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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 [redacted] (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

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