February 03, 2014

BY COURIER

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061, HFA-305
Rockville Maryland 20852

RE: Use of Non-Enteric Coated Naproxen in Generic Versions of VIMOVO® (naproxen/esomeprazole magnesium)

Ladies and Gentlemen:

CITIZEN PETITION

Horizon Pharma, Inc. ("Horizon") submits this Citizen Petition in accordance with the Food and Drug Administration's ("FDA's" or the "Agency's") regulations set forth in 21 CFR § 10.30. Horizon requests that the Commissioner of the FDA take the actions described below with respect to any Abbreviated New Drug Application ("ANDA") submitted to FDA and listing VIMOVO® (naproxen/esomeprazole magnesium) ("VIMOVO") as the reference listed drug ("RLD"). Horizon is the holder of the NDA for VIMOVO, having licensed the product on November 18, 2013 and accepted the NDA transfer on December 16, 2013.

As discussed in greater detail below, VIMOVO is specifically formulated to reduce the potential for damage to the gastric mucosal tissue induced by non-steroidal anti-inflammatory drugs ("NSAIDs"). VIMOVO consists of an immediate-release esomeprazole magnesium (proton pump inhibitor [PPI]) layer surrounding an enteric-coated naproxen (NSAID) core. Naproxen, like other NSAIDs, has been shown to increase the risk of stomach and intestinal problems, such as bleeding or an ulcer.[1] Esomeprazole, however, is a known gastroprotective agent that works by inhibiting the secretion of gastric acid thus decreasing the amount of acid in the stomach. Because the naproxen component is completely surrounded by enteric coating, VIMOVO releases its esomeprazole before the release of naproxen. This allows the gastroprotective effects of esomeprazole to take hold before naproxen is released, thus reducing the potential for gastric ulcers. This significant reduction in gastric ulcers was demonstrated in the two VIMOVO six-month clinical endoscopy trials in 854 patients.[2]

Horizon has received a notice letter from a generic manufacturer that the manufacturer has submitted an ANDA, referencing VIMOVO as the reference listed drug ("RLD"), for a generic product that contains a measurable amount of naproxen outside of the enteric coating.[3]

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[1] Singh G, Mannalithara A, Sostek M, Mitha A, Triadafilopolous G. *Naproxen Use Increases the Risk for Complicated Gastroduodenal Ulcers in a Dose-Dependent Fashion,* Am J Gastroenterology 2009; 104 (Suppl 3) #136.
[2] *See* VIMOVO Prescribing Information, Section 14.
[3] In its Notice Letter dated November 20, 2012, Dr. Reddy's Laboratories, Inc. ("DRL") described the product which is the subject of its Abbreviated New Drug Application Number 204206 as follows:

The would-be generic manufacturer has done this not to increase efficacy or reduce safety concerns. To the contrary, failure to completely enclose the entire naproxen component in an enteric coating specifically obviates VIMOVO's careful design and allows release of a measurable amount of naproxen before the gastroprotective benefits of esomeprazole can take effect. This could cause that generic product to have more frequent or more severe gastrointestinal adverse events than does VIMOVO. Thus, we respectfully suggest that FDA take steps to ensure that any proposed generic version of VIMOVO that does not have all of the naproxen enterically coated will have a different GI adverse event profile than VIMOVO.

I. ACTIONS REQUESTED

Horizon requests that FDA take the following actions:

1. Require that any application listing VIMOVO as the RLD, which seeks approval for a generic product that employs less than a complete enteric coating around the naproxen component, be supported by either (a) pharmacokinetic data sufficient to show that the timing of release of naproxen in the generic product is equivalent to that of VIMOVO, or (b) data from clinical trials demonstrating that the proposed generic product does not cause more frequent or more severe gastrointestinal adverse events than does VIMOVO;

2. If additional clinical trials described above are necessary to support safety of the proposed generic product, require that any such application be filed as a 505(b)(2) application, rather than as an ANDA; and

3. Refuse to approve any currently pending ANDA for such a product, and require the applicant to withdraw its ANDA and resubmit as a 505(b)(2) application, accompanied by the additional clinical testing described above.

