



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

¹ Singh G, Mannalithara A, Sostek M, Mitha A, Triadafilopoulos 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

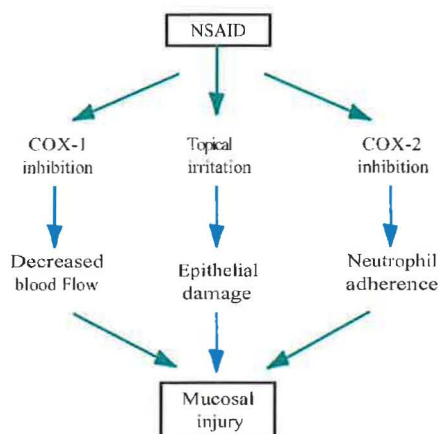
"A measurable portion of the entire amount of the naproxen (NSAID) in DRL's proposed product is not surrounded by a coating that prevents release at a pH of less than 3.5 but instead is coated in a polymer that completely dissolves at a much lower pH, and is released at that pH."

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.



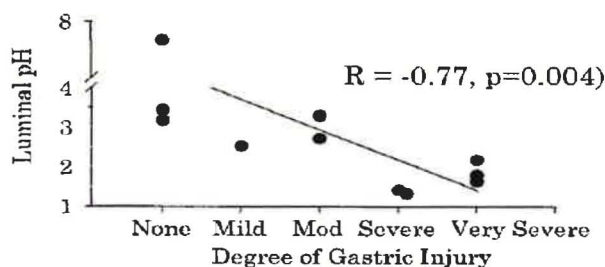
Regardless of the cause(s) for increased risk of GI complications, evidence increasingly makes clear that raising the pH of the gastric environment has a gastroprotective effect. According to Wallace, for example,

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.



2. EC naproxen 500 mg BID + esomeprazole 20 mg (VIMOVO);
3. EC naproxen 500 mg BID + esomeprazole 10 mg; and
4. Non-EC naproxen 500 mg BID + EC esomeprazole 20 mg¹²

The study measured the percentage of time over 24 hours that intragastric pH was greater than 4.0, on days one and nine respectively. The results of the study, set forth in Table 1, show that increasing doses of esomeprazole clearly led to raised gastric pH over time. At day 1, for example, the mean percentage of time with intragastric pH of 4.0 or greater was 27.8%, 20.5%, 12.8%, and 21.3% for each of the four listed formulations, respectively. By contrast, on day nine, these percentages had increased to 76.5%, 71.4%, 40.9%, and 59.9%, respectively (see Table 1). The various study treatments were well tolerated. No endoscopic assessment was performed, however, which is a primary efficacy endpoint for evaluating products intended to prevent NSAID-associated upper GI toxicity. Further, this was a small study of short duration.¹³ Ultimately, the EC naproxen 500 mg BID + esomeprazole 20 mg formulation was chosen for VIMOVO to be tested in Phase 3 gastroprotection endoscopy studies of six-months treatment duration.

Table 1. Percentage of time with gastric pH >4.0 over 24 h on days 9 and 1 (PP population)

Time pH >4.0 (%)	Day 9				Day 1			
	PN400/E30, n = 25	PN400/E20, n = 25	PN400/E10, n = 25	Naproxen+EC E20, n = 25	PN400/E30, n = 25	PN400/E20, n = 25	PN400/E10, n = 25	Naproxen+EC E20, n = 25
Mean (s.d.)	76.5 (12.3)	71.4 (13.0)	40.9 (22.5)	56.9 (10.1)	27.8 (22.6)	20.5 (16.6)	12.8 (11.1)	21.3 (13.6)
Median	78.8	70.4	35.8	55.1	20.0	15.3	9.1	16.8
% coefficient of variation	16	18	55	18	81	81	87	64
Range	49.8-95.3	51.8-97.6	10.3-85.3	40.6-75.5	1.8-89.6	4.4-74.4	3.0-53.8	3.2-58.2
LS mean (S.E.)	76.8 (3.0)	71.5 (3.0)	41.1 (3.0)	57.2 (3.0)	27.9 (3.3)	20.6 (3.3)	12.7 (3.4)	21.5 (3.3)
LS mean difference vs. naproxen + EC E20 (S.E.)	19.5 (3.3)	14.2 (3.3)	-16.1 (3.3)	—	6.4 (3.2)	-0.92 (3.2)	-8.9 (3.2)	—
95% CI	13.0-26.0	7.8-20.7	-(22.3-9.7)	—	0.0-12.8	-(7.3-5.4)	-(15.3-2.4)	—

PP, per protocol; EC, enteric coated; s.d., standard deviation; LS, least-squares; S.E., standard error; CI, confidence interval.

Second, as noted above, VIMOVO is specially formulated to release its esomeprazole component prior to release of naproxen. VIMOVO is designed for immediate release of the esomeprazole component, which is located just underneath the drug's outer shell. By contrast, VIMOVO's naproxen component is located in the tablet core, and is completely surrounded by

¹² Miner P, Jr., et al., *Clinical trial: evaluation of gastric acid suppression with three doses of immediate-release esomeprazole in the fixed-dose combination of PN 400 (naproxen/esomeprazole magnesium) compared with naproxen 500 mg and enteric-coated esomeprazole 20 mg: a randomized, open-label, Phase I study in healthy volunteers*, *Aliment Pharmacol Ther* 2010; 32:414-424.

