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**APPLICATION NUMBER:
22511Orig1s000**

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	April 22, 2010
From	Ruyi He, MD Acting Deputy Director/Medical Team Leader Division of Gastroenterology Products/ODE III
Subject	Cross-Discipline Team Leader Review
NDA	22-511
Applicant	POZEN Inc
Date of Submission	June 30, 2009
PDUFA Goal Date	April 30, 2010
Proprietary Name / Established (USAN) names	VIMOVO (naproxen/esomeprazole magnesium) Tablets.
Dosage forms / Strength	<ul style="list-style-type: none">• 375 mg enteric coated naproxen and 20 mg esomeprazole (as magnesium trihydrate) Tablet, or• 500 mg enteric coated naproxen and 20 mg esomeprazole (as magnesium trihydrate) Tablet.
Proposed Indication(s)	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.
Recommended:	NDA 22-511 VIMOVO (naproxen/esomeprazole magnesium) Tablets be approved for the indication of the relief of signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis and risk reduction of developing gastric ulcers in patients at risk of developing NSAID-associated gastric ulcers.

1. Introduction

PN 400 (VIMOVO) is a fixed dose combination tablet containing 375 mg or 500 mg naproxen in the core and 20 mg esomeprazole in the film coat. Esomeprazole is immediately released from the film coat, whereas the release of naproxen from the enteric coated core is delayed as it is dependent on elevated pH. Oral administration of PN 400 Tablets on a twice daily regimen is intended for *the treatment of the signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis in patients at risk for developing NSAID-associated gastric ulcers.*

Like other non-steroidal anti-inflammatory drugs (NSAIDs), naproxen inhibits cyclooxygenase enzyme activity. This inhibition reduces prostaglandin synthesis and leukocyte activation resulting in anti-inflammatory, and analgesic activity.

Esomeprazole is a gastric proton pump inhibitor (PPI) that inhibits the final common pathway of acid production in the stomach and thus inhibit both basal and stimulated gastric acid secretion.

NSAIDs remain the primary therapy for the management of signs and symptoms of chronic inflammatory conditions such as osteoarthritis. However, chronic NSAID therapy is associated with a substantial risk of upper gastrointestinal (UGI) ulcerations and ulcer complications, such as bleeding and perforations. The cumulative incidence of gastroduodenal ulcers with conventional NSAID use has been reported to be as high as 25-30% at 3 months and 45% at 6 months, while that of placebo is 3-7%. Important risk factors for UGI ulcers in NSAID users are advancing age, a history of UGI ulcer or bleeding, and concomitant aspirin use. Up to 4% of NSAID users experience serious UGI adverse events, such as bleeding, perforation or obstruction. Ulcer formation and complications associated with having an ulcer may also be asymptomatic. In fact, up to 80% of those who develop an ulcer complication have no warning signs or symptoms.

In clinical practice, the use of PPIs to inhibit gastric acid secretion has been shown to mitigate the risk from daily NSAID use by significantly reducing the development of gastric ulcers.

As such, the sponsor developed a combination product to increase compliance with the 2-drug regimen with every dose since it combines both agents into a single tablet. Tablets are formulated to immediately release esomeprazole followed by release of naproxen after dissolution of the enteric coat at pH above 5.0.

2. Background

The development program to support this 505(b)2 application for PN 400 Tablets was discussed and agreed with the Agency. EC-Naprosyn is approved for the indications of Rheumatoid Arthritis, Osteoarthritis and Ankylosing Spondylitis at both 500 mg and 375 mg doses for twice daily administration. Esomeprazole is approved for risk reduction of NSAID-associated gastric ulcer 20 mg or 40 mg once daily for up to 6 months.

The sponsor conducted 2 controlled pivotal efficacy and safety studies, PN400-301 and PN400-302, to demonstrate a reduction in gastric ulcer formation in subjects who took PN 400 Tablets bid compared with those who took EC naproxen 500 mg bid on a daily basis for 6 months. Those 2 trials are evaluated by the division of gastroenterology products (DGP).

The sponsor also conducted two controlled studies (PN400-307 and PN400-309) to compare PN 400 Tablets with celecoxib in the management of signs and symptoms of osteoarthritis of the knee. These 2 trials are evaluated by the Division of Analgesics, Anesthetics, and Rheumatology Products (DAARP).

