.4%)	103 (47.7%)	136 (64.8%)	102 (48.6%)
Discontinued gastric ulcer free		38 (17.4%)	63 (29.2%)	59 (28.1%)	57 (27.1%)
Difference (95% CI[a]) of (EC naproxen – PN 400)	Missing = Success	19.0% (13.0%, 25.6%)		17.1% (10.4%, 24.1%)	
	Missing = Failure	30.8% (21.9%, 39.3%)		16.2% (6.6%, 25.5%)	
p-value[b]		< 0.001		< 0.001	

CI: Confidence Interval
[a] Exact CI.
[b] CMH test on ulcer occurrence stratified by LDA use (Yes/No).
Source: Reviewer's Table (the results concur with those from the sponsor)

The statistical reviewer recommended that the 3 key secondary endpoints proposed by the Applicant (two tolerability endpoints and the duodenal ulcer incidence endpoint) not be included in the efficacy section of the label because they were redefined late in the study. She had concern that the plan for statistical testing of the duodenal ulcer endpoint as a key endpoint was not included until late in the study.

Exploratory analyses by gender, race, age, history of ulcer and use of low dose aspirin did not reveal internal inconsistencies for the primary endpoint.

I concur with the reviewers' conclusions that the Applicant has established that Vimovo is effective for reducing naproxen induced gastric ulcers. Esomeprazole carries the indication of reducing the risk of NSAID-induced gastric ulcers at doses of 20 mg/d and 40 mg/d (once daily dosing). The esomeprazole in Vimovo is an immediate release formulation that makes it vulnerable to degradation in gastric acid. The product is dosed twice daily. The single dose PK studies of Vimovo described in Section 5 of this review revealed that Vimovo was associated with lower esomeprazole exposures than Nexium 20mg. Repeat dose PK studies of Vimovo demonstrated higher exposures at Day 14. The two phase 3 trials demonstrated that immediate release esomeprazole in Vimovo is effective in this twice daily regimen for reducing naproxen induced gastric ulcers.

Although Vimovo will be marketed in two dose levels of naproxen in the fixed combination, 375 mg and 500 mg, the efficacy trials were only conducted at the 500 mg naproxen dose level. Esomeprazole efficacy in reducing gastric ulcers was demonstrated at the highest naproxen dose, so it is reasonable to assume that esomeprazole will contribute to the fixed combination at the lower naproxen 375 mg dose. A precedent for approving multiple dose levels of naproxen combined with a single dose level of a proton pump inhibitor can be found in the approval of the NDA for NapraPAC. The clinical review of that NDA indicates that patients in the clinical efficacy dataset were taking a range of naproxen doses, with the overwhelming majority taking 700-1000mg /day; however, the review does not indicate what

proportion were taking 375 mg BID vs. 500 mg BID. Efficacy was not presented by dose level.

Higher doses of NSAIDs are a risk factor for developing NSAID induced gastric ulcers; however, the Applicant submitted literature to support that naproxen 375 mg is associated with a risk for development of gastric ulcers. They cited a retrospective study (meeting abstract by Singh, Gurkirpal, et al.) of the MediCal database (California Medicaid program), that found that use of both naproxen 375 mg bid (750 mg/day) and naproxen 500 mg bid (1 g/day) significantly increases the risk of serious GI complications, defined as hospitalizations for complicated GU or DU (hemorrhage, perforation, or obstruction). The patients on 750 mg/day demonstrated a 2.95 increased risk ratio (RR) for hospitalization for complications of gastric and duodenal ulcers compared with controls (remote [>60 days previous] history of NSAID use). The corresponding RR for patients on naproxen 1 g/day was 3.13. This epidemiological analysis suggests that naproxen 375 mg twice daily is associated with GI risk, which in this study was slightly lower than that associated with the 500 mg twice a day. The Applicant also cited a short term (4 week) endoscopy trial (randomized, double blind) reported by Gomes, JA Melo, et al in Annals of the Rheumatic Diseases, 1993; 52: 881-885, in which 8.6% of patients treated with naproxen 375 mg BID developed gastroduodenal ulcers in that short time frame (6.9% developed gastric ulcers). A higher dose of naproxen was not studied in that trial. In comparison, the 1-month cumulative incidences of gastric ulcers in the EC-naproxen 500 mg arm of Study 301 and 302 were 13% and 10%, respectively.