II. STATEMENT OF GROUNDS

A. Factual Background

1. *NSAIDs and Gastrointestinal Adverse Events*

NSAID therapy is one of the most common and effective treatments available for musculoskeletal diseases such as osteoarthritis.[4] Unfortunately, chronic use of NSAIDs can give rise to several serious safety concerns which are clearly outlined in class-labeling assigned to all NSAIDs. Among the more prevalent of these is that chronic use of NSAIDs is associated with an increased risk for significant gastrointestinal adverse events. These can range from

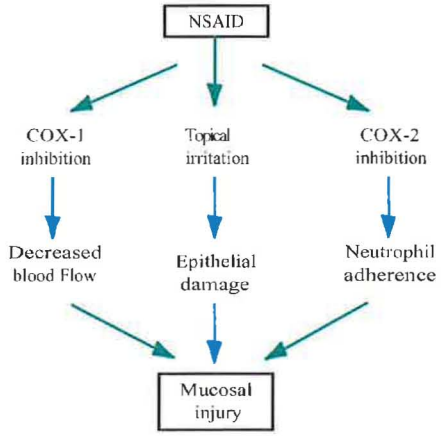
"A measurable portion of the entire amount of the naproxen (NSAID) in DRL's proposed product is not surrounded by a coating that prevents release at a pH of less than 3.5 but instead is coated in a polymer that completely dissolves at a much lower pH, and is released at that pH."

[4] Goldstein J.L., et al. *Clinical Trial: the incidence of NSAID-associated endoscopic gastric ulcers in patients treated with PN 400 (naproxen plus esomeprazole magnesium) vs. enteric-coated naproxen alone*, Aliment Pharmacol Ther 2010; 32:401-413.

endoscopic gastric ulcers (15-46% of NSAID users),[5] to clinically relevant symptomatic ulcers and serious ulcer complications.[6]

The etiology of NSAID induced damage to the gastric mucosa is likely multifactorial as depicted in Figure 1 below.[7] Although a number of possible mechanisms have been suggested, the predominant effect on gastric mucosa induced by NSAID systemic exposure is inhibition of the enzymes cyclooxygenase 1 and 2. The former is predominantly responsible for generating a protective barrier to the mucosal surface of the stomach to alleviate tissue exposure to the acidic noxious environment of the gastric lumen to allow for normal digestion of food. Once the mucosal barrier is compromised by inhibition of these enzymes, then local effects become very important; in particular the exposure to gastric acid. In addition, COX-2 inhibition can lead to greater adherence of neutrophils to endothelium and slowed healing of mucosal insults.

Figure 1.



In addition to the inhibition of cyclooxygenase enzymes, some believe that damage to the gastric mucosa is enhanced by the local presence of NSAIDs, almost all of which are formulated as weak organic acids. NSAIDs may locally damage the gastric mucosa by close approximation to the mucosal cells leading to superficial cell death leaving holes, which can be widened and deepened with ongoing exposure to the acidic environment. The enteric coating of the NSAID in VIMOVO prevents that exposure. By contrast, drugs that are not completely enteric coated might lead to this effect of increased damage by exposure of the drug in the stomach lumen.

[5] Geis GS, Stead H, Wallemark C-B, Nicholson PA. *Prevalence of Mucosal Lesions in the Stomach and Duodenum Due to Chronic Use of NSAID in Patients with Rheumatoid Arthritis or Osteoarthritis, and Interim Report on Prevention by Misoprostol of Diclofenac Associated Lesions,* J Rheumatol 1991; (Suppl 28) 18:11-14.
[6] Goldstein J.L., et al. *Clinical Trial: the incidence of NSAID-associated endoscopic gastric ulcers in patients treated with PN 400 (naproxen plus esomeprazole magnesium) vs. enteric-coated naproxen alone*, Aliment Pharmacol Ther 2010; 32:401-413.
[7] Wallace J, *Pathogenesis of NSAID-induced gastroduodenal mucosal injury*, Best Pract. & Res. Clin Gastroenterology 2001; 15(5):691-703.

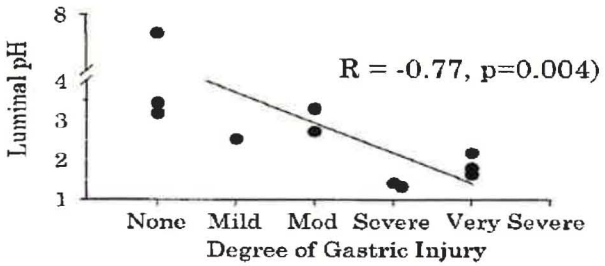
Regardless of the cause(s) for increased risk of GI complications, evidence increasingly makes clear that raising the pH of the gastric environment has a gastroprotective effect. According to Wallace, for example,

> While the presence of acid in the lumen of the stomach may not be a primary factor in the pathogenesis of NSAID-induced gastroenteropathy it can make an important contribution to the chronicity of these lesions and to bleeding by impairing the restitution process, interfering with haemostasis and inactivating several growth factors that are important in mucosal defense and repair.[8]