In addition, the 12-month open-label safety study PN400-304 provides the long-term safety of PN 400 Tablets in subjects at risk of developing NSAID-associated gastrointestinal ulcers and provided safety and tolerability data.

3. CMC

PN 400 Tablets have been designed as a single combination tablet of two distinct formulations, an inner enteric coated (delayed release) component of naproxen containing either 375 mg or 500 mg of naproxen and an outer immediate release film coat of esomeprazole containing 20 mg of esomeprazole (present as 22.3 mg of esomeprazole magnesium trihydrate). The tablet is designed to release the active ingredients in a coordinated, yet independent fashion.

The tablet consists of a naproxen core tablet that is coated with (b) (4)

PN 400 Tablets use conventional pharmaceutical ingredients and manufacturing processes that are well established for use in solid oral dosage forms.

A 24 months shelf-life is proposed for PN 400 Tablets 500mg/20 mg and 375 mg/20 mg stored at controlled room temperature, 25°C (77°F) excursions 15°C to 30°C (59°F to 86°F), in the proposed commercial container closure system.

The dissolution data submitted are acceptable based on Dr. Tien-Mien Chen's evaluation; however, the currently proposed dissolution methodology by the sponsor for Vimovo tablets can only be used on an interim basis. As a Phase 4 commitment, the sponsor agreed to submit additional dissolution testing/data on the naproxen of Vimovo tablets for review. See Dr. Tien-Mien Chen's review for details.

Based on Dr. Rajiv Agarwal's review (CMC reviewer), this NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. The final "Acceptable" recommendation from the Office of Compliance is received on 24-MAR-2010. The labeling information on immediate container and carton labels is adequate. This NDA is recommended for APPROVAL from the CMC perspective.

4. Nonclinical Pharmacology/Toxicology

This NDA is submitted under section 505(b) (2) and is supported by reference to the Agency's previous findings of safety and publicly available information on the toxicology of naproxen and esomeprazole (including omeprazole) to meet the nonclinical assessment requirements as part of the PN 400 new drug application.

There are no nonclinical study reports in this NDA except a PK study on determination of urinary and plasma metabolite profiles following 4 days oral administration of buffered- and unbuffered-omeprazole to female Sprague Dawley rats. In addition, the sponsor provided published studies to support the safety of the drug from a nonclinical standpoint.

Pharmacologic, pharmacokinetic and toxicological properties of individual components of PN 400 (naproxen and esomeprazole, including omeprazole) are well-established. From a nonclinical standpoint, approval of the NDA application is recommended. Please see Dr. Charles Wu's review dated March 17, 2010 for detail.

5. Clinical Pharmacology/Biopharmaceutics

The 10, 20 and 30 mg bid dose for esomeprazole were tested. After 9 days of bid dosing, esomeprazole 20 mg resulted in a greater percent time with intragastric pH > 4.0 than esomeprazole 10 mg (71.4% vs 40.6%). Mean % time pH>4 following Vimovo increased with esomeprazole dose with 41%, 71%, and 77%, for 10 mg, 20mg, and 30 mg, respectively. The 20 mg dose for esomeprazole is reasonable.

At 375 mg dose of naproxen, PN 400 was bioequivalent to EC-NAPROSYN. At 500 mg dose of naproxen, the first bioequivalence study with less frequent sampling failed to demonstrate bioequivalence (BE) for C_{max}. With more frequent sampling in a second bioequivalence study, PN 400 was bioequivalent to EC NAPROSYN. Based on Dr. Bai and Dr. Jappar's Clinical Pharmacology review, Vimovo is bioequivalent to EC-NAPROSYN. At 20 mg, average esomeprazole AUC following Vimovo was approximately 50% of that following Nexium, indicating that immediate release of esomeprazole without protection against gastric acidic degradation resulted in significantly lower esomeprazole exposure.

Co-administration of naproxen and esomeprazole in PN 400 did not alter the PK profile of either drug regardless of esomeprazole formulation (IR or EC), suggesting the absence of pharmacokinetic drug-drug interaction between naproxen and esomeprazole. The afternoon dose had lower esomeprazole AUC and C_{max} than the morning dose. AUC and C_{max} following multiple doses were higher than following single dose. Esomeprazole component of PN 400 has very high inter- and intra-individual variability regardless of single dose or multiple dose administration.