The proportion of patients who developed ulcers on the naproxen only comparator in the NapraPAC data set was higher than observed in the naproxen only arm of the two trials submitted this Vimovo NDA. This may be attributed to the risk of the population studied. In the NapraPAC study all patients had a history of gastric ulcer, compared to <15% of patients in the Vimovo trials. A lower dose of naproxen, 375 mg, may be associated with a lower proportion of patients developing gastric ulcers (which is supported by the information described above), which might result in a lower incremental improvement of risk for gastric ulcers with the addition of the esomeprazole magnesium in the fixed combination of Vimovo, particularly in patients who are not at high risk for developing ulcers; however, there is a substantial safety experience with esomeprazole and the risk benefit ratio supports approval in the lower dose naproxen combination. Should a definitive significant risk associated with esomeprazole use be identified in the future, the risk/benefit of this unstudied dose level may need to be re-examined.

Osteoarthritis Trials

Studies 307 and 309, reviewed by the Division of Anesthesia and Analgesia Products (DAAP), were double blind, randomized, placebo and active controlled trials of 12 weeks duration conducted to assess the efficacy of Vimovo for treatment of signs and symptoms of osteoarthritis (OA). The naproxen component of Vimovo has been approved as a single agent for treatment of signs and symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. The trials were identical and included 3 arms: Vimovo (500mg/20 mg), placebo and celecoxib 200 mg once daily. Patients were randomized 2:2:1 (Vimovo:placebo:celcoxib).

The planned primary efficacy analysis was a noninferiority analysis comparing Vimovo to celecoxib for the 3 primary endpoints: WOMAC pain subscale; WOMAC function subscale; and the Patient Global assessment (all 0-100 mm visual analogue scales). The DAAP clinical reviewers found all 3 efficacy endpoints acceptable. The Statistical reviewer noted that there was no plan for adjustment for multiplicity in the statistical plan but the Applicant had specified in the protocol that because noninferiority had to be demonstrated for all 3 primary endpoints, no adjustment was necessary.

The protocol plan to use a noninferiority margin of 10 mm on each of the 0-100 VAS scales was not subject to agreement from FDA prior to study conduct, and the Applicant did not provide justification for selection of this margin. In a June 10, 2008, teleconference between the Applicant and FDA, the Applicant was advised that the FDA did not agree that a delta of 10 mm for the noninferiority margin could be supported, and that the totality of evidence from the trials would be used to assess the Applicant's desired comparison to celecoxib (since the trials contain a placebo arm). The clinical trials that established the efficacy of celecoxib did not utilize the same scales and the questions used to assess symptoms were worded differently. The Statistical reviewers and Clinical reviewers concluded that the celecoxib treatment effect relative to placebo (as a foundation for the noninferiority analysis) was best determined within Studies 307 and 309. Because the observed treatment effect of celecoxib vs. placebo in these trials was less than 10 mm (6-7 mm range across the endpoints in Study 307) and because celecoxib was not significantly different from placebo in Study 309 (with treatment effect sizes of 1-1.5 mm), the reviewers concluded that the 10 mm noninferiority margin proposed by the Applicant was not acceptable. The study results did not establish noninferiority of Vimovo to celecoxib (b) (4)

The reviewers, however, determined that the comparison of Vimovo to placebo established its efficacy for the indication of treatment of signs and symptoms of OA. Vimovo was found to be statistically significantly different from placebo for all 3 efficacy endpoints. The statistical reviewer stated that the efficacy results were "consistent across the 3 endpoints and the alternative imputation methods." I concur with the DAAP Clinical and Statistical reviewers that the results of these two studies provide sufficient evidence to support the efficacy of Vimovo (naproxen component) for the indication of treatment of signs and symptoms of osteoarthritis, (b) (4) Although the analysis comparing Vimovo to placebo in these trials was a prespecified secondary endpoint, one could argue that it technically should not have been tested after failure to establish noninferiority in the primary analysis. However, I agree that the bioequivalence of the naproxen component of Vimovo to the reference drug EC-Naprosyn, which is approved for the Applicant's proposed indications for the naproxen component of Vimovo, supports the validity of the observed outcome of the comparison to placebo in these trials.