Indeed, inhibition of acid secretion, which raises gastric pH, has been directly shown to reduce the degree of gastric injury in patients on chronic NSAID therapy. This fact is demonstrated, for example, by a study conducted by Shiotani, et al., investigating whether the severity of acute and chronic mucosal inflammation, *H. pylori* density, mucosal IL-8 levels, or gastric mucosal and juice nitrite levels had predictive value in relation to the severity of NSAID-induced gastric mucosal damage.[9] After receiving placebo for three days, volunteers underwent upper gastrointestinal endoscopy for histology and determination of IL-8 and nitrite levels. Following a three week washout period, each patient then received naproxen (500 mg BID) and endoscopy was repeated on day four. Fasting gastric juice pH and nitrite levels were assessed at each endoscopy.

As shown in Figure 2, the results of this study clearly demonstrate that gastrointestinal complications from NSAID therapy are inversely related to gastric pH:

Figure 2.



Efforts to reduce gastrointestinal adverse events in chronic NSAID therapy have met with mixed results. In light of the well-known risks for gastrointestinal problems, many physicians prescribe a gastroprotective agent to patients needing chronic NSAID therapy, and who have an increased risk for gastrointestinal complications. Unfortunately, adherence is frequently an

[8] Wallace J, *Pathogenesis of NSAID-induced gastroduodenal mucosal injury*, Best Pract. & Res. Clin Gastroenterology 2001; 15(5):691-703.
[9] Shiotani A, Yamaoka Y, Hala M, El-Zimaity T, Ali Saeed M, Qureshi W, Graham D, *NSAID Gastric Ulceration Predictive Value of Gastric pH, Mucosal Density of Polymorphonuclear Leukocytes, or Levels of IL-8 or Nitrite,* Digestive Diseases and Sciences, 2002, 47(1); 38-43.

issue. Recent studies have shown that even when prescribed alongside an NSAID, patients adhere to prescribed gastroprotective therapy only half the time.[10]

2. *VIMOVO*

VIMOVO combines a well-established NSAID (naproxen) with a proven PPI gastroprotective agent (esomeprazole magnesium). The addition of the esomeprazole component to naproxen is intended to provide gastroprotection. Thus, VIMOVO is indicated to relieve the signs and symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis, and to decrease the risk of gastric ulcers in patients at risk of developing such ulcers from treatment with NSAIDs. Indeed, in two clinical studies conducted to support approval, VIMOVO showed a clear reduction in the incidence of gastric ulcer formation as compared to enteric-coated naproxen alone.[11]

VIMOVO is specifically formulated to allow esomeprazole (a proton pump inhibitor) to achieve its gastroprotective impact before naproxen is released into the system. VIMOVO is a single-tablet formulation comprising an enteric coated naproxen core surrounded by an immediate release esomeprazole mantle. Proton pump inhibitors, such as esomeprazole, work by decreasing the generation of hydrochloric acid in the gastric lumen, which increases the gastric pH, thereby protecting the gastric mucosa. VIMOVO's design is intended to produce a sequential delivery of gastroprotective esomeprazole before systemic (or local) exposure to naproxen.

3. *Generic Versions with Only a Portion of Naproxen Enteric Coated*

Several generic manufacturers recently have filed ANDAs listing VIMOVO as the RLD. Horizon understands based on a notice letter received that at least one of those ANDA applications is for a product that includes a portion of the naproxen component that is not surrounded by an enteric coating. As discussed below, such a product would allow for earlier release of potentially significant amounts of naproxen.

B. Discussion

1. *VIMOVO's Sequential Delivery Mechanism is Essential to Reduction of Gastrointestinal Adverse Events*

VIMOVO addresses the issue of gastrointestinal adverse events in two ways. First, by adding the proton-pump inhibitor esomeprazole, VIMOVO acts to reduce overall gastric acid, thereby raising gastric pH. Esomeprazole's impact on gastric pH is clearly demonstrated by a study conducted by Miner, et al., which to guide formulation selection for Phase 3 clinical testing compared gastric acid suppression at days 1 and 9 in the following four formulations:

1. EC naproxen 500 mg BID + esomeprazole 30 mg;

[10] Van der Linden MW, *Gastroprotection among new chronic users of non-steroidal anti-inflammatory drugs: a study of utilization and adherence in The Netherlands*, Current Med Res Opin. 2009 Jan;25(1):195-204.
[11] *See* VIMOVO Prescribing Information, Section 14.

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