High-fat meal significantly reduced esomeprazole bioavailability by 50% and delayed naproxen absorption by 10 hr from Vimovo. When Vimovo was administered 30 min or 60 min prior to food intake, food had less effect on esomaprozole and naproxen absorption. This observed food effect was taken into consideration in Phase 3 clinical trials as patients were instructed to take Vimovo 30-60 min before breakfast or dinner.

From the clinical pharmacology perspective, the application is acceptable provided the labeling comments are adequately addressed by the sponsor. Please see Dr. Bai and Dr. Jappar's Clinical Pharmacology review dated April 7, 2010 for details.

6. Clinical Microbiology

N/A

7. Clinical/Statistical- Efficacy

Studies PN400-307 and PN400-309 in the management of signs and symptoms of osteoarthritis of the knee

The sponsor conducted two controlled studies (PN400-307 and PN400-309) to compare PN 400 Tablets with celecoxib in the management of signs and symptoms of osteoarthritis of the knee. These 2 trials are evaluated by the Division of Analgesics, Anesthetics, and Rheumatology Products (DAARP).

DAARP was consulted on the study design of the two pivotal trials (Studies 307 and 309) and attended EOP2 meeting on June 10, 2008 and Pre-NDA meetings on March 23, 2009. The following main issues were discussed and conveyed to the Sponsor:

Primary endpoint must be the change from baseline to the end of treatment (12 weeks) in WOMAC Pain, WOMAC Function and Patient Global Assessment.

Handling dropouts: a conservative imputation method for dropouts should be used as most of the dropouts are nonrandom.

Pediatric studies

(b) (4)

Substantial evidence of analgesic efficacy of PN400 will be based on bioequivalence to EC-Naprosyn. The Studies 307 and 309 are intended to demonstrate comparability of PN-400 to celecoxib and is not possible to establish an "acceptable" non-inferiority margin at that time.

The sponsor submitted three bioequivalence studies (Studies 102, 114 and 105) to establish bioequivalence of naproxen in PN400 tablets vs. EC-Naprosyn that were evaluated by clinical biopharmacology team (see reviews by Dr. Dilara Jappar and Dr. Jane Bai).

Based on the evaluation by Dr. Dilara Jappar and Dr. Jane Bai, PN400 is bioequivalent to EC-Naprosyn. Therefore, analgesic efficacy of PN400 is established based on bioequivalence to EC-Naprosyn.

Study 307 and Study 309 were designed identically as 12-week, multi-center, randomized, double-blind, placebo-controlled, active-controlled, non-inferiority (NI) studies. A total of 619 (Study 307) and 615 (Study 309) patients with the knee OA were enrolled from 75-82 study sites in the US and were randomized into three groups with a ratio of 2:2:1 (PN400:celecoxib: placebo). The planned enrollment for each study was 570 patients with a study power of 90% based on the proposed NI margin of 10 mm difference (2-sided 95% CI) in three co-primary endpoints between PN400 and celecoxib. The subjects were treated with PN400 tablets (500 mg naproxen/20 mg esomeprazole) bid, celecoxib capsules 200 mg qd or placebo for 12 weeks.

The standard three co-primary endpoints for the OA indication were used: *the mean change from baseline at Week 12 in WOMAC Pain, WOMAC Function and Patient Global Assessment*. The secondary endpoints included common supportive efficacy variables for OA and variables for GI tolerability.

The Applicant's analyses of the primary endpoints for both noninferiority (PN400 vs. celecoxib) and superiority (PN400 and celecoxib vs. placebo) were consistent with the re-analyses performed by DAARP's statistical reviewer. See both the medical review by Dr. Jin Chen and statistical review by Ms. Katherine Meaker for details.

According to Dr. Chen, the upper bound of the 95% CI of the differences in three co-primary endpoints between PN400 and celecoxib were 4-5 mm, within the pre-specified NI margin of 10 mm, based on the primary analysis, secondary analyses and sensitivity analyses in both studies. Also, the effect sizes of PN400 compared to placebo were similar to celecoxib (Table 1 in Dr. Chen's review).