The submitted trials only evaluated osteoarthritis and only evaluated the 500 mg naproxen dose level. The Applicant proposes that the indication for Vimovo include treatment of signs and symptoms of rheumatoid arthritis and ankylosing spondylitis, and they propose to market a Vimovo dose combination that includes 375 mg of naproxen. Naproxen is already approved

and marketed as a single agent for treatment of signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. Both of the proposed naproxen dose levels (375mg and 500 mg) are approved for treatment of these indications. The pharmacokinetic evaluation of Vimovo found no evidence of drug drug interaction between the naproxen and esomeprazole in Vimovo. The clinical pharmacology reviewers found that both doses of the referenced naproxen product, EC-Naprosyn, were bioequivalent to the respective Vimovo doses that contained the same amount of naproxen. Therefore there is adequate evidence that the naproxen component of Vimovo will contribute to the labeled treatment effect in all 3 conditions and at both dose levels.

In summary, I concur with the Clinical and Statistical reviewers of this application that the Applicant has established the efficacy of each component of this fixed combination product.

8. Safety

This is a 505(b)(2) application. The two product components of Vimovo, naproxen and esomeprazole, have been marketed in the US since 1976 and 2001, respectively. The Clinical pharmacology reviewers found that the naproxen component is bioequivalent to the referenced approved naproxen product, EC-Naprosyn, and determined in a single dose study that the AUC of the 20 mg immediate release esomeprazole component of Vimovo was approximately half that of the Nexium 20 mg reference after a single dose. Multiday dosing increases the esomeprazole exposure, as discussed in Section 5 above, but even with this increased exposure, the reviewers concluded that Vimovo is not be expected to exceed the exposure associated with the Nexium 40 mg product, which is approved for reduction of the risk of NSAID-associated gastric ulcers.

The CDTL noted in his review that 1326 subjects have been exposed to at least one dose of Vimovo in the clinical development program. Of the 1157 patients treated with Vimovo in the 5 major phase 3 clinical trials that were submitted in support of this NDA (the two ulcer trials, the two osteoarthritis trials and the 12 month safety study), most were female and the median age was 60 years. Approximately one third were greater than or equal to 65 years of age. The Clinical reviewer noted that half the patients studied had a history of cardiovascular disease.

There were no deaths in the clinical trials.

Across the clinical trials, in the combined safety population, the naproxen only arms had the highest proportion of dropouts for adverse events (40.6%), followed by Vimovo, then celecoxib. Gastric ulcers were included as adverse events leading to discontinuation. The dropout profile is summarized in the table below, which is reproduced from the Clinical Reviewer's review. Note that the misoprostol arm reflects patients from Study 303 (a high risk population), which was discontinued early due to poor accrual.

Table 36 Dropout Profile for All Phase III Trials

Dropout Profile: Incidence of Dropout by Treatment Group and Reason for Phase 3 Clinical Trials with New Drug					
Reasons For Dropout	Treatment Groups				
	Vimovo N = 1166	Placebo N = 246	Naproxen N = 426	Celecoxib N=488	Misoprostol* N = 11
Adverse Event	142 (12.2%)	12 (4.9%)	173 (40.6%)	38 (7.8%)	6 (54.5%)
Withdrew Consent	84 (7.2%)	22 (8.9%)	31 (7.3%)	38 (7.9%)	1 (9%)
Lost to Follow-Up	22 (1.9%)	1 (0.4%)	9 (2.1%)	6 (1.2%)	3 (2.7%)
Other	53 (4.5%)	9 (3.7%)	11 (2.6%)	17 (3.5%)	0 (0%)
Total Dropouts	301 (25.8%)	44 (17.9%)	329 (77.2%)	99 (20.3%)	10 (90.9%)

[1]Reviewers Table * Trial PN400-303 discontinued prematurely due to poor enrollment .

The Applicant conducted a one year trial to assess safety with longer term exposure to Vimovo, Study 304. The safety population in this study included 239 patients who had a mean duration of exposure of 270.7 days. Fifty-seven percent of patients completed 12 months on study. Of the 96 patients who withdrew, 45 did so for an adverse event. Nineteen of those 45 patients withdrew due to gastrointestinal adverse events, of which the most common adverse event was dyspepsia (N=6). The next most common category of adverse events was musculoskeletal complaints. The list of discontinuations related to adverse events is shown in the table below which is reproduced from Dr. Wynn's Clinical review. The musculoskeletal events may be related to inadequate efficacy, as may the gastrointestinal events.

