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APPLICATION NUMBER:
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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	• 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.

(b) (4)

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 form 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 Cmax. 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 Cmax than the morning dose. AUC and Cmax 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.

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