However, the pre-specified NI margin is considered to be inadequate as determined by both the clinical and statistical review teams in DAARP. The conclusion is based on the observed effect size of celecoxib over placebo from this study and the effect sizes were too small as compared with similar OA trials on the similar products. Dr. Chen pointed out in his review that the upper bound of the 95% CI of the observed effect sizes of celecoxib (vs. placebo) were only 0.28-1.75 mm less than the pre-specified NI margin (10 mm) for WOMAC pain and Function in both studies. Dr. Chen indicated that PN400 might be similar to placebo if a non-inferiority is established based on this NI margin. The non-inferiority of PN400 compared to celecoxib cannot be established as demonstrated by the re-analyses of non-inferiority performed by the statistical review team using a re-defined NI margin (see the statistical review for details).

In both studies PN400 was statistically superior to placebo in all three co-primary endpoints in the primary analysis.

In summary, I concurred with Dr. Chen and Ms. Katherine Meaker that PN400 is efficacious for the treatment of signs and symptoms of osteoarthritis of the knee based on superiority analyses comparing PN400 with placebo in both trials. Because the bioequivalence of PN400 to the reference drug EC-Naprosyn (naproxen PK profile) is adequately established, the Applicant's proposed indication "*for the relief of signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis*" and dosing regimen would be acceptable. The non-inferiority of PN400 (500/20 mg bid) compared to celecoxib (200 mg qd) cannot be established based on the totality of efficacy outcomes from both trials. The DAARP's statistical review team re-defined the NI margin based on the observed effect size of celecoxib and concluded that PN400 was not noninferior to celecoxib in both studies.

No new safety signals have been identified from either study, as compared to the reference drugs. Please see Dr. Chen's review for detail clinical evaluation.

PN400-301 and PN400-302 for a reduction in gastric ulcer formation

The sponsor conducted 2 controlled pivotal efficacy and safety studies, PN400-301 and PN400-302, to demonstrate a reduction in gastric ulcer formation in subjects who took PN 400 Tablets bid compared with those who took EC naproxen 500 mg bid on a daily basis for 6 months. Those 2 trials are evaluated by the division of gastroenterology products (DGP).

Studies PN400-301 and PN400-302 were identical as 6 month, Phase 3, randomized, double-blind, parallel group, multicenter, outpatient studies at sites throughout the United States. Studies PN400-301 and PN400-302 each had 2 arms; the PN 400 and the EC naproxen.

These studies enrolled subjects with risk factors for developing NSAID-associated gastric ulcer. Specifically, the inclusion required that subjects 18 years or older, but less than 50 years old must have had a documented, uncomplicated gastric or duodenal ulcer within 5 years of the study enrollment. Subjects 50 years or older did not require such a history but were not excluded if such a history existed.

Efficacy endpoints in PN400-301 and PN400-302 were identical. The primary endpoint to support product approval was the cumulative proportion of subjects developing endoscopically visualized gastric ulcers (GU) through 6 months of treatment with PN 400 relative to the EC naproxen control. Endoscopies were conducted at baseline and at 1, 3 and 6 months of treatment; treatment emergent endoscopies were to be conducted in response to certain hemodynamic events and in response to dyspeptic symptoms. The definition of GU, both for the purposes of patient inclusion/exclusion and assessment of response, was a mucosal break \geq 3mm in diameter with depth.

The key secondary efficacy and tolerability endpoint assessments included:

1. Pre-specified NSAID-associated UGI AEs
2. Discontinuation from the study due to NSAID-associated UGI AEs
3. Duodenal ulcers throughout 6 months of study treatment

Both pivotal studies enrolled a majority of females (63- 69%) equally into both arms. The population was predominantly White (84- 90%), and had mean ages between 58 and 62 years. Approximately one quarter of the subjects in PN400-301 used low-dose aspirin (LDA) distributed equally between treatment groups, and there were equal histories of documented ulcer within the past 5 years. In PN400-302, slightly fewer subjects in the PN 400 group (21.9%) used LDA compared to subjects taking EC naproxen (24.3%).

A significantly lower proportion of subjects who took PN 400 in both trials had gastric ulcers (GU) than subjects who used EC naproxen at 1 month, 3 months and at 6 months ($p < 0.001$ at each time point, Table 1).