Table 18 Adverse Events Leading to Discontinuation in Trial PN400-304

System Organ Class/ Preferred Term	**Vimovo Safety Population N = 239**
Study Participants with at least 1 adverse event leading to discontinuation	45 (18.8%)
Gastrointestinal Disorders	19 (17.9%)
Dyspepsia	6 (2.5%)
Abdominal pain upper	2 (0.8%)
Constipation	2 (0.8%)
Gastroesophageal reflux disease	2 (0.8%)
Musculoskeletal and Connective Tissue Disorders	11 (4.6%)
Arthralgia	2 (0.8%)
Back pain	2 (0.8%)
Osteoarthritis	2 (0.8%)
General disorders and administration site conditions	3 (1.3%)
Peripheral edema	2 (0.8%)

There were 58 SAEs reported by 53 patients in the phase 3 studies, and the SAE rate was similar between Vimovo and patients treated with EC-Naprosyn. The most common SAEs were cardiac disorders (0.5% in the Vimovo group, 0.5% in the EC-Naprosyn group and 0.2% in celecoxib). Four of the Vimovo events were atrial fibrillation/flutter. There were 2 SAE events of pneumonia in patients treated with Vimovo, 1 case in the EC-Naprosyn group and none in patients treated with celecoxib.

Thirteen patients experienced at least one SAE in Study 304, the 12 month safety study. The Clinical Reviewer considered 3 SAEs to be possibly related to study drug, i.e. hematemesis secondary to hemorrhagic gastritis (n= 1), worsening back pain (n= 1) and worsening left knee pain (n= 1). The latter two events may be related to inadequate efficacy for the naproxen component.

With regard to laboratory evaluations in the phase 3 trials, the CDTL noted in his review that over a period of 3-12 months, there were no increases in the mean for ALT, AST, alkaline phosphatase or bilirubin for Vimovo treated patients. Group mean, median and shifts in ALT and AST, and in bilirubin, were similar and consistent between the active treatment groups. He stated that elevations in transaminases greater than 3x ULN were noted in subjects in all treatment groups and were rare. He concluded that observations with regards to the liver function tests performed in this program are consistent with the medical literature and the product labels for the individual components of Vimovo. The primary reviewer summarized the transaminases from the phase 3 trial population in the table below, which is reproduced from her review:

Table 43 Clinically Relevant Hepatic Transaminases from the Expanded Safety Population

Assessment	Vimovo N = 1157	Naproxen N = 426	Celecoxib N = 488	Placebo N = 246
Total Study Participants with ALT Changes (normal 0-55 U/L)	3 (0.26%)	2 (0.47%)	0 0	1 (0.41%)
ALT ≥ 3X ULN	3 (0.26%)	2 (0.47%)	0	1 (0.41%)
ALT ≥ 5X ULN	2 (0.17%)	0	0	0
ALT ≥ 10X ULN	1 (0.09%)	0	0	0
ALT ≥ 20X ULN	1 (0.09%)	0	0	0
Total Study Participants with AST Changes (Normal 0-45 U/L)	5 (0.43%)	0	0	1 (0.41%)
AST ≥ 3X ULN	5 (0.43%)	0	0	1 (0.41%)
AST ≥ 5X ULN	2 (0.17%)	0	0	0
AST ≥ 10X ULN	1 (0.09%)	0	0	0
AST ≥ 20X ULN	1 (0.09%)	0	0	0
Total Study Participants with bilirubin changes	4 (0.35%)	0	2 (0.41%)	3 (1.2%)
Total bilirubin ≥ 1.5X ULN	1 (0.09%)	0	0	1 (0.41%)
Total bilirubin ≥ 2.0X ULN	1 (0.09%)	0	0	1 (0.41%)
Total Study Participants with Alkaline Phosphate changes	7 (0.61%)	1 (0.23%)	0	0
Alk Phos≥ 1.5X ULN	7 (0.61%)	1 (0.23%)	0	0
Alk Phos≥ 3.0X ULN	1 (0.09%)	0	0	

Sponsor's Table 5.3.5.3.2.37 Integrated Summary of Safety p112/2911.

She noted that although the number of patients with abnormal liver function tests was greater in the Vimovo treated group relative to the other treatment arms, the overall rate was still less than 1%. She noted that current naproxen labeling states that elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDS, and that these abnormalities may progress, remain unchanged, or be transient with continued therapy. In the ALT section of the table above, there are a total of 3 patients with an ALT ≥ 3 times the upper limit of normal (ULN). One patient had an ALT ≥ 3 times the ULN, one had an ALT ≥ 5 times the ULN and one exceeded 10 times the ULN. The two with the highest levels are described below because they also had concomitant elevation of AST. Only one of those patients developed an elevated bilirubin, and it was associated with an elevation in alkaline phosphatase.