¹³ Summary Minutes of Gastrointestinal Drugs Advisory Committee (GIDAC), November 4, 2010.



an enteric coating. This enteric coating is designed to release naproxen only in a pH ≥ 5.5 environment.¹⁴ Because the normal pH environment of the stomach typically ranges between 1.5 to 3.5, this enteric coating ensures that naproxen is not released until the enteric-coated core passes through the stomach and reaches the small intestine. Thus, by the time VIMOVO begins to release its naproxen, VIMOVO's esomeprazole has already begun to impact gastric pH. This provides a less favorable environment for the development of gastric ulcers.¹⁵ Two Phase 3 studies subsequently demonstrated the effect of VIMOVO to decrease the risk of developing gastric ulcers in patients at risk of developing NSAID associated gastric ulcers.¹⁶

2. *Non-Enteric Coated Naproxen Would Reduce the Benefit of Sequential Release*

Horizon understands that at least one ANDA applicant for generic VIMOVO has formulated its proposed product with a portion of the naproxen not enteric coated. Although it is not known precisely what percentage of the proposed generic product's naproxen is outside the enteric-coated core, locating any naproxen outside the enteric-coated core will result in the immediate release of at least some portion of the naproxen at the same time as esomeprazole is released.¹⁷

Any portion of the generic product's naproxen that is released prematurely in the stomach will act both topically and systemically without the benefit of the raised gastric pH produced by the esomeprazole component. As noted in Figure 2, the gastric injury that can be caused by naproxen is inversely related to gastric pH. In other words, unlike VIMOVO, which releases its naproxen component only after its esomeprazole component has begun to raise gastric pH, a generic product without all of the naproxen enterically coated would release at least some portion of its naproxen in a less gastroprotective environment, before gastric pH has begun to rise.

3. *FDA Should Take Steps to Ensure That a Generic Product Does not Jeopardize Patient Safety*

As FDA knows, the potential for GI adverse events with chronic NSAID therapy in patients at risk for gastrointestinal complications is significant. Like all NSAIDs, VIMOVO's package insert includes a "black" box warning relating to the potential for "serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal."¹⁸ Thus, a reduction in the enteric coating surrounding the naproxen core could subject patients to significantly increased risk of potentially fatal side-effects. As a result, FDA should take steps to ensure that patients taking the proposed generic product are not exposed to such an increased risk unnecessarily. This is particularly so where, as

¹⁴ See VIMOVO Prescribing Information, Section 12.1.

¹⁵ Roberts DN, Miner PB. *Safety aspects and rational use of naproxen + esomeprazole combination in the treatment of rheumatoid disease.* Drug, Healthcare and Patient Safety 2011;3 1-8.

¹⁶ See VIMOVO Prescribing Information, Section 14.

¹⁷ Miner P, Plachetka J, Orlmans E, et al. *Clinical trial: evaluation of gastric acid suppression with three doses of immediate-release esomeprazole in the fixed-dose combination of PN 400 (naproxen/esomeprazole magnesium) compared with naproxen 500 mg and enteric-coated esomeprazole 20 mg: a randomized, open-label, phase 1 study in healthy volunteers.* Aliment Pharmacol Ther 2010;32:414-424.

¹⁸ See VIMOVO Prescribing Information (Highlights).



here, the increased safety risk is not justified by a commensurate increase in overall effectiveness.

At a minimum, we suggest FDA require that any ANDA applicant for a product that lists VIMOVO as the RLD, and includes a portion of naproxen outside of the enteric coated core, includes with its ANDA pharmacokinetic data adequate to show that the timing of release of naproxen from the generic product is equivalent to the timing of release of naproxen in VIMOVO.¹⁹ Such a demonstration cannot be made with reference to FDA's traditional requirements for bioequivalence testing, which measure only maximum concentration (C_{max}) and area under the concentration-time curve (AUC), but do not address the timing of naproxen release relative to esomeprazole. For example, a product that contained a portion of naproxen outside of the enteric-coated core would release naproxen before the esomeprazole component is able to begin raising gastric pH, even though the overall values of naproxen are within the specified 80-125 confidence interval range for C_{max} and AUC.

In the absence of clear pharmacokinetic evidence described above, FDA should require that the generic applicant provide data from clinical trials demonstrating that the proposed product does not result in more frequent, or more severe, gastrointestinal adverse events than does VIMOVO. Of course, where clinical trials are necessary to support approval, an ANDA is not the appropriate pathway for approval. As a result, any such product should be required to submit its application as a 505(b)(2) application rather than an ANDA. In the case of applications already on file with FDA, FDA should require the applicant to withdraw its ANDA and resubmit as a 505(b)(2).²⁰

III. ENVIRONMENTAL IMPACT

Horizon claims a categorical exclusion under 21 C.F.R. § 25.31.

IV. ECONOMIC IMPACT STATEMENT

Horizon will, upon request by the Commissioner, submit economic impact information, in accordance with 21 C.F.R. § 10.30(b).

V. CERTIFICATIONS

The undersigned certifies that, to the best knowledge and belief of the undersigned, this Petition includes all information and views on which the Petition relies, and that it includes representative data and information known to Horizon which are unfavorable to the Petition.

¹⁹ See VIMOVO Prescribing Information, Section 12.3.

²⁰ See, e.g., 57 Fed. Reg. 17950, 17953 (April 28, 1992) ("Section 505(j) of the act permits ANDAs only for duplicate and related versions of previously approved drug products. The ANDA applicant relies on a prior agency finding of safety and effectiveness based on the evidence presented in a previously approved new drug application. *If investigations on a drug's safety or effectiveness are necessary for approval, an ANDA is not permitted.*"). (emphasis added). See also 54 Fed. Reg. 28872, 28879 (1989) ("Such a product would require investigations to show its safety and effectiveness; thus an ANDA would not be appropriate.").



Horizon makes the following certification pursuant to FDC Act § 505(q)(1)(H): I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: September 20, 2013 (during product licensing due diligence). If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Horizon. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,

A handwritten signature in black ink that reads 'Timothy P. Walbert'.

Timothy P. Walbert
Chairman, President and Chief Executive Officer

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