Table 1: Analysis of Cumulative Observed Incidence of Gastric Ulcers at 1, 3 and 6 Months – ITT Population, PN400-301 and PN400-302

Gastric ulcer n (%)	Study 301		Study 302	
	PN 400 N=218	EC naproxen N=216	PN 400 N=210	EC naproxen N=210
1 month	3 (1.4)	28 (13.0)	4 (1.9)	21 (10.0)
3 months	4 (1.8)	42 (19.4)	10 (4.8)	37 (17.6)
6 months	9 (4.1)	50 (23.1)	15 (7.1)	51 (24.3)

P is <0.001 for both studies at 1 month, 3 months and at 6 months. P-value for ulcer occurrence is from a CMH test stratified by low-dose aspirin use, at randomization, as reported on the concomitant medications CRF page.

Fewer subjects assigned to PN 400 developed GU throughout 6 months in PN400-301 (4.1%) compared to those in PN400-302 (7.1%), while approximately the same percentage of those assigned to EC naproxen developed GU (23.1 % and 24.3%, respectively).

PN 400 treatment also demonstrated improvements in the key secondary upper GI endpoints, including duodenal ulcer (Table 2).

Table 2: Outcomes of Key Secondary Endpoints

Key Secondary Endpoint	Study 301		Study 302	
	PN 400 N=218 % (95% CI)	EC naproxen N=216 % (95% CI)	PN 400 N=210 % (95% CI)	EC naproxen N=210 % (95% CI)
NSAID Associated Upper GI AE and/or Duodenal Ulcers (DU)	52.3% (45.4 – 59.1%) (p< 0.001)	69.0% (62.4 – 75.1%)	54.3% (47.3 – 61.2%) (p< 0.001)	71.9% (65.3 – 77.9%)
Incidence of DU at 6 months	0.5% (p= 0.003)	5.1%	1.0% (p= 0.007)	5.7%
Discontinuation due to NSAID Associated Upper GI AE or DU 6 months	3.2 % (1.3 - 6.5%) (p< 0.001)	12% (8.0 - 17%)	4.8 % (2.3, 8.6%) (p= 0.009)	11.9% (7.9, 17.1%)

Significantly fewer subjects in both trials who took PN 400 had a pre-specified NSAID-associated upper GI adverse event and/or duodenal ulcer than did those who took EC naproxen. Additionally, more subjects in both studies who took EC naproxen discontinued due to upper GI AE or DU compared to subjects who took PN 400; and subjects in both studies treated with EC naproxen had a higher incidence of duodenal ulcers, compared to those taking PN 400 (Table 2).

Analyses were performed on subgroups of patients who did and did not take low-dose aspirin, subgroups of age and in subgroups of subjects who entered the trial with and without a history of gastric ulcer. The factors known to increase the risk of GU with the use of naproxen are increasing age, use of low dose aspirin (LDA), and history of gastric ulcer within 5 years of the study. Table 3 summarizes the findings at 6 months in these pre-defined subpopulations on the combined dataset.

Table 3: Cumulative Proportion of Patients with Gastric Ulcers at 6 Months by Risk Factors, Combined Studies PN400-301 and PN400-302

Risk Factor	Vimovo N	% GU (95%CI)	EC naproxen N	% GU
Used LDA	99	3.0 (0.6-8.6)	102	28.4 (19.9-38.2)
Did not use LDA	329	6.4 (4.0-9.6)	324	22.2 (17.8-27.1)
Age < 60 years	216	8.3 (5.0-12.9)	217	21.2 (16.0-27.2)
Age ≥ 60 years	212	2.8 (1.0-6.1)	209	26.3 (20.5-32.8)
Age ≥ 50 years/ no history of ulcer	393	5.1 (3.1-7.8)	390	21.5 (17.6-26.0)
Age ≥ 50 years/ history of ulcer	21	4.8 (0.1-23.8)	27	55.6 (35.3-74.5)

P < 0.001 between Vimovo and Naproxen groups for all risk factors listed.

The effectiveness of PN 400 in the reduction in occurrence of gastric ulcers was not decreased when analyzed by the risk factors of age, or the concomitant use of low dose aspirin.

The efficacy of PN 400 is also supported by significant improvement in the secondary endpoints of reduction of pre-specified NSAID-associated UGI adverse events, duodenal ulcers and discontinuations from therapy due to each of those endpoints. The improved tolerability profile of PN 400 was further demonstrated by the fact that a higher proportion of subjects in the combined analysis assigned to PN 400 (71.4%) completed 6 months of treatment without developing a gastric or duodenal ulcer than subjects assigned to EC naproxen (47.6%). Importantly, the reductions in rates of DU and pre-specified NSAID-associated UGI adverse events in those who took PN 400 were not impacted by age or concomitant use of LDA.