In the Vimovo treated patients, there were 3 with concurrent elevations in ALT and AST greater than or equal to 3 times the upper limit of normal. Dr. Wynn considered two of particular interest (the two described in the preceding paragraph) and they are described in detail in her review. One patient entered the study with a normal ALT and AST but experienced elevations to ALT 2948 and AST 4046 on Day 33. The investigator considered the elevation unrelated to study drug and the patient was withdrawn from study due to duodenal ulcer documented on endoscopy on Day 33. This patient had a history of hypertension, dyslipidemia, insomnia and anxiety. Medications included aspirin, atenolol, clonazepam, trazodone, fenofibrate and valsartan. When he presented on Day 33 for endoscopy he had nausea, bronchospasm and cough. He had been using epinephrine inhalers

for the respiratory symptoms and was given an IM injection of dexamethasone. Bilirubin and alkaline phosphatase were within normal range and all other laboratory tests were normal; however, on follow up visits the total bilirubin and alkaline phosphatase were elevated, but then normalized. ALT and AST had markedly declined, but remained elevated (83 and 61 U/L). The investigator attributed these abnormalities to a viral syndrome, but the Clinical reviewer expressed concern that they might reflect naproxen toxicity.

Another patient experienced an increase in ALT and AST to >5 x upper limit of normal, but this patient had baseline elevations of transaminases. The investigator considered the elevation on study possibly related to study drug. This patient was a 55 year old female who was taking estrogen, methyl-testosterone and salmeterol fluticasone inhaler. The higher transaminases were documented at the one month visit, but they declined 10 days later.

One additional patient had elevated baseline transaminases that increased on study. The levels declined despite continuing treatment and the patient completed the study. Overall, among these 3 patients, only one had new onset of elevated transaminases. In that patient, the bilirubin was only documented to be elevated after the transaminases had declined, and was associated with an elevation of alkaline phosphatase. The investigator did not consider the changes related to study drug.

The CDTL noted that the post marketing safety review for esomeprazole (reports submitted to Astra Zeneca) in patients who were taking concomitant naproxen included events of pruritis, hypersensitivity, arthritis, confusional state, gait disturbance, nausea, peripheral edema, decreased platelet count and decreased WBC. There were no reports of liver function abnormalities in this combination group. The current Nexium label includes information on elevated transaminases under the Clinical Trials Experience section.

The Clinical reviewer also pointed out the rate of cardiovascular events in the safety data base was higher in Vimovo treated patients than placebo, but similar to patients treated with Naproxen. The table below is the summary of types of cardiovascular serious adverse events that occurred in the phase 3 trials, a modification of Table 35 in her Clinical Review. Four of Vimovo events were related to rhythm disturbance.

System Organ Class/ Preferred Term	Vimovo (N=1166)	Naproxen (N=426)	Celecoxib (N=488)	Misoprostol (N=11)	Placebo (N=246)
System Organ Class/ Preferred Term	Vimovo (N=1166)	Naproxen (N=426)	Celecoxib (N=488)	Misoprostol (N=11)	Placebo (N=246)
Number of Study Participants with Any Serious Adverse Events	31 (2.7%)	13 (3.1%)	8 (1.6%)	0	1 (0.4%)
All Serious Adverse Events	34	14	9	0	1
Cardiac Disorders	6 (0.5%)	2 (0.5%)	1 (0.2%)	0	0
Coronary artery disease	1 (<0.1%)	1 (0.2%)	1 (0.2%)	0	0
Atrial Flutter	2 (0.2%)	0	0	0	0
Unstable Angina	1 (<0.1%)	0	0	0	0
Atrial Fibrillation	1 (<0.1%)	0	0	0	0
Complete AV Block	1 (<0.1%)	0	0	0	0
Myocardial Infarction	1 (<0.1%)	0	0	0	0
Palpitations	0	1 (0.2%)	0	0	0

As of 2005, all prescription NSAIDs have been required to include a Boxed Warning and a Medication Guide in the product label due to the risk of cardiovascular and gastrointestinal adverse events. Vimovo contains naproxen as a component, and the label will include the class Boxed Warning and the Medication Guide.

The clinical reviewers concluded that the adverse events reported in the safety dataset submitted in support of this NDA were consistent with the currently labeled adverse events for the component products in this fixed combination. The reviewers concluded that risk/benefit supports approval of this product. Nexium's labeled indication for risk reduction of NSAID-associated gastric ulcer states "Controlled studies do not extend beyond 6 months." In keeping with this, the reviewers recommended that the indication for Vimovo included the language, "Controlled studies do not extend beyond 6 months."