In conclusion, Studies PN400-301 and PN400-302 demonstrated individually and when combined that the use of PN 400 results in a significantly lower proportion of subjects with NSAID-associated gastric or duodenal ulcers over 6 months of treatment. The effect was consistent through the six months of treatment.

8. Safety

The active ingredients in PN 400, naproxen and esomeprazole, have been commercially available in the US since 1976 and 2001, respectively and have been used together in clinical practice since 2004 when esomeprazole was first approved to reduce the gastric injury that can result from chronic use of NSAIDs. There are no known interactions between naproxen and esomeprazole that would indicate any novel adverse pharmacology, toxicology, physical or chemical interaction or tolerability issues as a result of their combination. Accordingly, no new non-clinical pharmacology, pharmacokinetic or toxicology studies have been conducted with PN 400.

At least one dose of PN 400 was given to 1326 subjects in the Phase 1 and Phase 3 studies. Of these, 135 subjects took PN 400 for 12 months and 491 for six months. More than 360 doses were taken by 264 subjects and more than 180 doses were taken by 561 subjects.

The Expanded Safety Population (ESP) included studies PN400-301, PN400-302, PN400-304, PN400-307, and PN400-309. The ESP examines only subjects who were assigned to the PN 400 treatment group (N= 1157). The population was predominantly white (83%), female (67%) and had a mean age of 61 years. About 7% of subjects were greater than or equal to 75 years of age and approximately 33.4% were ≥ 65 years.

In the ESP, 88.5% of subjects reported taking NSAIDs for osteoarthritis, 4.7% for rheumatoid arthritis (RA), 0.4% for ankylosing spondylitis (AS) and 13% had other reasons for use of NSAIDs. Twenty five point seven percent (25.7%) used Low Dose Aspirin, 51.9% entered with a history of upper GI disorders and 56.4% entered with a history of cardiovascular disease.

Common Treatment Emergent Adverse Events (TEAEs) in the Primary Safety Population

More subjects who took EC naproxen reported related TEAEs (75.8%) compared to subjects who took PN 400 (53.5%). This difference was primarily due to reports of TEAEs in GI Disorders. The most common preferred term, erosive gastritis, was found in 38.0% of subjects taking EC naproxen and 19.4% of those taking PN 400. Subjects assigned to EC naproxen also had more dyspepsia, gastric ulcer, esophagitis, erosive duodenitis, GERD, duodenal ulcer, and erosive esophagitis than did subjects who took PN 400. The preferred term gastritis was the only related TEAE more frequently reported in subjects taking PN 400 (15%) than in subjects taking EC naproxen (12.2%). The only related TEAE in Cardiac Disorders was a single case of angina in a subject from the EC naproxen group.

Deaths

There were no deaths reported in any subject participating in any of the studies reported in this application.

Other Serious Adverse Events

All 58 SAEs were reported by 53 subjects in the 6 Phase 3 studies. Overall, the frequency of SAEs was similar between PN 400 (2.7%) and EC naproxen (3.1%). When adjusted for exposure, the rate of SAEs was similar in the PN 400, EC naproxen and celecoxib groups. In the PN 400 group, there were 6.8 SAEs per 100 patient-years compared with 9.1 SAEs per 100 patient-years in the EC naproxen group and 7.9 SAEs per 100 patient-years in the celecoxib group.

The most common SAEs were in Cardiac Disorders. The frequency of Cardiac Disorders was 0.5% in the PN 400 group, 0.5% in the EC naproxen group and 0.2% in the celecoxib group. There were 4 reports of atrial fibrillation/flutter in subjects assigned to PN 400, 3 of which were SAEs. One subject entered the study with irregular rhythm that was later confirmed to be atrial fibrillation and a second subject developed atrial fibrillation approximately 3 weeks after stopping study drug. There were 2 cases of atrial fibrillation that occurred while the subjects were taking PN 400. However, none of the events were considered to be related to study drug by the Principal Investigator.

Serious adverse events were next most commonly reported from the SOC of Infections and Infestations. There was a similar frequency of pneumonia in the PN 400 treatment group with 2 cases (0.2%) compared to the EC naproxen group with 1 case (0.2%). There were no reports of pneumonia in the celecoxib group.

Serious Adverse Events and Treatment Emergent Adverse Events Leading to Discontinuation

More subjects discontinued from the EC naproxen group (40.6%) than from PN 400 (12.2%) and celecoxib (7.8%). This difference was due to discontinuation from GI Disorders including gastric ulcer, duodenal ulcer, and dyspepsia. More subjects assigned to PN 400 withdrew due to TEAEs from Investigations (0.9%) than did celecoxib (0.6%) or naproxen (none) or placebo (none) although no pattern was detected.

Withdrawal from clinical studies due to TEAEs from Cardiac Disorders occurred in 0.4% and 0.5% of subjects assigned to PN 400 and EC naproxen, respectively. The TEAE of hypertension, using the combined preferred terms of 'hypertension' and 'blood pressure increase', led to the withdrawal of 4 subjects assigned to PN 400, 2 subjects assigned to EC naproxen, 3 subjects (in the celecoxib treatment group and 1 subject assigned to placebo).

Laboratory Values in Studies in Patients

More subjects shifted neutrophils from low or normal to high in the PN 400 treatment group (16.5%) than did celecoxib or placebo treatment groups (12.6% and 11.6%, respectively).

More subjects shifted eosinophils from low or normal to high in the PN 400 treatment group (18.1%) than did celecoxib or placebo treatment groups (10.3% and 7.1%, respectively)

Over a period of 3-12 months, there were no increases in the mean for ALT, AST, alkaline phosphatase or bilirubin for PN 400 subjects. Group mean, median and shifts in ALT and AST, and in bilirubin, were similar and consistent between the active treatment groups. Elevations in transaminases greater than 3x ULN were noted in subjects in all treatment groups and were rare. Similar proportions of subjects in all treatment groups had elevation of transaminases to greater than 3X ULN. The 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 PN 400.

The laboratory findings in this application were consistent with the changes in laboratory tests described in the Approved Product Labeling of the components of PN 400. The clinical laboratory changes seen in the PN 400 treatments group are generally similar to the active comparators, EC naproxen and celecoxib, in the trials.

Post Marketing Data

PN 400 tablets are currently not approved for marketing in any country and therefore there are no post marketing data on the use of PN 400.

The individual components of PN 400, esomeprazole and naproxen, have been marketed globally for a number of years and post-marketing adverse experience data are recorded in the individual prescribing information.

The concurrent prescribing of esomeprazole and NSAIDs such as naproxen is supported by NEXIUM Approved Product Labeling. POZEN is relying on previous findings of safety and efficacy of naproxen in this 505(b)2 application. The proposed information to be included in the PN 400 prescribing information regarding adverse experiences should be derived from naproxen labeling and esomeprazole labeling.

There are several published randomized controlled studies that address the safety and efficacy of esomeprazole when prescribed with NSAIDs including naproxen for the reduction in NSAID-associated gastric ulcer. However, specific safety information on esomeprazole and naproxen is not provided in these published studies.

The cumulative reported (inclusive to 11 May 2009) medically confirmed, spontaneous case reports to AstraZeneca with esomeprazole specifically with concomitant naproxen was 67 including 34 SAEs. The most common AE was pruritus (3 AE reports) and the most common SAE was hypersensitivity (2 SAE reports). Other reported AEs include arthritis, confusional state, gait disturbance, nausea; peripheral edema, decreased platelet count and decrease WBC count. There were no reports of liver function abnormalities or of liver disease.

In general the types of spontaneous adverse events reported are consistent with the adverse event profile of esomeprazole and naproxen. Moreover, the types of adverse events were generally consistent with the adverse event profile reported in the PN 400 development program.

9. Advisory Committee Meeting

N/A

10. Pediatrics

PREA is triggered for this application because this is a new indication. In addition, the new combination also triggers PREA as a “new active ingredient.” [REDACTED] (b) (4)

PMHS was consulted and recommended:

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.

I concurred with PMHS recommendations and the above recommendations were conveyed to the sponsor. The sponsor submitted a new pediatric plan to defer pediatric study under PREA for VIMOVO in 2- to 11-year-olds and in 12- to 17-year-olds with JRA.

The sponsor proposed a single safety/population PK study in children with JRA who are 2 years to 11 years of age to support dosing and safety information in this population. Following formulation development and PK/PD in adults, [REDACTED] (b) (4) and will be a 6month, multicenter, open-label study to evaluate the safety and dosing of VIMOVO in this age range. It is to be conducted in approximately 60 patients with JRA who require treatment with NSAIDS to permit comparison to historical controls from published studies in JRA with naproxen. Protocol will be submitted on Jan. 15, 2013; Study will be completed on June 30, 2014; and Final Report will be submitted on Nov. 30, 2014.