9. Advisory Committee Meeting

There was no Advisory Committee for this application. The product does not contain a new molecular entity and there were no scientific issues that required discussion in an Advisory Committee.

10. Pediatrics

(b) (4)

Both naproxen and Nexium carry pediatric indications (juvenile rheumatoid arthritis [JRA] in patients 2 years and older for Naprosyn suspension and GERD for patients 1-17 years for Nexium); however, Nexium does not carry an NSAID-associated gastric ulcer risk reduction indication for children.

The DAAP Clinical reviewers did not recommend waiving studies in children with juvenile rheumatoid arthritis since the product is likely to be used in this population and Naprosyn suspension is approved in this population. The DAAP reviewers recommended that comparative PK studies in pediatric patients >2 years of age with an age-appropriate formulation of VIMOVO should be required under PREA. This would be used to bridge to the JRA indication for Naprosyn. The DAAP reviewers agreed that pediatric studies in osteoarthritis and ankylosing spondylitis could be waived.

The DGP Clinical reviewer stated in her review that "Essentially all patients on NSAID therapy are at risk of developing ulcers. In general the histology of pediatric gastric ulcers is similar to adults." In her review of the literature she found that there have been many attempts to determine the prevalence of NSAID gastropathy in children and the conclusions from these investigations have varied. She stated that the percentage of children who experience NSAID toxicity appears to be less than that of adults. She cautioned, however, that used on a chronic basis, NSAIDs can lead to gastropathy in children. DGP consulted the Pediatric and Maternal Health staff (PMHS) on this issue and the PMHS reviewers recommended the following:

1. For the indication, relief of signs and symptoms of **osteoarthritis** in patients at risk of developing NSAID-associated gastric ulcers, PMHS would concur with a request for a full waiver because studies would be impossible or highly impracticable.
2. For the indication, relief of signs and symptoms of **rheumatoid arthritis** (RA) in patients at risk of developing NSAID-associated gastric ulcers, PMHS recommends a partial waiver for patients under 2 year of age because studies would be highly impracticable, and a deferral for pediatric patients 2 year through 16 years. The rationale for going down to age 2 years is that although esomeprazole is approved down to one year of age, naproxen has been found to be safe and effective down to 2 years of age.
3. For the indication, relief of signs and symptoms of **ankylosing spondylitis** (AS) in patients at risk of developing NSAID-associated gastric ulcers, PMHS would concur with a request for a full waiver because studies would be impossible or highly impracticable.

The pediatric issues were taken to PeRC on April 14, 2010, and the committee concurred with the DAAP, DGP and Pediatric and Maternal Health reviewers. PeRC agreed with the plan to conduct PK studies to create a bridge to the existing data for children with JRA that has been established for naproxen. These studies to evaluate Vimovo tablets for patients ages 2 years to

16 years with JRA and to reduce the risk of naproxen induced gastric ulcers in patients with JRA will be deferred.

The following summarizes the decisions regarding pediatric requirements for this product:

1. For the indication relief of signs and symptoms of **osteoarthritis (OA)** and to decrease the risk of developing gastric ulcers in OA patients at risk of developing NSAID-associated gastric ulcers, we are waiving the pediatric study requirement for ages birth to 16 years, 11 months. Osteoarthritis is one of the "adult-related" conditions that does not occur in pediatrics and qualifies for a waiver because studies would be impossible or highly impractical.

2. For the indication relief of signs and symptoms of **ankylosing spondylitis (AS)** and to decrease the risk of developing gastric ulcers in AS patients at risk of developing NSAID-associated gastric ulcers, we are waiving the pediatric study requirement for ages birth to 16 years, 11 months. Necessary studies are impossible or highly impracticable because there are too few pediatric patients with this disease to study. Ankylosing spondylitis typically presents in young adulthood.

3. For the indication relief of signs and symptoms of **rheumatoid arthritis (RA)** and to decrease the risk of developing gastric ulcers in RA patients at risk of developing NSAID-associated gastric ulcers, we are waiving the pediatric study requirement for ages birth to 1 year, 11 months. Necessary studies for pediatric patients in this age range are impossible or highly impracticable because Juvenile Rheumatoid Arthritis does not usually present at birth and fewer than 2% of all pediatric visits to a physician for an NSAID prescription for arthritis and arthropathy occur in this age group. The very low prevalence of JRA in this age group would make it extremely difficult to conduct a study with a sufficient number of patients to evaluate safety. Additionally, neither of the active components of Vimovo has been approved for the entirety of this age group. Safety and effectiveness of naproxen below the age of 2 years has not been established and esomeprazole was found to be ineffective for GERD in patients less than 1 year of age. The current labeling for esomeprazole does not establish the safety of this drug in children less than 1 year of age.