The sponsor also proposed a single safety/population PK study in adolescents (12- to 17) with JRA. Following formulation development and PK in adults, this study will be a 6-month, multicenter, open-label study to evaluate the safety and PK of VIMOVO in adolescents with JRA. It is to be conducted in approximately 60 patients with JRA who require treatment with NSAIDS to permit comparison to historical controls from published studies in JRA with naproxen. Protocol will be submitted on Dec. 15, 2011; Study will be completed by May 30 2013; and Final Report will be submitted by Oct. 31, 2013.

The new pediatric study plan seems reasonable. We discussed the proposed plan with PeRC on April 14 and PeRC concurred with the plan.

11. Other Relevant Regulatory Issues

Four clinical investigators were inspected in support of the application as part of a routine data audit: Drs. Riff, Kavitz, Shamim, and Portnoy. No regulatory violations were noted at Drs. Kavitz and Shamim's sites, and although minor regulatory violations were noted at the sites of Drs. Riff and Portnoy, these are unlikely to significantly impact data integrity. Division of Scientific Investigations concluded that the data generated from the above 4 sites can be used in support of the NDA.

12. Labeling

Vimovo is the proposed proprietary name for the combination product of enteric coated Naproxen and Esomeprazole Magnesium Tablets. This proposed name was evaluated from a safety and promotional perspective based on the product characteristics provided by the Applicant.

The Proprietary Name Risk Assessment findings indicate that the proposed name, Vimovo, is not vulnerable to name confusion that could lead to medication errors nor is it promotional. The assessment supports the findings of the External Study submitted by the Applicant. Thus the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proprietary name, Vimovo for this product at this time.

I concurred with review team's labeling recommendations that incorporated in the final labeling.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I concurred with Dr. Erica Wynn and Jin Chen's recommendations that NDA 22-511 VIMOVO (naproxen/esomeprazole magnesium) tablets be approved for the indication of 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.

- Risk Benefit Assessment

PN400 is a tolerated and effective oral therapy for the relief of signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis in patients at risk of developing NSAID-associated gastric ulcers. Efficacy of PN 400 is demonstrated by bioequivalence of both tablet strengths (containing 500 mg and 375 mg naproxen) to the corresponding strength of EC-NAPROSYN. PN 400 Tablets bid reduces the occurrence of gastric ulcers, NSAID-associated upper gastrointestinal adverse events and duodenal ulcer compared to EC naproxen 500 mg bid. The effectiveness of PN 400 in the reduction in occurrence of gastric ulcers was not decreased when analyzed by the risk factors of age, or the concomitant use of low dose aspirin.

The overall safety profile of PN 400 is consistent with the profile that has been established for oral naproxen or esomeprazole monotherapy. PN 400 provides improved upper gastrointestinal safety for subjects who require NSAIDs. As expected, this improvement is accompanied by some treatment emergent adverse events (TEAE) that are associated with the long term use of esomeprazole. No alteration of the known safety profile of naproxen was observed including no changes in the known TEAE profile, the clinical laboratory profile or alterations of vital signs or physical examinations.

Group mean changes in physical examinations, blood pressure and heart rate were not different between PN 400 and EC naproxen at 6 months.

Risks associated with the use of PN 400 are those of the component drugs which are known and have been replicated in the reported clinical trials.

In conclusion, the results of studies conducted in this development program and submitted in this NDA confirm that PN 400 is a safe and effective oral therapy for the relief of signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis in patients at risk of developing NSAID-associated gastric ulcers.

- Recommendation for Postmarketing Risk Management Activities

None

- Recommendation for other Postmarketing Study Commitments

As a Phase 4 commitment, within one year post approval, submit new dissolution data on the testing of naproxen in Vimovo FDC tablets using the Agency's recommended USP dissolution methodology for enteric coated (i.e., delayed release) drug products (refer to

Biopharmaceutical review dated 9-MAR- 2010). The applicant has committed to the proposal via amendment dated 4-MAR-2010.

- Recommended Comments to Applicant

None

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/

RUYI HE
04/23/2010