   We are deferring submission of your pediatric studies for ages 2 to 16 years, 11 months because this product is ready for approval for use in adults and the pediatric studies have not been completed.

See the Approval letter and Section 13 of this review for the studies required under PREA.

11. Other Relevant Regulatory Issues

Financial Disclosures: Dr. Erica Wynn noted in her review that the Applicant submitted an FDA form 3454 certifying that it had not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study. The Applicant certified that, with the exception of one

investigator, no investigator disclosed a proprietary interest in the product or significant equity in the applicant. The Applicant submitted a form 3455 "Disclosure: Financial Interests and Arrangements of Clinical Investigators" for one investigator.

DSI: The DSI report for inspections at the 4 sites that enrolled the largest number of study participants concluded that the data generated from all 4 sites could be used in support of the NDA.

Combination Rule and Labeling: The proposed product is a fixed combination drug product. The Applicant has established that each component contributes to the purported treatment effect of the product, meeting the requirements of the combination rule. The Applicant's proposed indication (see below), however, does not clearly state the role/indication for the esomeprazole component of Vimovo and does not make clear that there are two component products, each with a separate role.

VIMOVO is indicated for the relief of signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis in patients at risk of developing NSAID-associated gastric ulcers. (b) (4) . VIMOVO is not recommended for initial treatment of acute pain because the absorption of naproxen is delayed compared to absorption from other naproxen containing products.

To address this issue, the product indication was revised during labeling negotiations to the following:

VIMOVO is a combination product that contains naproxen and esomeprazole. It is indicated for the relief of signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis and to decrease the risk of developing gastric ulcers in patients at risk of developing NSAID-associated gastric ulcers. VIMOVO is not recommended for initial treatment of acute pain because the absorption of naproxen is delayed compared to absorption from other naproxen-containing products. Controlled studies do not extend beyond 6 months.

Medication Guide and REMS: Because the naproxen component is an NSAID, Vimovo is subject to the class labeling for NSAID, including a Box Warning and Medication Guide. The Applicant was notified on October 9, 2010, that a risk evaluation and mitigation strategy (REMS) was required for Vimovo (naproxen/esomeprazole magnesium) to ensure that the benefits of the drug outweigh the risks of cardiovascular and gastrointestinal adverse events. The Applicant was told that the REMS must include a Medication Guide and a timetable for submission of assessments of the REMS.

The Applicant submitted a REMS on November 11, 2010. After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we reconsidered the need for a REMS for this product. We believe that a Medication Guide is necessary to inform patients of the serious risks of cardiovascular and gastrointestinal adverse events. However, since other drugs currently approved in the NSAID class have Medication Guides with identical safety information regarding these risks that are not included in a REMS, we will not require a REMS.

12. Labeling

I concur with the reviewers' recommendations for labeling. The DMEPA reviewers found the proprietary name, Vimovo, acceptable.

The label will include the class labeling Box Warning and Medication Guide for the NSAID (naproxen) component of Vimovo.

In addition, since esomeprazole was approved, we have become aware of reports of osteoporosis-related bone fractures in patients taking proton pump inhibitors for an extended period of time. Data were evaluated from several epidemiology studies and reports published in the peer-reviewed biomedical literature which compare patients receiving proton pump inhibitors (PPIs) to patients who were not receiving PPIs [1,2,3,4,5]. In four of the five published studies, there was a small increased risk of osteoporosis-related bone fracture in patients taking PPIs. Taken together these findings support the association between PPI exposure and bone fracture. We consider this information to be new safety information.

We requested that the Applicant include the following information in the product label for the esomeprazole component of Vimovo under Warnings and Precautions, and the Applicant agreed to the wording:

Bone Fracture
Several studies and literature reports indicate that proton pump inhibitor (PPI) therapy is associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. Those patients with the highest risk received high-dose or long-term PPI therapy (a year or longer). Patients should use the lowest effective dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to the established treatment guidelines. Adequate vitamin D and calcium intake is recommended.

In addition, the Medication Guide includes this in the Vimovo section under "What are the possible side effects of Vimovo?" as follows:

[1] Yang YX et.al. Long-term proton pump inhibitor therapy and risk of hip fracture. JAMA 2006; 296:2947-53.
[2] Targownik LE et.al. Use of proton pump inhibitors and risk of osteoporosis-related fractures. CMAJ 2008 Aug 12; 179(4):319-26.
[3] Vestergaard P et.al. Proton pump inhibitors, histamine H2 receptor antagonists, and other antacid medications and the risk of fracture. Calcif Tissue Int. 2006; 79: 76-83.
[4] Corley DA et.al. Proton Pump Inhibitors and Histamine-2 Receptor Antagonists are associated with Hip Fractures Among A-Risk Patients. Gastroenterology 2010 Mar 27 [Epub ahead of print]
[5] Kaye JA et al. Proton Pump Inhibitor Use and Risk of Hip Fractures in Patients without Major risk Factors. Pharmacotherapy 2008; 28:915 – 59.

"Bone Fracture. Talk to your healthcare provider about your risk for fractures if you take VIMOVO for a long period of time."

This was included in the Medication Guide because a Medication Guide existed already for the NSAID safety issue. The reviewers agree that a Medication Guide would not be necessary for this particular safety issue.

Use of the lowest effective is mentioned in the bone fracture warning and in Section 2 Dosage and Administration ("Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals.") In light of the fact that in this fixed combination, the lowest possible esomeprazole dose is 20 mg twice daily, while the Nexium lowest approved dose for reduction of risk of NSAID-associated gastric ulcers is 20 mg once daily, the Division added the following language to the Dosage and Administration section of Vimovo: "Vimovo does not allow for administration of a lower daily dose of esomeprazole. If a dose of esomeprazole lower than a total daily dose of 40 mg is more appropriate, a different treatment should be considered."

The Applicant proposed (b) (4) This deviated from current labeling of Nexium and naproxen. The reviewers did not agree with incorporating this language in the indication.

See additional information on labeling included in other sections of this review.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action –Approval.

- Risk Benefit Assessment – I concur with the CDTL that the risk and benefit characteristics of this fixed combination product are favorable, for the proposed indication. Both products have been marketed for years for the same indications proposed for this product. As discussed in my review, although the dosing regimen for esomeprazole differs from Nexium for the same indication, the total daily dose does not exceed the maximum Nexium dose approved for the indication and the clinical pharmacology reviewers have concluded that the daily exposure should not exceed that associated with the Nexium 40 mg once daily. The Dosage and Administration section of the label will state, "Vimovo does not allow for administration of a lower daily dose of esomeprazole. If a dose of esomeprazole lower than a total daily dose of 40 mg is more appropriate, a different treatment should be considered."

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

  Because this fixed combination product contains the NSAID naproxen, it will be approved with the Medication Guide that all NSAID products carry in labeling. A REMS will not be required. (See Approval Letter and Section 11 above.)

- Recommendation for other Postmarketing Requirements and Commitments

The following deferred studies are required under the Pediatric Research Equity Act (PREA):

1634-1 Deferred pediatric study under PREA in children 2 years to 11 years of age with Juvenile Rheumatoid Arthritis (JRA)

A safety and population pharmacokinetic (PK) study in children with JRA who are 2 years to 11 years, 11 months of age and require treatment with NSAIDs will be conducted. This study will be a 6 month, multicenter, open-label study to evaluate the dose, safety and PK of VIMOVO in this age group.

Final Report Submission: November 2014

1634-2 Deferred pediatric study under PREA in children 12 years to 16 years and 11 months of age with Juvenile Rheumatoid Arthritis (JRA)

A safety and population pharmacokinetic (PK) study in adolescents with JRA who are ages 12 years to 16 years and 11 months and require treatment with NSAIDs will be conducted. This study will be a 6 month, multicenter, open-label study to evaluate the safety and PK of VIMOVO in this age group.

Final Report Submission: October 2013

In addition, there was a single non-PREA Postmarketing Commitment (PMC):

1634-3 Within one year post-approval, [the Applicant] will transition from the naproxen dissolution test currently in the NDA to the USP method that tests naproxen continuously, i.e. acid followed by buffer, using the same tablet.

Protocol Submission: July 2010
Final Report Submission: April 2011

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22511	ORIG-1	POZEN INC	PN 400 NAPROXEN/ESOMEPRAZOLE MAGNESIUM

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

/s/

DONNA J GRIEBEL
04/30/2010